SYNTHETIC APPROACHES TO NITRENE PRECURSORS

A thesis submitted to the University of Keele in part fulfilment of the requirements for the Degree of Doctor of Philosophy

by

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ABSTRACT

Chapter One describes the search for a synthetic route to 2-azidodiphenylmethanes and 2-azidotriphenylmethanes carrying electron withdrawing substituents in the 4'- and 4"- positions. Extensive use is made of the new Grignard reagent, 4-(1,3-dioxan-2-yl)phenylmagnesium bromide to prepare many novel diphenyl- and triphenyl-methanols, and benzophenones. The reduction of these compounds to the required diphenyl- and triphenyl-methanes is difficult, however, and although 2-amino-4'-carboxymethyldiphenylmethane is obtained in one instance, the reaction is not reproducible.

Further uses for the 3- and 4-(1,3-dioxan-2-yl)phenylmagnesium bromide synthons are investigated in Chapter Two. These Grignard reagents provide a useful synthetic route to many known compounds, and also to some previously unprepared compounds such as 3- and 4-(1-hydroxyethyl)benzaldehyde, and 4-(1,3-dioxan-2-yl)benzyl bromide.

Chapter Three describes the preparation and decomposition of 2-azido-4',4",bis(dimethylamino)triphenylmethane and 2-azidophenyl-2-thiazolylmethane. Extensive tar formation occurs during both decompositions. 2-Aminophenyl-2-thiazolylmethane is the only identified product from the thermolysis of 2-azidophenyl-2-thiazolylmethane. The thermolysis of 2-azido-4',4"-bis(dimethylamino)triphenylmethane, however, results in the formation of 3-dimethylamino-9-(4'-dimethylaminophenyl)acridine, and the "rearranged" 2-dimethylamino-9-(4'-dimethylaminophenyl)acridine. "Rearranged" acridines have not previously been obtained from the decomposition of members of the 2-azidotriphenylmethanes.

EXPERIMENTAL MATERIALS AND APPARATUS

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Elemental analyses for C, H, and N were determined on a Perkin Elmer Elemental Analyser 240, at the University of Keele. Exact mass measurements were carried out by the P.C.M.U.

Low resolution mass spectra were recorded on a Hitachi-Perkin Elmer RMU-6 instrument.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on Hitachi-Perkin Elmer R24 60 MHz and Jeol JNM FX100 Fourier Transform instruments. Chemical shifts are reported as δ values in parts per million (ppm) using tetramethylsilane as an internal standard, and coupling constants (J) are reported in Hertz. Abbreviations used are: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, cplx = complex, ax = axial, eq = equatorial, H_d = dioxan proton.

Infrared absorption spectra were recorded on a Perkin Elmer 257 spectrophotometer as liquid films, nujol mulls, or in solution (e.g. CCl_4). Abbreviations used are: w = weak, s = strong, m = medium intensity, br = broad.

Ultraviolet and visible absorption spectra were recorded on solutions in 95% ethanol using a Unicam SP800 instrument.

Column chromatography was carried out using Woelm neutral alumina which had been deactivated by the addition of water. The activity values quoted refer to the Brockmann scale. A sample to alumina ratio of 1 : 30 (w/w) was used unless otherwise stated. All samples were adsorbed onto alumina before being placed on the column.

Preparative layer chromatography (P.L.C.) was carried out on glass plates (40 x 20 cm) coated with a 1.5 mm layer of silica gel (Merck Kieselgel PF_{254}). The separated components, visualized under ultraviolet light, were isolated by scraping off the silica and extracting with methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. This residue was dissolved in hot ethyl acetate, filtered and evaporated.

Medium pressure chromatography was carried out on silica gel (Merck Kieselgel PF_{254}) columns at pressures of 15 - 20 p.s.i.

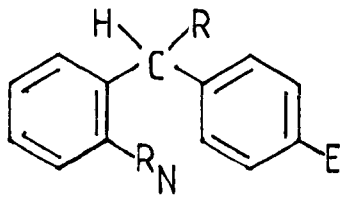
Thin layer chromatography (t.l.c.) was carried out on glass slides (20 x 7.5 cm) coated with silica gel and the separated components were observed under ultraviolet light.

All solvents used in chromatography were distilled before use.

GENERAL INTRODUCTION

This thesis continues the investigation of intramolecular nitrene insertion reactions into aromatic rings.[1-10] At the time of embarking on this section of the work insertions into electron deficient aromatic rings had not been investigated.

Chapter one describes the quest for a possible synthetic route to compounds of type (I) which would have an electron deficient benzene ring available for nitrene insertion.



(I)

R_N = NO_2, NH_2, N_3

E = an electron withdrawing group

R = H, $-C_6H_5$, $-4-C_6H_4E$

Unfortunately, the usual syntheses of di- and tri-phenylmethanes cannot be carried out on starting materials containing an electron withdrawing group. Furthermore, addition of the electron withdrawing moiety to the di- or tri-phenylmethane skeleton was found to be impractical, due to the restrictions imposed by the requirement of a "potential nitrene" in the 2-position of the other ring. Hence it appeared that a masked electron withdrawing group would provide the best route to the required compounds. It was noted in the literature[11] that it is possible to prepare the Grignard reagent from 2-(1,3-dioxan-2-yl)ethyl bromide, and that the cyclic acetal protecting group is particularly versatile and may be subsequently converted to either an aldehyde or an ester.[12,13] Since the synthesis of di- and tri-phenylmethanes require an aromatic

ring attached to the protecting group, 4-(1,3-dioxan-2-yl)-phenylmagnesium bromide became an important synthon in attempts to obtain an electron withdrawing nitrene precursor.

In the course of these investigations the potential use of 4-(1,2-dioxan-2-yl)phenylmagnesium bromide for the production of aromatic compounds having Grignard-reactive acid, ester or aldehydic substituents was noted. Chapter two describes the use of this Grignard reagent for the preparation of a series of 3- and 4-disubstituted benzene compounds, of deceptively simple structure, containing groups of "mixed oxidation states". In addition it was possible to synthesize 4-(1,3-dioxan-2-yl)-benzyl bromide from 4-(1,3-dioxan-2-yl)phenylmagnesium bromide and so open another possible route to the electron withdrawing nitrene precursor.

Finally, Chapter three describes two further examples of intramolecular nitrene reactions. Both precursors, 2-azido-4',4''-dimethylaminotriphenylmethane and 2-azido-2-thiazolyl-methane, had nitrogen containing moieties associated with the nitrene receiving ring. Their decompositions produced large amounts of tar, as does the thermolysis of analogous pyridine compounds.[14]

CHAPTER ONE

SYNTHESIS OF ELECTRON-POOR NITRENE PRECURSORS IN THE DIPHENYL- AND TRIPHENYL- METHANE SERIES

INTRODUCTION

PART I : NITRENES

Nitrenes are uncharged molecular intermediates containing a monovalent nitrogen atom which has only six electrons in its valence shell - two bonding electrons, a lone pair, and two non-bonding electrons. The two non-bonding electrons may be spin paired (singlet nitrene) or have parallel spins (triplet nitrene). The singlet nitrene would be expected to behave as an electrophilic species, whereas the triplet nitrene would exhibit the properties of a diradical. In agreement with Hund's rule,[15] theoretical calculations and electron spin resonance measurements indicate[16] that most nitrenes have a triplet ground state.

The work described in this thesis is concerned mainly with arylnitrenes which have been obtained by solution thermolysis of the corresponding azides. The points discussed in this introduction will therefore be of particular relevance to these species.

For arylnitrenes in the triplet state it is possible that mixing of the ring π-orbitals with one of the nitrogen 2p orbitals, containing a non-bonding electron, can occur (Figure 1.1). However, this interaction is considered to be fairly weak in order to account for the observation (by electron spin resonance) of low lying triplet states in phenylnitrene.[16] If a very strong interaction were present

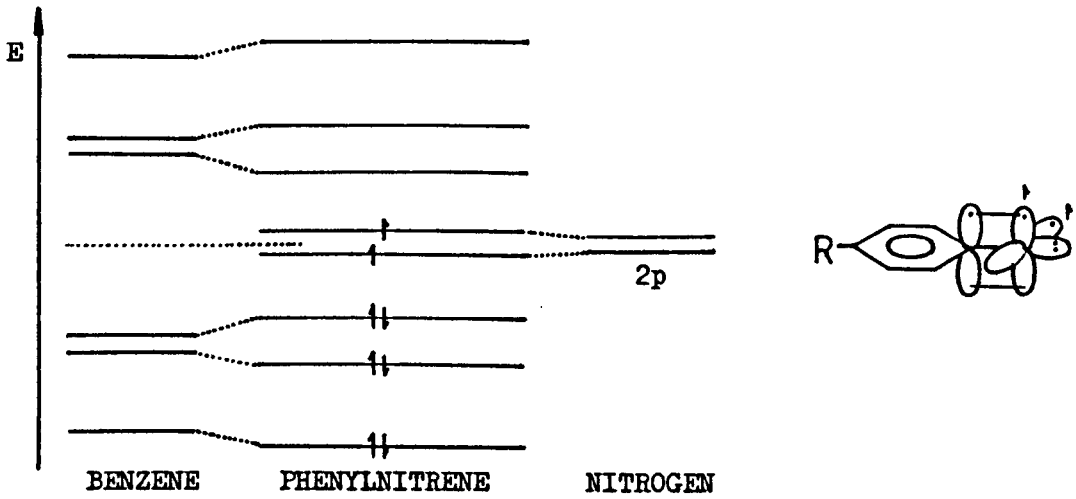


Figure 1.1: Schematic diagram[16] for the aromatic and nitrogen 2p orbitals in triplet phenylnitrene

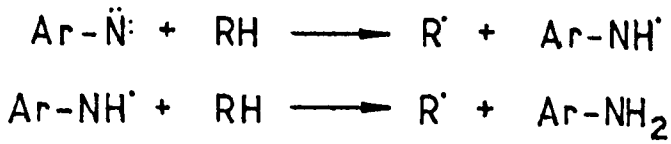
this would lift the degeneracy of the 2p orbitals to such an extent that a singlet ground state would be favoured. Recently electron spin resonance measurements have been used to predict[17] the extent of spin delocalization in triplet para-substituted phenylnitrenes. Combination of these measurements with INDO calculations indicated that the total spin density on nitrogen remains almost constant (and equal to approximately 1.83) irrespective of the electronegativity of the substituent. It should be noted, however, that spin conservation laws dictate[18] that the nitrene intermediate produced by thermal decomposition of an azide has to be formed initially in the singlet state (since the lowest triplet state for nitrogen is 140 kcal above the ground state).

The rate of reaction of the initially formed singlet nitrene will depend on its affinity for the substrate, and will be matched against the rate at which it undergoes intersystem crossing to the triplet configuration. The final distribution of products from the decomposition of an azide will therefore reflect this competition - the nature of the products being determined by either

the electrophilic or diradical tendencies of the participating nitrene.

A number of reactions, considered to be typical of arylnitrene intermediates, and relevant to the experimental work described in this thesis are discussed below.

1. HYDROGEN ABSTRACTION:



Scheme 1.1

Perhaps the most general reaction of arylnitrenes which have been produced in solution, is the abstraction of hydrogen (from the solvent or the nitrene precursor) to form primary amines. The isolation of dehydrogenatively coupled solvent molecules from the reaction mixture indicates[19] that in many cases the hydrogen atoms are probably abstracted one at a time by a radical mechanism (Scheme 1.1). Such a reaction is to be expected of a triplet nitrene.

2. INSERTION INTO A C-H BOND:

* chiral centre

Scheme 1.2

The observed order[19] of reactivity of nitrene insertions into C-H bonds is that primary C-H is preferred to secondary C-H, which in

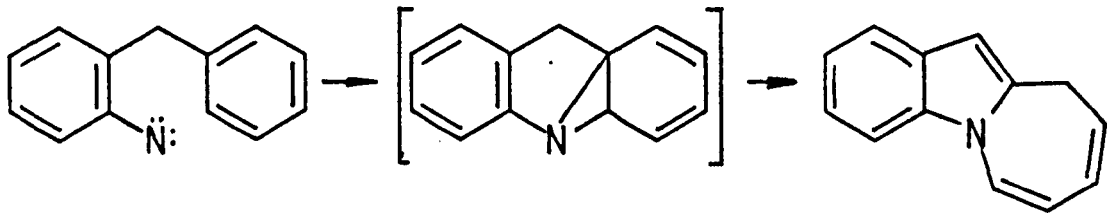
turn is preferred to tertiary and aromatic C-H. The term "C-H insertion reaction", however, describes the overall reaction rather than the detailed mechanism. Thus, it is possible that a C-H insertion reaction may result from an intramolecular hydrogen abstraction by a triplet nitrene. This possibility has been invoked[19] to explain the preference for cyclization to a five membered ring during intramolecular C-H insertion reactions. If the attack of a triplet nitrene proceeds <u>via</u> a cyclic transition

Figure 1.2

state, then the preferred geometry is that of a six membered ring, resulting in a five membered ring in the product molecule (Figure 1.2). This radical mechanism is in accord with the order of reactivity of C-H insertions described above.

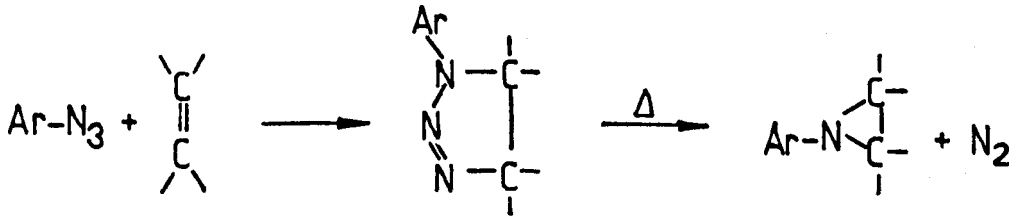
However, it has been demonstrated that C-H insertions may also occur <u>via</u> a concerted mechanism, and hence involve a singlet nitrene (Skell hypothesis).[20] For example, the high degree of retention of configuration observed for the reaction shown in Scheme 1.2 indicates that some of the molecules are reacting by a concerted mechanism.

3. ADDITION TO UNSATURATED C-C BONDS:



Scheme 1.3

By analogy with the products observed from the reactions of some carbenes with multiple bonds, an aziridine intermediate has been postulated[19] for some comparable arylnitrene reactions (e.g. Scheme 1.3). However, evidence for the direct addition of arylnitrenes to unsaturated C-C bonds is scarce since the operation of other mechanisms (C-H insertion, H-abstraction) could result in formation of the observed products. Further confusion can arise when the nitrene is generated by thermolysis of an azide. Although azides can decompose to give nitrenes, they can also react with multiple bonds at temperatures below those necessary to produce the free nitrene. In the latter reaction the initial product is a 1,2,3-triazoline but this breaks down on further heating to give the same products as those observed when the azide decomposes <u>via</u> the nitrene intermediate (Scheme 1.4).

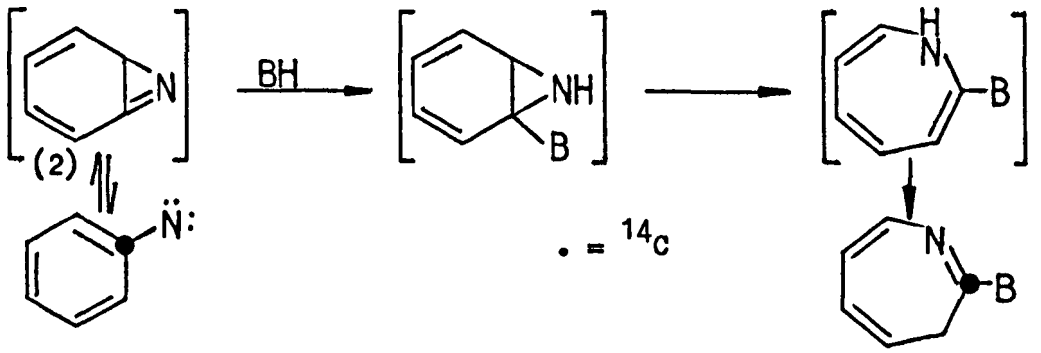


Scheme 1.4

Nevertheless, there are a few examples of direct addition of arylnitrenes to C-C double bonds in the literature. Aziridine formation (18-35%) has been observed[21] when pentafluorophenylnitrene (generated by the triethylphosphite deoxygenation of pentafluoronitrosobenzene) is added to some olefins. The less electrophilic species, phenylnitrene, generated by the thermal ∝-deoxysilylation of N,O-bis(trimethylsilyl)-N-phenylhydroxylamine in cyclohexene, adds to the C-C double bond of the solvent to give a 2% yield of the aziridine, 7-phenyl-7-azabicyclo[4.1.0]heptane[22] (Scheme 1.5).

Scheme 1.5

4. AZEPINE FORMATION:

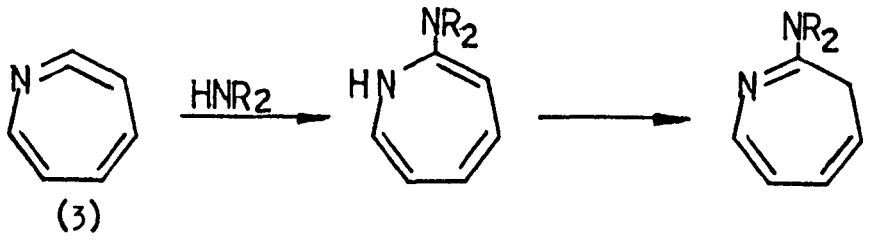


Scheme 1.6

The ring expansion of arylnitrenes generated in the presence of a base to give 2-substituted-3H-azepines has been generally thought[23] to proceed via nucleophilic attack on a 7-azabicyclo[4.1.0]heptatriene intermediate (Scheme 1.6). The unsymmetrical nature of the proposed azirine intermediate (2) is indicated by ^{14}C labelling studies which

show[24] that the 2-position of the azepine arises exclusively from C-1 of the phenylnitrene (obtained by thermolysis of suitably labelled phenyl azide).

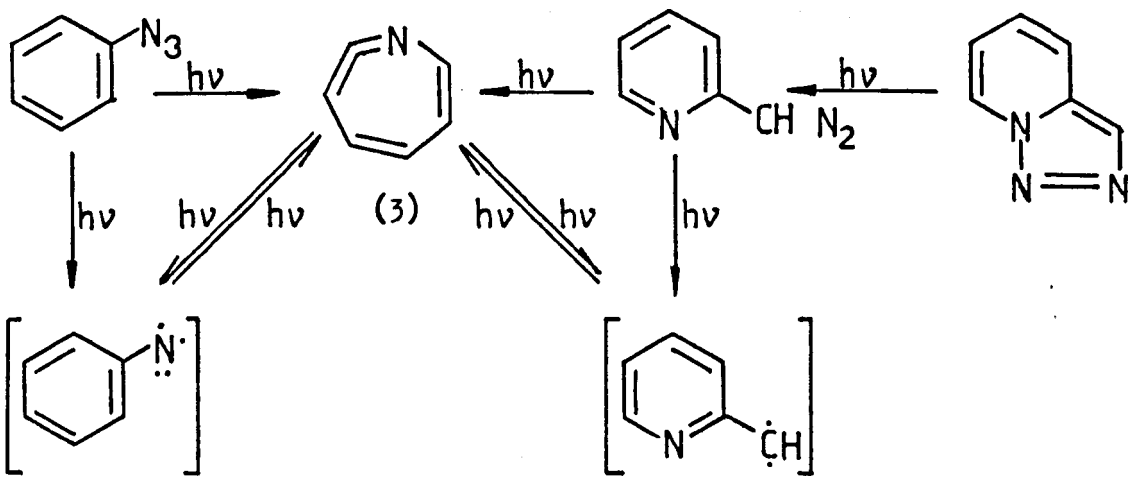
The mechanism of azepine formation has been discussed in the literature recently by Chapman *et al.*[25] They observed (by infra-red spectroscopy) the formation of 1,2,4,6-cycloheptatetraene (3) in an argon matrix after irradiation (at $\lambda > 2160$ Å) of phenyl azide, and suggested that this intermediate (rather than an azirine) reacts with nucleophiles to form 2-substituted-3-H-azepines.



(3)

Scheme 1.7

Later, the same workers carried out electron spin resonance studies,[26] on matrix isolated phenyl azide and *vic*-triazolopyridine, from which they concluded that triplet phenylnitrene was being converted into the strained allene intermediate (3) (Scheme 1.8). They have suggested that this intermediate could also be involved in the thermolytic decomposition of phenyl azides. It would be interesting to see whether a study of the kinetics of the solution thermolysis of phenyl azide in the presence of an amine by infra-red spectroscopy would provide more information about the applicability of Scheme 1.8 to azepine formation. Although this scheme is compatible with the ^{14}C labelling studies discussed above, it seems doubtful, in view of the chemical evidence, that triplet nitrenes can be the main precursors involved in azepine formation. Irradiation of phenyl azide solution (2-100% v/v tetrahydrofuran/diethylamine) gives 2-diethylamino-3H-azepine in

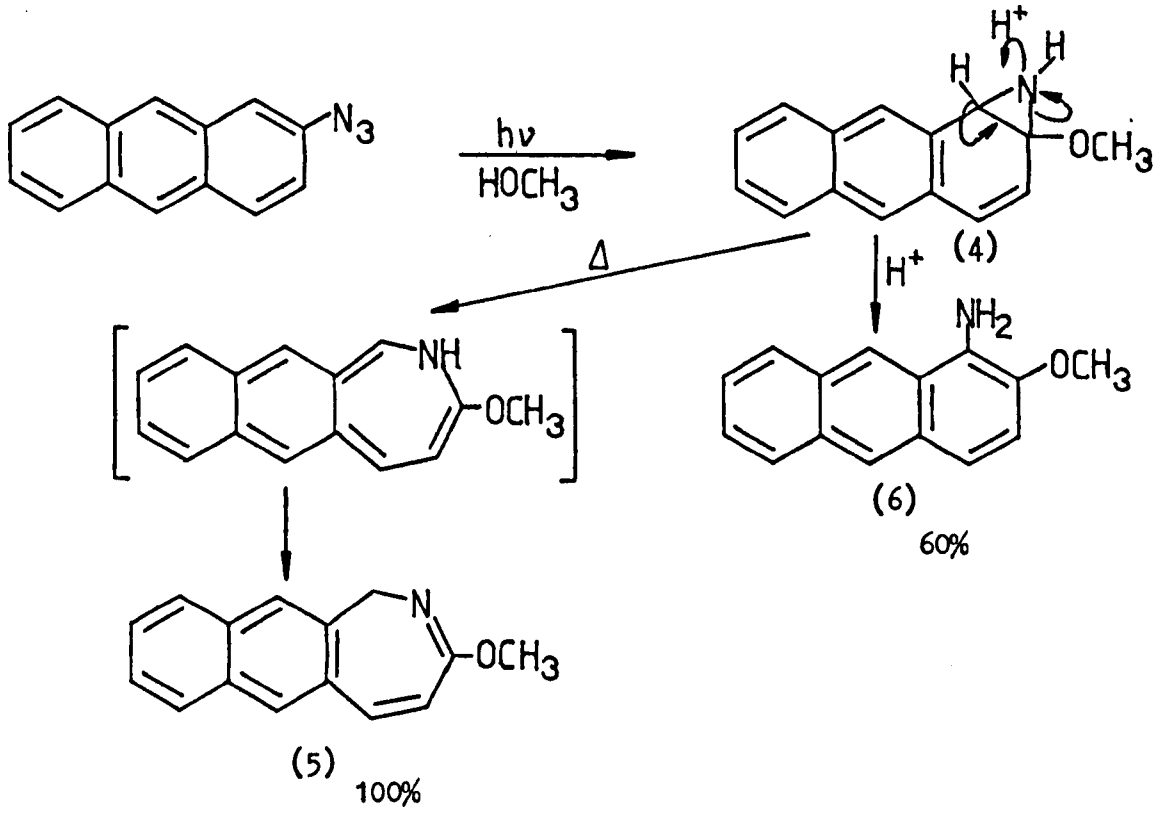


Scheme 1.8

70% yield[27] and a small amount of aniline, whereas the triplet sensitized photolysis of phenyl azide in diethylamine solution using an equimolar amount of p-dimethylaminobenzaldehyde gives a 70-80% yield of aniline and only 7% azepine.[28] As a result of these and similar observations, it is generally thought that it is the singlet state of arylnitrenes which gives rise to azepines.[16]

Rigaudy and his co-workers[29,30] have presented evidence that an azirine intermediate is involved in the photolytic decomposition of polycyclic aromatic azides in the presence of a nucleophile. They have found[29] that the photolysis of 2-azidoanthracene (or 2-azidonaphthalene) in a methanol-potassium

methoxide/dioxane* mixture affords either an azepine (5) if the reaction mixture is heated before work-up, or the methoxy-amine (6) when the reaction mixture is neutralized immediately after photolysis. In addition, the ultra-violet spectrum of the reaction solution immediately after irradiation is characteristic of a 1,2-dihydroanthracenic compound such as (4) - the product expected from the action of base on an azirine.



Scheme 1.9

In order to substantiate the intermediacy of the methoxy-azirine (4), the photolytic decomposition of 2-azidoanthracenes

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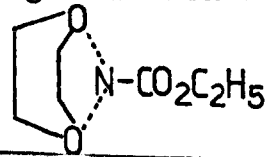
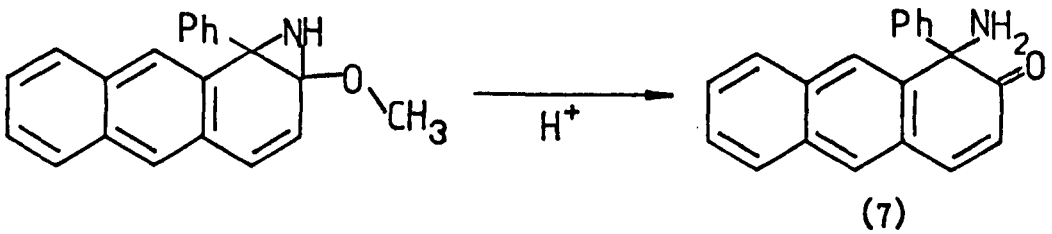
* It should be noted that Takeuchi et al.[31,32] have recently concluded that the reactive species when singlet ethoxycarbonylnitrene is generated in the presence of 1,4-dioxan is a complex such as



and not the free nitrene.

bearing C_1 substituents, capable of preventing easy rearomatization of the aziridine intermediate (2-azido-1-phenylanthracene and 2-azido-1-methoxyanthracene), was investigated.[30] It was not possible to isolate the aziridines as such, but the nature of the products obtained indicated that an aziridine was the most likely species to have been present in the solution immediately after photolysis.

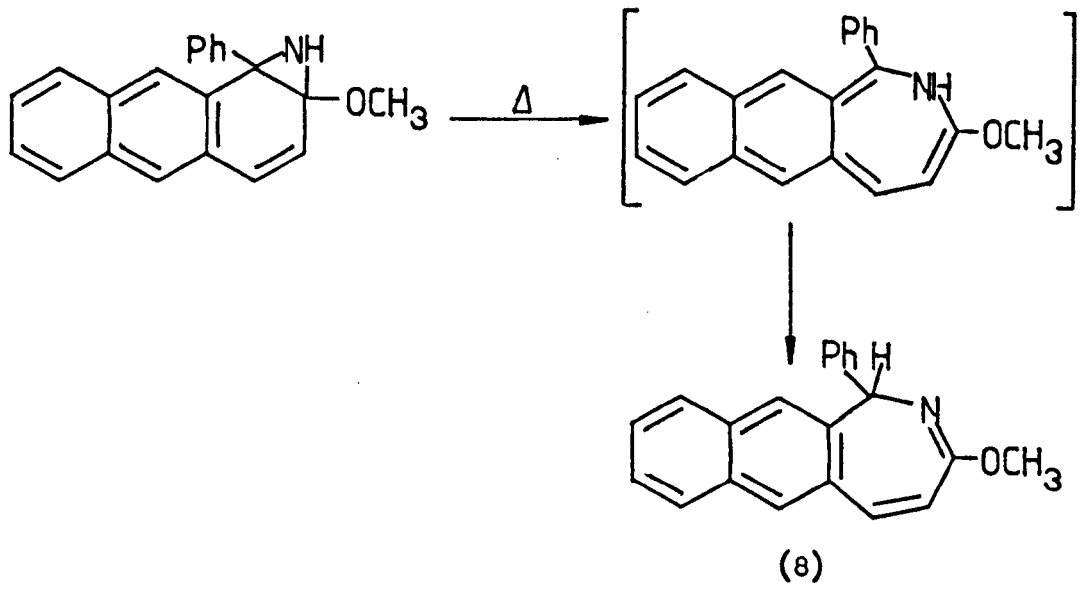
2-Azido-1-phenylanthracene yielded 1-amino-1-phenyl-1,2-dihydroanthracen-2-one (7) providing that the reaction mixture was treated with acid immediately after it had been photolysed in three molar methanol-potassium methoxide/dioxane. (In this case the phenyl C_1 substituent prevented rearomatization occurring after acid catalysed cleavage of the N-C_2 bond - compare Schemes 1.9 and 1.10). Heating the photolysis solution before neutralization



(7)

Scheme 1.10

apparently overcomes the energy barrier to electrocyclic ring opening and the subsequent loss of aromaticity, and 3-methoxy-1-phenyl-1H-naphth[2,3-c]azepine (8) is formed (Scheme 1.11). Analogous products were obtained when the base was changed to dimethylamine. A similar set of experiments using 2-azido-1-methoxyanthracene also



(8)

Scheme 1.11

implied that an azirine intermediate was involved. It remains to be seen whether an azirine is the ubiquitous precursor involved in azepine formation, or if it is restricted to the polycyclic series where it is favoured over 1-aza-1,2,4,6-cycloheptatetraenes as a result of structural constraints.[30]

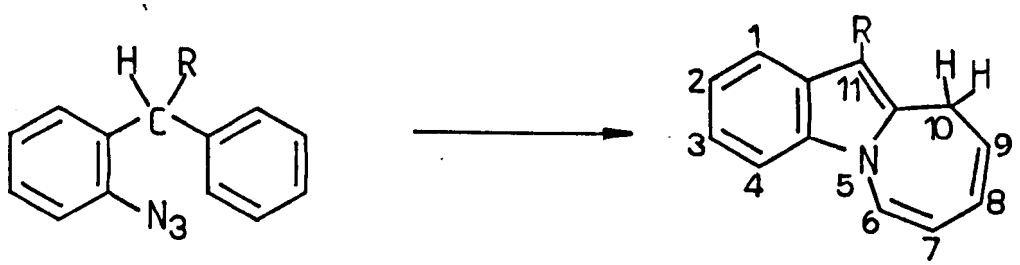
5. AZO-COMPOUND FORMATION:

The formation of azo-compounds during the solution thermolysis of azides is thought to occur mainly via attack of triplet nitrene on unreacted azide[33] since dimerization of the nitrene intermediate is unlikely to occur in dilute solutions. Meth-Cohn and his co-workers[34,35] have decomposed (both thermally and photolytically) various 2-azido biphenyl compounds over a range of

temperatures and under both singlet and triplet nitrene forming conditions. One of the conclusions reached by them as a result of these experiments, that the formation of azo-compound is indicative of a "lazy" triplet nitrene, and only occurs when the triplet nitrene has insufficient energy, or lacks a suitable substrate, for hydrogen abstraction.

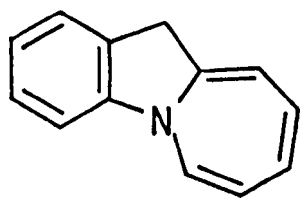
The intramolecular cyclization of aromatic nitrenes derived from 2-azidodiphenylmethanes and 2-azidotriphenylmethanes has been of interest to Jones and his co-workers[1-10] at Keele for a number of years. These reactions have been found to have considerable mechanistic interest and to provide a profitable source of old and new heterocyclic systems.

The investigation of these reactions was initiated by their discovery[2] that the thermolysis of 2-azidodiphenylmethane in 1,2,4-trichlorobenzene solution at 200° yields 10H-azepino[1,2-a]indole (9), and not 11H-azepino[1,2-a]indole (10) as had been previously suggested.[36] To confirm this structural assignment the methylazepinoindole, (11), was



(9) R = H, 56% yield

(11) R = CH_3, 38% yield

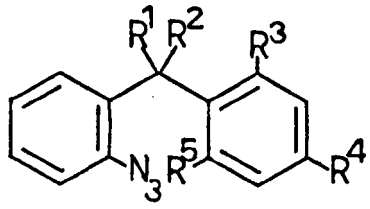


(10)

synthesized by thermolysis of 1-(2-azidophenyl)-1-phenylethane at 200° in 1,2,4-trichlorobenzene.

