Halogenated diazines and triazines

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UNIVERSITY OF DURHAM

A THESIS

entitled

HALOGENATED DIAZINES AND TRIAZINES

Submitted by

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A candidate for the degree of Doctor of Philosophy

1978

To my Mother and Father

with thanks for all that they have done

ACKNOWLEDGEMENTS

I would like to express my thanks to Professor R D Chambers under whose guidance this research was undertaken, for considerable encouragement, advice and discussion

Thanks are due to Dr R S Matthews for his expert advice with n m r. data, to many technical and laboratory staff for their assistance, and to Mrs B A McGonigle for typing this thesis.

Finally, thanks are also due to the Science Research Council for a maintenance grant.

MEMORANDUM

The work described in this thesis is original except where specifically stated to the contrary. It has not previously been submitted either wholly, or in part, for a degree at this or any other university.

ABSTRACT

PART I A convenient synthesis of 3,5,6-trichloro-1,2,4-triazine was developed using 3,5-dihydroxy-1,2,4-triazine and 6-bromo-3,5-dihydroxy-1,2,4-triazine as precursors

No product was obtained on photolysis of 3,5,6-trichloro-1,2,4-triazine but nitrogen elimination occurred on pyrolysis to give trichloroacrylonitrile The red colouration from the pyrolyzate (at -196°) was deduced to be from trichloroazete This reaction is the first evidence of azete generation from a 1,2,4-triazine

The fluorination of 3,5,6-trichloro-1,2,4-triazine was attempted with potassium and caesium fluorides, with and without a solvent 3,5,6-Trifluoro-1,2,4-triazine was formed in many of the reactions but was always detected as a minor product in unstable mixtures

Polyfluoroalkylations of 3,5,6-trichloro-1,2,4-triazine were attempted with tetrafluoroethylene, hexafluoropropene, n-octafluorobut-2 ene and hexafluorocyclobutene Alkylation was successful only with hexafluoropropene where perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine was prepared in good yields. Attempts to prepare mono- and di-alkyl derivatives were unsuccessful

Photolysis of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine gave three products, perfluoro-isobutyronitrile and perfluoro-2,5-dimethylhex-3-yne by nitrogen elimination and perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine by rearrangement Pyrolysis gave nitrogen elimination but there was no evidence of any azete formation

PART II The novel cyclisation observed with 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine was studied A process of internal nucleophilic substitution occurred, with elimination of hydrogen fluoride, to give a product with an ambiguous bicyclic structure The vivid purple coloured intermediate

formed on loss of fluoride ion was trapped as a tetrafluoroborate salt

In an aid to determine the structure of the bicyclic product, various dimethylamino heptafluoroisopropylpyridazines were prepared

CONTENTS

APPENDICES

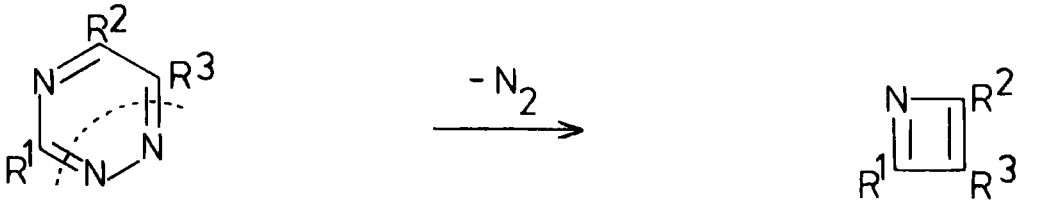
PART I

CHAPTER 1

THE ELIMINATION OF NITROGEN FROM 1,2,4-TRIAZINES

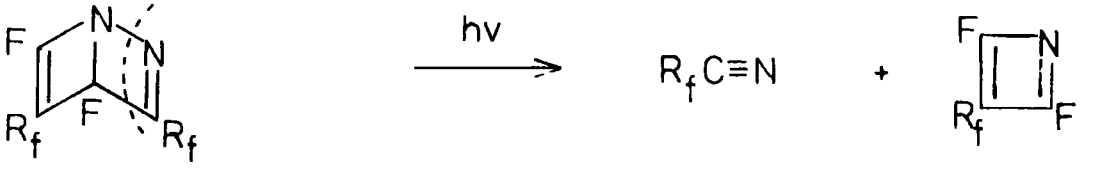
1 1 GENERAL INTRODUCTION

The aim of this work was to investigate a rational method for generating azetes (2) by nitrogen elimination from 1,2,4-triazines (1)



(1) (2)

This follows from earlier work[1] at these laboratories where a fluorinated azete (4) was produced by elimination of $R_FC{\equiv}N$ from a para-bonded valence isomer (3) of a pyridazine



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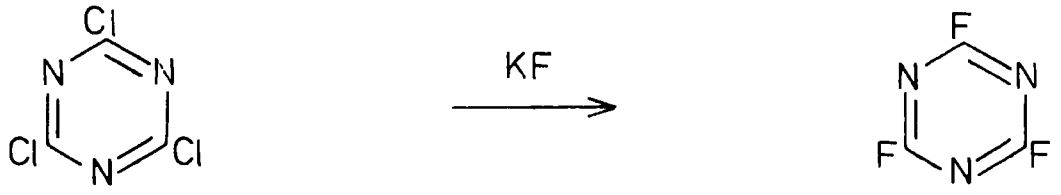
This chapter is concerned with nitrogen elimination reactions The mechanisms and reactive intermediates involved are discussed This discussion includes the competing process of rearrangement A summary of the reports of generated azetes is also given

The following chapter discusses the synthesis of 1,2,4-triazines Although many 1,2,4-triazines have been prepared, prior to this work, no

perfluoro-derivatives were known A general procedure for the preparation of perfluoroaromatic compounds is by fluorination of the perchloro-derivative using an alkali-metal fluoride, e g 2,4,6-trichloro-1,3,5-triazine (5) is converted to 2,4,6-trifluoro-1,3,5-triazine (6)



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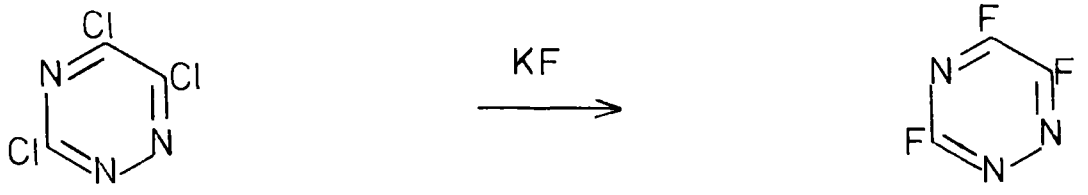
By adopting this general procedure the most obvious route to 3,5,6-trifluoro-1,2,4-triazine (8) is by fluorination of 3,5,6-trichloro-1,2,4-triazine (7)



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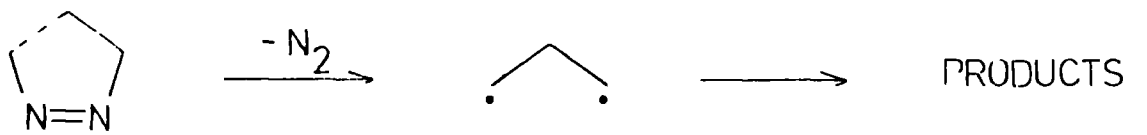
1 2 NITROGEN ELIMINATION REACTIONS

A MECHANISMS AND REACTIVE INTERMEDIATES

There are many ring-cleavage reactions in the literature,[2,3] of which a steady growing number concern nitrogen-elimination The reactions do not follow any set pattern, in some cases several mechanisms and intermediates are involved Thus, any classification of these reactions is rather arbitrary and the following classification has been made for convenience only

(i) DIRADICALS

The thermal, direct photochemical and triplet sensitised decomposition reaction of cyclic azo-compounds are generally believed[4] to yield hydrocarbons via diradical intermediates For example, 1-pyrazolines (9) are believed to rearrange via diradicals [5]



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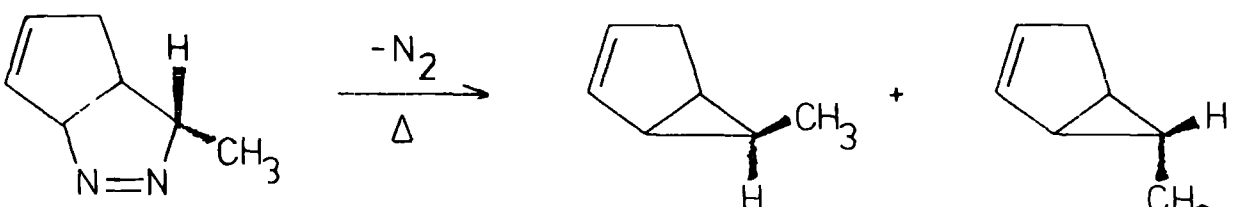
Similarly, a series of bicyclic 1-pyrazolines gave the expected products of a diradical intermediate [5] The gas phase thermolysis of compound (10)

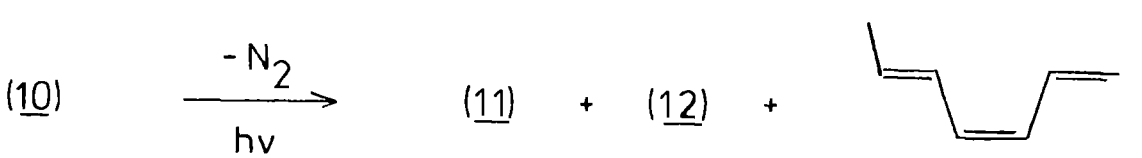


(10) (11) (12)

produces only the exo and endo bicyclic compounds (11) and (12) No open chain or other rearrangement products were observed

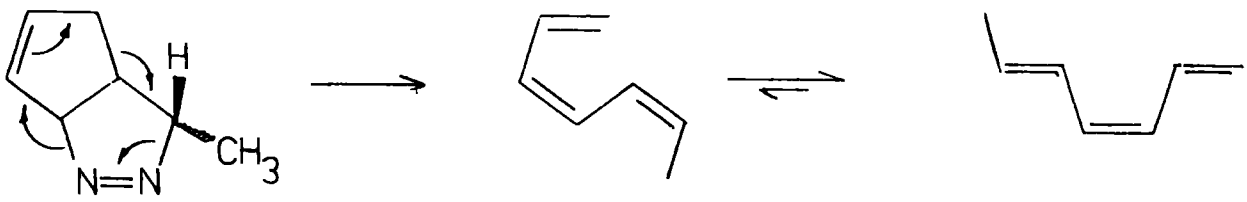
(ii) ELECTROCYCLIC PROCESSES

An additional product was obtained from (10) on photolysis As the reaction was carried out in methanol, the possibility of a carbene



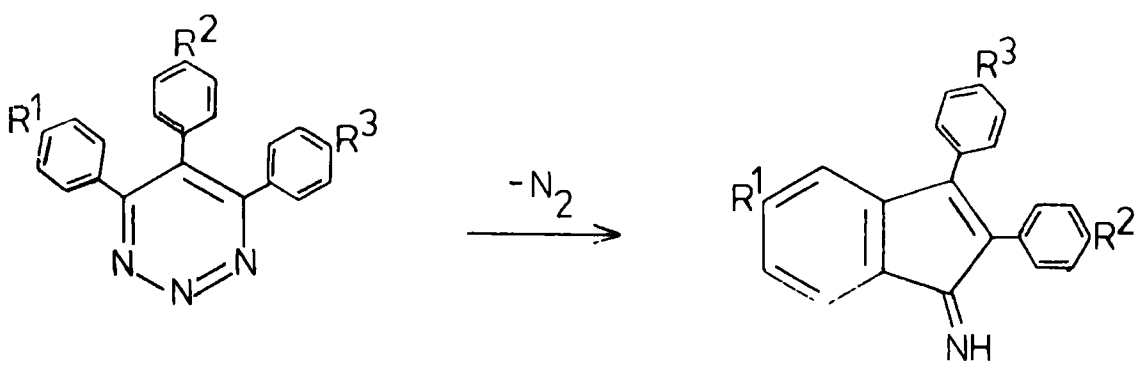
(13)

intermediate, formed by a retro-1,3-dipolar cycloaddition, was unlikely This additional product (13) was attributed[5] to an electrocyclic nitrogen elimination



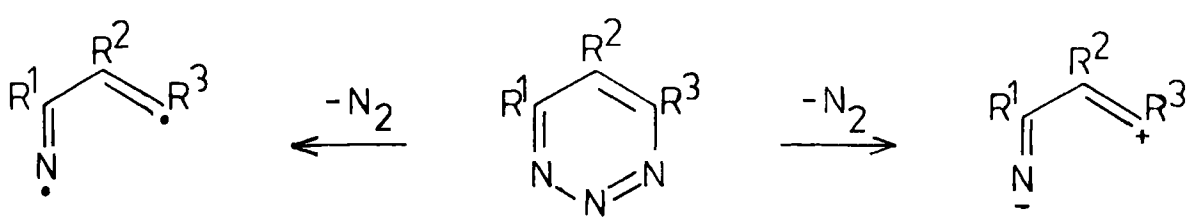
(iii) ZWITTERIONS

When tri-aryl-1,2,3-triazines (14) were pyrolysed at 250°, rearrangement via indenimines (15) occurred[6] The mechanism by which this reaction occurs



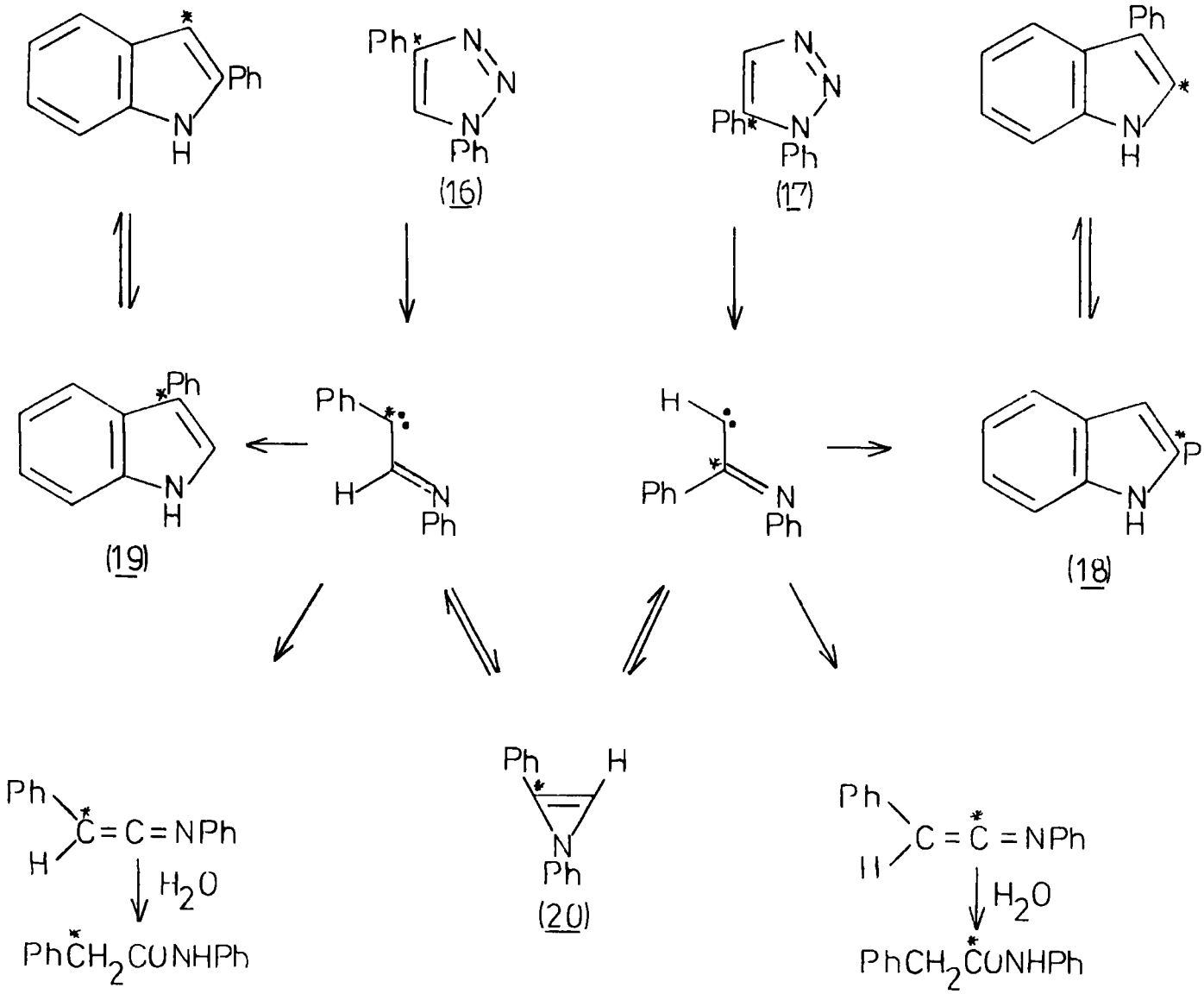
(14) (15)

is in dispute It is believed that either a diradical, or a zwitterion, are involved



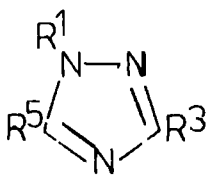
(iv) CARBENES

Five membered aromatic compounds containing adjacent doubly bonded nitrogen atoms commonly undergo thermal or photochemical reactions involving loss of molecular nitrogen [7] Such reactions have been observed with tetrazoles,[8] 1H-1,2,3-triazoles,[9] 1,2,3-thiadiazoles,[10] and 1,2,3-selendiazoles [11] Recent work by Rees et al [12] has shown that in triazoles, intermediate carbenes and diradicals are involved, depending upon the substituents Vapour phase pyrolysis of 1,4- and 1,5-diphenyl-1,2,3-triazoles (16,17) both yield 2- and 3-phenylindoles (18) and (19) respectively,



and N-(phenylvinylidene)anilide, which was isolated as its hydrolysis product, phenylacetanilide Results from ^{13}C studies show that the products are principally those derived from carbenes and that 1H-azirines (20) may be possible intermediates due to a substantial degree of scrambling of the ^{13}C label

In 1,2,4-triazoles there are two adjacent nitrogen atoms, but in the aromatic 1-H and 4-H derivatives (21) and (22), these are not doubly bonded and there is no direct way in which molecular nitrogen can be extruded Only in the unknown, non-aromatic 3-H derivatives (23), are the nitrogen atoms suitably bonded for extrusion



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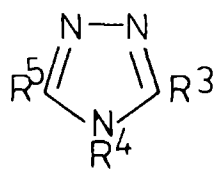

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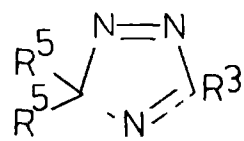
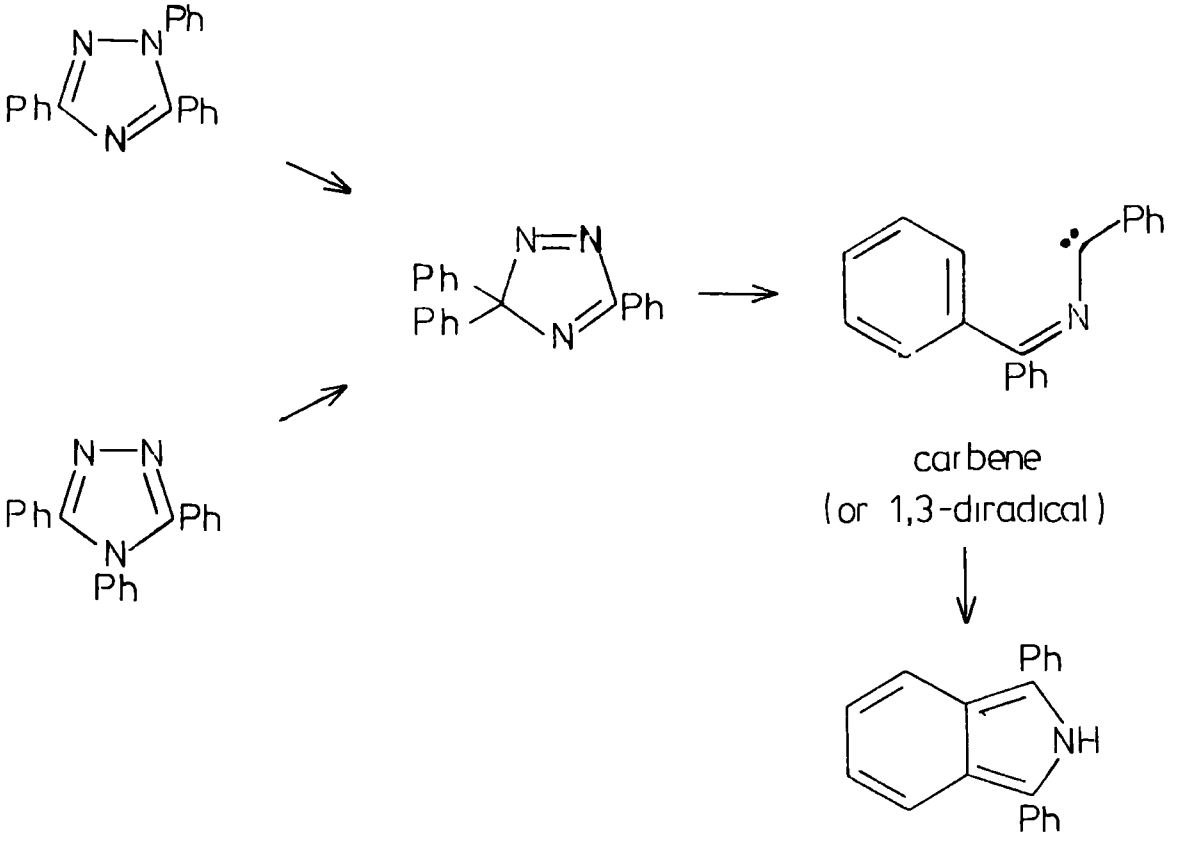


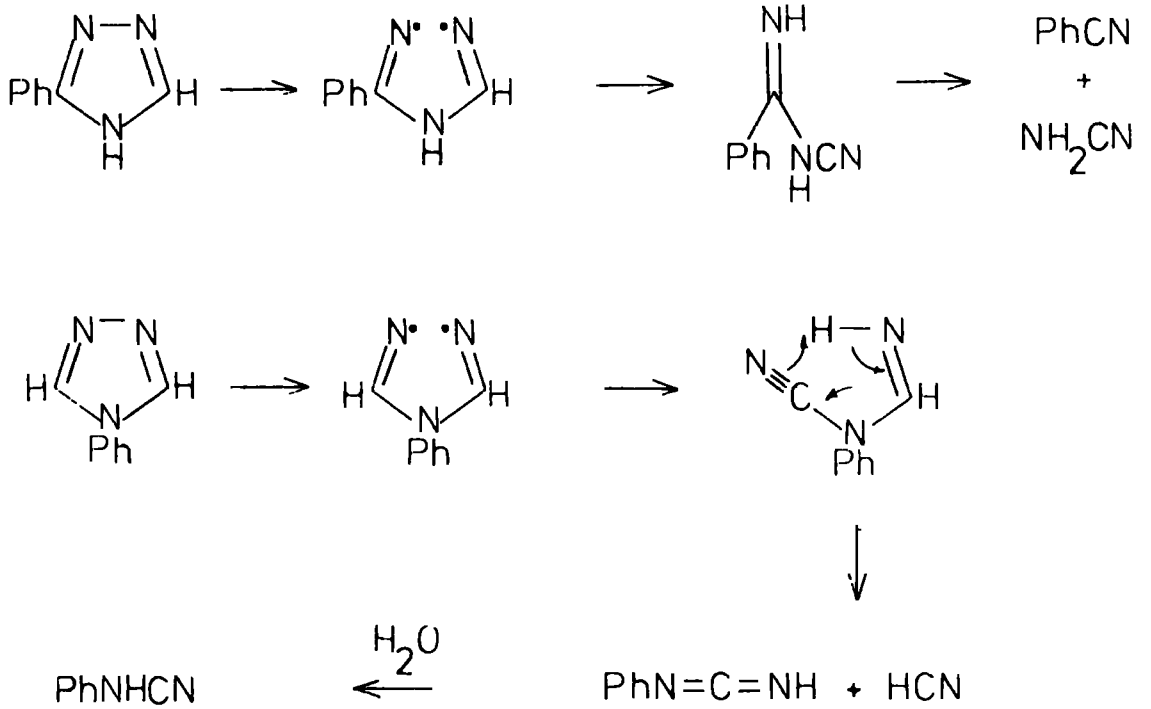
(23)

The results of flash vacuum pyrolysis[7] of phenyl-substituted-1,2,4-triazoles have shown that there are two major pathways for fragmentation One involving rearrangement and extrusion of molecular nitrogen (SCHEME 1) and the other involving extrusion of a nitrile fragment, either directly or indirectly (SCHEME 11) There is some evidence that the second type of reaction involving the extrusion of a nitrile, is a stepwise process with the homolysis of the N-N bond as the first step

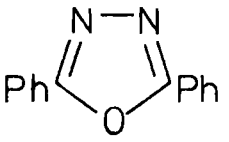
SCHEME I



SCHEME II



The two types of reaction must be very similar energetically Apparently increased phenyl substitution favours the [1,5] rearrangement process, so that this is the only reaction observed with di- and tri-phenyl-1,2,4-triazoles When this type of reaction is precluded, however, as in 2,5-diphenyl-1,3,4-oxadiazole (24), the alternative type of cleavage (SCHEME II) takes place under identical conditions

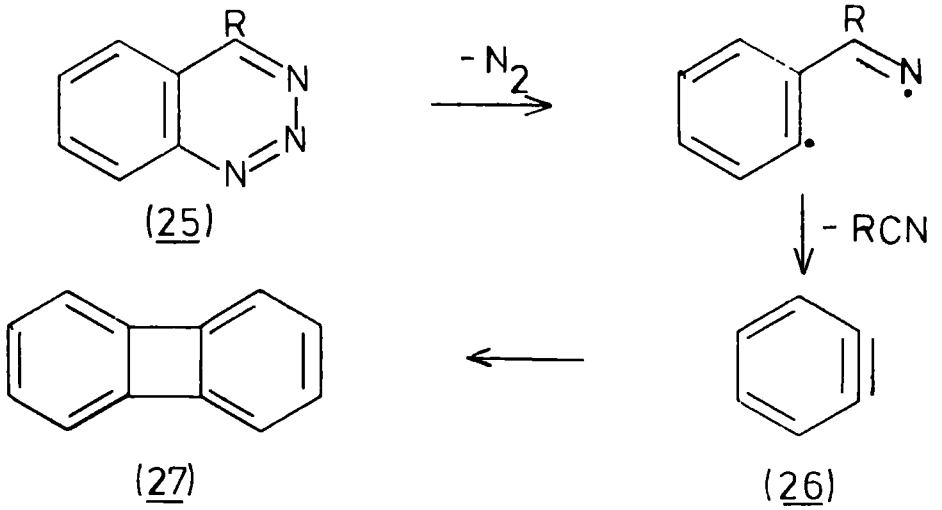


(24)

The nitrogen extrusion and subsequent cyclisation have a close parallel in the photochemical conversion of 3,3-diphenylindazole into 9-phenylfluorene and nitrogen [7] Similar high temperature conversions of pyrazoles,[13] and indazoles,[14] into non-aromatic isomers by migration of hydrogen,[14] cyano,[13] and methyl[13] substituents have been proposed to explain the results of other fragmentations

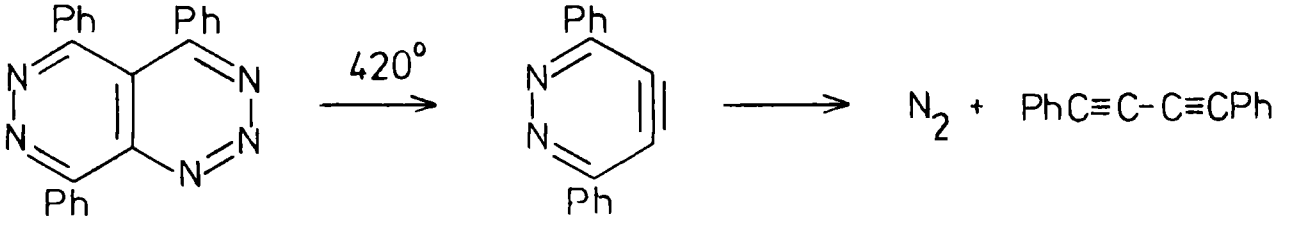
(v) DEHYDROAROMATICS

Dehydroaromatics such as benzyne (26) can be generated by nitrogen elimination reactions Biphenylene (27) is produced when 4-phenyl-benzo-1,2,3-triazine (25) is pyrolysed at 500°, though the reaction is believed to be concerted with loss of nitrogen the first step [15]



(25) (27) (26)

3,6-Diphenyl-4,5-dehydropyridazine (29) is generated in the vapour phase, by pyrolysis of the pyridazotriazine (28) and reacts by extrusion of nitrogen to give diphenylbutadiyne rather than by dimerisation [16]

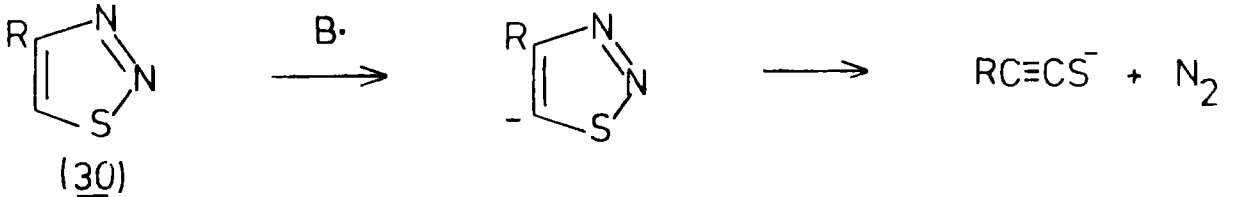


(28) (29)

Benzyne and most other dehydroaromatic intermediates dimerise when they are generated in the vapour phase 3,6 Diphenyl-4,5-dehydropyridazine (29) is exceptional in that, although a small amount of dimer is formed the major reaction involves unimolecular fragmentation of the aromatic system The difference has been ascribed[16] to differences in bond energies and resonance energies, totalling about 38 kcal mol^{-1}, which should favour the fragmentation compared with that of benzyne

(vi) CARBANIONS

Elimination reactions can also be induced by reactions with bases, after initial formation of carbanions Thus, 4-substituted-1,2,3- thiadiazoles ((30), R = t-butyl,[17] or isothiazol-5-yl[18]) react with a variety of bases to form salts of acetylenic thiols.



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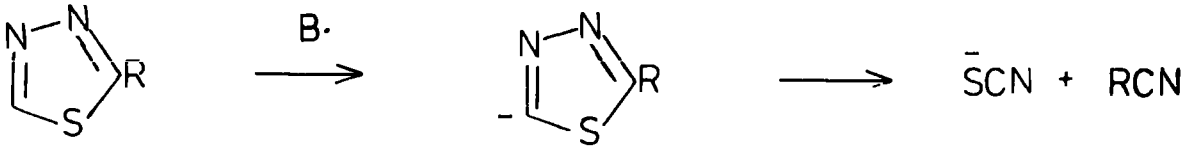
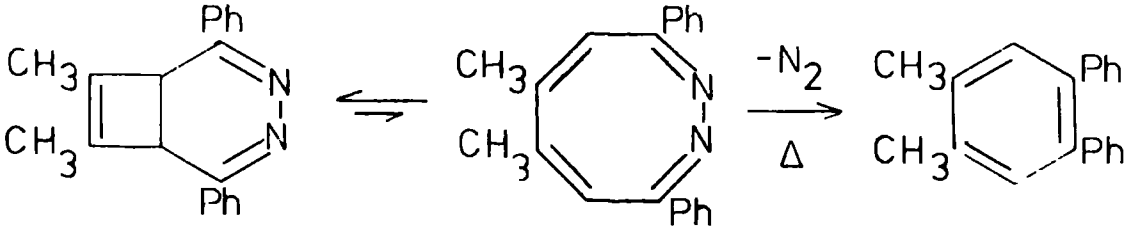
Similarly, 5-substituted-1,3,4-thiadiazoles (31) give nitriles and isothiocyanate anions in high yield with sodium ethoxide [2]



(31)

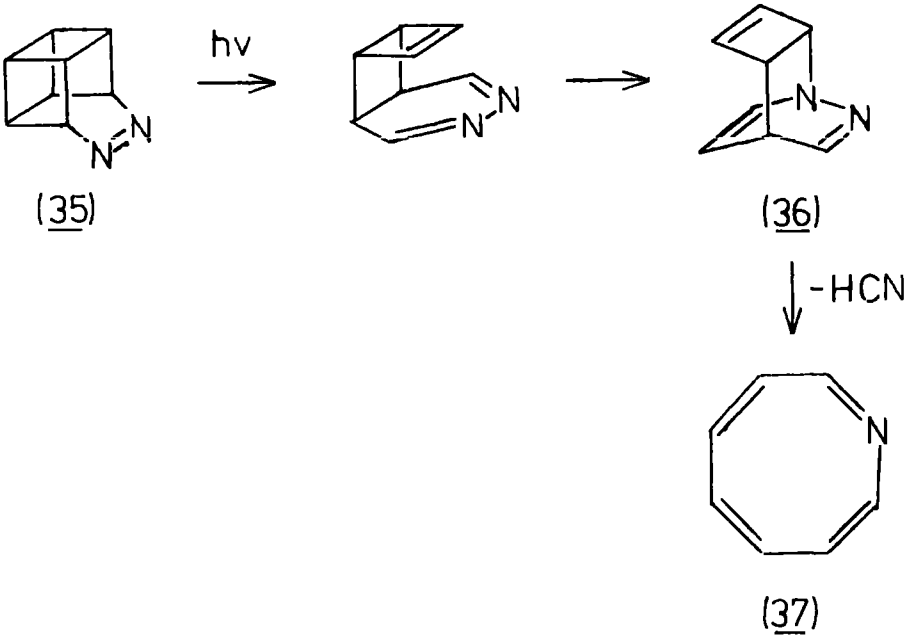
B COMPETING ELIMINATION REACTIONS

It is still generally accepted that in thermal and photochemical reactions of cyclic azo-compounds, elimination of nitrogen is the normal course of reaction. For example, 1,2-diazacyclo-octatetraene, with phenyl and methyl substituents (which exists as the bicyclic tautomer (32)) on heating splits off nitrogen, affording a benzene derivative (34) [19,20]



(32) (33) (34)

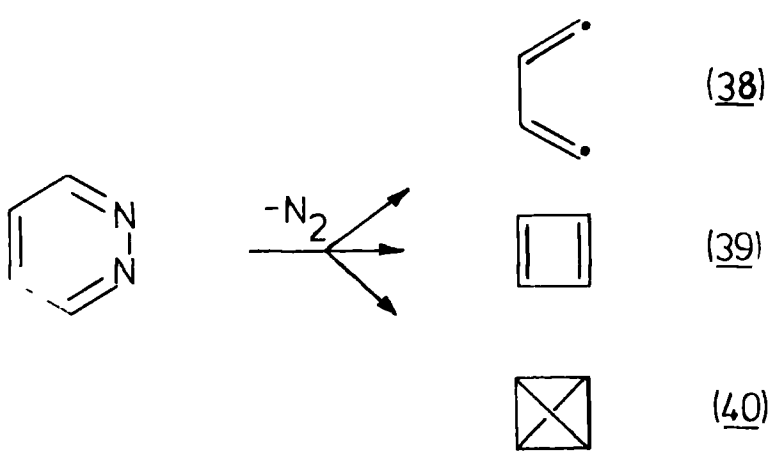
Whereas, the reaction of 1,2-diaza-basketene (35) is described[21] as giving the unexpected product, an unsubstituted azocine (37) This occurs by loss of hydrogen cycanide from the diazaderivative (36) of the Nenitzesceu hydrocarbon, formed as an intermediate



(35) (36) (37)

C ELIMINATION OF NITROGEN FROM HALOCARBONS

Initial work on the pyrolysis of perfluoro-compounds, such as perfluoro-pyridazine, found that rearrangement to pyrimidines and pyrazines, was the dominant process [22] However, it was later found that polyhalo-pyridazines can eliminate nitrogen on thermolysis [23] The C_4 fragment obtained can have any of a variety of structures There are three main possibilities· a diradical (38), a cyclobutadiene (39), or even a tetrahedrane (40).



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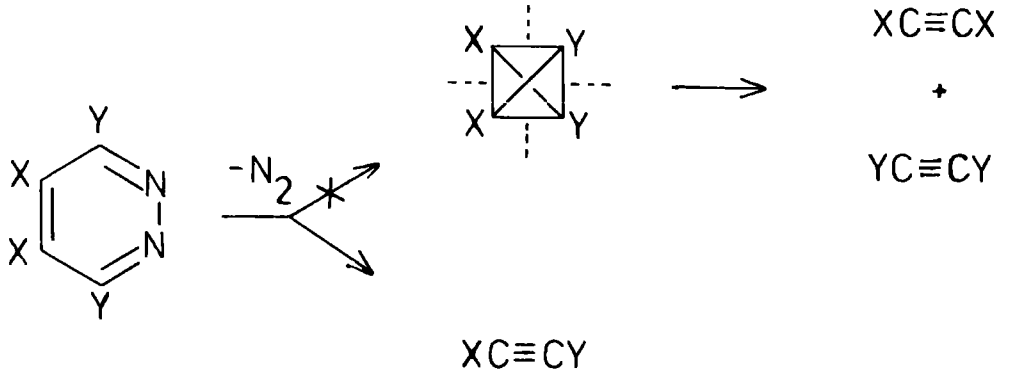
(39)

(40)

With the pyridazine system shown below, where X ≠ Y, only unsymmetrical acetylenes were isolated [23]



(i) X = Y = C_6F_5

(ii) X = CF_2CF_3, Y = C_6F_5

(iii) X = $CF(CF_3)_2$, Y = C_6F_5

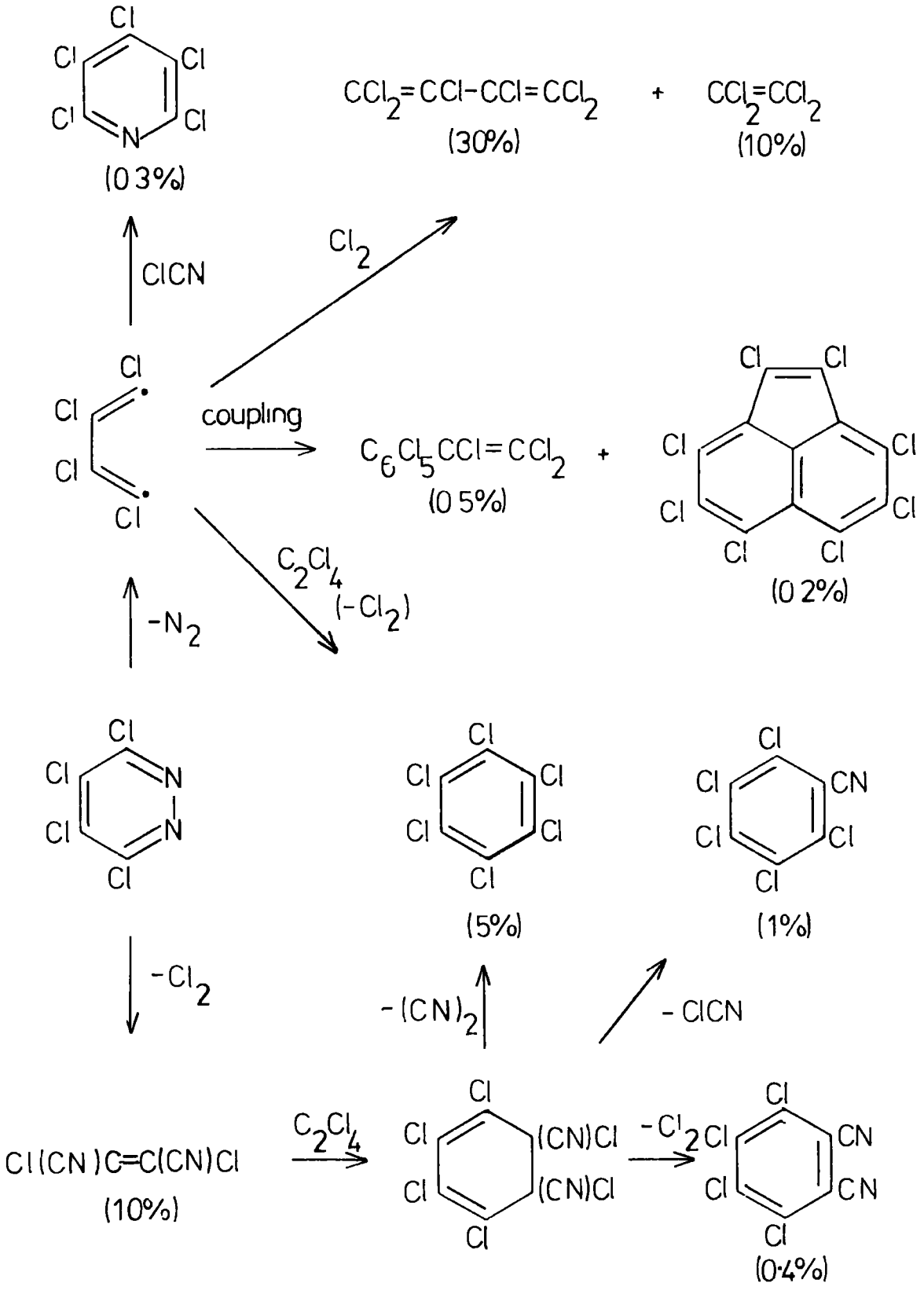
(iv) X = $CF(CF_3)_2$, Y = 4 - C_5F_4N

As there were no symmetrical acetylenes detected i e XC ≡ CX, or YC CY, one can conclude that intermediate diradicals were involved With an intermediate tetrahedrane, or possibly a cyclobutadiene, one would have anticipated more random fission to produce symmetrical as well as unsymmetrical acetylenes There does appear though to be symmetrical acetylenes present in the mass spectra It is pointed[23] out that this would indicate a degree of scrambling which is only consistent with an intermediate ion derived from tetrahedrane or cyclobutadiene

In contrast to tetrafluoropyridazine, pyrolysis of tetrachloropyridazine proceeded with loss of nitrogen rather than rearrangement as the principal process [23] Scheme III shows the main processes, the main products were hexachlorobutadiene and molecular chlorine The compounds can be divided into two groups (i) those which arise from an initial loss of nitrogen from tetrachloropyridazine, followed by combination of C_4Cl_4 fragments, and

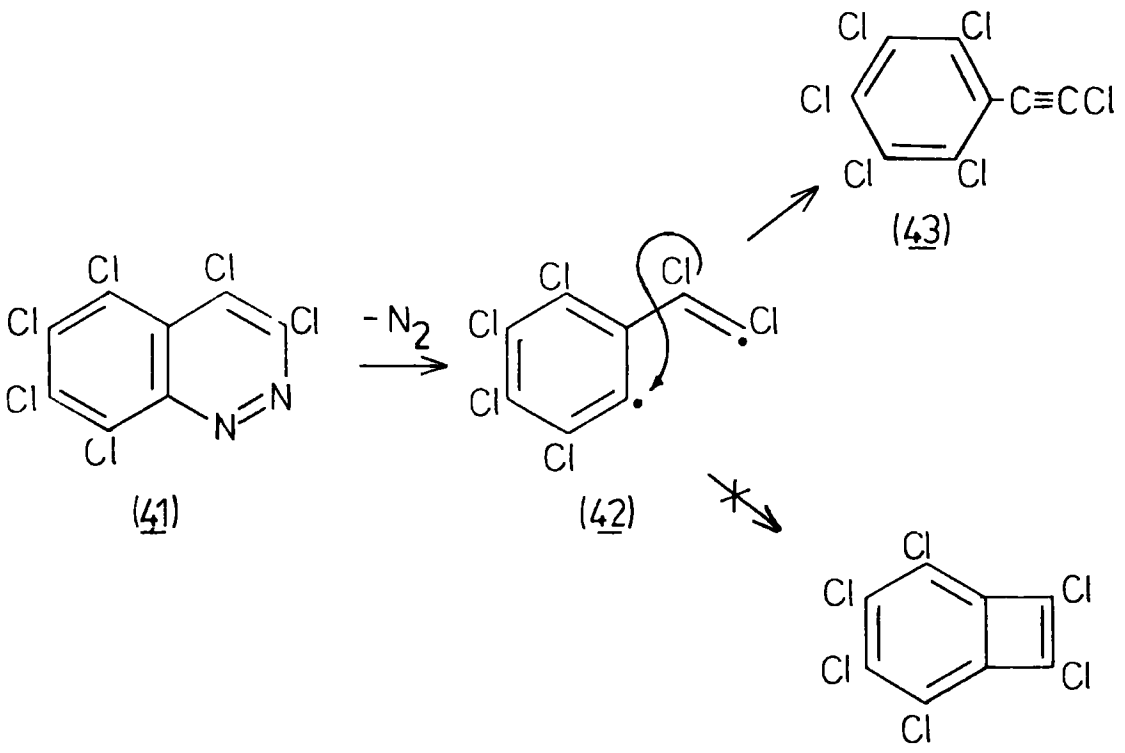
(ii) those formed by initial cleavage of the N-N bond in tetrachloropyridazine, followed by the reactions indicated

SCHEME III

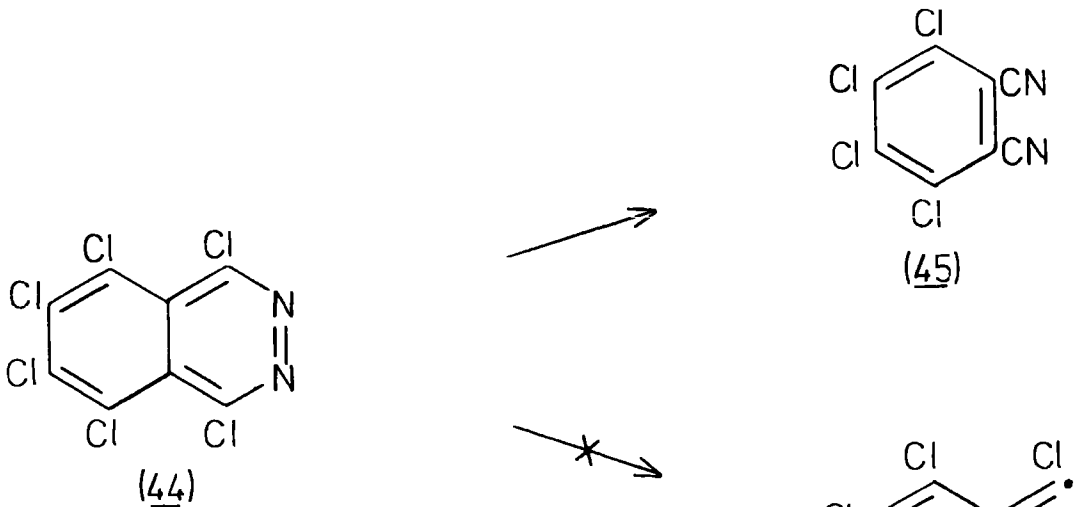


Again a diradical process is in good agreement with the results

With the perchlorobenzopyridazines, two distinct processes are apparent [23] Perchlorocinnoline (41) lost nitrogen on pyrolysis giving perchlorophenylacetylene (43) and not the corresponding benzocyclobutadiene, this is consistent with the intermediacy of a diradical (42) and transfer of a chlorine atom



In contrast, perchlorophthalazine (44) lost chlorine on pyrolysis, giving tetrachlorophthalonitrile (45) The difference in behaviour is attributed to the diradical (42) having a greater stability than the diradical (46)



The bulk of the evidence available suggests the formation of diradical intermediates in these extrusion reactions This is believed[23] to be consistent with conclusions drawn from orbital symmetry considerations, that concerted nitrogen extrusion from pyridazines by either photolysis or pyrolysis is unfavourable

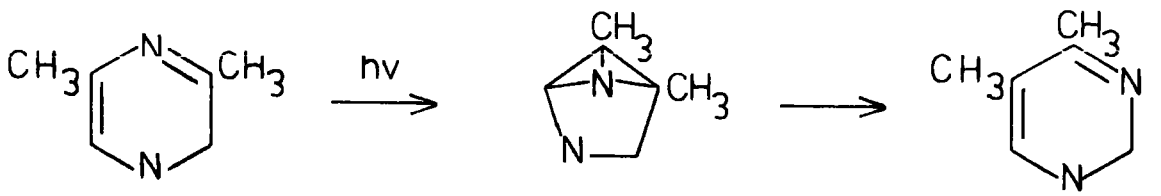
1 3 REARRANGEMENT VERSUS ELIMINATION

In the previous section, it was demonstrated that elimination of nitrogen is not always the most favoured process Different diazo-compounds undergo cleavage of different types, either C-N cleavage or N-N cleavage. However, a third type, C-C cleavage, can occur giving rise to the process of rearrangement In some cases, rearrangement is the dominant process

A HYDROCARBONS

In recent years there have been many accounts[24] of light induced isomerisation of simple benzenoid compounds into benzvalene, Dewar benzene, prismane and fulvene derivatives For example, the products observed[25] in

the photorearrangement of dihydropyrazines are consistent with those expected for a benzvalene type intermediate (47)



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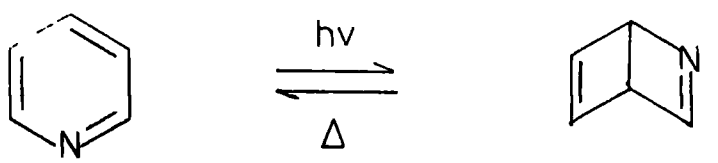
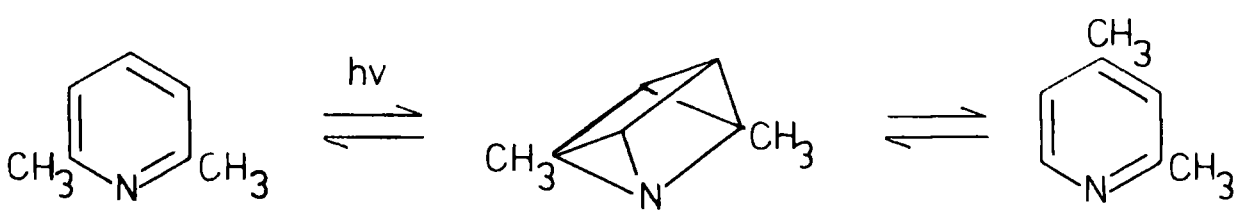
Irradiation of neat pyridine at 254 nm gave para-bonded pyridine (48) with a half-life of 2 minutes at 25° [26]



(48)

Similar studies by other workers,[27] invoke azaprismane type intermediates (49) with picolines



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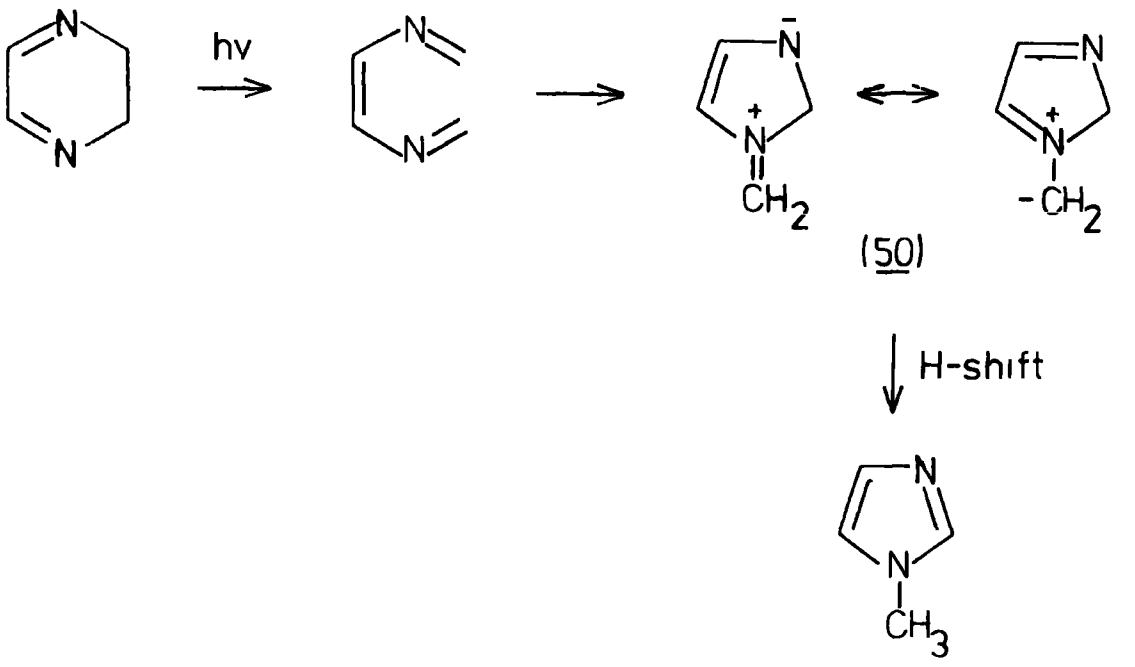
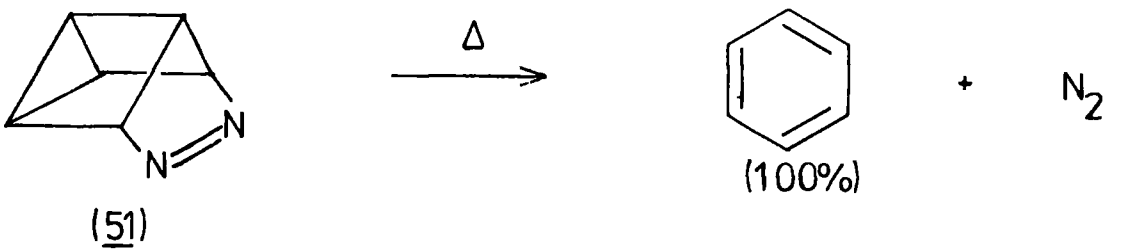
The conversion of 2,3-dihydropyrazines to imidazoles has been formulated to proceed via enediimine intermediates (50) formed by photolytic ring opening.[28]



Ring contraction-expansion processes account for some of the major processes in photoisomerisations, especially with five-membered rings [24]