A variety of 2-azidodiphenylmethanes have since been thermolysed under the same conditions and the results are summarized in Table 1.1.

TABLE 1.1

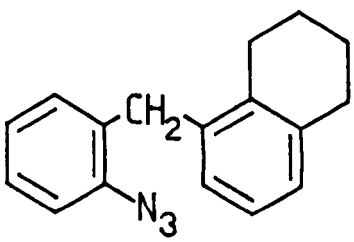


Cpd No.	Starting Material R^1	R^2	R^3	R^4	R^5	Products % Azepine	% Acridine + % Acridan	% Others	Total Recovery	Ref No.
12	H	H	H	H	H	56 [a]	-	-	56%	2
13	D	D	H	H	H	60 [b]	-	-	60%	37
14	CH_3	H	H	H	H	38 [c]	-	-	38%	2
15	CH_3	H	H	CH_3	H	19 [d]	0.5 + 0 = 0.5	-	19.5%	38
16	H	H	H	OCH_3	H	48 [e]			48%	3
17	H	H	CH_3	H	H	36.5 [f]	-	-	36.5%	1, 3
18	H	H	OCH_3	H	H	1 [g]	10[i] + 36[j] = 46	8 [m]	55%	1, 3
19	H	H	CH_3	CH_3	CH_3	74.3 [h]	-	-	74.3%	3
20	H	H	OCH_3	OCH_3	OCH_3	-	24.5[k] + 21.5[l] = 46	22.5[n]	68.5%	3

a) 10H-azepino[1,2-a]indole (9); b) 10,11-dideuterio-10H-azepino[1,2-a] indole; c) 11-methyl-10H-azepino[1,2-a]indole (11); d) 8-methyl-10H-azepino[1,2-a]indole; e) 8-methoxy-10H-azepino[1,2-a]indole; f) 27.5% 10-methyl-10H-azepino[1,2-a]indole, 9% 6-methyl-10H-azepino[1,2-a]indole; g) 10-methoxy-10H-azepino[1,2-a]indole, 6-methoxy-10H-azepino[1,2-a]indole; h) 41% 6,8,10-trimethyl-6H-azepino[1,2-a]indole, 20.4% 6,8,10-trimethyl-10H-azepino[1,2-a]indole, 12.9% 6,8,10-trimethyl-8H-azepino[1,2-a]indole; i) 3% acridine, 7% 1-methoxyacridine; j) 26% 1-methoxyacridan, 10% acridan; k) 1,3-dimethoxyacridine; l) 1,3-dimethoxyacridan; m) azepino-[1,2-a]indol-6-one; n) 8,10-dimethyoxyazepino[1,2-a]indol-6-one.

Thus, it appears that azepines may be regarded as the normal reaction products in the diphenylmethane system, and that the reaction mechanism is altered to favour the production of acridines and acridans when an ortho-methoxy substituent is present in the nitrene receiving ring.

Intramolecular nitrene insertions where the receiving ring of the "diphenylmethane" is part of a naphthalene or tetralin system have also been investigated[3] and the results are summarized in Table 1.2. As one might expect, the tetralins (22) and (24) behave similarly to diphenylmethanes, and azepine formation is greatly favoured over any other reaction.



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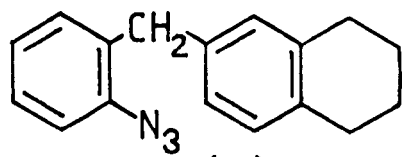
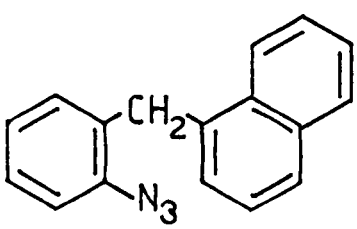


(24)

If, however, the nitrene receiving ring is part of a naphthalene system, (21) and (23), the overwhelming preference is for acridine/acridan production.



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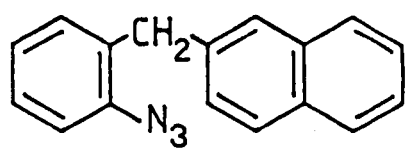


(23)

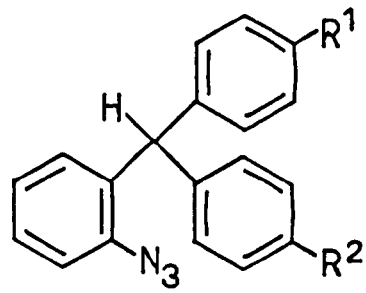
Although the reaction path for intramolecular nitrene insertion is unaltered by the presence of a methyl substituent on the central methane carbon atom (compounds (14) and (15), Table 1.1) it is considerably affected by a phenyl substituent in this position. The results obtained from the thermolysis of various 2-azidotriphenylmethanes are summarized in Table 1.3. It can be seen that almost equal amounts of

TABLE 1.2

Cpd No.	% Azepine	% Acridine + % Acridan	% Others	Total Recovery	Ref No.
21	3 [a]	25 [d] + 65 [h] = 90	3 [j]	96%	5
22	38 [b]	10 [e] + 0 = 10	18 [k]	56%	5
23	0	36 [f] + 38.5 [i] = 74.5	3.5 [l]	78%	5
24	70 [c]	2 [g] + 0 = 2	0	72%	5

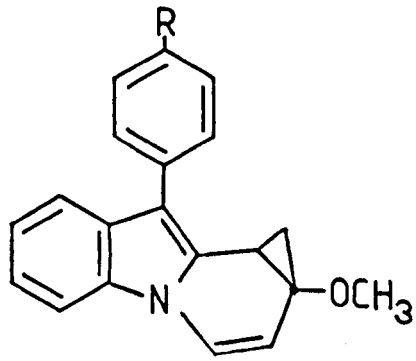
a) 3% 7H-indolo[1,2-a][1] benzazepine, v. small amount of 7H-indolo[2,1-a][2] benzazepine; b) 18% 2,3,4,7-tetrahydro-1H-indolo 1,2-a 1 benzazepine, 12% 2,3,4,7-tetrahydro-1H-indolo - [2,1-a][2] benzazepine, 8% 2,3,4,13b-tetrahydro-1H-indolo[2,1-a][2] - benzazepine; c) 8,9,10,12-tetrahydro-7H-indolo[1,2-b][2] benzazepine; d) benz[a]acridine; e) 1,2,3,4,7,12-hexahydrobenz[a]acridine; f) benz[c]acridine; g) 1,2,3,4-tetrahydrobenz[c]acridine; h) benz-[a]acridan; i) benz[c]acridan; j) 1-(2-aminobenzyl)naphthalene; k) 4,5,6,6a,7,12-hexahydronaphtho[1,8-bc][1] benzazepine; l) 2-(2-aminobenzyl)naphthalene.

TABLE 1.3



Starting Material Cpd No.	R^1	R^2	Products % Azepine	% Acridine + % Acridan	% Others	Total Recovery	Ref No.
25	H	H	31 [a]	14[d] + 19[g] = 33	8.5 [j]	72.5%	37
26	H	OCH_3	17 [b]	16[e] + 26[h] = 42	34 [k]	93%	37
27	OCH_3	OCH_3	1 [c]	28[f] + 8.8[i] = 36.8	13.6 [l]	50.4%	37

a) 11-phenyl-10H-azepino[1,2-a]indole; b) 11-(4-methoxyphenyl)-10H-azepino[1,2-a]indole; c) 8-methoxy-11-(4-methoxyphenyl)-10H-azepino-[1,2-a]indole; d) 9-phenylacridine; e) 10% 3-methoxy-9-phenylacridine, 6% 9-(4-methoxyphenyl)acridine; f) 3-methoxy-9-(4-methoxyphenyl)-acridine; g) 9,10-dihydro-9-phenylacridine; h) 14% 9,10-dihydro-3-methoxy-9-phenylacridine, 12% 9,10-dihydro-9-(4-methoxyphenyl)acridine; i) 9,10-dihydro-3-methoxy-9-(4-methoxyphenyl)acridine; j) 7.5% 2-aminotriphenylmethane, 1% azo-2,2'-bisdiphenylmethylbenzene; k) 8,9-dihydro-8,9-methano-8-methoxy-10-phenylpyrido[1,2-a]indole (28); l) 8,9-dihydro-8,9-methano-8-methoxy-10-(4-methoxyphenyl)pyrido[1,2-a]indole (29).



(28) R = H
(29) R = OCH_3

azepine and acridine-type products are obtained when the nitrene receiving rings are unsubstituted, and that the yield of azepine is further diminished by the presence of 4'- and 4"-methoxy substituents in the 2-azidotriphenylmethane molecule.

With the reaction products from these intramolecular nitrene insertion reactions so clearly divided into two types, azepines (resulting from expansion of the receiving ring) and acridines (where the receiving ring remains unexpanded), the most attractive explanation is that one is produced by a singlet nitrene and the other by a triplet nitrene. Photolysis and triplet sensitized thermolysis experiments[37] have confirmed that this is so.

Photolysis of 2-azidotriphenylmethane (25) and 2-azido-4',4"-dimethoxytriphenylmethane (27) in benzene solutions yielded mainly azo-compound (referred to by Meth-Cohn and his co-workers[35] as a "lazy" triplet product) and acridines and acridans, but no azepines. Thus it appears that acridines and acridans may be "triplet nitrene products" and that, as has been observed elsewhere,[16] expansion of an aromatic ring to an azepine requires a singlet nitrene.

This observation is supported by a series of triplet sensitized thermolysis experiments[37] on 2-azidotriphenylmethane (25), the triplet sensitization being effected by using either the "heavy atom effect" of bromobenzene, or an adiabatic singlet-triplet exchange interaction with naphthalene or biphenyl. The yield of acridine-type products was increased and the yield of azepines was considerably diminished under conditions favouring the formation of triplet rather than singlet nitrenes.

The results summarized in Tables 1.1, 1.2 and 1.3 may now be rationalized, but not completely explained, in terms of singlet and triplet nitrene intermediates. Fundamentally, the ratio of singlet

to triplet products (i.e. azepines to acridines and acridans) will be determined by the rate of reaction of the initially formed singlet nitrene with the receiving ring, compared with the rate at which it undergoes intersystem crossing to a triplet configuration.

The intramolecular transfer of singlet and triplet energy is known[39] to occur with high efficiency in compound (30) and related systems which have two separated chromophores with suitably related electronic energy levels (Figure 1.3).

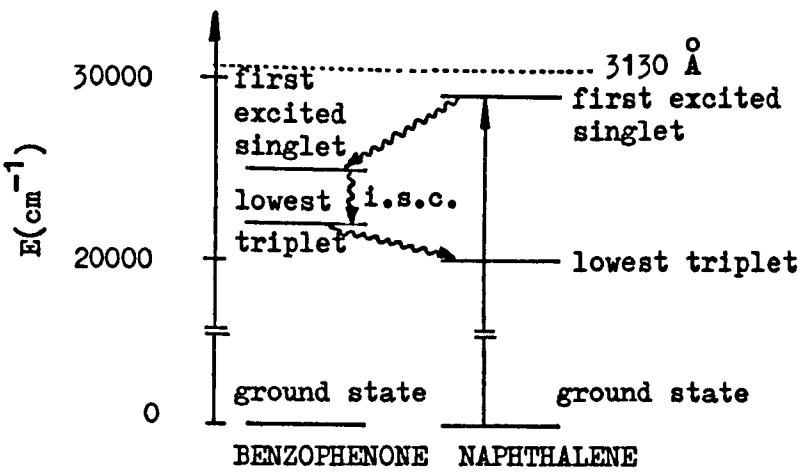
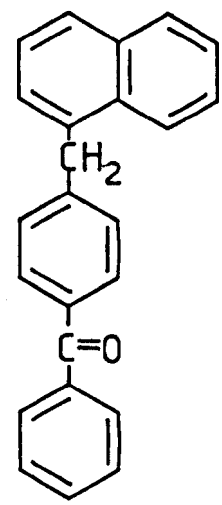


Figure 1.3 Electronic transitions in 4-(1-naphthylmethyl)benzophenone (30)[39]

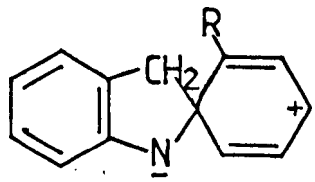


(30)

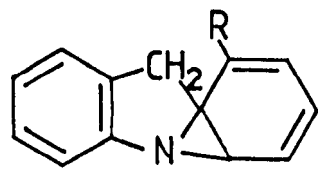
Thus, it is possible to promote the naphthalene moiety of compound (30) to an excited singlet state by irradiation at $\lambda = 3130$ Å. Singlet energy transfer to the benzophenone chromophore, intersystem crossing to form the benzophenone triplet, and then triplet energy transfer to form the naphthalene triplet can then occur with an overall efficiency of 98%. The high yields of triplet products obtained from the thermolysis of azides (21) and (23) indicate that a similar energy transfer process may be operating on the singlet nitrenes initially formed in the decomposition. That is, the singlet nitrene transfers energy to the naphthalene chromophore which then

undergoes intersystem crossing to the triplet state and subsequently transfers triplet energy back to the phenylnitrene moiety.

A complete explanation for the predominance of acridine/acridan production over azepine formation in 2-methoxy substituted diphenylmethanes has not yet emerged. The complex mixture of products obtained by thermolysis of 2-azido-2'-methoxydiphenylmethane suggests that a number of competing mechanisms may be operating. It is possible that spirodiene (31) and/or norcaradiene (32) intermediates may be involved in the nitrene insertion reaction. Mechanisms have been proposed[3] which may account for some of the observed products. For example, if a norcaradiene intermediate is

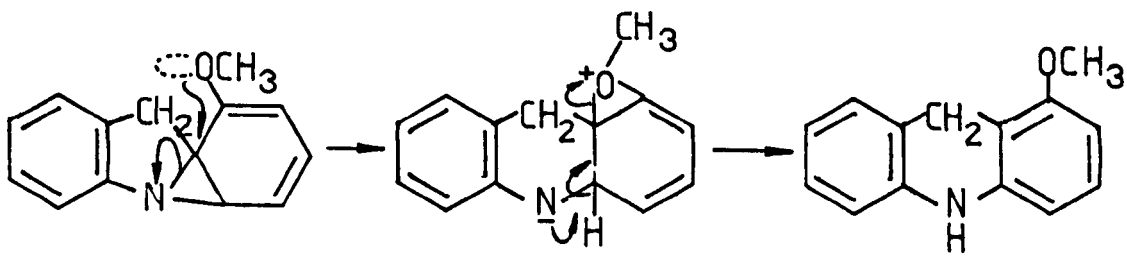


(31)



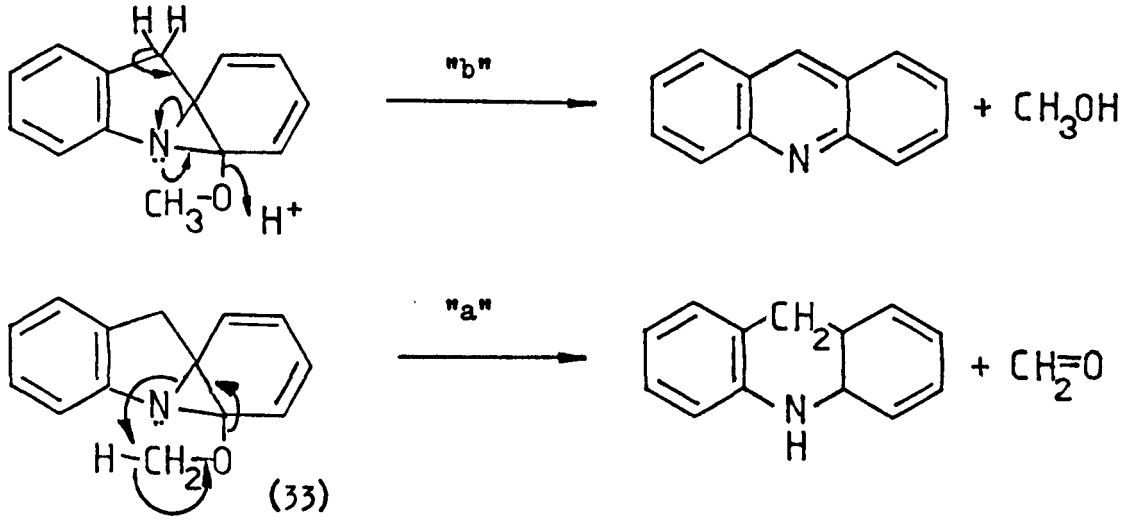
(32)

involved, then the formation of 1-methoxyacridan, rather than ring opening to give an azepine, would be assisted by the presence of an ortho-methoxy group (Scheme 1.12). Elimination of methanol to form



Scheme 1.12

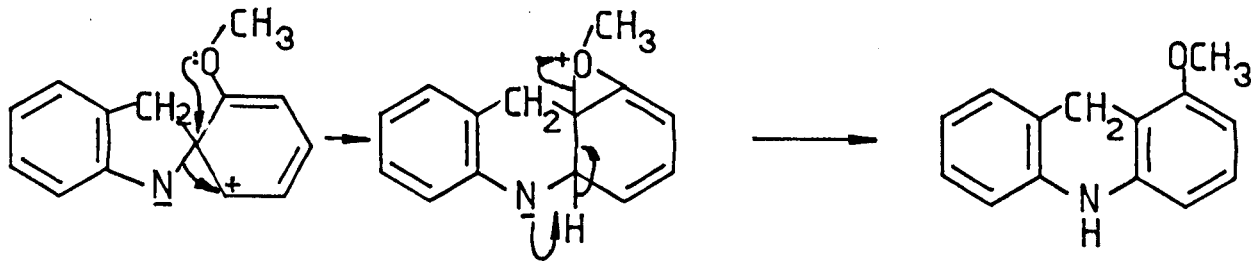
acridine (route "a"), or of formaldehyde to form acridan (route "b"), can theoretically occur if the nitrene inserts into the 1'-2' bond to give the norcaradiene (33). It is unlikely that acridan formation occurs <u>via</u> route "a", however, since formaldehyde



(33)

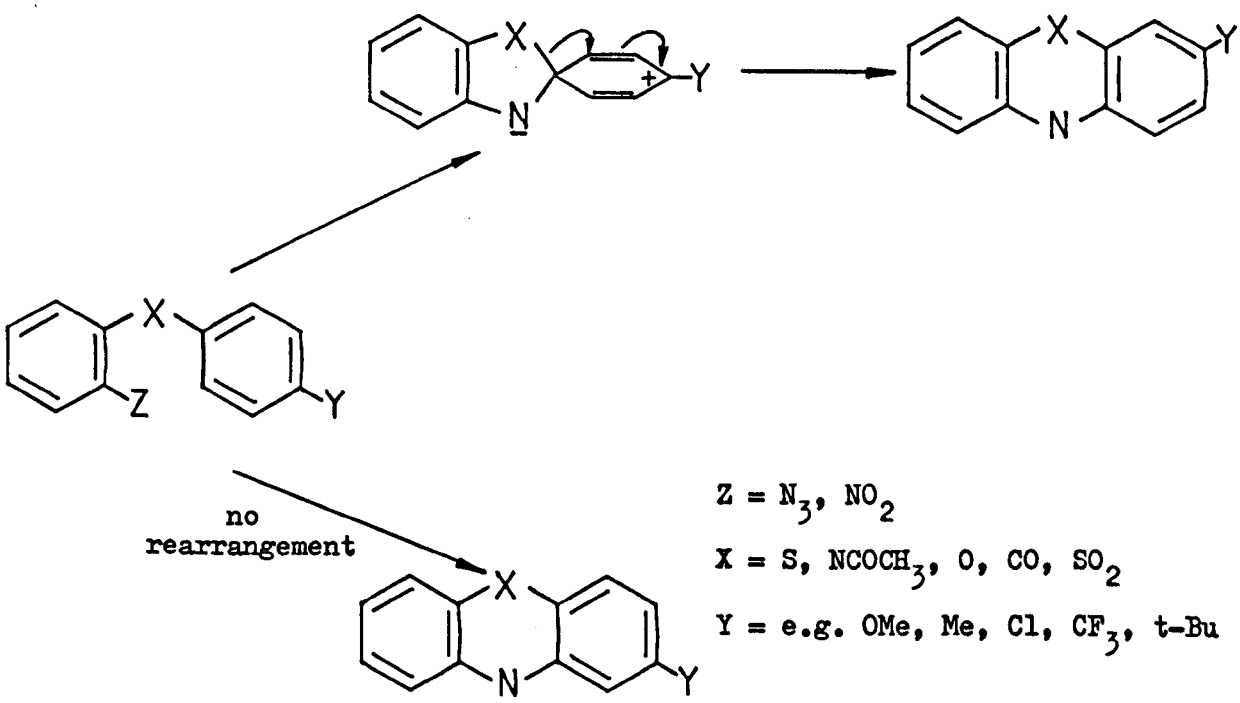
evolution is not detected during the decomposition. On the other hand it appears that acridine formation must involve some kind of internal oxidation-reduction system, such as that proposed in route "b", since rigid exclusion of oxygen does not prevent its production or that of 1-methoxyacridine.

Similar mechanisms may be drawn for the loss of formaldehyde or methanol from a spirodiene intermediate to form acridan or acridine respectively. However, formation of 1-methoxyacridan from a spirodiene intermediate would involve an unusual nitrogen migration (Scheme 1.13).



Scheme 1.13

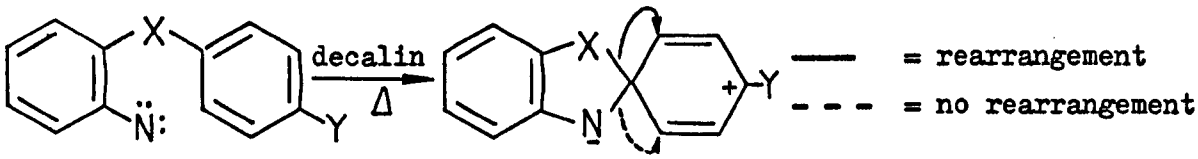
The spirodiene intermediate has been proposed by Cadogan[40] to account for the phenothiazine rearrangement (Scheme 1.14) and has been extended to cover cases where the "bridgehead group" (X) is oxygen, nitrogen, carbonyl, or sulfonyl.[41]



Scheme 1.14

It should be noted, however, that there are a number of differences between the type of products obtained from these systems and those obtained from the diphenylmethanes. Consequently, it is not easy to assess how closely their reaction mechanisms are related. For example, although 2-aminodiphenylmethane is the only product obtained from the decomposition of 2-azidodiphenylmethane in decalin,[36] it is only a minor component of the decomposition products from the compounds listed in Scheme 1.14 (see Table 1.4). It is interesting to note that the results summarized in Table 1.4 indicate that the amount of rearrangement occurring is directly related to the extent of conversion of singlet to triplet nitrene.

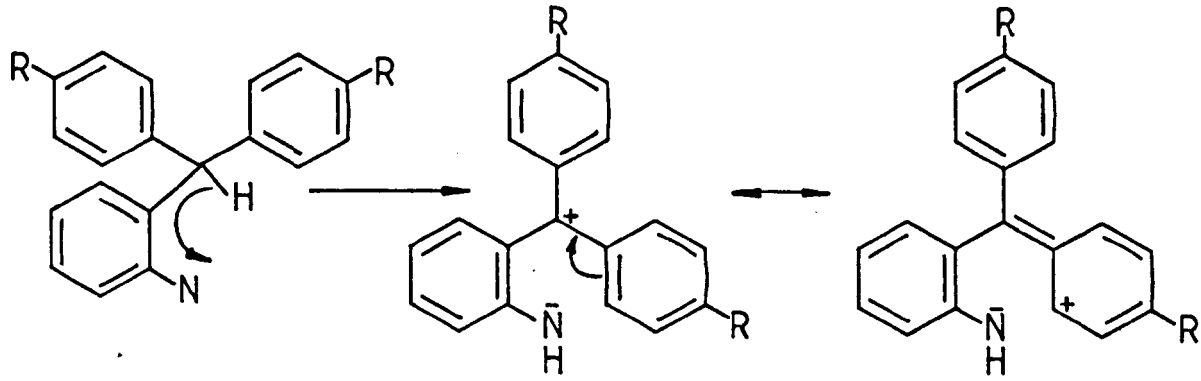
TABLE 1.4



X	Y	% rearrangement	% amine	Reference
SO_2	OMe	73	2	41
S	OMe	100	None reported	42
SO_2	Me	30	10	41
S	Me	100	None reported	42
SO_2	t-Bu	42	23	41
S	t-Bu	100	None reported	42
SO_2	Cl	41	20	41
S	Cl	100	None reported	42

The decomposition of aryl 2-azidodiphenyl sulfides also differs from that of 2-azidodiphenylmethanes when ortho-methoxy substituents are present in the receiving rings of both systems. The evolution of formaldehyde was detected[40] when an ortho-methoxy group was eliminated from the sulfide during phenothiazine formation, but not when an ortho-methoxy group was lost during the decomposition of a 2-azidodiphenylmethane. In addition, a methoxy group is only eliminated from the sulfide if both ortho-groups are "blocked", whereas methoxyl-elimination occurs to some extent even if only one of the ortho-positions of the receiving ring in 2-azidodiphenylmethanes is occupied.

A mechanism which accounts for the products obtained from the decomposition of the triphenylmethanes (Table 1.3) has been proposed[37] (Scheme 1.15).



(34) (35) (36)

Scheme 1.15

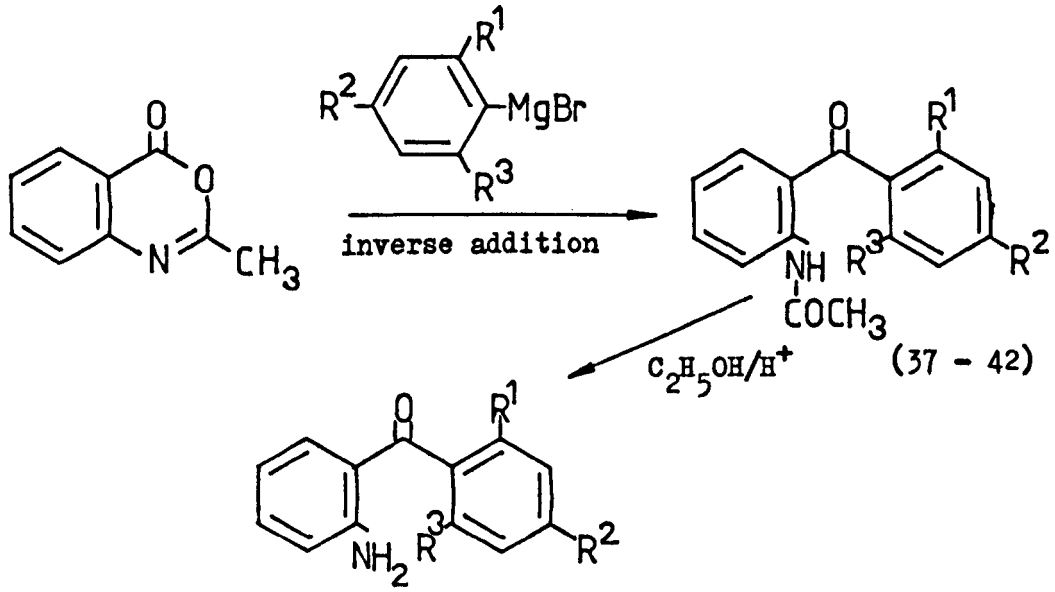
Nitrene abstraction (presumably by a singlet nitrene) of the proton attached to the bridging carbon atom can occur via a five membered transition state (34) to give the species (35 ⟷ 36) which is capable of cyclization to an acridan. The C-H bond strength, which

is directly related to the stability of the incipient carbonium ion would determine the probability of such a reaction. Thus, acridine/acridan formation by this mechanism can successfully compete with azepine formation in the triphenylmethane series. The stability of the carbonium ion is enhanced by the presence of electron donating substituents and thus almost exclusive acridan/ acridine formation results when R is a methoxy group.

As yet, no study has been carried out with electron withdrawing groups in the nitrene "receiving rings" of the diphenyl- and triphenyl-methanes. Such compounds could provide a valuable test for the mechanistic pathways which have been suggested for the intramolecular nitrene insertion reactions previously discussed. They may also give some further insight into the factors governing these reactions. We have therefore attempted to devise convenient synthetic routes to 2-azidodiphenyl- and 2-azidotriphenyl-methanes which have electron withdrawing substituents on the nitrene "receiving rings".

PART II : SYNTHESIS OF 2-AZIDO-DIPHENYL- AND TRIPHENYL- METHANES

The 2-azidodiphenylmethanes (12) - (20) which have been used in previous investigations of intramolecular nitrene insertions into aromatic rings[1-3] have all been synthesized *via* the corresponding 2-aminobenzophenones. A comprehensive survey of the synthetic routes to 2-aminobenzophenones has been given by Simpson *et al.*[43] The method chosen by Cliff and Jones[3] for the synthesis of benzophenones (37) - (42) was that devised by Lothrop and Goodwin[44] (Scheme 1.16) which caters for a wider range of substituents in the non-basic ring than are possible by other methods.



Scheme 1.16

(37),(38) R^1, R^3 = H; R^2 = OCH_3, CH_3

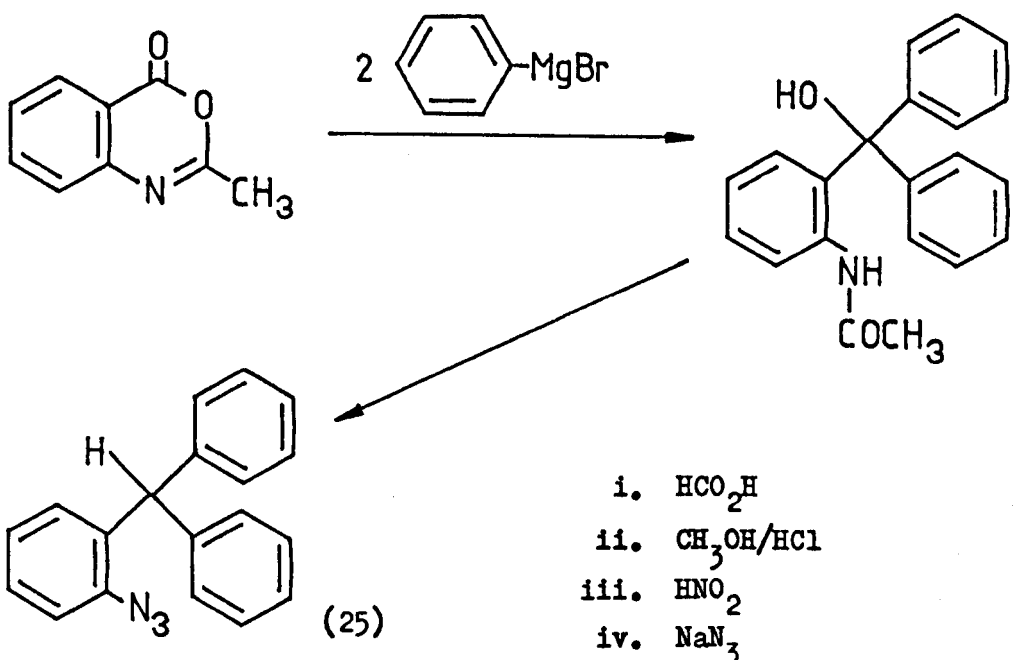
(39),(40) R^1, R^2 = H; R^3 = OCH_3, CH_3

(41),(42) R^1, R^2, R^3 = OCH_3, CH_3

2-Aminobenzophenone, itself, is usually prepared by an aluminium chloride catalysed Friedel-Crafts reaction between N-tosyl-anthraniloyl chloride and benzene.[45]

All the 2-aminobenzophenones previously mentioned can be reduced to 2-aminodiphenylmethanes by a dissolving-metal (sodium in ethanol) reduction. Diazotization of the resulting amines, followed by treatment with sodium azide gives the required 2-azido-diphenylmethanes.

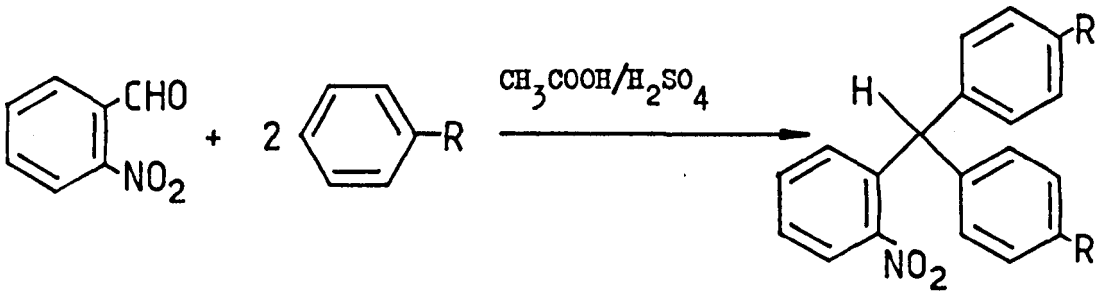
The synthesis of various triphenylmethanes has been described by Jones and his co-workers.[37] Their preparative route to 2-azidotriphenylmethane (25) is shown in Scheme 1.17. It contains a modification of the method due to Lothrop and Goodwin[44] which had been used for the preparation of the 2-acetamidobenzophenones (37) - (42).



Scheme 1.17

Jones and his co-workers[37] have also prepared 2-azido-4'-methoxytriphenylmethane (26) by reaction of 2-acetamido-4'-methoxybenzophenone (37) with phenylmagnesium bromide to give 2-acetamido-4'-methoxytriphenylmethanol, which was subsequently reduced in boiling formic acid and converted to the azide.

They also synthesized[37] 2-azido-4',4"-dimethoxytriphenylmethane (27) from 4,4'-dihydroxy-2"-nitrotriphenylmethane (43) by methylation (CH_3I/K_2CO_3) of the hydroxyl groups, catalytic (Pd/C) hydrogenation of the nitro group, and conversion of the resulting amine to the corresponding azide (HNO_2,NaN_3).

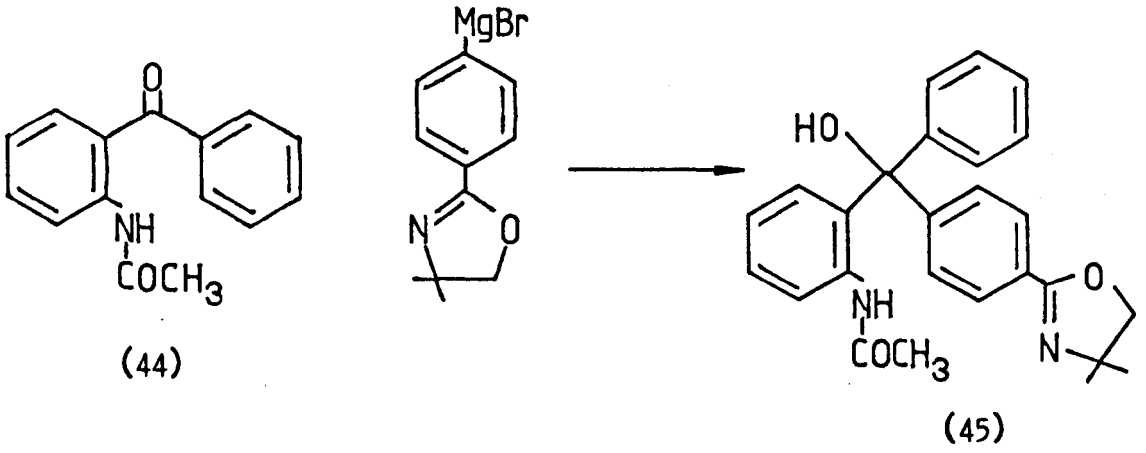


(43) R = OH

Scheme 1.18

The starting material (43) for the previous reaction was prepared by the acid catalyzed condensation shown in Scheme 1.18. This method is, however, only suitable when R is a strongly electron-donating group.

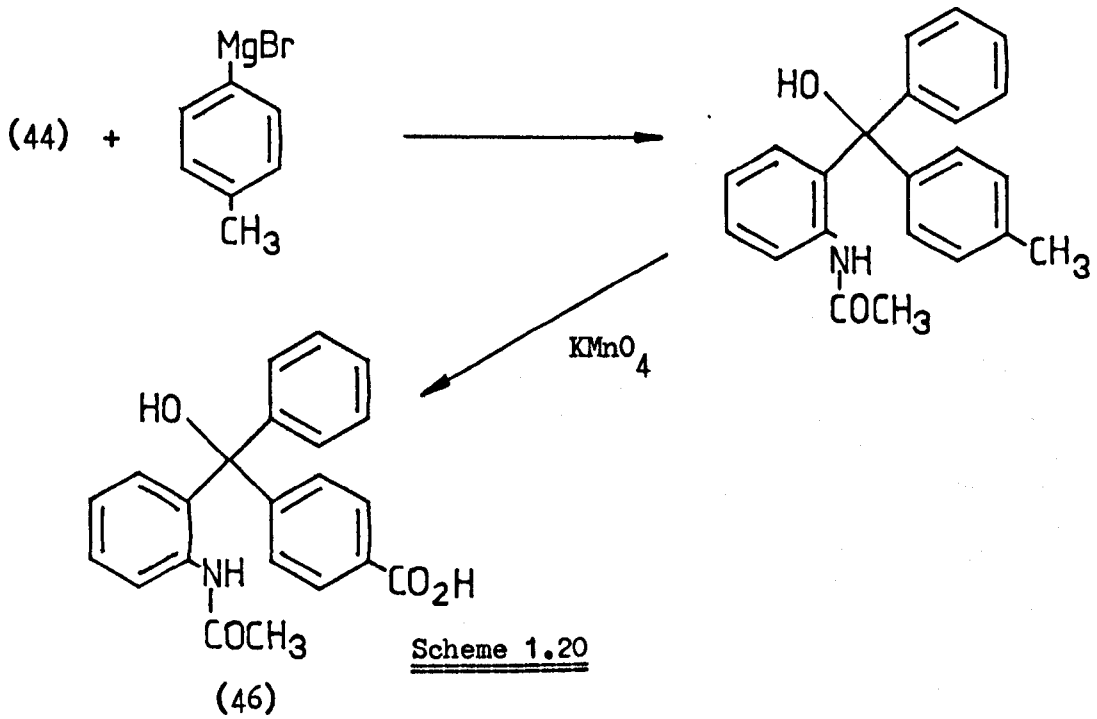
In the past, two attempts have been made[46] to synthesize the mixed "electron-withdrawing" nitrene precursor, 2-amino-4'-methoxycarbonyltriphenylmethane. One approach made use of the Grignard resistant oxazoline protecting group[47] (Scheme 1.19), but was abandoned when severe difficulties were encountered during attempts to reduce (45) to the corresponding triphenylmethane.



(44) (45)

Scheme 1.19

The other route (Scheme 1.20) involved the oxidation of a methyl substituent with neutral potassium permanganate. Only a small amount of the starting material was oxidized and the synthesis of



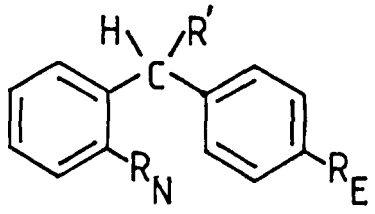
(46)

Scheme 1.20

2-amino-4'-methoxycarbonyltriphenylmethane *via* (46) was not continued.

DISCUSSION

Our aim in the work discussed below was the synthesis of examples of each of the three classes of compounds (47), (48), (49) indicated below.



R_N = NO_2, NH_2, N_3

R_E = electron-withdrawing substituent

(47) $R^1 = H$

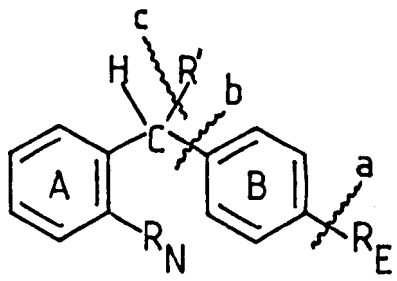
(48) $R^1 = -C_6H_5$

(49) $R^1 = -4\text{-}C_6H_4R_E$

In practice, the potential nitrene moiety, R_N, can be any of the three groups listed. The nitro group can be converted to a nitrene by deoxygenation with triethyl phosphite,[41] or readily reduced to an amino group. The amino group on the other hand can only be converted to a nitrene via the azide. Fortunately, conversion of the amine to an azide can be carried out in the presence of a wide range of functional groups although, ideally, this reaction should occur at the end of the synthesis in order to avoid losses caused through instability of the azido group.

There are a number of electron-withdrawing groups which may be considered for incorporation in the molecule at R_E, including ketones, esters, hydroxycarbonyl, hydroxysulfonyl, cyano, and nitro

groups. However, since compounds which have both strongly acidic and basic components present in the same molecule are difficult to handle, the synthesis of (47) - (49) which have hydroxycarbonyl or hydroxysulfonyl substituents was avoided. Apart from this consideration, the choice of R_E was largely primarily determined by the nature of the synthetic route chosen to obtain the target molecule.



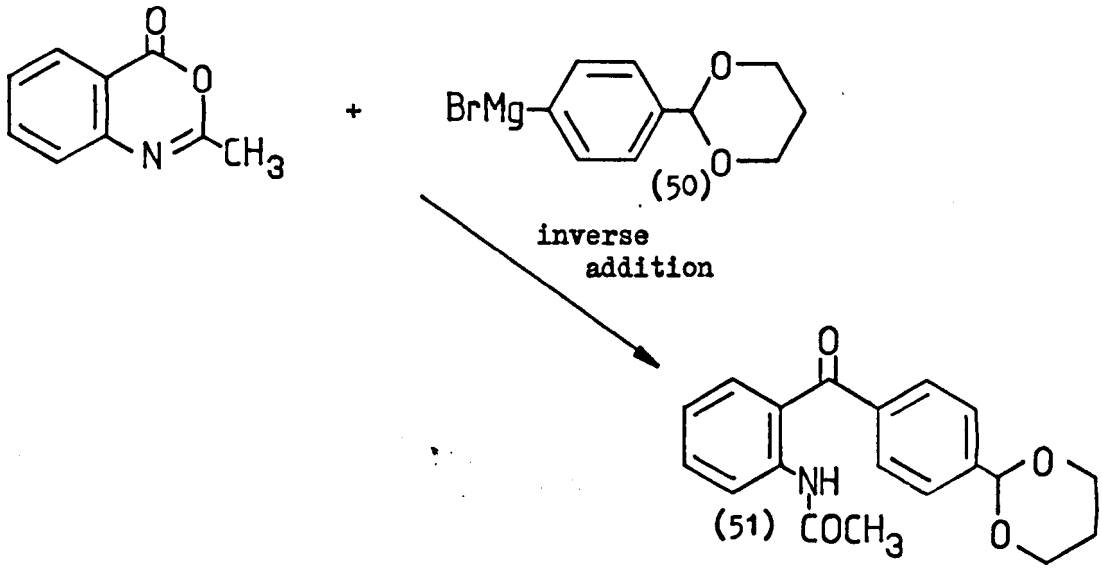
(47) - (49)

Figure 1.4

The strategic bond disconnections a and b, for diphenylmethanes, and b and c, for triphenylmethanes guided our synthetic approach. The traditional synthetic routes to these compounds either, rely on the presence of electron donating groups in the B ring (Friedel-Crafts and related syntheses of triphenylmethanes[47-50]) or depend on the absence of electron-withdrawing groups in the reactants (Grignard reactions to give triphenylmethanols[51,44] or benzophenones[44]).

The reported[11] resistance of the 1,3-dioxan moiety to attack by Grignard reagents prompted us to incorporate this versatile[12,13] group into the synthetic routes to compounds (47) - (49).

Lothrop and Goodwin's method[44] was chosen for the preparation of 2-acetamido-4'-(1,3-dioxan-2-yl)benzophenone (51).



Although 4-(1,3-dioxan-2-yl)bromobenzene was found to be resistant to Grignard reagent formation in ether solution (as are 4-(1,3-dioxolan -2-yl)bromobenzene[52] and 4-(2-methyl-1,3-dioxolan -2-yl)-bromobenzene[53]) (50) could be readily obtained in tetrahydrofuran solution.

A section of the 100 MHz ^{1}H n.m.r. spectrum of 4-(1,3-dioxan-2-yl)bromobenzene is shown in Figure 1.5. The approximate chemical shifts and coupling constants of the protons attached to C_4, C_5 and C_6 of the 1,3-dioxan ring have been derived from this spectrum with the help of decoupling experiments and are summarized in Table 1.5.

An X-ray crystal study[54] of 4-(1,3-dioxan-2-yl)chloro-benzene has indicated that the phenyl group is in an equatorial orientation with respect to the dioxane ring in its chair conformation. The similarity of this structure to that suggested by the ^{1}H n.m.r. data[55] for this molecule shows that the conformation adopted in the solid state is that which predominates in solution.

Since the nature of the halogen will have little effect on the conformation adopted by the molecule in solution we can reasonably assume that the conformation of 4-(1,3-dioxan-2-yl)bromobenzene is very similar to that of 4-(1,3-dioxan-2-yl)chlorobenzene.

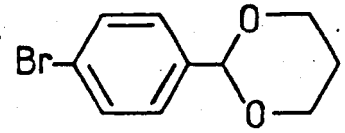


Figure 1.5

TABLE 1.5

Chemical Shifts (p.p.m.)			Coupling Constants (Hz)
5e*	1.42	(1.23)**	Geminal
5a*	2.26	(1.98)	5a, 5e = 13.4 (13.2)
4a, 6a	3.98	(3.60)	4a, 4e; 6a, 6e = 11.7 (11.2)
4e, 6e	4.28	(4.00)	Vicinal
			5e, 4a; 5e, 6a = 2.5 (2.8)
			5e, 4e; 5e, 6e = 1.4 (1.7)
			5a, 4a; 5a, 6a = 11.2 (11.0)
			5a, 4e; 5a, 6e = 5.0 (5.0)

* e = equatorial, a = axial

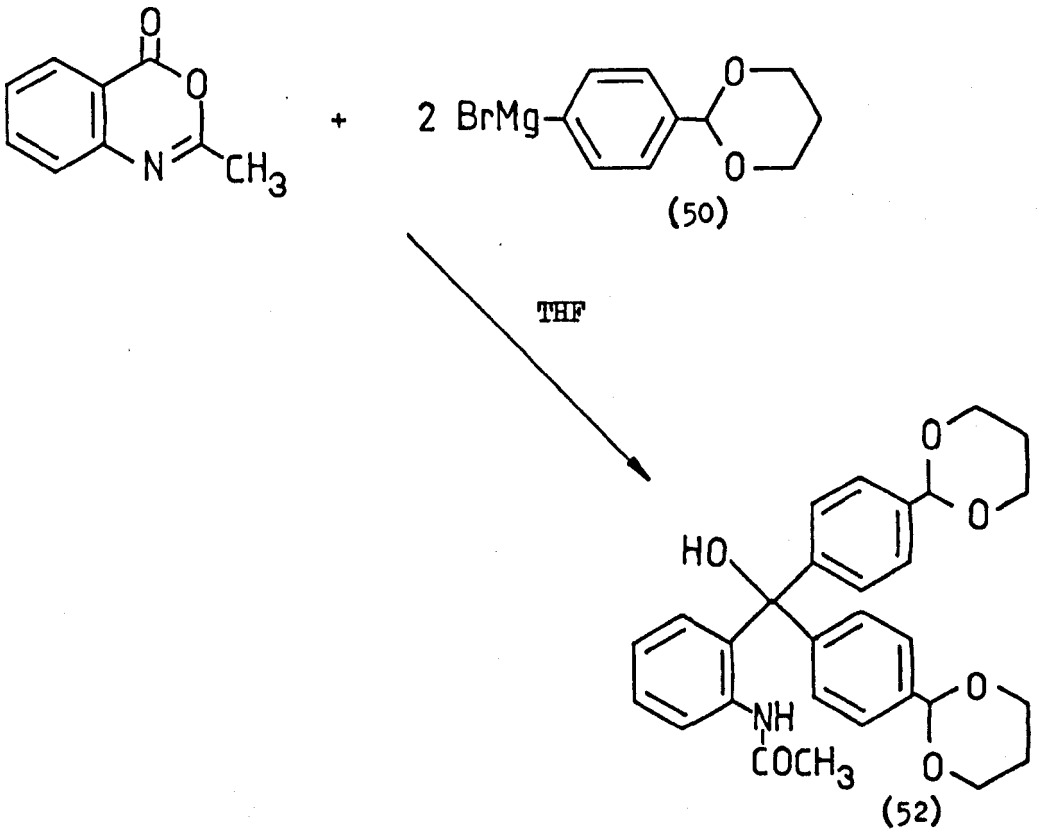
** values reported[56] for unsubstituted 1,3-dioxan

Since it had been reported[57] that the 1,3-dioxolane protecting group was unaffected by the Wolf-Kishner reduction, an attempt was made to reduce 2-acetamido-4'-(1,3-dioxan-2-yl)benzophenone (51) by the Huang-Minlon modification[58] of this method. The 1,3-dioxan protecting group, however, did not survive the reaction and a complex mixture of products was obtained. The methyl signal due to the acetamido group was also absent from the ^{1}H n.m.r. spectrum of the crude product mixture.

Having observed that the acetamido group had been apparently cleaved under the alkaline conditions of the previous reaction it was found that treatment with methanolic sodium hydroxide could also be used as an alternative to acid catalysed hydrolysis of the acetamido

group to obtain 2-amino-4'-(1,3-dioxan-2-yl)benzophenone from compound (51). This method avoids exposing the 1,3-dioxan moiety to acidic conditions in which it is known to be unstable.

Our attention was then directed towards 2-acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethanol (52). A small amount of this material had been obtained as a by-product during the preparation of 2-acetamido-4'-(1,3-dioxan-2-yl)benzophenone (51) but to obtain larger quantities we used the method outlined in Scheme 1.21.



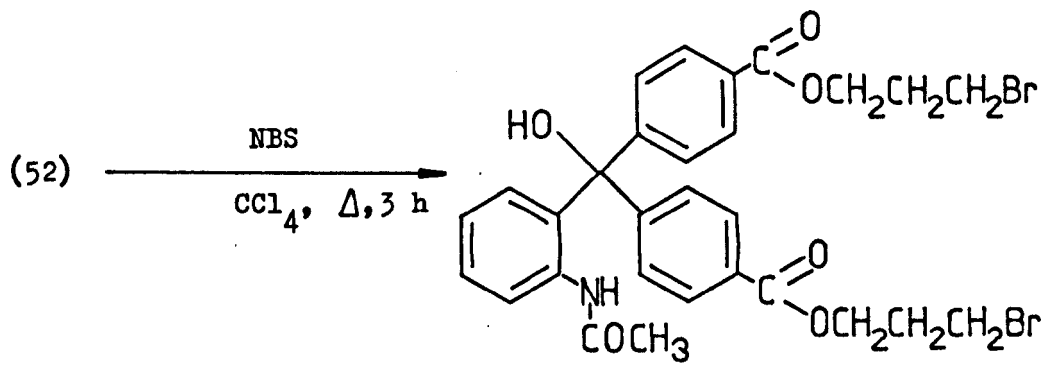
Scheme 1.21

In the past a number of methods have been successfully employed to reduce triphenylmethanols to triphenylmethanes. For example Baeyer and Villiger[51] used zinc dust and acetic acid to reduce 2-aminotriphenylmethanol to 2-aminotriphenylmethane, and the conversion of triphenylmethanol to triphenylmethane has been carried out using anhydrous formic acid,[59] isopropanol in concentrated

sulfuric acid,[60] and sodium borohydride and boron trifluoride in diethylene glycol.[61]

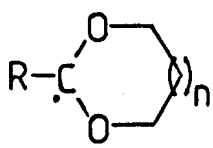
It was decided to attempt to use anhydrous formic acid to reduce 2-acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethanol (52) since this reagent had proved very successful in the preparation of the 2-azidotriphenylmethanes (25) and (26).

To avoid exposing the acid sensitive 1,3-dioxan protecting groups to formic acid these were converted to ester groups using N-bromosuccinimide (Scheme 1.22).

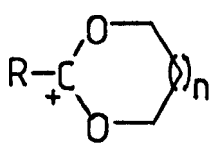


Scheme 1.22

There has been some uncertainty over the mechanism of the reaction of N-bromosuccinimide with cyclic acetals and both radical hydrogen abstraction mechanisms[62-64] giving (54), and ionic hydrogen abstraction mechanisms[65-69] giving (55), have been proposed. The experimental



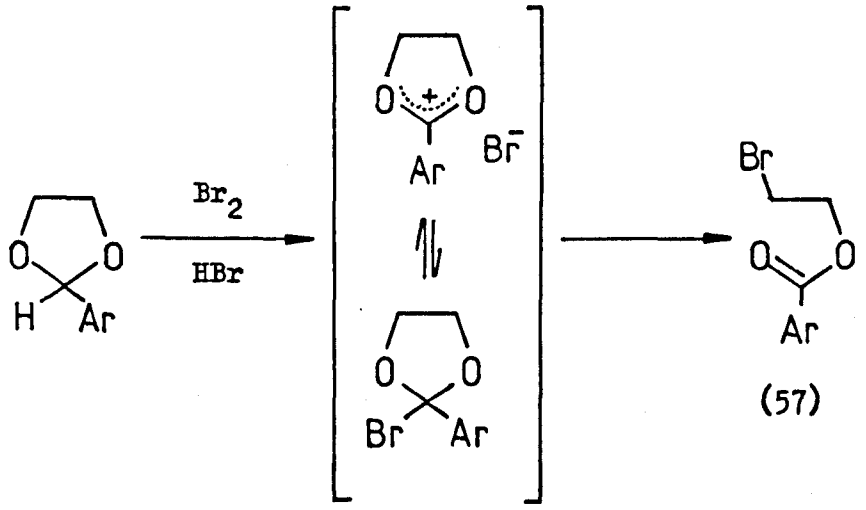
(54)



(55)

n = 0 or 1

evidence now appears to be weighted in favour of the aryloxonium ion intermediate (55). Scheme 1.23 shows the bromination of 2-aryl-1,3-dioxolane as depicted by Perst.[66]



(56) (57)

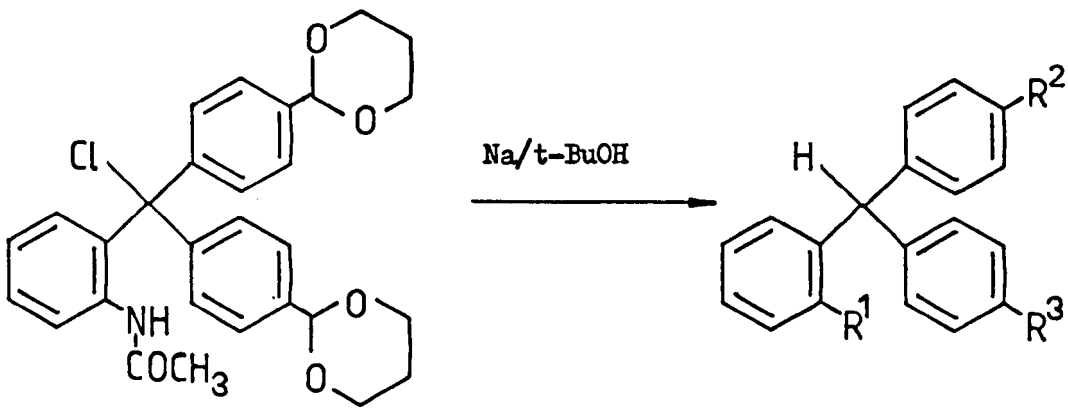
Scheme 1.23

Unfortunately treatment of 2-acetamido-4',4"-di-(3-bromopropylformate)triphenylmethanol (53) with formic acid[59] yielded an intractable green tar.

Since the nature of the ester groups in (53) were unnecessarily complex it was felt that the reaction might be more successful if these groups were simplified. For this reason an attempt was made to convert (53) to the dimethyl ester by heating it under reflux with dry hydrogen chloride in methanol. The large number of components obtained (n.m.r., t.l.c.) in the product mixture indicated that such a conversion was not viable at this stage.

It was then thought that the triphenylmethylchloride might

prove easier to reduce than the triphenylmethanol and so 2-acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethanol (52) was treated with acetyl chloride to produce this material (58). Dehalogenation of (58), by the hydridotetracarbonylferrate anion[70] gave a very complex mixture of products (as did the reaction of



(58)

(59) R^1 = -NH-$COCH_3$, R^2 = -CH_3, R^3 = -1,3-dioxan-2-yl

(60) R^1 = -NH-$COCH_3$, R^2 = R^3 = CH_3

(61) R^1 = -NH_2, R^2 = R^3 = -CH_3

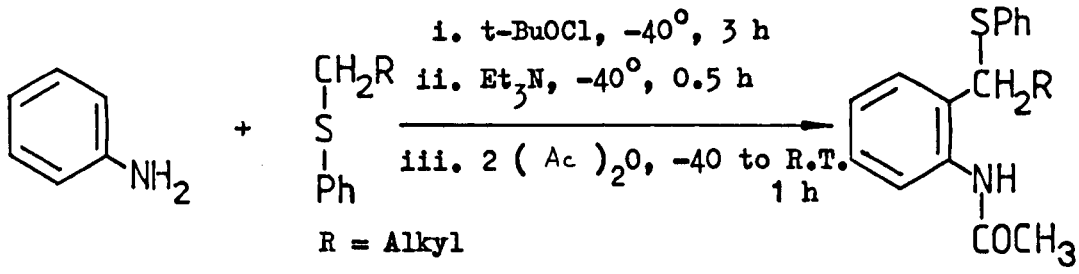
2-acetamidotriphenylmethyl chloride with this reagent) which were not further investigated.

It was, however, possible to isolate the "mixed" triphenylmethane (59) after the dissolving-metal reduction[71] of 2-acetamido-4',4"-(1,3-dioxan-2-yl)triphenylmethyl chloride (58). The nature of the other products, (60) and (61), isolated from this reaction would suggest that a shorter reaction time or a lower temperature may avoid the observed extensive reduction of the 1,3-dioxan rings.

It is worth noting that the reaction between 2-acetamidobenzophenone and 4-(1,3-dioxan-2-yl)phenylmagnesium bromide (analogous to Scheme 1.19) gave 2-acetamido-4'-(1,3-dioxan-2-yl)triphenylmethane in

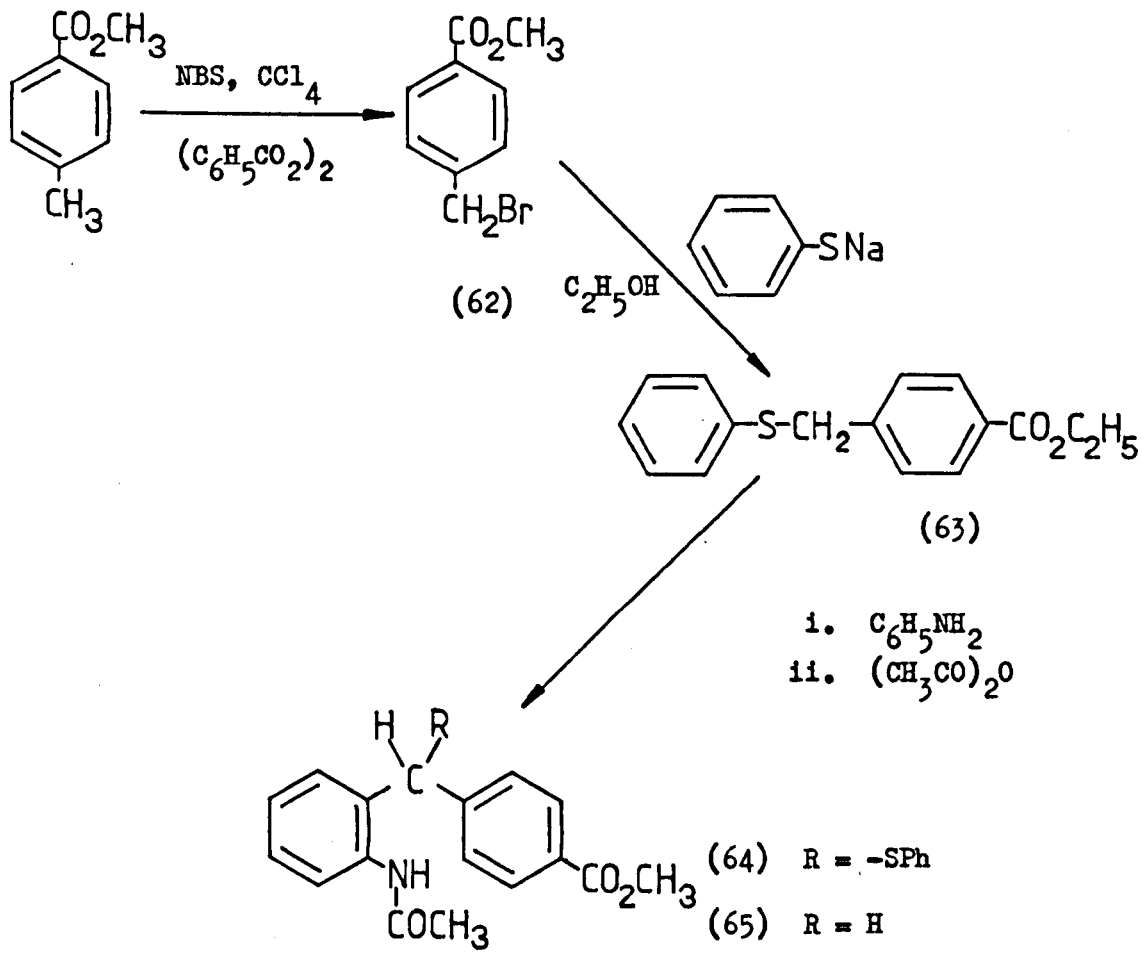
reasonable yield and this could also provide a "mixed" triphenylmethane once a suitable method of reduction is found.

While we were investigating the previous reaction Gassman and Parton published[72] an interesting and apparently useful method for the ortho-alkylation of anilines (Scheme 1.24, followed by Raney nickel desulfurization to remove the thiophenoxyl moiety).



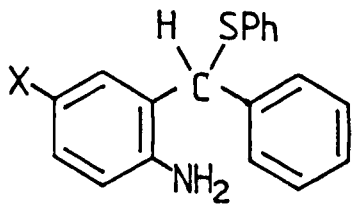
Scheme 1.24

We attempted to use this method for the synthesis of 2-acetamido-4'-methoxycarbonyldiphenylmethane (65) (i.e. R = aryl, unlike the published examples[72] where R = alkyl). The synthetic route which was followed is shown in Scheme 1.25. Schmid and Karrer's method for the preparation of benzylbromide[73] was used to obtain (62), which was then treated with sodium thiophenoxide[74] to yield 4-(ethoxycarbonyl)-benzyl phenyl sulfide (63). Gassman's ortho-alkylation method[72] was totally unsuccessful on this substrate, however, and column chromatography of the dark coloured oily product yielded only acetanilide, the sulfide (63) and diphenyldisulfide, along with a large number of other unidentified compounds which were present in minute quantities.



Scheme 1.25

A literature search then revealed that Gassman and Drewes[75] had previously prepared compounds (66) under slightly different conditions from those shown in Scheme 1.25. In the same communication[75] they also reported methods for the desulfurization of these compounds (except 66e) which gave high yields of the corresponding o-benzylanilines.



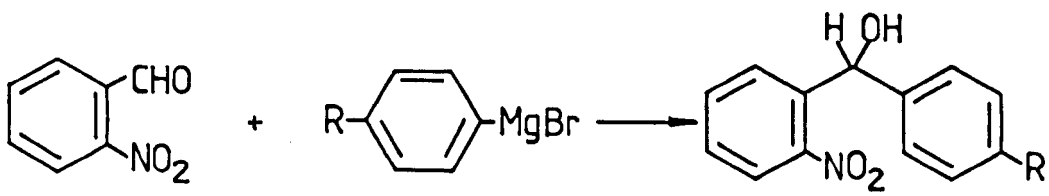
(66)

	X	Yield
a)	CH_3	73%
b)	H	72%
c)	Cl	76%
d)	CO_2CH_3	61%
e)	NO_2	65%

We therefore repeated the reaction of 4-(ethoxycarbonyl)benzyl phenyl sulfide (63) with aniline under modified conditions,[76] which were later published,[77] but once again the starting material (63) was recovered unchanged.

At this point it was decided to carry out the modified procedure for the preparation of 2-amino-5-methyldiphenylthiophenoxymethane (66a), the compound for which the method had been described.[76] However, reaction of benzyl phenyl sulfide with 4-methylaniline did not occur under these conditions and the starting materials were recovered. Further investigation of this route to 2-aminodiphenylmethanes was postponed until more information became available from the original workers.

The preparation of 3-nitrodiphenylmethanol has been reported[78] as part of a study of the reactions of Grignard reagents at low temperatures and we found that this method could be used to give an almost quantitative yield of 2-nitrodiphenylmethanol (67).