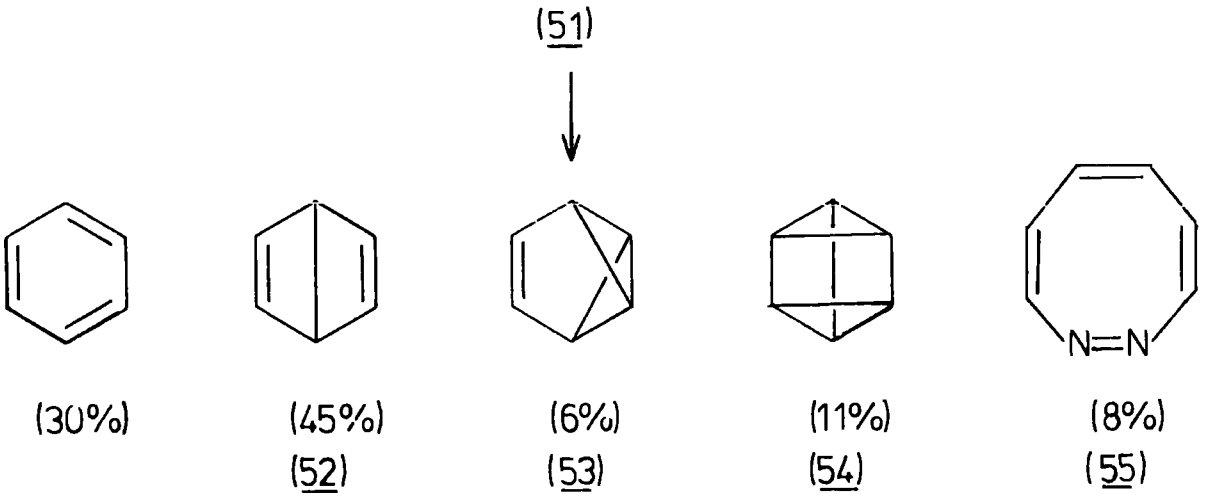
A recent study has shown that several valence isomers are formed from the tetracyclic azo-compound (51), where elimination and rearrangement can both be dominant processes [4] Thermolysis of (51) in n-dodecane results in quantitative formation of benzene and nitrogen



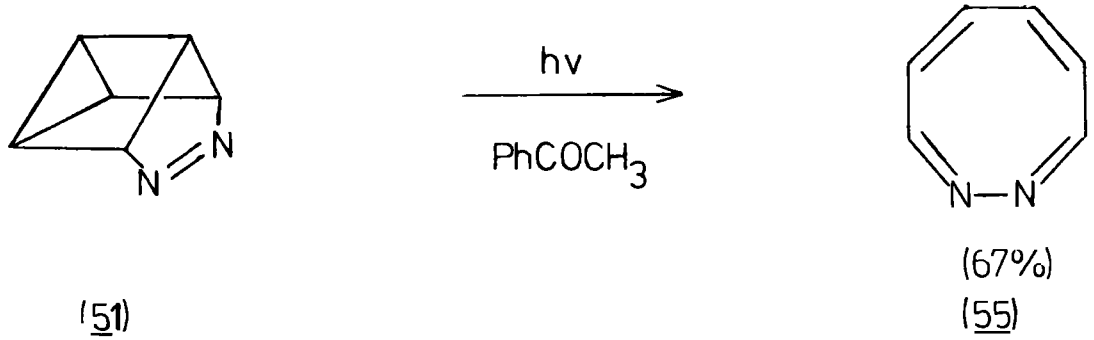
(51)

At 25°, direct photolysis of (51) (366 nm) in deuterated cyclohexane results in formation of benzene, Dewar benzene, benzvalene, prismane and 1,2-diazocyclooctatetraene, as shown in SCHEME IV

SCHEME IV



These observations were concluded[4] to be the result of two pathways from S_1 (singlet excited state) of (51) One is temperature independent ($S_1 \rightarrow T_1$, where T_1 is the triplet excited state) and the other is temperature dependent (C-N cleavage) Thus at low temperatures, inter-system crossing from S_1 to T_1 dominates This was confirmed by the sensitised decomposition of (51) by acetophenone which produced (55) as the predominant product

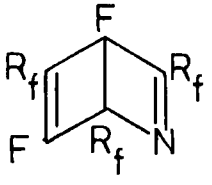


(51)

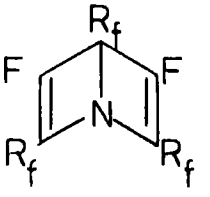
Thus, while C-N bond cleavage was the major chemical process undergone by S_1, C-C bond cleavage is the major process undergone by T_1

B HALOCARBONS

The halocarbons have produced results which are richer in variation than the analogous hydrocarbons This can be attributed to the value of fluorine as a passive substituent in compounds where reactions of the molecular skeleton, induced by pyrolysis or photolysis, can be observed with less interference from C-F bond fission than is encountered from C-H fission in corresponding hydrocarbon systems Transient non-aromatic isomers were postulated as intermediates in the rearrangements of hydrocarbons and relatively few of these have been isolated and characterised compared with their fluorocarbon counterparts Para-bonded species such as (56) and (57) have both been isolated and are stable at room temperature though they are rearomatised at 160° [29]

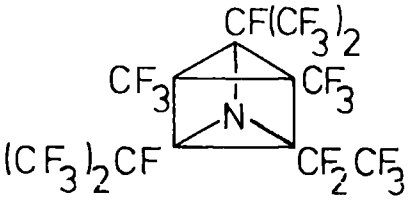


(56)

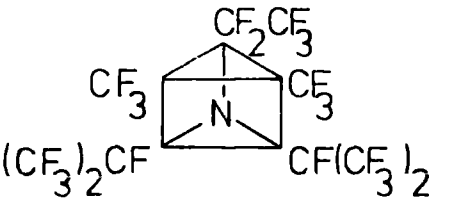


(57)

There have been no reports of the isolation of perfluoro-heterocyclic benzvalenes, but two azaprismane derivatives (58) and (59) have been prepared[30] and are slowly converted at 175°, into pyridines

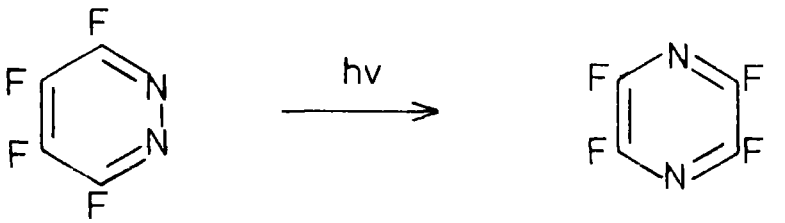


(58)



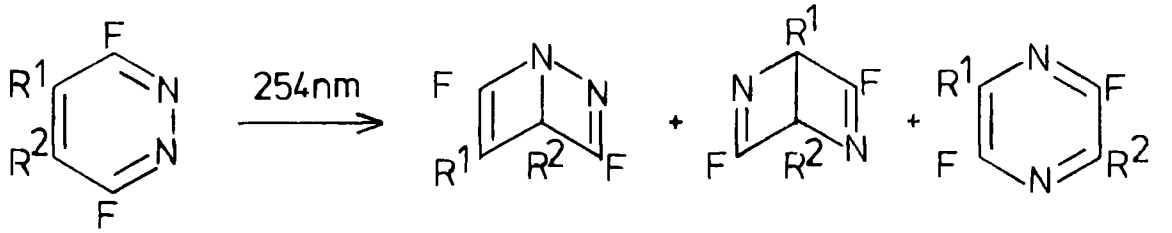
(59)

Perfluorinated pyridazines have been isomerised to perfluoropyrazines and perfluoropyrimidines. The major products obtained with u v irradiation are perfluoropyrazines, e g tetrafluoropyridazine (60) is isomerised to tetrafluoropyrazine (61) [22]



(60) (61)

Para-bonded intermediate species have been isolated from a number of 4,5-disubstituted pyridazines [31]

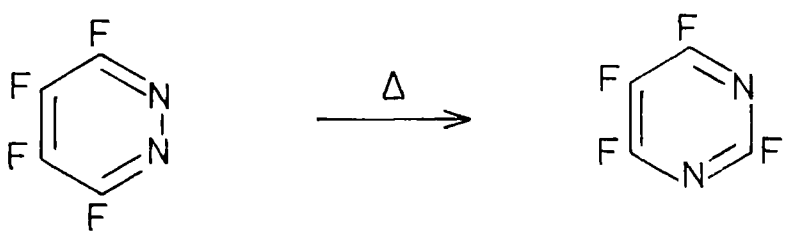


(i)	$R^1 = R^2 = CF(CF_3)_2$	(ia)	(ib)	(ic)
(ii)	$R^1 = R^2 = CF(CF_3)CF_2\ CF_3$	(iia)	(iib)	(iic)
(iii)	$R^1 = R^2 = F$	(iiia)*	(iiib)	(iiic)
(iv)	$R^1 = R^2 = CF_2CF_3$	(iva)*	(ivb)	(ivc)
(v)	$R^1 = CF(CF_3)_2$, $R^2 = F$	(va)*	(vb)	(vc)
(vi)	$R^1 = CF(CF_3)\ CF_2CF_3$, $R^2 = F$	(via)*	(vib)	(vic)
(vii)	$R^1 = CF_2CF_3$, $R^2 = F$	(viia)*	(viib)	(viic)

* not isolated

It was from a para-bonded species that elimination of $R_F C{\equiv}N$ occurred to give a fluorinated azete [1] This is discussed in the following section

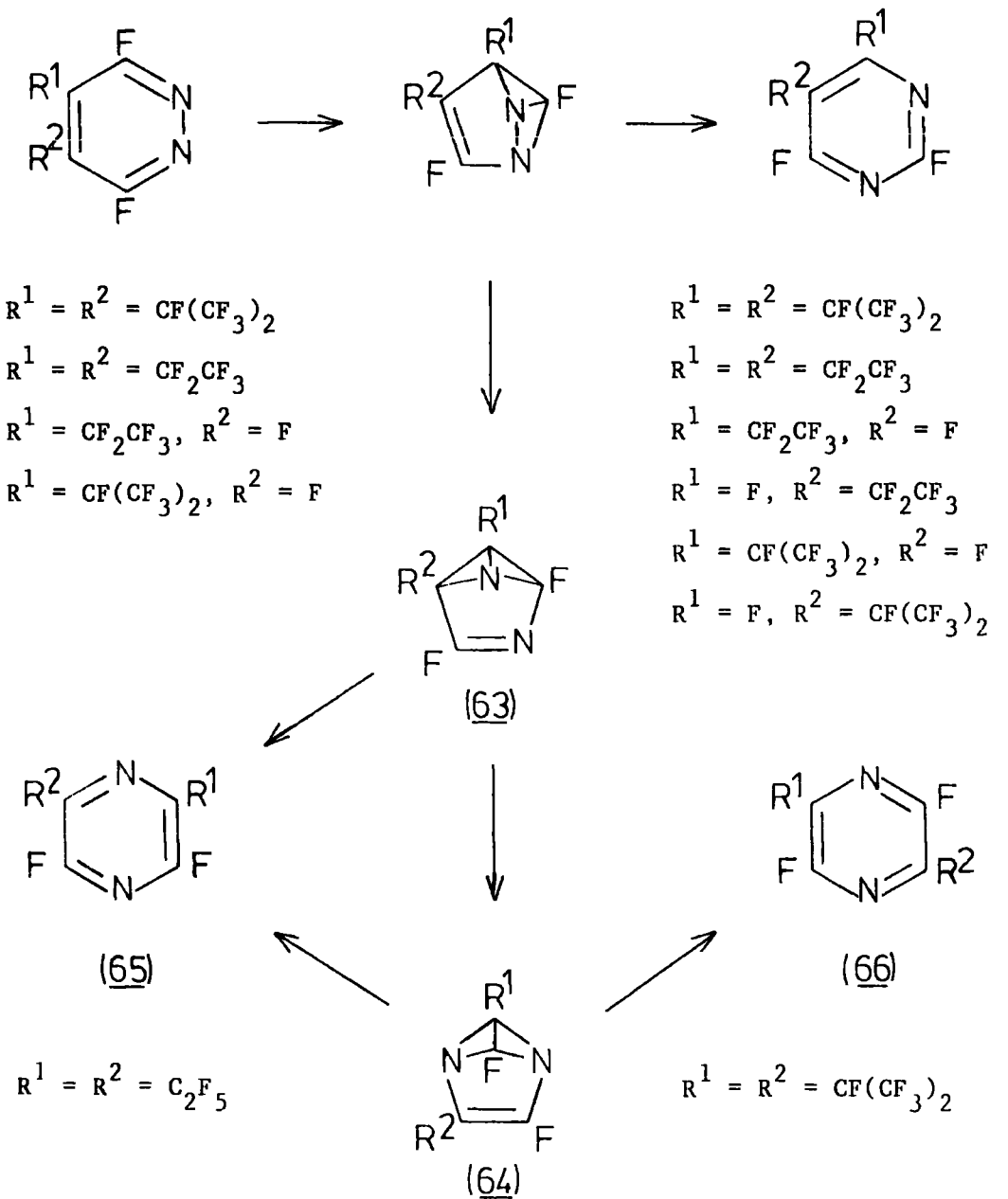
Whereas the major products obtained upon u v irradiation were pyrazines, the major products obtained on thermolysis were pyrimidines, e g tetrafluoropyridazine (60) was isomerised to tetrafluoropyrimidine (62) [22]



(60) (62)

The results of the thermal rearrangements can be accounted for by postulating diazabenzvalene intermediates, [32] as shown in SCHEME V

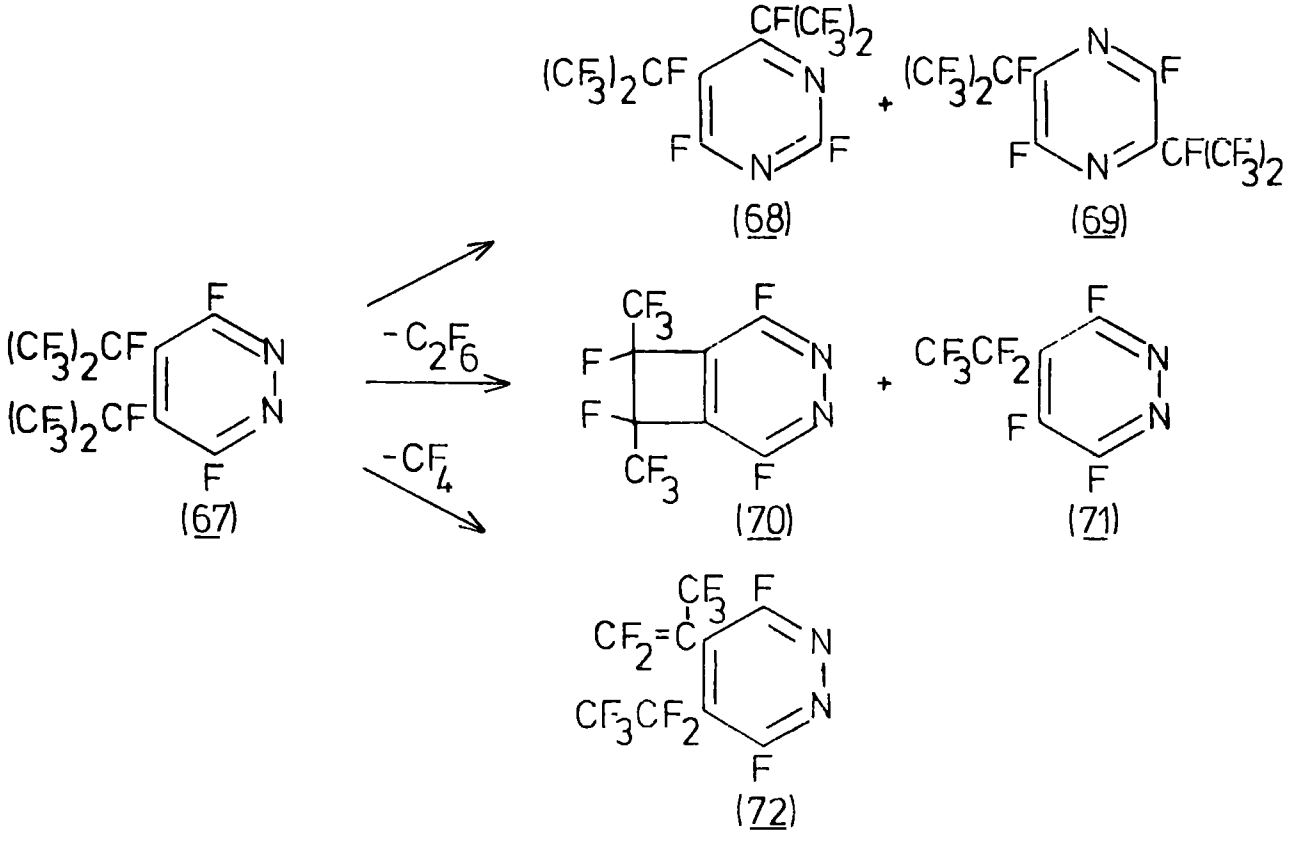
SCHEME V



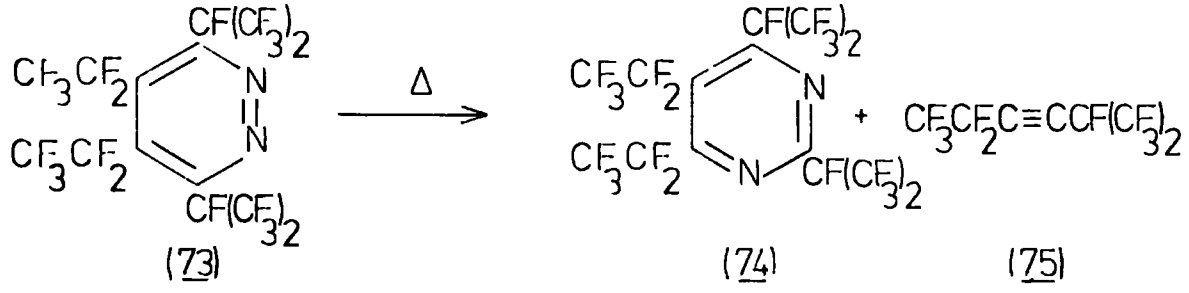
The difference between the pyrazines (65) and (66), minor products, is thought to arise from a greater driving force to separate perfluoroisopropyl than the smaller perfluoro-ethyl groups in the sequence (63) → (64)

When perfluoro-4,5-di-isopropylpyridazine (67) was pyrolysed[32] at higher temperatures, fragmentation products were isolated together with pyrimidine (68) and pyrazine (69) The structures of these products are

possibly those shown below, (70), (71) and (72), depending upon whether CF_4 or C_2F_6 was lost from the starting material



However, perfluoro-4,5-diethyl-3,6-di-isopropyl-pyridazine (73) pyrolysed[32] to give the pyrimidine (74) and perfluoro-5-methylhex-3-yne (75)



Therefore, a whole spectrum of possibilities exists during pyrolysis from preferential elimination of nitrogen from pyridazines, for example, in the case of perfluorotetra-aryl derivatives, to rearrangement to

pyrimidines and pyrazines in the reaction of (60) and (67), the production of both pyrimidine and acetylene from the pyridazine (73) demonstrates an intermediate situation

From these results, it can be concluded that the major factor governing competition between nitrogen extrusion and rearrangement is probably the ability of the substituents adjacent to nitrogen in the pyridazine to stabilise radicals i e aryl > Cl > polyfluoroalkyl > F.

1.4 AZETES (AZACYCLOBUTADIENES)

Over the last few years the chemistry of cyclobutadiene (76), the classic antiaromatic 4π hydrocarbon has been extensively studied In comparison, there are few reported attempts to obtain azetes (77) Other 4π heterocyclic analogues of cyclobutadiene such as oxirens, thiirens and

(76)

(77)

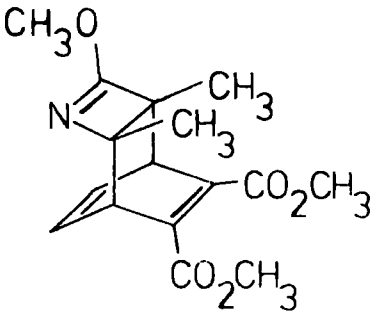
(78)

1 H-azirines (78, X = O, S or NR respectively) have been postulated as reaction intermediates[33] but have not been isolated

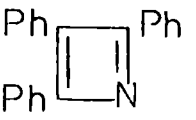
A negative resonance energy of 15.5 Kcal mol^{-1} has been calculated for azete [34] This is somewhat less than that for cyclobutadiene (-18 Kcal mol^{-1})[35] but significantly large to allow the prediction that azacyclobutadiene would exist only as an extremely reactive transient species Thus, techniques have been developed whereby the azete is generated at low temperatures, or the system has been stabilised by benzo-fusion and conjugative stabilisation of the imine function

A MONOCYCLIC AZETES

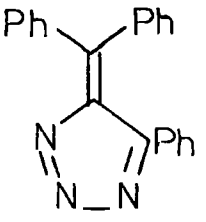
The first reported attempts at the preparation of monocyclic azetes were unsuccessful An attempt by Paquette using an apparently ideal precursor (79) to generate an azete by retro-Diels-Alder reaction failed [36] Triphenylazete (80) was suggested, though without supporting evidence as a possible reactive intermediate in the photolysis of triazafulvenes (81) and (82) [37]



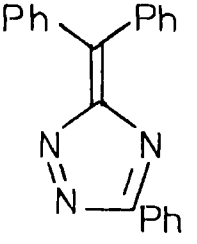
(79)



(80)

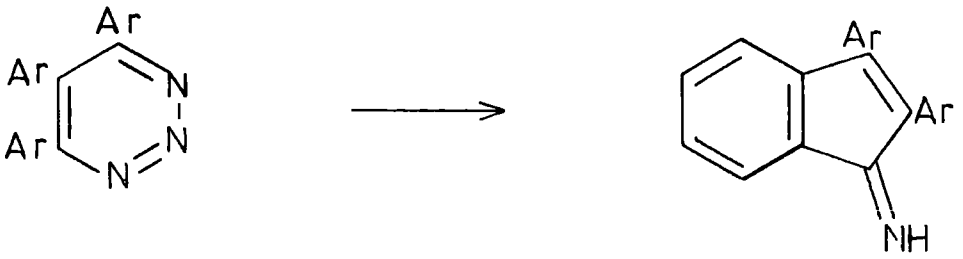


(81)



(82)

Pyrolysis or photolysis of trimethyl- and triphenyl-1,2,3-triazines afforded only acetylenes and nitriles, [38] though recently it was shown [6] that prolonged heating of various triaryl-triazines at the m p lead to the extrusion of nitrogen and formation of indenimines (83)

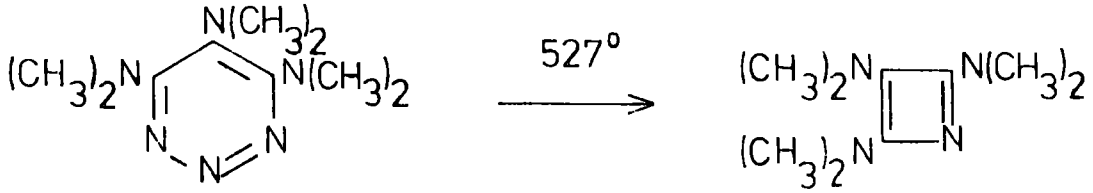


(83)

Recently, pyrolysis of a monocyclic 1,2,3-triazine has lead to the formation of tris(dimethyl-amino)azete [39] Two other reports of azetes have been made, one via oxazinones[40] and the other via a fluorinated pyridazine [1] Each of these is discussed in succession where elimination of nitrogen, carbon dioxide and nitrile occurred respectively No classification was made.

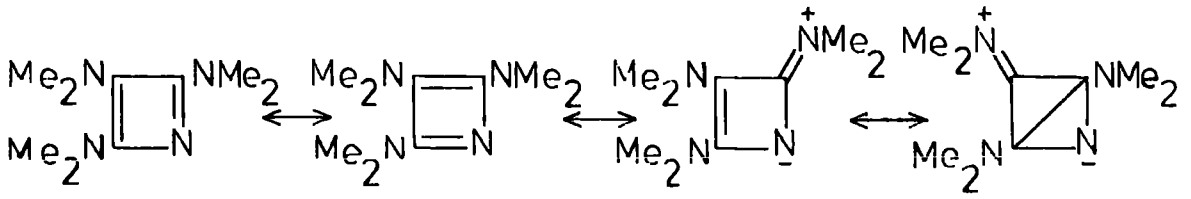
(i) TRIS(DIMETHYLAMINO)AZETE

Flash pyrolysis of triazine (84) gave the deep red tris(dimethyl-amino) azete (85) in approximately 30% yield, which was stable at room temperature for ca. 12h [39] This relatively high thermal stability indicates that (85)



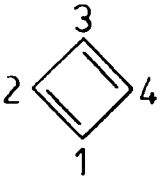
(84) (85)

should be described as the resonance hybrid (85a) - (85d)

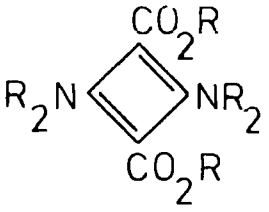


(85a) (85b) (85c) (85d)

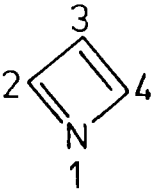
It has been argued[41] that cyclobutadiene (76) may be stabilised by push-pull substitution (86) Analogously, azacyclobutadiene which is energetically favoured in comparison with (76) by introduction of the ring nitrogen can be further stabilised by two donor groups at position 2 and 4 (87).



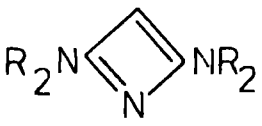
(76)



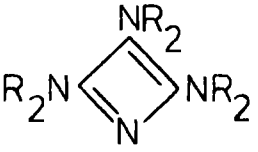
(86)



(77)



(87)



(88)

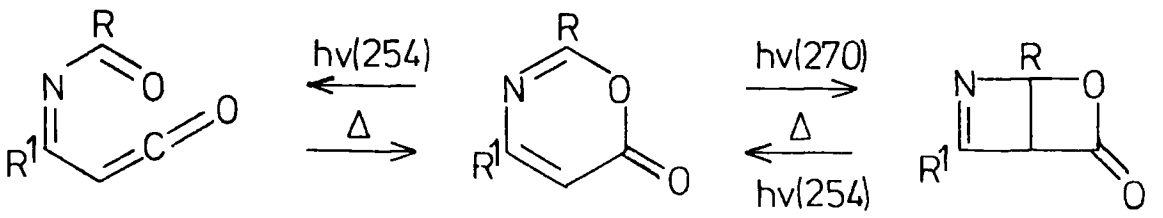
(89)

However, it is thought[41] that a donor group in position 3 (88,89) of the azete will have a destabilising effect

(ii) AZETE AND ALKYL-AZETES

Oxazinones of the type (91) are favourable starting materials for the photochemical generation of the parent compound, azete, or its alkyl derivatives A report[40] of the generation of azetes by this route is very recent

Careful selection of temperature, matrix-material and wavelength of irradiation were required Photo-reaction (254 nm) in a 2-methyl-tetrahydro-



(90) a,d,g (91) b,e,h (92) c,f,i

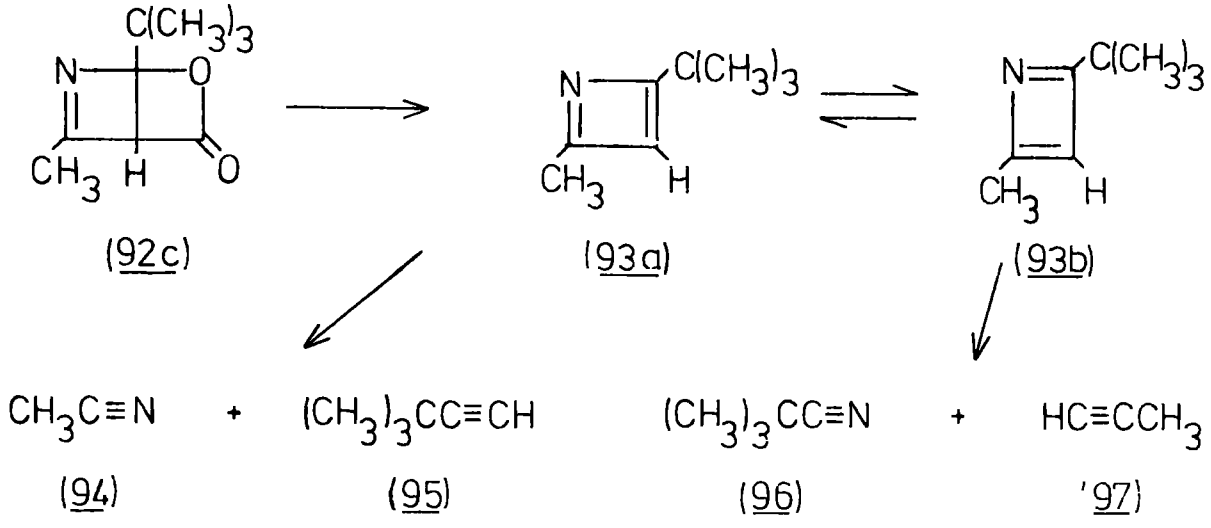
a, b, c $R = C(CH_3)_3$ $R^1 = CH_3$

d, e, f $R = CF_3$ $R^1 = CH_3$

g, h, i $R = H$ $R^1 = H$

furan matrix at -196° produced a mixture of the bicyclic (92c) and the ketene (90a) when (91b) was irradiated However, irradiation with light of wavelength 270 nm at -70° produced the bicyclic (92c) as the only product Longer irradiation (270 nm, -70°) gave quantitative elimination of CO_2 from (92c), but it was found that the azete once formed immediately dimerised When the reaction was repeated (270 nm, 7°K) using an argon matrix, in

addition to CO_2, four other components were detected Moreover, as shown below, the products obtained were consistent with an azete intermediate and that a fast valence isomerisation (93a ⇄ 93b) exists, provided (93) possesses a singlet ground state with alternating bond lengths



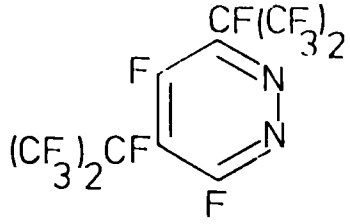
The product ratio (96 97) (94 95) was 6 5

Analogous results[40] were obtained with 1,3-oxazin-6-ones (91e) and (91h), the later giving the expected products from the parent compound, azete

(iii) FLUORO-AZETE

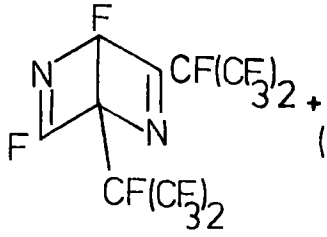
Evidence for the generation of a fluorinated azete was obtained when perfluoro-3,5-di-isopropyl-pyridazine (98) was photolysed in a flow system [1] Rearrangement products (100) and (101) were produced, in addition to four other compounds (A, B, C and D) which have been shown to be dimers of the intermediate (99)

The structures of these dimers have been tentatively assigned, as shown below Isomer (D), not shown, has a monocyclic structure similar to that of (C)

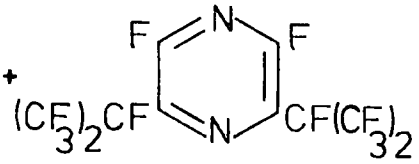


(98)

254nm



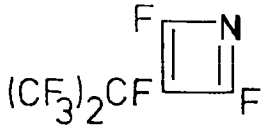
(100)



(101)

$(CF_3)_2CFC{\equiv}N$

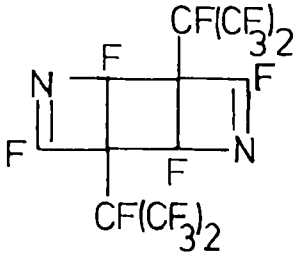
+



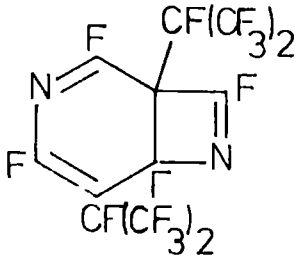
(99)

DIMERS

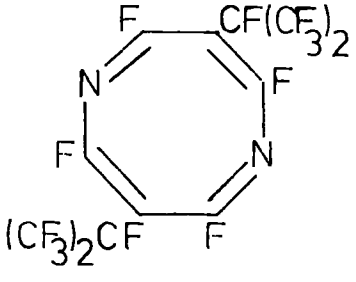
(A),(B),(C) AND (D)



(A)



(B)



(C)

(A) AND (B) $\xrightarrow{150^\circ}$ (C)

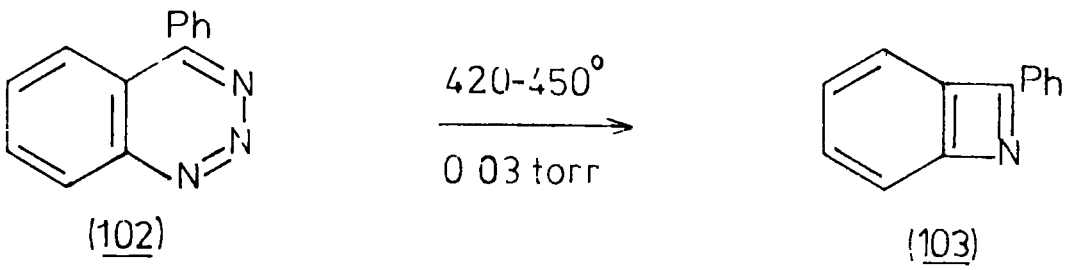
Dimerisation of (99) can occur in a number of ways but so far no attempt has been possible to distinguish between some of the possibilities

B POLYCYCLIC AZETES

There is only one reported route to the polycyclic azetes which is via 1,2,3-triazines by nitrogen elimination

(i) 2-ARYLBENZAZETES

The first polycyclic azete to be isolated was prepared[30] by the pyrolysis of 4-phenyl-benzo-1,2,3-triazine (102)

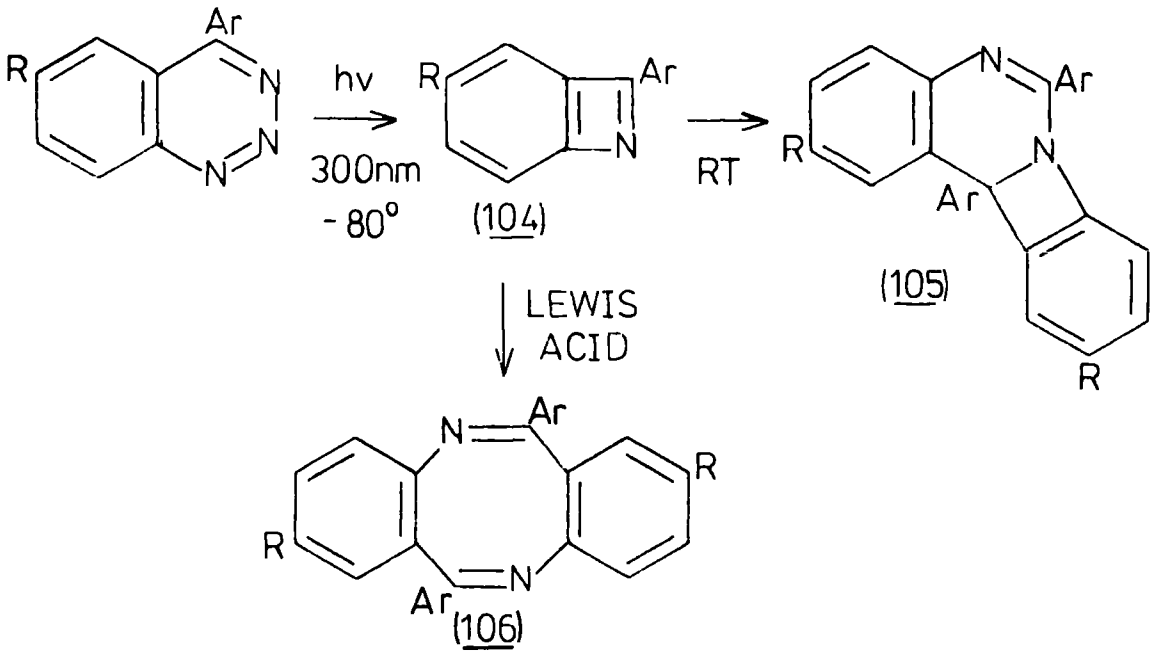


(102) (103)

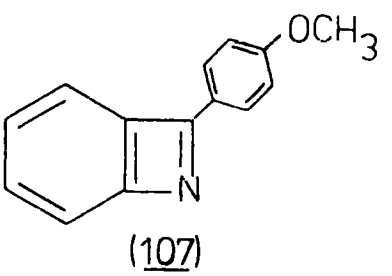
Red 2-phenylbenzazete (103) was found to dimerise and react with nucleophiles and dienes very rapidly, though it is surprisingly stable at -80° The red colour of this azete was expected by analogy with known cyclobutadiene derivatives

The 2-arylbenzazetes (104), where R = H, Me, Cl, have been prepared by photolysis of 4-aryl-benzo-1 2,3-triazines and can be intercepted in cyclo-addition reactions, the benzazetes dimerise thermally to give angular dimers (105), and in the presence of Lewis acids, the linear dimers (106) [42]

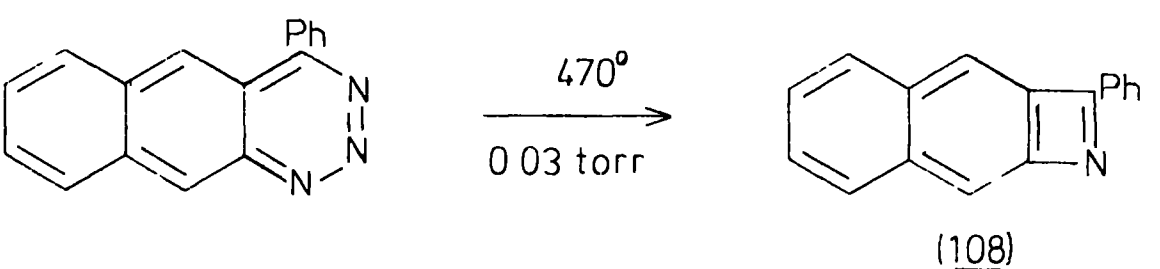
The 2-(p-methoxyphenyl)-benzazete (107) is even more stable than 2-phenylbenzazete, due to the electron release of the methoxy group reducing



the antiaromatic character of the 4-membered ring [43]

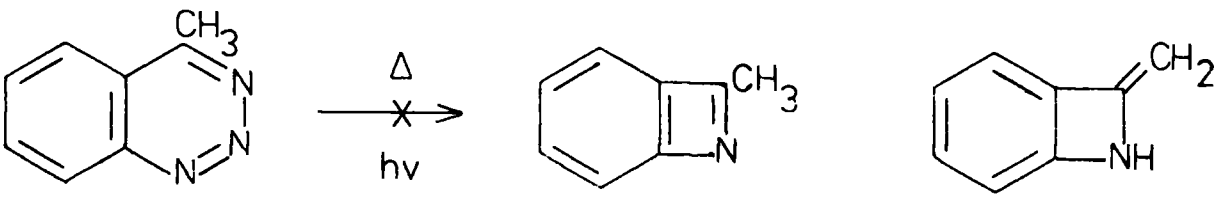


2-Phenylnaph-(2,3-b)-azete (108) has been prepared and is even appreciably stable at room temperature as an orange solid [43]



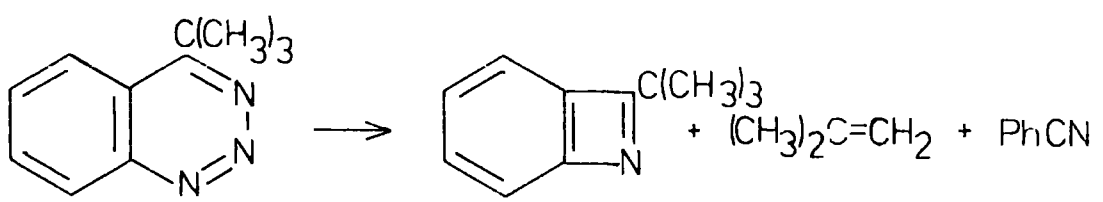
(ii) 2-ALKYLBENZAZETES

There is no evidence for the formation of 2-methylbenzazete Pyrolysis and photolysis of 4-methylbenzo-1,2,3-triazine did not give any benzazete products, neither dimers nor addition products were isolated [44]



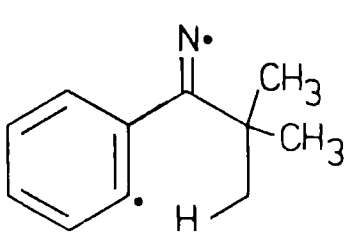
(109)

A possible explanation for the difference between aryl- and methyl-benzotriazines and benzazetes is the presence of reactive α-hydrogens in the methyl derivative Thus, 2-methylbenzazete may rapidly isomerise to the more stable tautomer (109) This complication is not present with 2-t-butyl-benzazete (110) but the yield was found to be low due to elimination of isobutene to give benzonitrile



(110)

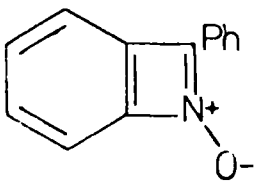
This has been rationalised by elimination of isobutene from an intermediate such as (111)



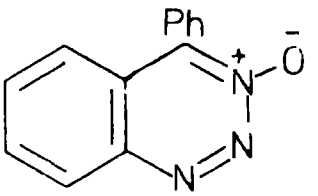
(111)

(iii) BENZAZETE-N-OXIDES

Enhanced stability of the benzazete system was expected[38] to result from the reduced C-N bond order in benzazete N-oxides such as (112)



(112)



(113)

However, pyrolysis of the N-oxide (113), gave a complex mixture and has shown than benzazete N-oxides, if formed, are not markedly more stable than the azetes

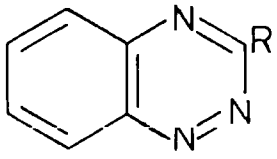
(iv) ALKOXYBENZAZETES

4-Methoxy-1,2,3-benzotriazine on pyrolysis was either recovered unchanged or gave a complex mixture of unidentified products [38] No evidence was found for 2-methoxy-benzazete, which, it was anticipated, would be stable This azete, like the starting material, was considered to readily suffer O → N methyl migration.

1 5 FRAGMENTATION STUDIES OF 1,2,4-TRIAZINES

A BENZO-1,2,4-TRIAZINES

Pyrolysis of benzo-1,2,4-triazines could also give benzazetes, however, these triazines (114) are considerably more stable than the corresponding 1,2,3-isomers No fragmentation occurred below 700° and above this temperature benzyne, and hence biphenylene, was produced [15]



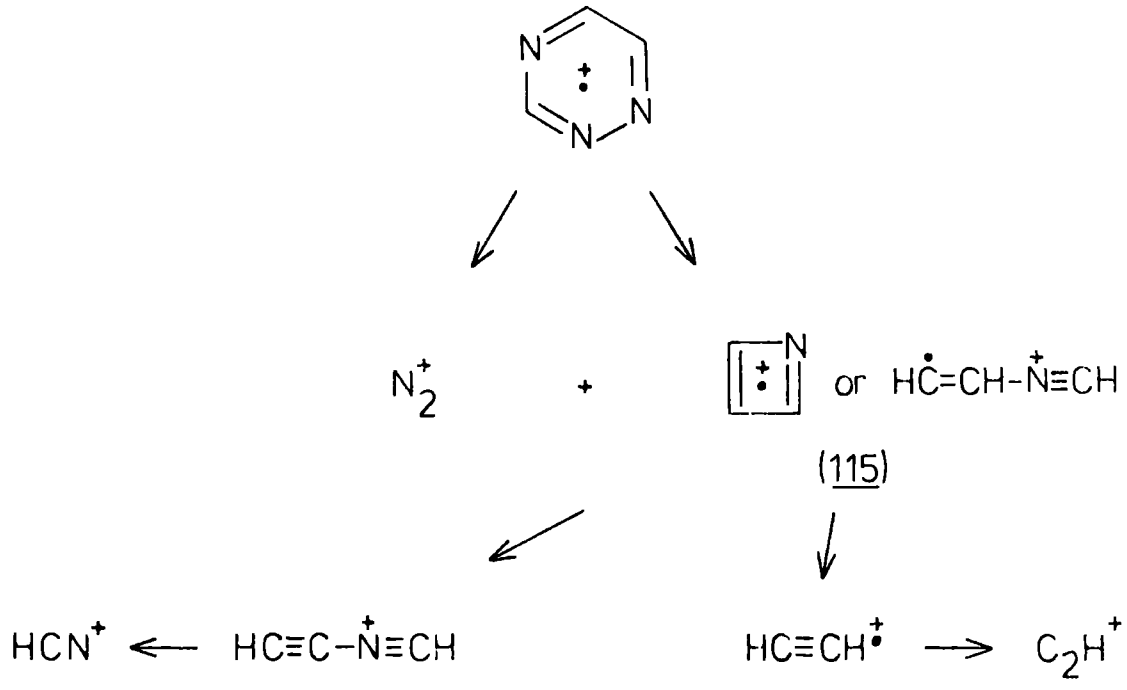
(R = H,CH_3,Ph)

(114)

B MASS SPECTROMETRIC STUDIES OF 1,2,4-TRIAZINES

Surprisingly, in view of the lack of actual studies of nitrogen elimination from 1,2,4-triazines there are numerous reports of their mass spectra

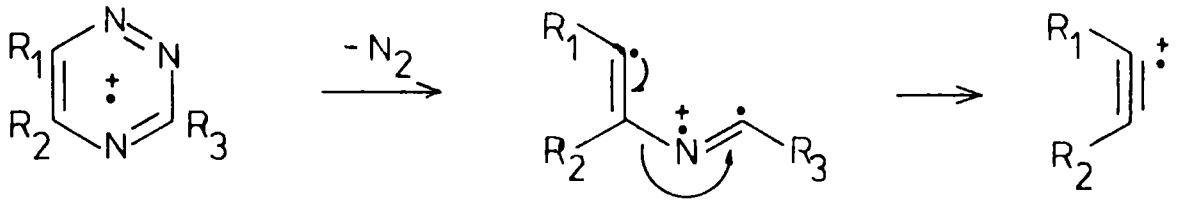
Paudler, et al [45] reported the spectra of the parent compound and found that one of the most abundant fragment ions was due to the loss of nitrogen It is not possible to predict the structure of the $[C_3H_3N]^+$ species (115)



(115)

Sasaki, et al [46] have reported the mass spectra of numerous phenyl substituted 1,2,4-triazine compounds, where again nitrogen elimination was deduced to be a major process Azirine type intermediates were postulated, as shown in SCHEME VI

SCHEME VI



(i) $R_1 = R_2 = Ph$, $R_3 = OMe$

(ii) $R_1 = R_2 = Ph$, $R_3 = OPh$

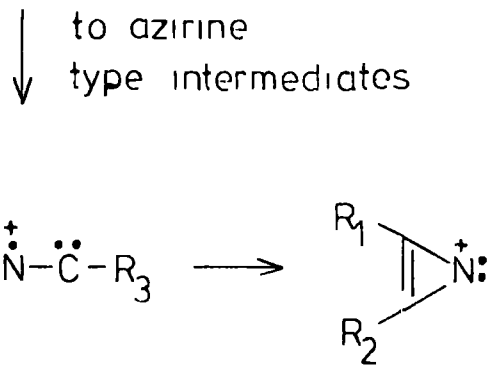
(iii) $R_1 = R_2 = Ph$, $R_3 = NH_2$

(iv) $R_1 = R_2 = Ph$, $R_3 = NHPh$

(v) $R_1 = H$, $R_2 = Ph$, $R_3 = NH_2$

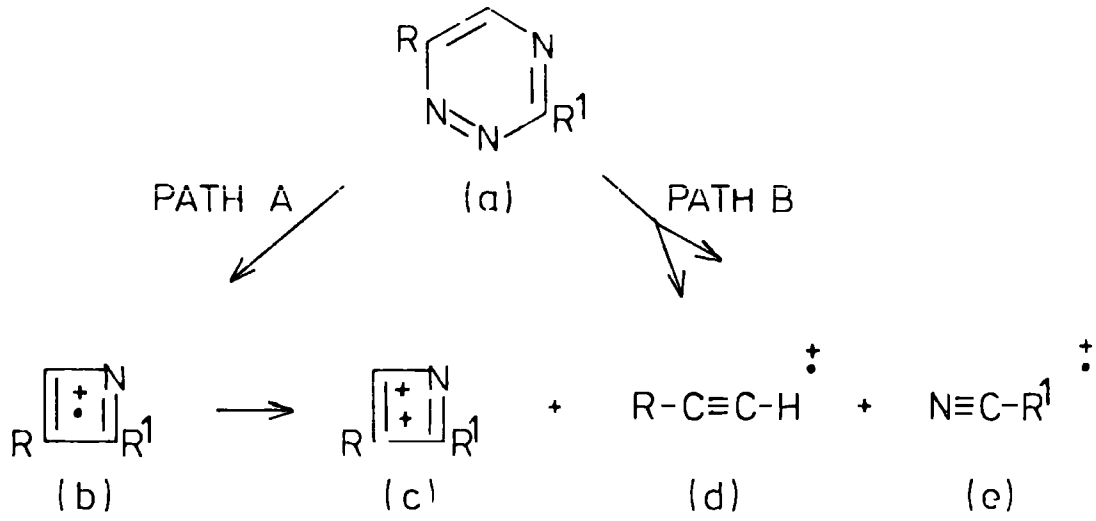
(vi) $R_1 = Ph$, $R_2 = H$, $R_3 = NH_2$

(vii) $R_1 = R_2 = OMe$, $R_3 = NH_2$



Studies of a number of 6-aryl- and 3-substituted 6-aryl-1,2,4-triazines, indicate two general modes of fragmentation, paths A and B, as shown in SCHEME VII [47]

SCHEME VII



(i) R = R^1 = Ph

(ii) R = Ph, R^1 = p-Me-Ph

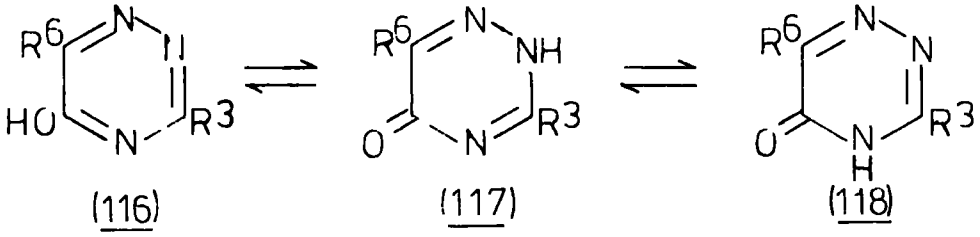
(iii) R = P-Me-Ph, R^1 = Ph

(iv) R = Ph, R^1 = 2-FURYL

(v) R = Ph, R^1 = TRIMETHYL GALLYL

Interestingly, compound (V) in SCHEME VII, only follows path B, evidenced by the absence of peak m/e values corresponding to fragments (b) and (c)

However, mass spectra data of a series of 1,2,4-triazines with oxo, thioxo and methoxy, and/or methylthio groups in 3 and 5 positions, detected five ring cleavage processes related mainly to the 5-substituent [48] Rupture at N-1-N-2 and C-5-C-6 occurred in all cases Loss of nitrogen or carbon monoxide was not observed This is probably due to the fact that tautomeric equilibriums exist whereby in the vapour phase paraquinoid structures predominate This is a common feature of triazines, especially the hyroxy derivatives e g (116) - (118)



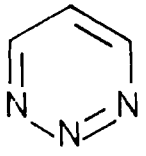
(116) (117) (118)

CHAPTER 2

THE SYNTHESIS AND THE CHEMISTRY OF 1,2,4-TRIAZINES

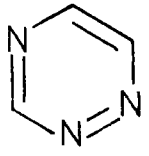
2 1 INTRODUCTION

There are three families of triazines which are the 1,2,3-(119), 1,2,4-(120) and 1,3,5-(121) triazines, derivatives of all three are known Preparations of the parent substances have been long known for the 1,3,5-triazine, are comparatively recent for the 1,2,4-triazine and are still not known for 1,2,3-triazine



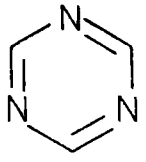
1,2,3

(119)



1,2,4

(120)



1,3,5

(121)

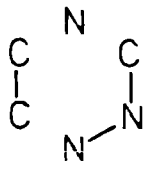
[49,50]

The published chemistry of the 1,2,4-triazines is largely that of its derivatives, though there are now several preparations of the parent compound A steadily growing interest in this system stems from the findings[50] that several 1,2,4-triazines show antimalarial, antimicrobial and antiviral activity

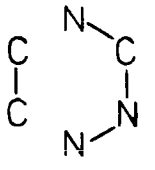
2 2 SYNTHESES OF 1,2,4-TRIAZINES

A GENERAL COMMENTS

These compounds are prepared by two general methods which correspond to condensation of the units shown below [51]

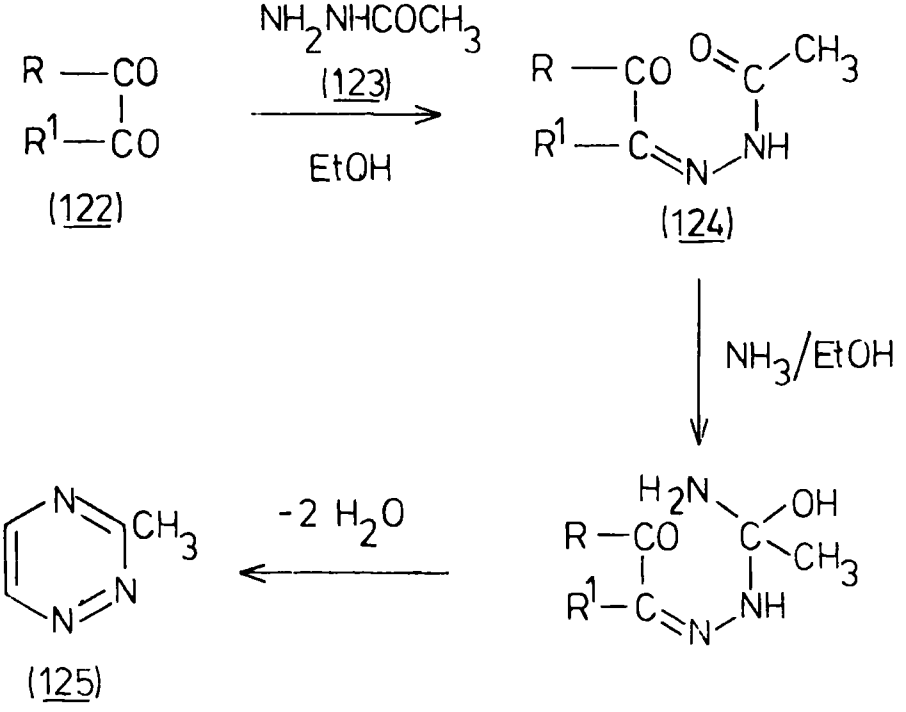


(I)