(67) R = H

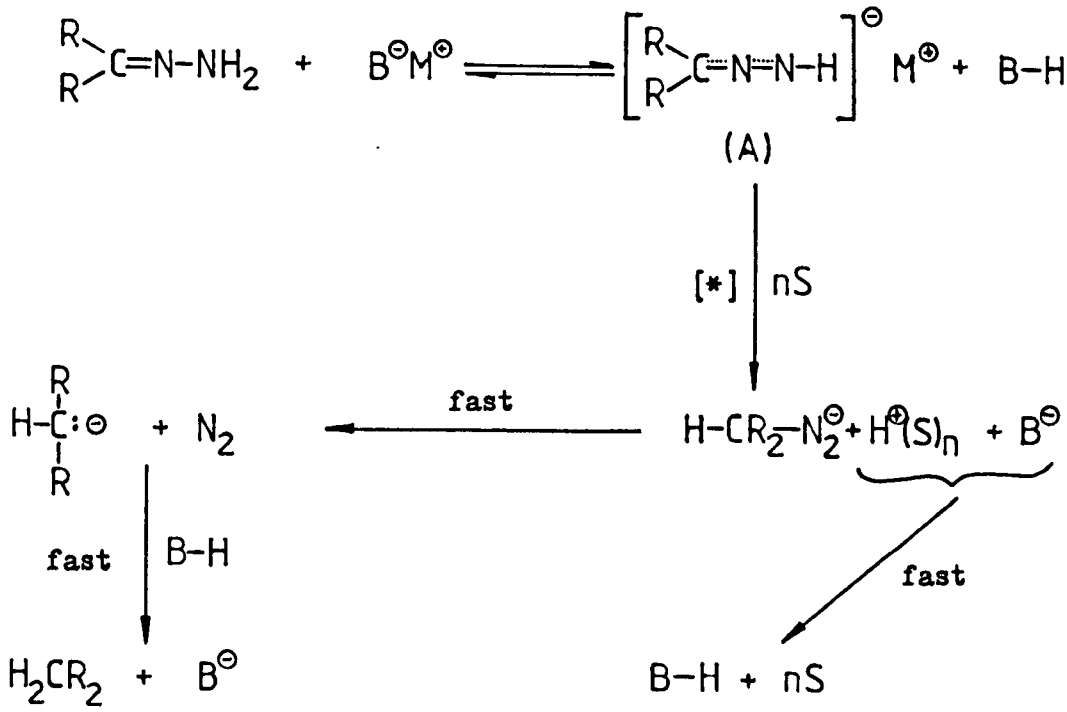
(68) R = 1,3-dioxan-2-yl

Scheme 1.26

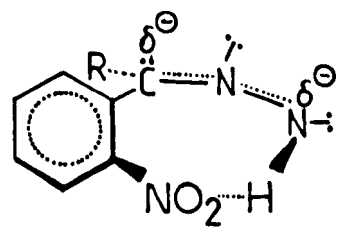
The high yield of this reaction prompted us to investigate the use of 2-nitrodiphenylmethanol as a better precursor of 2-nitrodiphenylmethane[43] than those previously used. It might then be possible to introduce an electron withdrawing substituent into the 4'-position of 2-nitrodiphenylmethane *via* a Friedel-Crafts type reaction (probably catalysed by $NaCl.AlCl_3$ rather than $AlCl_3$[79]) without affecting the other aromatic ring which would be deactivated by its nitro substituent.

2-Nitrodiphenylmethanol (67) was successfully oxidized to 2-nitrobenzophenone[80] in high yield but Wolf-Kishner reduction[58] (with either simultaneous, or separate addition of hydrazine hydrate and base) failed to give any of the required 2-nitrodiphenylmethane, as did an attempt to reduce (67) with hydriodic acid.[81]

The failure of the Wolf-Kishner reduction in this case is surprising since it has been reported[82] that the reduction of hydrazones of aromatic carbonyl compounds which contain an *ortho*-nitro group is extremely facile. Two reasons for this have been suggested[82] from a consideration of the generally accepted mechanism of the Wolf-Kishner reduction (Scheme 1.27). The initial carbanion formation will be



In our system: $B^{\ominus} = HO^{\ominus}$, S = $HOCH_2CH_2OH$, $M^{\oplus} = K^{\oplus}$.
[*] = rate determining step



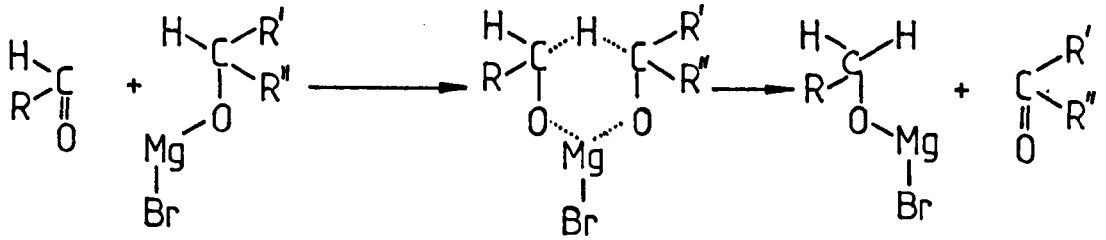
(A)

Scheme 1.27

favoured by the strongly electron withdrawing nature of the nitro substituent, and the "internal solvation" of the terminal N-H will

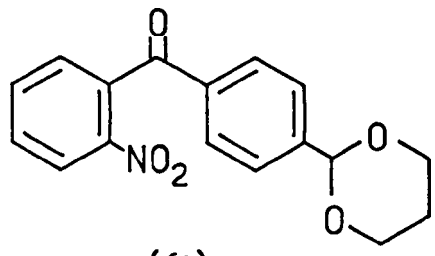
considerably lower the enthalpy of activation in the rate determining step.

4-(1,3-Dioxan-2-yl)-2'-nitrodiphenylmethanol (68) was also prepared according to Scheme 1.26. Some difficulties were encountered, however, in following Newman and Smith's exact method[78] which calls for an excess of aldehyde to be used. We found, as has been observed elsewhere,[83] that in reaction with the Grignard reagent an excess of aldehyde could operate as an oxidizing reagent. Such oxidation/reduction reactions are thought[83] to involve a quasi six-membered transition state as shown in Scheme 1.28.



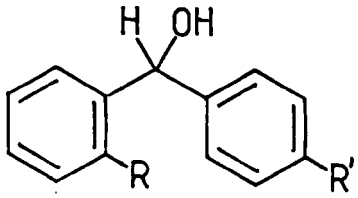
Scheme 1.28

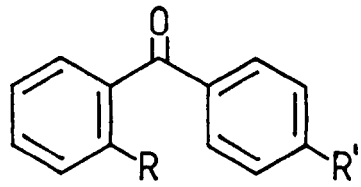
Thus, if an excess of 2-nitrobenzaldehyde and 4-(1,3-dioxan-2-yl)-phenylmagnesium bromide are reacted at -70° for four hours and the reaction mixture is worked up at that temperature, the alcohol (68) is obtained. If, however, the reaction mixture is allowed to warm to room temperature before being hydrolysed the corresponding benzophenone (69) is obtained.



(69)

The 1,3-dioxan moiety of both (68) and (69) was converted to the 3-bromopropyl ester substituent using N-bromosuccinimide, to give high yields of (70) and (71) respectively.





(70) R = NO_2; R' = $-CO_2(CH_2)_3Br$

(74) R = NH_2; R' = $-CO_2(CH_2)_3Br$

(78) R = NH_2; R' = $-CO_2CH_3$

(71) R = NO_2; R' = $-CO_2(CH_2)_3Br$

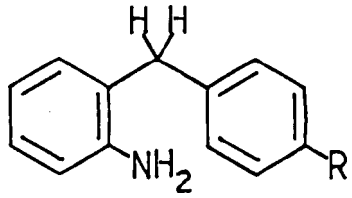
(75) R = NH_2; R' = $-CO_2(CH_2)_3Br$

(76) R = NO_2; R' = $-CO_2CH_3$

(77) R = NH_2; R' = $-CO_2CH_3$

Hydrogenation of an ethanolic solution of (70) over 10% palladium on charcoal yielded 2-amino-4'-(3-bromopropylformate)diphenylmethane (72) which was readily converted into the methyl ester (73)

using dry hydrogen chloride in methanol.



(72) R = $-CO_2(CH_2)_3Br$

(73) R = $-CO_2CH_3$

Numerous subsequent attempts to repeat the hydrogenation and obtain compound (72) were unsuccessful. On one occasion the 2-aminodiphenylmethanol (74) was formed but on most occasions the hydrogenations gave extremely complex mixtures. The aluminium chloride/palladium catalysed reduction of compound (74) by hydrogen transfer from cyclohexene[84] yielded an intractable tar.

As an alternative to hydrogenation it was thought that desulfurization of the dithioketal of 4-(3-bromopropyl formate)-2'-nitrobenzophenone (71) might provide a route to the diphenylmethanes. No reaction occurred, even when (71) was treated with ethanedithiol and borontrifluoride etherate in methanol for three days and such reactions are normally complete in one hour.[85]

A palladium catalysed transfer hydrogenation[86,87] was, however, used very successfully, to convert (71) into the corresponding 2-amino compound (75).

It had been reported[88] that benzophenones can be reduced in 90-100% yields (determined by gas-liquid chromatography) by catalytic hydrogen transfer from limonene using a palladium on charcoal catalyst

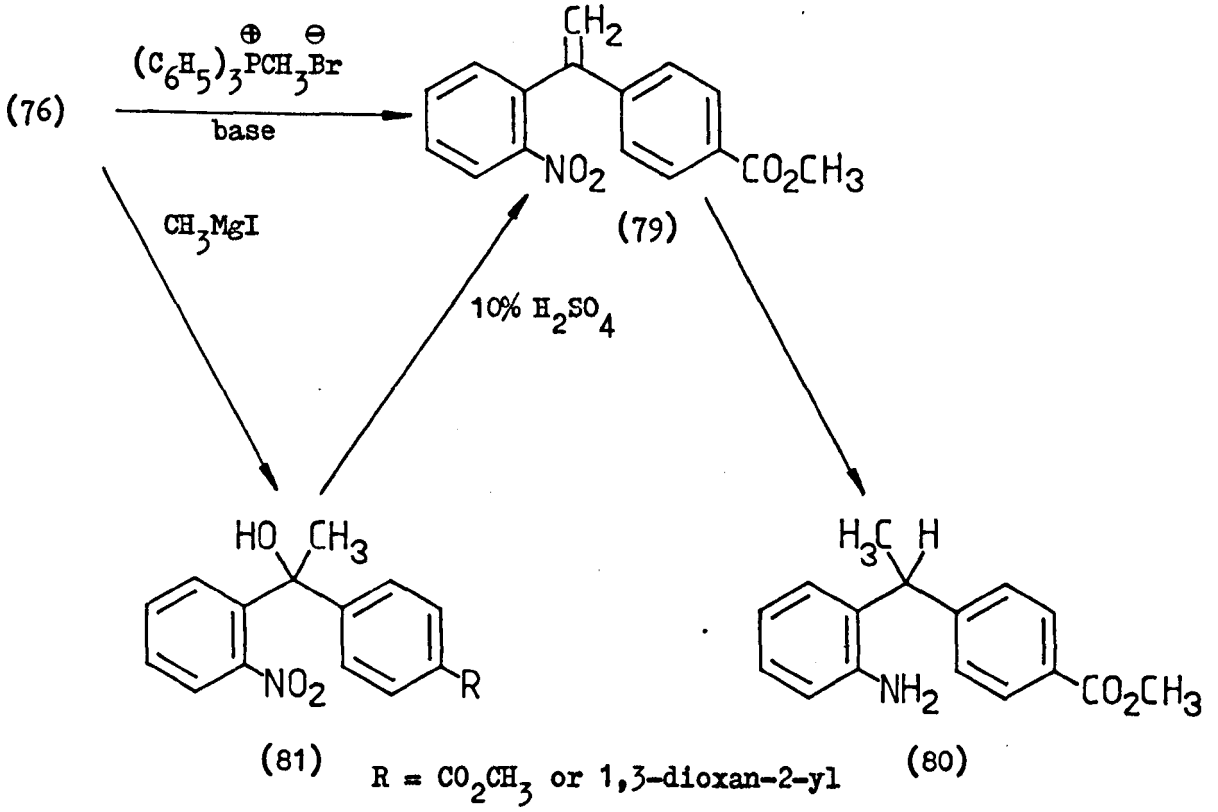
and ferric chloride promoter. The reduction of (75) was attempted by this method but severe difficulties were encountered during the work-up. Although it was not possible to remove all traces of limonene from the product mixture, there was no sign in this material of the n.m.r. signal at 3.9 p.p.m. observed previously for the protons attached to the central carbon atom of the diphenylmethane (72).

A mixture of sodium borohydride and trifluoroacetic acid in methylene chloride has been used[89] to reduce a number of benzophenones. However we found that this method was not suitable for the reduction of 2-amino-4'-(3-bromopropyl formate)benzophenone (75) as shown by the exceedingly complex nature of the n.m.r. spectrum of the crude product mixture.

It was therefore decided to simplify our substrate to a methyl ester (76) and hence reduce the number of possible side reactions which could occur during the reduction.

Treatment of a methylene chloride solution of this methyl ester (76) with a mixture of sodium borohydride and trifluoroacetic acid[89] did not, however, yield the required product. Use of the Huang-Minlon[58] modification of the Wolf-Kishner reaction was also unsuccessful on this substrate, as were attempts to prepare[90] the dithioketal.

It has now been shown to be possible[91] to reduce (76) to 2-amino-4'-methoxycarbonylbenzophenone (77) by palladium catalysed transfer hydrogen transfer from cyclohexene and then to convert this compound to the diphenylmethanol (78) using sodium borohydride in methanol and this may provide a viable route to the desired diphenylmethane in the future.



Scheme 1.29

A preliminary investigation of possible synthetic routes to compound (80), which could be subsequently converted to an azide and then thermolysed, was carried out.

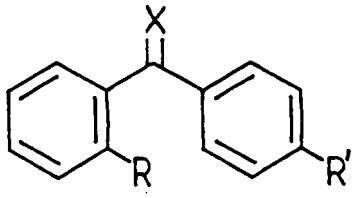
The Wittig reaction was attempted with four different bases; phenyllithium,[92] n-butyllithium,[93] sodamide,[94,95] and sodium hydride. In all cases the starting ketone (76) was recovered unchanged.

Ketones (69) and (76) were treated with methylmagnesium iodide, at -70° (since they have nitro-substituents), but no reaction occurred. This reaction could, perhaps, be carried out successfully on the corresponding amino compounds at higher temperatures. This

possibility has yet to be investigated.

It can be seen from the preceding discussion that the synthetic routes investigated so far have all presented severe difficulties at the "reduction stage". Obviously, there are numerous methods of reduction which could still be attempted at various stages of the synthesis. Some of these possibilities are listed in Table 1.6.

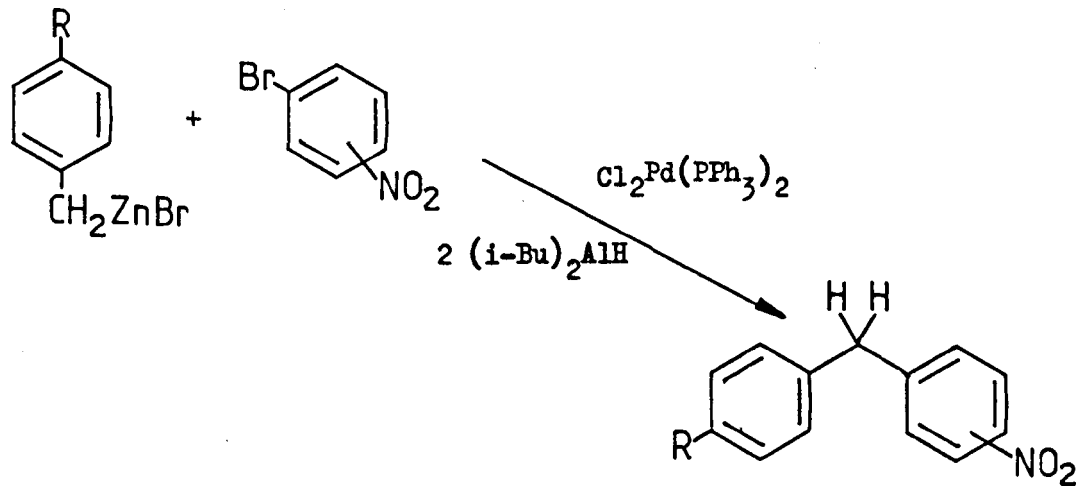
TABLE 1.6



Starting Material			Reagents	Expected Product			Ref.No.
R	R'	C=X		R	R'	C=X	
NO_2	Diox*	C=O	cyclohexene/10% Pd-C/ethanol	NH_2	Diox	C=O	86
NH_2	Diox	C=O	10% NaOH soln./Ni-Al alloy	NH_2	Diox	CH_2	96
NO_2	CO_2CH_3	C=O	trifluoroacetic acid/Et_3SiH	NO_2	CO_2CH_3	CH_2	97
NH_2	CO_2CH_3	CHOH	$AlCl_3$/cyclohexene/10% Pd-C	NH_2	CO_2CH_3	CH_2	84
NO_2	Diox	CHOH	i) R'N=C=NR'/CuCl ii) Pd-C/H_2/ethyl acetate	NH_2	Diox	CH_2	98
NH_2	Diox	C=O	i) $SiHCl_3/(C_3H_7)_3N$ ii) ethanol/KOH	NH_2	Diox	CH_2	99
NO_2	CO_2CH_3	CPhCl	$CH_3COOH/SiHEt_3$	NO_2	CO_2CH_3	CHPh	97
NH_2	CO_2CH_3	C·OHPh	$AlCl_3$/cyclohexene/10% Pd-C	NH_2	CO_2CH_3	CHPh	84

* 1,3-dioxan-2-yl

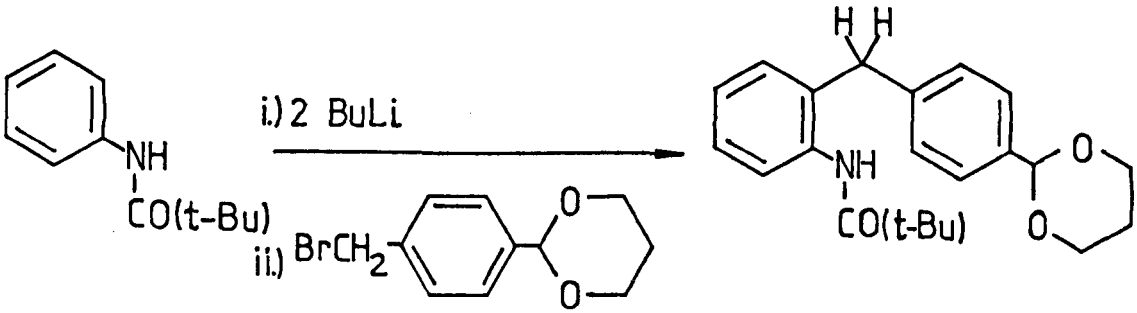
On the other hand, it may be more fruitful to pursue synthetic paths which avoid the necessity for a reduction step. For example, Negishi et al.[100] have recently devised a direct synthesis of diphenylmethanes which tolerates the presence of electrophilic functional groups such as nitrile and ester. Although most of the examples of this reaction that have been carried out have had para-substituents (e.g. Scheme 1.30; R = H; p-NO_2) it



Scheme 1.30

may be possible to carry out Scheme 1.30 with R = 1,3-dioxan-2-yl and an ortho-nitro substituent on bromobenzene.

Alternatively, it may be possible to adapt Fuhrer and Gschwend's method[101] for the ortho-functionalization of aromatic amines to synthesize the diphenylmethane systems we require (Scheme 1.31). This synthetic route is discussed in more detail in Chapter 2 of this thesis.



EXPERIMENTAL

2-Methyl-3,1-benzoxazin-4-one[102] -

2-Aminobenzoic acid (100 g, 0.73 mole) and acetic anhydride (200 ml, 2.1 mole) were heated together under reflux, on a steam bath. After 3 h, the excess acetic anhydride was removed (b.p. 48°/55 mm), and the product (70 g, 0.44 mole, 60%) was obtained by distillation (b.p. 164-165°/40 mm) of the residue. It had m.p. 79-80° (ethanol/petrol)(lit[103] 79-80°), and δ ($CDCl_3$) 2.4 (3H, s, $-CH_3$), 7.3-8.3 (4H, cplx m, aromatic).

4-(1,3-dioxan-2-yl)bromobenzene (52) -

4-Bromobenzaldehyde (69.3 g, 0.37 mole), 1.3-propanediol (30 g, 0.37 mole), 4-toluenesulfonic acid monohydrate (400 mg), and toluene (375 ml) were boiled together under reflux, using a Dean and Stark apparatus for 16 h (6.5 ml water collected). The mixture was then cooled, washed with saturated sodium bicarbonate solution (2 x 50 ml), water (2 x 50 ml), dried (Na_2SO_4), and the solvent evaporated to give a crystalline solid (78.6 g, 0.32 mole, 87%). Distillation of the crude product at 94-100°/0.01 mm and recrystallisation from ethanol yielded pure 4-(1,3-dioxan-2-yl)bromobenzene which had m.p. 63°. (Found: C, 49.6; H, 4.55. $C_{10}H_{11}O_2Br$ requires C, 49.4; H, 4.55%), m/e 244 ($M^{+\cdot}$, 72%), 243 (87), 242 ($M^{+\cdot}$, 74), 241 (100), 188 (13), 187 (11), 186 (51), 185 (92), 184 (36), 183 (77), 163 (36), 158 (15), 157 (23), 156 (15), 155 (21), 107 (17), 106 (11), 105 (36), 104 (11), 89 (11), 87 (47), 86 (49), 79 (15), 78 (15), 77 (55), 76 (34), 75 (28), 74 (11), 59 (13), 51 (28), 50 (34), 42 (32) 41 (17), 39 (11), and δ ($CDCl_3$), 1.42 (1H, br d, J13.4, $-5_{eq}H_d$),

1.95 - 2.38 (1H, cplx m, $-5_{ax}H_d$), 3.84 - 4.33 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.44 (1H, s, $-2H_d$), 7.24 - 7.53 (4H, cplx m, aromatic).

2-Acetamido-4'-(1,3-dioxan-2-yl)benzophenone (51) -

The Grignard reagent from 4-(1,3-dioxan-2-yl)bromobenzene (9 g, 40 mmole) in dry tetrahydrofuran (100 ml) was added slowly during 0.5 h to a vigorously stirred solution of freshly distilled 2-methyl-3,1-benzoxazin-4-one (6.44 g, 40 mmole) in a mixture of dry toluene (100 ml) and dry ether (50 ml) at -5°. Stirring was continued at 0° for 2 h, and at room temperature overnight. The yellow complex which had formed was then hydrolysed with a saturated solution of ammonium chloride in aqueous ammonia (100 ml, s.g. 0.880). The organic layer was separated and the aqueous phase was extracted with ether (3 x 50 ml). The ethereal extracts and the organic layer were combined and washed with saturated sodium chloride solution, dried ($MgSO_4$), concentrated, and adsorbed onto alumina. Column chromatography (activity IV alumina, 250 g) of the resulting yellow oil yielded 2-acetamido-4'-(1,3-dioxan-2-yl)benzophenone (2.1 g, 6.46 mmole, 17.5%), m.p. 121 - 122.5° (methanol). (Found: C, 70.55; H, 5.75; N, 4.5. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3%), m/e 325 (23%), 324 ($M^{+\cdot}$, 81%), 283 (27), 282 (26), 267 (20), 266 (100), 227 (10), 226 (27), 225 (41), 198 (13), 197 (43), 196 (11), 181 (13), 167 (13), 149 (14), 134 (17), 120 (29), 105 (17), 92 (14), 87 (29), 77 (17), 65 (13), 43 (33), 41 (14), and $\delta(CDCl_3)$ 1.2 - 1.5 (1H, cplx m, $-5_{eq}H_d$), 1.7 - 2.5 (4H, cplx m, $-CH_3$ and $-5_{ax}H_d$), 3.6 - 4.3 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.4 (1H, s, $-2H_d$), 6.5 - 7.6 (8H, cplx m, aromatic and -NH), 8.5 (1H, brd, J10, 6H), and 2-acetamido-4',4"-di(1,3-dioxan-2-yl)triphenylmethanol (1.7 g, 3.5 mmole, 11.6%), m.p. 176-177° (CH_2Cl_2). (Found: C, 71.0; H, 6.55; N, 2.7. $C_{29}H_{31}O_6N$ requires C, 71.15; H, 6.4; N, 2.85%), m/e 489 ($M^{+\cdot}$, 6%), 473 (17), 472 (21),

471 (65), 431 (12), 430 (19), 429 (10), 414 (12), 412 (12), 372 (12), 371 (35), 370 (100), 343 (10), 342 (29), 312 (19), 284 (25), 266 (38), 256 (10), 255 (10), 254 (15), 208 (10), 180 (12), 149 (33), 106 (10), 101 (19), 87 (65), 77 (10), 59 (17), 57 (12), 44 (52), 43 (19), 41 (12), 40 (12), 39 (10), 36 (15), and $\delta(CDCl_3)$ 1.25 (1H, br s, $-5_{eq}H_d$), 1.45 (4H, br s, $-CH_3$ and $-5_{eq}H_d$), 1.75 - 2.5 (2H, cplx m, $-5_{ax}H_d$), 3.6 - 4.4 (8H, cplx m, $-4H_d$ and $-6H_d$), 4.9 (1H, br s, -OH), 5.4 (2H, br s, $-2H_d$), 6.4 - 7.4 (11H, cplx m, aromatic), 7.95 (1H,br d, J10, -6H), 9.0 (1H, br s, -NH).

2-Amino-4'-(1,3-dioxan-2-yl)benzophenone -

2-Acetamido-4'-(1,3-dioxan-2-yl)benzophenone (100 mg, 0.3 mmole) was added to methanolic sodium hydroxide (3 ml, 10% NaOH and the resulting solution was boiled under reflux for 45 min. The methanol was removed in vacuo and the residue was extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$) and evaporated to give a yellow solid which had m/e 283 ($M^{+\cdot}$, 30%), 282 (16), 232 (14), 224 (20), 207 (18), 196 (20), 193 (20), 163 (18), 151 (20), 149 (24), 139 (18), 137 (22), 127 (16), 125 (30), 124 (18), 123 (36), 121 (18), 120 (20), 113 (18), 112 (16), 111 (52), 110 (22), 109 (50), 107 (20), 105 (20), 99 (22), 98 (18), 97 (74), 96 (30), 95 (76), 94 (32), 93 (28), 91 (20), 87 (32), 85 (56), 84 (22), 83 (76), 82 (28), 81 (72), 80 (20), 79 (40), 77 (28), 71 (88), 70 (32), 69 (100), 68 (20), 67 (42), 65 (20), 59 (20), 58 (92), 57 (92), 56 (36), 55 (92), 49 (20), 45 (36), 44 (92), 43 (96), 42 (20), 41 (100), 39 (24), and $\delta(CDCl_3)$ 0.5 - 2.5 (obscured by hydrocarbon impurities present in the starting material), 3.7 - 4.4 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.5 (1H, s, $-2H_d$), 5.9 - 6.2 (2H,br s, $-NH_2$), 6.5 - 6.8 (1H, t, -3H).

2-Acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethanol (52) -

A solution of 2-methyl-1,3-benzoxazin-4-one (1.13 g, 0.07 mole) in benzene (30 ml) and tetrahydrofuran (20 ml) was added dropwise over 30 min to a cold solution of 4-(1,3-dioxan-2-yl) phenylmagnesium bromide (34 g, 0.14 mole) in dry tetrahydrofuran (420 ml). The mixture was boiled under reflux for 4 h, allowed to cool, and then hydrolysed with a saturated solution of ammonium chloride in aqueous ammonia (170 ml, s.g. 0.880). The organic layer was separated and the aqueous phase extracted with ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. Trituration of the resulting red oil with methanol yielded a white solid (7.65 g, 0.016 mole, 22%) more of which was obtained (2.85 g, 5.8 mmole, 8.3%) by column chromatography of the residue. The characteristics of the product were identical to those of 2-acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethanol which was obtained as a by-product during the preparation of 2-acetamido-4'-(1,3-dioxan-2-yl)benzophenone (51).

2-Acetamido-4',4"-di-(3-bromopropylformate)triphenylmethanol (53) -

N-Bromosuccinimide (3.2 g, 18 mmole) was added to a solution of 2-acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethanol (4.6 g, 9.4 mmole) in carbon tetrachloride (25 ml). The resulting mixture was boiled under reflux for 2 h, cooled, filtered, and the carbon tetrachloride evaporated from the filtrate to yield a fluffy cream-coloured solid (4.56 g, 7.0 mmole, 78%). The product had $\delta(CDCl_3)$ 1.5 (3H, s, $-CH_3$), 2.35 (4H, quintet, J6, $-2H_{propyl}$), 3.55 (4H, t, J6, $-3H_{propyl}$ or $-1H_{propyl}$), 4.45 (4H, t, J6, $-3H_{propyl}$ or $-1H_{propyl}$), 6.05 (1H, br s, -OH), 6.5 - 8.0 (12H, cplx m, aromatic),

9.0 (1H,br s, -NH), and $\bar{\nu}(CHCl_3)$ 3590 (w, O-H stretch), 3400 (w, N-H stretch), 1725 cm^{-1} (s, C=O stretch).

2-Acetamido-4',4"-di(1,3-dioxan-2-yl)triphenylmethyl chloride (58) -

Acetyl chloride (0.44 ml, 5.9 mmole) was added to a solution of 2-acetamido-4',4"-di(1,3-dioxan-2-yl)triphenylmethanol (2.9 g, 5.9 mmole) in dry benzene (5.8 ml). The solution was gently warmed to boiling and then allowed to stand for 5 days at room temperature. The pale yellow solid which precipitated (2.1 g, 4.1 mmole, 69%) was filtered off, washed with petroleum ether containing a small amount of acetyl chloride, and dried at 0.05 mm/70°. It had m.p. 176 - 179°. (Found: C, 68.45; H, 6.1; N, 2.85. $C_{29}H_{30}O_5NCl$ requires C, 68.55; H, 5.9; N, 2.75%), $\delta(CDCl_3)$ 1.45 (2H, brd, J15, $-5_{eq}H_d$), 1.75 - 2.5 (5H, cplx m, $-5_{ax}H_d$ and $-CH_3$), 3.5 - 4.4 (8H, cplx m, $-4H_d$ and $-6H_d$) 5.5 (2H, s, $-2H_d$), 6.6 - 8.0 (13H, cplx m, aromatic and -NH), and $\bar{\nu}(CDCl_3)$ 3300 (w and br, -NH stretch), 2960 and 2920 (m, aromatic C-H stretch), 2860 (s, aliphatic C-H stretch), 2720 (w, $-OCH_2O$ C-H stretch), 1660 (s, amide I, C=O stretch), 1605 and 1590 (m, aromatic C-C stretch), 1510 cm^{-1} (m, amide II, C=O stretch).

Reaction of 2-acetamido-4',4"-di-(1,3-dioxan-2-yl)triphenylmethyl chloride with sodium in t-butanol -

Finely chopped sodium metal (0.45 g, 0.02 g atom) was added to a vigorously stirred solution of 2-acetamido-4',4"-di-(1,3-dioxan-2-yl) triphenylmethyl chloride (0.3 g, 0.6 mmole), in dry t-butanol (0.8 ml) and tetrahydrofuran (3.4 ml), under nitrogen. The mixture was boiled under reflux for 18 h, cooled and then excess methanol slowly added. This solution was then poured into cold water (25 ml), extracted with ether (3 x 10 ml), and the ethereal extract dried ($MgSO_4$) and concentrated to give a yellow foam which had five components by TLC. Separation by PLC (25% ethyl acetate : 75% toluene) showed that the major products were 2-acetamido-4',4"-dimethyltriphenylmethane [m/e 329 ($M^{+\cdot}$, 14%), 328 (44), 286 (41), 285 (100), 195 (9), 194 (36), 193 (13), 180 (14), 179 (12), 178 (10), 149 (14), 92 (58), 91 (62), 65 (16), 63 (10), 57 (13), 55 (10), 51 (10), 43 (33), 41 (12), 39 (14), and $\delta(CDCl_3)$ 1.9 (3H, s, $-COCH_3$), 2.3 (6H, s, $-CH_3$), 5.45 (1H, s, $-H_{methine}$), 6.8 - 7.8 (13H, cplx m, aromatic and $-NH_2$)] , 2-amino-4',4"-dimethyltriphenylmethane [m/e 287 (26%), 286 (97), 285 (57), 272 (25), 197 (12), 196 (30), 195 (14), 194 (35), 193 (16), 181 (18), 180 (27), 179 (23), 178 (15), 167 (19), 165 (21), 149 (73), 125 (25), 123 (25), 111 (38), 91 (26), 85 (40), 84 (16), 83 (47), 82 (18), 81 (40), 71 (66), 70 (25), 69 (60), 67 (30), 57 (100), 56 (26), 55 (75), 44 (16), 43 (74), 41 (61), 39 (18), and $\delta(CDCl_3)$ 2.3 (6H, s, $-CH_3$), 5.35 (1H, s, $-H_{methine}$), 6.6 - 7.2 (14H, cplx m, aromatic and $-NH_2$)] , and 2-acetamido-4'-methyl-4"-(1,3-dioxan-2-yl)triphenylmethane [m/e 401 ($M^{+\cdot}$, 19%), 400 (63), 343 (31), 342 (100), 327 (16), 301 (14), 300 (28), 272 (11), 270 (10), 208 (10), 207 (10), 194 (23), 181 (11), 180 (23), 179 (16), 165 (10), 149 (14), 87 (11), 43 (16), 41 (10), 40 (13), m^* 292 (401 → 342), and $\delta(CDCl_3)$

1.2 - 1.5 (1H, cplx m, $-5_{eq}H_d$), 1.8 - 2.5 (1H, cplx m, $-5_{ax}H_d$), 1.9 (3H, s, $-COCH_3$), 2.3 (3H, s, $-CH_3$), 3.6 - 4.3 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.45 (2H, br s, $-2H_d$ and $H_{methine}$), 6.6 - 7.8 (13H, cplx m, aromatic and -NH)].

2-Acetamidotriphenylmethyl chloride -

This was prepared from 2-acetamidotriphenylmethanol as described for the preparation of compound (58). A 69% yield of white solid was obtained with m.p. 146 - 148°. (Found: C, 75.35; H, 5.5; N, 4.4. $C_{21}H_{18}NOCl$ requires C, 75.1; H, 5.35; N, 4.15%), m/e 299 (15), 257 (13), 256 (65), 254 (15), 180 (20), 77 (38), 76 (14), 75 (10), 63 (13), 51 (30), 50 (13), 43 (100), 40 (15), 39 (15), 38 (10), 36 (30) and δ ($CDCl_3$) 2.7 (3H, s, $-CH_3$), 6.1 - 8.1 (15H, cplx m, -NH and aromatic).

2-Acetamido-4'-(1,3-dioxan-2-yl)triphenylmethanol -

2-Acetamido-4'-(1,3-dioxan-2-yl)benzophenone (10 g, 31 mmole) in dry tetrahydrofuran (31 ml) was added dropwise to a solution of phenylmagnesium bromide (69.1 mmole) in boiling ether (116 ml). The resulting mixture was stirred and boiled under reflux for 4 h, cooled, hydrolysed with a saturated solution of ammonium chloride in aqueous ammonia (75 ml, s.g. 0.880), and filtered. The organic layer of the filtrate was separated and the aqueous layer was extracted with benzene (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a yellow oil which was then adsorbed onto alumina. Chromatography on an alumina column (500 g, activity V) yielded 2-acetamido-4'-(1,3-dioxan-2-yl)triphenylmethanol (7.24 g, 18 mmole, 58%) which had m.p. 163 - 166° (CH_2Cl_2). (Found: C, 74.1; H, 6.15; N, 3.45. $C_{25}H_{25}NO_4$ requires C, 74.45; H, 6.2; N, 3.45), m/e 403 ($M^{+\cdot}$, 16%), 386 (14), 385 (44), 343 (28), 342 (50), 341 (11), 326 (11), 286 (11), 285 (32), 284 (100), 266 (13), 257 (13), 256 (50), 255 (22), 254 (18), 190 (13), 180 (22), 165 (10), 120 (10), 105 (19), 101 (14), 93 (10), 87 (58), 77 (19), 39 (10), 43 (27), 41 (10), and δ($CDCl_3$) 1.3 - 2.4 (2H, cplx m, $-5H_d$), 1.5 (3H, s, $-CH_3$), 3.7 - 4.7 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.2 (1H, s, -OH), 5.4 (1H, s, $-2H_d$), 6.4 - 8.0 (13H, cplx m, aromatic), 8.8 (1H, br s, -NH).

Methyl 4-(bromomethyl)benzoate (62) -

N-Bromosuccinimide (24 g, 0.14 mole) was added to a solution of methyl 4-methylbenzoate (19.5 g, 0.13 mole) in carbon tetrachloride (35 ml). The resulting mixture was heated and illuminated with a tungsten lamp for 5 h, then N-bromosuccinimide (8 g, 0.045 mole) and carbon tetrachloride were added to it and illumination continued for a further 5 h. The cooled reaction mixture was filtered, concentrated *in vacuo* and distilled. The product (21.6 g, 0.094 mole, 72%), obtained at 80-100°/0.1 mm, was recrystallized from absolute alcohol to give a white solid which had m.p. 55 - 55.5°, (lit.[104] 54 - 55°). (Found: C, 46.8; H, 3.85. Calc. for $C_9H_9O_2Br$: C, 47.1; H, 3.95%), m/e 230 ($M^{+\cdot}$, 10%), 228 ($M^{+\cdot}$, 10), 199 (13), 197 (11), 150 (26), 149 (100), 121 (19), 119 (13), 118 (31), 90 (23), 89 (16), 82 (11), 80 (10), 63 (13), 39 (11), δ ($CDCl_3$) 3.8 (3H, s, $-CH_3$), 4.4 (2H, s, $-CH_2Br$), 7.22 - 8.94 (4H, AA'BB', aromatic), and $\bar{\nu}$ (CCl_4) 1725 cm^{-1} (s, C=O).

4-(Ethoxycarbonyl)benzyl phenyl sulfide (63) -

Thiophenol (9.0 ml, 88 mmole) was added to sodium (2.2 g, 88 mmole) dissolved in dry ethanol (52 ml). Methyl 4-(bromomethyl) benzoate (20 g, 8.8 mmole), dissolved in the minimum quantity of dry ethanol, was added dropwise to the sodium thiophenoxide solution over 1 h. The resulting mixture was boiled under reflux for 2 h, cooled, and poured onto crushed ice (40 g). The crude product (26.1 g) was filtered off and recrystallized from 40-60° petrol. It had m.p. 30-32°. (Found: C, 70.35; H, 5.95. $C_{16}H_{16}O_2S$ requires C, 70.6; H, 5.9%), m/e 273 (19%), 272 ($M^{+\cdot}$, 100%), 227 (20), 164 (34), 163 (70), 149 (18), 135 (53), 118 (24), 109 (22), 107 (48), 92 (16), 91 (48), 90 (32), 77 (21), 65 (20), 63 (16),

51 (13), 39 (19), and $\delta(CDCl_3)$ 1.25 (3H, t, J7.2, $-CH_3$), 4.0 (2H, s, $-SCH_2$), 4.25 (2H, q, J7.2, $-CH_2$), 7.15 - 8.0 (9H, cplx m, aromatic).

2-Nitrodiphenylmethanol (67) -

An ethereal solution (50 ml) of phenylmagnesium bromide was prepared from bromobenzene (12.9 ml, 0.125 mole) and magnesium turnings (3 g, 0.125 mole), and added over a period of 2 h to a solution of 2-nitrobenzaldehyde (30 g, 0.199 mole) in toluene (415 ml) at -70°. The solution was stirred for a further 2 h at -70° and then allowed to warm to room temperature. Ethanol (100 ml) was added to decompose any residual Grignard reagent and then the reaction mixture was treated with dilute hydrochloric acid. The organic layer was washed with water, dried (Na_2SO_4) and concentrated to give a brown oil (31.0 g). The product had b.p. 150-153°/0.15 mm, m/e 212 (11%, $M^{+\cdot}$ 17), 211 (14), 197 (16), 196 (20), 195 (34), 194 (43), 181 (27), 178 (18), 177 (100), 176 (39), 175 (16), 154 (14), 153 (25), 152 (45), 151 (16), 134 (14), 121 (11), 105 (59), 104 (11), 93 (11), 92 (11), 79 (16), 78 (16), 77 (100), 76 (18), 65 (14), 64 (11), 63 (14), 51 (41), 50 (14), 44 (59), 40 (34), $\delta(CDCl_3)$ 3.3 (1H, br s, -OH), 6.3 (1H, br s, -CH), 7.1 - 7.9 (9H, cplx m, aromatic), and $\bar{\nu}$ (liq. film) 3370 (m, br, O-H stretch), 1515 and 1345 cm^{-1} (s, N-O stretch, NO_2 group).

2-Nitrobenzophenone[81] -

A solution of potassium dichromate (9 g), concentrated sulfuric acid (7.5 ml) and water (42 ml) was added in one portion with stirring to 2-nitrophenylmethanol (5 g, 22 mmole). When the mixture had cooled to room temperature it was poured into water (80 ml) and the crude product was filtered off and washed with water. It was then dissolved in a mixture of chloroform and ethyl acetate dried (Na_2SO_4), and the solvent was evaporated to yield a light brown solid (4.6 g, 20 mmole, 91%) which had m/e 227 ($M^{+\cdot}$, 27%), 167 (21), 155 (35), 154 (100), 153 (78), 152 (75), 151 (23), 150 (30), 135 (10), 134 (78), 128 (10), 127 (10), 126 (10), 121 (24), 115 (11), 107 (14), 106 (92), 105 (25), 103 (10), 92 (27), 78 (13), 77 (84), 76 (59), 75 (16), 74 (16), 65 (48), 64 (14), 63 (19), 52 (10), 51 (60), 50 (35), 43 (14), 39 (21), δ (D_6 acetone/D_6 DMSO) 7.2 - 8.4 (cplx m, aromatic), $\bar{\nu}$ (Nujol mull) 1670 (s, C=O stretch), 1525 and 1352 cm^{-1} (s, N-O stretch, NO_2 group).

4-(1,3-Dioxan-2-yl)-2'-nitrodiphenylmethanol (68) -

4-(1,3-Dioxan-2-yl)phenylmagnesium bromide (0.24 mole) in tetrahydrofuran (700 ml) was added over 3 h to a solution of 2-nitrobenzaldehyde (36.2 g, 0.24 mole) in dry toluene (780 ml) kept at -90 to -70°. The reaction mixture was stirred at -70° for a further 2 h and then allowed to warm to -5° over 1 h. It was then hydrolysed with a saturated solution of ammonium chloride in aqueous ammonia (500 ml, s.g. 0.880). The organic layer was separated, washed with water, then with saturated sodium metabisulfite solution, and then with water, dried (Na_2SO_4), and concentrated to give a yellow oil (56.5 g). Column chromatography (activity IV alumina ,1400 g) of the oil yielded

4-(1,3-dioxan-2-yl)-2'-nitrodiphenylmethanol (30.1 g, 0.096 mole, 40%), m.p. 98 - 99° (ethyl acetate). (Found: C, 64.85; H, 5.45; N, 4.35. $C_{17}H_{17}NO_5$ requires C, 64.75; H, 5.4; N, 4.45%), δ($CDCl_3$) 1.35 (1H,br d, J12, $-5_{eq}H_d$), 1.8 - 2.55 (1H, cplx m, $-5_{ax}H_d$), 3.5 (1H,br d, J5, -OH), 3.65 - 4.35 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.4 (1H, s, $-2H_d$), 6.25 (1H,br d, J5, -CH), 7.1 - 7.9 (8H, cplx m, aromatic).

4-(1,3-Dioxan-2-yl)-2'-nitrobenzophenone (69) -

4-(1,3-Dioxan-2-yl)phenylmagnesium bromide (0.24 mole) in tetrahydrofuran (700 ml) was added over a period of 2 h to a solution of 2-nitrobenzaldehyde (56.4 g, 0.38 mole) in dry toluene (780 ml) at -70°. The resulting mixture was stirred at -70° for 3 h and then allowed to warm to room temperature overnight. It was then hydrolysed with a saturated solution of ammonium chloride in ammonia (500 ml, s.g. 0.880). The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated to give a brown oil (85 g) which partly solidified. This oily solid was triturated with methanol to obtain the product, a cream coloured solid (33 g, 0.11 mole, 46%) with m.p. 126 - 127° (methanol). (Found: C, 65.35; H, 4.75; N, 4.5%. $C_{17}H_{15}NO_5$ requires C, 65.15; H, 4.8; N, 4.5%), m/e 314 (23%), 313 ($M^{+\cdot}$, 78), 312 (80), 297 (22), 296 (100), 255 (23), 254 (74), 238 (14), 211 (23), 209 (10), 208 (10), 196 (10), 195 (23), 194 (49), 184 (10), 182 (10), 181 (15), 180 (23), 179 (20), 178 (20), 177 (78), 176 (25), 173 (12), 164 (12), 163 (25), 162 (52), 161 (28), 160 (68), 135 (14), 134 (77), 133 (75), 127 (11), 121 (12), 106 (18), 105 (75), 103 (52), 87 (72), 79 (17), 78 (29), 77 (72), 76 (69), 65 (10), 63 (12), 59 (28), 52 (12), 51 (52), 50 (20), 42 (25), 41 (29), 39 (15), δ($CDCl_3$) 1.4 (1H,br d, J12, $-5_{eq}H_d$), 1.7 - 2.5 (1H, cplx m, $-5_{ax}H_d$), 3.6 - 4.3 (4H, cplx m,

$-4H_d$ and $-6H_d$), 5.4 (1H, s, $-2H_d$), 7.2 - 8.15 (8H, cplx m, aromatic) and $\bar{\nu}(CDCl_3)$ 1675 (s, C=O stretch), 1525 and 1345 cm^{-1} (s, N-O stretch, NO_2 group). The brown oil which was recovered from the methanol after trituration was chromatographed on an alumina column (activity IV, 1300 g) to give 2-nitrobenzyl alcohol (13.4 g, 88 mmole) [m/e 135 (12), 105 (28), 92 (12), 91 (34), 79 (78), 78 (38), 77 (100), 76 (16), 66 (10), 65 (28), 64 (16), 63 (10), 53 (20), 52 (44), 51 (70), 50 (26), 41 (14), 39 (48), 38 (16), and $\delta(CDCl_3)$ 3.1 (1H,br s, -OH), 4.85 (2H, s, $-CH_2$), 7.1 - 8.0 (4H, cplx m, aromatic)] and 2-nitro-4'-(1,3-dioxan-2-yl)diphenylmethanol (12.6 g, 40 mmole, 17%).

4-(3-Bromopropylformate)-2'-nitrodiphenylmethanol (70) -

4-(1,3-Dioxan-2-yl)-2'-nitrodiphenylmethanol (0.5 g, 1.6 mmole) was dissolved in hot carbon tetrachloride (5 ml) and N-bromosuccinimide (0.23 g, 1.6 mmole) was added to the solution. The resulting mixture was boiled under reflux for 3 h, cooled, filtered and the filtrate washed with saturated sodium thiosulfate solution and then with water before drying (Na_2SO_4). The solvent removed on a rotary evaporator to give an orange oil (0.5 g, 1.3 mmole, 80%) which was purified for analysis by PLC (50% ethyl acetate : 50% toluene, 25% ethyl acetate : 75% toluene). (Found: C, 51.65; H, 4.0; N, 3.6. $C_{17}H_{16}NO_5Br$ requires C, 51.8; H, 4.05; N, 3.55%), $\delta(CDCl_3)$ 2.2 (2H, quintet, J6, $-2H_{propyl}$), 3.4 (2H, t, J6, -1 or $-3H_{propyl}$), 3.75 (1H, s, -OH), 4.3 (2H, t, J6, -1 or $-3H_{propyl}$), 6.3 (1H, s, -CH), 7.1 - 7.9 (8H, cplx m, aromatic).

4-(3-Bromopropylformate)-2'-nitrobenzophenone (71) -

4-(1,3-Dioxan-2-yl)-2'-nitrobenzophenone (10 g, 32 mmole) was dissolved in hot carbon tetrachloride (100 ml), and N-bromosuccinimide (5.7 g, 32 mmole) was added to the solution. The resulting mixture was boiled under reflux for 3 h, cooled and then filtered. The filtrate was washed with saturated sodium thiosulfate solution, then with water, before drying (Na_2SO_4). The solvent was removed on a rotary evaporator to give a pale yellow oil (12.4 g, 31.5 mmole, 98%) which had $\delta(CDCl_3)$ 2.25 (2H, quintet, J7, $-2H_{propyl}$), 3.45 (2H, t, J7, -1 or $-3H_{propyl}$), 4.4 (2H, t, J7, -1 or $-3H_{propyl}$), 7.3 - 8.2 (8H, cplx m, aromatic), and $\bar{\nu}$(liq. film) 1725 (s, C=O stretch, ester), 1690 (s, C=O stretch, ketone), 1535 and 1355 cm^{-1} (s, N-O stretch, NO_2 group).

2-Amino-4'-(3-bromopropylformate)diphenylmethane (72) -

10% Palladium on charcoal (0.3 g) was added to a solution of 4-(3-bromopropylformate)-2'-nitrodiphenylmethanol (0.5 g, 1.27 mmole) in ethanol (50 ml, 95%). The resulting mixture was stirred in a hydrogen atmosphere at room temperature for 30 min (3.8 mmole H_2 absorbed), then hydrochloric acid (1.5 ml, 2N) was added and hydrogenation was continued for a further 1.5 h (1-3 mmole H_2 absorbed). The reaction mixture was then filtered and the ethanol removed on a rotary evaporator. The residue was neutralized with sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4) and the solvent was removed to yield a pink solid (0.32 g). PLC (25% ethyl acetate : 75% toluene) yielded the product (0.12 g, 0.35 mmole, 28%) from a band at R_f 0.5. It had $\delta(CDCl_3)$ 2.25 (2H, quintet, J6, $-2H_{propyl}$), 3.3 (2H,br s, $-NH_2$), 3.45 (2H, t, J6, -1 or $-3H_{propyl}$), 3.9 (2H, s, $-CH_2$), 4.35 (2H, t, J6, -1 or $-3H_{propyl}$), 6.5 - 8.0 (8H, cplx m, aromatic).

2-Amino-4'- methoxycarbonyldiphenylmethane (73)-

A solution of 2-amino-4'-(3-bromopropylformate)diphenylmethane (0.12 g, 0.35 mmole) and dry hydrogen chloride in methanol was boiled under reflux for 7 h. The solvent was then removed on a rotary evaporator and the residue was taken up in ether, washed with water, dried (Na_2SO_4), and the ether evaporated. The residue was bulb distilled at 260° - 270°/0.1 mm, and had m/e 242 (41%), 241 ($M^{+\cdot}$, 82), 240 (100), 239 (16), 226 (12), 211 (15), 210 (22), 199 (10), 198 (25), 197 (24), 196 (10), 184 (19), 183 (62), 182 (68), 181 (32), 180 (26), 167 (12), 166 (16), 165 (35), 107 (28), 106 (31), 105 (22), 105.5 (12), 104 (10), 91 (21), 90.5 (24), 90 (21), 89.5 (10), 89 (12), 86 (12), 84 (13), 78 (12), 77 (15), 57 (10), and $\delta(CDCl_3)$ 3.8 (3H, s, $-CH_3$), 4.0 (2H, s, $-CH_2$), 6.0 (2H, br s, $-NH_2$), 6.9 - 7.9 (8H, cplx m, aromatic).

2-Amino-4'-(3-bromopropylformate)diphenylmethanol -

Palladium on charcoal (3 g, 10% Pd) was added to a solution of 4-(3-bromopropylformate)-2'-nitrodiphenylmethanol (5.6 g, 14.2 mmole) in 1,2-dimethoxyethane (400 ml) and hydrochloric acid (18 ml, 2N). The resulting mixture was stirred under a hydrogen atmosphere for 5½ h at 16°C and 750 mm pressure (955 ml hydrogen were consumed), then filtered and the 1,2-dimethoxyethane removed on a rotary evaporator. The residue was neutralized with saturated sodium bicarbonate solution and then extracted with methylene chloride. The extract was washed with water, dried and the solvent removed to yield the product (3.6 g, 9.9 mmole, 70%) which had m.p. 116 - 117° (benzene). (Found: C, 56.45; H, 5.0; N, 4.05. $C_{17}H_{18}NO_3Br$ requires C, 56.05; H, 4.95; N, 3.85%), m/e 365 ($M^{+\cdot}$, 17%), 363 ($M^{+\cdot}$, 17), 347 (13), 345 (10), 226 (11), 225 (22), 224 (100), 181 (22), 180 (100), 179 (11), 82 (28), 80 (22), 79 (10), 78 (61), 77 (22), 76 (17), 69 (44), 52 (17), 51 (34), 50 (17), 44 (28), 41 (22), 40 (34), 39 (10), and $\delta(CDCl_3)$, 2.25 (2H, quintet, J6, $-2H_{propyl}$), 3.5 (5H, t, J6, -1 or $-3H_{propyl}$, -OH, and $-NH_2$), 4.35 (2H, t, J6, -1 or $-3H_{propyl}$), 5.8 (1H, s, -CH), 6.5 - 8.0 (8H, cplx m, aromatic).

2-Amino-4'-(3-bromopropylformate)benzophenone (75) -

Palladium on charcoal (0.57 g, 10% Pd) was added to a solution of 4-(3-bromopropylformate)-2'-nitrobenzophenone (10 g, 25.5 mmole) in ethanol (100 ml, 95%) and cyclohexene (31 ml). After having been boiled under reflux for 3½ h, the mixture was cooled, filtered, and the solvent was removed from the filtrate on a rotary evaporator. The resulting yellow oil (6.5 g, 18 mmole, 70%) had m/e 363 ($M^{+\cdot}$, 2%), 362 (7),

361 ($M^{+\cdot}$, 2), 360 (7), 281 (5), 238 (12), 218 (29), 210 (10), 209 (66), 208 (75), 203 (100), 195 (19), 194 (42), 161 (17), 143 (10), 120 (18), 119 (10), 118 (48), 117 (34), 105 (20), 104 (29), 103 (54), 90 (29), 89 (38), 86 (18), 84 (88), 82 (88), 80 (29), 79 (10), 78 (29), 77 (10), 75 (34), 63 (30), 56 (41), 55 (39), 49 (34), 47 (88), 45 (21), 44 (28), 43 (48), 41 (21), 39 (29), 36 (20), 35 (23), 34 (54), 33 (18), and $\delta(CDCl_3)$ 2.25 (2H, quintet, J7, $-2H_{propyl}$), 3.5 (2H, t, J7, -1 or $-3H_{propyl}$), 4.4 (2H, t, J7, -1 or $-3H_{propyl}$), 5.65 (2H, br s, $-NH_2$), 6.3 - 8.1 (8H, cplx m, aromatic).

4-Methoxycarbonyl-2'-nitrobenzophenone (76) -

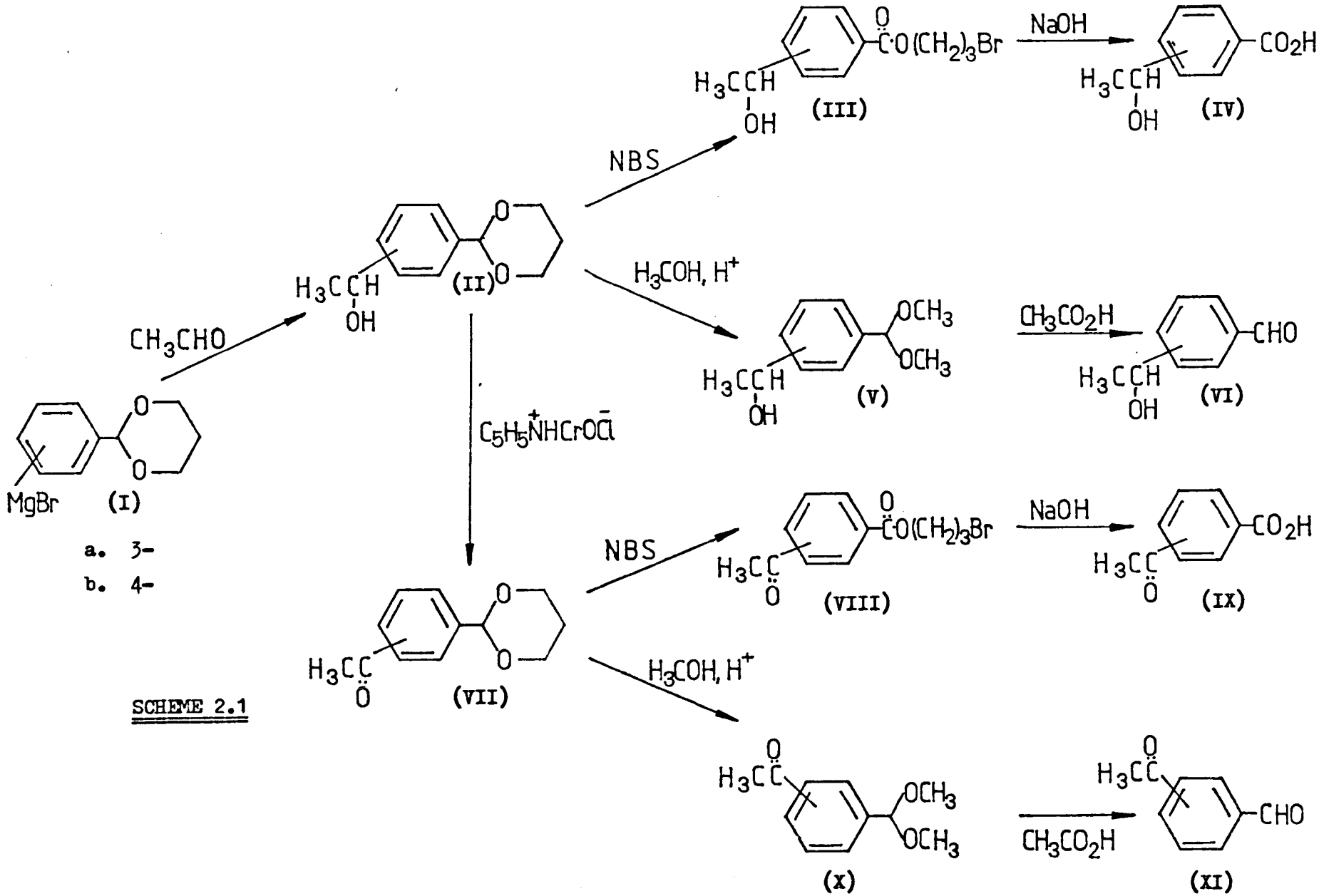
4-(3-Bromopropylformate)-2'-nitrobenzophenone (9.7 g, 24.7 mmole) was dissolved in a saturated solution of dry hydrogen chloride in methanol (100 ml). The resulting solution was boiled under reflux for 18 h, cooled, and a small quantity of the solvent was removed on a rotary evaporator. The product which crystallized out (7 g, 24.6 mmole, 99%) had m.p. 130 - 132° (methanol). (Found: C, 62.8; H, 3.8; N, 4.95. $C_{15}H_{11}NO_5$ requires C, 63.15; H, 3.85; N, 4.9%), m/e 285 ($M^{+\cdot}$, 10%), 254 (26), 163 (85), 150 (26), 135 (23), 134 (100), 104 (21), 103 (13), 77 (10), 76 (28), 75 (10), 51 (10), 50 (10), and $\delta(CDCl_3)$ 3.9 (3H, s, $-CH_3$), 7.2 - 8.2 (8H, cplx m, aromatic).

CHAPTER TWO

SYNTHETIC APPLICATIONS OF 3- AND 4-(1,3-DIOXAN-2-YL)PHENYL MAGNESIUM BROMIDE

INTRODUCTION

Much of the work described in the previous Chapter involves the new intermediate, 4-(1,3-dioxan-2-yl)phenylmagnesium bromide. This Chapter investigates its wider application, and that of 3-(1,3-dioxan-2-yl)phenylmagnesium bromide, to the synthesis of disubstituted benzene compounds. We have found that it is possible, using these Grignard reagents, to obtain compounds with the two substituents in different oxidation states. Molecules of this type have often proved difficult to synthesize in the past. Their preparation from 3- and 4-(1,3-dioxan-2-yl)phenylmagnesium bromide (I) is outlined in Scheme 2.1.


MgBr
(I)
a. 3-
b. 4-
CH3CHO
H3CCH
OH
(II)
NBS
H3COH, H+
C5H5NHCrOCl
(III)
NaOH
CO2H
(IV)
OCH3
OCH3
(V)
CH3CO2H
CHO
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)

SCHEME 2.1

No reference to the preparation of either 3- or 4-(1-hydroxyethyl)benzaldehyde (VI), or of 3-(1-hydroxyethyl)benzoic acid (IVa), could be found in the literature. However, the other products shown in Scheme 2.1 have been prepared previously by other routes.

Tinapp and Moltgen[105] have recently obtained 3-acetylbenzaldehyde (XIa) (in 75% yield), and 4-acetylbenzaldehyde (XIb) (in 79% yield) by hydrogenation of the corresponding nitriles in the presence of Raney nickel and dilute sulfuric acid. This appears to be the only method available for the preparation of 3-acetylbenzaldehyde, although 4-acetylbenzaldehyde has also been synthesized from 4-isopropyltoluene[106] and from 4-acetylbenzoic acid (in 30% yield).[107]

3-Acetylbenzoic acid (IXa) has usually been prepared from 3-aminoacetophenone by diazotization, cyanolysis, and alkaline hydrolysis; a synthetic route which was first reported by Rupe and von Majewski[108] at the beginning of this century. Alternative routes to IXa have since been reported by Braz et. al.[109] (less than 12.7% yield) and Pearson et. al.[110] (8% yield).

A large number of preparative routes to 4-acetylbenzoic acid (IXb) have been reported[53,107,110-127] and are summarized in Table 2.1. The syntheses most relevant to the present work are those of Pearson et. al.[110] and Feugeas.[53] In both these cases the acetyl moiety was protected so that the carboxyl group could be introduced via a Grignard reaction. This is the reverse of the synthetic approach outlined in Scheme 2.1, which employs a masked carbonyl group to allow introduction of the acetyl substituent.

Various reducing systems have been used to prepare 4-(1-hydroxyethyl)benzoic acid (IVb) from 4-acetylbenzoic acid (IXb)[114]

and its esters.[115,117,119]

In general, preparation of these disubstituted benzene compounds, carrying substituents of mixed oxidation state, is greatly facilitated by the use of the new Grignard reagents (I). Furthermore, it has been possible to prepare hitherto unknown disubstituted benzenoid molecules. These, in turn, should provide useful synthons for the preparation of other compounds.

Another apparently new and useful molecule, 4-(1,3-dioxan-2-yl)benzyl bromide, can also be synthesized from 4-(1,3-dioxan-2-yl)phenylmagnesium bromide (Ib). This material was obtained by treatment of 4-(1,3-dioxan-2-yl)benzyl alcohol (the product of the reaction of Ib with formaldehyde) with phosphorous tribromide. A recent report in the literature[101] suggests that it should be possible to heat the di-lithio derivative of N-pivaloyl-aniline with 4-(1,3-dioxan-2-yl)benzyl bromide and hence obtain 2-pivalamido-4'-(1,3-dioxan-2-yl)diphenylmethane. Conversion of the acetal to an ester group and acid hydrolysis of the pivaloyl protecting group should then yield an electron withdrawing nitrene precursor of the type desired (see Chapter one). Such a route to the nitrene precursor has a major advantage over those attempted previously in that it avoids the need for reduction of substituents attached to the central carbon atom in the di- or tri-phenyl-methanes - a process which has proved to be unreliable in the syntheses attempted to date.