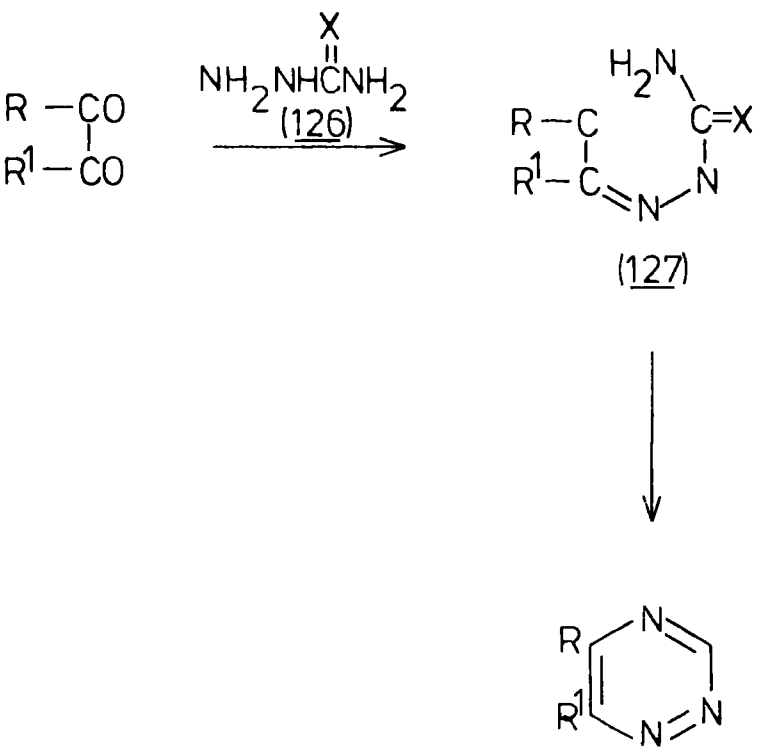


(II)

(1) Condensation of an α-diketone (122) with an acethydrazide (123) gives the corresponding hydrazone (124) which on treatment with alcoholic ammonia gives the 5,6-disubstituted-3-methyl-1,2,4-triazine (125) The last step in this reaction is reminiscent of pyridine formation from 1,5-diketones With unsymmetrically substituted diketones ($R \neq R^1$), the most reactive carbonyl forms the hydrazone and fixes the substitution pattern in the triazine

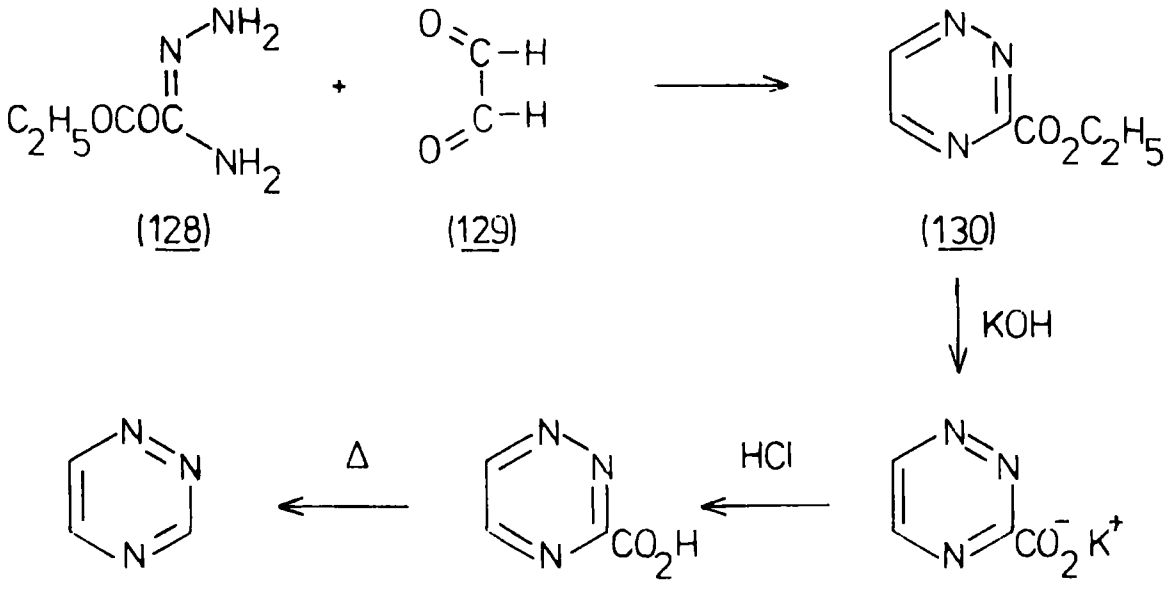


(ii) α-diketones react with semicarbazide (126, X = O), thiosemicarbazide (126, X = S), or aminoguanidine (126, X = NH) to give the mono-(127) and bis-substituted hydrazones Compound (127) is readily converted to 1,2,4-triazines by hot dilute alkali (when X = O) or by heating the reaction medium (when X = S, NH)



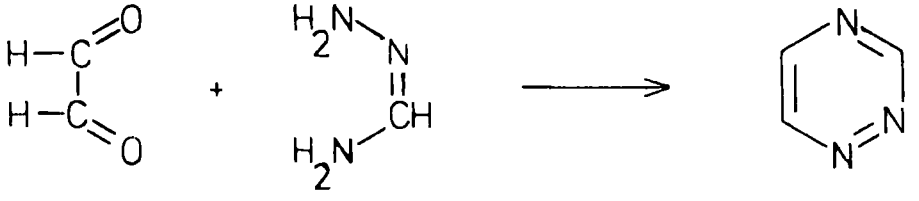
B SYNTHESIS OF 1,2,4-TRIAZINE

There have been many unsuccessful[49] attempts to prepare 1,2,4-triazine, however 1,2,4-triazine was eventually synthesised by the decarboxylation of 1,2,4-triazine-3-carboxylate Condensation of glyoxal (129) with compound (128) gave the 3-carboxylate derivative (130) which was converted by saponification and decarboxylation to the desired product [52]



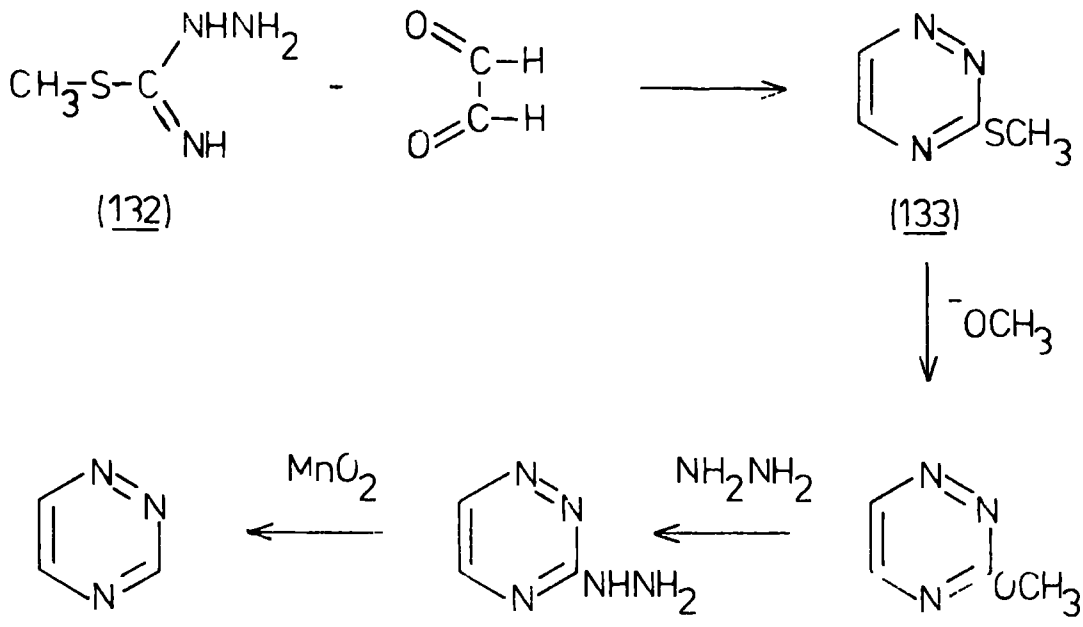
(128) (129) (130)

The first primary synthesis of 1,2,4-triazine was effected by condensation of glyoxal monomer with compound (131) in methanol in the presence of triethylamine at -75° [53]



(131)

A convenient synthesis, in terms of overall yield, was recently developed by Paudler et al ,[54] whereby condensation of S-methylthiosemicarbazide (132) with glyoxal readily affords the 3-methythio-1,2,4-triazine (133) The following steps, shown below, all give high yields

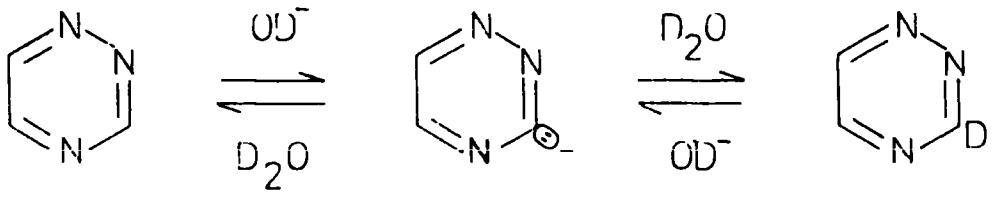


(132) (133)

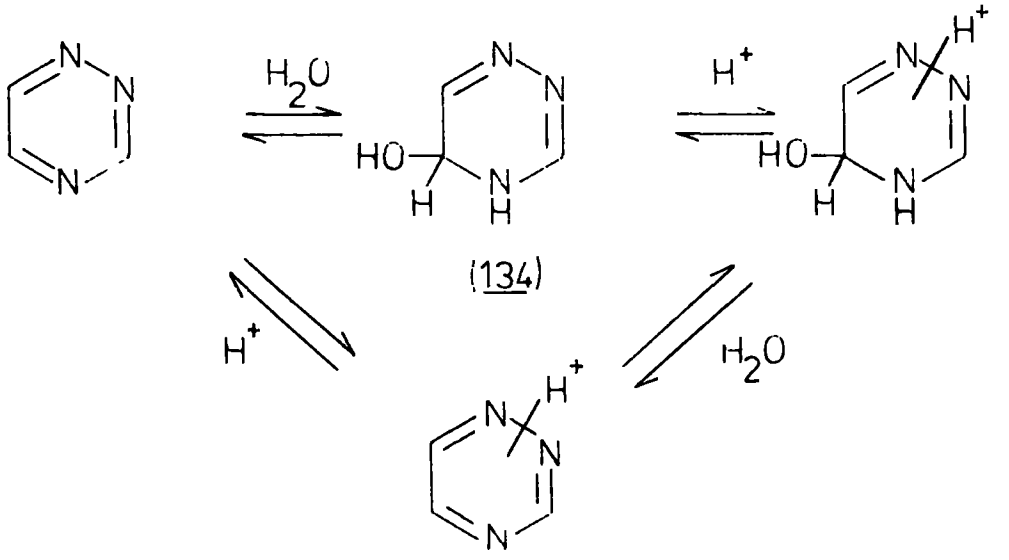
C CHEMISTRY OF 1,2,4-TRIAZINES

There are reviews of 1,2,4-triazine[49] and the related compound, 3,5-dihydroxy-1,2,4-triazine (more commonly known as 6-azauracil)[55] The chemistry discussed is largely that of amino-, hydroxy-, mercapto- and carboxy-derivatives of dihydro- and tetrahydro-1,2,4-triazines References to the fully aromatic parent compound are few However, this is not surprising in view of the difficulty of preparing 1,2,4-triazine, where in its preparation, low overall yields have been characteristic Thus the compound has been mainly a curiosity for physical and theoretical studies, its derivatives being made more readily via alternative condensation reactions

1,2,4-Triazine is a yellow liquid above its m p (16-17 5°) and undergoes exchange reactions in the presence of bases and acids The base-catalysed reactions can be represented by the following equilibrium[56]

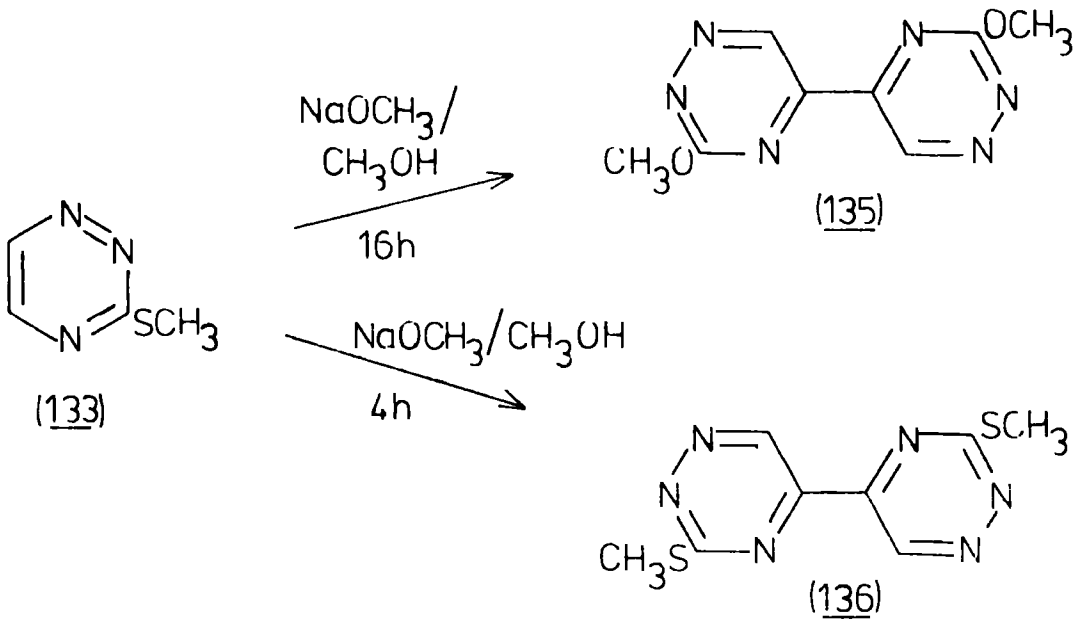


H-3 → D-3 exchange occurs under neutral conditions via a covalently hydrated intermediate (134), which is readily generated in acidic media [54] A situation involving all the indicated equilibria is believed to prevail Addition of base to the aqueous solution quantitatively regenerates 1,2,4-triazine



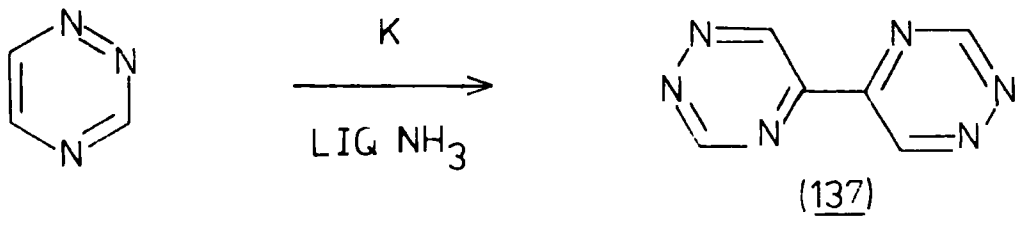
An interesting dimerisation of 1,2,4-triazines was recently reported[57] where 5,5'-bi-1,2,4-triazinyl compounds are obtained by treatment of various 1,2,4-triazines with either sodium methoxide or with aqueous potassium cyanide This process was first found in the preparation of 3-methoxy-1,2,4-triazine from 3-methylthio-1,2,4-triazine (133) Dimerisation to (135) became the

major process when sodium was added to a solution of 3-methylthio-1,2,4-triazine in absolute methanol When the reaction was interrupted, the methythio dimer was obtained (136)



(133) (135) (136)

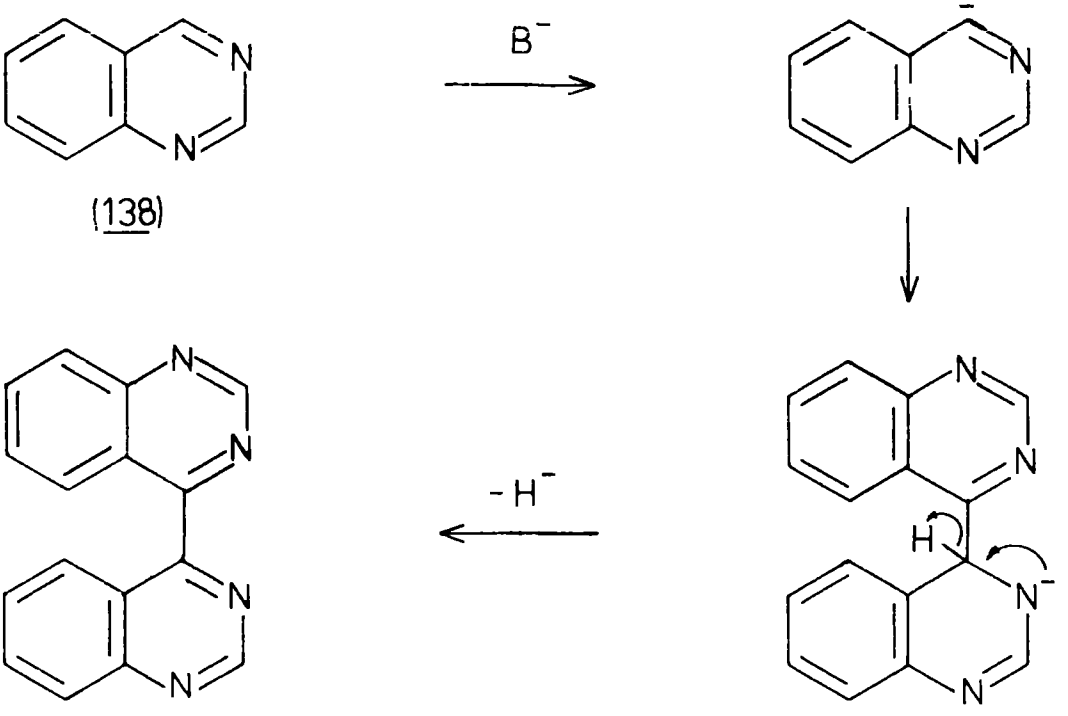
Similarly, when potassium was added to a solution of 1,2,4-triazine in liquid ammonia, 5,5'-bi-1,2,4-triazinyl (137) was produced [57]



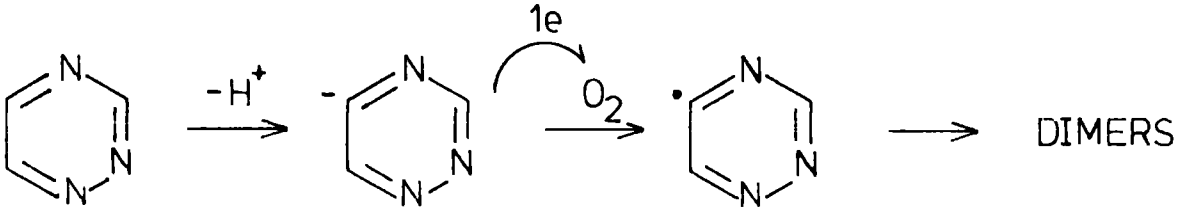
(137)

Dimerisations of some pyridine derivatives are well known phenomena Dry pyridine when treated with sodium at room temperature gives a mixture of 2,2'- and 4,4'-bipyridyl Similarly, quinazoline affords 4,4'-biquinazolyl It has been suggested that these dimerisations occur by either free radical

or carbanionic mechanisms Specifically, the dimerisation of quinazoline (138) is presumed to occur by the following sequence, where it is assumed[57] that hydride ion is lost in the last step

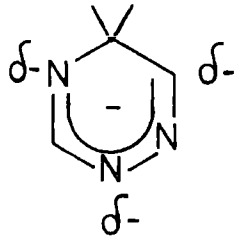


It is more probable that the process involves loss of hydrogen ion, followed by oxidation to form free radicals



Thus, the chemistry of 1,2,4-triazines is still at its infancy However, considerations of charge stabilisation in the transition state led to the postulation that the order of susceptibility of the three ring positions to nucleophilic attack should be 5 > 3 > 6 [51] This follows from

anticipation that nitrogen atoms ortho and para to the position of nucleophilic attack will be strongly activating

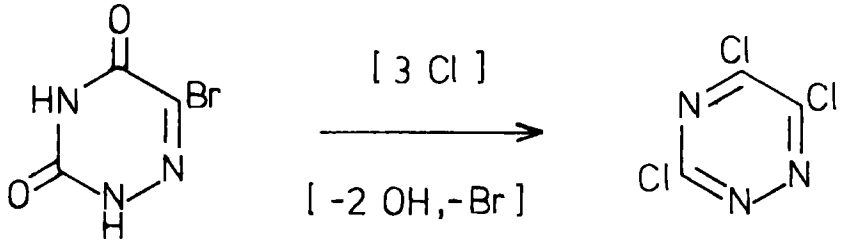


This relationship is consistent with the reactivity of 3,5-disubstituted and 3,5,6-trisubstituted chloro-derivatives in those cases where the structure of the products have been established

2 3. SYNTHESIS AND CHEMISTRY OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

A. INTRODUCTION

The aim of this work was to synthesise 3,5,6-trichloro-1,2,4-triazine (7) using 6-bromo-3,5-dihydroxy-1,2,4-triazine (139), as a precursor since it can be readily prepared

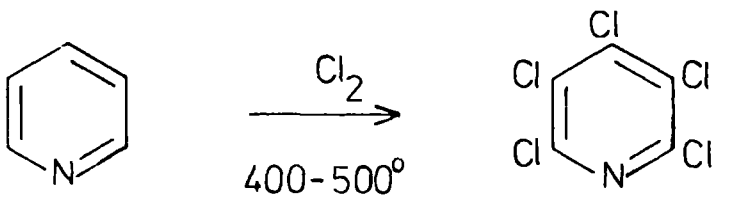


(139) (7)

The following is a general discussion of chlorination methods

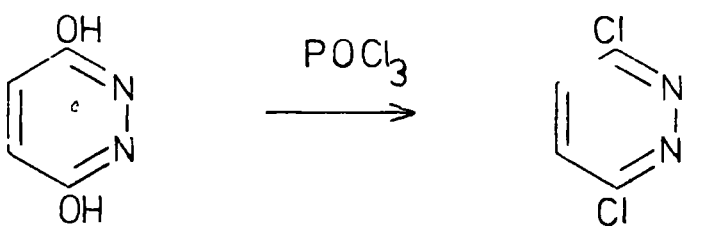
B GENERAL METHODS FOR CHLORINATION OF N-HETEROCYCLES

Elemental chlorine has been used to prepare highly chlorinated compounds such as pentachloropyridine (140),[58] but high temperatures are often required

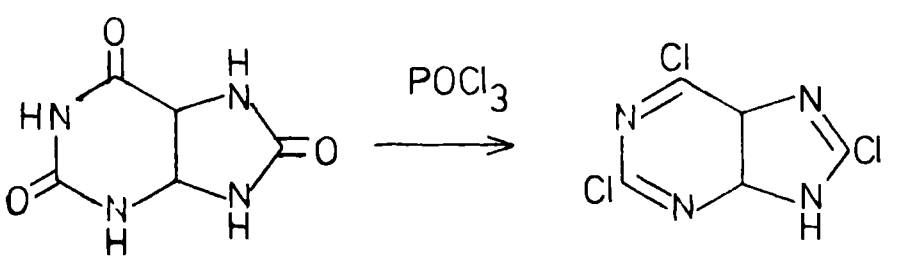


(140)

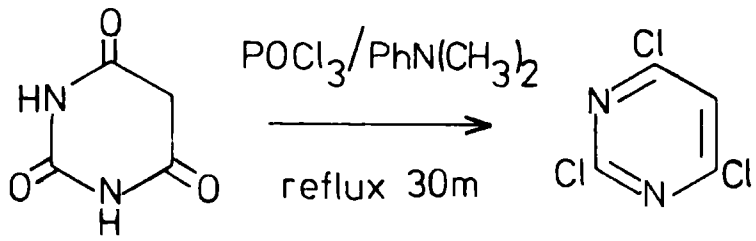
The reagent frequently used is refluxing phosphoryl chloride Group V elements, as well as replacing hydrogen by chlorine, frequently aid the replacement of hydroxyl by chlorine Phosphorous pentachloride or dimethyl-aniline are sometimes added to the reaction mixture A method developed in these laboratories uses phosphorus pentachloride alone The following are some examples of these methods



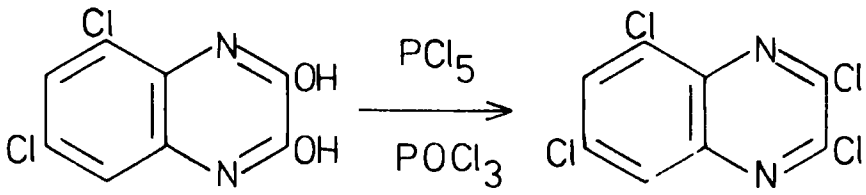
59



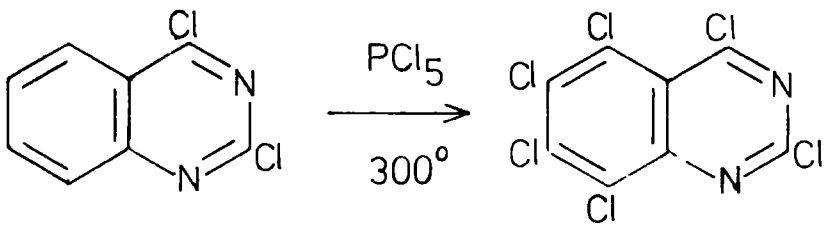
60


POCl3/PhN(CH3)2
reflux 30m

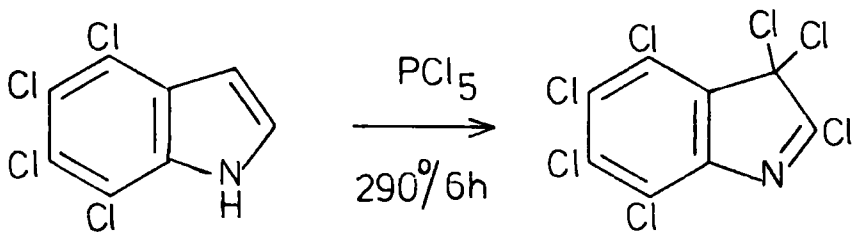
61


PCl5
POCl3

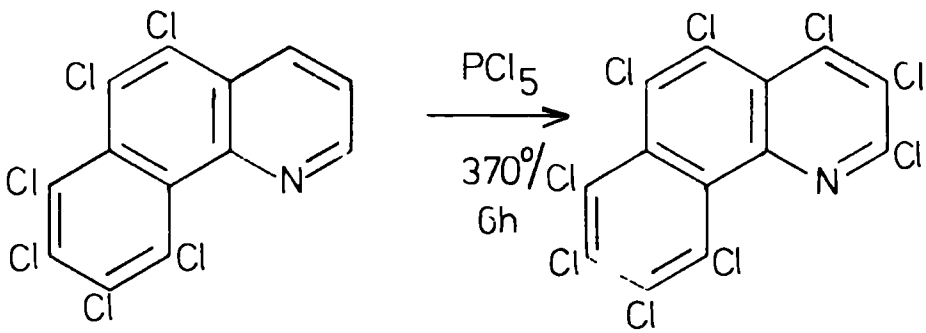
62


PCl5
300°

63


PCl5
290°/6h

64


PCl5
370°/Cl
6h

65

Phosphorus pentachloride is often used to complete chlorination of a N-heterocycle.

Other chlorinating reagents such as sulphur monochloride, sulphuryl chloride and Ballesters 'BMC' reagent[66] (a complex mixture of sulphur monochloride, sulphuryl chloride and aluminium chloride), have not generally found widespread use in the chlorination of N-heterocycles

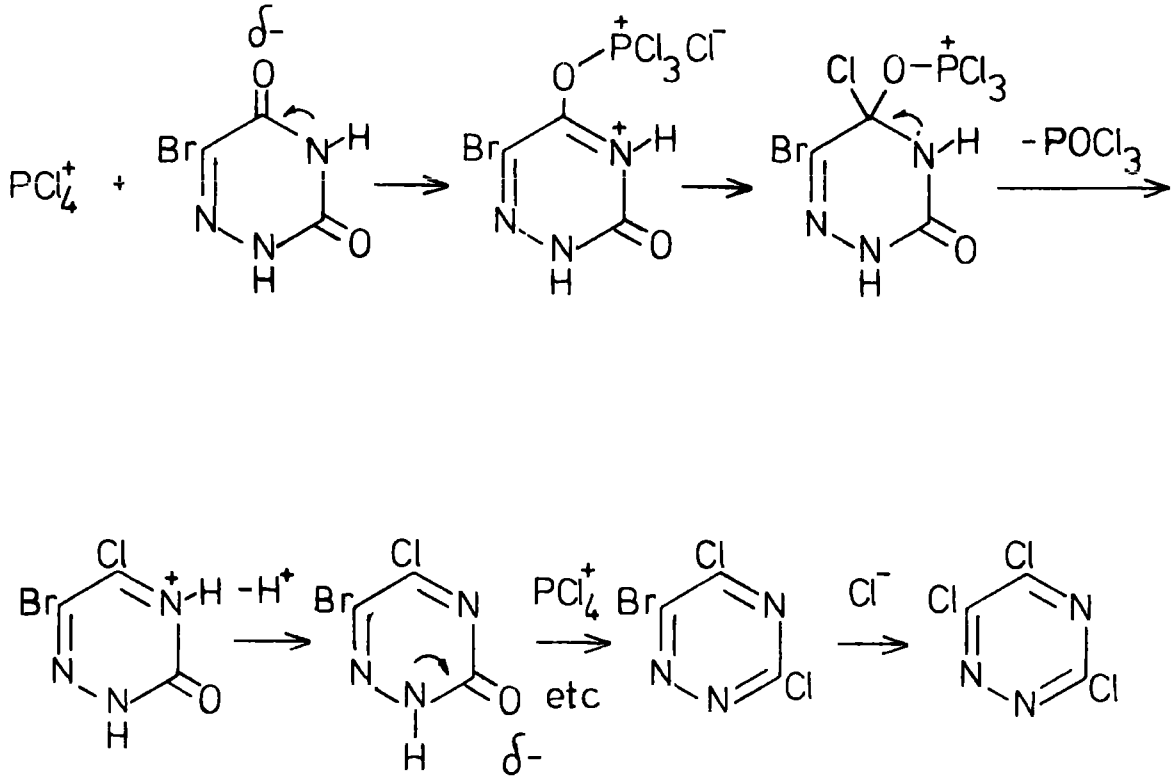
C SYNTHESIS OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

(1) PREVIOUS WORK

The first report[67] of an attempt to isolate 3,5,6-trichloro-1,2,4-triazine (7) was made by Chang, where the chlorination of 3,5-dihydroxy-1,2,4-triazine (144) was studied However, no product was identified from the reaction of (144) with phosphoryl chloride with or without dimethylaniline and/or phosphorus pentachloride Therefore 6-bromo-3,5-dihydroxy-1,2,4-triazine (139), which was considered[67] to be less reactive was reacted with phosphoryl chloride A moisture sensitive oil was obtained in ca 30% yield This was deduced to be 3,5,6-trichloro-1,2,4-triazine by characterisation of the hydrolysis product 6-chloro-3,5-dihydroxy-1,2,4-triazine Other workers[68] found this method could afford purer material but no report of the yield was made.

This work was repeated by Loving and was found to give (7) in yields of only 9-11%[69] Following this work Loving claimed an improved method of preparing (7) involving phosphoryl chloride, N,N'-diethylaniline and phosphorus pentachloride[69] A maximum yield of 78% was obtained though it was found that yields dropped substantially with large scale reactions This was apparently overcome by employing continuous liquid extraction methods on the reaction mixtures where yields of 50-60% were claimed An attempt[69] was made to rationalise this complex reaction and is summarised below, in SCHEME VIII

SCHEME VIII



(ii) PREPARATION OF THE STARTING MATERIALS

(a) GLYOXYLIC ACID SEMICARBAZONE[67]

Glyoxylic acid semicarbazone (143) was prepared readily from chloral hydrate (141) and semicarbazide hydrochloride (142).

$$\underset{(141)}{CCl_3CH(OH)_2} + \underset{(142)}{NH_2NHCONH_2.HCl} \xrightarrow[H_2O]{\Delta} \underset{(143)}{HO_2CCH=NNHCONH_2} \quad (74\,5\%)$$

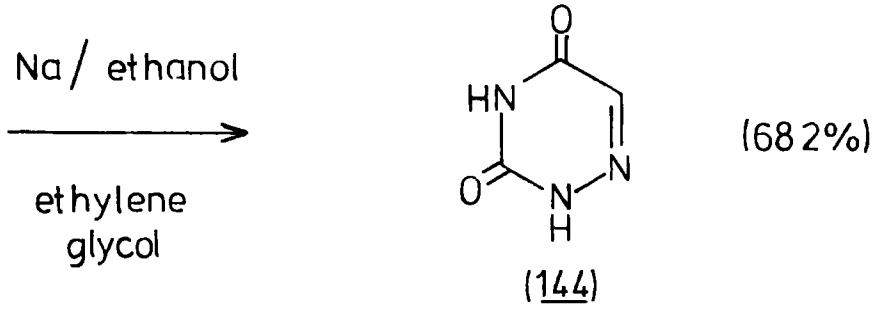
(b) 3,5-DIHYDROXY-1,2,4-TRIAZINE[67]

3,5-Dihydroxy-1,2,4-triazine (144) was prepared by cyclising gloxylic acid semicarbazone with sodium ethoxide. Apparently, the sodium salt formed from (143) is insoluble in ethanol but by employing a mixture of ethanol and

ethylene glycol a suitable reaction medium and reflux temperature was achieved.

$H_2OCCH{=}NNCONH_2$

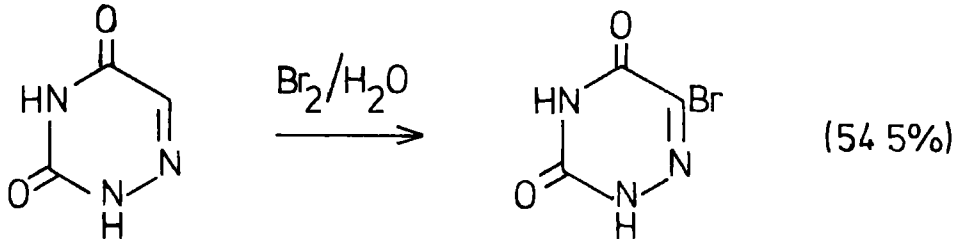
(143)



(144)

(c) 6-BROMO-3,5-DIHYDROXY-1,2,4-TRIAZINE[70]

(144) was readily brominated in the 6-position by stirring with a mixture of water and bromine.

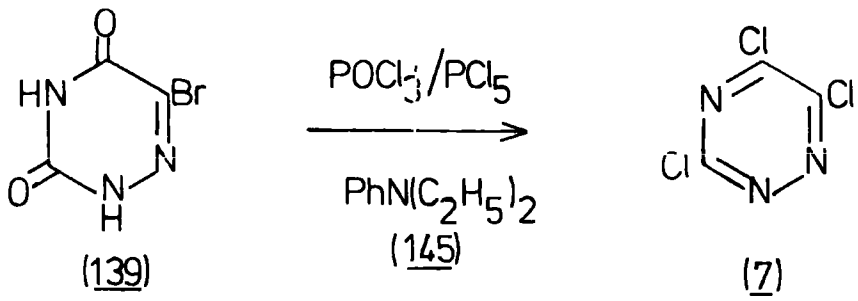


(144) (139)

(iii) CHLORINATION OF 6-BROMO-3,5-DIHYDROXY-1,2,4-TRIAZINE

(a) SOLVENT PHASE REACTIONS

The procedure[69] used by Loving was initially adopted.



(139) (145) (7)

Several difficulties were encountered in trying to repeat Loving's procedure An error in the reported experimental raises the question of what proportions of N,N'-diethylaniline were actually used Several attempts using the same amounts of reactants quoted [(139) (145) = 1 2 5] failed to give any product. When the reaction was repeated using the claimed molar quantities [(139) (145) = 1 3.0], yields of 21 4 - 33 1% were obtained.

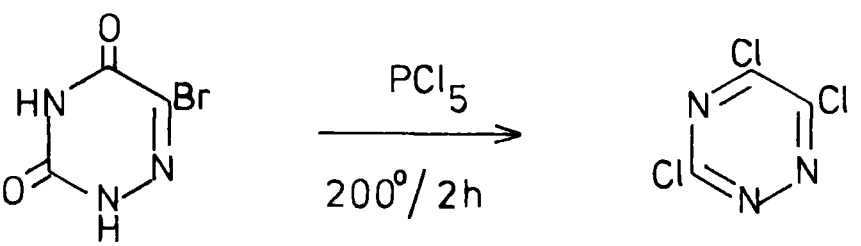
Another difficulty was one of extraction. The reaction mixtures were found to be miscible with organic solvents thus making liquid-liquid extraction impossible. When all the solvents were removed, the material obtained was very intractable. It was from this material that small amounts of 3,5,6-trichloro-1,2,4-triazine was obtained by distillation under reduced pressure.

The reactions were repeated with, and without, N,N'-diethylaniline or phosphorus pentachloride and with different reactant ratios but the yields were invariably very low Contrary to Loving's results,[69] the use of pyridine instead of N,N'diethylaniline, did assist in the formation of small yields of 3,5,6-trichloro-1,2,4-triazine Another base tried was triethylamine but with no success.

Overall, small scale reactions with this procedure gave low yields and with large scale reactions the yields were always reduced to zero.

(b) AUTOCLAVE REACTIONS

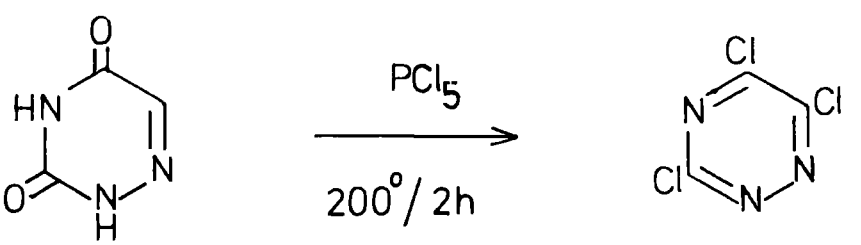
As mentioned earlier, a common procedure for preparing highly chlorinated -N- heterocycles is to use phosphorus pentachloride at high temperatures under autogenous pressure This method has now been successfully employed in the chlorination of 6-bromo-3,5-dihydroxy-1,2,4-triazine 3,5,6-Trichloro-1,2,4-triazine was isolated in yields of 36 2-48 8% when an optimum temperature of 200° for 2h. was employed



The product was isolated from the reaction mixture by distillation under reduced pressure and then recrystallised from hexane This procedure was simpler than the solvent phase reaction, and moreover, gave consistent yields with large scale reactions.

(iv) CHLORINATION OF 3,5-DIHYDROXY-1,2,4-TRIAZINE

Several chlorinations were carried out using 6-azauracil as the substrate Optimum conditions for the reaction and isolation of the product were found to be the same as those employed for chlorination of 6- bromo-3,5-dihydroxy-1,2,4-triazine, although lower yields of 19 1-33 6% were obtained

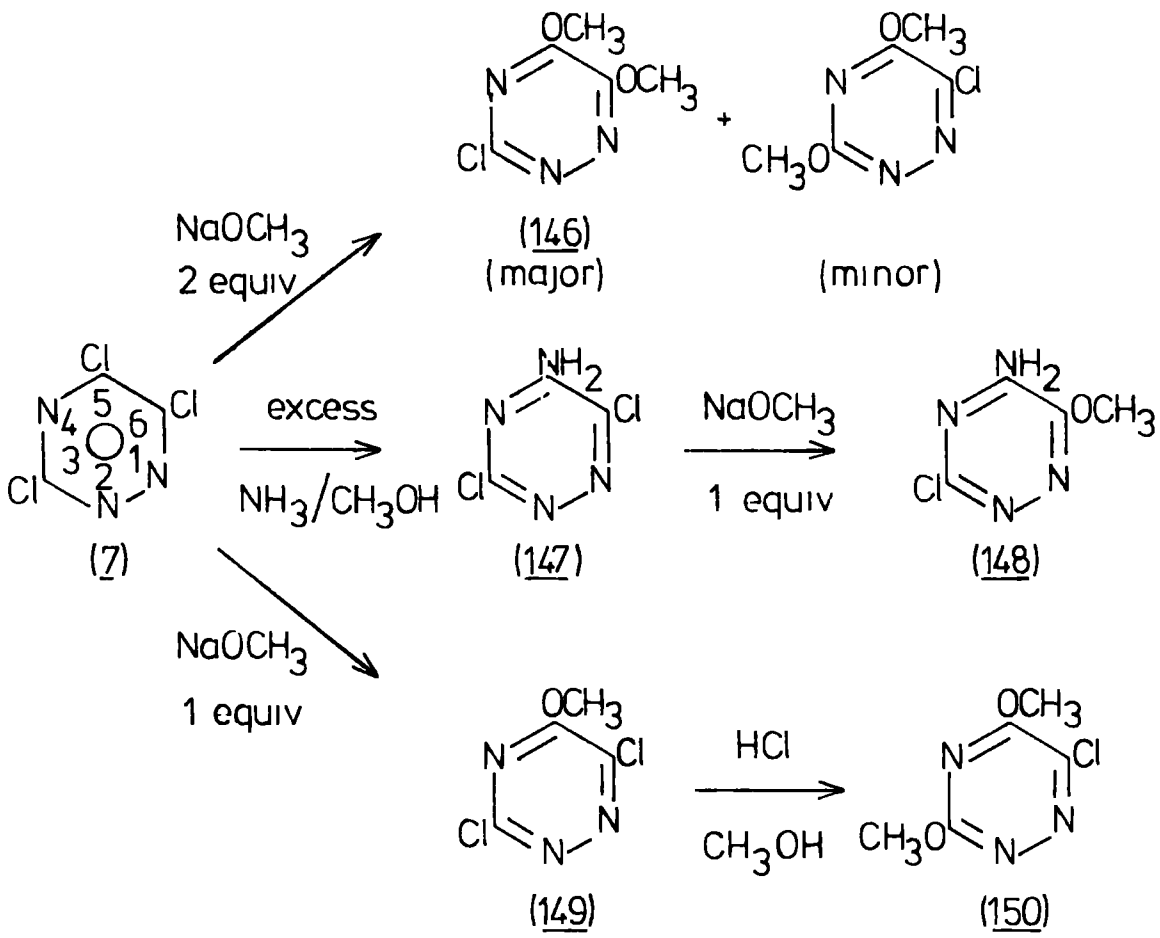


D CHEMISTRY OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

The chemistry of 3,5,6-trichloro-1,2,4-triazine, like that of the parent triazine, has only been studied briefly. The compound is very unstable with respect to hydrolysis and not surprisingly the reactions reported for this nitrogen heterocycle, are nucleophilic aromatic substitutions

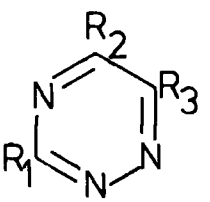
Piskala[68] has shown that the 5-position is the most susceptible to nucleophilic substitution The position of further substitution depends upon the reaction conditions In the experiments summarised in SCHEME IX, the positional order was found to be 5 > 6 > 3 with anionic nucleophiles and in the order 5 > 3 > 6 with neutral nucleophiles This is demonstrated by the reaction of compound (7) with two equivalent amounts of sodium methoxide

SCHEME IX



where the 5,6-disubstituted compound (146) is the major product Also, compound (147) gives only the 6-methoxy product (148) on reaction with one equivalent of sodium methoxide On the other hand, when compound (149) is treated with alcoholic hydrogen chloride the 3-methoxy product (150) is obtained

In more recent studies[71,72] by Piskala various dialkylamino-1,2,4-triazines have been prepared



$R_1 = R_3 = Cl$, $R_2 = NMe_2$

$R_1 = R_2 = NMe_2$, $R_3 = Cl$, OMe

$R_1 = R_3 = H$; $R_2 = NMe_2$, OMe

$R_1 = R_2 = NMe_2$, NEt_2; $R_3 = H$

$R_1 = R_2 = NMe_2$, NEt_2; $R_3 = OMe$, NMe_2

$R_1 = H$; $R_2 = OMe$, NMe_2, $R_3 = OMe$

$R_1 = H$; $R_2 = OMe$, $R_3 = NMe_2$

$R_1 = R_2 = OMe$; $R_3 = H$

A similar series of compounds has been prepared by Neunhoeffer [73]

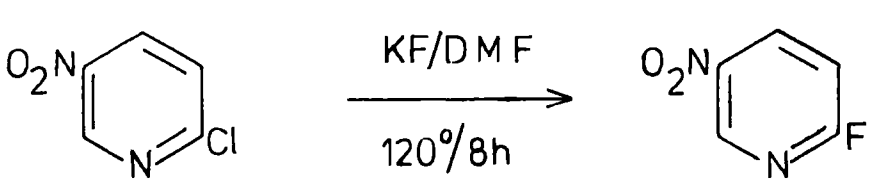
2 4 ATTEMPTED SYNTHESIS OF 3,5,6-TRIFLUORO-1,2,4-TRIAZINE

A. INTRODUCTION

As mentioned earlier the most obvious route to the synthesis of 3,5,6-trifluoro-1,2,4-triazine is by fluorination of 3,5,6-trichloro-1,2,4-triazine Polyfluorination of polychlorocompounds can be achieved by a halogen exchange reaction using an alkali metal fluoride, with or without a solvent The following section is a discussion involving this particular method of fluorination and where the substrates are chloro-N-heterocycles The most practical alkali metal fluoride is potassium fluoride though sometimes the more expensive and reactive caesium fluoride is used.

B FLUORINATION OF CHLORO-N-HETEROCYCLES

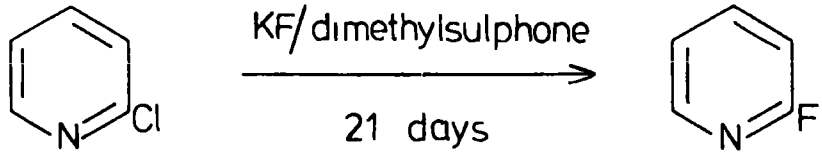
The halogen exchange reactions considered here are essentially nucleophilic aromatic substitutions and is therefore a process which will be favoured with the more activated systems This is demonstrated in the reactivity of 2-chloro-pyridines to potassium fluoride in dimethylformamide Although the pyridine system is activated by the ring nitrogen present no reaction occurs with 2-chloropyridine When the aromatic system is further activated by a nitro group para to the chlorine atom, reaction does proceed to give 2-fluoro-5-nitropyridine (151).[74]



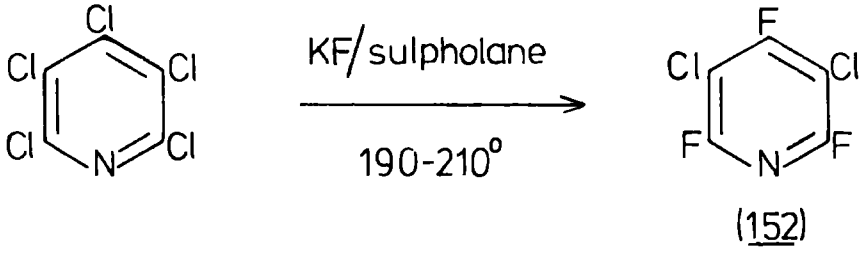
(151)

More polar aprotic solvents such as dimethylsulphone, N-methyl-2-pyrrolidone and sulpholane, allow halogen exchange reactions to occur on less

activated systems Thus 2-chloropyridine can be fluorinated in dimethyl-sulphone but a long reaction time is required [75]

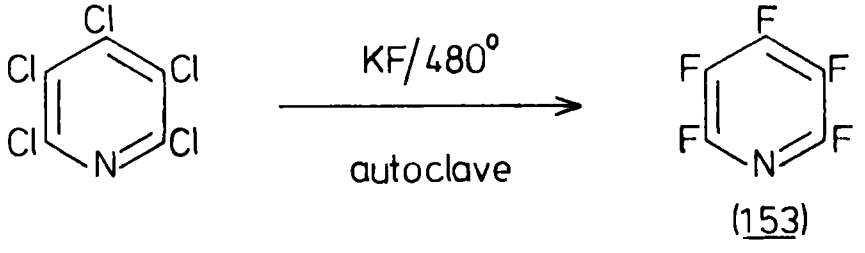


With perchloropyridine the main product obtained on reaction with potassium fluoride and sulpholane is 2,4,6-trifluoro-3,5-dichloropyridine (152)



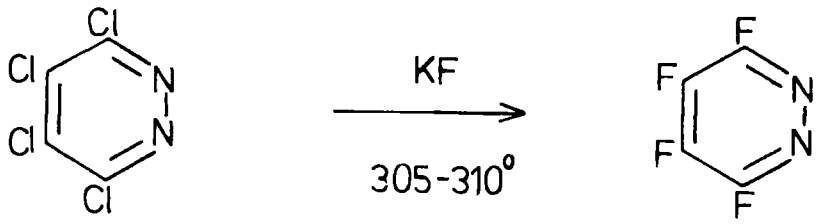
(152)

The feature limiting the extent of this and many other fluorinations is the thermal stability of the solvent This problem is avoided by employing potassium fluoride at high temperatures in an autoclave in the total absence of a solvent Pentafluoropyridine (153) is thus prepared by heating pentachloropyridine with potassium fluoride at 480° [76,77]

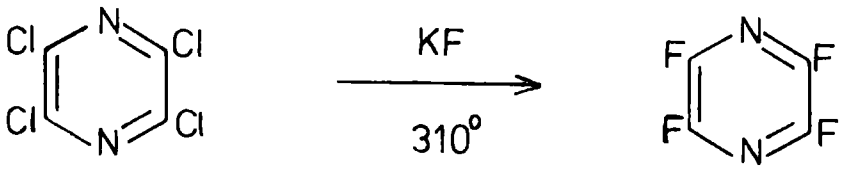


(153)

This technique is a general process for the synthesis of highly fluorinated N-heterocycles For example, perfluoropyridazine (60)[78] and perfluoropyrazine (61)[79] are prepared from perchloropyridazine and perchloropyrazine respectively.

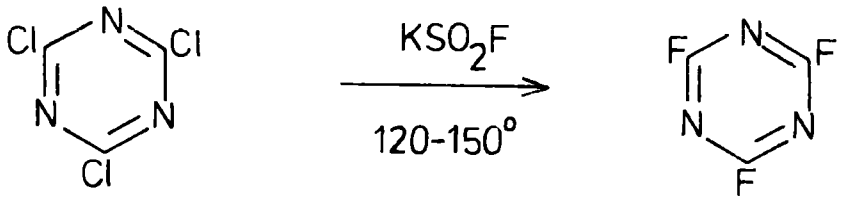


(60)



(61)

Milder reaction conditions give cyanuric fluoride from cyanuric chloride [80]



(6)

Other compounds which have been prepared by halogen exchange reactions are perfluoroquinoline,[81] perfluoroisoquinoline,[81] perfluoropyrimidine,[82,83] perfluoroquinoxaline,[84] perfluoroquinazoline[63] and perfluorocinnoline.[85]

C FLUORINATION OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

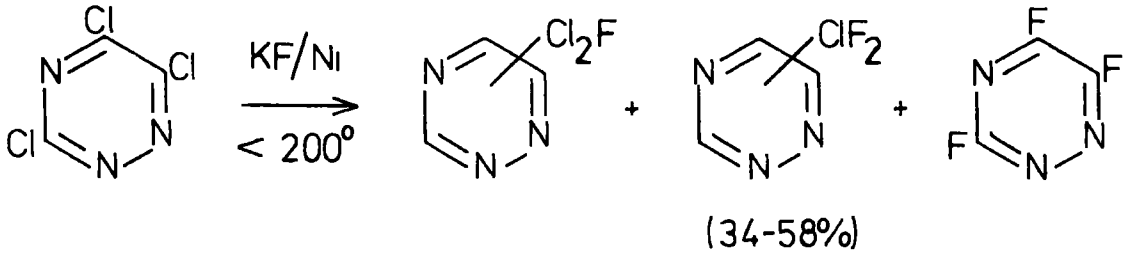
(i) SOLID PHASE REACTIONS

(a) POTASSIUM FLUORIDE

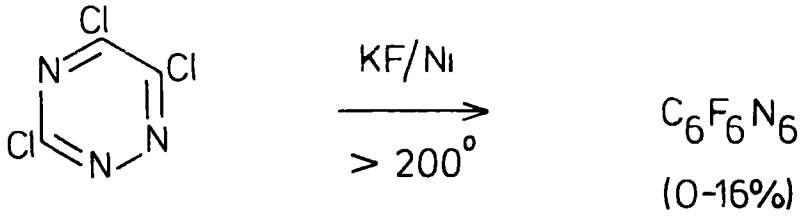
The fluorination of 3,5,6-trichloro-1,2,4-triazine with potassium fluoride in a nickel autoclave was attempted at a variety of temperatures The reactions gave mixtures of chloro-fluoro-1,2,4-triazines, the extent of

fluorination increased with temperature but there was a corresponding decrease in the yields.

Below 200° fluorination of 3,5,6-trichloro-1,2,4-triazine was the favoured process, 140-150° favoured the dichloromonofluoro-1,2,4-triazine(s) and 170-200° favoured the difluoromonochloro-1,2,4-triazine(s). Trace amounts of 3,5,6-trifluoro-1,2,4-triazine were observed in all these reactions



Above 200° only 3,5,6-trifluoro-1,2,4-triazine dimers were obtained in very low yields



The reaction mixtures obtained were readily hydrolysed, even on glass surfaces which had been previously baked in hot ovens.

(b) CAESIUM FLUORIDE

That caesium fluoride is a more reactive fluorinating agent than potassium fluoride was remarkably demonstrated when caesium fluoride and 3,5,6-trichloro-1,2,4-triazine were mixed together at room temperature Exothermic reaction occurred between the two substrates to give a fused coloured mass. It was not possible to characterise this mass by ^{19}F n.m.r. due to poor

solubility, therefore no other techniques were used, on what was probably a complex mixture.

(ii) SOLVENT PHASE REACTIONS

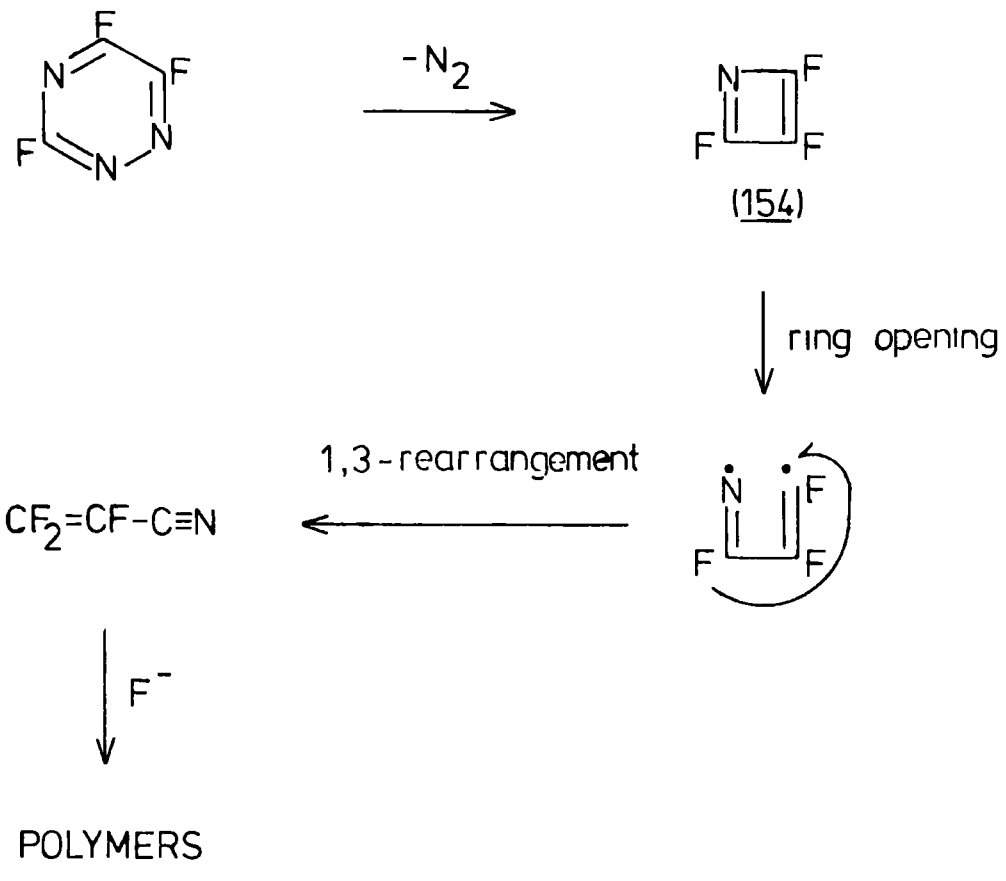
Attempts at fluorination of 3,5,6-trichloro-1,2,4-triazine in sulpholane with either potassium fluoride or caesium fluoride at room temperature and at 120° were unsuccessful. The most surprising feature was that no volatiles could be isolated from these mixtures, which gave polymeric tars on removal of solvent.

D CONCLUSIONS ON FLUORINATIONS OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

It is apparent that fluorination of 3,5,6-trichloro-1,2,4-triazine with potassium fluoride in nickel autoclaves at temperatures above 200° gave the desired product, 3,5,6-trifluoro-1,2,4-triazine, but the system then suffers by either ring opening or undergoes further reaction with the excess fluoride ion present

Evidence for ring opening was found in the infrared spectra of residue remaining in the nickel autoclaves used in the fluorinations (a medium band at 2120 cm^{-1} is indicative of a C≡N function) Study of the mass spectra of the chlorofluoro- and 3,5,6-trifluoro-1,2,4-triazines revealed that after ionisation loss of nitrogen was a major pathway in fragmentation.

Extrusion of nitrogen with the formation of transient trifluoroazete (154), followed by ring opening and a 1,3-rearrangement, could generate trifluoro-acrylonitrile, (155) a compound which would be prone to polymerisation

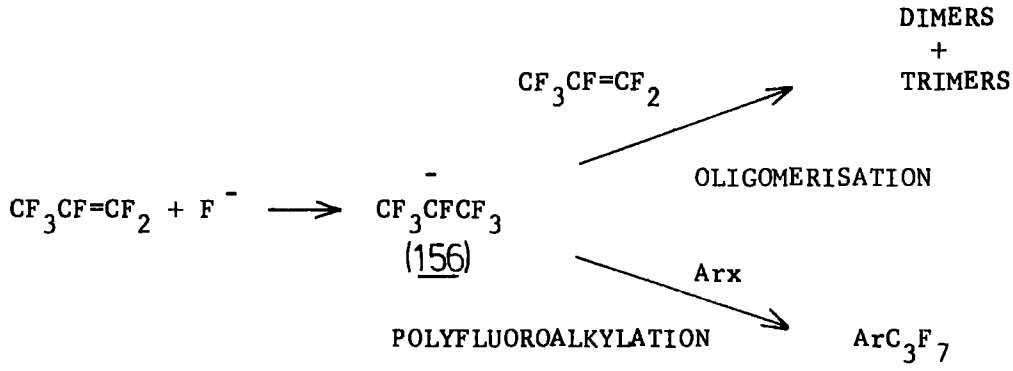


By analogy with 3,5,6-trichloro-1,2,4-triazine the product of hydrolysis would be expected to be 3,5-dihydroxy-6-fluoro-1,2,4-triazine There was no evidence for the formation of this compound (Attempts to prepare 3,5-dihydroxy-6-fluoro-1,2,4-triazine by other workers have failed due to ring rupture)[70]

An alternative process to ring rupture was one of dimerisation It is difficult to speculate upon the structure of these dimers with no other information than their molecular weight.

Thus attempts to isolate 3,5,6-trifluoro-1,2,4-triazine from reactions of 3,5,6-trichloro-1,2,4-triazine with an excess of fluoride ion were of little success With hindsight, however, it appears that the presence of excess fluoride ion may have been the major problem.

In a later experiment, which was an attempt at mono-(polyfluoroalkyl)-ation, an excess of 3,5,6-trichloro-1,2,4-triazine was used in a mixture with potassium fluoride and sulpholane under an atmosphere of hexafluoro-propene The hexafluoropropene was recovered unchanged, that is, neither polyfluoroalkylation of the 3,5,6-trichloro-1,2,4-triazine nor oligomerisation of the hexafluoropropene had occurred. Both of these processes involve the generation of the perfluoroisopropyl anion (156), a species which is known to be readily formed under these conditions

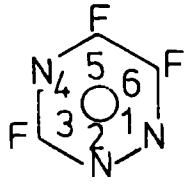


It can therefore be concluded that the entire amount of fluoride ion present in the reaction mixture reacted only with 3,5,6-trichloro-1,2,4-triazine

The principle volatiles isolated from the solution were 3,5,6-trichloro-1,2,4-triazine and an unstable liquid. The liquid attained a bright red colour and decomposed over a period of two days with the gaseous evolution. The ^{19}F n m r spectrum gave three signals of equal intensity at 58.95 p.p.m , 60.82 p p m. and 63.12 p p m (relative to external $CFCl_3$) It is possible that this liquid was 3,5,6-trifluoro-1,2,4-triazine but the absence of other data makes inference difficult The formation of 3,5,6-trifluoro-1,2,4-triazine as an intermediate in polyfluoroalkylations of 3,5,6-trichloro-1,2,4-triazine is dissussed further in the following section

Calculations of substituent chemical shifts (SCS) allow predictions of chemical shifts of hitherto unknown compounds The changes in chemical shift of various fluorine atoms in aromatic fluorocarbons caused by the replacement of C-F by N in the aromatic rings can be calculated. The calculations of such systems as the quinolines,[86] have been found to be in good agreement with observed shifts.

The SCS values obtained from hexafluorobenzene and pentafluoropyridine, pentafluoropyridine and the three tetrafluorodiazines, were very inconsistent. The results, which are summarised below, show that there is no reliable way of predicting the chemical shifts of 3,5,6-trifluoro-1,2,4-triazine.



	SHIFT	POSITION
	10.01 - 34.79	3
	49.85 - 76.11	5
	84 11 - 100.05	6

2 5 POLYFLUOROALKYLATION OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

A. INTRODUCTION

A very useful preparation of polyfluoroalkyl substituted aryl compounds is the reaction of polyfluoroalkyl anions, with activated haloaromatic compounds.

This type of reaction can be seen to be complementary to the Friedel-Crafts type of reaction in hydrocarbon chemistry

$$F^- + F_2C{=}\dot{C}- \longrightarrow CF_3-\dot{C}^-- \xrightarrow{Ar_F} CF_3-\dot{C}-Ar + F^-$$

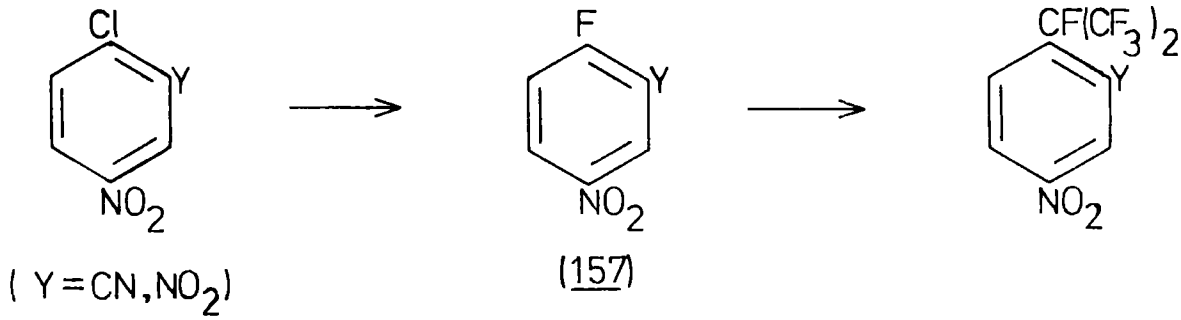
$$H^+ + H_2C{=}\dot{C}- \longrightarrow CH_3-\dot{C}^+- \xrightarrow{Ar_H} CH_3-\dot{C}-Ar + H^+$$

The following discussion relates the differences found on going from fluorocarbons to chlorocarbons in nucleophilic substitution, which is the type of reaction involved with polyfluoroalkyl anions

B. POLYFLUOROALKYLATION OF HALOCARBONS

The general method for polyfluoroalkylation of fluorocarbons involves reaction of the respective fluorocarbon in an atmosphere of the appropriate polyfluoroolefin, with or without a solvent (such as glymes, acetonitrile, sulpholane) in the presence of fluoride ion (either potassium fluoride or caesium fluoride) at temperatures ranging from 25° to 180°

This general method, however, has not been extended to the chlorocarbons. There is only one reported[87] example where a chlorine atom was substituted for a polyfluoroalkyl group It is probable, though, that the fluorocompound (157) was formed in situ as an intermediate



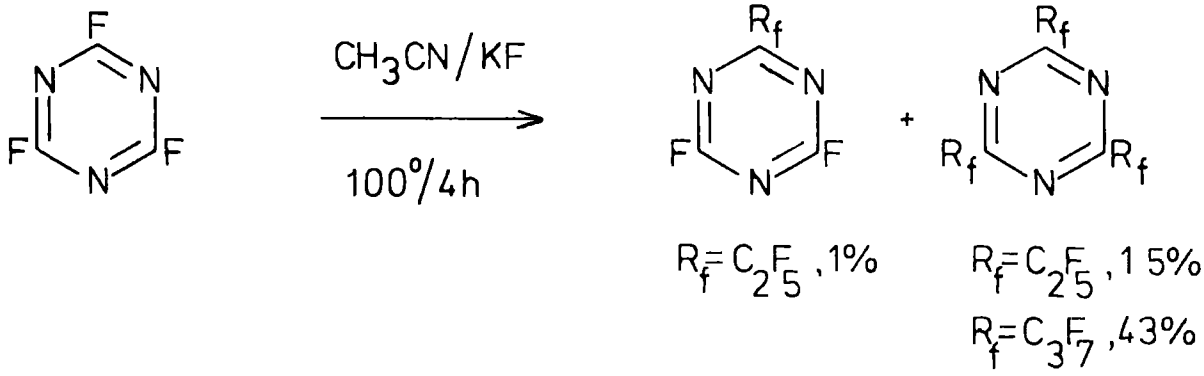
(Y = CN, NO_2) (157)

The reason why chlorocarbons are less suited for polyfluoroalkylations is easily understood Highly chlorinated compounds are generally less reactive than the corresponding highly fluorinated compounds as the carbon chlorine bond is less readily attacked by nucleophiles than the carbon fluorine bond It is commonly thought that fluoride ion is displaced more readily than chloride ion because the fluorine bond is more polar and the carbon atom is therefore more positive and open to nucleophilic attack

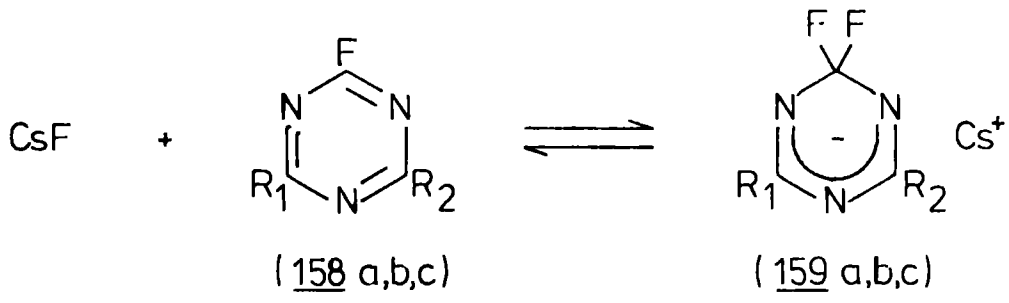
It is interesting to note the reactions of the isomeric 1,3,5-triazines, cyanuric fluoride and cyanuric chloride, to polyfluoroalkylation With cyanuric fluoride, the derivatives from tetrafluoroethylene and hexafluoropropene are all known. The reaction conditions involve heating cyanuric

fluoride, caesium fluoride and perfluoroalkene in an autoclave at temperatures of 80-130° with pressures of 3-50 atmospheres.[88] Although three compounds are formed in these reactions, the reaction can be directed toward any of the derivatives by altering the reactant ratio.

An unusual feature, not evident in other activated fluorocarbons, is the difference in the yields observed with tetrafluoroethylene and hexafluoropropene, under the same reaction conditions.



This may be due to competition between cyanuric fluoride and the perfluoroalkenes for fluoride ion i.e. hexafluoropropene competes better than tetrafluoroethylene for fluoride ion in the presence of cyanuric fluoride The formation of σ-complexes has been proven for the compounds shown below though only the σ-complex formed from cyanuric fluoride (158,a) and caesium fluoride has been isolated.[89]



a $R_1=R_2=F$

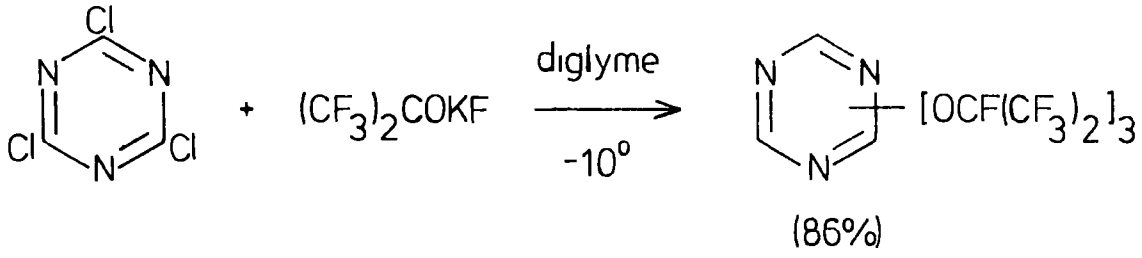
b $R_1=F, R_2=CF(CF_3)_2$

c $R_1=R_2=CF(CF_3)_2$

Polyfluoroalkyl derivatives have also been obtained from reactions involving cyanuric fluoride with n-octafluoro-2-butene and hexafluoro-2-butyne in the presence of fluoride ion

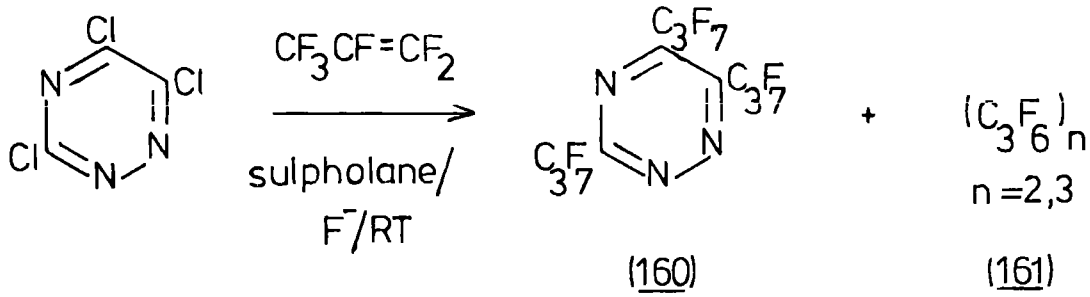
Although the possibility has been suggested in the literature,[90] there are no reported polyfluoroalkylations of cyanuric chloride In the formation of polyfluoroalkoxy derivatives cyanuric chloride rather than cyanuric fluoride is used The probable advantage of using the perchlorocompound lies in reducing the possibility of a back reaction when X = Cl in the sequence shown.[91]

$$R_fO^- + ArX \rightleftharpoons ArOR_f + X^- \ (X=Cl,F)$$



C POLYFLUOROALKYLATION OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE

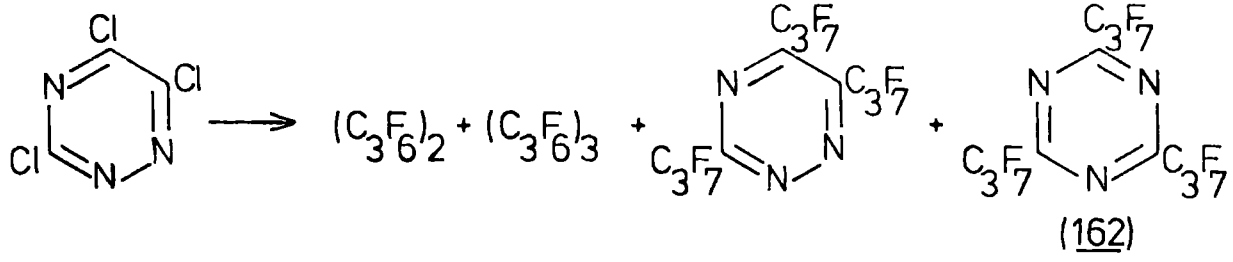
Polyfluoroalkylation of 3,5,6-trichloro-1,2,4-triazine was attempted with tetrafluoroethylene, hexafluoropropene, n-octafluoro-2-butene and hexafluorocyclobutene. Sufficient fluoride for both halogen exchange and catalysis was used In the reactions with tetrafluoroethylene, n-octafluoro-2-butene and hexafluorocyclobutene, the perfluoroalkenes were recovered unchanged whereas with hexafluoropropene the main products obtained were perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (160) and hexafluoropropene oligomers (161).



(160) (161)

The reaction products were found to vary with the source of the fluoride ion.

It is worth recording that in a preliminary reaction, with caesium fluoride as the fluoride ion source, four principal products were obtained as shown below.



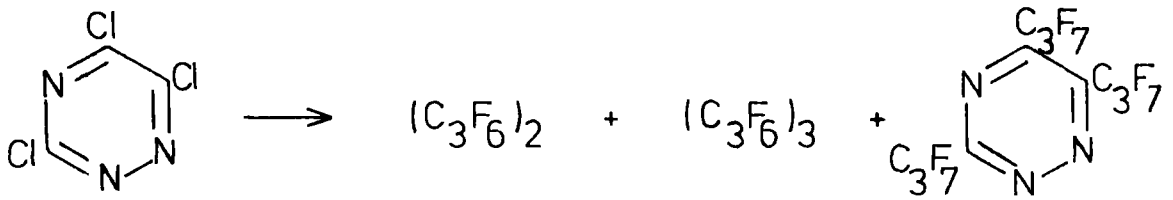
(162)

molar ratios	18·1	63·5	16·0	2·4

The yield of the perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine was only 1.9%.

A remarkable feature of this reaction was the formation of perfluoro-2,4,6-isopropyl-1,3,5-triazine (1,2). However, this experiment was repeated but no perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine was detected though the other components were obtained in almost identical ratios.

When potassium fluoride was used for the fluoride ion source the major product was perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine. No perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine was detected in any of the reaction mixtures.

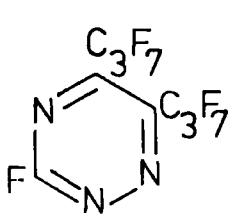


molar ratios	15 1	11 4	73·5

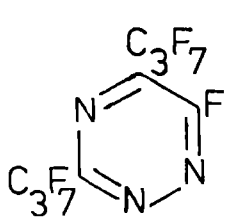
The yield of the perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine was 62 7%

Distillation of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine gave crude fractions containing perfluoro-di-isopropyl-1,2,4-triazines Separation of these perfluoro-di-isopropyl-1,2,4-triazines could not be achieved by preparative gas-liquid chromatography. It should be emphasised that they were minor components making only an estimated 3.2% of the perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine fraction

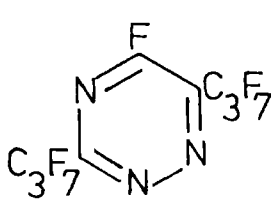
^{19}F n.m r data supported the presence of only two of the three possible perfluoro-di-isopropyl-1,2,4-triazines (163) - (165), though it was not possible to determine their structures.



(163)



(164)

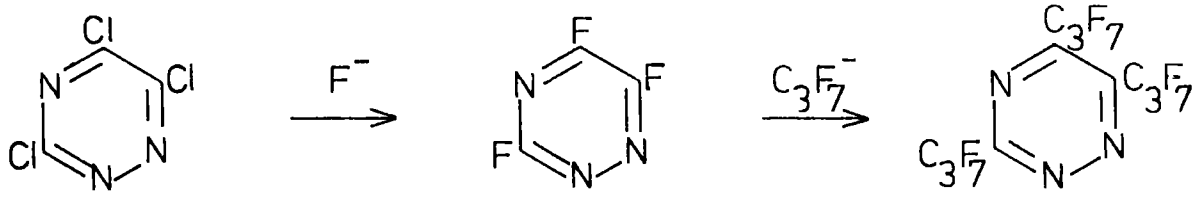


(165)

D. CONCLUSION

In the polyfluoroalkylation reactions which have been described only the reaction of 3,5,6-trichloro-1,2,4-triazine with hexafluoropropene, in the presence of fluoride ion, gave a perfluoroalkyl-1,2,4-triazine. This reaction is very unusual in that it is the only known example where a highly chlorinated aromatic compound is directly converted to a polyfluoroalkyl-compound. Furthermore, there are very few systems where polyfluoroalkylation gives the highest possible degree of substitution and none which are achieved under such mild reaction conditions

The mechanism of this reaction probably involves six steps, with 3,5,6-trifluoro-1,2,4-triazine being formed as an intermediate

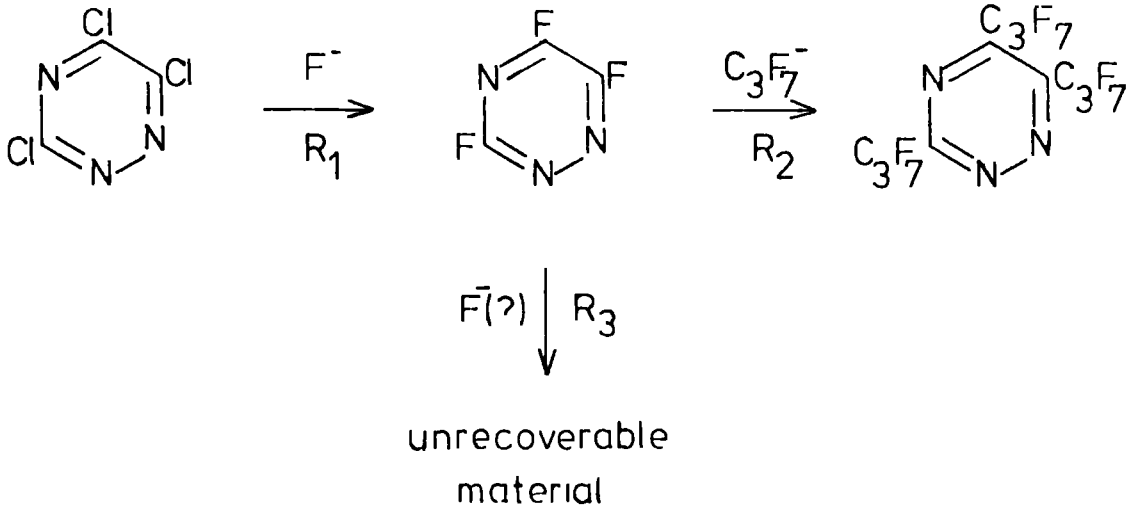


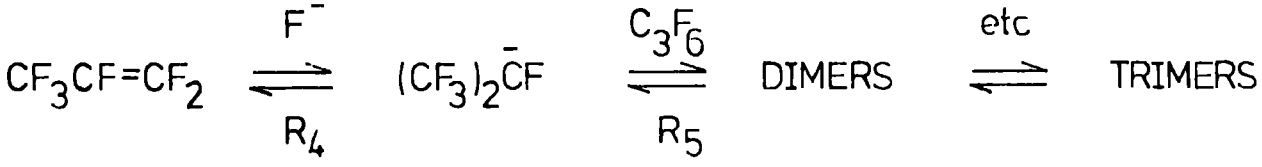
This follows from the observations that when there was insufficient fluoride ion for both halogen exchange and catalysis, neither polyfluoroalkylation of 3.5,6-trichloro-1,2,4-triazine nor oligomerisation of hexafluoropropene occurred.

There is no evidence to suggest direct substitution of chlorine with perfluoroisopropyl.

The results can be represented by the rate determining sequences shown in SCHEME X The reaction can be seen to involve five distinct processes:- (1) fluorination of 3,5,6-trichloro-1,2,4-triazine where three fluorine atoms are substituted for three chlorine atoms. For simplification these

SCHEME X





RATE DETERMINING AND COMPETING PROCESSES IN THE REACTION OF 3,5,6-TRICHLORO 1,2,4-TRIAZINE AND HEXAFLUOROPROPENE WITH FLUORIDE ION

three reactions are denoted by the rate constant R_1

(2) polyfluoroalkylation, again involving three substitutions at different reaction centres, but being represented by one rate constant R_2.

(3) further reaction of 3,5,6-trifluoro-1,2,4-triazine, presumably with fluoride ion, to give unrecoverable material. This is denoted by the rate constant R_3.

(4) formation of the perfluoroisopropyl anion with a rate constant R_4.

(5) oligomerisation of hexafluoropropene with a rate constant R_5.

When the source of fluoride ion is potassium fluoride there are two distinct competing processes The reactions of polyfluoroalkylation and oligomerisation both compete for the perfluoroisopropyl anion, i e. R_2 via R_5 It is assumed that the rate of fluorination (R_1) and the rate of formation of the perfluoroisopropyl anion (R_4) are both very fast

When the fluoride ion source is caesium fluoride a further apparent complication is introduced The rate at which 3,5,6-trifluoro-1,2,4-triazine undergoes side reactions (R_3) becomes very significant and this is reflected in the very low yields of perfluoro 3,5,6-tris-isopropyl-1,2,4-triazine

It is interesting to note that introduction of a perfluoroisopropyl group into the 1,2,4-triazine ring system must cause considerable activation to further substitution. No mono-alkyl derivatives and only trace amounts of di-alkyl derivatives were detected.

2.6 REACTION OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE WITH PENTAFLUOROPHENYL LITHIUM

With most polychloroaromatics, reaction with organo-lithium compounds give products which are derived by metal-halogen exchange processes. Alkylation has been found to occur in exceptionally few cases. Pentachloropyridine undergoes some alkylation by n-butyl lithium in hydrocarbon solvents,[92] and tetrachloropyrazine has been alkylated by methyl lithium and phenyl lithium [93,94]

Pentafluorophenyl lithium was prepared in situ and 3,5,6-trichloro-1,2,4-triazine was added to the reaction mixture. However, it was not possible to obtain any tractable material from the reaction

CHAPTER 3

EXPERIMENTS WITH 3,5,6-TRICHLORO-1,2,4-TRIAZINE AND PERFLUORO-3,5,6-TRIS-ISOPROPYL-1,2,4-TRIAZINE

3.1. INTRODUCTION

This chapter describes investigations into the generation of azetes from 1,2,4-triazines described in the preceding chapter. Photolytic and pyrolytic methods were employed and, under those conditions where nitrogen elimination occurred, trapping of the reactive intermediates was attempted. Reaction of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine with fluoride ion was also studied.

3.2. 3,5,6-TRICHLORO-1,2,4-TRIAZINE

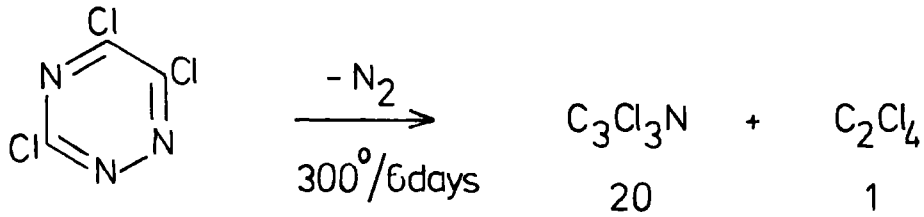
A. PHOTOLYSIS

Irradiation (300 n.m.) of 3,5,6-trichloro-1,2,4-triazine (λ 290 mμ, ε = 4445, 302mμ, ε = 2805, 365mμ, ε = 440) failed to give any product by rearrangement or nitrogen elimination. There was partial decomposition, probably due to carbon chlorine bond fission.

B. PYROLYSIS

(i) STATIC PYROLYSIS

3,5,6-Trichloro-1,2,4-triazine was heated at a variety of temperatures in pyrex carius tubes and nickel autoclaves. The optimum conditions for nitrogen elimination in pyrex carius tubes are shown below (yield ca 9%).



In nickel autoclaves breakdown of triazine occurred at 250° but no pyrolysis products were isolated

(ii) FLOW PYROLYSIS

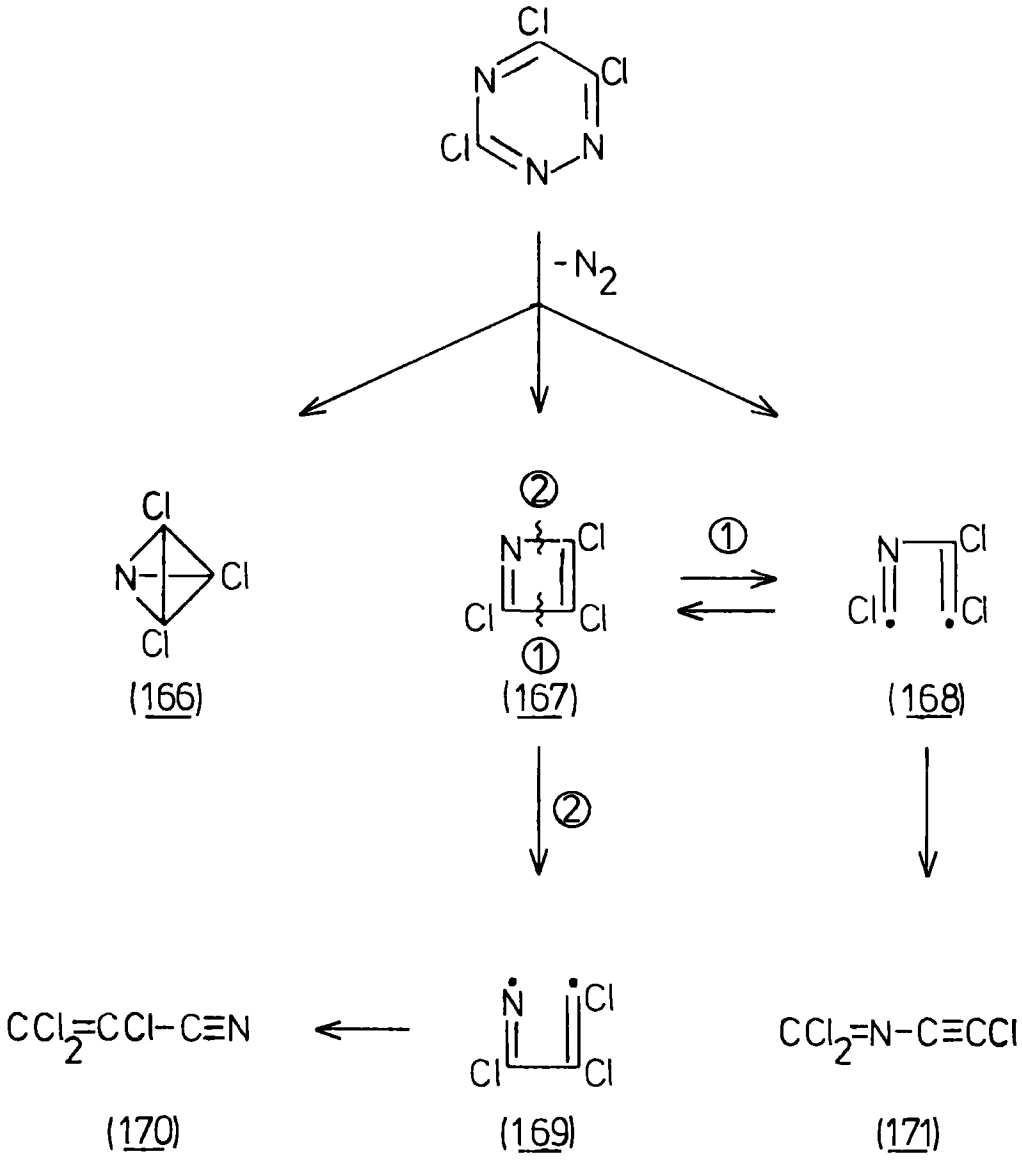
3,5,6-Trichloro-1,2,4-triazine was passed through a silica tube packed with platinum foil at 660°, under a flow of dry nitrogen estimated to give a contact time of about 12 seconds. Products of ring fragmentation were again obtained and proved to be identical with that produced from static pyrolysis (yield ca 53%), and in the same proportions (20·1).

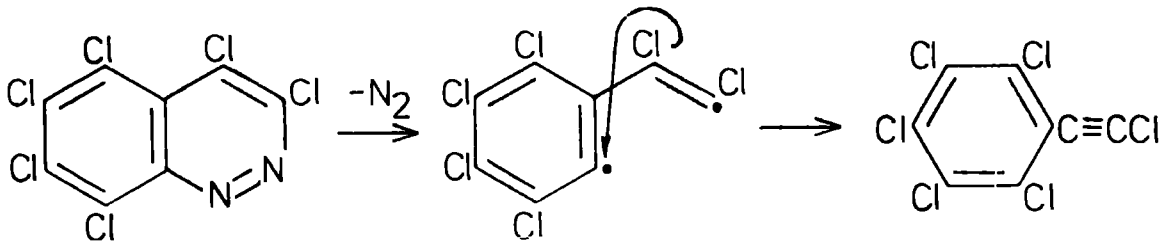
(iii) MECHANISM OF NITROGEN ELIMINATION AND STRUCTURE OF THE PYROLYSIS PRODUCT

The possible reactive intermediates which may be anticipated in the pyrolysis of 3,5,6-trichloro-1,2,4-triazine are a tetrahedrane (166), an azete (167) and diradicals, (168) and (169). There are though, only two products which could be obtained from these intermediates, compounds (170) and (171) shown in SCHEME XI.

In the event of the diradical (168) being generated on the immediate extrusion of nitrogen, then the most likely course of reaction would be a 1,3-rearrangement of a chlorine radical to give the acetylene (171). There is precedent for the formation of diradicals in the elimination reactions of the chlorocompounds tetrachloropyridazine and hexachlorocinnoline,[23] where the latter compound, in particular, has been shown to involve a 1,3-rearrangement.

SCHEME XI


Cl
N
Cl
Cl
N
N
-N2
Cl
N
Cl
Cl
(166)
②
N
Cl
Cl
Cl
①
(167)
①
N
Cl
Cl
Cl
(168)
②
CCl2=CCl-C≡N
(170)
N
Cl
Cl
Cl
(169)
CCl2=N-C≡CCl
(171)



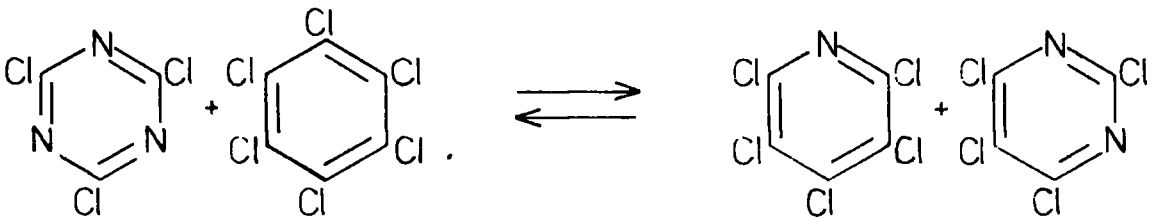
However, a red colouration was observed from the pyrolysate at -196°. This colouration is a phenomena observed in the generation of many azetes. If the azete (167) was generated in the elimination reaction then it is possible that this highly reactive species could give either of the structural isomers, (170) or (171), on warming to room temperature when the red colouration disappeared.

There are no reports of the acetylene (171) but the infra-red spectra of the pyrolysis product was identical with that given in the literature[95] for the nitrile (170). Further verification of the structure of the pyrolysis product was obtained from ^{13}C n.m.r. data where the spectra of the pyrolysis product was in favourable agreement with that of trichloroacrylonitrile synthesised from hexachloropropene (This synthesis is described in the next part of this section).

Thus, these observations suggest the elimination of nitrogen from 3,5,6-trichloro-1,2,4-triazine is concerted and the intermediate species generated is the azete. Moreover, rupture of the azete ring is specific where it is possible that the driving force is attributable to the difference in the carbon-nitrogen and carbon-carbon bond strengths (bond strengths C-N = 72.8 Kcals mol^{-1}, C-C = 82.6 Kcals mol^{-1}).[96] Rupture of the carbon-nitrogen bond (② in SCHEME XI) is followed by a 1,3-rearrangement of a chlorine radical to give trichloroacrylonitrile. It is not possible to rule out the existence

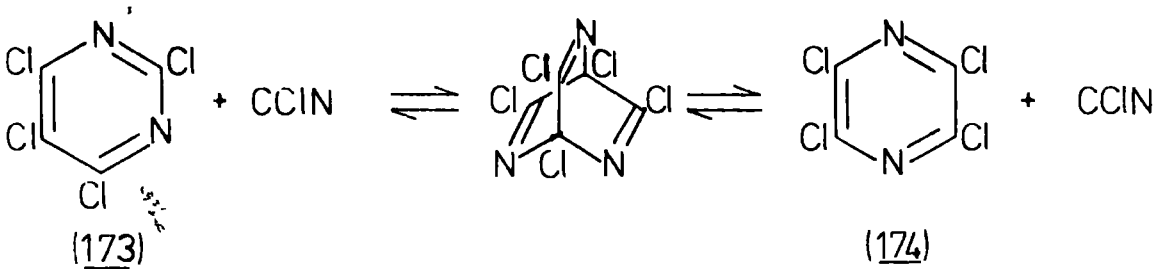
of the tetrahedrane intermediate (166) but the data presented here would appear to be the first evidence of an azete generated from a 1,2,4-triazine.

In the discussion so far, the fragmentation of 3,5,6-trichloro-1,2,4-triazine has been assumed to be uni-molecular. However, in the light of recent results obtained from the pyrolysis of 2,4,6-trichloro-1,3,5-triazine, Mahler and Fukunaga[97] have questioned the molecularity of such reactions. They claim that the perchlorinated aromatic nitrogen heterocycles, (5) and (172), undergo metathesis and approach equilibrium conditions at about 600° in three hours according to the equation shown below An equimolar mixture of 2,4,6-trichloro-1,3,5-triazine (5) and hexachlorobenzene (172) gave



(5) (172) (140) (173)

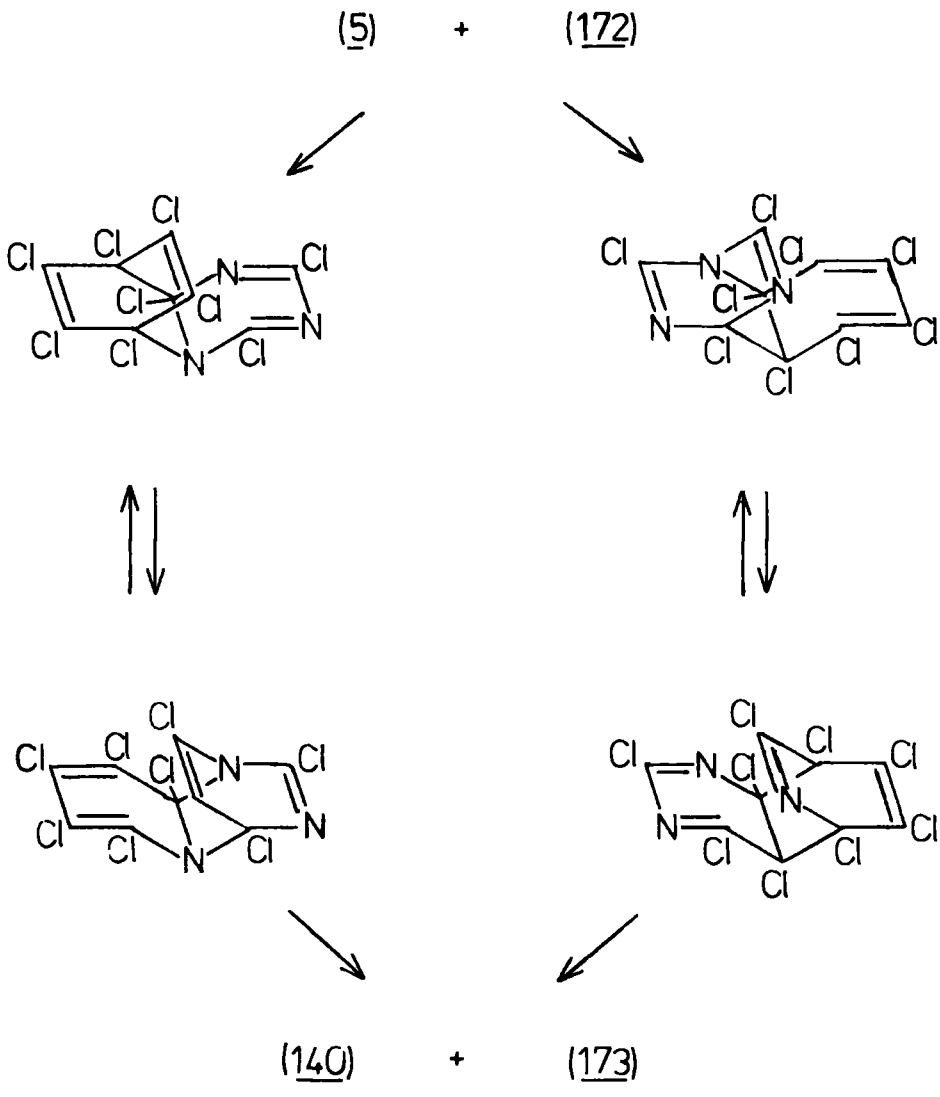
pentachloropyridine (140), tetrachloropyrimidine (173), and tetrachloropyrazine (174) in 91% yield and 14% conversion. The diazines (173) and (174) were considered to exist in an equilibrium where the conversion was by way of cyanogen chloride Diels-Alder adducts.



(173) (174)

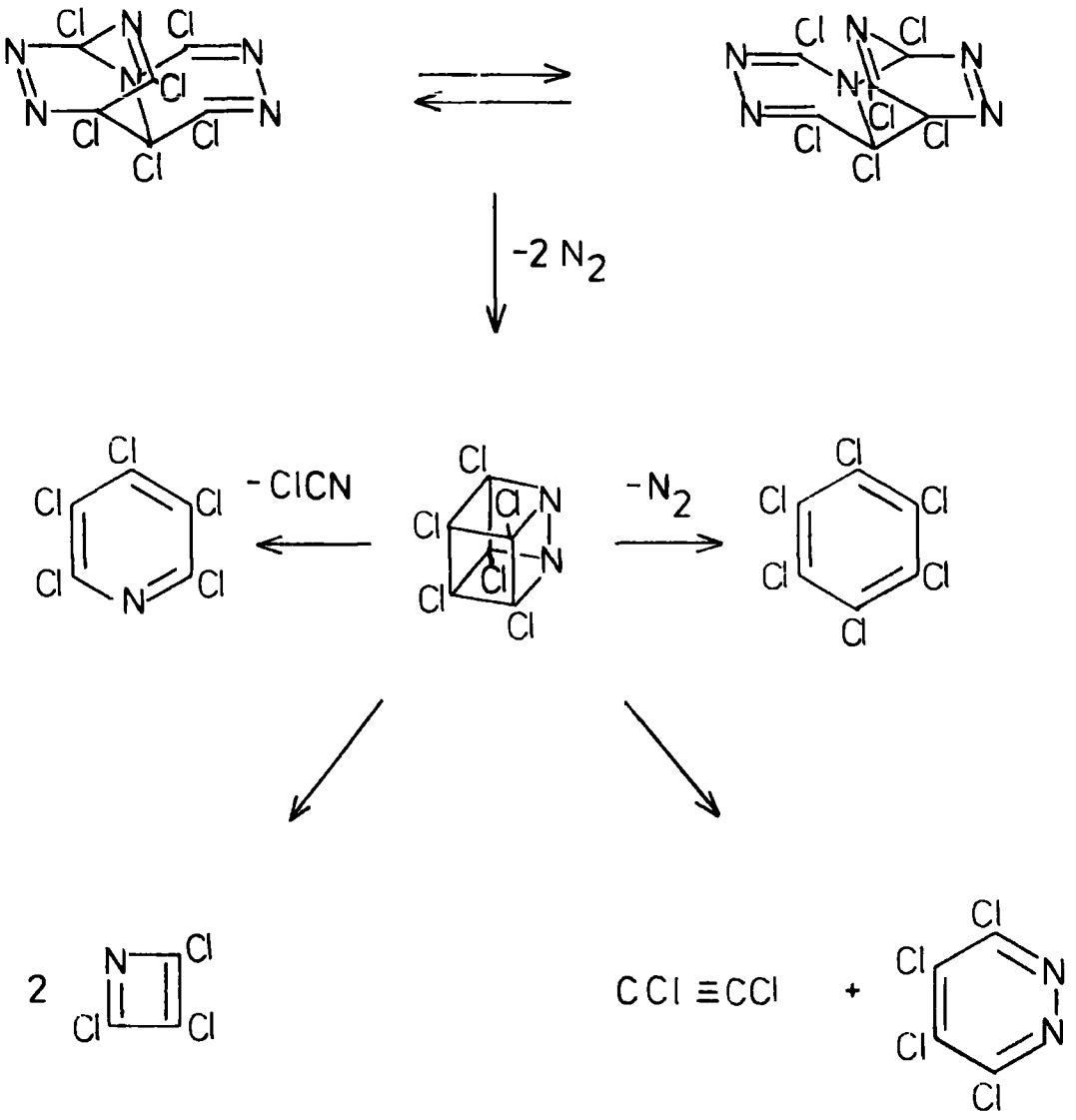
For the reaction of (5) with (172), Mahler and Fukunaga tentatively suggested the Diels-Alder adducts shown in SCHEME XII.

SCHEME XII



If the nitrogen elimination reaction of 3,5,6-trichloro-1,2,4-triazine was bi-molecular then it is possible to postulate several different Diels-Alder adduct intermediates An example is given in SCHEME XIII.

SCHEME XIII



The results are not consistent with a bi-molecular process. Although pentachloropyridine was detected in a static pyrolysis (< 0.1%) and hexachlorobenzene was detected in a flow pyrolysis (< 0 1%), the results could not be repeated

(iv) SYNTHESIS OF TRICHLOROACRYLONITRILE

The synthesis of trichloroacrylonitrile involved the following three preparations

(a) PREPARATION OF TRICHLOROACRYLIC ACID

The first step, which has been reported to be explosive, was the oxidation of hexachloropropene in sulphuric acid The procedure according to Bergmann and Haskelberg was followed.[98]

$$CCl_2 = CClCCl_3 \xrightarrow[H_2O/Al_2(SO_4)_3]{C.H_2SO_4} CCl_2 = CCl.CO_2H$$

Trichloroacrylic acid was obtained with a yield of 87 5%.

(b) PREPARATION OF TRICHLOROACRYLIC ACID AMIDE

The acid chloride was prepared in situ by refluxing trichloroacrylic acid in thionyl chloride After removing excess thionyl chloride, the acid chloride was dissolved in diethyl ether and reacted with an excess

$$CCl_2 = CClCO_2H \xrightarrow{SOCl_2} [CCl_2 = CClCOCl] \xrightarrow{NH_3} CCl_2 = CClCONH_2$$

of ammonia. Recrystallisation from cyclohexane gave the amide in a yield of 96.5% .

(c) PREPARATION OF TRICHLOROACRYLONITRILE

An intimate mixture of the dry powdered amide and phosphorus pentoxide was heated slowly under reduced pressure.

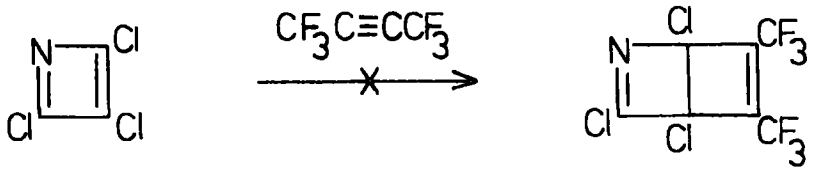
$$CCl_2 = CCl.CONH_2 \xrightarrow{P_2O_5} CCl_2 = CClC \equiv N$$

The volatile trichloroacrylonitrile was collected by vacuum transference with a yield of 43.5%. (The overall yield of trichloroacrylonitrile from hexachloropropene was 36.2%).

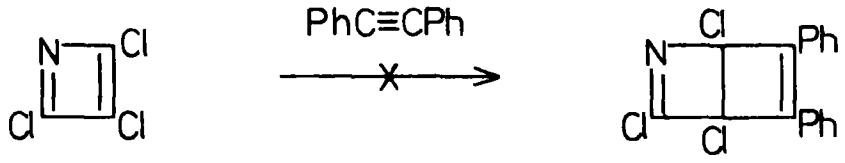
(v) TRAPPING EXPERIMENTS

Attempts were made to trap the azete generated on pyrolysis of 3,5,6-trichloro 1,2,4-triazine. Although benzazetes readily undergo 1,4-cycloaddition reactions[38], halo-olefins preferentially undergo 1,2-cycloadditions.[99] For this reason hexafluorobut-2-yne and diphenylacetylene were used as potential adducts.

In the reaction of 3,5,6-trichloro-1,2,4-triazine with hexafluorobut-2-yne the high pressure involved, required the use of a nickel autoclave. After heating at 250° for six hours the reaction mixture was analysed but no addition product could be isolated.



In the reaction with diphenylacetylene, the 3,5,6-trichloro-1,2,4-triazine was pyrolysed using a flow system described previously. The trapping reagent was coated on the inside of the trap where the pyrolysate was collected However, no addition product could be found

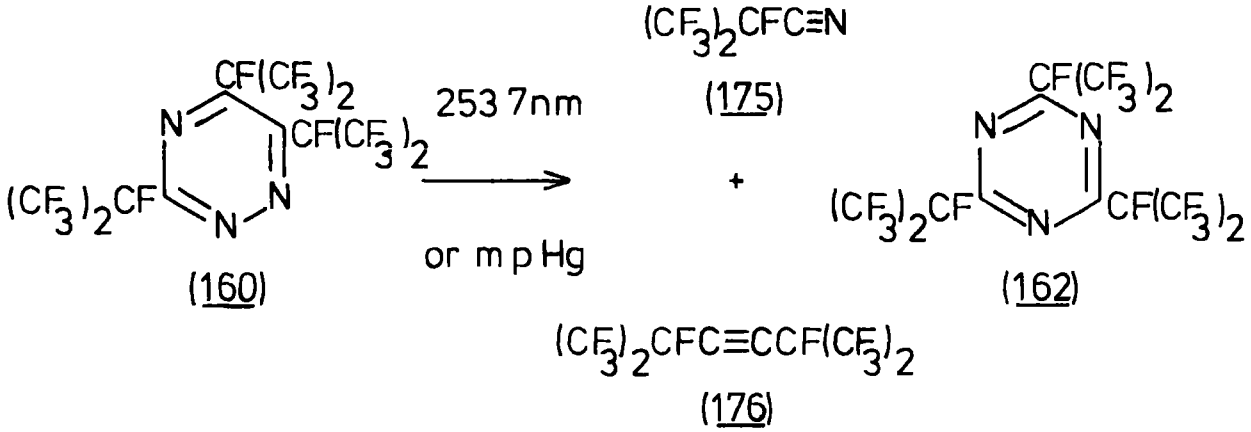


3.3 PERFLUORO-3,5,6-TRIS-ISOPROPYL-1,2,4-TRIAZINE

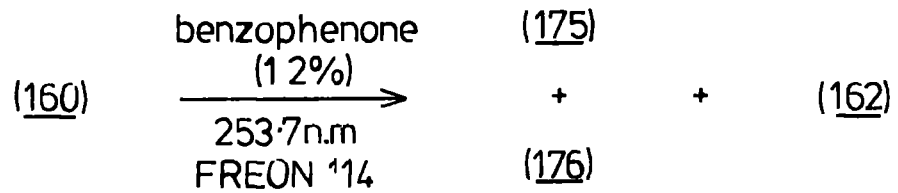
A. PHOTOLYSIS

Preliminary irradiations of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (λ_{max} 255 n.m., ϵ = 1435, 400 n.m., ϵ = 303) were carried out using low pressure arcs (253.7 n.m). The results were the same when the irradiation was carried out with medium pressure mercury arcs (which emits light at various wavelengths between 230 n.m and 600 n.m). The reactions were carried out both in the vapour phase and in solution where the solvents used were FREON 113 ($CF_2ClCFCl_2$) and FREON 114 (CF_2ClCF_2Cl).