TABLE 2.1

SYNTHETIC ROUTES TO 4-ACETYLBENZOIC ACID			YIELD, m.p.	REFERENCE
A. Syntheses involving oxidation of aromatic sidechains:				
$4\text{-}HO_2C\cdot C_6H_4\cdot C(CH_3)_2OH$	$\xrightarrow[3H_2SO_4,\ 100^\circ]{2K_2Cr_2O_7,5H_2O}$	IXb	not given, 200°	Meyer[111]
Curcumone ($C_{13}H_{18}O$, structure unknown)	$\xrightarrow{4\%\ K_2MnO_4}$	IXb	not given, 205°	Rupe and Steinbach[112]
$4\text{-}H_3C\cdot C_6H_4\cdot CH(CH_3)_2$	$\xrightarrow[90^\circ]{\text{electrochem, } INH_2SO_4}$	IXb	12.3%, 205°	Fichter and Meyer[113]
$4\text{-}H_3C\cdot CH{:}CH\cdot C_6H_4\cdot CO_2H$	$\xrightarrow{O_3,\ 10\ h}$	IXb	83%, 200°	Komppa[114]
$4\text{-}H_5C_2\cdot C_6H_4\cdot CO_2R$ $R = CH_3,\ C_2H_5$	$\xrightarrow[140\text{-}150^\circ,\ 24\ h]{CrO_3,\ CaCO_3,\ air}$	$4\text{-}H_3C\cdot CO\cdot C_6H_4\cdot CO_2R$	60-70%	Emerson et. al.[115] Emerson and Deebel[116] Monsanto[117]

TABLE 2.1 CONTINUED

SYNTHETIC ROUTES TO 4-ACETYLBENZOIC ACID		YIELD, m.p.	REFERENCE
$4\text{-}H_3C\cdot C_6H_4\cdot CO\cdot CH_3$	$\xrightarrow[56\ h,\ 115\text{-}120^\circ]{air,\ (C_6H_6O)_2Ni}$ IXb	70%, 205-206°	Sergeev and Sladkov[118]
$4\text{-}H_3C\cdot C_6H_4\cdot CO\cdot CH_3$	$\xrightarrow[60^\circ]{MgSO_4,\ KMnO_4,\ H_2O}$ IXb	54%, 200-201°	Bergman and Blum[119]
$4\text{-}HO_2C\cdot C_6H_4\cdot CH(CH_3)\cdot C_2H_5$	$\xrightarrow[Mn\ rosinate,\ 82\ h,\ 110^\circ]{Co(O\cdot CO\cdot CH_3)_2,\ Na\ stearate}$	30.5%, 203-204°	Shalganova and Zavgorondnii[120]

B. Syntheses involving hydrolysis of a nitrile group:

$4\text{-}H_2N\cdot C_6H_4\cdot CO\cdot CH_3$	$\xrightarrow[ii\quad CN^-]{i\ \ diazotize}$	$4\text{-}NC\cdot C_6H_4\cdot CO\cdot CH_3$	$\xrightarrow[reflux]{alc\ KOH}$ IXb	not given, 200°	Ahrens[121]

TABLE 2.1 CONTINUED

SYNTHETIC ROUTES TO 4-ACETYLBENZOIC ACID		YIELD, m.p.	REFERENCE
$4\text{-}H_2N\cdot C_6H_4\cdot CO\cdot CH_3$	$\xrightarrow{\substack{CH_3COOH \\ H_2SO_4}}$ IXb	30%, 208.6 - 209.4°	Detweiler and Amstutz[107]
"	$\xrightarrow[45\text{ min. reflux}]{50\%\ H_2SO_4}$ IXb	38%, 205° (from nitrile)	Langenbeck and Baltes[122]

$$H_2C{:}CH\cdot C(C{:}N){:}CH_2 + H_3C\cdot CO\cdot CH{:}CH_2 \longrightarrow 4\text{-}NC\cdot C_6H_8\cdot CO\cdot CH_3$$

$$\xrightarrow{\text{dehydrogenate}} 4\text{-}NC\cdot C_6H_4\cdot CO\cdot CH_3 \longrightarrow \text{IXb}$$

72%, not given — Tanaka[123]

C. Syntheses involving Grignard reactions:

$$Br\cdot C_6H_4\cdot C(CH_3){:}N\cdot N{:}C(CH_3)\cdot C_6H_4\ MgBr \xrightarrow[\text{ii } H^+]{\text{i } CO_2} \text{IXb}$$

34-40%, 207.5 - 209.5° — Pearson et. al[110]

TABLE 2.1 CONTINUED

SYNTHETIC ROUTES TO 4-ACETYLBENZOIC ACID		YIELD, m.p.	REFERENCE
$4\text{-Br}\cdot C_6H_4\cdot CO\cdot CH_3 \xrightarrow[HOCH_2CH_2OH]{4\text{-}CH_3\cdot C_6H_4\cdot SO_3H} 4\text{-Br}\cdot C_6H_4\cdot C(CH_3)(OCH_2CH_2O)$			
$\xrightarrow[\text{ii } CO_2/H^+]{\text{i Mg/THF}}$	IXb	47%, 208°	Feugeas[53]

D. Other methods:

$4\text{-}C_6H_4[CO\cdot CH\cdot(CO_2C_2H_5)_2]_2 \xrightarrow{\text{dil. } H_2SO_4}$	IXb	30%, 205°	Ingle[124]
$4\text{-}C_6H_4[CO\cdot CH(CO\cdot CH_3)\cdot CO_2C_2H_5]_2 \xrightarrow{35\%\ H_2SO_4}$	IXb	not given, 205°	Berend and Herms[125]
$4\text{-Br}\cdot C_6H_4\cdot CO\cdot CH_3 \xrightarrow[200°,\ 10\ atm,\ 10\ h]{CuCN,\ KCN,\ H_2O}$	IXb	not given, 206°	Feist[126]

TABLE 2.1 CONTINUED

SYNTHETIC ROUTES TO 4-ACETYLBENZOIC ACID	YIELD, m.p.	REFERENCE
$C_6H_5CCo_3(CO)_9 \xrightarrow[AlCl_3]{H_3CCOCl} 4\text{-}H_3C\cdot CO\cdot C_6H_4\cdot CCo_3(CO)_9$		
$\xrightarrow[H_2O,(H_3C)_2CO]{(NH_4)_2Ce(NO_3)_6}$ IXb	17%, 208–210°	Seyferth et. al.[127]

DISCUSSION

From a consideration of the structure of 3- and 4-(1,3-dioxan-2-yl)phenylmagnesium bromide one might expect these reagents to provide a convenient route for the production of a wide variety of disubstituted benzene compounds.

To establish whether this was so a preliminary investigation was carried out, using the synthetic routes outlined in Scheme 2.1 to prepare all the 4-substituted compounds and a selection of the 3-substituted compounds IV, VI, IX and XI. The details of the various stages of these syntheses are discussed below.

The initial reaction between the Grignard reagent (Ib) and acetaldehyde was carried out at low temperature using the method due to Newman and Smith[78] which employs a 1.5 M excess of aldehyde. Although pure 1-(1-hydroxyethyl)-4-(1,3-dioxan-2-yl)-benzene can be prepared in high yield in this way, it was later found that an excess of aldehyde often oxidizes the Grignard complex of the product alcohol to a ketone[83] (see Chapter one, page 50). To avoid this problem equimolar quantities of aldehyde and Grignard reagent were used for the preparation of the 1-(1-hydroxyethyl)-3-(1,3-dioxan-2-yl)benzene. This led to a quantity of (1,3-dioxan-2-yl)benzene being isolated along with the required product, the former arising from the hydrolysis of unreacted 3-(1,3-dioxan-2-yl)phenylmagnesium bromide. These two components could, however, be readily separated by distillation.

Oxidation of the 1-hydroxyethyl substituent to an acetyl

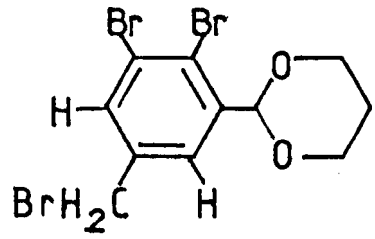
group (II → VII) was carried out cleanly and efficiently using sodium acetate-buffered pyridinium chlorochromate.[129] Barium manganate[130] was found to be totally ineffective for this purpose.

The 1,3-dioxan ring was converted to a 3-bromopropyl ester group, with N-bromosuccinimide in carbon tetrachloride following the procedure used by Rieche et. al.[13] for the cleavage of 1,3-dioxolane rings. The mechanism of this reaction is discussed in Chapter one. The yields for the conversion (II → III), when the benzene ring carried a 1-hydroxyethyl substituent, were low (30-45%). However, with the acetyl substituent present, an almost quantitative yield of 3-bromopropyl 4-acetylbenzoic acid was obtained. The reason for the low yields of the 3-bromopropyl esters of 1-hydroxyethyl benzoic acids is at present still unclear. Although preliminary steps have been made to determine the nature of the by-products formed during the preparation of 3-bromopropyl 3-(1-hydroxyethyl)benzoic acid no completely firm conclusions could be reached. During the isolation of the product by PLC an additional band at Rf 0.9 was observed whose contents were of equal weight to that of the product. Since the Rf of the desired product was 0.7 one must presume that these additional components are of lower polarity. Their ^{1}H NMR spectrum in deuterochloroform was unchanged by the addition of deuterium oxide to the solution. However, the gradual addition of dilute NaOD solution caused two sharp peaks at 5.7 p.p.m. and 7.5 p.p.m. to diminish and finally disappear, without any new signals appearing. It would appear that a component in the mixture was being extracted into the aqueous layer.

The spectrum of the small quantity of material which remained in the organic layer had signals similar to those which have been observed in molecules containing a 1,3-dioxan ring, and in addition a signal in the aromatic region with integral of four relative to the signal in the dioxane portion of the spectrum, suggests that the benzene ring is disubstituted. No other signals, which could be assigned to a 1-hydroxyethyl group, were observed. Thus it appears that we have a disubstituted benzene ring, one of the substituents being a 1,3-dioxan ring and a second substituent containing no hydrogen atoms. A mass spectrum of the components of the fast running PLC band contained peaks at m/e 242 and 244 indicating that the other substituent on the benzene ring could be a bromine atom. However, the NMR spectrum differs from that of the 3- and 4-(1,3-dioxan-2-yl)phenyl bromides (which have been made previously), so the molecule is possibly 2-(1,3-dioxan-2-yl)phenyl bromide. If this compound is present it is most likely to have arisen through bromination of the aromatic ring in (1,3-dioxan-2-yl)benzene, a small quantity of which may have contaminated the starting material. Bromination of aromatic rings by N-bromosuccinimide may occur if aged samples of this reagent are used.[131]

If a drop of a concentrated solution of NaOD (40%) was added to the deuterochloroform solution, rather than the dilute solution described previously, an orange oil separated out and the spectrum observed for the remaining solution was that which has been attributed to 2-(1,3-dioxan-2-yl)phenyl bromide above. The

oil isolated in this way was found to redissolve in D_6-acetone. The ^1H NMR spectrum of this solution had signals typical of the 4, 5 and 6 protons of a 1,3-dioxan system and the signal at 5.9 p.p.m. was still present. However, the signal in the aromatic region of the spectrum had moved upfield to 7.2 p.p.m. implying that the sodium hydroxide had brought about some chemical change in the molecule. If we assume that the signal at 5.9 p.p.m. is due to the 2-proton in a 1,3-dioxan ring then the signal at 7.2 p.p.m. integrates for two protons. Thus it appears that we have a benzene ring with four substituents arranged in such a way that the two remaining protons are in similar magnetic environments, both before and after reaction of one of the substituents with NaOD. The most likely type of substituent to be present in this case and to react with NaOD is an alkyl bromide, and there is some evidence from the integral of the peaks between 3.5 and 4.3 p.p.m. that a bromomethyl group may have been present, but obscured by the dioxan resonances. (The signal due to the CH_2Br moiety in 4-(1,3-dioxan-2-yl)benzyl bromide is observed at 4.35 p.p.m.). Signals from the resulting hydroxymethyl would also be obscured in the same way. In addition the absence of any signals due to a 1-hydroxyethyl group indicates that this group has been modified during the initial reaction with N-bromosuccinimide. The mass spectrum contains a series of peaks centred about m/e 417 ± 3 with a pattern typical of that observed for a molecule containing three bromine atoms.



XII

From a consideration of the available information a structure such as XII can be postulated. This structure is consistent with the presence of 3 bromine atoms and the molecular weight indicated by the mass spectrum. One would expect the bromomethyl substituent to be hydrolysed by alkali to a hydroxymethyl group, and this is consistent with the observed reactions with sodium hydroxide and with the upfield shift of the aromatic signal after such treatment. The position of the bromomethyl substituent between the two aromatic protons would best account for the symmetrical nature of the aromatic signal both before and after hydrolysis. It is far from clear, however, as to why a compound of this type should be formed in the reaction of 1-(1-hydroxyethyl)-3-(1,3-dioxan-2-yl)benzene with N-bromosuccinimide.

Alkaline hydrolysis of the 4-acetyl and 4-(1-hydroxyethyl) substituted 3-bromopropyl esters (IIIa and VIIIa) in aqueous methanol gave 65 - 85% yields of the corresponding acids (IVa and IXa).

Initially the aldehydes (VI, XI) were prepared by direct removal of the 1,3-dioxan protecting group with dilute hydrochloric acid. Later, a method due to Howell and Keith[132] was found to be more satisfactory. This method involved

trans-acetalation of the 1,3-dioxan in acidic methanol and then hydrolysis of the more labile dimethylacetal with aqueous acetic acid.

3-(1-Hydroxyethyl)benzaldehyde (VIa) appears not to have been previously reported, and was characterized as the 2,4-dinitrophenylhydrazone.

The identity of 3-acetylbenzaldehyde (XIa), which has also been prepared by Tinapp and Moltgen,[105] was confirmed by the properties of its bis-phenylhydrazone.

Characterization of the two 4-substituted aldehydes (VIb, XIb) presented some difficulties, the bis-2,4-dinitrophenylhydrazine derivative of XIb giving a consistently low nitrogen analysis. However, nuclear magnetic resonance spectra consistent with the correct structures have been obtained. Attempts to prepare the oxime of 4-(1-hydroxyethyl)benzaldehyde (VIb) and the bis-phenylhydrazone of 4-acetylbenzaldehyde (XIb) resulted in oily mixtures. This was probably caused by incomplete reaction of one of the carbonyl groups yielding a mixture of bis- and mono- oxime or -phenylhydrazone. It is interesting to note, however, that widely differing melting points have been reported for the analytically pure bisphenylhydrazone (121°, 189.6 - 190.8°) and dioxime (177°, 180.6 - 181.2°) derivatives of 4-acetylbenzaldehyde.[106,107] This phenomenon can probably be attributed to geometrical (syn-anti) isomerism, which is thought to be responsible for many literature discrepancies concerning the melting points of aryl hydrazones.[133] As previously mentioned, the 2,4-dinitrophenylhydrazones of VIb and XIb were also prepared but these could not be adequately purified due to their extreme insolubility in a wide range of solvents.

EXPERIMENTAL

1-(1-Hydroxyethyl)-4-(1,3-dioxan-2-yl)benzene -

A solution of 4-(1,3-dioxan-2-yl)phenylmagnesium bromide (96 mmole) dry tetrahydrofuran (285 ml), prepared from 4-(1,3-dioxan-2-yl)bromobenzene (23.3 g, 96 mmole) and magnesium turnings (2.33 g, 96 mmole), was added over a period of 2 h to a solution of acetaldehyde (6.7 g, 152 mmole) in dry toluene (320 ml) at -70°. The reaction mixture was then allowed to warm to room temperature over 1 h. After a further 5 h, it was hydrolysed with a saturated solution of ammonium chloride in ammonia (s.g. 0.880), washed with water, dried (Na_2SO_4) and concentrated to give a pale yellow oil (16.5 g, 79 mmole, 83%) which later solidified. The product had mp 67-68°. (Found: C, 68.9; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.25; H, 7.7%), m/e 208 (20%, $M^{+\bullet}$), 207 (60), 205 (10), 165 (10), 164 (55), 163 (93), 149 (28), 147 (10), 135 (25), 134 (10), 133 (15), 131 (10), 107 (28), 106 (48), 105 (100), 104 (13), 103 (30), 91 (13), 89 (13), 87 (60), 86 (13), 79 (25), 78 (15), 77 (45), 59 (30), 58 (10), 51 (15), 50 (13), 45 (13), 43 (35), 42 (33), 41 (33), 39 (13), $\delta(CDCl_3)$ 1.35 (3H, d, J6, $-CH_3$), 1.35 (1H, br d, J12, $-5_{eq}H_d$), 1.75-2.45 (1H, cplx m, $-5_{ax}H_d$), 2.05 (1H, br s, -OH), 3.65-4.35 (4H, cplx m, $-4H_d$ and $-6H_d$), 4.7 (1H, q, J6, -CH), 5.45 (1H, s, $-2H_d$), 7.1, 7.4 (4H, AA'BB', aromatic), and $\bar{\nu}(CHCl_3)$ 3450 cm^{-1} (m, broad, H-bonded O-H stretch), 3590 cm^{-1} (m, sharp, free O-H stretch).

3-Bromopropyl 4-(1-hydroxyethyl)benzoate -

N-Bromosuccinimide (1.8 g, 10 mmole) was added to a solution of 1-(1-hydroxyethyl)-4-(1,3-dioxan-2-yl)benzene (2.5 g, 12 mmole) in hot carbon tetrachloride (30 ml). The resulting mixture was boiled under reflux for 1 h, cooled, filtered, and the filtrate concentrated to give a yellow oil (3.2 g). Purification by PLC (25% ethyl acetate, 75% toluene) gave the product (1.3 g, 4.5 mmole, 45%). (Found: C, 50.5; H, 5.35. $C_{12}H_{15}O_3Br$ requires C, 50.15; H, 5.25%), m/e 288 (2%, $M^{+\cdot}$), 286 (2, $M^{+\cdot}$), 274 (13), 273 (74), 272 (13), 271 (55), 246 (10), 245 (45), 244 (10), 243 (74), 207 (10), 165 (10), 151 (16), 149 (84), 147 (10), 133 (19), 123 (35), 121 (32), 106 (19), 105 (29), 104 (10), 103 (29), 91 (10), 87 (16), 86 (16), 84 (16), 79 (29), 78 (13), 77 (39), 76 (10), 59 (39), 58 (16), 51 (10), 45 (16), 44 (26), 43 (81), 41 (100), and $\delta(CDCl_3)$ 1.45 (3H, d, J6, $-CH_3$), 2.25 (2H, quintet, J7, $-2CH_2$), 3.5 (2H, t, J7, $-CH_2$), 3.85 (1H, br s, -OH), 4.35 (2H, t, J7, $-CH_2$), 4.85 (1H, q, J6, -CH), 7.25, 7.4, 7.8, 7.95 (4H, AA'BB', aromatic).

4-(1-Hydroxyethyl)benzoic acid -

A solution of 3-bromopropyl 4-(1-hydroxyethyl)benzoate (1.1 g, 3.83 mmole), in aqueous methanol (100 ml, 80%) containing sodium hydroxide (1.0 g), was stirred at room temperature overnight. The reaction mixture was diluted with ether and washed thoroughly with water. The aqueous extracts were acidified (HCl), extracted with methylene chloride, and the methylene chloride extracts were dried (Na_2SO_4) and evaporated to give a white solid. Recrystallization of the solid from benzene containing a few drops

of ethanol yielded the product (0.3 g, 1.81 mmole, 47%) which had mp 135 - 137°. (Found: C, 65.0; H, 6.1. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.05%), m/e 166 (10%, $M^{+\cdot}$), 152 (10), 151 (85), 149 (21), 124 (13), 123 (100), 121 (13), 106 (17), 105 (23), 104 (10), 103 (10), 80 (10), 79 (58), 78 (15), 77 (58), 76 (10), 75 (10), 65 (10), 51 (23), 50 (15), 43 (46), and $\delta(CDCl_3/D_6$ DMSO) 1.4 (3H, d, J7, - CH_3), 4.77 (1H, q, J7, -CH), 6.0-7.3 (1H, br s, -OH), 7.23, 7.38, 7.79, 7.91 (4H, AA'BB' aromatic), ~14.6 (1H, br s, -COOH).

4-(1-Hydroxyethyl)benzaldehyde -

Nitrogen was bubbled through a mixture of 1-(1-hydroxyethyl)-4-(1,3-dioxan-2-yl) benzene (1.0 g, 4.8 mmole) and hydrochloric acid (25 ml, 1N) for 12 h at room temperature. The reaction mixture was then extracted with methylene chloride, and the extract dried (Na_2SO_4) and concentrated to obtain a pale yellow oil (0.4 g, 2.7 mmole, 56%) which had $\delta(CDCl_3)$ 1.45 (3H, d, J6, -CH_3), 3.6 (1H, br s, -OH), 4.85 (1H, q, J6, -CH), 7.25-7.95 (4H, cplx m, aromatic), 9.85 (1H, s, -$H_{aldehyde}$). The aldehyde was converted to its 2,4-dinitrophenylhydrazone which proved to be unsuitable for characterization due to its high insolubility in the wide range of solvents available. The crude material had mp 206-208° (absolute alcohol). (Found: C, 53.25; H, 4.05; N, 16.4. $C_{15}H_{14}N_4O_5$ requires C, 54.55; H, 4.25; N, 16.95%).

1-Acetyl-4-(1,3-dioxan-2-yl)benzene -

1-(1-Hydroxyethyl)-4-(1,3-dioxan-2-yl)benzene (3.12 g, 15 mmole) in methylene chloride (26 ml) was added in one position to a magnetically stirred suspension of pyridinium chlorochromate[129] (6.47 g, 30 mmole) and sodium acetate (0.49 g, 6 mmole) in methylene chloride (26 ml). After 2 h, dry ether (50 ml) was added to the reaction mixture and the supernatant liquid was decanted from a black gum. This insoluble residue was washed thoroughly with dry ether (3 x 10 ml), and the combined organic solutions were filtered through a short pad of Florisil. Evaporation of the solvent, *in vacuo*, gave a pale brown oil (2.6 g, 13 mmole, 84%), which later solidified and was recrystallized from cyclohexane. It had mp 61.5-63.5. (Found: C, 69.65; H, 6.55. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%), *m/e* 206 (34%, $M^{+\cdot}$), 205 (38), 149 (14), 148 (17), 147 (62), 134 (14), 133 (100), 106 (10), 105 (62), 104 (34), 103 (14), 91 (10), 87 (48), 78 (10), 77 (38), 76 (14), 65 (10), 63 (10), 59 (10), 51 (10), 43 (76), 42 (28), 41 (17), and $\delta(CDCl_3)$ 1.4 (1H, br d, J12, $-5_{eq}H_d$), 1.7-2.4 (1H, cplx m, $-5_{ax}H_d$), 2.5 (3H, s, $-CH_3$), 3.7-4.35 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.4 (1H, s, $-2H_d$), 7.2-7.85 (4H, cplx m, aromatic).

3-Bromopropyl 4-acetylbenzoate -

N-Bromosuccinimide (0.86 g, 4.8 mmole) was added to a solution of 1-acetyl-4-(1,3-dioxan-2-yl)benzene (1.0 g, 4.8 mmole) in hot carbon tetrachloride (12 ml). The resulting mixture was boiled under reflux for 3 h, cooled, filtered, and the filtrate washed with saturated sodium thiosulfate solution (twice), water (twice), dried (Na_2SO_4), and concentrated to give a pale yellow oil

(1.24 g, 4.4 mmole, 92%). The oil had m/e 286 (3%, $M^{+\cdot}$), 284 (3, $M^{+\cdot}$), 271 (22), 269 (22), 205 (19), 181 (13), 169 (13), 163 (22), 149 (22), 147 (38), 133 (19), 131 (19), 122 (19), 119 (16), 106 (13), 105 (100), 104 (13), 77 (25), 76 (13), 69 (91), 51 (28), 50 (13), 44 (31), 43 (28), 41 (31), 39 (13), $\delta(CDCl_3)$ 2.3 (2H, quintet, J7, $-2CH_2$), 2.6 (3H, s, $-CH_3$), 3.53 (2H, t, J7, $-CH_2$), 4.45 (2H, t, J7, $-CH_2$), 7.3-8.1 (4H, cplx m, aromatic), and $\bar{\nu}(CDCl_3)$ 1690 cm^{-1} (s, C=O stretch, ketone), 1722 cm^{-1} (s, C=O stretch, ester).

4-Acetylbenzoic acid -

A solution of 3-bromopropyl 4-acetylbenzoate (1.1 g, 3.86 mmole), in aqueous methanol (100 ml, 80%) containing sodium hydroxide (1.0 g), was stirred at room temperature overnight. The reaction mixture was then diluted with ether and washed thoroughly with water. The aqueous extracts were acidified (HCl), extracted with methylene chloride, and the organic phase was dried and evaporated to give a solid product (0.54 g, 3.29 mmole, 85%). The product was recrystallized from water and then benzene containing a few drops of ethanol to give a pale yellow solid mp 209° (lit[127] 208°-210°), m/e 164 (18%, $M^{+\cdot}$), 149 (100), 121 (24), 77 (11), 65 (24), 51 (11), 50 (13), 43 (22), and $\delta(CDCl_3/D_6DMSO)$ 2.6 (3H, s, $-CH_3$), 7.75-8.1 (4H, cplx m, aromatic).

4-Acetylbenzaldehyde dimethyl acetal -

1-Acetyl-4-(1,3-dioxan-2-yl)benzene (2.6 g, 13 mmole) and 4-toluenesulfonic acid (0.09 g, 0.46 mmole) in methanol (114 ml) were boiled under reflux in a nitrogen atmosphere for 2 h. The cooled reaction mixture was neutralized with anhydrous sodium carbonate and the methanol removed on a rotary evaporator. The product was taken up in methylene chloride, washed with water, dried (Na_2SO_4) and the methylene chloride evaporated. The resulting pale yellow oil (2.2 g, 11.3 mmole, 87%) had m/e 194 (4%, $M^{+\cdot}$), 178 (10), 165 (12), 164 (100), 149 (10), 133 (20), 120 (10), 105 (18), 91 (10), 77 (16), 75 (18), 51 (10), 43 (18), and $\delta(CDCl_3)$ 2.53 (3H, s, $-CH_3$), 3.27 (6H, s, $-OCH_3$), 5.32 (1H, s, $-CH_{acetal}$), 7.25-7.9 (4H, cplx m, aromatic).

4-Acetylbenzaldehyde -

A solution of 4-acetylbenzaldehyde dimethyl acetal (2.2 g, 11.3 mmole) in water (10 ml) and acetic acid (40 ml) was stirred at room temperature, under nitrogen, for 4 h. It was then neutralized with saturated sodium bicarbonate solution and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and concentrated to obtain the product, a yellow oil (1.1 g, 7.4 mmole, 65%*), which had $\delta(CDCl_3)$ 2.6 (3H, s, $-CH_3$), 7.55-8.05 (4H, cplx m, aromatic), 9.98 (1H, s, $-CH_{aldehyde}$). A quantity of the product was immediately converted to the bis-2,4-dinitrophenylhydrazone (using Brady's reagent) for further characterization. As in the case of 4-(1-hydroxyethyl)benzaldehyde, this derivative was found to be unsatisfactory.

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* A quantity of material was lost during work up. Estimated yield is 90%.

3-(1,3-Dioxan-2-yl)bromobenzene -

3-Bromobenzaldehyde (100 g, 0.54 mole), 1,3-propanediol (41.1 g, 0.54 mole), 4-toluenesulfonic acid monohydrate (1.0 g), and benzene (100 ml) were boiled together under reflux, using a Dean and Stark apparatus, for 12 h (10 ml water collected). The resulting mixture was cooled, washed with saturated sodium bicarbonate solution and then with water, dried (Na_2SO_4), and concentrated to give a pale yellow oil (140.6 g). Pure 3-(1,3-dioxan-2-yl)bromobenzene (106.2 g, 0.44 mole, 80%) was obtained by distillation of the crude product at 100-125°/0.25 mm. (Found: C, 49.05; H, 4.45. $C_{10}H_{11}O_2Br$ requires C, 49.4; H, 4.55%), m/e 244 (40%, $M^{+\cdot}$), 243 (60), 242 (46, $M^{+\cdot}$), 241 (54), 186 (57), 185 (97), 184 (66), 183 (100), 163 (31), 158 (14), 157 (34), 156 (14), 155 (46), 127 (20), 105 (40), 87 (91), 86 (29), 78 (14), 77 (66), 76 (37), 75 (34), 74 (20), 59 (20), 51 (46), 50 (49), 44 (69), 42 (31), 41 (17), and $\delta(CDCl_3)$ 1.35 (1H, br d, J14, $-5_{eq}H_d$), 1.65-2.5 (1H, cplx m, $-5_{ax}H_d$), 3.6-4.3 (4H, cplx m, $-4\ H_d$ and $-6H_d$), 5.32 (1H, s, $-2H_d$), 6.9-7.5 (4H, cplx m, aromatic).

1-(1-Hydroxyethyl-3-(1,3-dioxan-2-yl)benzene -

The preparation was carried out as described for 1-(1-hydroxyethyl)-4-(1,3-dioxan-2-yl)benzene using 3-(1,3-dioxan-2-yl)-phenylmagnesium bromide (192 mmole) in tetrahydrofuran (600 ml) and acetaldehyde (10.8 ml, 192 mmole) in toluene (640 ml). The two components of the crude product (31.1 g), (1,3-dioxan-2-yl)benzene (5.93 g, 36 mmole, bp 66-90°/0.04 mm) and 1-(1-hydroxyethyl)-3-(1,3-dioxan-2-yl)benzene (18.54 g, 89 mmole, 57%, bp 140-158°/0.06 mm), were separated by distillation. (1,3-Dioxan-2-yl)benzene

had m/e 164 (46%, $M^{+\cdot}$), 163 (98), 106 (34), 105 (100), 87 (46), 79 (16), 78 (20), 77 (48), 51 (27), 50 (14), 42 (18), 41 (18), and $\delta(CDCl_3)$ 1.1-1.4 (1H, cplx m, $-5_{eq}H_d$), 1.6-2.4 (1H, cplx m, $-5_{ax}H_d$), 3.5-4.3 (4H, cplx m, $-4H_d$ and $-6H_d$), 5.32 (1H, s, $-2H_d$), 7.1-7.5 (5H, cplx m, aromatic). 1-(1-Hydroxyethyl)-3-(1,3-dioxan-2-yl)benzene had m/e 208 (48%, $M^{+\cdot}$), 207 (95), 193 (19), 170 (19), 169 (24), 153 (62), 150 (14), 149 (57), 147 (14), 135 (57), 133 (29), 107 (67), 106 (14), 105 (38), 104 (14), 103 (76), 91 (14), 87 (100), 79 (52), 78 (19), 77 (57), 76 (14), 65 (19), 63 (14), 59 (43), 58 (29), 57 (24), 52 (14), 51 (24), 50 (19), 45 (33), 44 (24), 43 (52), 42 (33), 41 (43), 39 (24), and $\delta(CDCl_3)$ 1.4 (3H, d, J6, $-CH_3$), 1.25-1.6 (1H, cplx m, $-5_{eq}H_d$), 1.65-2.55 (1H, cplx m, $-5_{ax}H_d$), 2.65 (1H, br s, -OH), 3.65-4.35 (4H, cplx m, $-4H_d$ and $-6H_d$), 4.75 (1H, q, J7, -CH), 5.4 (1H, s, $-2H_d$), 6.5-7.4 (4H, cplx m, aromatic).

3-Bromopropyl 3-(1-hydroxyethyl)benzoate -

N-Bromosuccinimide (1.17 g, 9.6 mmole) was added to a solution of 1-(1-hydroxyethyl)-3-(1,3-dioxan-2-yl)benzene (2.0 g, 9.6 mmole) in carbon tetrachloride (24 ml). The resulting mixture was boiled under reflux for 3 h, cooled, and filtered. The filtrate was washed with saturated sodium thiosulfate solution, and then with water, dried (Na_2SO_4) and concentrated to give a pale yellow oil (2.7 g). Purification of a portion of the crude product (1.6 g, 59%) by PLC (50% ethylacetate, 50% toluene) gave pure 3-bromopropyl 3-(1-hydroxyethyl)benzoate (0.5 g, 1.7 mmole, 30%), m/e 288 (5%, $M^{+\cdot}$), 286 (3, $M^{+\cdot}$), 273 (49), 271 (53), 245 (44), 243 (51), 165 (14), 163 (12), 151 (14), 150 (12), 149 (53), 148 (16), 147 (14), 134 (12), 133 (100), 131 (12), 123 (35), 121 (16), 106 (21), 105 (60), 104 (14), 103 (46), 91 (19), 87 (23),

79 (21), 78 (14), 77 (49), 58 (37), 57 (19), 51 (26), 50 (14), 45 (21), 44 (19), 43 (77), 42 (12), 41 (65), 39 (26), and $\delta(CDCl_3)$ 1.45 (3H, d, J6, $-CH_3$), 2.35 (2H, quintet, J7, $-2CH_2$), 2.4 (1H, br s, -OH), 3.47 (2H, t, J7, $-CH_2$), 4.35 (2H, t, J7, $-CH_2$), 4.83 (1H, q, J6, -CH), 7.1-7.9 (4H, cplx m, aromatic).

3-(1-Hydroxyethyl)benzaldehyde -

3-(1-Hydroxyethyl)benzaldehyde dimethyl acetal (1.0 g, 5.5 mmole), in acetic acid (20 ml) and water (5 ml), was stirred at room temperature, under nitrogen for 4 h. The solution was then neutralized with saturated sodium bicarbonate solution, extracted with methylene chloride, dried (K_2CO_3) and the solvent removed on a rotary evaporator. The product, a pale yellow oil (0.63 g, 4.2 mmole, 76%), had $\delta(CDCl_3)$ 1.45 (3H, d, J6, $-CH_3$), 3.8 (1H, br s, -OH), 4.85 (1H, q, J6, -CH), 7.15-7.75 (4H, cplx m, aromatic), 9.75 (1H, s, $-CH_{aldehyde}$). The aldehyde was immediately converted to the 2,4-dinitrophenylhydrazone using Brady's reagent.[134] It had mp 204-205°. (Found: C, 54.0; H, 4.25; N, 16.95. $C_{15}H_{14}N_4O_5$ requires C, 54.55; H, 4.25; N, 16.95%), m/e 330 (51%, $M^{+\cdot}$), 297 (18), 296 (23), 295 (100), 265 (15), 251 (18), 250 (33), 219 (15), 193 (15), 166 (15), 165 (13), 149 (13), 133 (23), 132 (15), 107 (13), 106 (13), 105 (26), 104 (15), 103 (28), 91 (23), 90 (13), 89 (31), 79 (31), 78 (20), 77 (41), 76 (15), 75 (13), 65 (15), 64 (15), 63 (28), 51 (23), 45 (41), 43 (38), 39 (20).