Starting material was recovered in good yield from these reactions though in most cases a small conversion ($\sim$ 2%) was detected where three products, perfluoroisobutyronitrile (175)*, perfluoro-2,5-dimethyl-hex-3-yne (176)+ and perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine (162), were identified in almost equimolar quantities



When benzophenone (λ_{max} 252 n.m., ϵ = 20,000, 325 n m , ϵ = 180) was employed as a sensitiser there was an increase in the extent of photochemical conversion



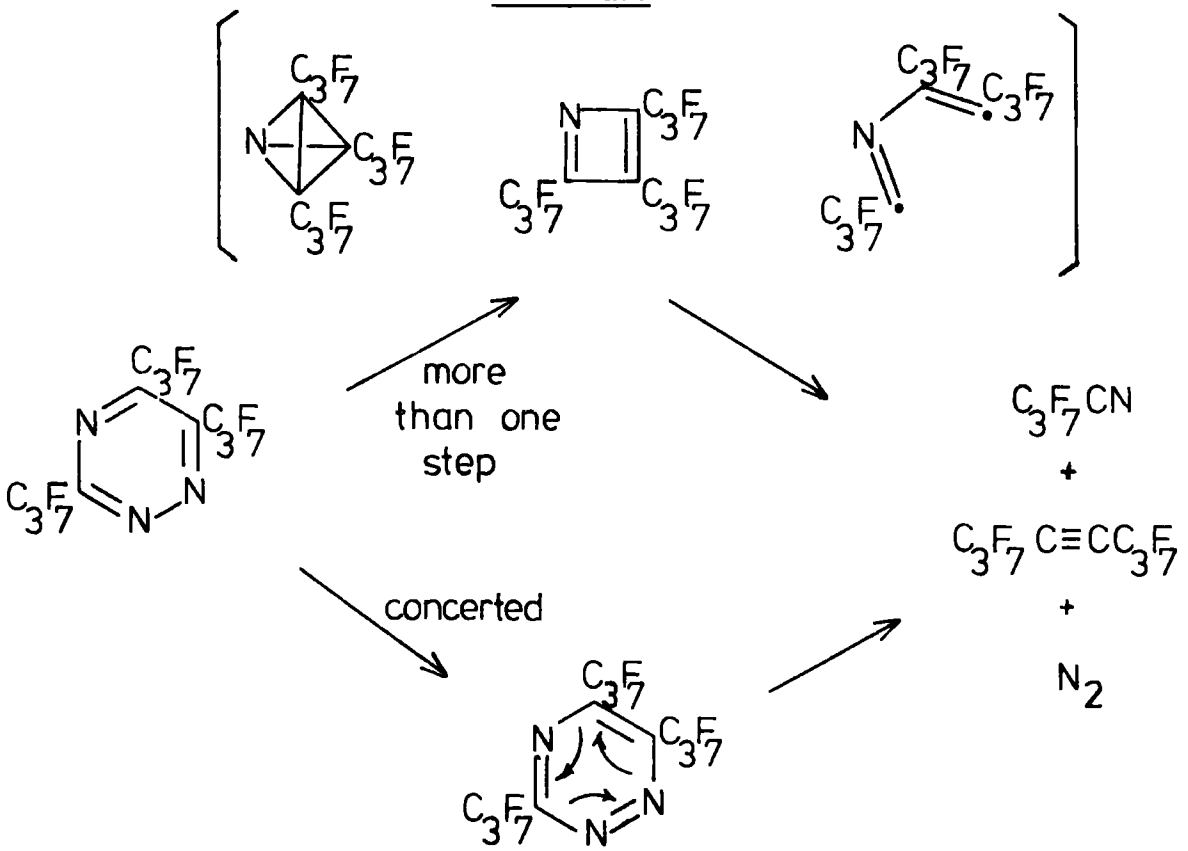
% conversion	11 3	5 8

Although benzophenone appeared to have increased the extent of photochemical conversion it was not specific in that both elimination and rearrangement reactions were promoted

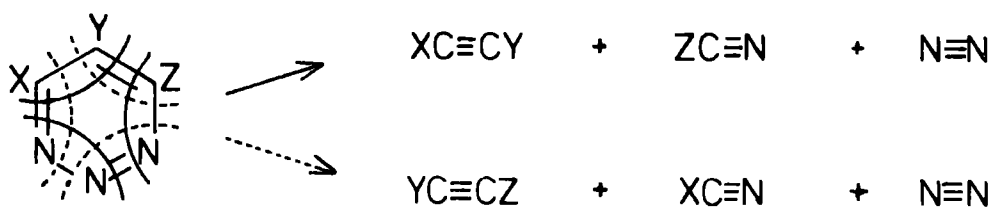
A technique used to trap reactive valence isomers generated by photolysis, is the irradiation of substrates whilst under transference whereby volatile products are collected in a trap cooled in liquid air With perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine the material recovered was largely starting material (> 98%) with trace amounts of the nitrile (175) and acetylene (176)

These reactions do reveal that upon ultra-violet irradiation of (160), both elimination and rearrangement processes do occur In principle the photochemical elimination of nitrogen could occur via a tetrahedrane, an azete or a diradical, or alternatively a concerted fragmentation is possible where all three products are formed simultaneously

SCHEME XIV



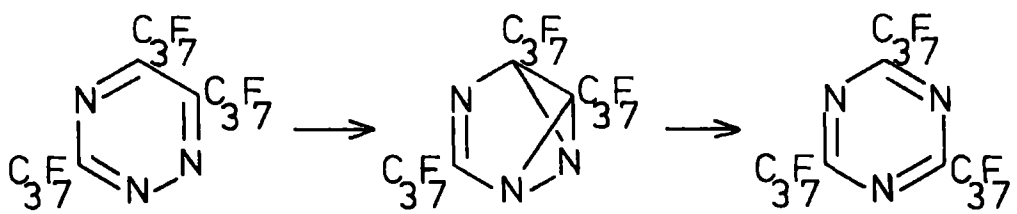
A concerted process similar to that in SCHEME XIV was observed in the fragmentation of 1,2,3-triazines [100]



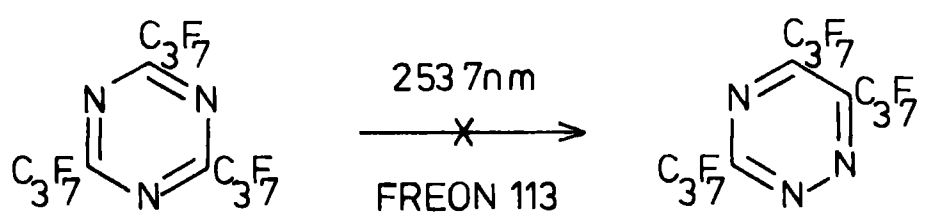
(X,Y,Z = substituted phenyl groups)

However, there is no evidence available to distinguish between these alternative processes since it was not possible to prepare perfluoromono- and di-isopropyl derivatives for comparative studies

Formation of the sym-triazine could be explained using a mechanism which involves the intermediacy of triaza-benzvalene intermediates.



A sample of perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine was irradiated (253.7 n.m.) in solution (FREON 113). No products of elimination or rearrangement could be identified

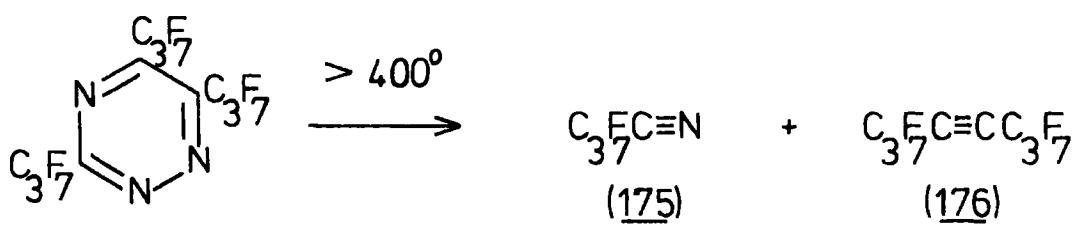


B PYROLYSIS

(i) STATIC PYROLYSIS

Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine was heated at a variety of temperatures in nickel autoclaves Fragmentation was minimal until 400° where the products (175) and (176) were detected. Also present in trace amounts were defluorination products i.e derivatives of perfluoro-tris-isopropyl-1,2,4-triazines where the alkyl side chains had suffered varying degrees of F_2 loss

At a temperature of 400° substantial fragmentation of the triazine occurred ($\sim$ 50% after 1 hr.) and at 450° only the pyrolysis products were recovered (100% after 40 mins.).

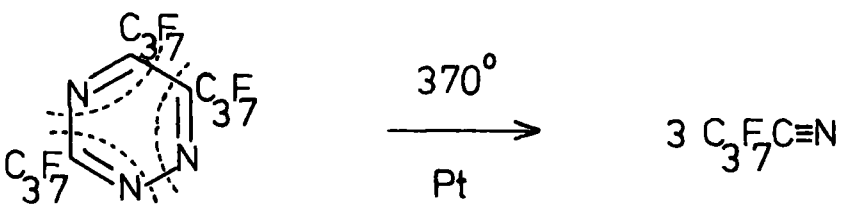


Trapping experiments were attempted with diphenylacetylene and toluene. (Cyclo-addition adduct and radical scavenger, respectively) The conditions required for elimination of nitrogen were too drastic for diphenyl-acetylene which decomposed and with toluene only the pyrolysis products and starting material could be identified

(ii) FLOW PYROLYSIS

Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine was passed through a silica tube packed with platinum foil at various temperatures, under a flow of dry nitrogen estimated to give a contact time of about 12 seconds Below 600°

the triazine was recovered virtually unchanged although at 370° trace amounts of the nitrile (175) were detected. This was surprising in that no acetylene (176) was detected. The absence of acetylene, the least volatile of the fragmentation products, may be due to the concerted process shown below.



At 500°, trace amounts of the nitrile (175) and acetylene (176) were detected in a ratio 1.1.

Finally, at 600° there was fragmentation of all the triazine passed through the pyrolysis tube and in addition to the nitrile and acetylene, trace amounts of hexafluoropropane were detected. This suggests that the trifluoromethyl radical is generated, and dimerises.

In conclusion, there is no evidence for the generation of an azete but the elimination may involve radicals and concerted processes.

C. REACTIONS WITH FLUORIDE ION

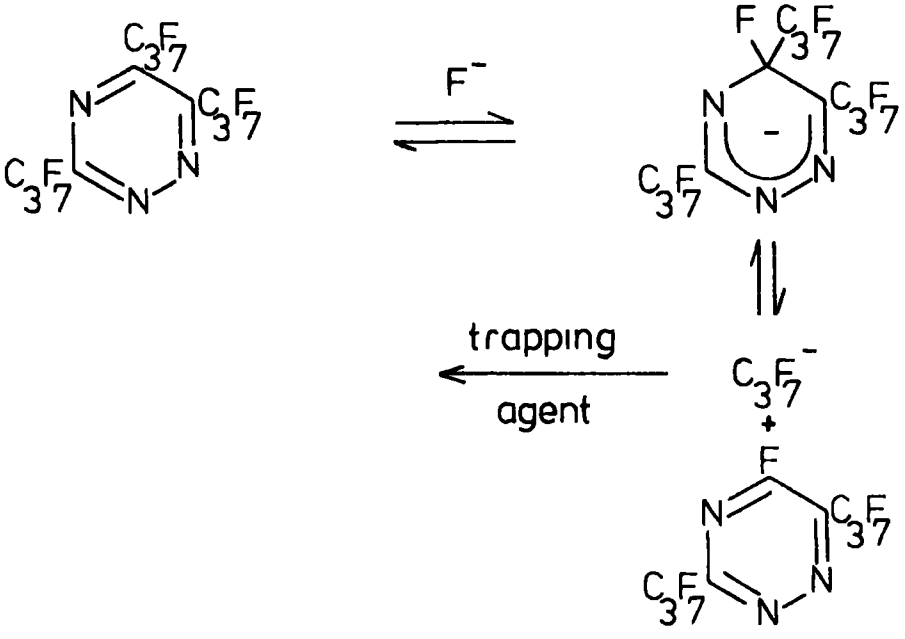
Various experiments were carried out with perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine in the presence of fluoride ion. The purpose of these experiments was two fold: (i) to establish whether the asym-triazine can rearrange to the sym-triazine in the presence of fluoride ion, and (ii) to synthesise mono- and di-alkyl-1,2,4-triazines by means of an 'exchange' reaction.

(i) WITH FLUORIDE ION

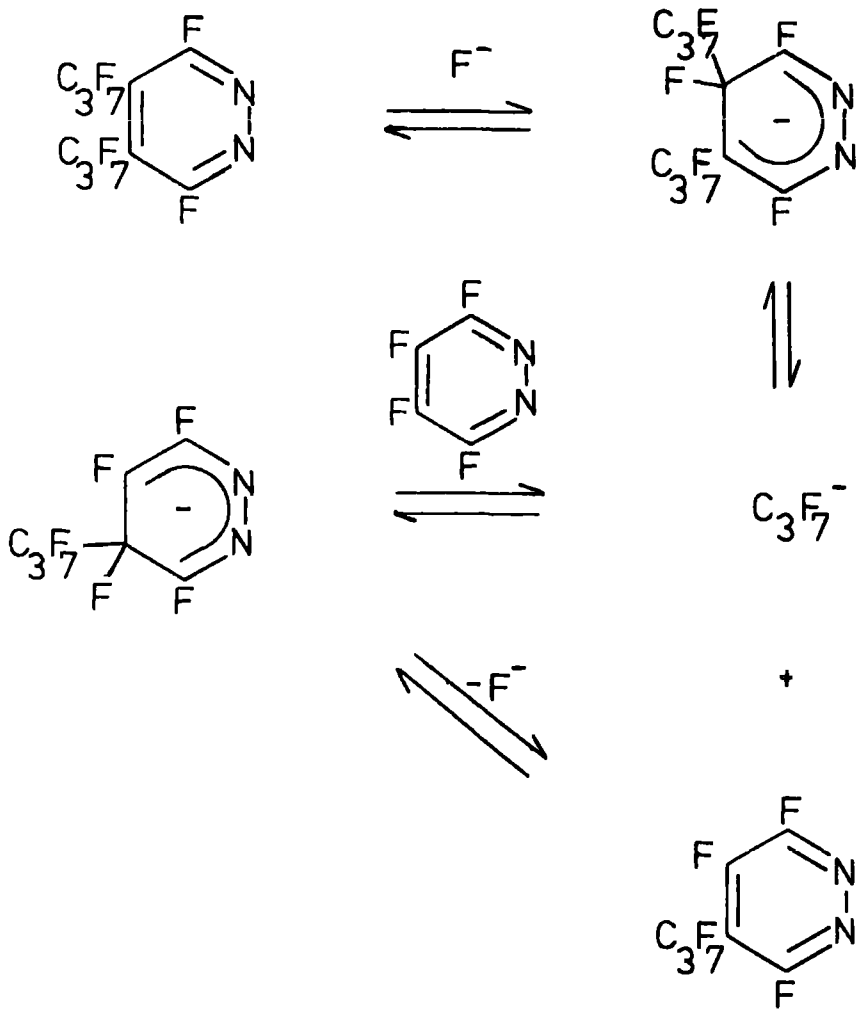
In an experiment where perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine was synthesised from 3,5,6-trichloro-1,2,4-triazine, perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine was identified as a reaction product. Attempts were made to reproduce the experimental conditions with only perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine, caesium fluoride and sulpholane. Reaction was observed in only one experiment in which the oligomers of hexafluoropropene were isolated as the sole products

(ii) WITH FLUORIDE ION IN THE PRESENCE OF A TRAPPING AGENT

A type of reaction by which an alkyl group migrates from one aromatic nucleus to another is commonly referred to as an exchange reaction. The transient alkyl group exists as an anion and the aromatic nucleus to which it migrates can be regarded as a trapping agent. With perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine a partial reversal of its synthesis was attempted whereby the intermediate mono- and di-alkyl triazines could be isolated.

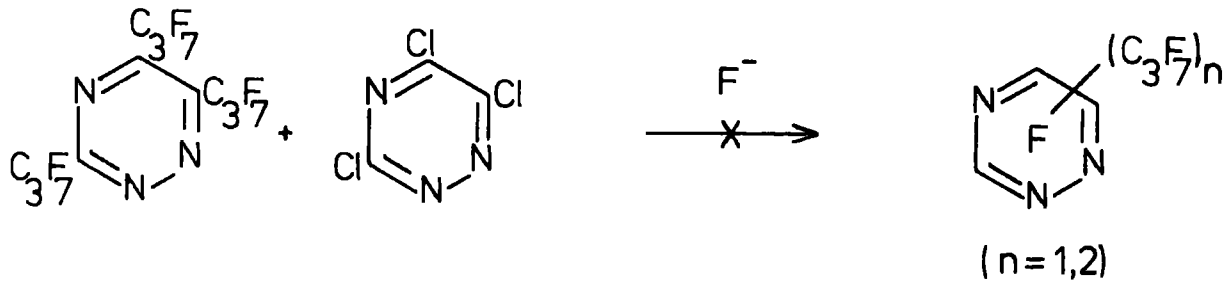


The scheme shown above is analogous to that for the preparation of perfluoro-4-isopropyl-pyridazine.[101]



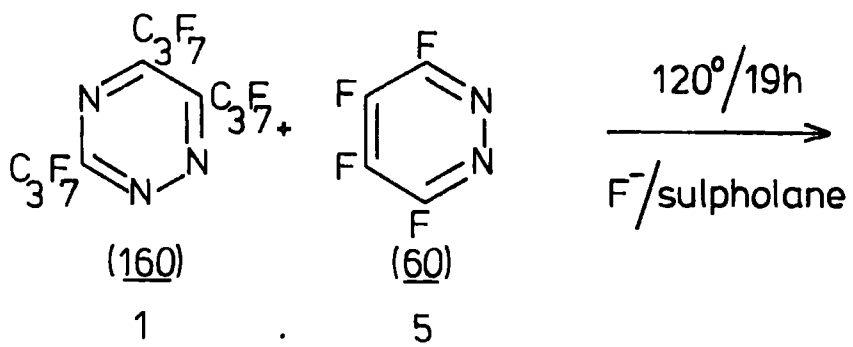
(a) 3,5,6-TRICHLORO-1,2,4-TRIAZINE

When a mixture of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine, trichloro-1,2,4-triazine and potassium fluoride (1 3·12, respectively) was stirred in a mixture of sulpholane for 14 days only the tri-alkyl-1,2,4-triazine was recovered. There was no evidence for an exchange reaction.



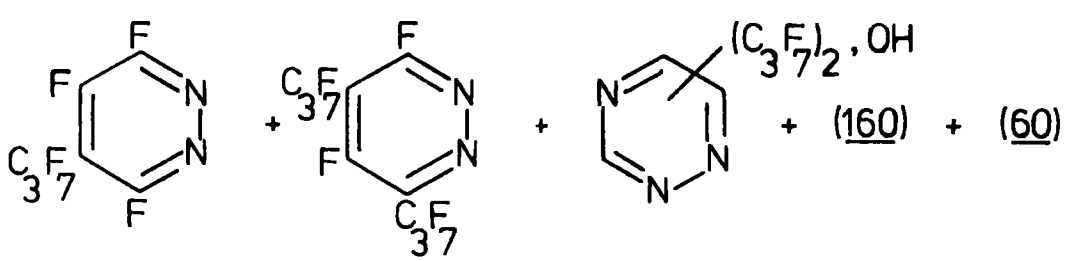
(b) TETRAFLUOROPYRIDAZINE

Initial attempts at exchange reaction between tetrafluoropyridazine and perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine at room temperature were unsuccessful. When the reaction was repeated using similar conditions as those used in the preparation of perfluoro-4-isopropyl-pyridazine,[101] five compounds were isolated from the reaction mixture.



(160) (60)

1 . 5



(177) (98) (178)

7·8% 53 5% 28 7% 5 4% 4·6%

Compounds (177), (98), (160) and (60) were isolated as volatiles, and compound (178) was isolated after diethyl ether/water extraction of the reaction mixture.

These results demonstrate that an exchange reaction did proceed to give a di-alkyl-1,2,4-triazine but that once formed it remained in the mixture as an involatile. Evidently it must prefer to exist as a complex with fluoride ion (cf cyanuric fluoride and caesium fluoride) which is destroyed in the aqueous extraction In conclusion there is apparently no simple way of preparing perfluoromono- and di-isopropyl-1,2,4-triazines.

CHAPTER 4

EXPERIMENTAL

4 1 GENERAL

A REAGENTS

Chloral hydrate and semicarbazide hydrochloride were obtained from British Drugs Houses Ltd Tetrafluoroethylene was prepared by pyrolysis of polytetrafluoroethylene at these laboratories.[102] Other perfluoro-alkenes used in the polyfluoroalkylations were obtained from Peninsular Chemical Research Inc

Caesium fluoride was dried by heating at 160° under high vacuum for several days, powdered in a glove bag filled with dry nitrogen, heated under vacuum again, and stored under a dry nitrogen atmosphere.

Potassium fluoride was dried by strong heating in the air, followed by grinding, and then heating under high vacuum It was stored under a dry nitrogen atmosphere.

Sulpholane was purified by fractional vacuum distillation The middle fraction was collected over dried molecular sieve (TYPE IVA) and stored at room temperature under an atmosphere of dry nitrogen.

B. INSTRUMENTS

Infra-red spectra were recorded on Perkin-Elmer 547 or 577 spectro-photometers Solid samples were recorded as KBr discs, liquid or low melting point solids as contact films between KBr plates and gaseous or low boiling point liquids in a gas cell with KBr windows

Mass spectra were recorded on an A.E I. MS9 spectrometer or on a V.G Micromass 12B linked with a Pye Series 104 gas chromatograph. Molecular weights in this thesis are from mass spectrometric measurements

Quantitative vapour phase chromatographic analysis was carried out on a Griffin and George D6 Gas Density Balance (GDB) using columns packed with 30% gum rubber SE-30 on Chromsorb P (column 'O'), or 20% Di-isodecyl-phthalate on Chromsorb P (column 'A') Preparative scale vapour phase chromatography was performed on a Varian Aerograph instrument using column 'O' or 'A'.

Thin layer chromatographs were recorded on thin glass plates coated with an even layer of silica (Silicic gel/CT, Reeve Angel Scientific Ltd.), containing a fluorescing agent The position of compounds on the plates was revealed by the way they quenched the fluorescence normally excited by ultra-violet light

Ultraviolet spectra, in cyclohexane (Spectrosol grade) as solvent, were recorded on a Unicam S P.800 spectrophotometer.

Fluorine (^{19}F) nuclear magnetic resonance spectra were recorded on a Varian A56/60D spectrometer operating at 56 4 Mc/s at the ambient probe temperature (40^{o}) Chemical shifts are quoted in p.p m relative to $CFCl_3$.

Carbon (^{13}C) spectra of natural samples were recorded on a Brüker HK90 with Fourier Transform facility by the S.R.C. Physico-Chemical Measurements Unit and Services of the Chemistry Department Natural abundance T M.S. was used as reference and the shifts are quoted in p p.m

Carbon, nitrogen and hydrogen analyses were obtained using a Perkin-Elmer 240 Elemental Analyser Analysis for halogens were carried out as described in the literature [103]

Melting points and boiling points were determined at atmospheric pressure and are uncorrected. Boiling points were measured by the Siwoloboff method.

4 2 EXPERIMENTAL FOR CHAPTER 2 - THE SYNTHESIS AND CHEMISTRY OF 1,2,4-TRIAZINES

A PREPARATION OF STARTING MATERIALS

(i) GLYOXYLIC ACID SEMICARBAZONE

A solution of semicarbazide hydrochloride (65 5g, 0 587 mole) and chloral hydrate (108 5g, 0 657 mole) in water (1 2ℓ) was refluxed gently for 25 minutes The solution was chilled in ice, filtered, washed with ethanol and ether, and then dried in a vacuum desiccator over phosphorus pentoxide (57 3g, 74 5%), m p 199°, literature value 200-202°.[67] Identification was molecular weight (131)

(ii) 3,5-DIHYDROXY-1,2,4-TRIAZINE

A solution of glyoxylic acid semicarbazone (31 8g, 0 242 mole) in ethylene glycol (1ℓ) was added rapidly to sodium (18g, 0 78 mole) dissolved in absolute ethanol (0 5ℓ) and the solution was gently refluxed for 24 hours. After reducing the solution to dryness on a water aspirator at 120°, the residue was dissolved in hot water (0 5ℓ) and the hot solution adjusted to pH2 with concentrated hydrochloric acid The 3,5-dihydroxy-1,2,4-triazine crystallised on cooling and was recrystallised from water (18 7g, 68 2%), m p 266-9°, literature value 268-70°[67] Identification was by molecular weight (113)

(iii) 6-BROMO-3,5-DIHYDROXY-1,2,4-TRIAZINE

A mixture of 3,5-dihydroxy-1,2,4-triazine (18g, 0 16 mole), bromine (18g, 0 228 mole) and water (270 ml) was stirred for 27 hours The colourless crystalline product was filtered, recrystallised from water and dried under vacuo (16.7g, 54 5%), m p 239-41°, literature value 232-4°[70]

Identification was by molecular weight (191 (Br = 79) with one bromine atom)

B CHLORINATION REACTIONS

(1) 6-BROMO-3,5-DIHYDROXY-1,2,4-TRIAZINE

(a) SOLVENT PHASE REACTIONS

The method used for all these chlorinations was the same and the quantitative differences between the various runs are summarised in TABLE I The most successful was run No 3 which is described here All the apparatus was dried before using, by rinsing with acetone and drying in an oven, both before and during the reaction it was continually purged with dry nitrogen gas

6-Bromo-3,5-dihydroxy-1,2,4-triazine (10g, 0 052 mole) in phosphoryl chloride (210 ml) was placed in a flask fitted with a gas inlet, reflux condenser and a teflon-bladed paddle stirrer Phosphorus pentachloride (21 5g, 0 103 mole) and diethylaniline (23 3g, 0.156 mole) were added and the mixture stirred and heated under reflux for 2 hours The excess solvent was removed under reduced pressure and the residue remaining was extracted with diethyl ether Distillation (50-70°, 0 5-0 1 mm) of the residue from the ether phase gave 3,5,6-trichloro-1,2,4-triazine which was further purified by vacuum sublimation (3 18g, 33 1%), m p 57-9°, literature 60-62° [69] (Found C, 19 8, Cl, 57 9, N, 22 4%, M (mass spectrum) 183 Calcd.for $C_3Cl_3N_3$, C, 19 5, Cl, 57 7, N, 22 8%, M, 183) Infra-red spectrum No 1 Ultra-violet spectrum No 1 ^{13}C n m r spectrum No 1.

Note that in runs No 12 and No 13-14 the base used was triethylamine and pyridine respectively

(b) AUTOCLAVE REACTIONS

6-Bromo-3,5-dihydroxy-1,2,4-triazine (34 5g, 0.179 mole) and phosphorus pentachloride (150g, 0 720 mole) were sealed in a nickel-lined autoclave This was placed in a preheated furnace at 200° and heated at this temperature for two hours The autoclave was then removed from the furnace, allowed to

TABLE I

SOLVENT PHASE CHLORINATIONS OF 6-BROMO-3,5-DIHYDROXY-1,2,4-TRIAZINE

No OF RUN	AMOUNT OF SUBSTRATE (139) (g)	PCl_5/ SUBSTRATE	DIETHYLANILINE/ SUBSTRATE	YIELD (%)
1	4 8	2 0	2 5	-
2	20.3	2 0	2 5	-
3	10 0	2 0	3 0	33 1
4	16 5	2 0	3.0	21.4
5	32 0	2 0	3 0	-
6	5 0	-	2 0	-
7	13 9	2 0	-	14.0
8	10 0	6 0	2.0	9 5
9	4 8	4 0	3 0	-
10	8.0	2 0	2.0	19.8
11	8 9	2 0	2 0	-
12	5.9	2 0	3.0*	-
13	16.3	2 0	3.0Δ	51.6
14	31 8	2.0	3.0Δ	-

* BASE USED WAS TRIETHYLAMINE

Δ BASE USED WAS PYRIDINE

cool, vented, and opened

Phosphoryl chloride formed in the reaction was removed under reduced pressure and crude 3,5,6-trichloro-1,2,4-triazine was obtained by distillation (50-70°, 0 05 - 0 1 mm) The product was recrystallised from hexane (16 2g, 48 8%) Identification was by comparison with infra-red No. 1 and molecular weight (183) Higher temperatures or longer reaction times reduced the yield

(ii) 3,5-DIHYDROXY-1,2,4-TRIAZINE

3,5-Dihydroxy-1,2,4-triazine (30 6g, 0 271 mole) and phosphorus pentachloride (180g, 0 865 mole) were heated at 200° for two hours in an autoclave The work up was the same as that described in the previous section (16 8g, 33 6%) Identification was by comparison with infra-red No 1 and molecular weight (183) Again, higher temperatures or longer reaction times reduced the yield

C ATTEMPTED FLUORINATION REACTIONS

(i) SOLID PHASE REACTIONS

(a) POTASSIUM FLUORIDE

The fluorination reactions described here are the attempts at preparing 3,5,6-trifluoro-1,2,4-triazine from 3,5,6-trichloro-1,2,4-triazine by reaction with potassium fluoride The general procedure for all these reactions was the same and quantitative details are given in Table II.

The nickel autoclaves and the glassware used were meticulously dried by rinsing with acetone and drying in a hot oven The nitrogen used was dried by passing through towers containing phosphorus pentoxide, potassium hydroxide pellets and silica gel, respectively, and then through a trap cooled with liquid air The reaction mixtures were prepared in a glove bag filled with dry nitrogen The tubes were sealed at atmospheric pressure and placed in preheated furnaces After reaction they were allowed to cool, and then further cooled to -196° before opening

TABLE II

AUTOCLAVE FLUORINATIONS OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE (7)

No OF RUN	AMOUNT OF (7) (g)	TEMPERATURE (°C)	TIME (h)
1	7 0	140	16
2	13 5	150	72
3	4.0	170	6
4	4 0	180	13
5	3 9	200	6
6	4 0	225	6
7	4 0	250	6
8	1.8	300	2 5

(In all the reactions the ratio of substrate (7) potassium fluoride was 1 9)

The first four runs produced liquid/solid mixtures The products were obtained by pumping under high vacuum and collecting the volatiles in a trap cooled in liquid air Only glassware was used as 3,5,6-trichloro-1,2,4-triazine, when molten, was found to react with rubber The nickel autoclave was heated at 120° for several hours to aid transfer of the reaction products

In runs No 5-8, the volatiles were collected in traps fitted with 'rotaflo' taps and the volatiles allowed to warm to room temperature in the absence of any other atmosphere Analysis of all runs was by gas-liquid chromatography and mass spectrometry

The reactions below 200° were found to give mixtures of chloro-fluoro-1,2,4-triazines where 3,5,6-trifluoro-1,2,4-triazine was always a minor component Identification was by mass spectra, m/e = 167 ($C_3Cl_2FN_3$), m/e = 151 ($C_3ClF_2N_3$) and m/e = 135 ($C_3F_3N_3$) Above 200°, only dimers of trifluoro-1,2,4-triazine were identified, m/e = 270 ($C_6F_6N_6$)

The residue remaining in the autoclave from run No 5 was refluxed with $CHCl_3$ (100 ml) for two hours The cooled mixture was filtered and the solvent was removed from the filtrate to give a gum (The infra-red spectrum gave a broad band at 2120 cm^{-1})

(b) CAESIUM FLUORIDE

3,5,6-Trichloro-1,2,4-triazine (4.3g, 0.023 mole) and caesium fluoride (29 4g, 0 192 mole) were ground in a mortar under a dry nitrogen atmosphere. After mixing thoroughly heat was generated and a fused mass was formed It was not possible to obtain an n m r (^{19}F) spectrum due to poor solubility, therefore no further characterisation was attempted on what was probably a complex mixture

(ii) SOLVENT PHASE REACTIONS

(a) POTASSIUM FLUORIDE

(1) 3,5,6-Trichloro-1,2,4-triazine (1 8g, 0.010 mole), potassium fluoride (5.6g, 0 098 mole) and sulpholane (15 ml) were stirred together for 12 hours at room temperature. No volatiles were collected on pumping under high vacuum The solvent was removed by distillation under reduced pressure to give a polymeric tar

(2) The results were the same when the reaction was repeated at 120° for 12 hours

(b) CAESIUM FLUORIDE

(1) 3,5,6-Trichloro-1,2,4-triazine (2.0g, 0.011 mole), caesium fluoride (10g, 0.065 mole) and sulpholane (30 ml.) were stirred at 95° for 20 hours No volatiles could be isolated from the reaction mixture. The reaction mixture was stirred for a further 28 hours at 150° but again, no volatiles could be isolated

(2) 3,5,6-Trichloro-1,2,4-triazine (3.0g, 0.016 mole), caesium fluoride (7 4g, 0 049 mole) and sulpholane (20 ml.) were stirred together for 10 minutes. No volatiles were collected on pumping under high vacuum. Water (200 ml) was added to the mixture which was then extracted with diethyl ether (200 ml.) The ether was separated, washed with water several times (3 x 100 ml.), dried over $MgSO_4$, and after removal of solvent, a polymeric tar was obtained.

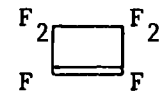
D POLYFLUOROALKYLATION REACTIONS

The experiments described here are all attempts at polyfluoroalkylation of 3,5,6-trichloro-1,2,4-triazine. The experimental procedure, developed by previous workers at these laboratories, was the same for all the attempted polyfluoroalkylations The required quantities of dry fluoride, sulpholane and 3,5,6-trichloro-1,2,4-triazine, were rapidly introduced into a baked conical flask, fitted with

a gas-tap and variable volume reservoir, against a flow of dry nitrogen The apparatus was evacuated and then filled with the requisite amount of gaseous perfluoroalkene to equilibriate it to atmospheric pressure On completion of reaction, i e collapse of the perfluoroalkene reservoir, the products were vacuum transferred into a cold trap (liquid air), at temperatures up to 100°

The reactions carried out are summarised in TABLE III The molar ratios of 3,5,6-trichloro-1,2,4-triazine, fluoride and perfluoroalkene were always in the ratio 1 4 3 respectively

TABLE III

No OF RUN	PERFLUOROALKENE	FLUORIDE	TEMPERATURE
1	$CF_3CF = CF_2$	CsF	RT
2	$CF_3CF = CF_2$	KF	RT
3	$CF_2 = CF_2$	KF	80°
4	$CF_3CF = CFCF_3$	CsF	RT
5	$CF_3CF = CFCF_3$	KF	RT
6		KF	RT

Only in runs Nos 1 and No 2, was there any alkylation These are described here in more detail

USING CAESIUM FLUORIDE Dry caesium fluoride (6 9g, 0.045 mole), dry sulpholane (75 ml.) and 3,5,6-trichloro-1,2,4-triazine (2 3g, 0 012 mole) were stirred together in a conical flask, fitted with a gas-tap and variable volume reservoir The apparatus was evacuated and then filled with hexafluoropropene (5 7g, 0 038 mole) The resulting mixture was stirred

for 3 weeks at R T by which time reaction, though incomplete, had ceased (i e the reservoir containing perfluoroalkene had not collapsed completely) Volatiles were then transferred out of the reaction (0 876g) mixture under vacuum, into a cold trap The mixture was analysed by quantitative vapour phase chromatography (GDB) and by mass spectra

It was estimated that this mixture consisted of 0 141g (1 93%) of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine Identification was by mass spectra (Parent peak at 585 and prominent peak at 557 due to nitrogen (N_2) loss) A small amount of perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine (estimation, 0 021g (0 29%)) was present in the mixture Identification was by mass spectra (Parent peak at 585 and no nitrogen (N_2) lost from parent ion This spectra was also compared with that from an authentic sample) The other compounds in the mixture were hexafluoropropene oligomers

USING POTASSIUM FLUORIDE Dry potassium fluoride (5 03g, 0 087 mole), dry sulpholane (20 ml) and 3,5,6-trichloro-1,2,4-triazine (4 0g, 0 022 mole) were stirred together in a conical flask, fitted with a gas-tap and variable volume reservoir The apparatus was evacuated and then filled with hexafluoropropene (9 78g, 0 065 mole) The resulting mixture was stirred at room temperature for 24 hours, by which time all the gas had been used up Volatiles were then transferred out of the reaction mixture under vacuum, into a cold trap The main component was separated by distillation and was found to be perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine, a yellow liquid, (7 9g, 61.4%), b p 155°, (Found C, 24.9, F, 68.6, N, 7.6%, M (mass spectrum), 585. $C_{12}F_{21}N_3$ requires C, 24 6, F, 68 2, N, 7.2%, M, 585). Infra-red spectrum No 2 Ultra-violet spectrum No 2. ^{19}F n.m.r. spectrum No. 2.

In the distillation of perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine, a fore-fraction was found to contain at least two other compounds An attempt to separate these two compounds by preparative g l c (Varian

Aerograph, Column 'A') was unsuccessful, though some enrichment of these other products in the fore-fraction, was achieved They were found to be perfluoro-di-isopropyl-1,2,4-triazines Identification was by molecular weight (435)

E REACTION OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE WITH PENTAFLUOROPHENYL LITHIUM

n-Butyl lithium (25 ml (1 6M), 0 040 mole) was added over a period of one hour to a mixture of pentafluorobromobenzene (10 87g, 0.044 mole), dry diethyl ether (30 ml) and dry hexane (20 ml) at -20°, under an atmosphere of dry nitrogen The mixture was stirred at this temperature for two hours

3,5,6-Trichloro-1,2,4-triazine (2 08g, 0.013 mole) in hexane (25 ml) was added over a period of ca 30 minutes The reaction mixture, which became red in colour, was maintained at -20° for a further hour and then left to warm up to room temperature overnight Water (100 ml) was added to the stirred mixture, which was then extracted with diethyl ether (2 x 100 ml) The organic layer was separated and dried over $MgSO_4$ Evaporation of the solvents gave an intractable material from which no products could be recovered by molecular distillation or sublimation

4 3 EXPERIMENTAL FOR CHAPTER 3 - SOME EXPERIMENTS WITH 3,5,6-TRICHLORO-1,2,4-TRIAZINE AND PERFLUORO-3,5,6-TRIS-ISOPROPYL-1,2,4-TRIAZINE

A 3,5,6-TRICHLORO-1,2,4-TRIAZINE

(1) PHOTOLYSIS

3,5,6-Trichloro-1,2,4-triazine (2.03g) and dry FREON 113 (50 ml.) were placed in a silica carius tube, which was cooled and evacuated, and then let down to an atmosphere of dry nitrogen gas several times to de-gas the solvent Finally, the tube was evacuated and sealed It was then irradiated (300 n m) for 21 h

The tube was then cooled, opened, and the contents washed out with FREON 113 The solvent was removed under reduced pressure and only 3,5,6-trichloro-1,2,4-triazine was recovered from the tarred residue by sublimation (Identified by a comparison of its infra-red and mass spectra with an authentic sample)

(ii) PYROLYSIS

(a) STATIC PYROLYSIS 3,5,6-Trichloro-1,2,4-triazine (1 085g, 5 98 x 10^{-3} mole) was placed in a pyrex carius tube which was then cooled, evacuated and sealed The tube was heated at 300° for 6 days After cooling, the tube was opened and the product transferred in to a cold trap under vacuum The product was trichloroacrylonitrile (0 072g, 9 1%) Identification was by molecular weight (155 with three chlorine atoms (Cl = 35)) and by comparison of its infra-red spectrum with an authentic sample (see 4 3B(iii))

(b) FLOW PYROLYSIS A flow of dry nitrogen was passed through molten 3,5,6-trichloro-1,2,4-triazine (5 357g, 0 029 mole) at 100° The vapour of the triazine was then allowed to pass in the stream of nitrogen through a silica tube packed with platinum foil at 660° at a rate estimated to give a contact time of ca 12 seconds The volatile product was collected in a cold trap and was identified as trichloroacrylonitrile (2 064g, 45.4%) (Identification was the same as in 4 3A(ii)(a)) Infra-red spectrum No 3 ^{13}C n m r spectrum No 3

(iii) ATTEMPTS AT TRAPPING TRICHLORO-AZETE

(a) WITH HEXAFLUORO-BUT-2-YNE 3,5,6-Trichloro-1,2,4-triazine (3 008g, 0 016 mole) and hexafluoro-but-3-yne (8 6g, 0 530 mole) were sealed in a nickel autoclave and heated at 250° for six hours After cooling, the autoclave was opened and the volatiles were collected under vacuum Only hexafluoro-but-2-yne was identified in the volatile mixture

by molecular weight (162)

The nickel autoclave was extracted with dry hexane (30 ml) Evaporation of the solvent left a degraded solid

(b) WITH DIPHENYLACETYLENE The experiment given in section 4 3A(ii)(b) was repeated with the exception that the cold receiver, attached to the heated silica tube, was coated internally with diphenylacetylene (8 85g, 0 049 mole) 3,5,6-Trichloro-1,2,4-triazine (4 028g, 0 022 mole) was passed through the packed platinum at 660° and the volatile pyrolysate was condensed onto the diphenylacetylene No addition product could be detected in the mixture of trichloroacrylonitrile and diphenylacetylene Compounds were identified by infra-red spectra and mass spectra (155 and 178, respectively).

B. PREPARATION OF TRICHLOROACRYLONITRILE FROM HEXACHLOROPROPENE

(i) CONVERSION OF HEXACHLOROPROPENE TO TRICHLOROACRYLIC ACID

Hexachloropropene (82 0g, 0.329 mole) was mixed with concentrated sulphuric acid (68 6g, 37 3 ml) and a solution of aluminium sulphate (0.67g) in water (6 67 ml) added The mixture was slowly heated in a round bottom flask, fitted with a reflux condenser and an efficient stirrer During the first four hours a temperature of more than 110° was avoided, otherwise, violent explosion would have occurred [98] Then it was heated for another eight hours at 110-130° The reaction mixture was ccoled to 0° and mixed with an equal volume of water The trichloroacrylic acid was filtered off and recrystallised from petroleum ether (40-60°) (50 3g, 87 2%), m p. 75-6°, literature value 76° [98] Infra-red spectrum No 4

(ii) CONVERSION OF TRICHLOROACRYLIC ACID TO TRICHLOROACRYLIC ACID AMIDE

Trichloroacrylic acid (45 8g, 0 261 mole) was refluxed with freshly distilled thionyl chloride (124 3g, 0 694 mole) for 24 h The excess thionyl chloride was removed under reduced pressure and the acid chloride was dissolved in dry ether (600 ml) Ammonia gas was passed through the solution, which was mechanically stirred and maintained at 0^{o}, until there was no further gas absorption The reaction mixture was washed with water, aqueous sodium carbonate, water, dilute hydrochloric acid (2N), water and finally, dried over $MgSO_4$. The ether was removed under reduced pressure to give the amide which was washed with cyclohexane (43 9g, 9 5%) Identification was by infra-red spectrum No 5 (N-H absorption at 3362 cm^{-1} and C=O absorption at 1660 cm^{-1})

(iii) CONVERSION OF TRICHLOROACRYLIC ACID AMIDE TO TRICHLOROACRYLONITRILE

Trichloroacrylic acid amide (9 85g, 0 572 mole) and phosphorus pentoxide (12 71g, 0 915 mole) were mixed together in a flask to give an intimate mixture The flask was evacuated and slowly heated to 120^{o} and maintained at this temperature for about 2 h Trichloroacrylonitrile was collected under vacuum in a trap cooled in liquid air (3 84g, 43 5%) M p 19-20^{o}, literature value 20^{o} [95] (Found, C, 23 3, Cl, 67.4, N, 8 6%, M(mass spectrum), 155. Calcd.for C_3Cl_3N,C, 23 0, Cl, 68 0, N, 8.9%, M, 155) Infra-red spectrum No 6 ^{13}C n m r spectrum No 4

C PERFLUORO-3,5,6-TRIS-ISOPROPYL-1,2,4-TRIAZINE

(i) PHOTOLYSIS

(a) IN THE VAPOUR PHASE AT 253 7 n m Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 073g) was placed in a dry silica tube which was cooled, evacuated and sealed It was then irradiated (with a 120 watt, low pressure mercury lamp) for 185 h The tube was then cooled, opened, and the

contents analysed by quantitative g l c (G D B) and the mass spectra of the individual compounds was obtained (Varian Micromass) The mixture consisted mainly of unchanged starting material (>95%) together with trace amounts of perfluoroisobutyronitrile, perfluoro-2,5-dimethyl-hex-3-yne and perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine. The products were identified by their mass spectra (m/e = 176 (parent - fluorine), m/e = 362, and m/e = 585, respectively (Further characterised in 4 3 C(ii) b).

(b) IN SOLUTION BY A MEDIUM PRESSURE ARC Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 045g) was introduced into a dry silica tube, then FREON 114 (ca 40 ml) was condensed into the tube which was sealed under vacuo The system was then irradiated by an Hanovia U V S. 1000 lamp, at a distance of ca 15 cms from the lamp, for a period of 11 days. The tube was cooled and opened, and then after evaporation of the solvent, the contents were shown by g.l c (G D B) to be a mixture with the same composition as that in the previous experiment This was further verified by mass spectra (Varian Micromass), as in the previous experiment.

(c) WHILST UNDER TRANSFERENCE AT 253 7 n m Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 962g) was introduced into a large silica vessel (81 x 340 mm.) which was attached by means of a transfer arm to a trap cooled in liquid air The triazine was frozen (liquid air), then the system was evacuated, allowed to warm up and let down to atmospheric pressure with pure dry nitrogen This procedure (to remove oxygen) was carried out three times, then the system was evacuated to 7 mm (residual pressure being due to nitrogen) The system was then irradiated at 253 7 n m. (120 watt, low pressure mercury lamp) whilst triazine transferred into the cold trap (liquid air) The transferred material was shown by g l.c (G D B) to be mainly unchanged starting material (>98%) with trace

amounts of perfluoroisobutyronitrile and perfluoro-2,5-dimethyl-hex-3-yne Identification was by mass spectra (same as in previous experiments)

(d) IN SOLUTION IN THE PRESENCE OF BENZOPHENONE AT 253 7 n m Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (0.9980g, 1 70 x 10^{-3} mole) and benzophenone (0 0038g, 2 08 x 10^{-5} mole, 1 2%) were placed in a dry silica tube, then FREON 114 (ca 30 ml) was condensed into the tube which was sealed under vacuo The system was then irradiated with ultra-violet light (120 watt, low pressure mercury lamp) for 129.4 h The tube was cooled and opened, then after evaporation of the solvent, the contents were shown by g l c (G D.B.) to be a mixture of starting material (83 0%), perfluoro-isobutyronitrile and perfluoro-2,5-dimethyl-hex-3-yne (11 3%), and perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine (5 7%) The products were identified by their mass spectra, as before

(ii) PYROLYSIS

(a) STATIC PYROLYSIS Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 894g) was sealed in a clean dry nickel autoclave and heated at 450° for 40 minutes. The autoclave was cooled, opened and the volatiles collected, under vacuum, in a cold trap fitted with 'rotaflo' taps (1 695g) A gas sample (26 cm^3 Hg + nitrogen to give atmospheric pressure) was analysed by g.l c (G D B.) and mass spectra The mixture was found to consist of a 50 50 mixture of perfluoroisobutyronitrile and perfluoro-2,5-dimethyl-hex-3-yne. They were identified as in previous experiments

(b) FLOW PYROLYSIS

(1) AT 370° Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1.139g) was passed through a silica tube packed with platinum foil at 370° under a stream of dry nitrogen (contact time ca 12s) The material recovered (1 043g) was mainly starting material (>98%) with a trace of perfluoro-

isobutyronitrile (G.D.B. and Varian Micromass). The spectra were the same as those obtained in previous experiments.

(2) AT 500° Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 153g) was passed through a silica tube packed with platinum foil at 500° under a stream of dry nitrogen (contact time ca 12s) The material recovered (1 060g) was mainly starting material (>95%) with two other compounds, in the ratio 1 1, which were perfluoroisobutyronitrile and perfluoro-2,5-dimethyl-hex-3-yne (G D.B)

(3) AT 600° Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 102g) was passed through a silica tube packed with platinum foil at 600° under a stream of dry nitrogen (contact time ca 12s). The volatile products (0.948g) were recovered in a cold trap and identified as in previous experiments (G D B and Varian Micromass). The products were perfluoroisobutyronitrile and perfluoro-2,5-dimethyl-hex-3-yne in the ratio 1 1 Infra-red spectra Nos 7 and 8; ^{19}F n m r. spectra Nos. 5 and 6, and m/e's 176 and 362, respectively

(iii) ATTEMPTED TRAPPING OF REACTIVE INTERMEDIATE(S) FORMED ON NITROGEN ELIMINATION

(a) WITH DIPHENYLACETYLENE (CO-PYROLYSIS) Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 751g, 2 99 x 10^{-3} mole) and diphenylacetylene (0.504g, 2 83 x 10^{-3} mole) were sealed in a clean dry nickel autoclave and heated at 250° for 6 h The autoclave was cooled, opened and the volatiles collected, under vacuum, in a trap cooled in liquid air Only perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 662g) was recovered together with trace amounts of defluorinated triazines (G D B and Varian Micromass).

(b) WITH TOLUENE (CO-PYROLYSIS) Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (2 039g, 3 49 x 10^{-3} mole) and toluene (3.118g, 33 89 x 10^{-3} mole) were sealed in a clean dry nickel autoclave and heated at 400° for 1 h The autoclave was cooled, opened and the volatiles collected in a trap fitted with 'rotaflo' taps (2 552g) Only starting materials and fragmentation products (same as 4 3 C(ii)) were identified (G D B and Varian Micromass).

(iv) REACTIONS WITH FLUORIDE ION

(a) WITH FLUORIDE ION

(1) Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (2 949g, 5 04 x 10^{-3} mole), caesium fluoride (4 069g, 26 77 x 10^{-3} mole) and dry sulpholane (10 ml) was stirred under an atmosphere of dry nitrogen for 20 days Volatiles were then collected, under vacuum, in a cold trap (liquid air) from the reaction mixture. The only products identified were oligomers of hexafluoropropene (i.e dimers and trimers). They were identified by their molecular weight (300 and 450 for the dimers and trimers, respectively)

(2) Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 069g, 1.83 x 10^{-3} mole), caesium fluoride (0 161g, 1 06 x 10^{-3} mole) and sulpholane (4 ml) was stirred under a dry nitrogen atmosphere for several days The mixture was analysed by ^{19}F n.m r periodically but no change in the starting material was observed. Only starting material was recovered by vacuum transference from the reaction mixture

(3) Experiment (2) was repeated except that the mixture was sealed in an n m r tube and heated at 100° No reaction was observed after 7 and 21 days

(b) WITH FLUORIDE ION IN THE PRESENCE OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (2 298g, 3 93 x 10^{-3} mole), 3,5,6-trichloro-1,2,4-triazine (1.953g, 10 59 x 10^{-3} mole), potassium fluoride (2 604g, 44 90 x 10^{-3} mole) and sulpholane (6 ml) were stirred under an atmosphere of dry nitrogen for 2 weeks The volatiles were transferred, under vacuum, into a dry flask The mixture partially hydrolysed on the glass surface on warming to room temperature, to give a solid mass This mass could not be identified by infra-red or mass spectra. The remaining liquid was removed and found to be perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 810g)

(c) WITH FLUORIDE ION IN THE PRESENCE OF TETRAFLUOROPYRIDAZINE

(1) Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 986g, 3 39 x 10^{-3} mole), tetrafluoropyridazine (1 568g, 10.32 x 10^{-3} mole), potassium fluoride (1 02g, 17.59 x 10^{-3} mole) and sulpholane (10 ml) were stirred under an atmosphere of dry nitrogen for 3 days When the volatiles were collected in a cold trap (liquid air), under vacuum, the unchanged starting materials were recovered

(2) The volatiles collected from experiment No 1 were added to a mixture of caesium fluoride (2 37g, 15 64 x 10^{-3} mole) and sulpholane (10 ml) The mixture was stirred under an atmosphere of dry nitrogen for 3 days. Again, the unchanged starting materials were recovered.

(3) Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (1 132g, 1 94 x 10^{-3} mole), tetrafluoropyridazine (9.88 x 10^{-3} mole), caesium fluoride (2 20g, 14 47 x 10^{-3} mole) and sulpholane (15 ml) were placed in a flask under a dry nitrogen atmosphere The stirred mixture was heated at 120^{o} for 19 5 h The volatiles were collected in a cold trap (liquid air), under vacuum (0 386g)

The volatile mixture was found to contain tetrafluoropyridazine (6 5%), perfluoro-4-isopropylpyridazine (11 0%), perfluoro-3,5-bis-isopropylpyridazine (75.0%) and perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (7 5%) These compounds were identified by their molecular weights (152, 302, 452 and 585, respectively) and their g.l c. retention times

Water (200 ml) was added to the reaction mixture which was then extracted with diethyl ether (2 x 200 ml.). The organic phase was separated, dried over $MgSO_4$, and evaporated The residue (0 155g) was identified as bis-heptafluoroisopropyl-monohydroxy-1,2,4- triazine by its molecular weight (433). Infra-red spectrum No 9 ^{19}F n m.r. spectrum No. 7

D PHOTOLYSIS OF PERFLUORO-2,4,6-TRIS-ISOPROPYL-1,3,5-TRIAZINE

Perfluoro-2,4,6-tris-isopropyl-1,3,5-triazine (0 967g) and FREON 113 (250 ml.) were placed in a dry silica tube, which was then cooled and sealed The tube was irradiated with ultra violet light (120 watt, low pressure mercury lamp) for 162 8 h The tube was then cooled, opened and the excess FREON 113 was removed by distillation Analysis by g.l c (G.D.B) and mass spectra (Varian Micromass) identified only starting material.

PART II

CHAPTER 5

CYCLISATIONS OF DIMETHYLAMINO POLYFLUOROISOPROPYLPYRIDAZINES

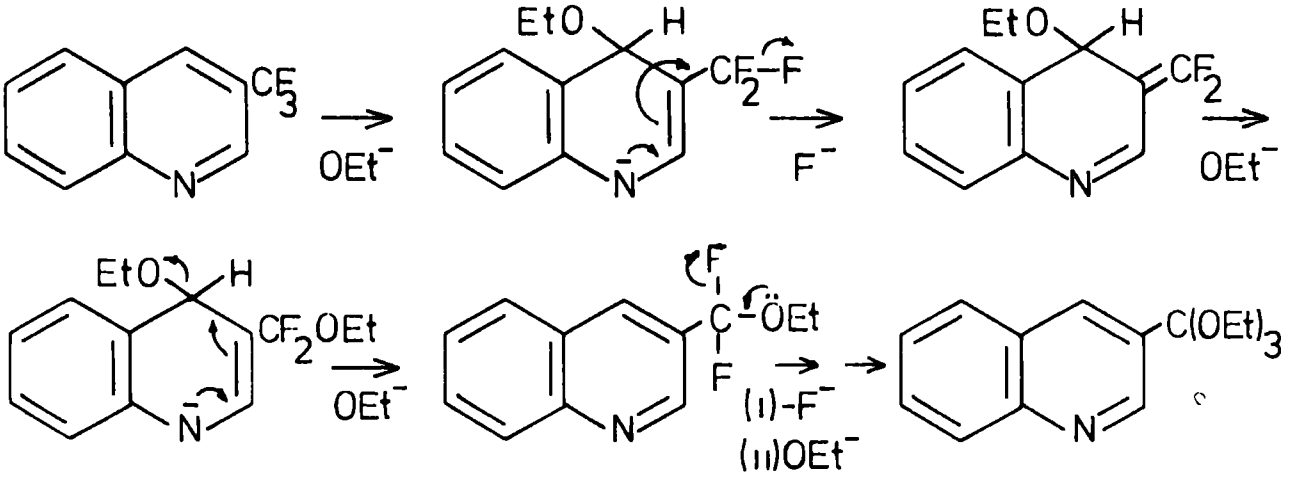
5.1. INTRODUCTION

This part of the thesis describes a study of a novel cyclisation discovered in a dimethylamino perfluoroisopropylpyridazine. The reaction involves a novel process of internal nucleophilic substitution, cyclisation occurred in a specific manner but the structures of the product remains ambiguous. In an attempt to distinguish between conformational and electronic effects other perfluoroisopropylpyridazines, their dimethylamino derivatives, and some of their methoxy derivatives were synthesised.

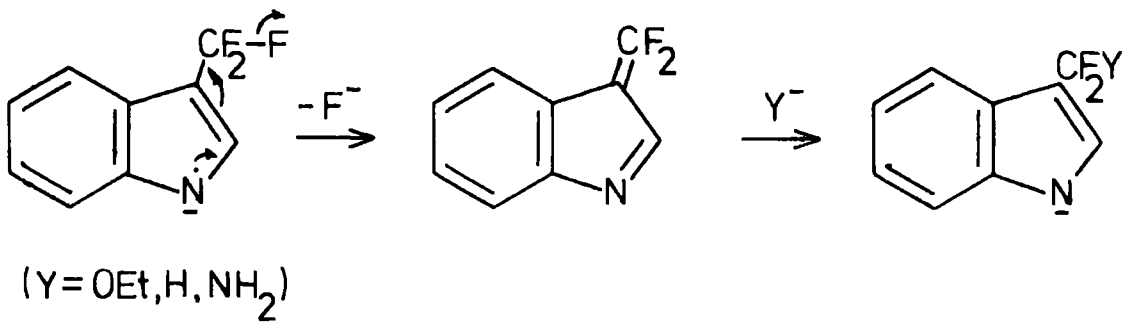
5.2. NUCLEOPHILIC DISPLACEMENT OF FLUORIDE ION FROM POLYFLUOROALKYL SIDE CHAINS

Nucleophilic displacement of fluoride ion from perfluoroalkyl groups is very rare. Those reactions reported involve intermolecular processes. For example, the fluorine atoms in 3-(trifluoromethyl) quinoline undergo nucleophilic displacement with ethoxy anions, as shown in SCHEME XV. The initial nucleophilic attack at the electron deficient 4-position leads to a C-F bond becoming labile due to charge donation in the intermediate anion (SCHEME XV).[104]

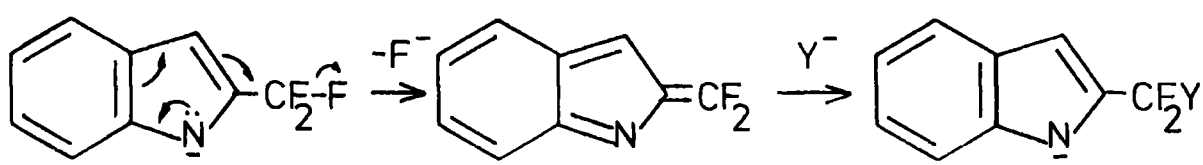
SCHEME XV



Substitution in the trifluoromethyl group has also been observed with 2- and 3-(trifluoromethyl)indoles.[105] In these cases the first step is an SN1- type cleavage of the C-F bond which has been attributed to the electronic effect of the π-electron rich indole ring.



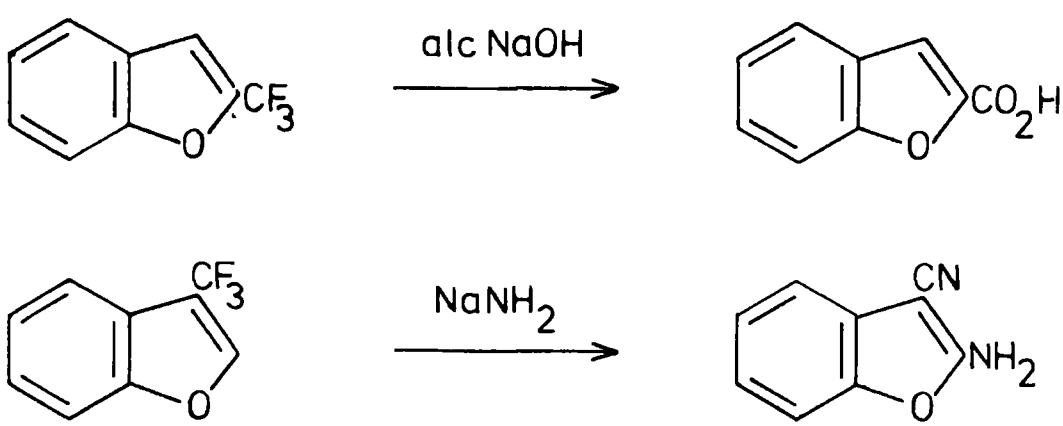
(Y=OEt,H,NH_2)



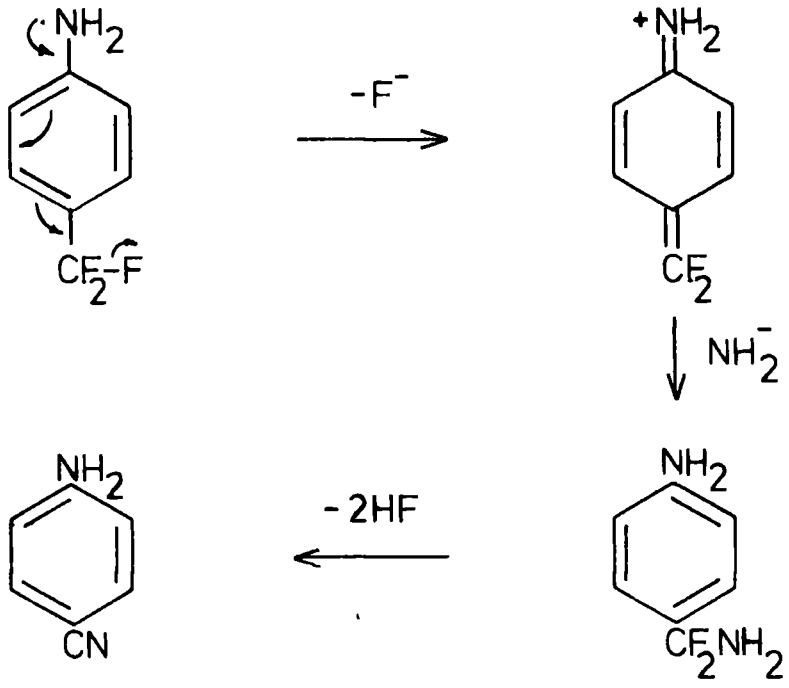
(Y=OEt,H; Y≠NH_2)

Kobayashi noted the similar reactivity of 3-(trifluoromethyl)indole and 3-(trifluoromethyl)quinoline and attributed this to enamine conjugation in the reactive intermediates.

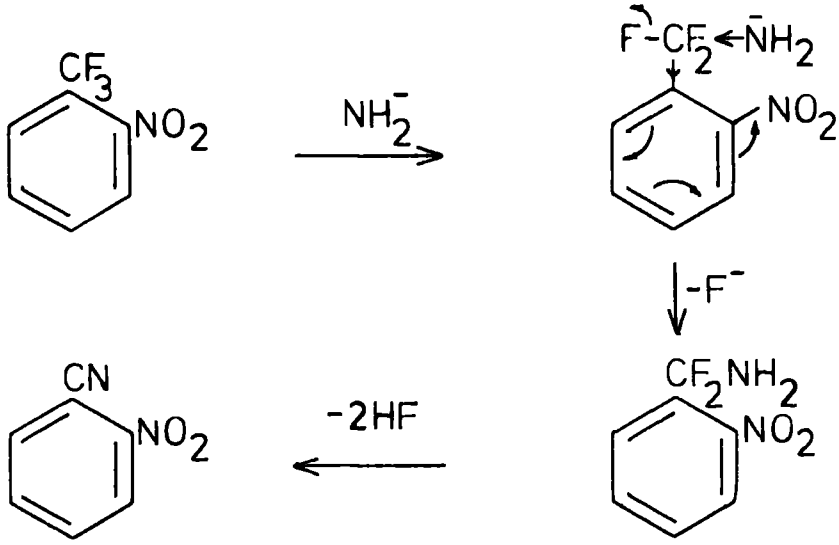
Other examples of nucleophilic displacement in the trifluoromethyl group, normally a very stable group, have been found in the benzofurans.[106]



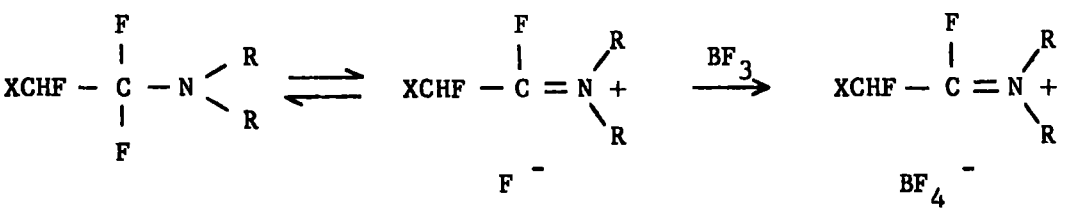
It has also been demonstrated[107] that the trifluoromethyl group present in benzotrifluoride will undergo reaction with nucleophiles if appropriate substituents are introduced into the benzene ring. Thus p-aminobenzotrifluoride, which has an electron-donating group in the para-position, gives p-aminobenzonitrile when reacted with sodium amide in liquid ammonia.



In contrast, if the substituent is electron-withdrawing, such as the nitro group in o-nitrobenzotrifluoride, an SN2-type reaction is claimed.[107]



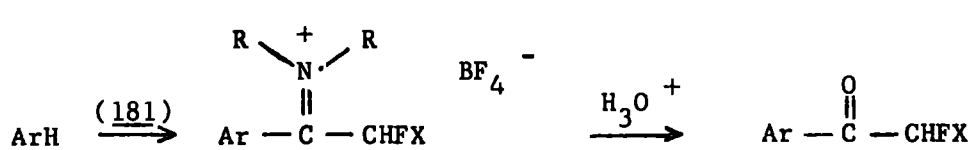
In none of the reactions of the N-heterocycles discussed, has the enamine intermediate been isolated. However, Wakselman, et al.,[108] have shown that such intermediates can be trapped with Lewis acids. They investigated the reactivity of fluoroamines (179), used extensively for the replacement of hydroxyl groups by fluorine,[109] and found that they readily reacted with boron trifluoride to produce immonium salts (181). The reactivity was explained by the following equilibria where (180) is an anionic form of (179).



(179) (180) (181)

(R = Et, X = Cl, F, CF_3)

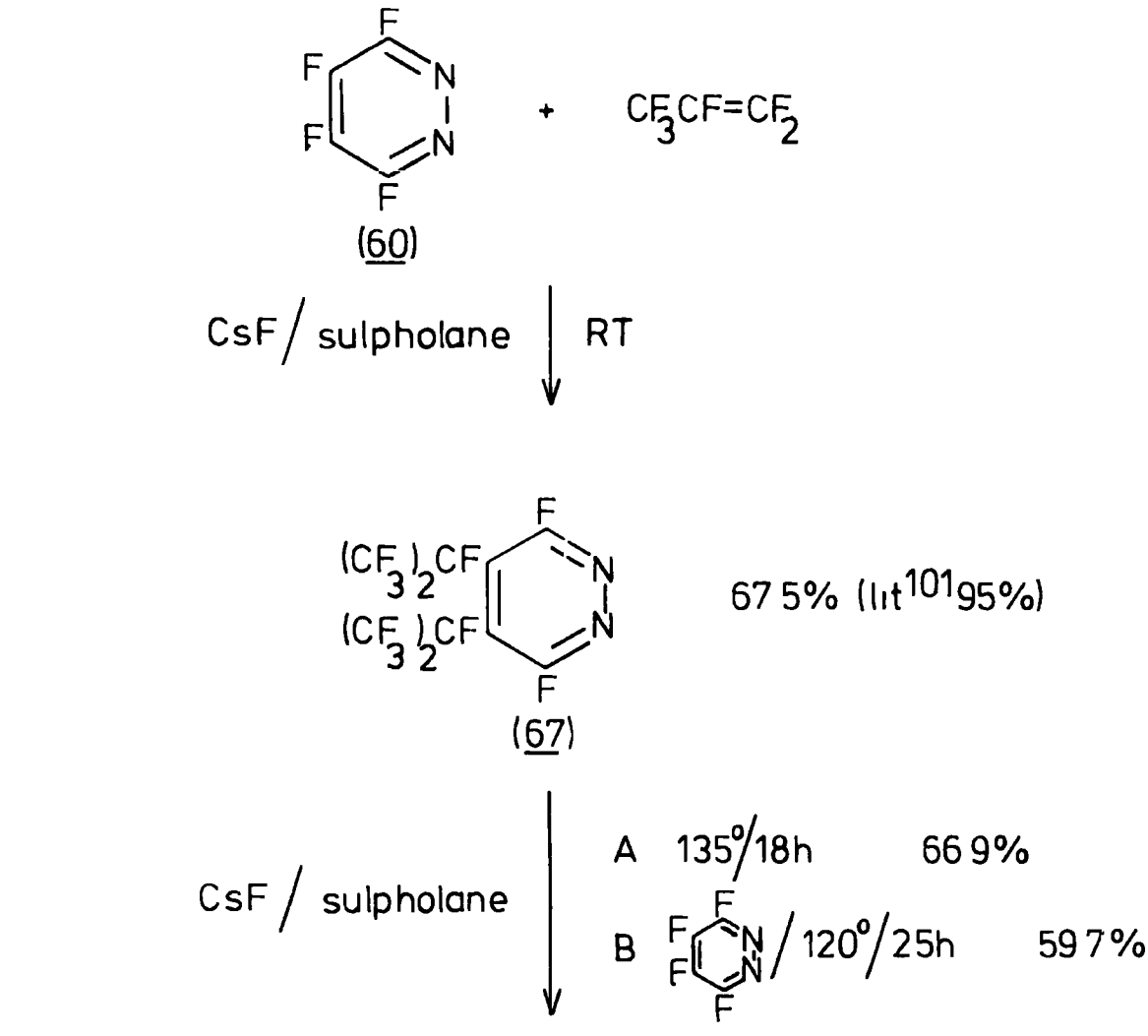
The immonium salts (181) have been used to acylate electron-rich aromatic compounds and provide an easy way to introduce an α-fluorinated carbonyl group into the molecule.[108]



5.2. PREPARATION OF PERFLUOROISOPROPYLPYRIDAZINES

The starting materials were made by known methods[101,110] and the yields recorded are given in the following SCHEME.

SCHEME XVI

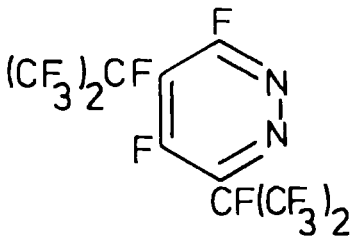


A	10%	86%	4%
(lit[101]	4%	81%	14%)
B	69%	24%	7%
(lit[110]	81%	19%	-)

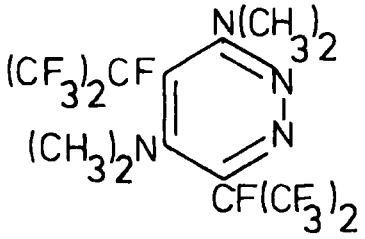
5.4. THE CYCLISATION OF 4,6-BIS-DIMETHYLAMINO-3,5-BIS-HEPTAFLUOROISO-PROPYLPYRIDAZINE

A. INITIAL WORK

In a study[111] of perfluoro-3,5-di-isopropylpyridazine (98), reaction with excess dimethylamine failed to give the expected product, 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine (183).

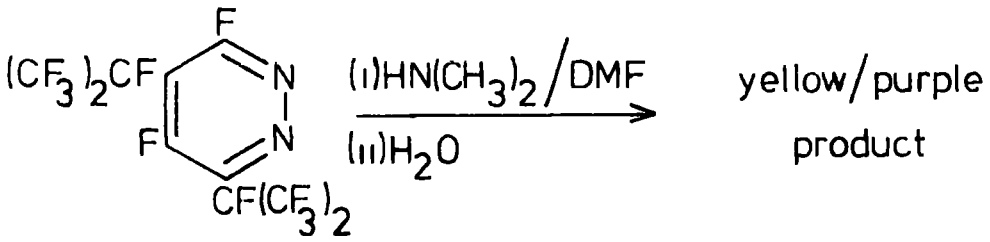


(98)



(183)

When this work was repeated, using the experimental conditions shown below, a yellow crystalline material was isolated.



(98)

This yellow material was unusual in that on standing several days, it was observed to change to a purple form. Moreover, it was found that recrystallisation would temporarily restore the original yellow colour. Only one product was detected (t.l.c.) in this material from which the following n.m.r. spectra (^{19}F and ^{1}H) were recorded (Table IV).

TABLE IV

BICYCLIC PRODUCT DERIVED FROM COMPOUND (183)

FLUORINE -19-NMR DATA

(solvent $(CD_3)_2CO$, int. ref. $CFCl_3$)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
69.30	S	6
72.91	D(J = 5Hz)	6
173.46	OCTET	1

HYDROGEN-1 NMR DATA

(solvent $(CD_3)_2CO$, ext. ref. TMS)

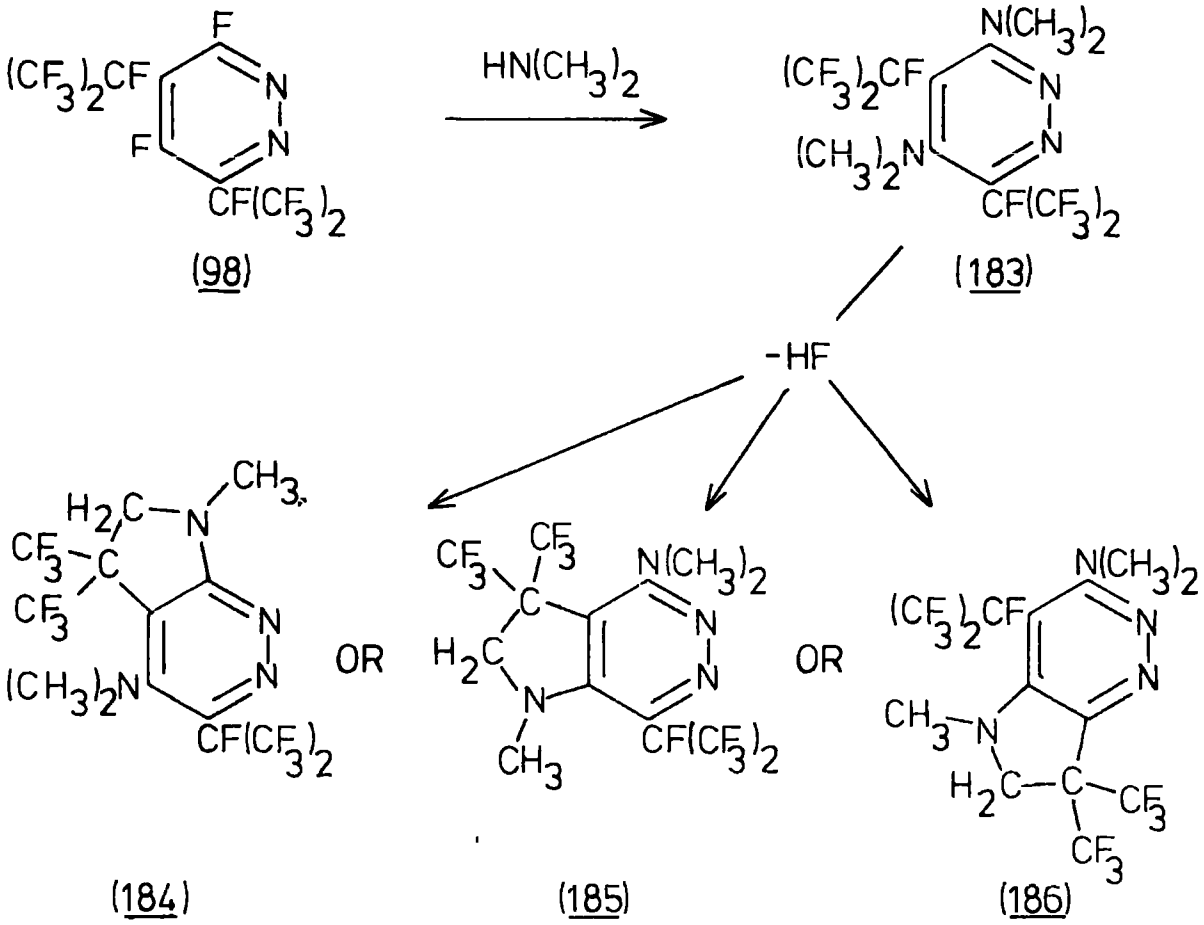
SHIFT (p.p.m.)	STRUCTURE	INTENSITY
2.57	S	6
3.10	D(J = 8Hz)	3
4.13	S	2

In the following sections, this compound is shown to have a bicyclic structure.

B. STRUCTURE OF THE BICYCLIC PRODUCT

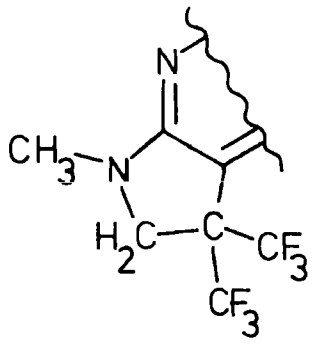
The mass spectra indicated that the product was derived from compound (183) by elimination of hydrogen fluoride and it was evident from the n m.r data (TABLE IV) that a 'tertiary' fluorine had been lost from one of the heptafluoroisopropyl groups and a proton had been lost from a methyl group. The product must therefore have one of three possible bicyclic structures, (184) - (186), SCHEME XVII

SCHEME XVII

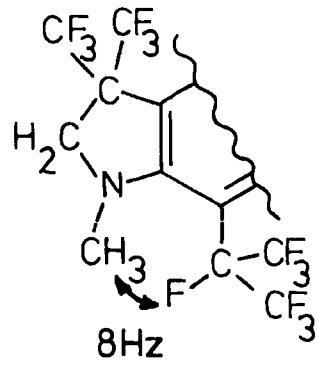


(98) (183) (184) (185) (186)

The n.m.r. data could not differentiate between structures (185) and (186) where coupling ($J_{CH_3,F}$ = 8Hz) between the methylamino (in the 2-pyrroline ring) and the adjacent tertiary fluorine (in the remaining heptafluoroisopropyl group) was observed. The data did eliminate structure (184) as the reaction product where no such coupling could be possible.



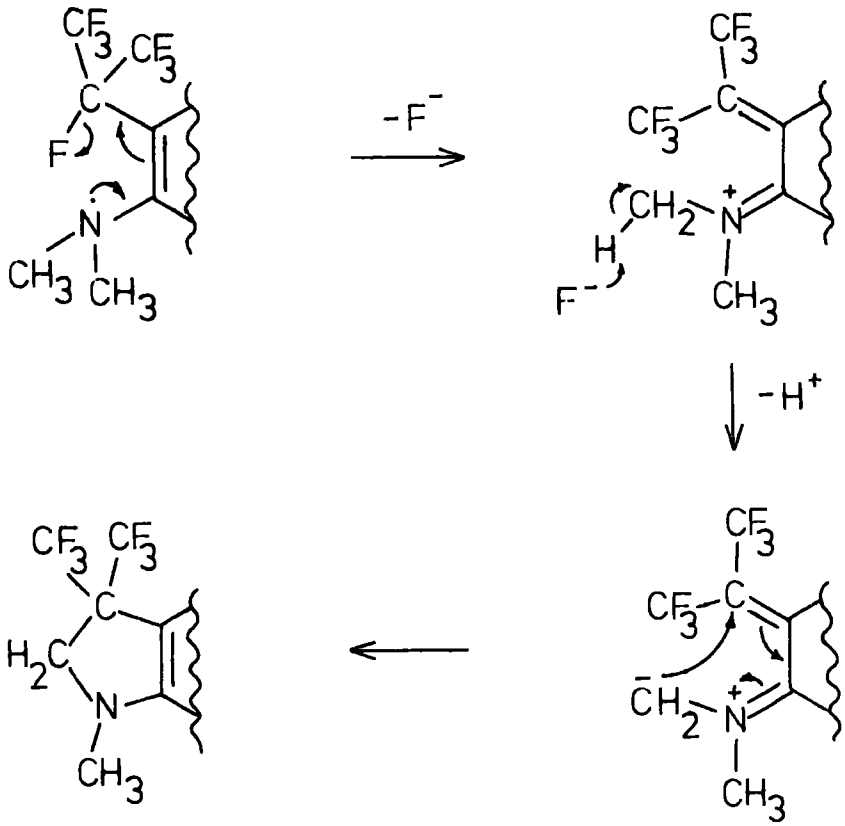
(184)



(185),(186)

C. MECHANISM OF THE CYCLISATION

The mechanism for this unique cyclisation is shown below. It is an



(187)

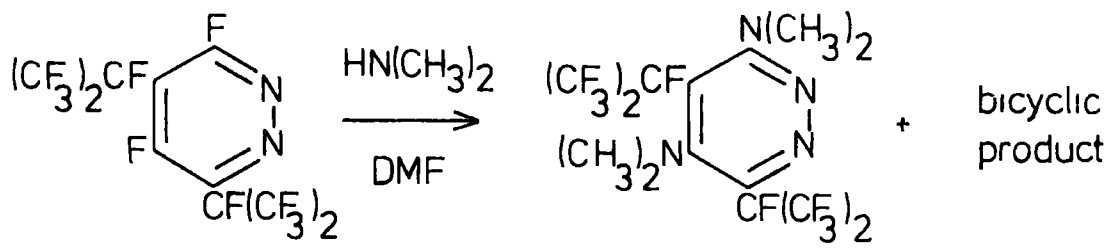
SN1-type reaction, where electron-donation by the nitrogen atom assists the loss of fluoride ion in the first step. Proton abstraction by the fluoride ion generates the reactive ylid (187) which then reacts by ring closure.

If the only requirement for this cyclisation was that an heptafluoro-isopropyl group be adjacent to a dimethylamino group in the aromatic ring, then the reaction would give three products, (184), (185) and (186), shown in SCHEME XVII.

The reaction though was specific in that only one bicyclic product was isolated. It is obvious that the reactive intermediate, and thus the reaction product, depend upon which position loses fluoride ion in the first step (SCHEME XVIII). If the fluoride ion is lost from the isopropyl group at position 5, then two products are possible, (184) and (185) On the other hand, loss of fluoride ion from the isopropyl group at position 3 can give only one bicyclic product (186), as the 'quinoid' type intermediate (191) cannot cyclise.

D ISOLATION OF 4,6-BIS-DIMETHYLAMINO-3,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE

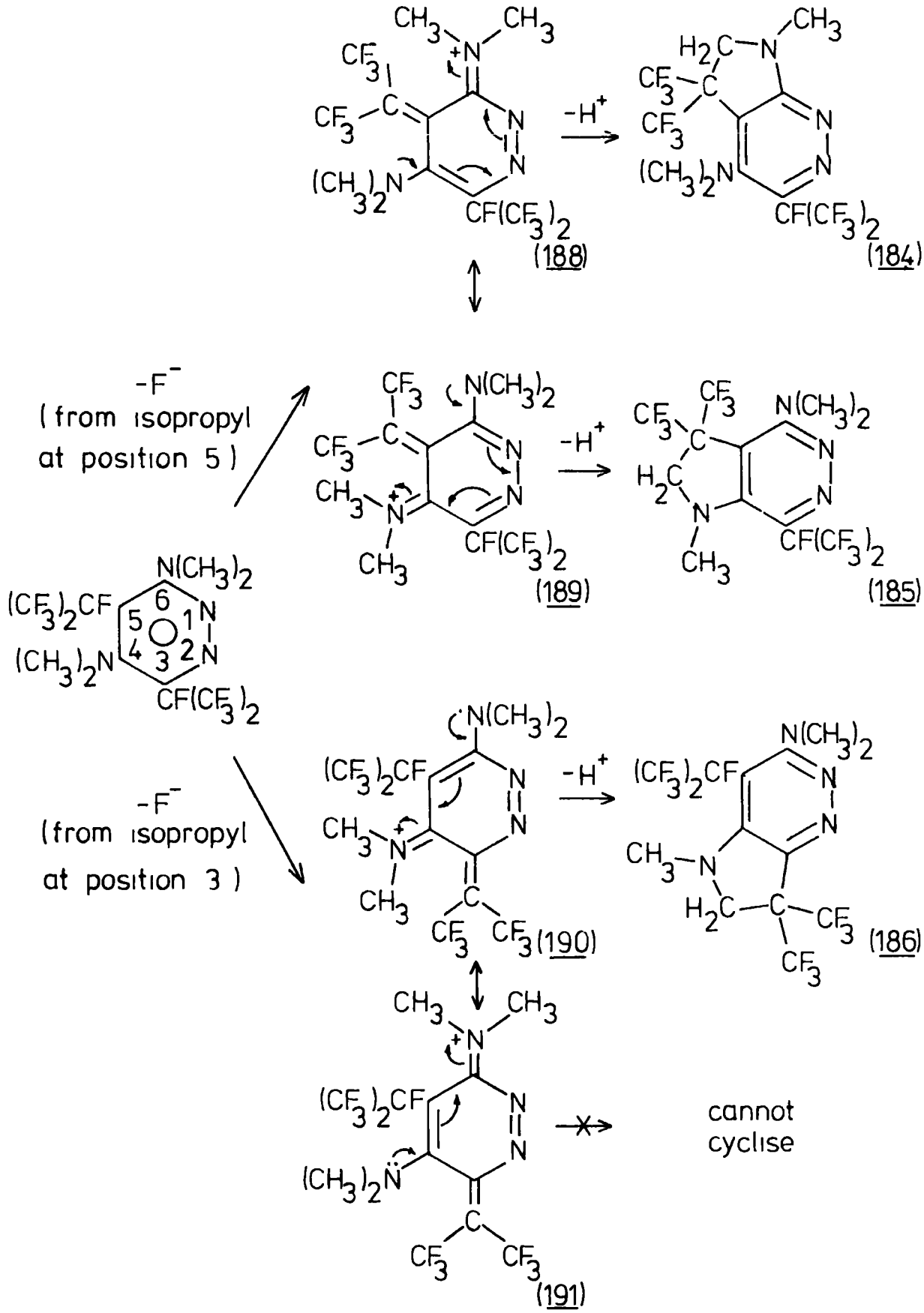
When the reaction mixture obtained from perfluoro-3,5-di-isopropylpyridazine and excess dimethylamine was excluded from any aqueous extraction, two reaction products were isolated.



(98) (183)

655% 43%

SCHEME XVIII



4,6-Bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine (183) was a brilliant yellow The n.m.r spectra recorded for this compound are given in TABLE V.

TABLE V

COMPOUND (183)

FLUORINE-19 NMR DATA

(solvent $(CD_3)_2CO$, int. ref. $CFCl_3$)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
72.49	S	6
73.33	D(J = 5Hz)	6
169.72	M(J = 4Hz)	1
187 22	M(J = 5Hz)	1

HYDROGEN-1 NMR DATA

(solvent $(CD_3)_2CO$, int. ref. TMS)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
2.57	D(J = 5Hz)	3
3.08	D(J = 4Hz)	3

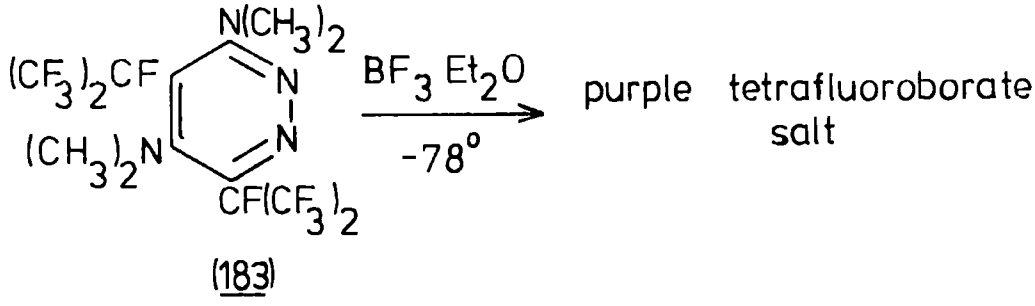
The bicyclic product isolated from this reaction was colourless but it was identical in all other respects (i.r., n.m.r., etc.) to the bicyclic product obtained in the initial reaction (5.4.A.).

The colour changes observed with 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine (183) were quite remarkable. After several days in solution ($(CD_3)_2CO$ or $CDCl_3$), or even when stored under a dry atmosphere, this compound was found to change from yellow to purple. However, the concentration of any purple species was too low to detect by

n m.r. Gradually, the concentration of (183) decreased, as did the intensity of the purple colour This process corresponded with the detection of the bicyclic compound, which increased in concentration until after several weeks it was the only species present in a colourless solution.

E. STRUCTURE OF THE REACTIVE INTERMEDIATE

The first step in the cyclisation is loss of a labile fluorine atom. The ease by which this fluorine is lost as fluoride ion, was demonstrated by the reaction of (183) with boron trifluoride etherate. Vivid purple crystals of a tetrafluoroborate salt were readily formed.



(183)

Surprisingly, the structure of this trapped intermediate was not that of any of the intermediates shown in SCHEME XVIII, (188)-(191)). It can be deduced from the ^{19}F n.m.r data (TABLE VI) that there are two non-equivalent trifluoromethyl groups with chemical shifts of 72.49 and 75.97 p.p.m. The peak at 151.68 p.p.m. can be assigned to the tetrafluoroborate ion, which is in the region of the ^{19}F spectra normally associated with such an ion.

The most interesting feature occurs in ^{1}H n.m.r. spectra where none of the methyl groups are equivalent. This is probably due to the dimethylamino groups adopting a planar configuration so as to stabilise π-bonding between the nitrogen atoms and the pyridazine ring. The trapped reactive intermediate

TABLE VI

TETRAFLUOROBORATE SALT DERIVED FROM COMPOUND (183)

FLUORINE-19 NMR DATA

(solvent $(CD_3)_2CO$, int. ref. $CFCl_3$)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
60.66	M	6
72.49	S	3
75.97	S	3
151.68	S	4
182.39	M	1

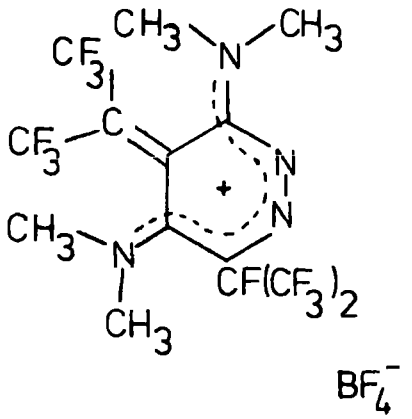
HYDROGEN-1 NMR DATA

(solvent $(CD_3)_2CO$, int. ref. TMS)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
3.50	S	3
3.63	S	3
3.93	D(J = 5Hz)	3
4.16	S	3

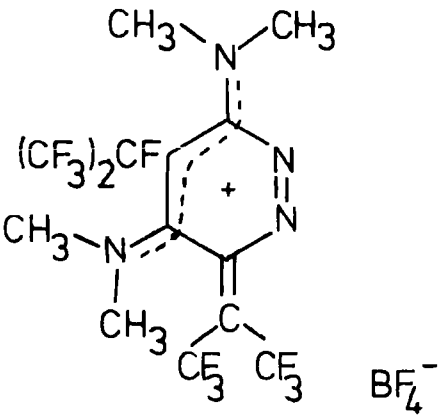
must therefore have a structure intermediate of the canonical forms (188) and (189), or, (190) and (191) (SCHEME XVIII). Two possible mesomeric structures are (192) and (193).

STRUCTURE OF THE TRAPPED INTERMEDIATE



(192)

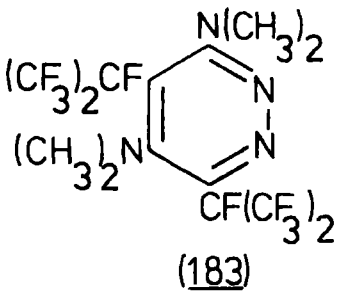
fluoride ion lost from isopropyl group at position 5



(193)

fluoride ion lost from isopropyl group at position 3

The tetrafluoroborate salt was unstable to moisture and reacted rapidly with moist acetone to give the colourless bicyclic compound. The cyclisation of (183) thus involves two colour changes, indicated below.



(183)

yellow

$\xrightarrow{-F^-}$ intermediate compound

purple

$\xrightarrow{-H^+}$ bicyclic compound

colourless

These observations explain the different colours found in the initial experiment (5.4.A.), where the bicyclic compound was yellow due to trace amounts of (183). This 'impurity' then cyclises to the bicyclic product via the purple intermediate.

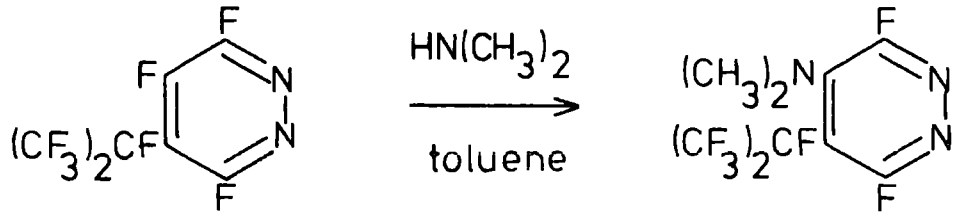
5.5. OTHER DIMETHYLAMINO DERIVATIVES OF PERFLUOROISOPROPYLPYRIDAZINES

In the previous discussion, it was not possible to distinguish between the relative importance of steric or electronic effects in the 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine system. To try and establish the influence of these effects, the following derivatives were prepared.

A. PERFLUORO-4-ISOPROPYLPYRIDAZINE

(i) 5-DIMETHYLAMINO DERIVATIVE

3,6-Difluoro-5-dimethylamino-4 heptafluoroisopropylpyridazine (194) was prepared by the reaction of perfluoro-4-isopropylpyridazine (177) with dimethylamine. The ortho/para orienteering effects of both ring nitrogen and heptafluoroisopropyl directed nucleophilic substitution to the 5 position.

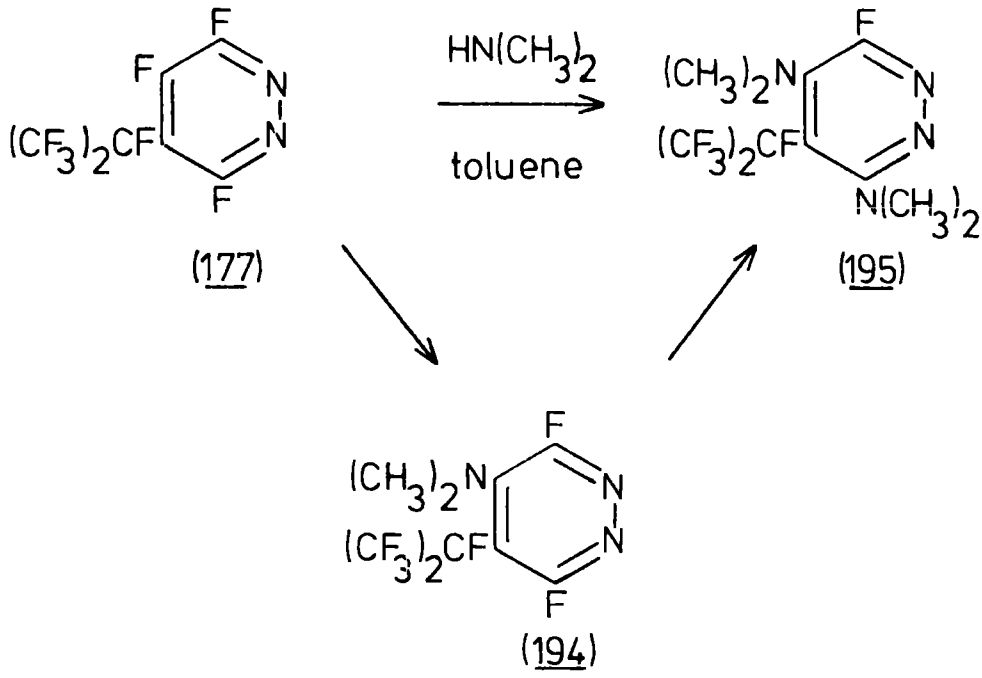


(177) (194)

This compound (194) was stable to prolonged heating at 120°, and was found to decompose at a temperature not much higher than its boiling point (~170°), without cyclisation. When stirred with boron trifluoride etherate, no reaction was observed.

(ii) 3,5-BIS-DIMETHYLAMINO DERIVATIVE

When reacted with sufficient dimethylamine for di-substitution, perfluoro-4-isopropylpyridazine (177) gave a mixture where the main product was 3,5-bis-dimethylamino-6-fluoro-4-heptafluoroisopropylpyridazine (195).

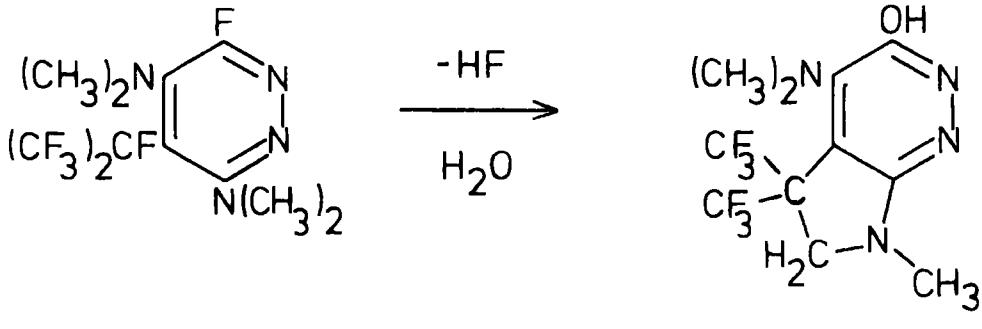


(177) (195)

(194)

Here, the ortho activating effect of the heptafluoroisopropyl group in the intermediate compound (194), effected substitution of the fluorine at the 3 position.

Pure (195) could not be isolated from the reaction mixture, which contained mono- and tris-dimethylamino products, by distillation or chromatographic methods. However, the product obtained by preparative thin layer chromatography had a bicyclic structure, (196)



(194) (196)

The n.m.r data of compound (196) is given in TABLE VII where the coupling (4Hz) between the hydroxy proton and a dimethylamino group (6 protons) means that cyclisation must have occurred via loss of a proton from the dimethylamino group at position 3.

This product must have been derived by a process of cyclisation analogous to that observed in 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine (183). Hydrolysis had also occurred where the remaining aromatic fluorine had been replaced by hydroxyl. It was not possible to say whether the process of hydrolysis had occurred before or after cyclisation.

TABLE VII

COMPOUND (196)

FLUORINE-19 NMR DATA

(solvent CCl_4, ext. ref $CFCl_3$)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
50.35	S	-

HYDROGEN-1 NMR DATA

(solvent CCl_4, ext. ref TMS)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
3.06	M(BROAD)	1
3.25	S	3
3.40	D(J = 4Hz)	6
4.33	S	2

TABLE VIII

BICYCLIC PRODUCT DERIVED FROM (197)

FLUORINE-19 NMR DATA

(solvent CCl_4, ext. ref. $CFCl_3$)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
69.68	S	-

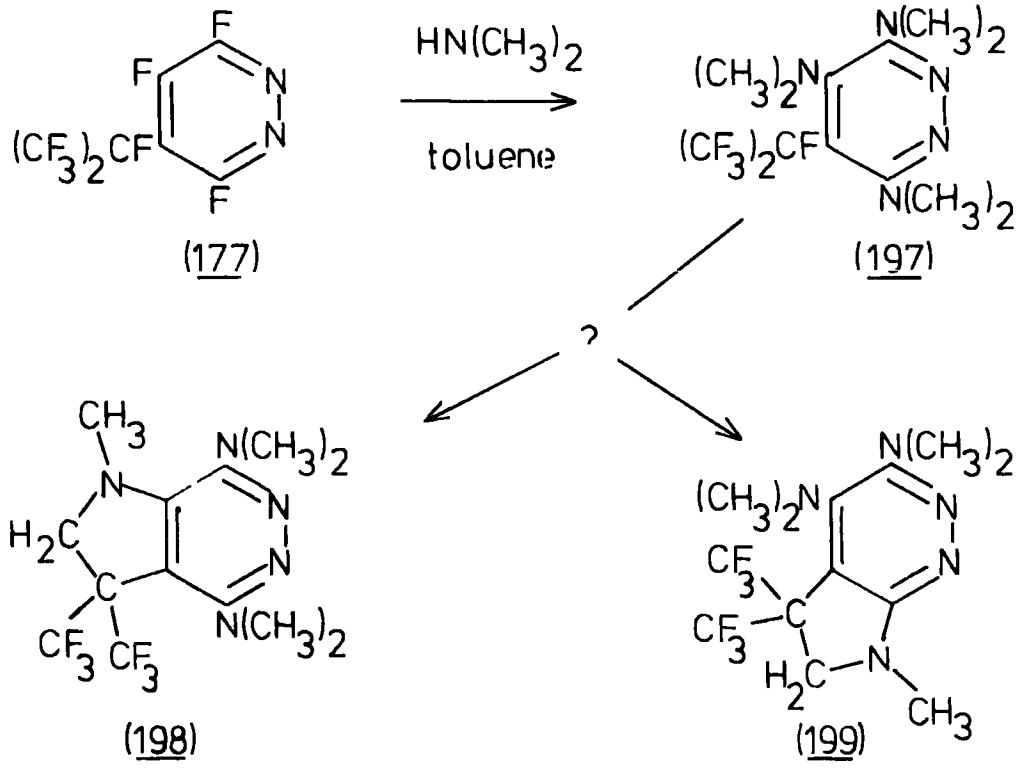
HYDROGEN-1 NMR DATA

(solvent CCl_4, ext. ref. TMS)

SHIFT (p.p.m.)	STRUCTURE	INTENSITY
3.20	S	6
3.37	S	6
3.55	S	3
4.27	S	2

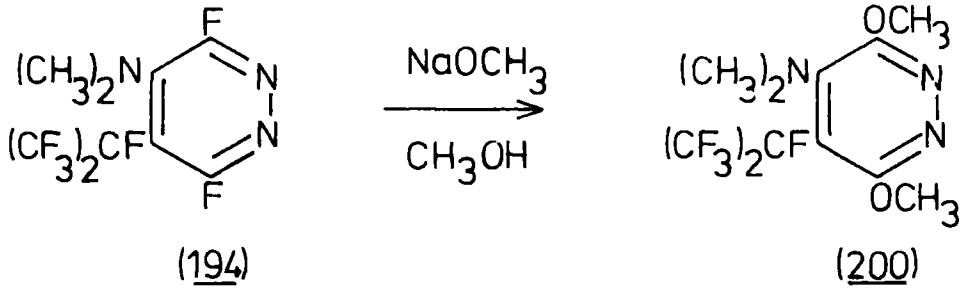
(iii) 3,5,6-TRIS-DIMETHYLAMINO DERIVATIVE

An attempt to prepare the tris-dimethylamino compound (197) led to the isolation of a third bicyclic compound. Once generated, the tris-dimethylamino compound undergoes immediate cyclisation, even at room temperature, as it could not be detected in the reaction mixture. Unfortunately, it was not possible to determine whether the structure of the product isolated was (198) or (199) (n.m.r. given in TABLE VIII).



(iv) 5-DIMETHYLAMINO-3,6-DIMETHOXY DERIVATIVE

Compound (194) was treated with sodium methoxide to give 5-dimethylamino-3,6-dimethoxy-4-heptafluoroisopropylpyridazine (200).

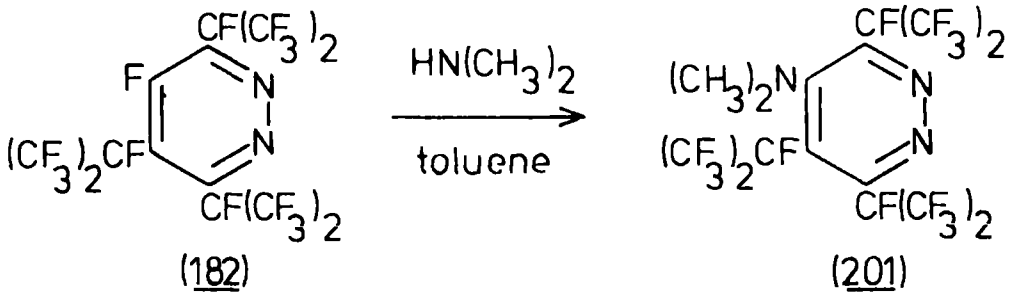


No cyclisation was observed even after heating at 240° for half an hour when decomposition became extensive.

B. PERFLUORO-3,4,6-TRIS-ISOPROPYLPYRIDAZINE

(i) 5-DIMETHYLAMINO DERIVATIVE

Reaction of perfluoro-3,4,6-tris-isopropylpyridazine (182) with dimethylamine gave the dimethylamino derivative (201).



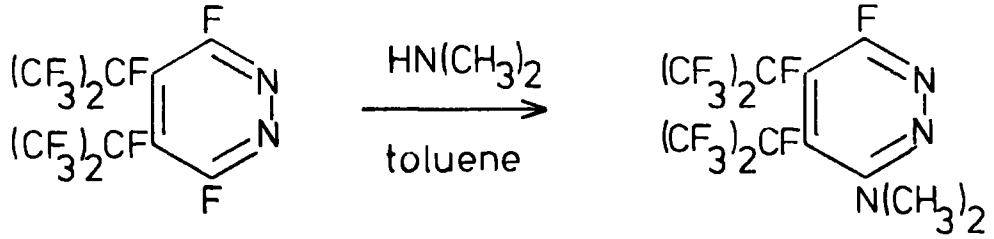
(182) (201)

This sterically crowded compound (201) did not undergo cyclisation after prolonged heating at 120°.

C. PERFLUORO-4,5-BIS-ISOPROPYLPYRIDAZINE

(i) 3-DIMETHYLAMINO DERIVATIVE

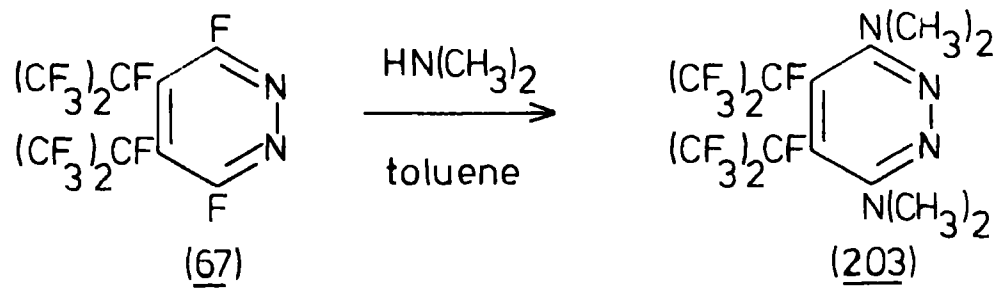
Reaction of perfluoro-4,5-bis-isopropylpyridazine (67) with the stoichiometric amount of dimethylamine gave compound (202).



(67) (202)

(ii) 3,6-BIS-DIMETHYLAMINO DERIVATIVE

The bis-dimethylamino compound (203) was readily prepared by the reaction of (67) with excess dimethylamine.



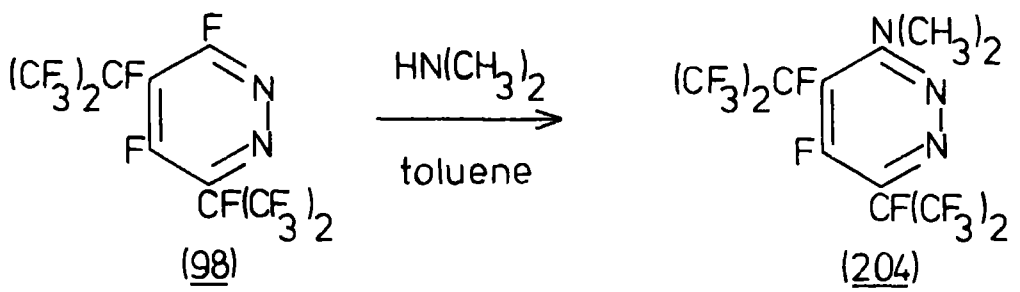
(67) (203)

Neither compounds, (202) or (203), were found to cyclise on heating at 120° for long periods. Photolysis of (203) caused extensive decomposition, where elimination of hydrogen fluoride was barely detectable and was obviously an unfavourable process

D PERFLUORO-3,5-BIS-ISOPROPYLPYRIDAZINE

(i) 6-DIMETHYLAMINO DERIVATIVE

Reaction of perfluoro-3,5-bis-isopropylpyridazine (98) with dimethylamine readily gave 3,5-bis-heptafluoroisopropyl-6-dimethylamino-4-fluoropyridazine (204) where substitution was probably controlled by steric interaction of the bulky isopropyl groups

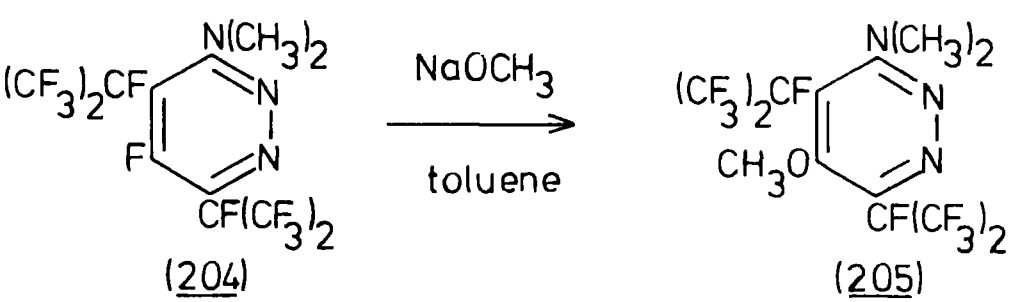


(98) (204)

No cyclisation was observed upon heating to 120°.

(ii) 6-DIMETHYLAMINO-4-METHOXY DERIVATIVE

Compound (204) was reacted with sodium methoxide in methanol to give 3,5-bis- heptafluoroisopropyl-6-dimethylamino-4-methoxypyridazine (205).

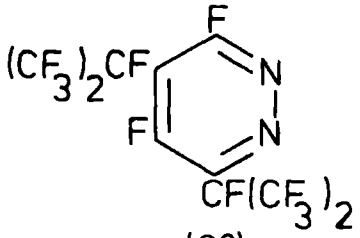


(204) (205)

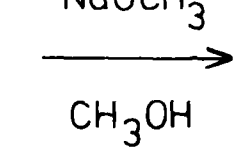
The compound was heated to 220° when it decomposed, and again no cyclisation was observed

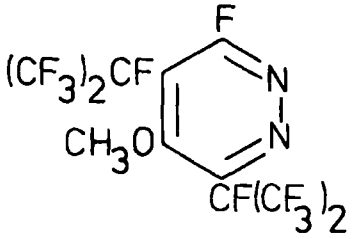
(iii) 4-METHOXY, 6-METHOXY AND 4,6-DIMETHOXY DERIVATIVES

When perfluoro-3,5-bis-isopropylpyridazine (98) was reacted with one equivalent of sodium methoxide in methanol, three products were isolated, in addition to starting material.



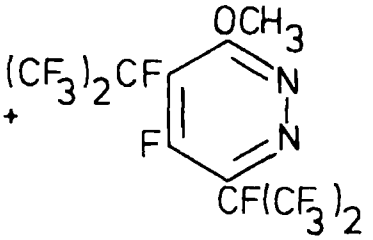
(98)





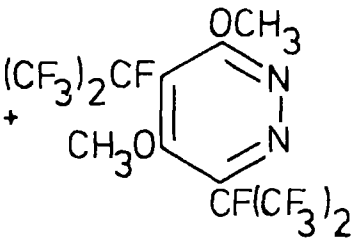
(206)

2



(207)

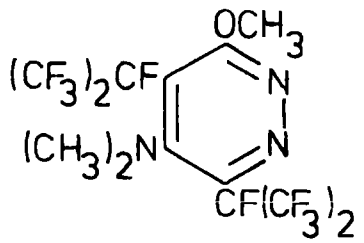
2



(208)

1

The dimethoxy derivative (208) was easily separated by preparative g.l.c. and was found to be stable at 280°. Separation of the mono-methoxy compounds, (206) and (207), could not be achieved by distillation or chromatography. Thus, a convenient synthetic route to 4-dimethylamino-6-methoxy derivative (209) was not found.



(209)

The conclusions of the substituent effects observed in these derivatives are given in the next section.

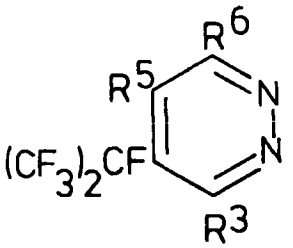
5.6. CONCLUSION

The result of preparing various perfluoroisopropylpyridazine derivatives demonstrated that the process of cyclisation was very specific, so much so that in only three derivatives was cyclisation observed Those derivatives which cyclised are indicated in SCHEME XIX.