1-Acetyl-3-(1,3-dioxan-2-yl)benzene -

The preparation was carried out as previously described for 1-acetyl-4-(1,3-dioxan-2-yl)benzene. The product (3.8 g, 18.4 mmole, 65%) was obtained from 1-(1-hydroxyethyl)-3-(1,3-dioxan-2-yl)benzene (6.1 g, 28.5 mmole) as a brown oil. A sample was purified by distillation to give a colourless oil bp 103-106°/0.1 mm. (Found: C, 69.65; H, 6.95. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%), m/e 206 (31%, $M^{+\cdot}$), 205 (56), 191 (22), 165 (19), 163 (14), 149 (19), 148 (22), 147 (94), 135 (10), 134 (14), 133 (94), 119 (31), 105 (53), 104 (28), 103 (17), 91 (17), 89 (10), 87 (100), 79 (10), 78 (10), 77 (39), 76 (17), 75 (14), 65 (10), 63 (10), 59 (14), 51 (31), 50 (14), 49 (10), 44 (33), 43 (67), 42 (17), 41 (25), 39 (17), $\delta(CDCl_3)$ 1.3 (1H, br d, J12, $-5_{eq}H_d$), 1.7-2.4 (1H, cplx m, $-5_{ax}H_d$), 2.5 (3H, s, $-CH_3$), 3.6-4.3 (4H, cplx m, $-4H_d$ and $6H_d$), 5.35 (1H, s, $-2H_d$), 7.1-7.9 (4H, cplx m, aromatic), and $\bar{\nu}(CDCl_3)$ 1685 cm^{-1} (s, sharp, C=O stretch).

3-Acetylbenzaldehyde -

The dimethylacetal was prepared from 1-acetyl-3-(1,3-dioxan-2-yl)benzene (1.0 g, 4.8 mmole) and then converted to 3-acetylbenzaldehyde (0.6 g, 4.05 mmole, 84%), as described previously for the 4-isomer. It had $\delta(CDCl_3)$ 2.6 (3H, s, $-CH_3$), 7.35-8.25 (4H, cplx m, aromatic), 9.9 (1H, s, $-H_{aldehyde}$). A portion of the aldehyde was converted to its bis-phenylhydrazone which had mp 162-164° (absolute alcohol) (lit[105] 163-166°), m/e 239 (24%), 238 ($M^{+\cdot}$, 100), 237 (32), 223 (16), 195 (42), 104 (13), 97 (13), 95 (10), 93 (50), 92 (82), 91 (16), 85 (13), 77 (18), 76 (18), 71 (18), 69 (18), 67 (13), 66 (18), 65 (53), 63 (16), 57 (18), 55 (16), 51 (16), 43 (21), 41 (16), 39 (21).

4-(1,3-Dioxan-2-yl)benzyl bromide[135]-

Formaldehyde (generated from paraformaldehyde) was added to 4-(1,3-dioxan-2-yl)phenylmagnesium bromide (0.17 mole) in tetrahydrofuran (500 ml) until all the Grignard reagent had been consumed. The reaction mixture was then hydrolysed with a saturated solution of ammonium chloride in ammonia. The aqueous phase was separated, washed with ether, and the combined organic layers were dried ($MgSO_4$), concentrated and distilled (164-167°/ 0.25 mm) to yield 4-(1,3-dioxan-2-yl)benzyl formate (12 g, 0.05 mole, 29%), $M^{+\cdot}$ 222, $\bar{\nu}$(Nujol mull) 1722 cm^{-1} (s, C=O stretch). The formate was dissolved in ether (100 ml) and added to lithium aluminium hydride (0.95 g, 0.025 mole). This mixture was boiled under reflux for 2 h, cooled, excess hydride decomposed with ethyl acetate, and the resulting mixture hydrolysed with a solution of ammonium chloride in ammonia (s.g. 0.880), and extracted with ether. After drying the organic layer, the solvent was removed to yield 4-(1,3-dioxan-2-yl)benzyl alcohol (8.6 g, 44 mmole, 88%), mp 106° (cyclohexane/benzene). (Found: C, 68.05; H, 7.35. $C_{11}H_{14}O_3$ requires C, 68.05; H, 7.2%), m/e 194 ($M^{+\cdot}$, 58%), 193 (100), 176 (10), 163 (65), 136 (21), 135 (77), 133 (10), 108 (13), 107 (85), 105 (23), 91 (29), 90 (10), 89 (19), 87 (46), 79 (52), 78 (10), 77 (42), 63 (10), 59 (17), 51 (19), 50 (10), 45 (15), 42 (17), 41 (23), 39 (19), and $\delta(CDCl_3)$ 1.4 (1H, brd, J12, $-5_{eq}H_d$), 1.75-2.65 (1H, cplx m, $-5_{ax}H_d$), 2.5 (1H, br s, -OH), 3.65-4.4 (4H, cplx m, $-4H_d$ and $-6H_d$), 4.55 (2H, s, $-CH_2$), 5.4 (1H, s, $-2H_d$), 7.1-7.45 (4H, cplx m, aromatic). Treatment of the alcohol with phosphorous tribromide yielded a mixture of 4-(bromomethyl)benzaldehyde and 4-(1,3-dioxan-2-yl)benzyl bromide

m/e 258 ($M^{+\cdot}$, 2%), 257 (8), 256 ($M^{+\cdot}$, 2), 255 (8), 200 ($M^{+\cdot}$, 4), 199 (8), 198 ($M^{+\cdot}$, 4), 197 (6), 178 (13), 177 (100), 120 (12), 119 (67), 118 (12), 105 (10), 91 (79), 90 (17), 89 (15), 87 (17), 77 (12), 65 (10), 63 (12), 51 (10), 41 (10), 39 (12), and

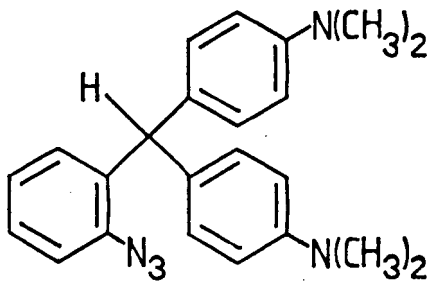
$\delta(CDCl_3)$ 1.35 ($^5/_9$H, brd, J12, $-5_{eq}H_d$), 1.7-2.95 ($^5/_9$H, cplx m, $-5_{ax}H_d$), 3.65-5.1 ($^{20}/_9$H, cplx m, $-4H_d$ and $-6H_d$), 4.35 (2H, s, $-CH_2Br$), 5.35 ($^5/_9$H, s, $-2H_d$), 7.1-7.4 (4H, cplx m, aromatic), 9.8 ($^4/_9$H, s, $-H_{aldehyde}$).

CHAPTER THREE

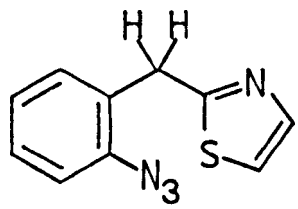
INTRAMOLECULAR NITRENE INSERTIONS INTO AROMATIC SYSTEMS

INTRODUCTION

This chapter describes the preparation and decomposition of 2-azido-4',4"-bis(dimethylamino)triphenylmethane (82) and 2-azidophenyl-2-thiazolylmethane (83).



(82)

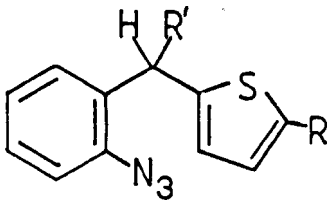


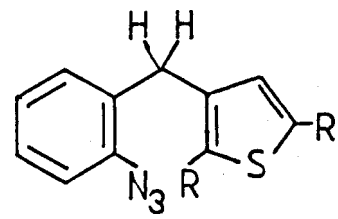
(83)

An outline of the methods available for the preparation of 2-azidotriphenylmethanes is given in the Introduction to Chapter 1, and the products which have been obtained by thermolysing 2-azidotriphenylmethanes containing electron-rich nitrene-receiving rings are summarized in Table 1.3. The thermolysis of 2-azido-4',4"-dimethylaminotriphenylmethane provides a further example of this type of reaction.

A number of nitrene insertions into π-excessive[136] heteroaromatics have been reported and various mechanisms have been proposed to account for the products obtained.

For example, Jones and his co-workers[4,6,9,10] have thermolysed azides (84) - (87) in 1,2,4-trichlorobenzene at 180-200°,

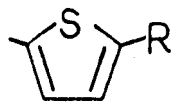




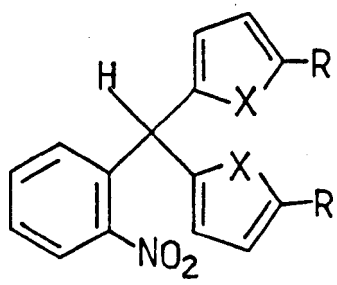
(87) R = CH_3

(84) R = R' = H

(85) R = CH_3, R' = H

(86) R = t-C_4H_9, R' = 

and have deoxygenated nitro compounds (88) - (96) with triethyl phosphite in boiling cumene. The intermediacy of a true nitrene in these decompositions is confirmed by the formation of the same products from both nitro and azide precursors.



(88) X = O, R = H (92) X = S, R = H

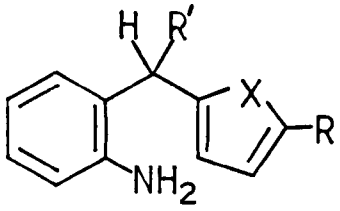
(89) X = O, R = CH_3 (93) X = S, R = CH_3

(90) X = O, R = C_2H_5 (94) X = S, R = C_2H_5

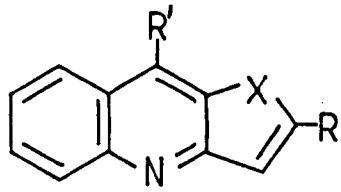
(91) X = O, R = t-C_4H_9 (95) X = S, R = t-C_4H_9

(96) X = NCH_3, R = H

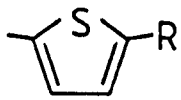
Decomposition of the 2-substituted thiophenes (84) - (86), (92) - (95) and pyrrole (96) yielded both amine (97) and acridine analogues (98) reminiscent of the decomposition products obtained in the diphenyl- and



(97)



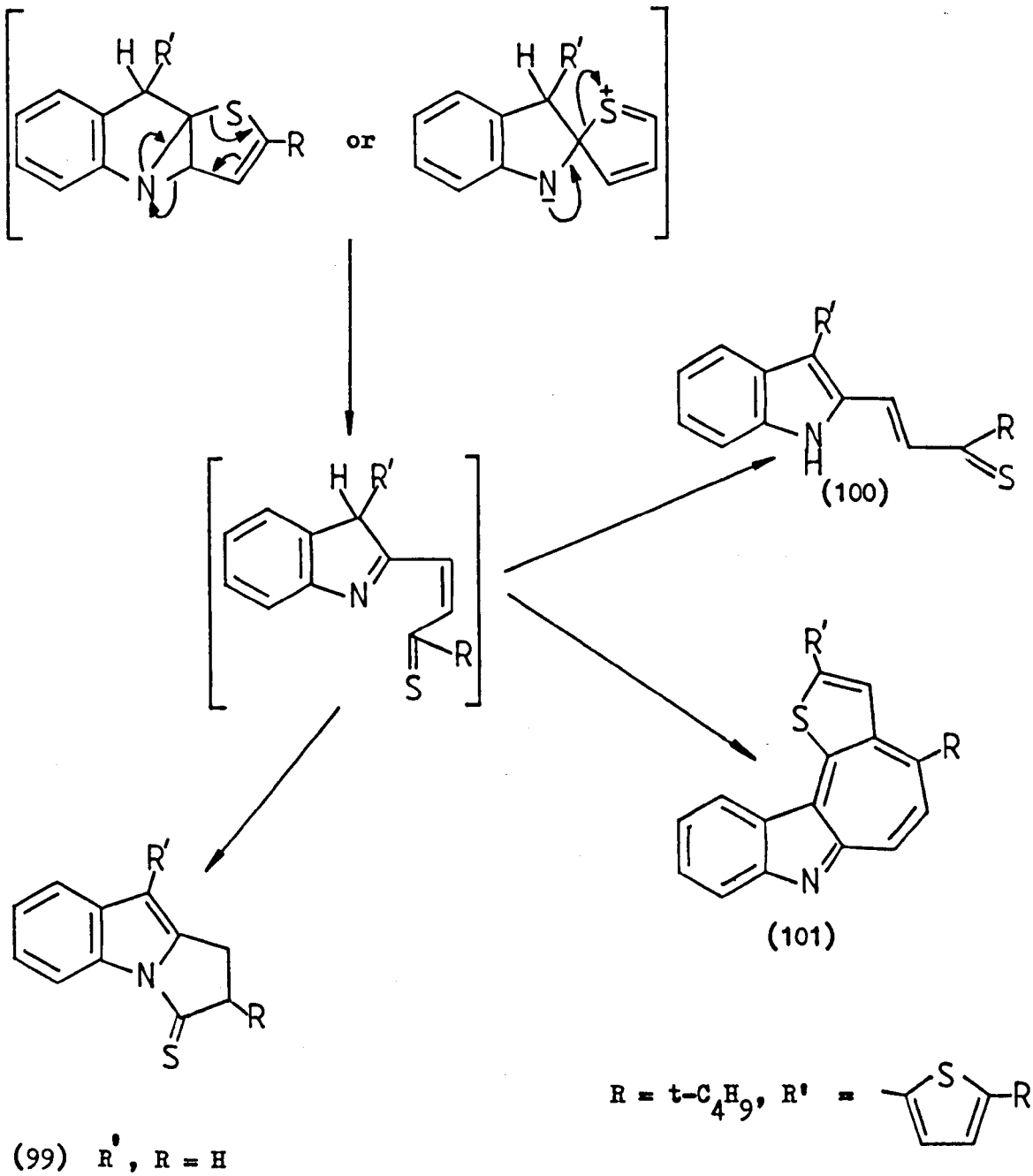
(98)

R' = H, 

R = H, CH_3, C_2H_5, t-C_4H_9

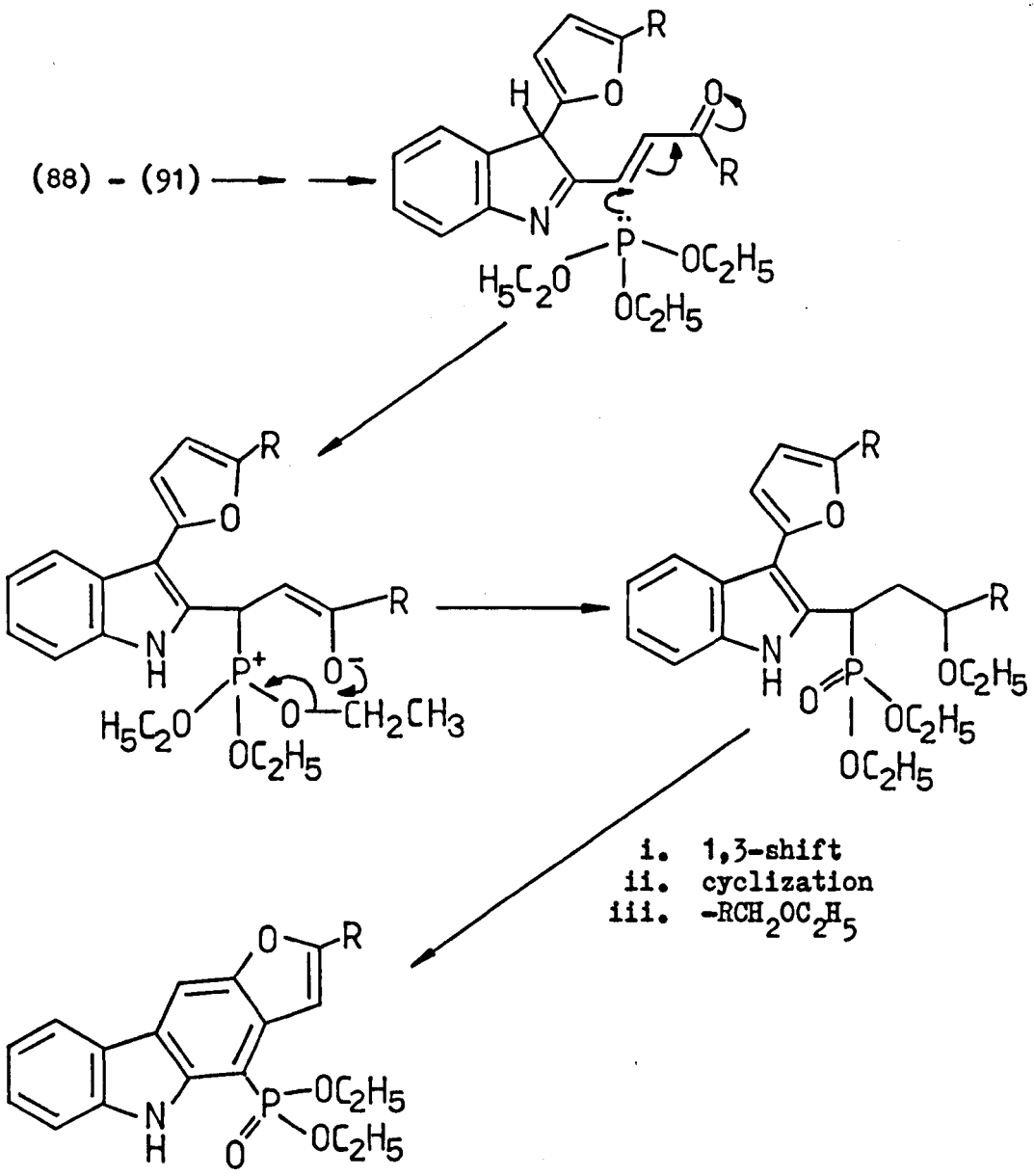
X = S, NCH_3

triphenyl-methane series. Ring opening of the heterocycle, as a result of nitrene insertion, has been postulated[9,137] to account for the preponderance of tars and other products which have been obtained from many of these decompositions. The ring opened "intermediate" (100) has actually been isolated[9] and mechanisms have been proposed for the formation of (99) and (101) from an analogous unsaturated sulfonyl precursor (Scheme 3.1).



Scheme 3.1

A similar ring opening process has been invoked[10] to account for the isolation of the diethyl 2-alkylfuro[3,2-c]carbazol-5-yl-phosphonates (102) - (104) as the only products after deoxygenation of the furans (89) - (91) (Scheme 3.2). Deoxygenation of the parent furan compound (88) yielded no identifiable compounds.



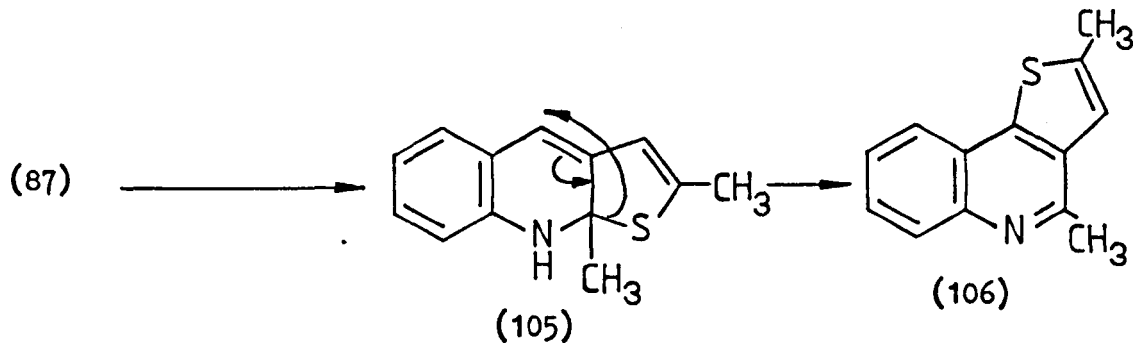
(102) R = CH_3

(103) R = C_2H_5

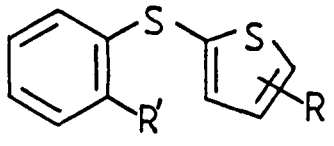
(104) R = t-C_4H_9

Scheme 3.2

It is thought[4] that nitrene insertion into the 2,3-bond is also the initial reaction during the decomposition of the 3-substituted thiophene (87). The resulting intermediate (105) probably then undergoes a 1,3-S shift and dehydrogenation to yield 2,4-dimethylthieno[3,2-c]-quinoline (106).



Lindley et al.[137] have thermolyzed a number of 2-azidophenyl thienyl sulfides, including compounds (107) - (110), under various conditions. The main decomposition products obtained under all conditions from the substituted thiophenes (108) - (110) were



(107) R = H, R' = N_3

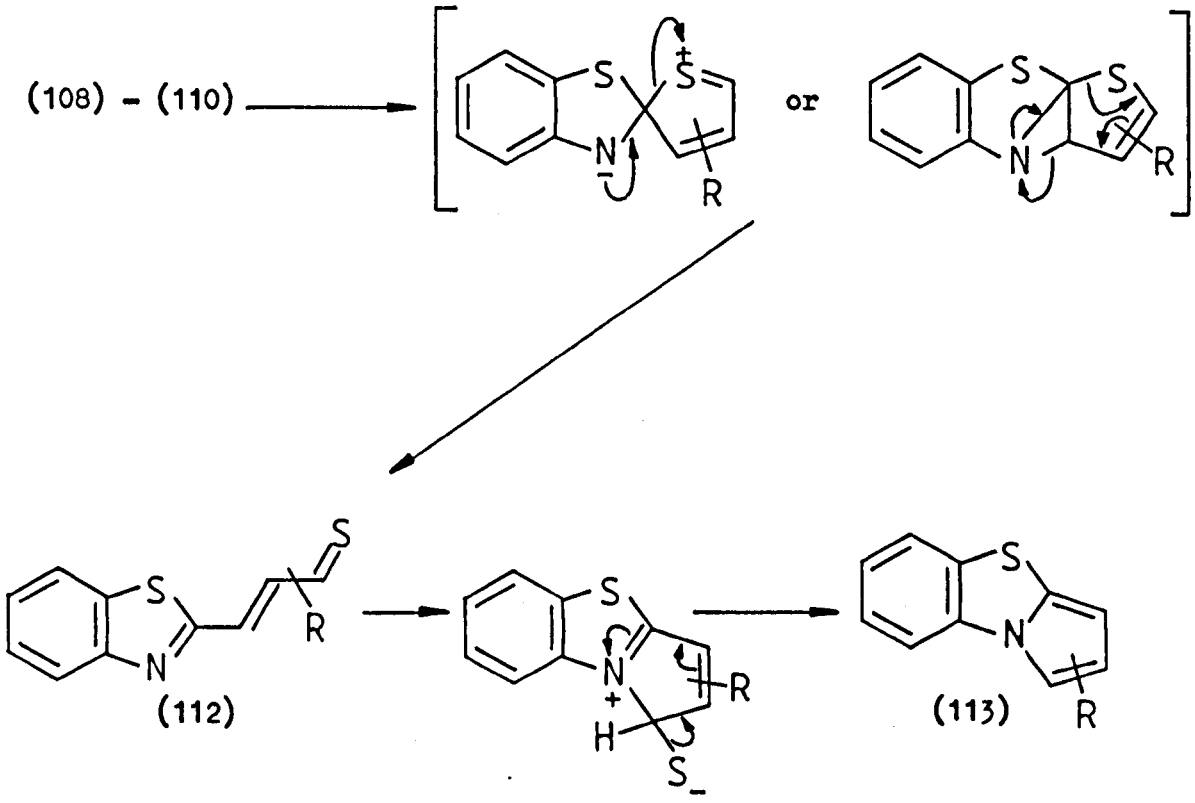
(108) R = 5-CH_3, R' = N_3

(109) R = 3-CH_3, R' = N_3

(110) R = 3,5-$(CH_3)_2$, R' = N_3

(111) R = H, R' = NH_2

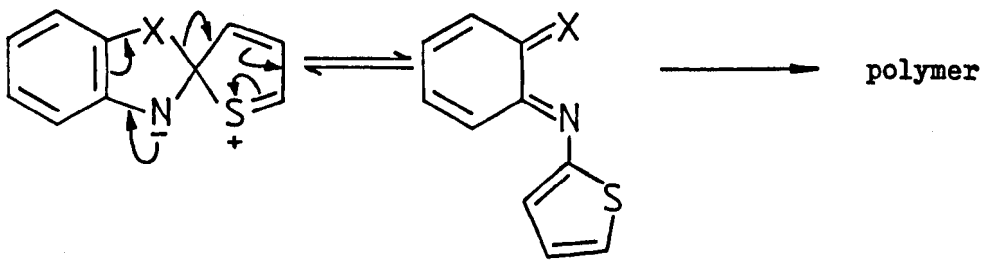
pyrrolo[2,1-b]benzothiazoles (113) whose formation apparently involves cleavage of the thiophene ring and then elimination of sulfur from the unstable thioketone intermediate (112) (Scheme 3.3). As shown



Scheme 3.3

above the presence of a methylene "bridgehead group" enables a relatively stable pyrroloindolethione (99) to be obtained from the thioketone intermediate. This is not possible when the bridgehead group is a sulfur atom and so sulfur elimination occurs instead, to give (113).

Thermolysis of the parent system (107) in trichlorobenzene solution has been shown[137] to yield mainly a purple polymer, and 10% of the amine (111). Lindley et al.[137] have suggested that extensive polymer formation occurs when stabilization of the initial nitrene adduct (eg a spirodiene) via an o-quinonoid structure (114) is favoured over thioketone (112) formation. Therefore, since the decomposition of (107) by the route shown in Scheme 3.3 would involve an extremely unstable α,β -unsaturated thioaldehyde intermediate, the initial nitrene adduct is more likely to isomerize to (114) and then polymerize as shown in Scheme 3.4.



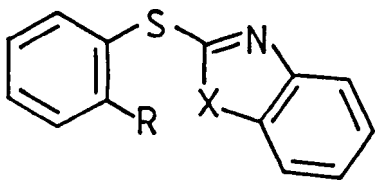
(114) X = S

(115) X = CH_2

Scheme 3.4

Since quinone methides are also highly reactive,[138] it seems likely that the decomposition of the unsubstituted thiophene (84) occurs via the intermediate (115), and that the involvement of similar quinonoid species could be the cause of the extensive polymer formation which has been observed[4,6,9,10] when the thiophene (92), furan (88) and pyrrole (96) are decomposed.

The sulfides (116) and (118) have also been thermolyzed.[137] Again, the only products obtained other than polymerized material were the amines (117) 14.5%, and (119) 60%.



(116) R = N_3, X = S

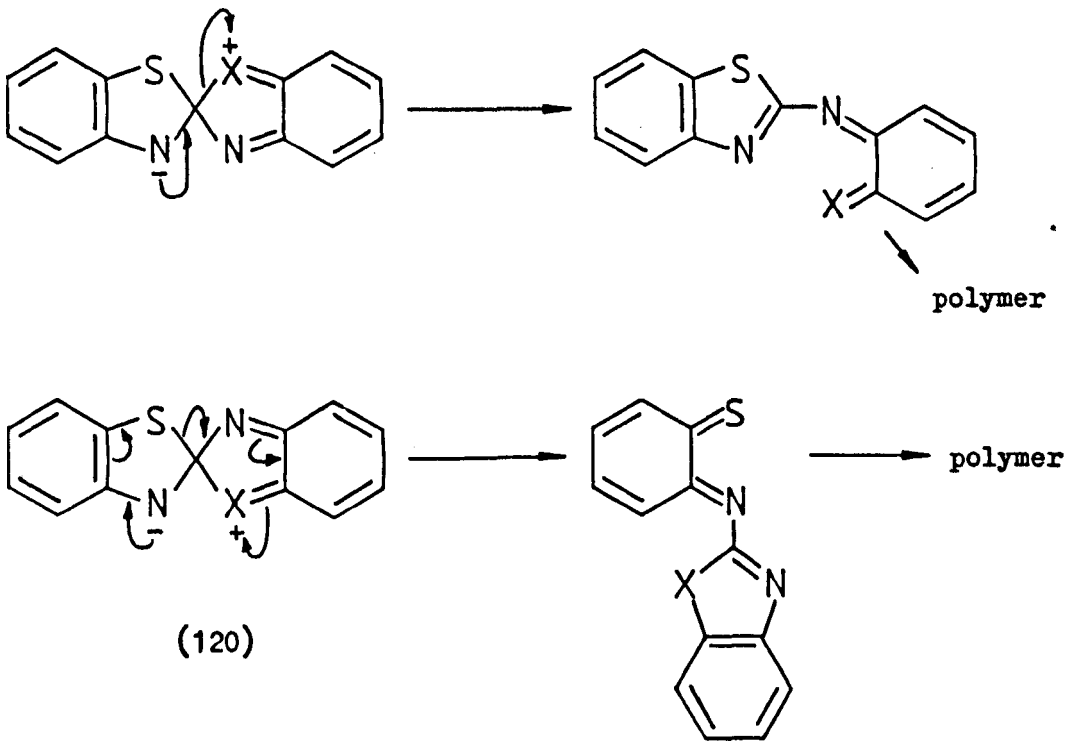
(117) R = NH_2, X = S

(118) R = N_3, X = NH

(119) R = NH_2, X = NH

These results have been attributed[137] to the π-deficient nature of the positions on the receiving ring available for nitrene attack although details of the mechanisms involved in polymer formation were

not discussed. It is interesting to note that either of the modes of isomerization of the spirodiene (120) suggested below yield a quinonoid intermediate capable of polymerization. Thus, although (116) appears superficially similar to 2-azidophenyl-2-thiazolylmethane



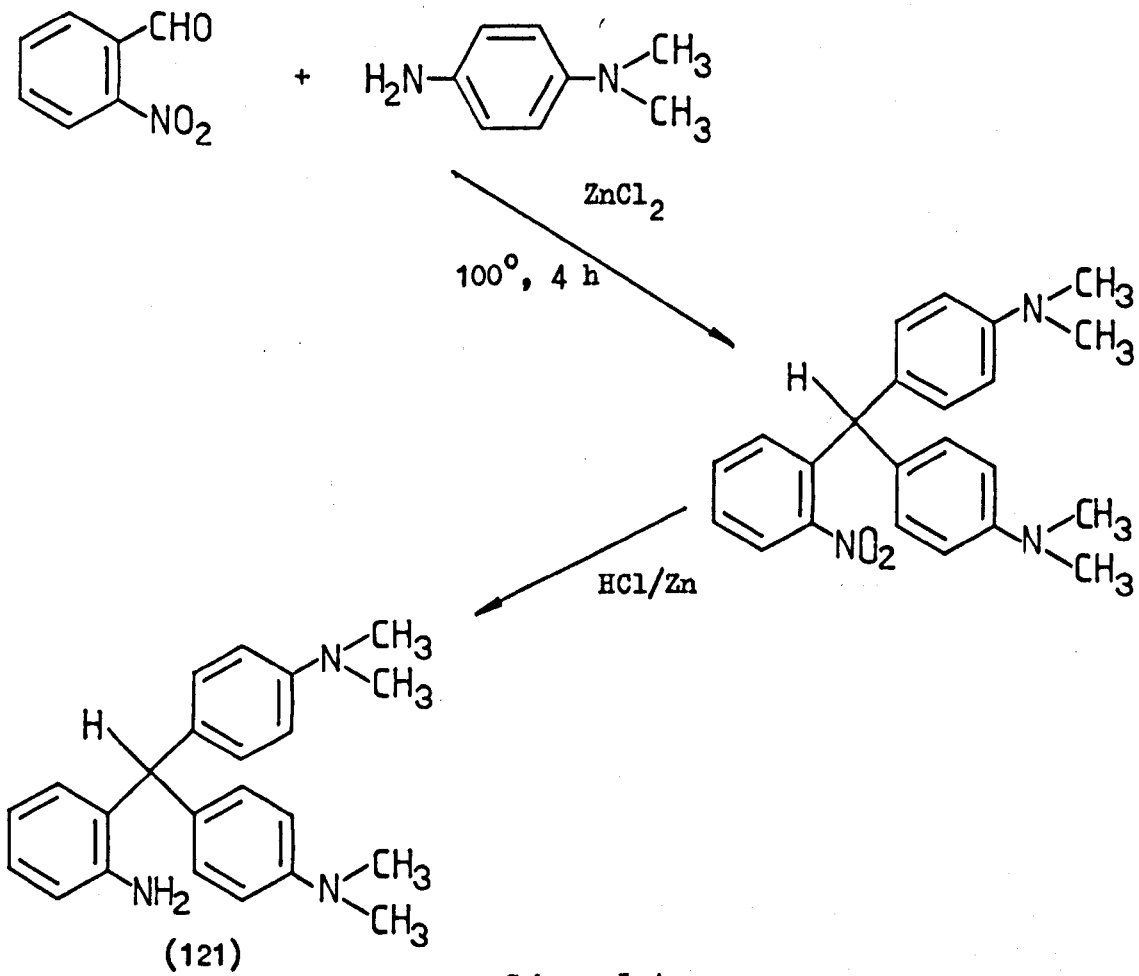
(120)

(83) whose thermolysis is discussed below, the fused benzene ring creates major differences in the type and reactivity of the intermediates which are thought to influence the path of the decomposition.