Initially it was thought that steric interaction was dominant in the cyclisation of compound (183) However, the fact that the 3,5-bis-dimethylamino derivative (195) cyclised whereas the 4-dimethylamino derivative (201) was stable established that electronic effects were more dominant than steric effects.

Clearly, substituents which will enhance the SN1-type reaction will be those which are electron-donors. Dimethylamino and methoxy, well known to activate aromatic systems to electrophilic substitution, were both used. With the perfluoroiospropylpyridazine derivatives where there was only one dimethylamino group ((194), (202) and (204), SCHEME XIX), no cyclisation was observed. When there was more than one dimethylamino group present cyclisation was observed in three cases ((183), (195) and (197)) but not in the fourth((203)) In the pyridazines where only methoxy groups were

SCHEME XIX

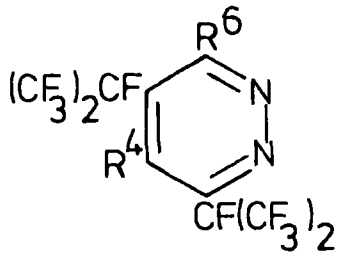


(194) $R^3 = R^6 = F$, $R^5 = N(CH_3)_2$

(195)* $R^3 = R^5 = N(CH_3)_2$, $R^6 = F$

(197)* $R^3 = R^5 = R^6 = N(CH_3)_2$

(200) $R^3 = R^6 = OCH_3$, $R^5 = N(CH_3)_2$



(204) $R^4 = F$, $R^6 = N(CH_3)_2$

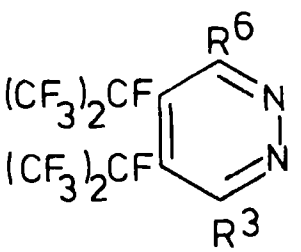
(183)* $R^4 = R^6 = N(CH_3)_2$

(205) $R^4 = OCH_3$, $R^6 = N(CH_3)_2$

(206) $R^4 = OCH_3$, $R^6 = F$

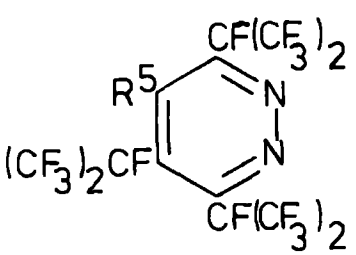
(207) $R^4 = F$, $R^6 = OCH_3$

(208) $R^4 = R^6 = OCH_3$



(202) $R^3 = N(CH_3)_2$, $R^6 = F$

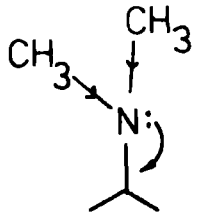
(203) $R^3 = R^6 = N(CH_3)_2$

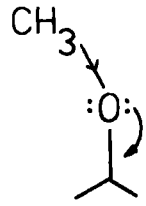


(201) $R^5 = N(CH_3)_2$

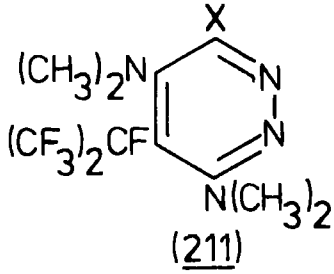
*DERIVATIVES WHICH CYCLISED

introduced (206), (207) and (208)), there was no evidence to suggest that there was any loss of fluoride ion Two derivatives were prepared where both dimethylamino and methoxy groups were present ((200) and (205)), surprisingly, neither of these compounds cyclised. This is probably a consequence of the fact that dimethylamino can donate electronic charge better than methoxy.

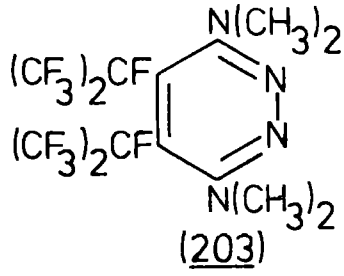




An important feature evident in the polydimethylamino derivatives (211) which cyclised, was the apparent necessity for two meta dimethylamino groups (derivative (203) with two para dimethylamino groups was stable).



(211)

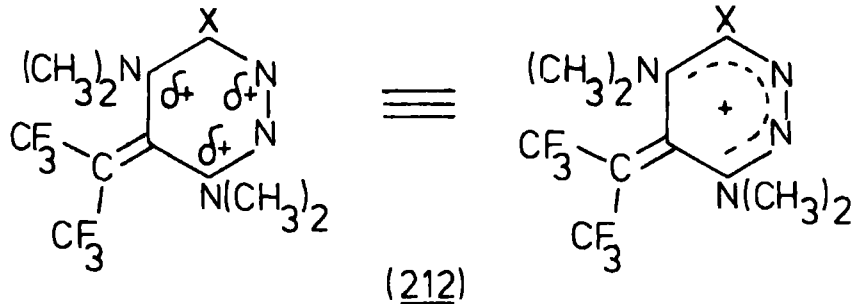


(203)

$X = F, CF(CF_3)_2, N(CH_3)_2$

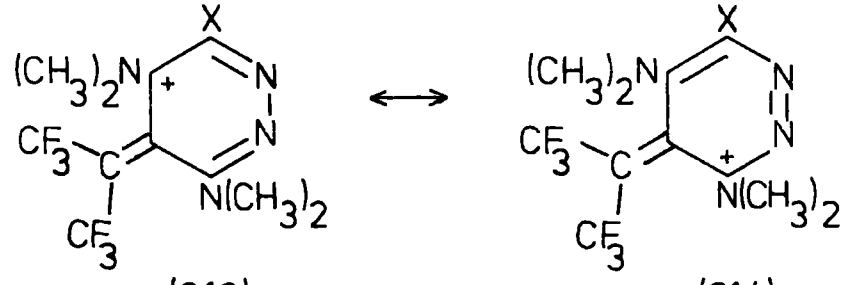
Moreover, that X can equal F or $N(CH_3)_2$ tends to suggest that the process of cyclisation is largely unaffected by the nature of X. This is because X is meta to the position losing fluoride ion and therefore cannot

contribute any charge stabilisation in the reactive intermediate. This is in contrast to the two nitrogen atoms, which are ortho to the reactive centre.



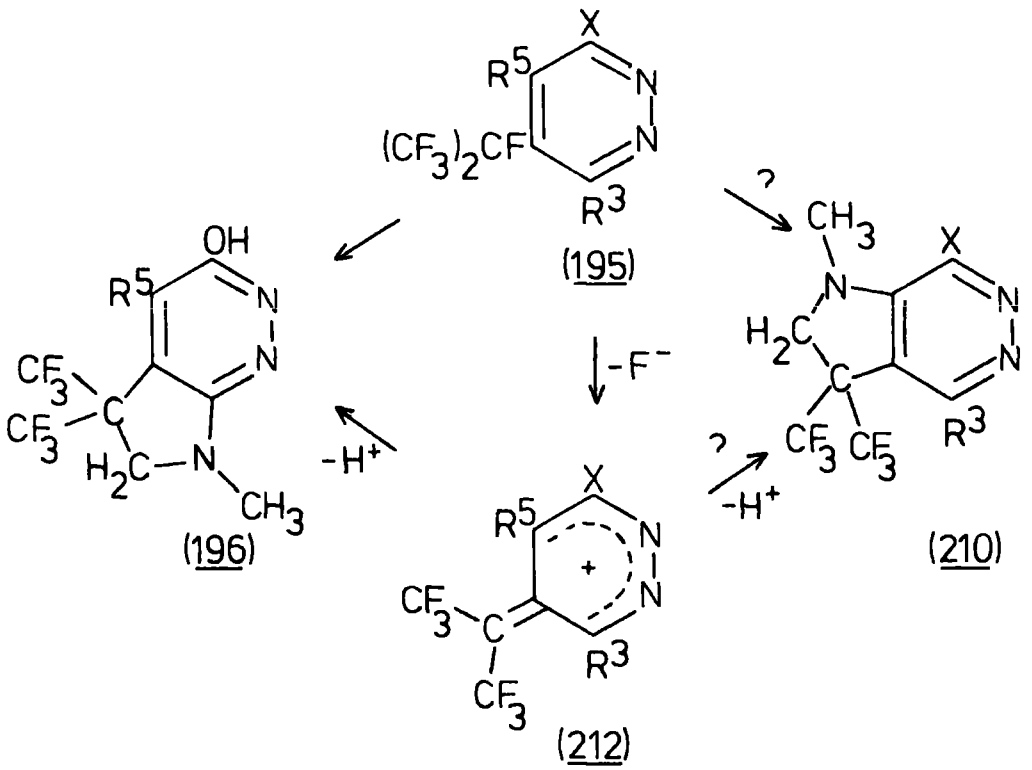
(212)

Structure (212) is, in fact, the resonance hybrid of two canonical forms (213)-(214).



(213) (214)

Compound (195) gave a bicyclic product which was identified as the structure (196) shown below. It is not obvious why compound (210), an alternative product which would be generated via the same intermediate (212), should not be formed. A consideration of the base strengths of R^3 and R^5 led to the prediction that R^5 would have a greater tendency to lose a proton than R^3. Whereas electronic factors dominated the first step (loss of fluoride ion), steric factors must influence the last step (loss

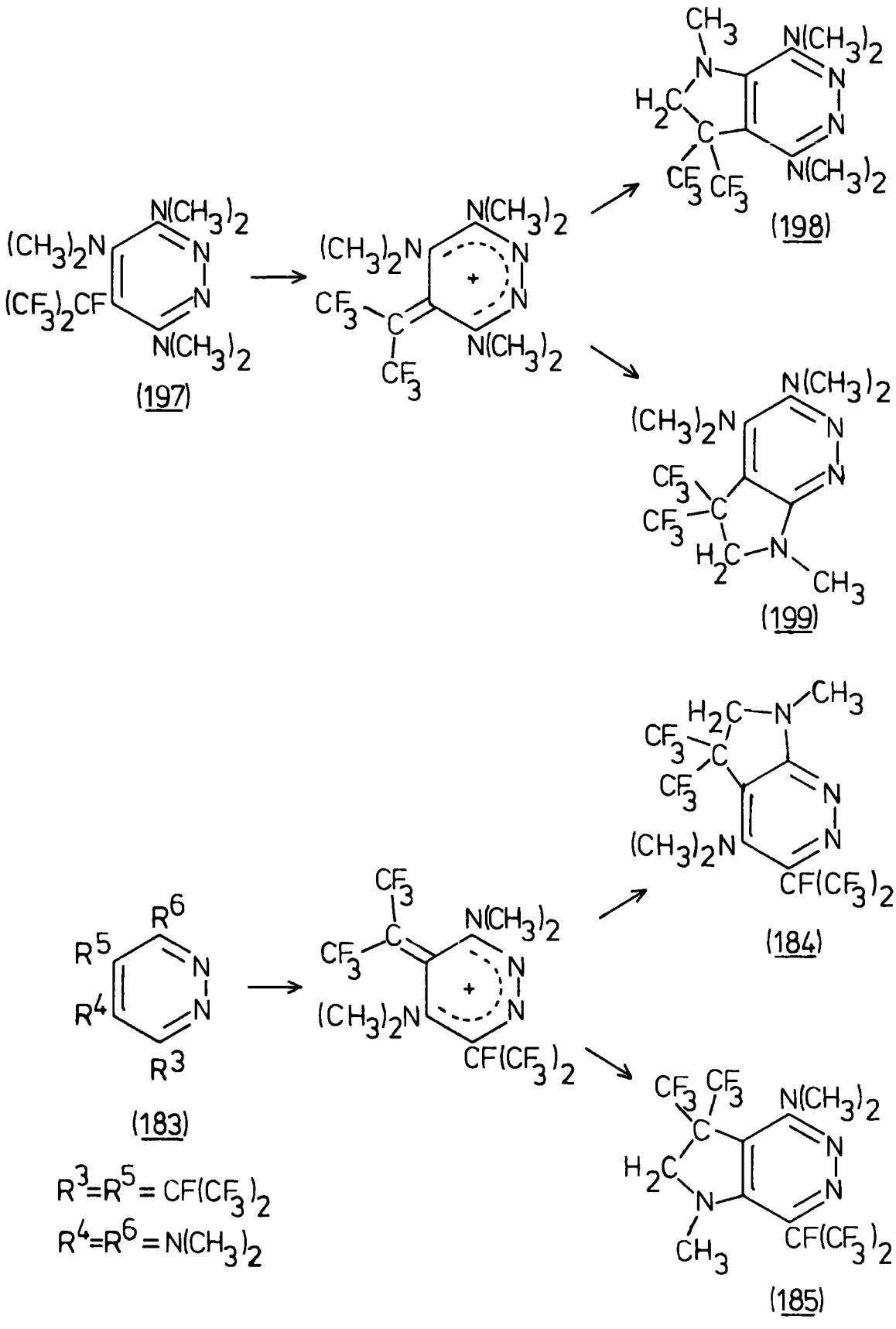


$R^3 = R^5 = N(CH_3)_2$; X = F or OH?

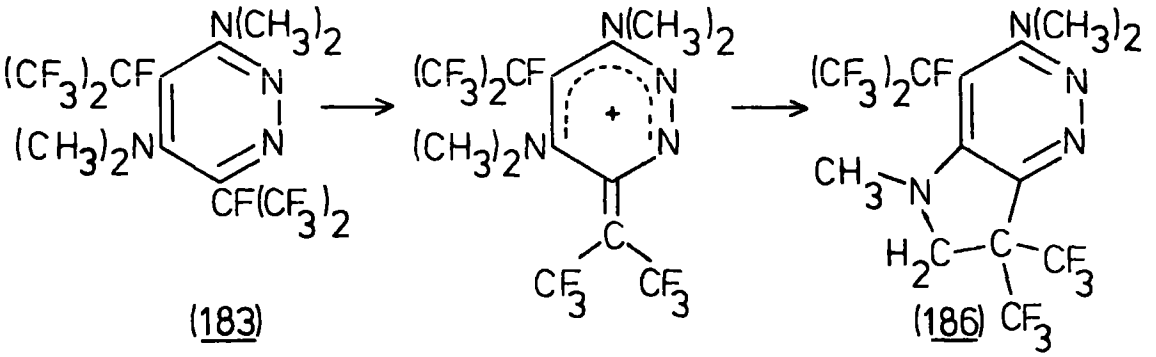
of hydrogen ion). R^3 is less configurationally restricted than R^5, in otherwords, R^3 can adopt a planar configuration necessary for cyclisation better than R^5. It is more probable that compound (196) was the preferred product and that compound (210) was formed as a minor product, though not detected.

With the tris-dimethylamino compound (197) only one product was detected when again two products were equally probable It is possible that configurational restriction favours product (199) and that a small amount of compound (198) was also produced, but not detected

In the perfluoro-3,5-di-isopropylpyridazine system, there are two positions where fluoride ion can be lost. If the fluoride ion was lost from R^5 (shown below), then there is precedent for predicting that compound (184) would be the preferred product (R^6 has more configurational freedom than R^4).


(197)
(198)
(199)
(183)
(184)
(185)
$R^3=R^5=CF(CF_3)_2$
$R^4=R^6=N(CH_3)_2$

However, as the n.m.r. data (TABLE IV) eliminated compound (184) as the reaction product, it would appear that compound (186) was the only reaction product, formed by loss of fluoride ion from R^3. Here the



(183)

(186)

reaction product would be formed by loss of a proton from the weaker base, R^4 (base strength $R^4 < R^6$). This is contrary to that which would be expected if one considered the cyclisation of compound (195) as an analogous case. Thus, it is not possible to conclude whether the reaction product obtained from the cyclisation of compound (183) was compound (185) or compound (186).

CHAPTER 6

EXPERIMENTAL

6.1. GENERAL

The reagents and instruments used for the second part of this thesis have already been described in Chapter 4. The Varian A56/60D spectrometer was operated at 60 M.c./s for the proton (^1H) nuclear magnetic resonance spectra.

6.2. EXPERIMENTAL FOR CHAPTER 6 - CYCLISATIONS OF DIMETHYLAMINO POLYFLUOROISOPROPYLPYRIDAZINES

A PREPARATION OF PERFLUOROISOPROPYLPYRIDAZINES

The syntheses described here were developed by previous workers at these laboratories

(i) PREPARATION OF PERFLUORO-4,5-BIS-ISOROPYLPYRIDAZINE (67)[110]

Perfluoro-4,5-bis-isopropylpyridazine was prepared on many occasions A typical experiment is given below.

A mixture of caesium fluoride (1.6g ,10.6m. moles) and sulpholane (50 ml.) was placed in a r b flask, fitted with a gas inlet to allow a continuous stream of dry nitrogen to purge through the apparatus. A variable volume reservoir was attached to the flask which was then evacuated. Hexafluoropropene (28.0g, 186 6m. moles) was introduced into the system and allowed to equilibriate to atmospheric pressure. Tetrafluoropyridazine (13 0g, 85 5m. moles) was injected through a serum cap into the mixture, which was then stirred at room temperature until all the gas was absorbed The product, perfluoro-4,5-bis-isopropylpyridazine (67), was obtained by vacuum transference from the reaction mixture and was recrystallised from hexane (26 0g, 67 5%) Identification was by comparison of its infra-red and ^{19}F n m r spectra with those of an authentic sample.

(ii) PREPARATION OF PERFLUORO-3,5-BIS-ISOPROPYLPYRIDAZINE (98)[110]

Perfluoro-4,5-bis-isopropylpyridazine (24.8g, 54.8m. moles), caesium fluoride (2 5g, 16 5m. moles) and sulpholane (20 ml.), were stirred vigorously for 18h at 135°. The volatile products (20.2g) were isolated by vacuum transference and shown by g l.c. (G.D.B.) to be a mixture of perfluoro-3,5- bis-isopropylpyridazine (86%), perfluoro-4-isopropylpyridazine (10%) and perfluoro-3,4,6-tris-isopropylpyridazine (4%). The main component, perfluoro-3,5-bis-isopropylpyridazine (98) was separated by fractional distillation (b.p 160-1°) and was identified by comparison of its infra-red and ^{19}F n.m r spectra with those of an authentic sample

(iii) PREPARATION OF PERFLUORO-4-ISOPROPYLPYRIDAZINE (177)[101]

A mixture of perfluoro-4,5-bis-isopropylpyridazine (14.9g, 32 9m. moles), tetrafluoropyridazine (5 9g, 38 8m moles), caesium fluoride (4 6g, 30.3m moles) and sulpholane (15 ml.) was stirred for 25h. at 120°. The volatile products (12 4g) were isolated by vacuum transference and shown by g.l.c (G D B) to be a mixture of perfluoro-4-isopropylpyridazine (69%), perfluoro-3,5-bis-isopropylpyridazine (24%) and perfluoro-3,4,6-tris-isopropylpyridazine (7%) The main component, perfluoro-4-isopropylpyridazine (177), was separated by preparative g.l.c. (Varian Aerograph, column 'A', 100°) and was identified by comparison of its infra-red and ^{19}F n.m r spectra with those of an authentic sample.

(iv) PREPARATION OF PERFLUORO-3,4,6-TRIS-ISOPROPYLPYRIDAZINE (182)

Perfluoro-3,4,6-tris-isopropylpyridazine (182) was always obtained as a minor product in preparations (ii) and (iii) Purification was effected by preparative g.l c (Varian Aerograph, column 'A', 100°)

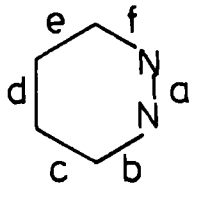
B DERIVATIVES OF PERFLUORO-3,5-BIS-ISOPROPYLPYRIDAZINE (98)

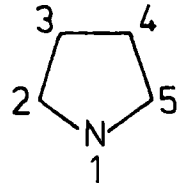
(i) REACTION OF PERFLUORO-3,5-BIS-ISOPROPYLPYRIDAZINE (98) WITH EXCESS DIMETHYLAMINE

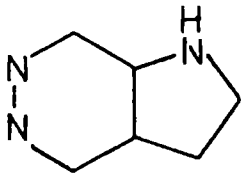
(a) Perfluoro-3,5-bis-isopropylpyridazine (5 68g, 12.6m moles), dimethylamine (10.0g, 222.2m moles) and dimethylformamide (50 ml.) were sealed in a carius tube at -196°. The reaction mixture, which was frequently shaken, was allowed to slowly warm up to room temperature. The mixture was filtered to give yellow crystals (4.13g, 65.5%) which were washed with cold dimethylformamide and dried under vacuum. These crystals were shown to 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine (183), m.p. 65-7°. (m/e = 502-recrystallisation or sublimation caused elimination of hydrogen fluoride). Infra-red spectrum No 10. ^{19}F n m.r spectrum No. 8 ^{1}H n.m.r spectrum No. 9. (n m r. also given in TABLE V)

Water (200 ml.) was added to the mother liquor, and the mixture was extracted with methylenedichloride (3 x 100 ml.) The organic phase was separated, dried ($MgSO_4$), and evaporated to give a colourless crystalline compound. (0.26g, 4 3%), m p 154-5° (m/e = 482). Infra-red spectrum No. 11. Ultra-violet spectrum No. 3 ^{19}F n m.r. spectrum No. 10. ^{1}H n m r spectrum No. 11. (n.m r also given in TABLE IV).

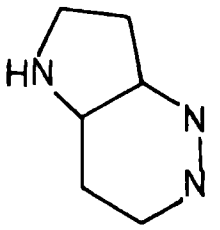
It was not possible to establish whether the latter compound was 3,3-bis-trifluoromethyl-2,3-dihydro-4-dimethylamino-7-heptafluoroisopropyl-1-methylpyrrolo-[2,3-d]-pyridazine (185) or 7,7-bis-trifluoromethyl-6,7-dihydro-3-dimethylamino-4-heptafluoroisopropyl-5-methylpyrrolo[2,3-c]-pyridazine (186)







1H-PYRROLO-[2,3-d]
-PYRIDAZINE



5H-PYRROLO-[2,3-c]
-PYRIDAZINE

(b) Perfluoro-3,5-bis-isopropylpyridazine (3.02g, 6 68m. moles), dimethylamine (2.5g, 55.5m mole) and dimethylformamide (100 ml.) were sealed in a carius tube at -196° and allowed to slowly warm to room temperature with occasional shaking. The tube was opened and the mixture added to water (100 ml.), which was then extracted with methylenedichloride (4 x 20 ml.). The organic layer was separated, dried ($MgSO_4$) and evaporated to give a purple residue This was recrystallised from cyclohexane to give yellow crystals (2 90g, 90 1%) which were identical (i.r , ^{19}F n m.r , ^{1}H n m.r) to the colourless crystalline compound obtained in (a), except for its colour

(ii) REACTION OF 4,6-BIS-DIMETHYLAMINO-3,5-BIS-HEPTAFLUOROISOPROPYL-PYRIDAZINE (183) WITH BORON TRIFLUORIDE ETHERATE

To a mixture of 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropyl-pyridazine (1.12g, 2 2m. moles) and dry diethyl ether (25 ml.) at -78°, was added boron trifluoride etherate (1 ml , 7.8m. moles) The stirred mixture was allowed to warm to room temperature where upon a purple crystalline precipitate was obtained. The mixture was filtered and the residue washed with dry diethyl ether The purple crystals (0 98g, 86 5%) obtained were

4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine tetrafluoroborate, m p 138-40°. (Found C, 29 9, H, 2 5, F, 56 5, N, 9.4%, M^+, 570. $C_{14}H_{12}BF_{17}N_4$ requires C, 29 5, H, 2 1, F, 56.7, N, 9 8%, M, 570) Infra-red spectrum No 12 ^{19}F n m r spectrum No. 12 ^{1}H n m r spectrum No. 13 (n.m r also given in TABLE VI)

(iii) PREPARATION OF 3,5-BIS-HEPTAFLUOROISOPROPYL-6-DIMETHYLAMINO-4-FLUOROPYRIDAZINE (204)

Perfluoro-3,5-bis-isopropylpyridazine (2.045g, 4.52m. mole) and toluene (5 ml) were placed in a 10 ml. r b. flask. This flask was connected by a 'vacuum transfer arm' to a trap (fitted with a 'rotaflo' tap) containing dimethylamine (0 415g, 9.22m mole) The system was partially evacuated (ca 30 cm^3Hg of residual nitrogen) and then the dimethylamine was allowed to react with the stirred pyridazine, maintaining a pressure below atmospheric When absorption of gas was complete, the mixture was filtered to remove dimethylamine hydrogen fluoride and the toluene was removed under reduced pressure. The remaining oil was molecularly distilled to give an orange liquid (1.82g, 84 4%) which was shown to be 3,5-bis-heptafluoroisopropyl-6-dimethylamino-4-fluoropyridazine (204). (Found C, 30 5, H, 1 0, F, 59.2, N, 8 8%, M^+, 477 $C_{12}H_6F_{15}N_3$ requires C, 30.2, H, 1 3, F, 59.7, N, 8 8%, M, 477). Infra-red spectrum No. 20 Ultra-violet spectrum No. 7 ^{19}F n m r spectrum No 30 ^{1}H n m r. spectrum No. 31

(iv) PREPARATION OF 3,5-BIS-HEPTAFLUOROISOPROPYL-6-DIMETHYLAMINO-4-METHOXYPYRIDAZINE (205)

To a stirred solution of 3,5-bis-heptafluoroisopropyl-6-dimethylamino-4-fluoropyridazine (0.511g, 1.07m. moles) in methanol (5 ml.) was added a solution of sodium (0 032g, 1.39m. moles) in methanol (5 ml.) The mixture was stirred at room temperature overnight, added to a large excess of water (300 ml) and then extracted with diethyl ether (4 x 25 ml.). The

organic phase was separated and dried ($MgSO_4$) Evaporation of the organic phase gave an orange oil, from which orange crystals (0.115g, 22.5%) of 3,5-bis-heptafluoroisopropyl-6-dimethylamino-4-methoxypyridazine (205) were obtained by sublimation, m.p. 75.5° Found C, 32 2, H, 1.8; F, 54.0, N, 8.9%, M^+, 489. $C_{13}H_9F_{14}N_3O$ requires C, 31.9, H, 1.8, F, 54.4, N, 8 6%, M, 489) Infra-red spectrum No. 21 Ultra-violet spectrum No. 8. ^{19}F n.m.r. spectrum No. 32 ^1H n.m.r spectrum No. 33.

(v) REACTION OF PERFLUORO-3,5-BIS-ISOPROPYLPYRIDAZINE (98) WITH SODIUM METHOXIDE

To a stirred solution of perfluoro-3,5-bis-isopropylpyridazine (2.01g, 4 45m. moles) in methanol (5 ml.) was slowly added a solution of sodium (0.1g, 4 39m moles) in methanol (5 ml.) over a period of ca 30 mins The mixture was stirred at room temperature overnight and then poured into a large excess of water (300 ml.). The mixture was extracted with methylenedichloride, which after drying ($MgSO_4$) and evaporating, gave a colourless liquid (1 76g). This was found to be a mixture of three compounds plus starting material. One compound was readily separated by preparative g l.c. (Varian Aerograph, column 'A', 150°) to give a white crystalline compound (O 35g, 16 5%), and was shown to be 3,5-bis-heptafluoroisopropyl-4,6-bis-methoxypyridazine (208), m.p. 61°. (Found C, 30.1, H, 1.1, F, 55 5, N, 6 3%, M^+, 476 $C_{12}H_6F_{14}N_2O_2$ requires C, 30 2, H, 1.2, F, 55 8, N, 5 9%, M, 476). Infra-red spectrum No. 23. Ultra-violet spectrum No. 9. ^{19}F n m r spectrum No. 36 ^1H n m.r. spectrum No 37.

The remaining two compounds were readily separated from the starting material but could not be separated from each other by preparative g.l.c , using columns with either polar or non-polar packing material The two compounds were 3,5-bis-heptafluoroisopropyl-6-fluoro-4-methoxypyridazine (206) and 3,5-bis-heptafluoroisopropyl-4-fluoro-6-methoxypyridazine (207)

(m/e = 464) (Analysis gave inconsistent results) Infra-red spectrum No. 22 ^{19}F n m r spectrum No 34 ^{1}H n m r. spectrum No. 35

C DERIVATIVES OF PERFLUORO-4-ISOPROPYLPYRIDAZINE (177)

(i) PREPARATION OF 3,6-DIFLUORO-5-DIMETHYLAMINO-4-HEPTAFLUOROISOPROPYLPYRIDAZINE (194)

A stirred mixture of perfluoro-4-isopropylpyridazine (2.088g, 6.91m. moles) and toluene (5 ml) was allowed to react with dimethylamine (0 60g, 13.3m. moles) under reduced pressure When gas absorption was complete, the mixture was filtered to remove dimethylamine hydrogen fluoride. The toluene was removed under reduced pressure and the product was molecularly distilled to give, on cooling, yellow crystals (1.66g, 73 2%) which were shown to be 3,6-difluoro-5-dimethylamino-4-heptafluoroisopropylpyridazine (194), m p 36-8°. (Found C, 32.8, H, 1.8, F, 52 6, N, 13.1%, M^+, 327. $C_9H_6F_9N_3$ requires C, 33 0, H, 1.8, F, 52.3, N, 12 8%, M, 327). Infra-red spectrum No. 13. Ultra-violet spectrum No 4 ^{19}F n m r spectrum No. 14 ^{1}H n m.r spectrum No. 15.

(ii) ATTEMPTED PREPARATIONS OF 3,5-BIS-DIMETHYLAMINO-6-FLUORO-4-HEPTAFLUOROISOPROPYLPYRIDAZINE (195) AND 4-HEPTAFLUOROISOPROPYL-3,5,6-TRIS-DIMETHYLAMINOPYRIDAZINE (197)

Several attempts were carried out to prepare these compounds Mixtures of mono-, bis- and tris-dimethylamino derivatives were always obtained, where the ratio of these products varied with the amounts of dimethylamine used. Techniques such as preparative t.l.c and molecular distillation failed to give the tris-dimethylamino derivative, but distillation in one experiment did give the crude bis-dimethylamino derivative. In another preparation where an aqueous extraction was employed two other pyridazine derivatives were isolated by preparative t.l.c.

(a) A stirred mixture of perfluoro-4-isopropylpyridazine (2 0g, 6.64m. moles) and toluene (5 ml) was allowed to react with dimethylamine (1.18g, 26.29m moles) under reduced pressure When gas absorption was complete, the dimethylamine hydrogen fluoride was filtered off. The toluene was removed under reduced pressure to give a mixture (1.52g, 64.8%) Molecular distillation gave a crude fraction of 3,5-bis-dimethylamino-6-fluoro-4-heptafluoroisopropylpyridazine (195) (m/e = 352) ^{19}F n m.r. spectrum No 16. ^{1}H n.m r spectrum No 17

(b) A large excess of dimethylamine (9.1g, 202.2m moles), perfluoro-4-isopropylpyridazine (4 59g, 15.18m. moles) and dimethylformamide (25 ml.) were sealed in a carius tube at -196^{o} The mixture was allowed to warm to room temperature with frequent shaking Water (200 ml.) was added to the reaction mixture which was then extracted with methylenedichloride. The organic phase was dried ($MgSO_4$) and evaporated to give a viscous mixture which was recrystallised from hexane. Part of this mixture (0.48g) was separated by preparative t l.c into its two components using a mixture of 2% $CH_3OH/CHCl_3$ as solvent. One compound (0.20g) was identified as 5,5-bis-trifluoromethyl-5,6-dihydro-4-dimethylamino-3-hydroxy-7-methylpyrrolo-[2,3-c]-pyridazine (196). (m/e = 332). Infra-red spectrum No. 14. ^{19}F n.m.r. spectrum No. 18 ^{1}H n m r.spectrum No. 19. (n.m.r also given in TABLE VII). It was not possible to establish whether the other compound (0.17g) was 4,7-bis-dimethylamino-3,3-bis-trifluoromethyl-2,3-dihydro-1-methylpyrrolo-[2,3-d]-pyridazine (198), or 3,4-bis-dimethylamino-5,5-bis-trifluoromethyl-5,6-dihydro-7-methylpyrrolo-[2,3-c]-pyridazine (199). (m/e = 357). Infra-red spectrum No. 15. ^{19}F n.m.r spectrum No. 20. ^{1}H n.m.r spectrum No. 21. (n.m.r. also given in TABLE VIII)

(iii) PREPARATION OF 3,6-DIMETHOXY-5-DIMETHYLAMINO-4-HEPTAFLUOROISOPROPYLPYRIDAZINE (200)

To a stirred solution of 3,6-difluoro-5-dimethylamino-4-heptafluoroisopropylpyridazine (0 75g, 2.29m. moles) in methanol (10 ml) was added a solution of sodium (0.11g, 4.74m. moles) in methanol (10 ml) over a period of 15 mins. at room temperature. The mixture was stirred for 24h., added to a large excess of water (300 ml), extracted with methylenedichloride (4 x 25 ml.) and dried ($MgSO_4$) The solvent was removed under reduced pressure and the product, an orange oil (0.71g, 87 9%) was obtained by distillation. This oil was shown to be 3,6-dimethoxy-5-dimethylamino-4-heptafluoroisopropylpyridazine (200) (m/e = 351) (Analysis gave inconsistent results) Infra-red spectrum No. 16 ^{19}F n m r. spectrum No. 22. ^{1}H n.m r. spectrum No 23.

D DERIVATIVE OF PERFLUORO-3,5,6-TRIS-ISOPROPYLPYRIDAZINE (182)

(i) PREPARATION OF 5-DIMETHYLAMINO-3,4,6-TRIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (201)

A stirred mixture of perfluoro-3,4,6-tris-isopropylpyridazine (1 92g, 3.19m. moles) and toluene (5 ml.) was allowed to react with dimethylamine (0 91g, 20 31m. moles) under reduced pressure at 55°. When reaction was complete, dimethylamine hydrogen fluoride was removed by hot filtration with hexane Pale yellow crystals (1.33g, 66 7%) were obtained on cooling and were shown to be 5-dimethylamino-3,4,6-tris-heptafluoroisopropylpyridazine (201) m p. 126-7° (Found C, 28 5, H, 0.9, F, 63 3, N, 7 1%, M^+, 627 $C_{15}H_6F_{21}N_3$ requires C, 28.7, H, 0 9, F, 63.6, N, 6 7%, M, 627) Infra-red spectrum No 17 Ultra-violet spectrum No. 5 ^{19}F n.m r spectrum No 24 ^{1}H n.m.r spectrum No. 25.

E DERIVATIVES OF PERFLUORO-4,5-BIS-ISOPROPYLPYRIDAZINE (67)

(i) PREPARATION OF 3-DIMETHYLAMINO-6-FLUORO-4,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (202)

A stirred mixture of perfluoro-4,5-bis-isopropylpyridazine (2.0g, 4.43m. moles) and toluene (15 ml.) was allowed to react with dimethylamine (0.43g, 9.95m. moles) under reduced pressure When adsorption of gas was complete, the mixture was filtered to remove dimethylamine hydrogen fluoride and the toluene was removed under reduced pressure. However, the last traces of starting material, perfluoro-4,5-bis-isopropylpyridazine, could not be separated from 3-dimethylamino-6-fluoro-4,5-bis-heptafluoroisopropyl-pyridazine (202), an orange oil, even by preparative g.l c (m/e = 477) Infra-red spectrum No. 18. ^{19}F n m r spectrum No 26. ^{1}H n m r spectrum No. 27.

(ii) PREPARATION OF 3,6-BIS-DIMETHYLAMINO-4,5-BIS-HEPTAFLUOROISOPROPYL-PYRIDAZINE (203)

Perfluoro-4,5-bis-isopropylpyridazine (3.89g, 8 6m. moles), dimethylamine (4 1g, 92.2m. moles) and hexane (20 ml) were sealed in a carius tube at -196°. The reaction mixture, which was frequently shaken, was allowed to warm up to room temperature and then filtered to remove dimethylamine hydrogen fluoride. Evaporation of the hexane and molecular distillation of the residue gave orange crystals (3.40g, 79.0%) of 3,6-bis-dimethylamino-4,5-bis-heptafluoroisopropylpyridazine (203), m.p 41-3°. (Found C, 33.6, H, 2.6, F, 53.4, N, 10.8%, M^+, 502. $C_{14}H_{12}F_{11}N_4$ requires C, 33 5, H, 2 4, F, 52.9, N, 11.2%, M, 502). Infra-red spectrum No 19. Ultra-violet spectrum No. 6. ^{19}F n.m.r. spectrum No. 28 ^{1}H n.m r spectrum No. 29.

F. N.M.R. EXPERIMENTS - THE COLOUR CHANGES OBSERVED IN THE CYCLISATION OF 4,6-BIS-DIMETHYLAMINO-3,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (183)

(i) On dissolving 4,6-bis-dimethylamino-3,5-bis-heptafluoroisopropyl-pyridazine (183) (~ 0.2g) in CD_3COCD_3 (or $CDCl_3$) in an n.m.r tube, the spectra were as recorded in TABLE V. After two days, the original yellow solution changed to give a vivid purple coloured solution, the n.m.r spectra recorded were unchanged. After five days, the purple solution was observed to be a mixture of compound (183) and the bicyclic product (TABLE IV), in the ratio ~ 2 1. The n.m.r. spectra recorded after a total of fourteen days showed that only the bicyclic product was present in a colourless solution.

(ii) After two days of storing a sample of compound (183) under a normal atmosphere, the crystals changed from yellow to purple The n.m r spectra obtained were identical to those recorded for the original yellow compound After two weeks, only the bicyclic product was present in a colourless solution ($CDCl_3$).

(iii) An n.m.r. solution (CD_3COCD_3) of the sparingly soluble tetra-fluoroborate salt of compound (183) was recorded (TABLE VI) The purple solution was observed to lose its colour after several days to give a colourless solution, again only the bicyclic product was present in solution

(iv) The tetrafluoroborate salt of compound (183) (0 3g) was added to aqueous acetone (10 ml , 10% water) and the mixture was gently refluxed Within minutes the solution became colourless The solvents were removed under reduced pressure and the oily residue was dissolved in $CDCl_3$ The n m r spectra were identical to those recorded for the bicyclic product (TABLE IV)

APPENDICES

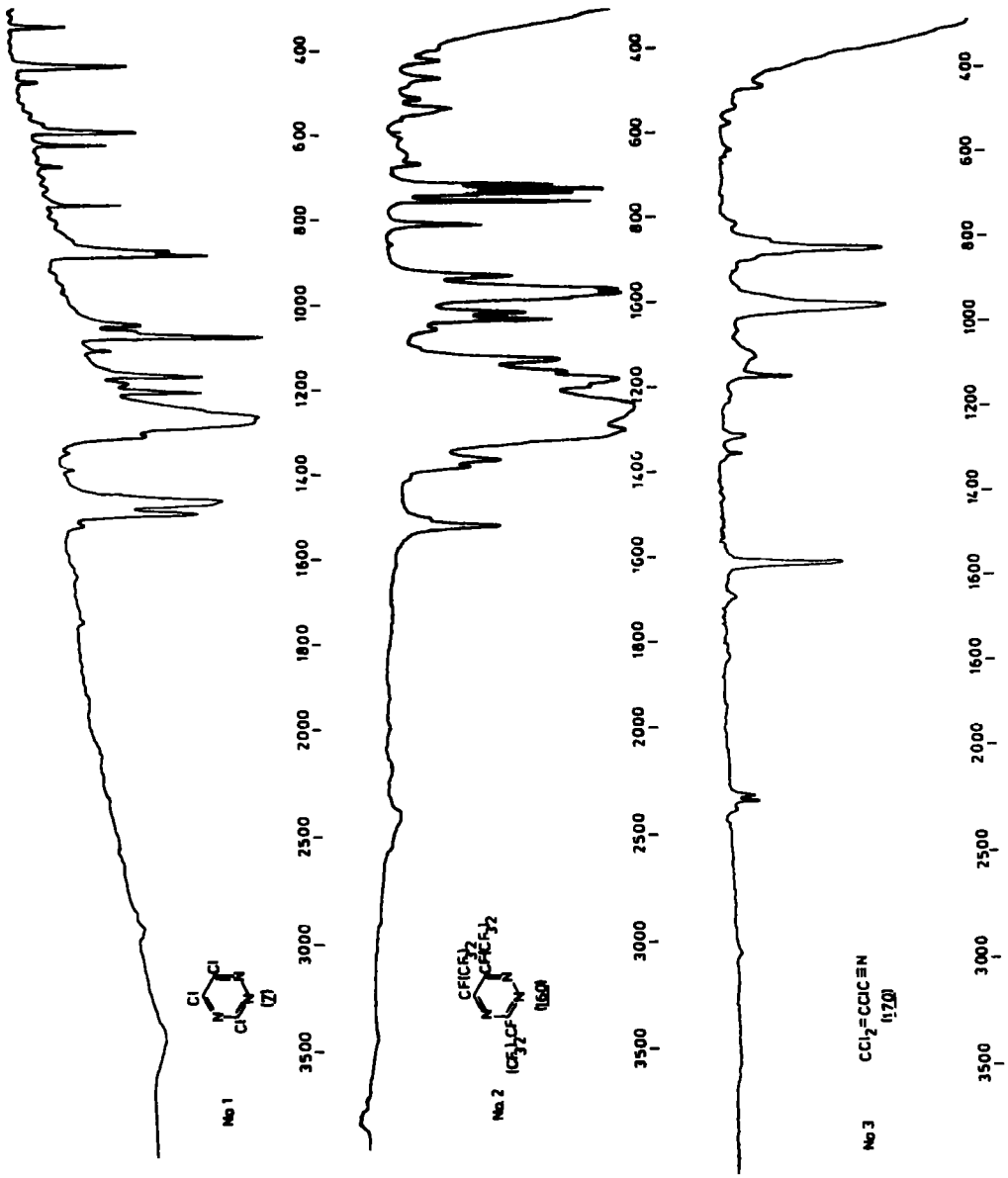
APPENDIX 1

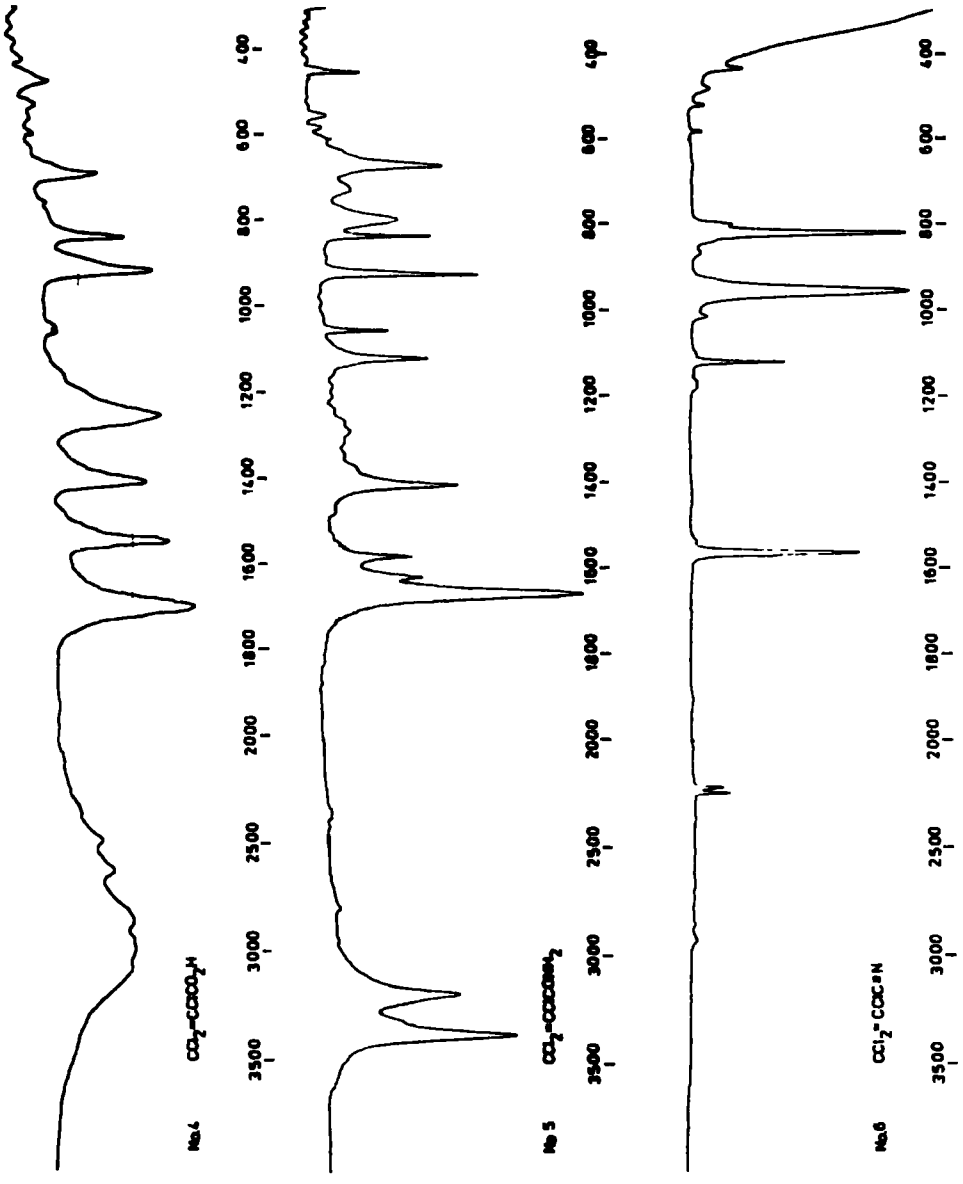
INFRA-RED SPECTRA

SPECTRUM No.	COMPOUND	STATE
1	3,5,6-Trichloro-1,2,4-triazine (7)	KBr Disc
2	Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine	Contact Film
3	Trichloroacrylonitrile (170)	Contact Film
4	Trichloroacrylic acid	KBr Disc
5	Trichloroacrylic acid amide	KBr Disc
6	Trichloroacrylonitrile	Contact Film
7	Perfluoroisobutyryl nitrile (175)	Gas Cell
8	Perfluoro-2,5-dimethylhex-3-yne (176)	Contact Film
9	Bis-heptafluoroisopropyl-mono-hydroxy-1,2,4-triazine (178)	KBr Disc
10	4,6-Bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine (183)	KBr Disc
11	3,3-Bis-trifluoromethyl-2,3-dihydro-4-dimethylamino-7-heptafluoroisopropyl-1-methylpyrrolo-[2,3-d]-pyridazine (185) or 5,5-Bis-trifluoromethyl-5,6-dihydro-3-dimethylamino-4-heptafluoroisopropyl-7-methylpyrrolo-[2,3-c]-pyridazine (186)	KBr Disc
12	4,6-Bis-dimethylamino-3,5-bis-heptafluoroisopropylpyridazine tetrafluoroborate (192) or (193)	KBr Disc

3	3,6-Difluoro-5-dimethylamino-4-heptafluoroisopropylpyridazine (194)	Contact Film
14	5,5-Bis-trifluoromethyl-5,6-dihydro 4-dimethylamino-3-hydroxy-7-methylpyrrolo-[2,3-c]-pyridazine (196)	KBr Disc
15	4,7-Bis-dimethylamino-3,3-bis-trifluoromethyl-2,3-dihydro-1-methylpyrrolo-[2,3-d]-pyridazine (198) or 3,4-Bis-dimethylamino-5,5-bis-trifluoromethyl-5,6-dihydro-7-methylpyrrolo-[2,3-c]-pyridazine (199)	KBr Disc
16	5-Dimethylamino-3,6-dimethoxy-4-heptafluoroisopropylpyridazine (200)	Contact Film
17	5-Dimethylamino-3,4,6-tris-heptafluoroisopropylpyridazine (201)	KBr Disc
18	3-Dimethylamino-6-fluoro-4,5-bis-heptafluoroisopropylpyridazine (202)	Contact Film
19	3,6-Bis-dimethylamino-4,5-bis-heptafluoroisopropylpyridazine (203)	KBr Disc
20	3,5-Bis-heptafluoroisopropyl-6-dimethylamino-4-fluoropyridazine (204)	Contact Film
21	3,5-Bis-heptafluoroisopropyl-6-dimethylamino-4-methoxypyridazine (205)	KBr Disc
22	Mixture of 3,5-bis-heptafluoroisopropyl-6-fluoro-4-methoxypyridazine (206) and 3,5-Bis-heptafluoroisopropyl-4-fluoro-6-methoxypyridazine (207)	Contact Film

23	3,5-Bis-heptafluoroisopropyl-4,6-dimethoxypyridazine (208)	KBr Disc


No 1
(7)
No 2
(160)
No 3
$CCl_2=CClC\equiv N$
(170)
400
600
800
1000
1200
1400
1600
1800
2000
2500
3000
3500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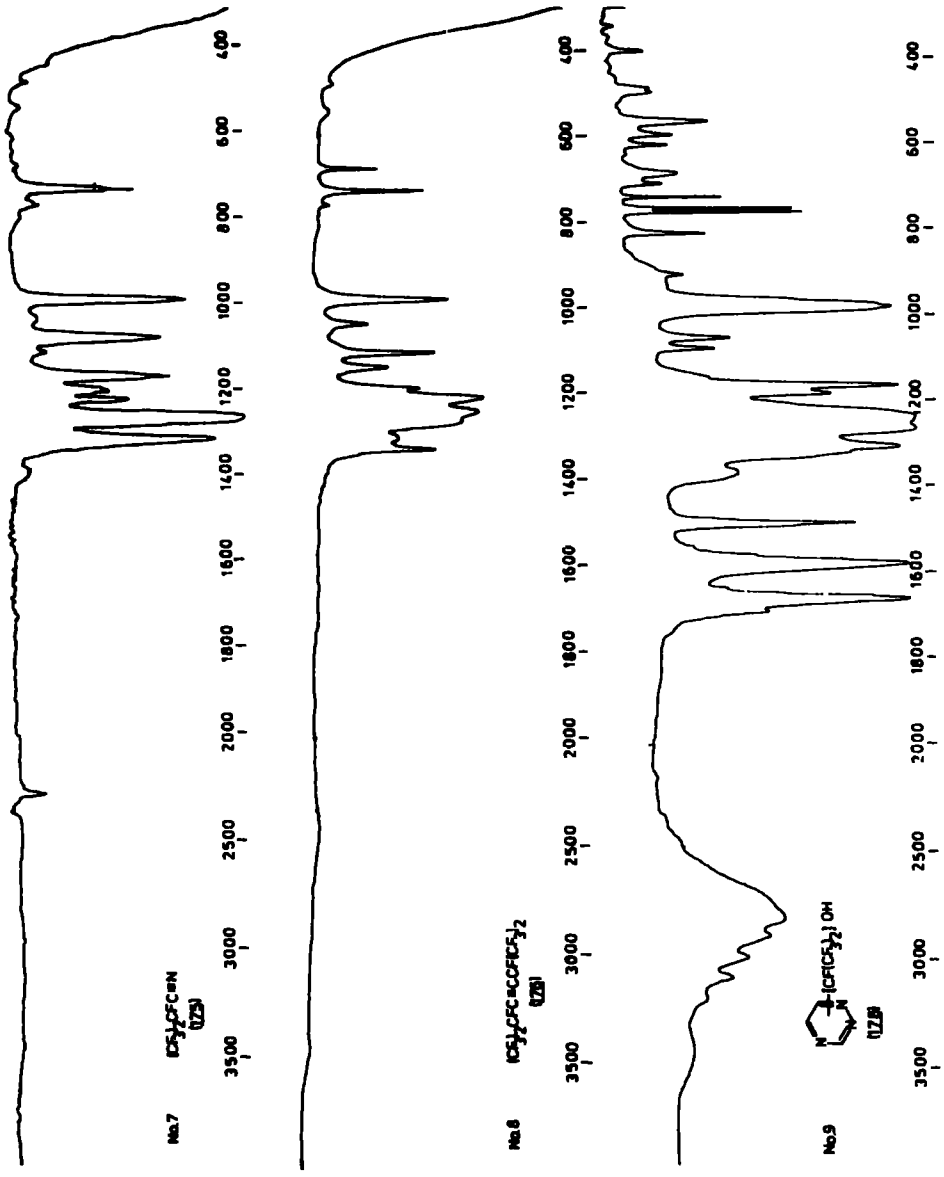
No.6
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400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No.8
No.9
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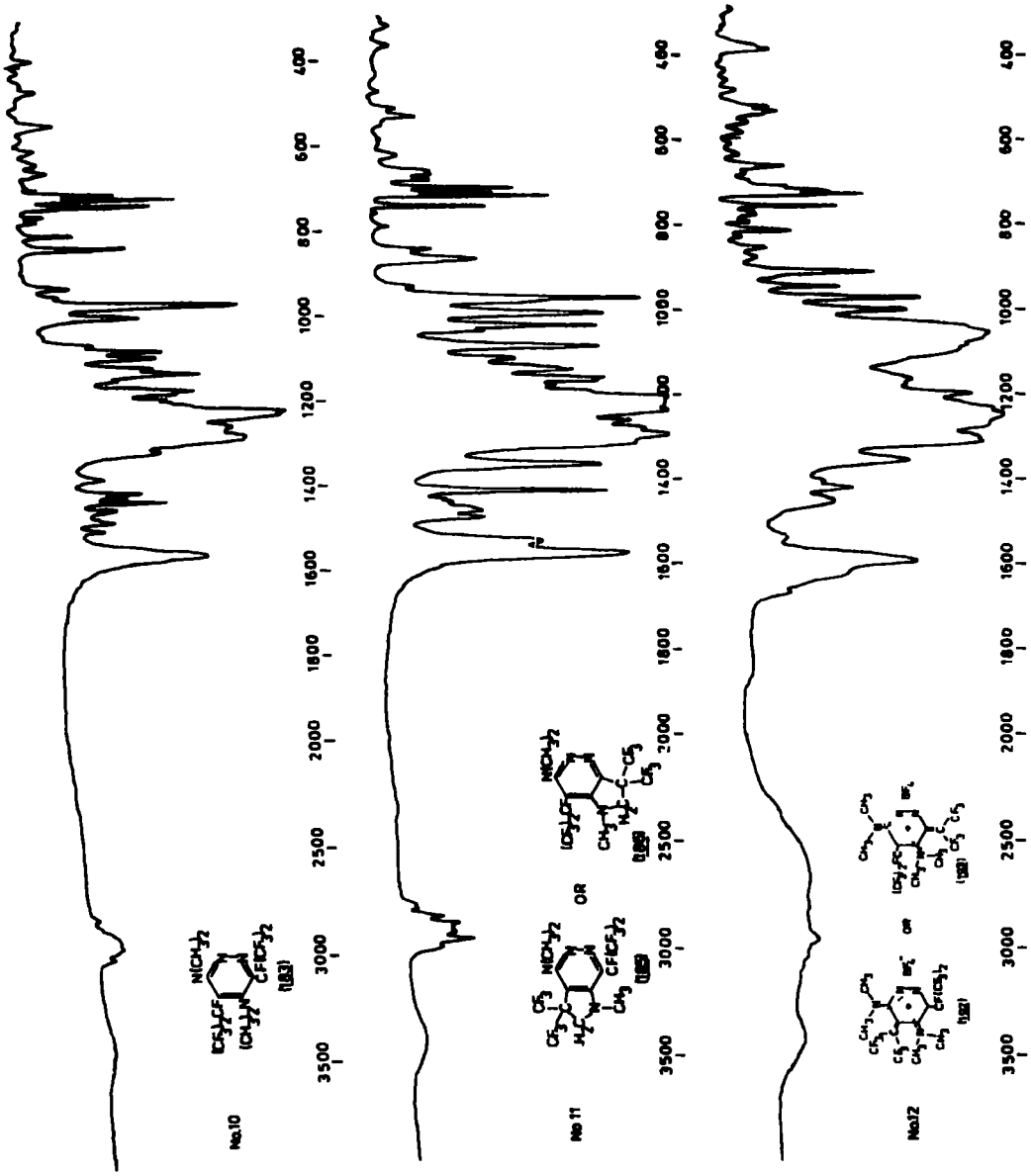
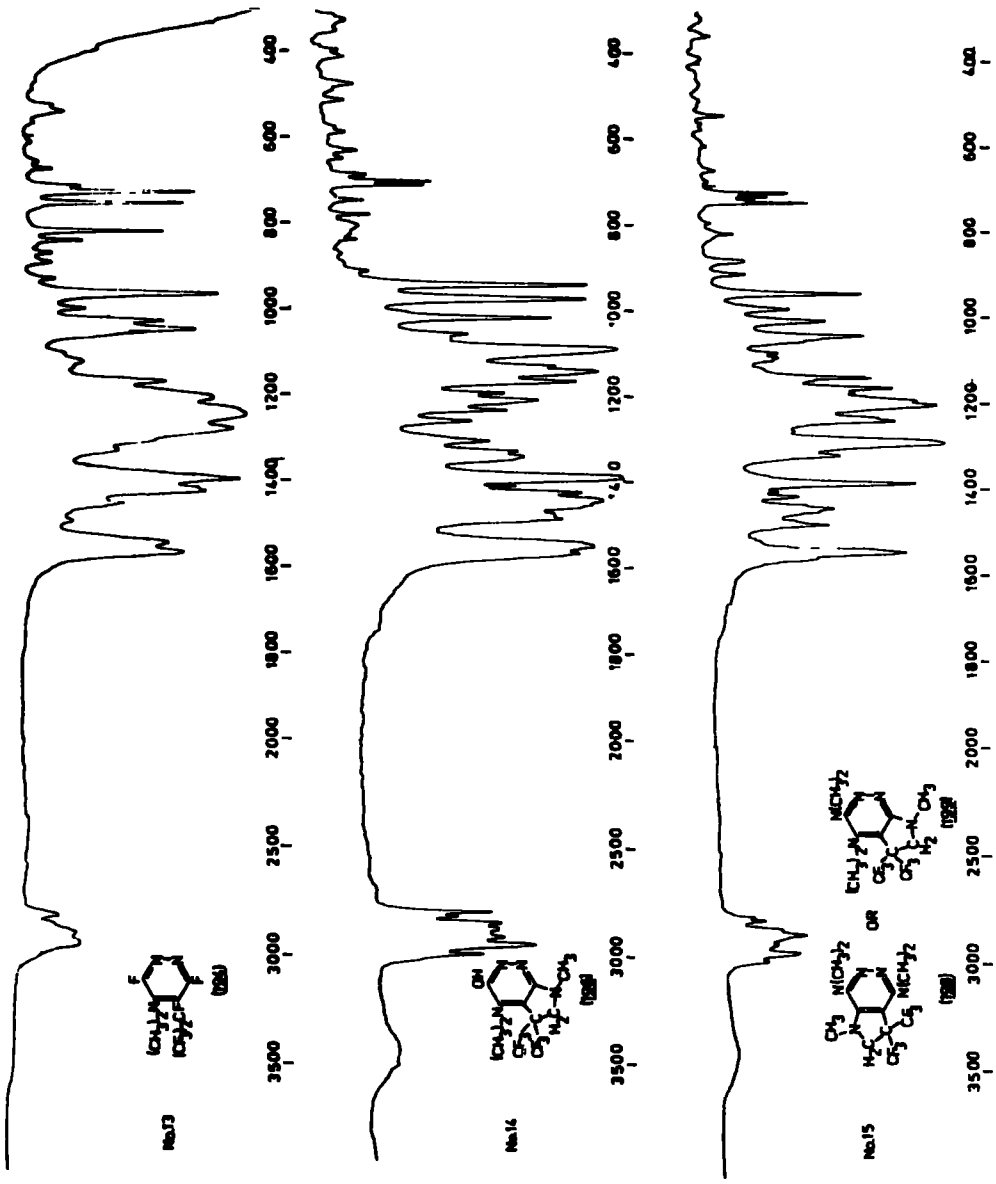
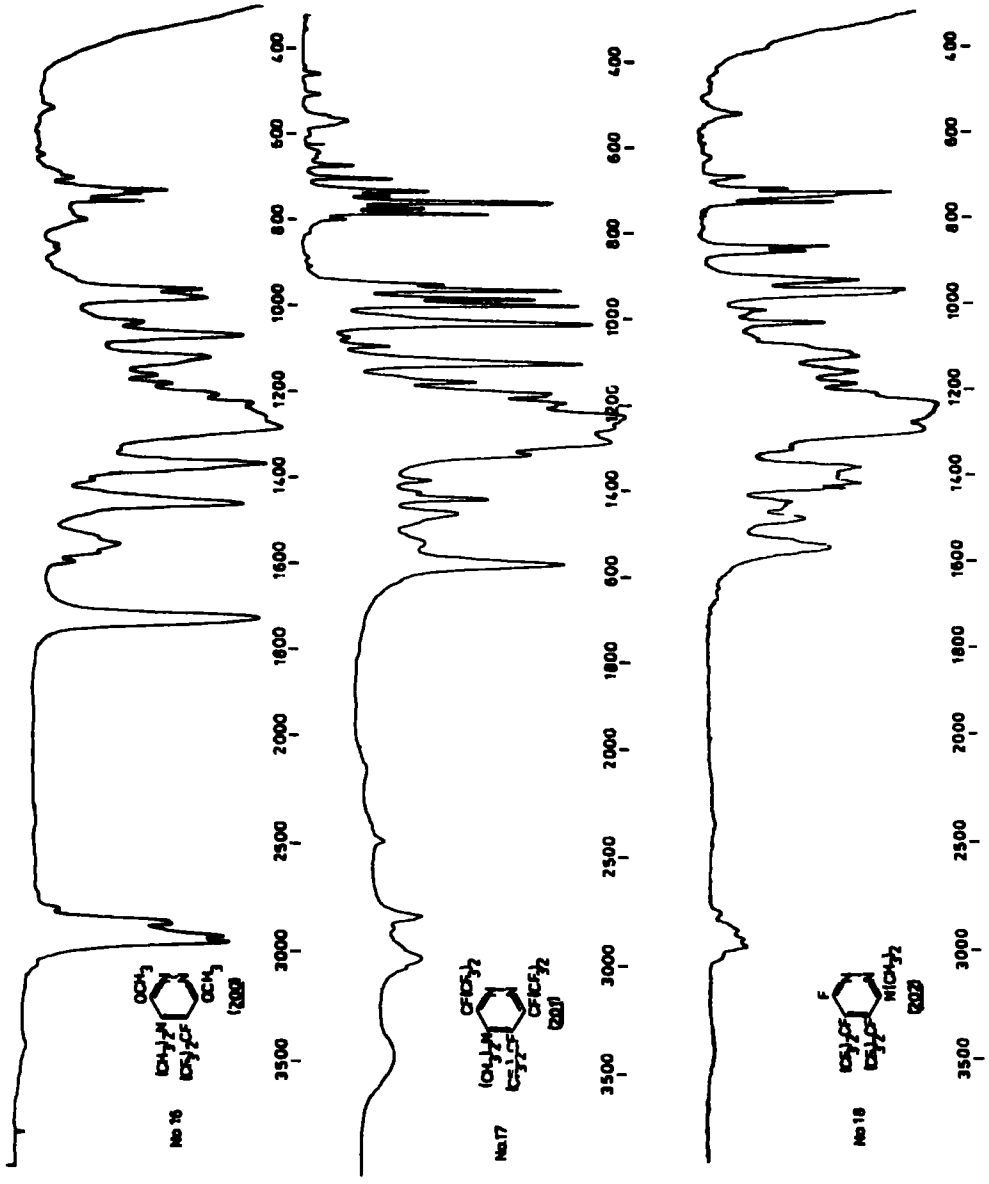
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400


4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
No.10
No.11
OR
No.12
OR


No.13
No.14
No.15
OR
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400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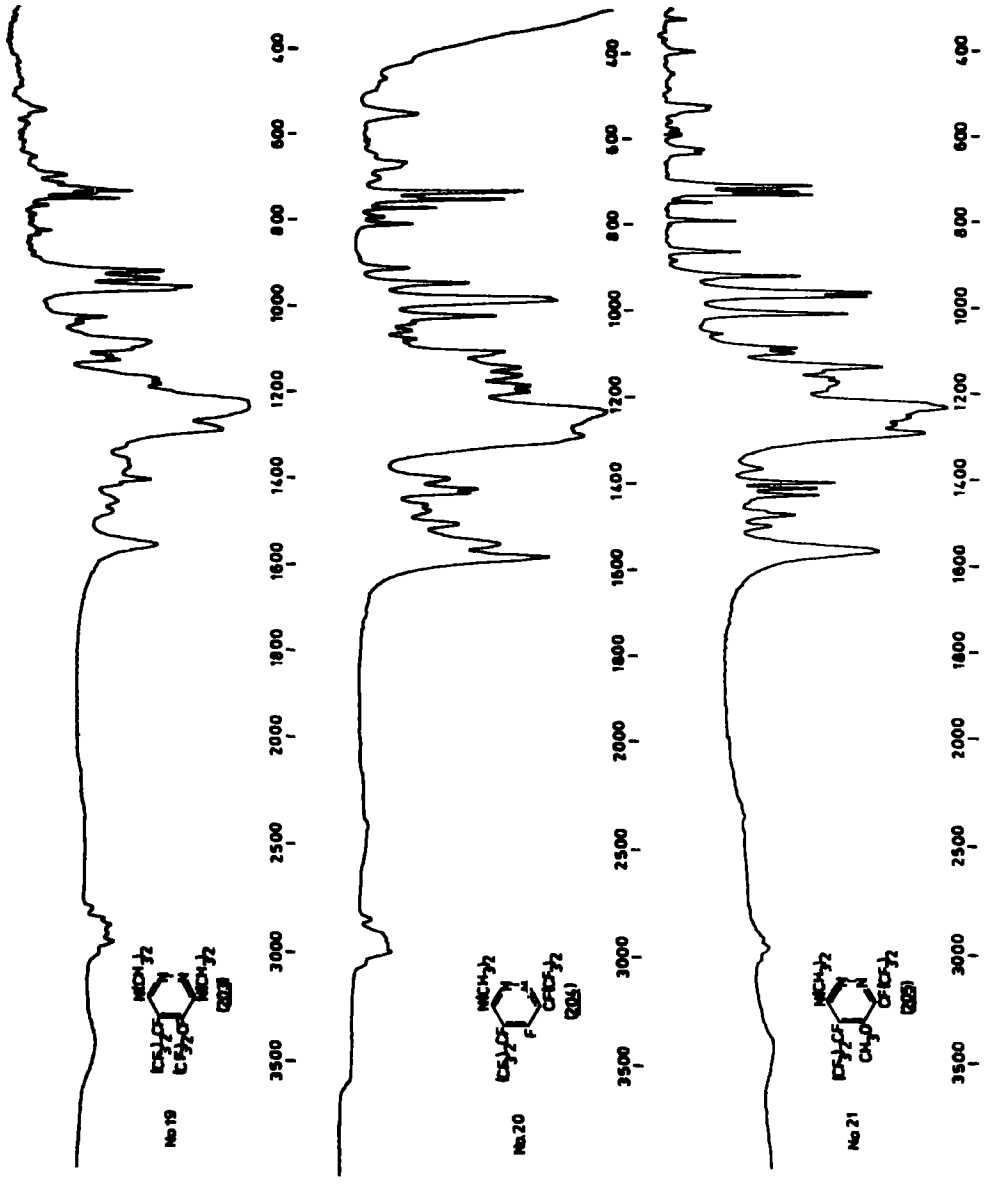
No 17
No 18
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400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3500
3000
2500
2000
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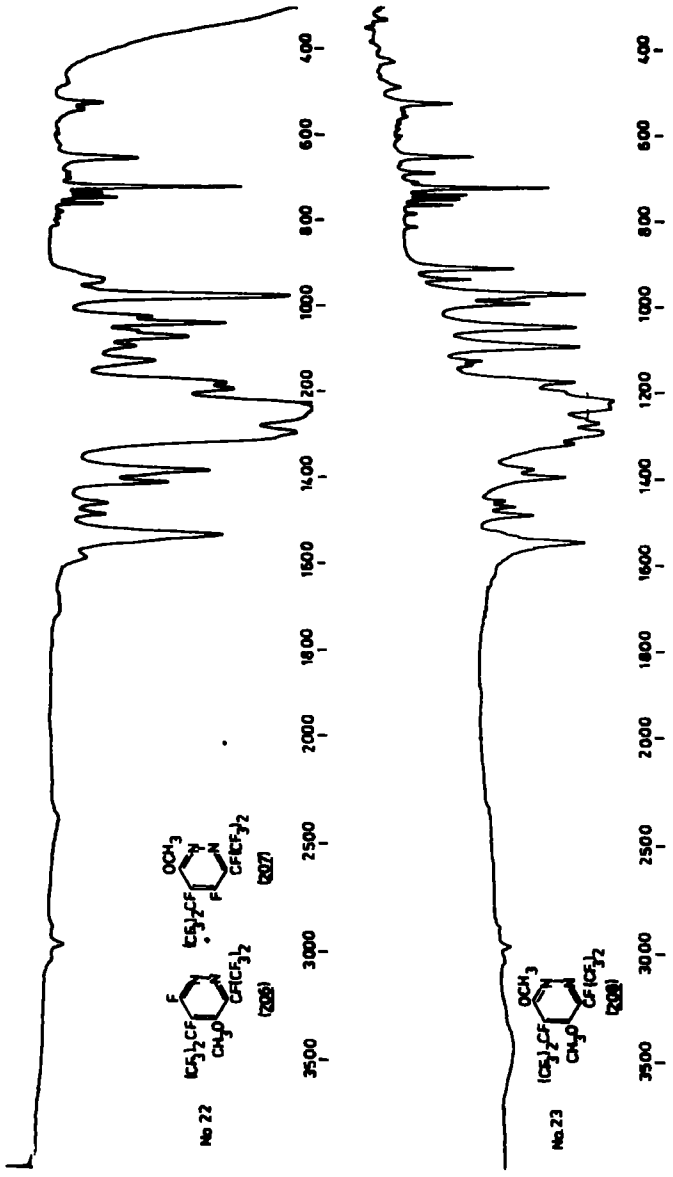
1600
1400
1200
1000
800
600
400
No.19
No.20
No.21

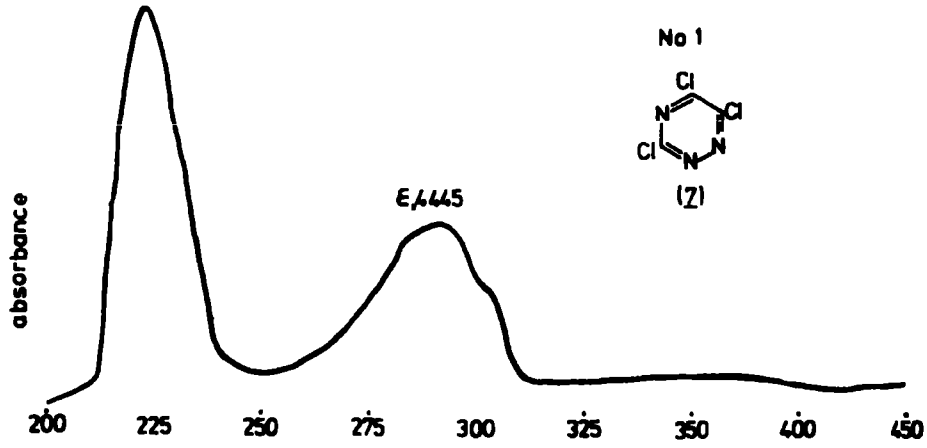

No.22
No.23
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400

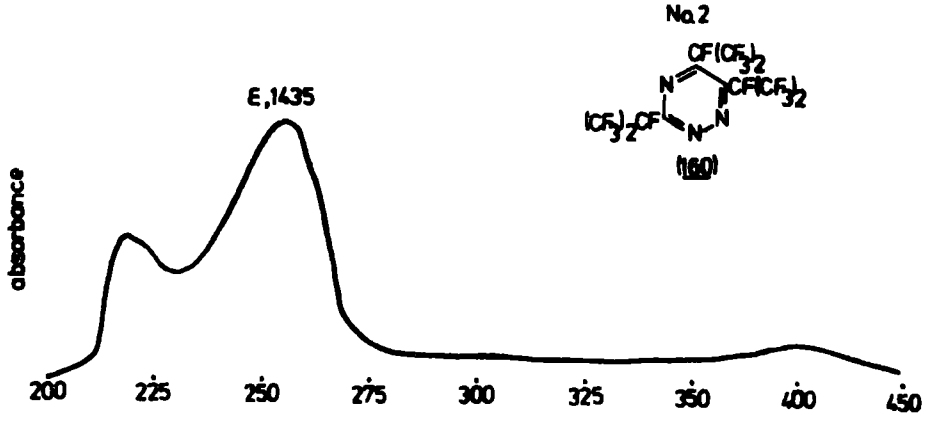
APPENDIX 2

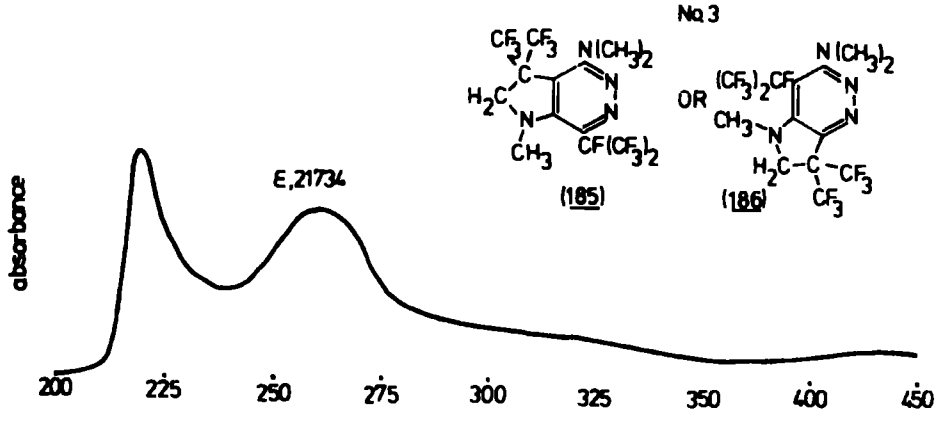
ULTRA-VIOLET SPECTRA

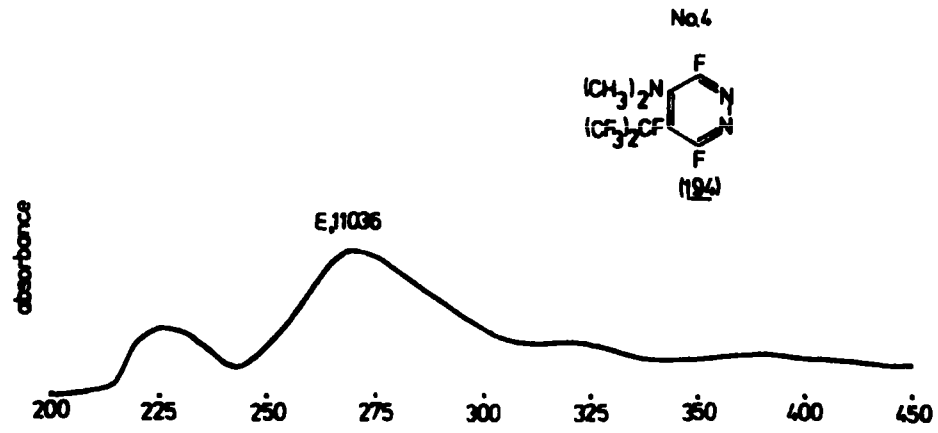
SPECTRUM No.	COMPOUND
1	3,5,6-Trichloro-1,2,4-triazine (7)
2	Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (160)
3	3,3-Bis-trifluoromethyl-2,3-dihydro-4-dimethylamino-7-heptafluoroisopropyl-1-methylpyrrolo-[2,3-d]-pyridazine (185) or 5,5-Bis-trifluoromethyl-5,6-dihydro-3-dimethylamino-4-heptafluoroisopropyl-7-methylpyrrolo-[2,3-c]-pyridazine (186)
4	3,6-Difluoro-5-dimethylamino-4-heptafluoroisopropyl-pyridazine (194)
5	5-Dimethylamino-3,4,6-tris-heptafluoroisopropylpyridazine (201)
6	3,6-Bis-dimethylamino-4,5-bis-heptafluoroisopropyl-pyridazine (203)
7	3,5-Bis-heptafluoroisopropyl-6-dimethylamino-4-fluoropyridazine (204)
8	3,5-Bis-heptafluoroisopropyl-6-dimethylamino-4-methoxypyridazine (205)
9	3,5-Bis-heptafluoroisopropyl-4,6-dimethoxypyridazine (208)

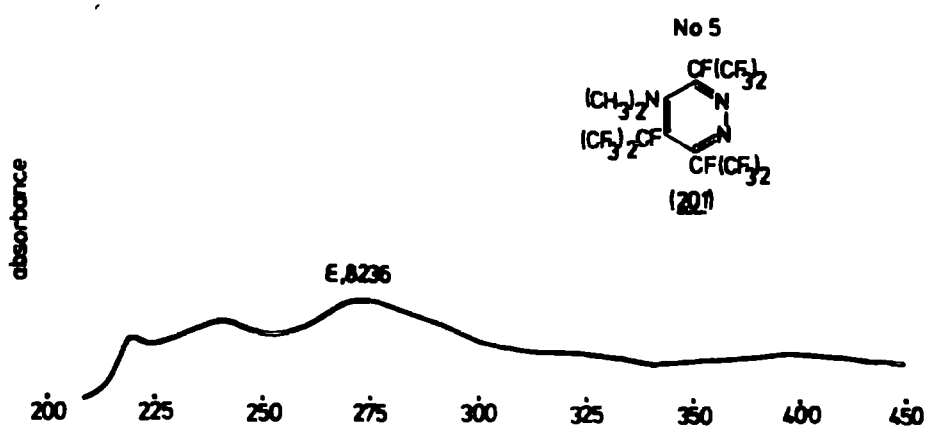
All spectra were recorded in cyclohexane (Spectrosol grade)

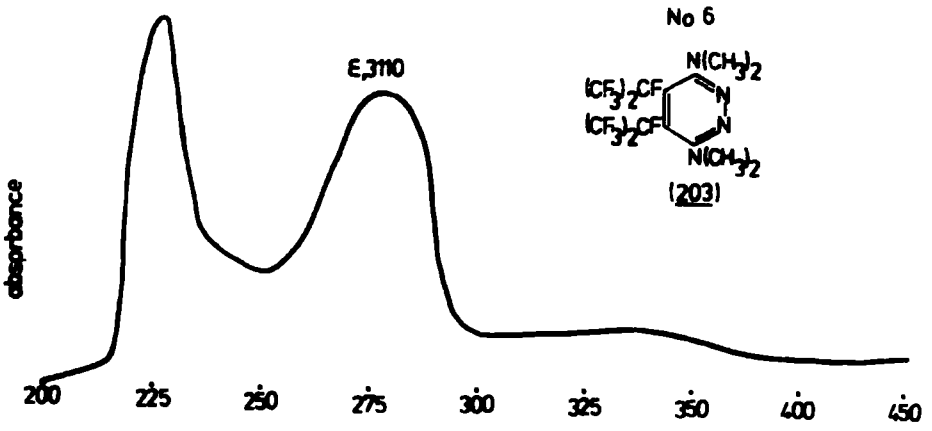

No 1
Cl
N
Cl
Cl
N
N
(7)
E,4445
absorbance
200
225
250
275
300
325
350
400
450


No 2
CF(CF3)2
N
CF(CF3)2
(CF3)2CF
N
N
(160)
E,1435
absorbance
200
225
250
275
300
325
350
400
450

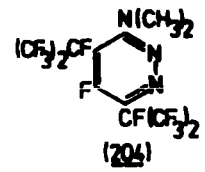

No 3
CF3 CF3
N(CH3)2
C
N
H2C
N
N
CH3
CF(CF3)2
(185)
OR
N(CH3)2
(CF3)2CF
N
CH3
N
N
H2C
C
CF3
CF3
(186)
E,21734
absorbance
200
225
250
275
300
325
350
400
450


No.4
F
$(CH_3)_2N$
N
N
$(CF_3)_2CF$
F
(194)
absorbance
E,11036
200
225
250
275
300
325
350
400
450


No 5
$CF(CF_3)_2$
$(CH_3)_2N$
N
N
$(CF_3)_2CF$
$CF(CF_3)_2$
(201)
absorbance
E,8236
200
225
250
275
300
325
350
400
450


No 6
$N(CH_3)_2$
$(CF_3)_2CF$
N
N
$(CF_3)_2CF$
$N(CH_3)_2$
(203)
absorbance
E,3110
200
225
250
275
300
325
350
400
450

No 7



(204)

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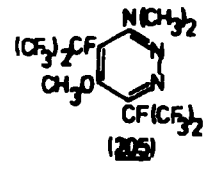
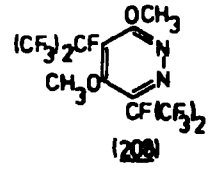
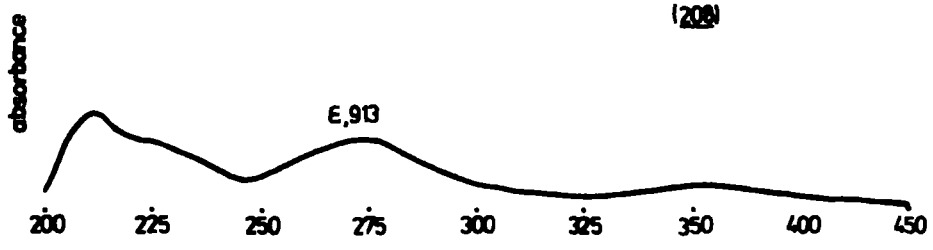


(205)

No 9



(208)



APPENDIX 3

N.M R. SPECTRA

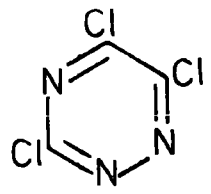
SPECTRUM No	COMPOUND	NUCLEUS
1	3,5,6-Trichloro-1,2,4-triazine (7)	^{13}C
2	Perfluoro-3,5,6-tris-isopropyl-1,2,4-triazine (160)	^{19}F
3	Trichloroacrylonitrile (170)	^{13}C
4	Trichloroacrylonitrile	^{13}C
5	Perfluoroisobutyryl nitrile (175)	^{19}F
6	Perfluoro-2,5-dimethylhex-3-yne (176)	^{19}F
7	Bis-heptafluoroisopropyl-mono-hydroxy-1,2,4-triazine (178)	^{19}F
8	4,6-Bis-dimethylamino-3,5-bis-	^{19}F
9	heptafluoroisopropylpyridazine (183)	^{1}H
10	3,3-Bis-trifluoromethyl-2,3-dihydro-4-dimethylamino-7-heptafluoroisopropyl-1-methylpyrrolo-[2,3-d]-pyridazine (185) or	^{19}F
11	5,5-Bis-trifluoromethyl-5,6-dihydro-3-dimethylamino-4-heptafluoroisopropyl-7-methylpyrrolo-[2,3-c]-pyridazine (186)	^{1}H
12	4,6-Bis-dimethylamino-3,5-bis-	^{19}F
13	heptafluoroisopropylpyridazine tetrafluoroborate (192) or (193)	^{1}H

14	3,6-Difluoro-5-dimethylamino-4-	^{19}F
15	heptafluoroisopropylpyridazine (194)	^{1}H
16	3,5-Bis-dimethylamino-6-fluoro-4-	^{19}F
17	heptafluoroisopropylpyridazine (195)	^{1}H
18	5,5-Bis-trifluoromethyl-5,6-dihydro-4-	^{19}F
19	dimethylamino-3-hydroxy-7-methylpyrrolo-[2,3-c]-pyridazine (196)	^{1}H
20	4,7-Bis-dimethylamino-3,3-bis-trifluoromethyl-2,3-dihydro-1-methylpyrrolo-[2,3-d]-pyridazine (198) or 3,4-Bis-	^{19}F
21	dimethylamino-5,5-bis-trifluoromethyl-5,6-dihydro-7-methylpyrrolo-[2,3-c]-pyridazine (199)	^{1}H
22	5-Dimethylamino-3,6-dimethoxy-4-	^{19}F
23	heptafluoroisopropylpyridazine (200)	^{1}H
24	5-Dimethylamino-3,4,6-tris-	^{19}F
25	heptafluoroisopropylpyridazine (201)	^{1}H
26	3-Dimethylamino-6-fluoro-4,5-bis-	^{19}F
27	heptafluoroisopropylpyridazine (202)	^{1}H
28	3,6-Bis-dimethylamino-4,5-bis-	^{19}F
29	heptafluoroisopropylpyridazine (203)	^{1}H
30	3,5-Bis-heptafluoroisopropyl-6-	^{19}F
31	dimethylamino-4-fluoropyridazine (204)	^{1}H

32	3,5-Bis-heptafluoroisopropyl-6-	^{19}F
33	dimethylamino-4-methoxypyridazine (205)	^{1}H
34	Mixture of 3,5-bis-heptafluoroisopropyl-6-fluoro-4-methoxypyridazine (206) and 3,5-	^{19}F
35	Bis-heptafluoroisopropyl-4-fluoro-6-methoxypyridazine (207)	^{1}H
36	3,5-Bis-heptafluoroisopropyl-4,6-	^{19}F
37	dimethoxypyridazine (208)	^{1}H

All shifts are given in p.p m and coupling constants in Hz. The following abbreviations have been used in presenting data concerning the fine structure of absorptions - S = singlet, D = doublet, T = triplet, H = heptet, O = Octet, M = Multiplet.

1 3,5,6-TRICHLORO-1,2,4-TRIAZINE (7)

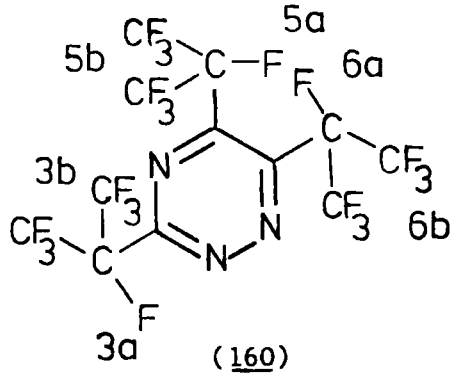


(7)

^{13}C	SHIFT
	154.7
	157 0
	160 8

(Recorded in $CDCl_3$ solution with an internal T M.S reference)

2. PERFLUORO-3,5,6-TRIS-ISOPROPYL-1,2,4-TRIAZINE (160)



(160)

^{19}F	SHIFT	FINE STRUCTURE	INTENSITY	ASSIGNMENT
	75 3	D(J = 5)	6	$CF(\underline{CF_3})_2$
	76.1	D(J = 5)	6	$CF(\underline{CF_3})_2$
	77.3	$D(J_{3b,3a} = 7)$	6	3b
	181 2	M	2	$2C\underline{F}(CF_3)_2$
	185.9	$H(J_{3a,3b} = 7)$	1	3a

(Recorded neat with an external $CFCl_3$ reference)

3 TRICHLOROACRYLONITRILE (170)

$$CCl_2{=}CClC{\equiv}N$$

(170)

^{13}C	SHIFT
	104 0
	112.0
	138 4

(Recorded in $CDCl_3$ solution with an internal T.M S reference).

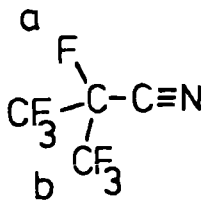
4 TRICHLOROACRYLONTRILE

$$CCl_2{=}CClC{\equiv}N$$

^{13}C	SHIFT
	103.5
	111.4
	138 0

(Recorded in $CDCl_3$ solution with an internal T.M S reference)

5. PERFLUOROISOBUTYRYL NITRILE (175)

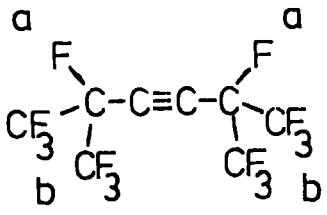


(175)

^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	76.4	$D(J_{b,a} = 10)$	6	b
	176.9	$H(J_{a,b} = 10)$	1	a

(Recorded neat with an external $CFCl_3$ reference)

6. PERFLUORO-2,5-DIMETHYLHEX-3-YNE (176)

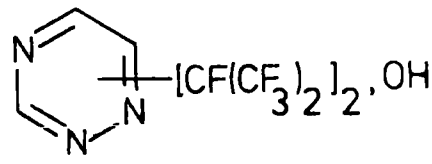


(176)

^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	80.1	$D(J_{b,a} = 10)$	6	b
	175.6	$H(J_{a,b} = 10)$	1	a

(Recorded neat with an external $CFCl_3$ reference).

7 BIS-HEPTAFLUOROISOPROPYL-MONO-HYDROXY-1,2,4-TRIAZINE (178)

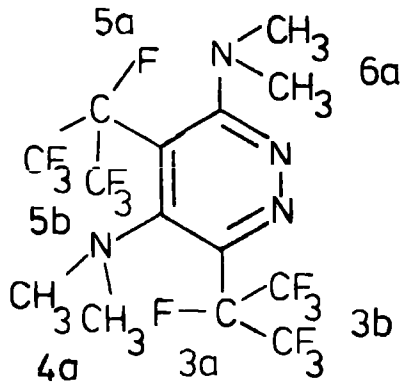


(178)

^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	73.6	D(J = 6)	1	$CF(\underline{CF_3})_2$
	74.2	D(J = 6)	1	$CF(\underline{CF_3})_2$
	183.7	M	-	$C\underline{F}(CF_3)_2$
	186.3	M	-	$C\underline{F}(CF_3)_2$

(Recorded in acetone solution with an external $CFCl_3$ reference)

8-9 4,6-BIS-DIMETHYLAMINO-3,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (183)



(183)

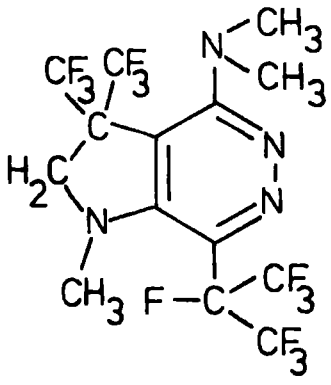
(8) ^{19}F	SHIFT	FINE STRUCTURE	ASSIGNMENT
	72 5	S	5b
	73 3	$D(J_{3b,3a} = 5)$	3b
	169.7	$M(J_{5a,6a} = 4)$	5a
	187.2	$M(J_{3a,3b} = 5)$	3a

(Recorded in $(CD_3)_2CO$ solution with an internal $CFCl_3$ reference)

(9) ^{1}H	SHIFT	FINE STRUCTURE	ASSIGNMENT
	2 57	$D(J_{4a,3a} = 5)$	4a
	3.08	$D(J_{6a,5a} = 4)$	6a

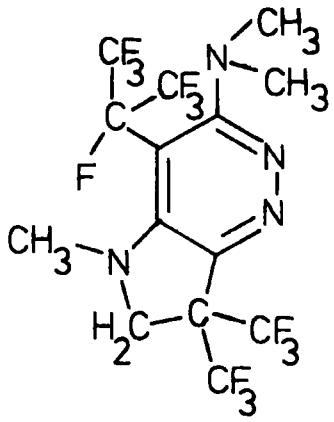
(Recorded in $(CD_3)_2CO$ solution with an internal T.M.S reference).

10-11. 3,3-BIS-TRIFLUOROMETHYL-2,3-DIHYDRO-4-DIMETHYLAMINO-7-HEPTAFLUOROISOPROPYL-1-METHYLPYRROLO-[2,3-d]-PYRIDAZINE (185) OR 5,5-BIS-TRIFLUOROMETHYL-5,6-DIHYDRO-3-DIMETHYLAMINO-4-HEPTAFLUOROISOPROPYL-7-METHYLPYRROLO-[2,3-c]-PYRIDAZINE (186)



(185)

or



(186)

(10) ^{19}F

SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
69.3	S	-	$C(C\underline{F}_3)_2$
72.9	D(J = 5)	-	$CF(C\underline{F}_3)_2$
173.5	0*	-	$C\underline{F}(CF_3)_2$

* Decoupling of the N-CH_3 doublet gave a septet.

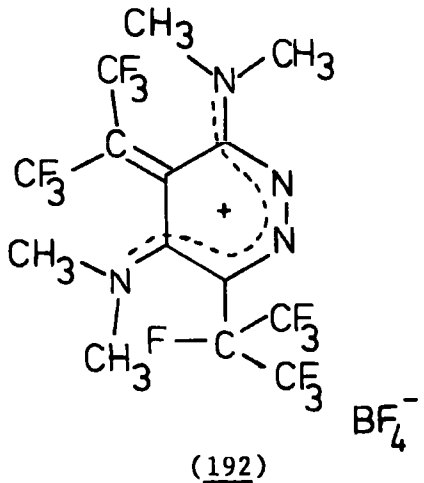
(Recorded in $(CD_3)_2CO$ solution with an internal $CFCl_3$ reference).

(11) ^{1}H

SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
2.57	S	6	$N(CH_3)_2$
3.10	D(J = 8)	3	CH_3
4 13	S	2	CH_2

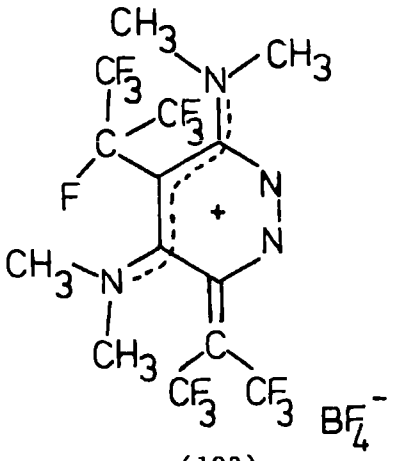
(Recorded in $(CD_3)_2CO$ solution with an external T.M S reference).

12-13. 4,6-BIS-DIMETHYLAMINO-3,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE TETRAFLUOROBORATE (192) OR (193)



(192)

or



(193)

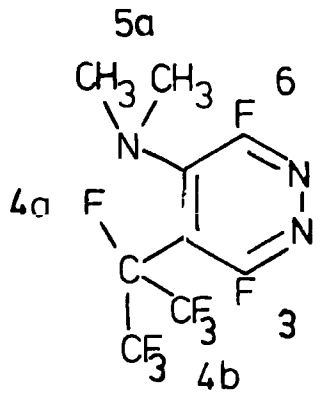
(12) ^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	60.7	M(BROAD)	6	$CF(CF_3)_2$
	72.5	S	3	CF_3
	76.0	S	3	CF_3
	151.7	S	4	BF_4^-
	182.4	S(BROAD)	1	$CF(CF_3)_2$

(Recorded in $(CD_3)_2CO$ solution with an internal $CFCl_3$ reference).

(13) ^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	3 50	S	3	CH_3
	3.63	S	3	CH_3
	3.93	D(J = 5)	3	CH_3
	4.16	S	3	CH_3

(Recorded in $(CD_3)_2CO$ solution with an external T.M.S. reference)

14-15 3,6-DIFLUORO-5-DIMETHYLAMINO-4-HEPTAFLUOROISOPROPYLPYRIDAZINE (194)



(194)

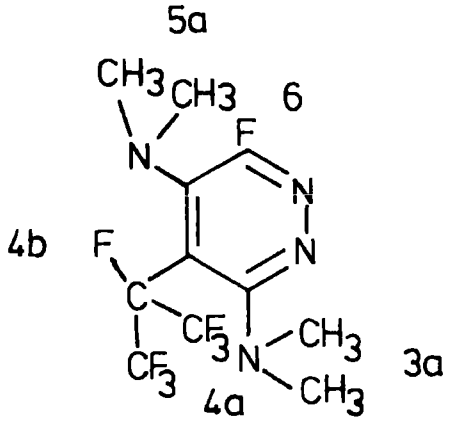
(14)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		74.0	S(BROAD)	7	3,4b
		84.1	M	1	6
		178.2	M(BROAD)	1	4a

(Recorded in $CDCl_3$ solution with an external $CFCl_3$ reference).

(15)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3.52	S	-	5a

(Recorded in $CDCl_3$ solution with an external T M.S reference).

16-17. 3,5-BIS-DIMETHYLAMINO-6-FLUORO-4-HEPTAFLUOROISOPROPYLPYRIDAZINE (195)



(195)

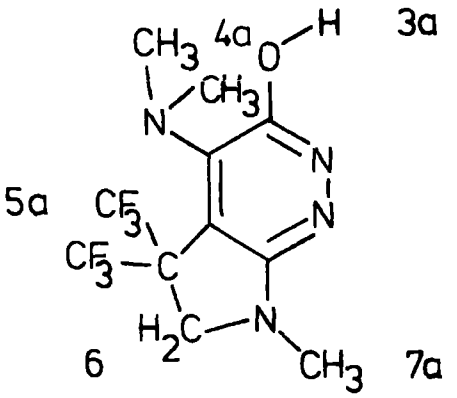
(16)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		73.1	D($J_{4b,4a}$ = 3)	-	4b
		91.4	S	-	6
		172.0	M(BROAD)	-	4a

(Recorded in CCl_4 solution with an external $CFCl_3$ reference).

(17)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		2.83	S	-	$N(CH_3)_2$
		2.86	S	-	$N(CH_3)_2$

(Recorded in CCl_4 solution with an external T.M.S reference).

18-19. 5,5-BIS-TRIFLUOROMETHYL-5,6-DIHYDRO-4-DIMETHYLAMINO-3-HYDROXY-7-METHYLPYRROLO-[2,3-c]-PYRIDAZINE (196)



(196)

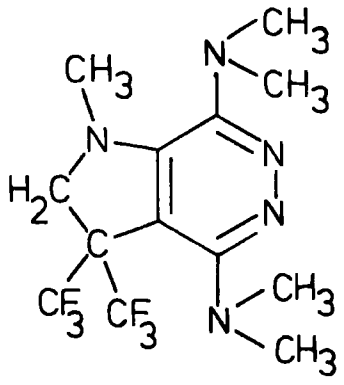
(18)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		50.4	S	-	5a

(Recorded in CCl_4 solution with an external $CFCl_3$ reference).

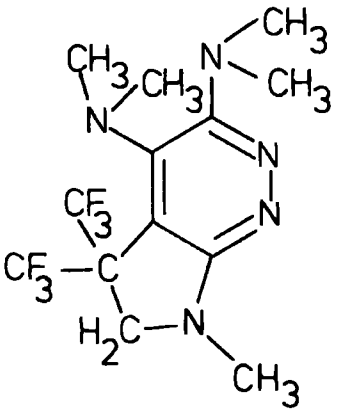
(19)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3.06	M(BROAD)	-	3a
		3.25	S	3	7a
		3.40	D($J_{4a,3a}$ = 4)	6	4a
		4.33	S	2	6

(Recorded in CCl_4 solution with an external T M.S. reference).

20-21 4,7-BIS-DIMETHYLAMINO-3,3-BIS-TRIFLUOROMETHYL-2,3-DIHYDRO-1-METHYLPYRROLO-[2,3-d]-PYRIDAZINE (198) OR 3,4-BIS-DIMETHYLAMINO-5,5-BIS-TRIFLUOROMETHYL-5,6-DIHYDRO-7-METHYLPYRROLO-[2,3-c]-PYRIDAZINE (199)



or



(198) (199)

(20)

^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	69.7	S	-	$2CF_3$

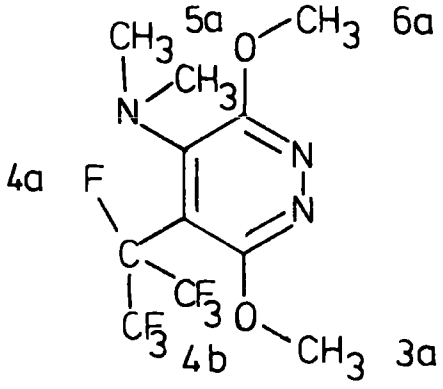
(Recorded in CCl_4 solution with an external $CFCl_3$ reference).

(21)

^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
	3.20	S	6	$N(CH_3)_2$
	3 37	S	6	$N(CH_3)_2$
	3 55	S	3	CH_3
	4 27	S	2	CH_2

(Recorded in CCl_4 solution with an external T.M S reference)

22-23 5-DIMETHYLAMINO-3,6-DIMETHOXY-4-HEPTAFLUOROISOPROPYLPYRIDAZINE (200)



(200)

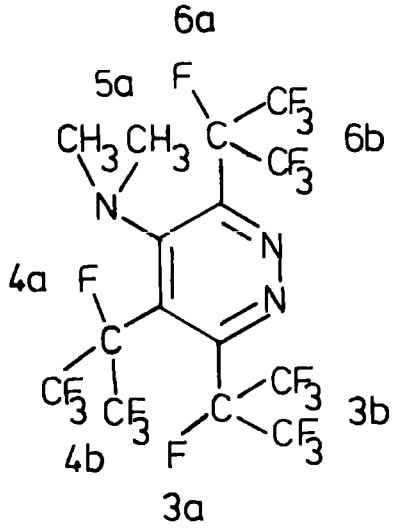
(22)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		74.6	D($J_{4b,4a}$ = 3)	-	4b
		177 7	M(BROAD)	-	4a

(Recorded in $CDCl_3$ solution with an external $CFCl_3$ reference)

(23)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3.00	D OF S(δ = 1Hz)	6	3a,6a
		4.35	D ($J_{5a,4a}$ = 3)	6	5a

(Recorded in $CDCl_3$ solution with an external T.M S reference).

24-25. 5-DIMETHYLAMINO-3,4,6-TRIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (201)



(201)

(24)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		67 0	D($J_{4b,3a}$ = 30)	6	4b
		73.3	S(BROAD)	12	3b, 6b
		154 2	M(BROAD)	1	$C\underline{F}(CF_3)_2$
		177.4	M(BROAD)	1	$C\underline{F}(CF_3)_2$
		182.1	M(BROAD)	1	$C\underline{F}(CF_3)_2$

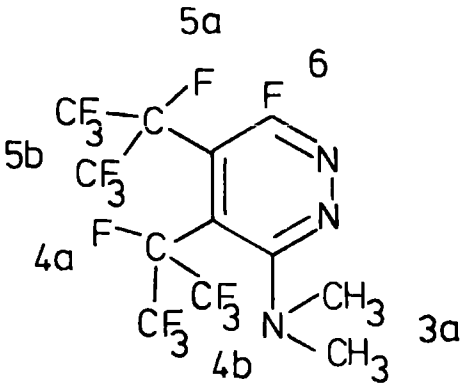
(Recorded in $(CD_3)_2CO$ solution with an internal $CFCl_3$ reference).

(25)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3 48	D OF D	-	5a

(J_1 = 4.5, J_2 = 1.5)

(Recorded in $(CD_3)_2CO$ solution with an internal T.M.S. reference).

26-27. 3-DIMETHYLAMINO-6-FLUORO-4,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (202)



(202)

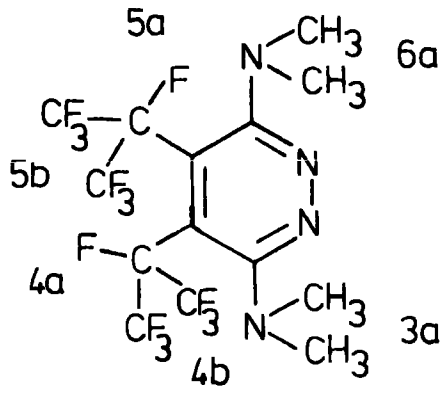
(26)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		73.3	S(BROAD)	-	4b,5b
		94.1	M(BROAD)	-	6
		163.3	M(BROAD)	-	4_a
		174.5	M(BROAD)	-	5_a

(Recorded in $CDCl_3$ solution with an external $CFCl_3$ reference).

(27)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3.42	S(BROAD)	-	3_a

(Recorded in $CDCl_3$ solution with an external T.M.S. reference).

28-29. 3,6-BIS-DIMETHYLAMINO-4,5-BIS-HEPTAFLUOROISOPROPYLPYRIDAZINE (203)



(203)

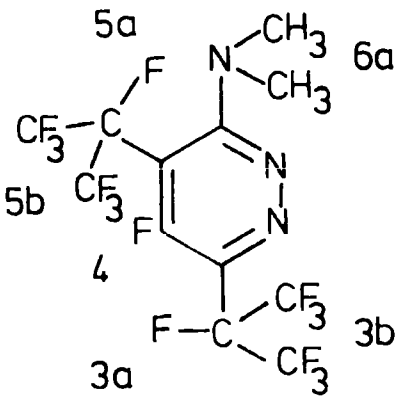
(28)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNEMENT
		69.7	S(BROAD)	-	4b,5b
		157.3	S(BROAD)	-	4a,5a

(Recorded in CCl_4 solution with an internal $CFCl_3$ reference)

(29)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3.26	S(BROAD)	-	3a,6a

(Recorded in CCl_4 solution with an external T.M.S. reference).

30-31. 3,5-BIS-HEPTAFLUOROISOPROPYL-6-DIMETHYLAMINO-4-FLUOROPYRIDAZINE (204)



(204)

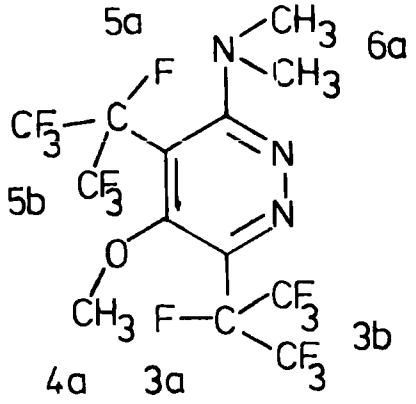
(30)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		76.8	D($J_{3b,3a}$ = 6)	6	3b
		77 0	D($J_{5b,4}$ = 6)	6	5b
		92.2	M(BROAD)	-	4
		179 2	M(BROAD)	-	5a
		185 5	D OF M ($J_{3a,4}$=40)	-	3a

(Recorded neat with an external $CFCl_3$ reference).

(31)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		3.30	D($J_{6a,5a}$ = 4)	-	6a

(Recorded neat with an external T M S. reference).

32-33. 3,5-BIS-HEPTAFLUOROISOPROPYL-6-DIMETHYLAMINO-4-METHOXYPYRIDAZINE (205)



(205)

(32)

^{19}F SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
74.8	$D(J_{3b,3a} = 6)$	-	3b
75.2	$D(J_{5b,5a} = 3)$	-	5b
175.7	M	-	5a
186 9	M	-	3a

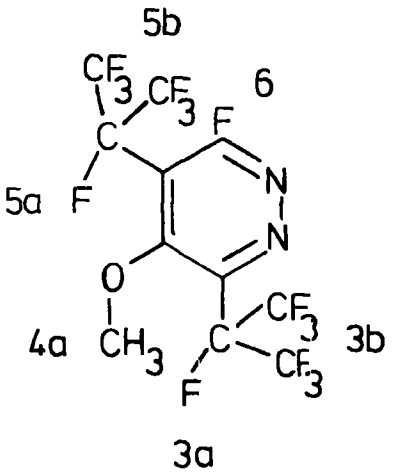
(Recorded in $CDCl_3$ solution with an external $CFCl_3$ reference)

(33)

^{1}H SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
3.23	$D(J_{6a,5a} = 4)$	6	6a
3 83	$D(J_{4a,3a} = 3)$	3	4a

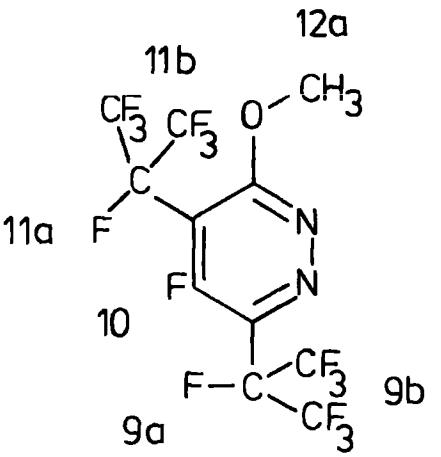
(Recorded in $CDCl_3$ solution with an external T.M.S reference).

34-35 MIXTURE OF 3,5-BIS-HEPTAFLUOROISOPROPYL-6-FLUORO-4-METHOXYPYRIDAZINE (206) AND 3,5-BIS-HEPTAFLUOROISOPROPYL-4-FLUORO-6-METHOXYPYRIDAZINE (207)



(206)

+



(207)

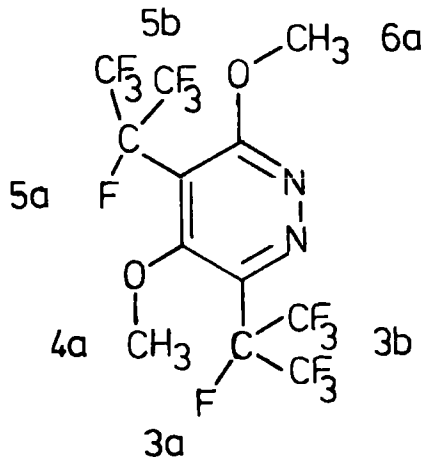
(34)	^{19}F	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		69.1	M(BROAD)	-	6
		72 6	M(BROAD)	-	10
		74.8	D(J = 6)	12	$2(CF(\underline{CF_3})_2$
		75.2	D(J = 6)	6	$CF(\underline{CF_3})_2$
		75.4	D(J = 6)	6	$CF(\underline{CF_3})_2$
		182.4	M(BROAD)	-	5a, 11a
		184.9	M(BROAD)	-	3a, 9a

(Recorded in $CDCl_3$ solution with an external $CFCl_3$ reference)

(35)	^{1}H	SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
		4.35 T ($J_{4a,3a}$=1, $J_{4a,5a}$=1)		3	4a
		4.38	S	3	12a

(Recorded in $CDCl_3$ solution with an external T.M.S reference)

36-37. 3,5-BIS-HEPTAFLUOROISOPROPYL-4,6-DIMETHOXYPYRIDAZINE (208)



(208)

(36) ^{19}F

SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
74.5	D($J_{3b,3a}$ = 3)	-	3b
74.7	D($J_{5b,5a}$ = 6)	-	5b
181.2	M(BROAD)	-	5a
185.3	M(BROAD)	-	3a

(Recorded in $CDCl_3$ solution with an external $CFCl_3$ reference).

(37) ^{1}H

SHIFT	FINE STRUCTURE	RELATIVE INTENSITY	ASSIGNMENT
3.98	T($J_{4a,3a}$=1, $J_{4a,5a}$=1)	1	4a
4.32	S	1	6a

(Recorded in $CDCl_3$ solution with an internal $CFCl_3$ reference).

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