DISCUSSION

PART I : PREPARATION OF THE AZIDES

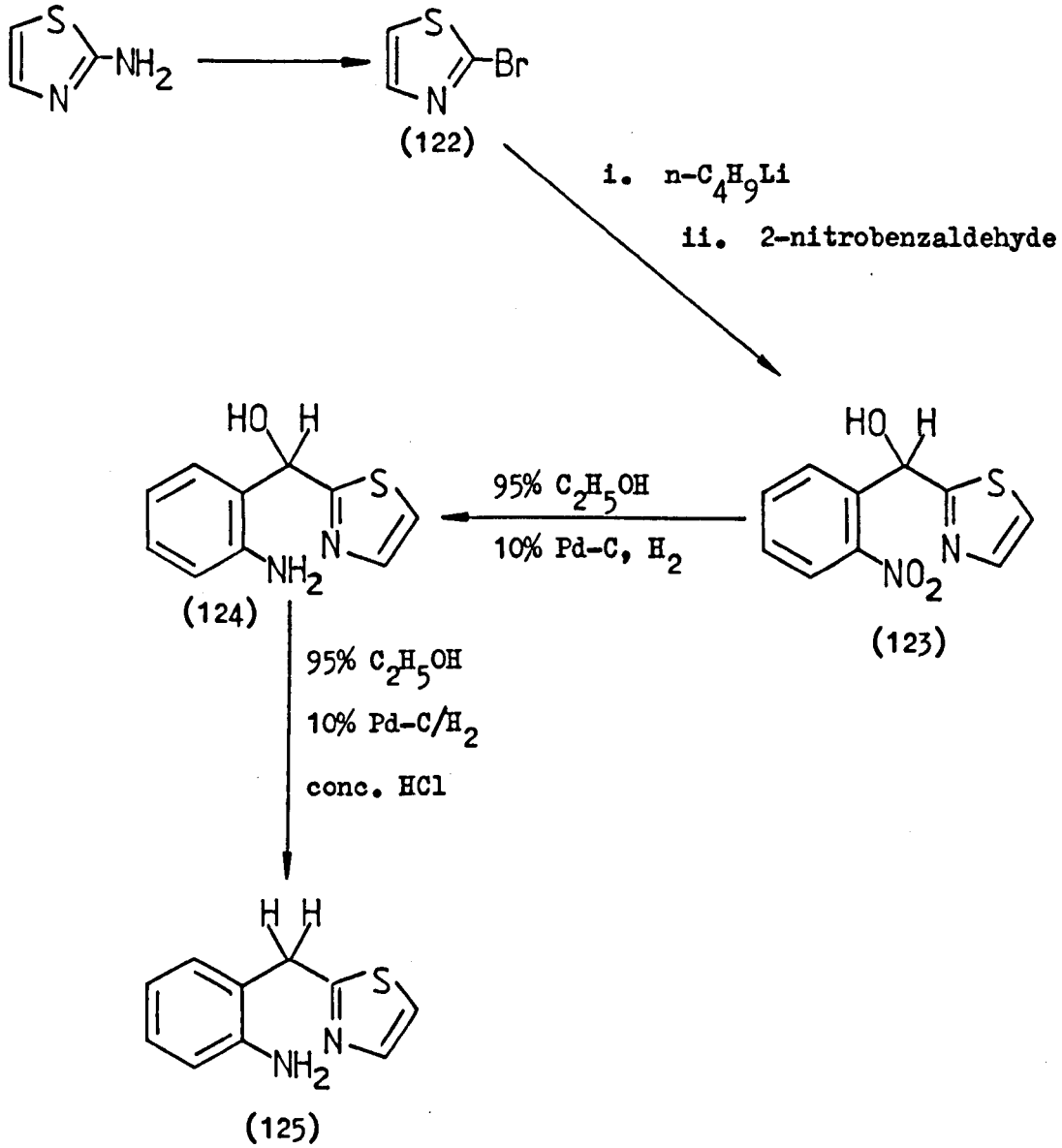
Preparation of 2-azido-4',4"-bis-(dimethylamino)triphenylmethane (82) was straightforward. The immediate precursor to the azide, 2-amino-4',4"-dimethylaminotriphenylmethane, is known,[139] although in this case it was prepared by the method which Fukui et al.[140] had used previously for the preparation of the analogous 4-aminotriphenylmethane (Scheme 3.4).



Scheme 3.4

Reaction of the diazonium salt of (121) with aqueous azide then yielded compound (82).

Scheme 3.5 shows the route by which 2-aminophenyl-2-thiazolylmethane (125) was obtained. A modification[141] of the

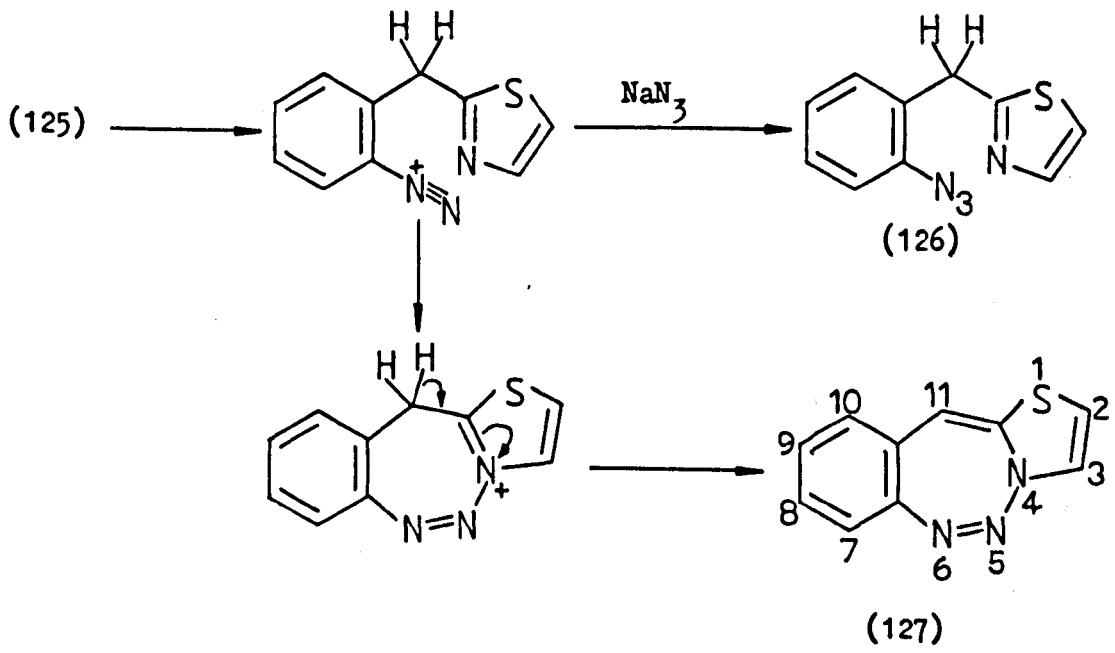


Scheme 3.5

Sandmeyer reaction was used to obtain 2-bromothiazole (122) from 2-aminothiazole. Reaction of (122) with n-butyl-lithium and then with 2-nitrobenzaldehyde at low temperature (-30 to -70°) yielded (123),[142] which was then catalytically reduced to the 2-amino-compound (124).

In line with previous observations,[143] reduction of the alcohol group required relatively large quantities of catalyst and long reaction times. Neither increasing the pressure of hydrogen to 50 p.s.i., nor the use of Adam's catalyst instead of palladium on charcoal, had any effect on the reaction rate. Attempts to carry out the reduction of (124) by transfer hydrogenation,[84] or by treatment with sodium borohydride in trifluoroacetic acid,[89] yielded complex mixtures which did not contain the required compound (125), and were therefore not further investigated.

Diazotization of the amine (125) in buffered solution[144] and subsequent treatment with sodium azide, yielded the two products (126) and (127). Thiazolo-[1,2-c]benzo[f]-1,2-3-triazepine (127)



appears to be a new compound, although nucleophilic substitution by a diazonium salt at the ring nitrogen of a thiazole has been previously observed[145] (Scheme 3.6).

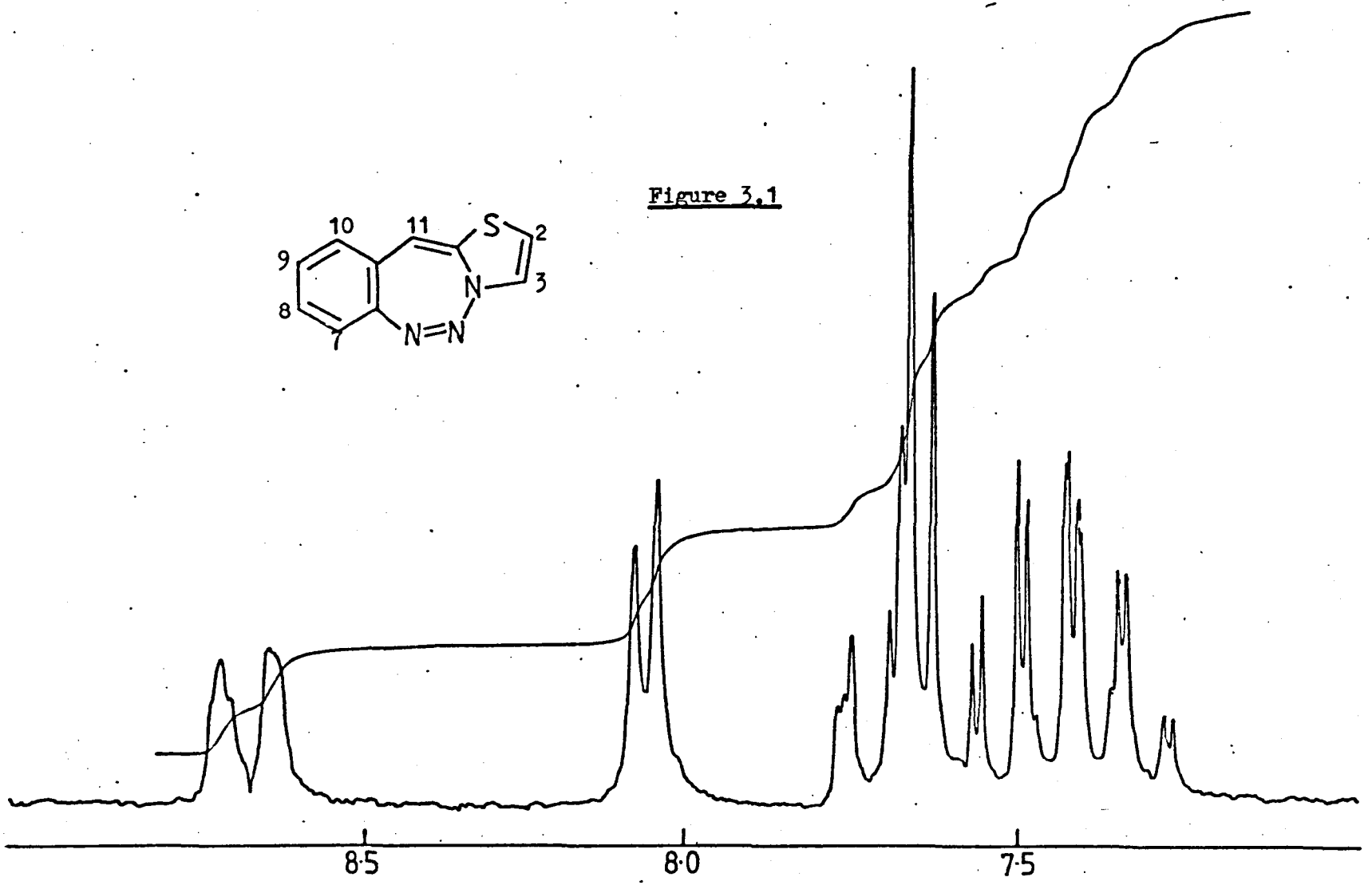
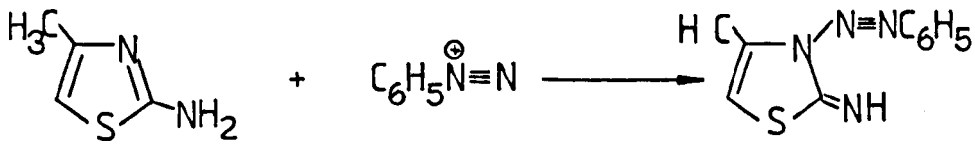


Figure 3.1



Scheme 3.6

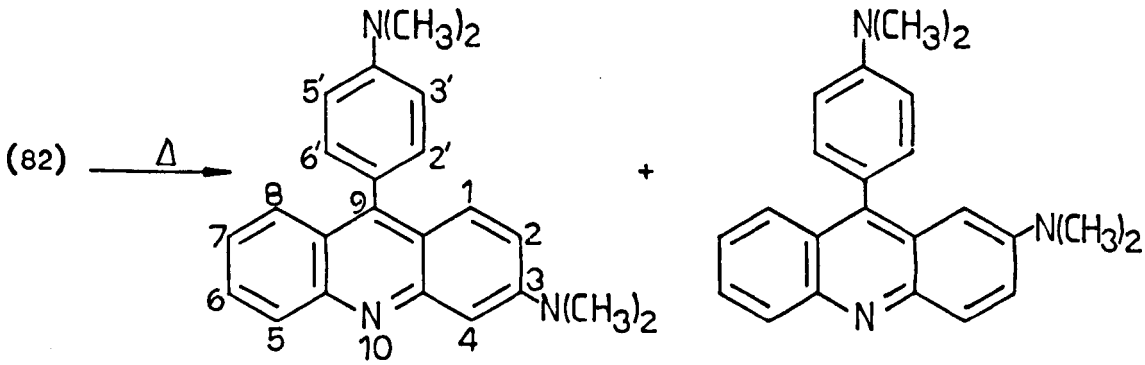
The ^{1}H n.m.r. spectrum of compound (127) is shown in Figure 3.1. The chemical shifts and coupling constants which have been derived from this spectrum together with the help of decoupling experiments are summarized in Table 3.1 below.

TABLE 3.1

Chemical Shifts (p.p.m.)		Coupling Constants (Hz)	
-2H	7.60	$J_{2,3}$	3.4
-3H	8.06	$J_{7,9}$	1.5
-7H	8.66	$J_{8,10}$	1.2
-8H	7.35	$J_{8,9} = J_{7,8} = J_{9,10}$	6.8
-9H	7.50		
-10H	7.73		
-11H	7.68		

PART II : THERMOLYSIS OF THE AZIDES

The thermolysis of 2-azido-4',4"-bis(dimethylamino)triphenylmethane (82) in 1,2,4-trichlorobenzene yielded two acridines, (128) and (129) and a considerable amount of brown polymeric material.

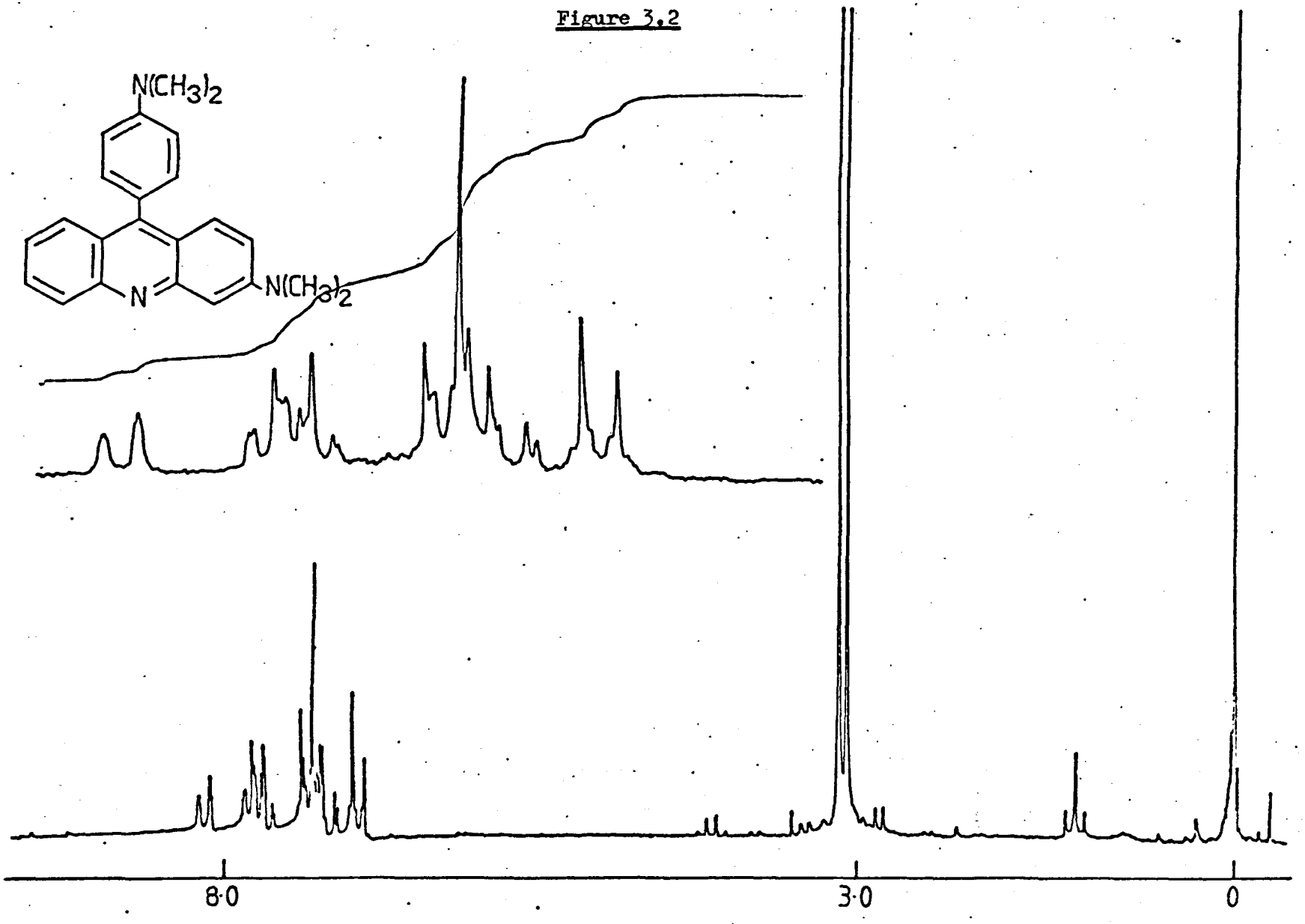


(128) (129)

This preponderance of acridine products is precisely what is expected if a carbonium ion intermediate (Scheme 1.15) is involved in acridine formation, since the stability of such an intermediate would be considerably enhanced by the strongly electron-donating dimethylamino substituents. Formation of the rearranged acridine (129), however, cannot be rationalized by this mechanism. Involvement of a spirodiene intermediate (as shown in Scheme 1.14) provides a more satisfactory explanation. This is the first time a rearranged acridine has been obtained from the decomposition of compounds in the diphenyl- and triphenyl-methane series, although decomposition products of this type have been obtained from aryl 2-azidophenyl sulfides (Table 1.4).

It was possible to distinguish between the two isomeric acridines, (128) and (129), on the basis of their 100 MHz ^{1}H n.m.r. spectra (Figures 3.2 and 3.3) and their visible spectra. In the n.m.r.

Figure 3.2



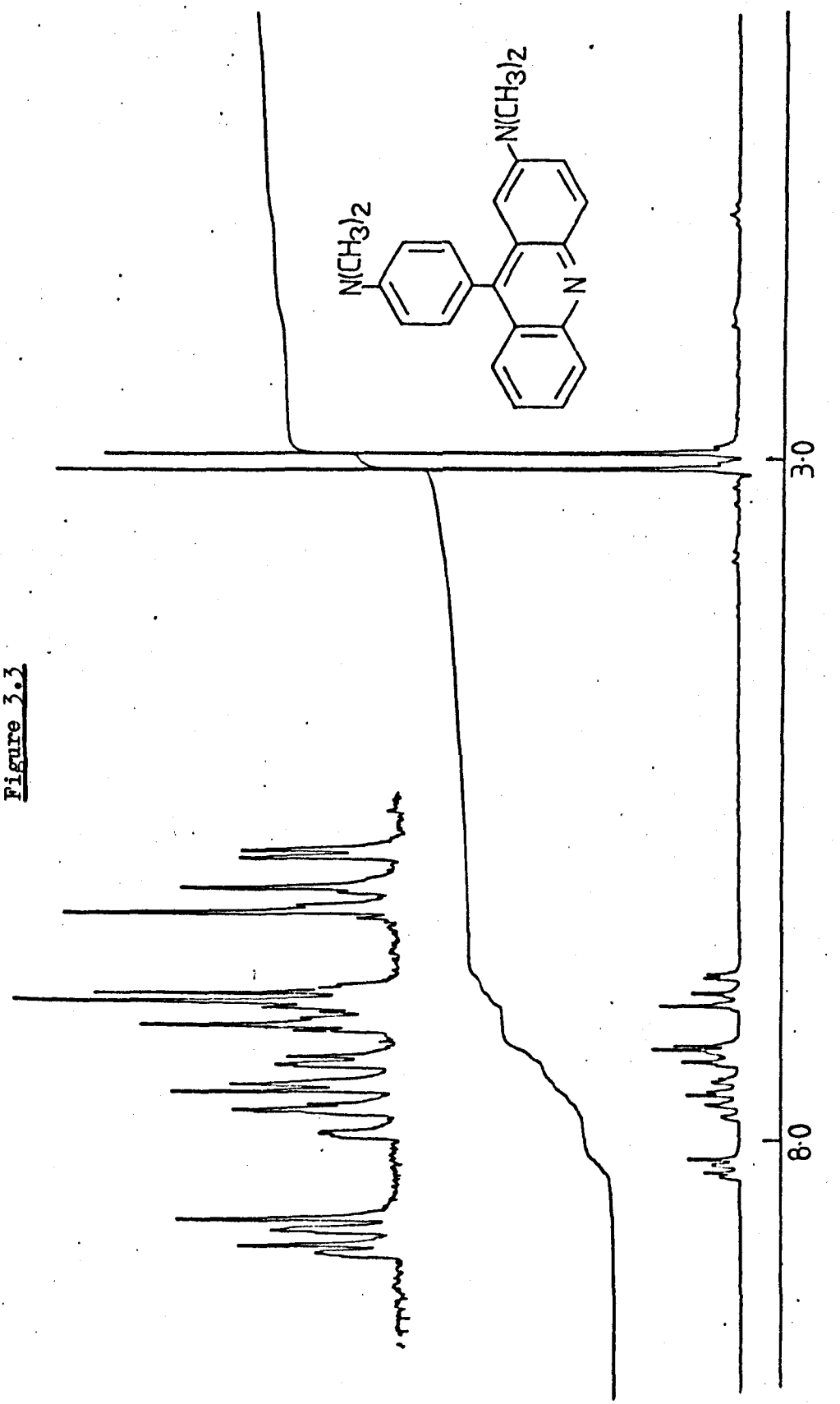
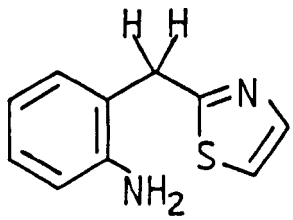


Figure 3.3

spectrum of (129) doublets due to -4H and -5H are both visible downfield from the main aromatic region. The spectrum of (128), on the other hand, has only one lowfield doublet (due to -5H), the signal due to -4H having been moved upfield by the dimethylamino group. In addition, the spectrum of (129) has a doublet (J = 2.5 Hz; m-coupling) upfield from the AA'BB' pattern (characteristic of the 4-dimethylaminophenyl moiety, and seen in both spectra) due to -1H. The coupling of -3H with -1H (J = 2.5 Hz) and with -4H (J = 9.5 Hz) results in the doublet of doublets seen at 7.55 p.p.m. The proton at position 4 in (129), coupled to -3H (J = 9.5 Hz), gives rise to the sharp doublet seen at 8.12 p.p.m. It was also possible to obtain chemical shifts and coupling constants for all the other protons in (129) and these are listed in the experimental section of this Chapter.

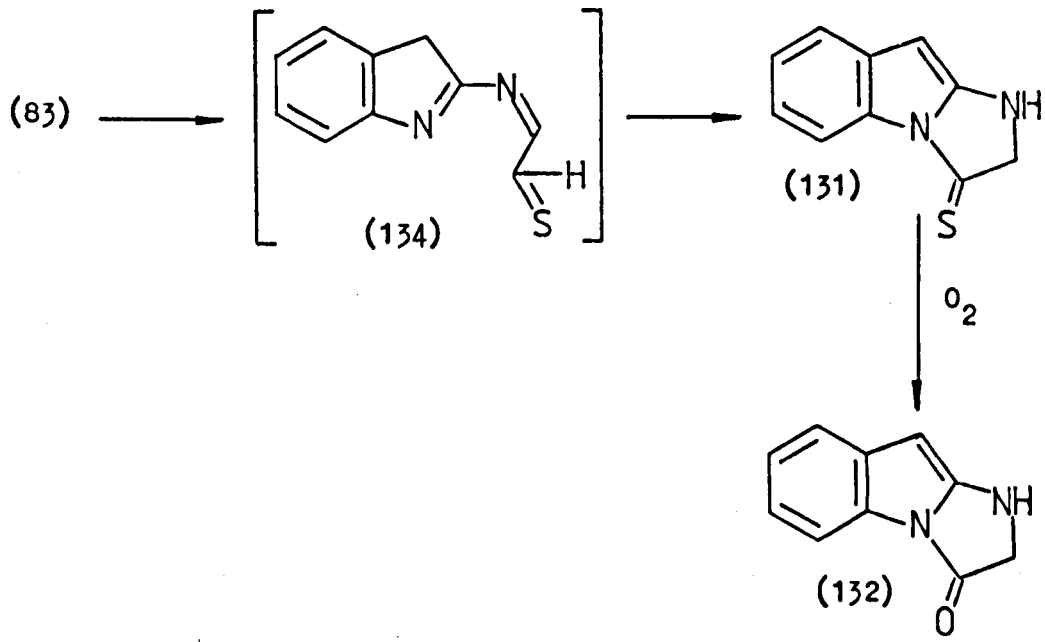
The structural assignment for the rearranged acridine was confirmed by observing the protonation of the isomers spectroscopically in the visible region and comparing this with similar measurements on 2-amino- and 3-amino-acridine.[146] Protonation of (129) caused a larger bathochromic shift in the longest wavelength absorption than it did for (128), but the intensity of the longest wavelength absorption of (128) increased the most. This is in agreement with the changes on protonation reported[146] for the aminoacridines.

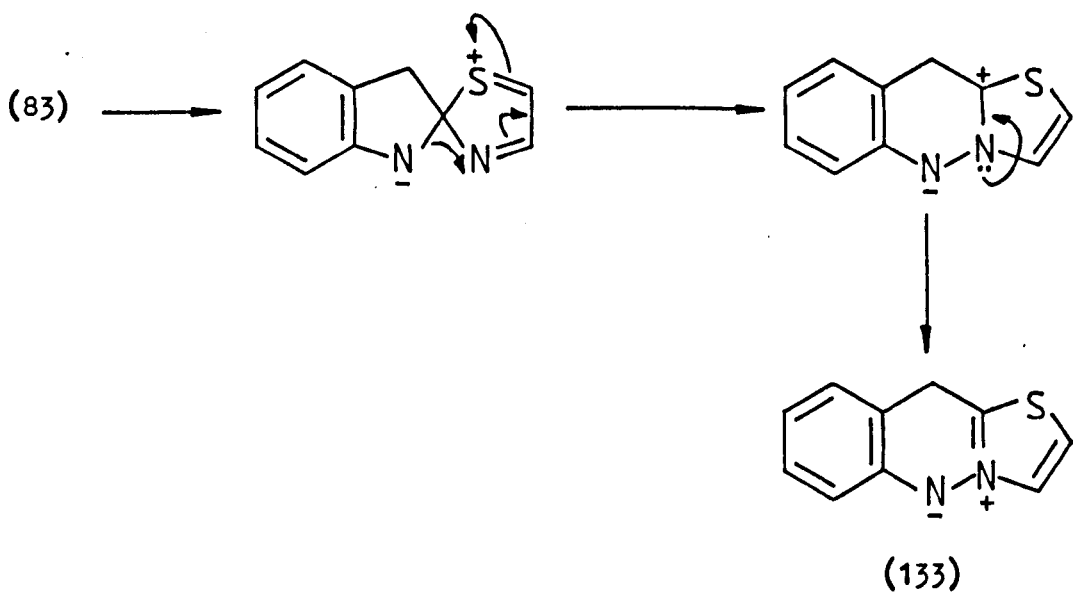
The thermolysis of 2-azidophenyl-2-thiazolylmethane (83) in 1,2,4-trichlorobenzene resulted in extensive polymer formation and the production of 9% of 2-aminophenyl-2-thiazolylmethane (130).



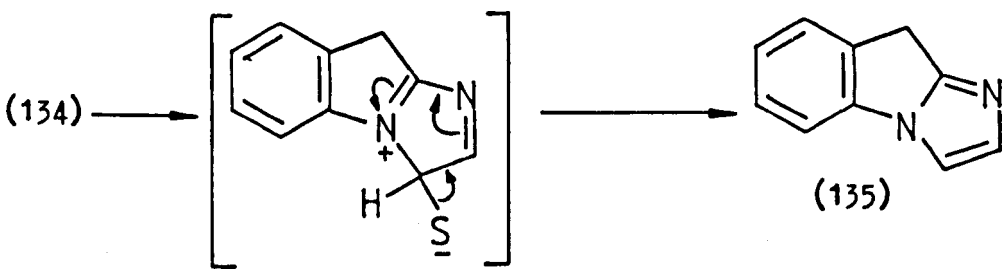
(130)

By analogy with nitrene insertions into other five-membered ring heterocycles, described in the introduction, a number of products might have been expected from the decomposition of (83). For example, by comparison with the mechanisms thought[6] to be operating during the decomposition of 2-azidophenyl-2-thienylmethane (84), compounds (131) - (133) would be expected to be amongst the decomposition products from (83).



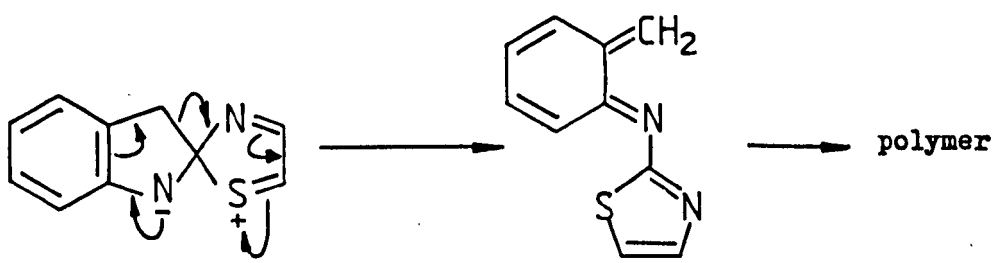


On the other hand, if after recyclization of the thioaldehyde (134) sulfur is eliminated, then compound (135) would be obtained. This type of reaction has, however, only been observed[137] when a "bridgehead" sulfur atom is present in the starting azide, (108) - (110).



(135)

Nitrene insertion into the thiazole nucleus appears, however, to closely resemble nitrene insertion into other unsubstituted five membered ring heterocycles in its overwhelming preference for tar and amine formation.



(120) (136)

In these situations it would appear that a mechanism involving formation

of the unstable unsaturated thioaldehyde (134) is less satisfactory than one which directly results in polymer formation. One such mechanism which has been previously suggested involves the isomerization of the spirodiene intermediate (120) to the quinonoid structure (136) which is capable of subsequent polymerization.

EXPERIMENTAL

2-Azido-4',4"-bis(dimethylamino)triphenylmethane -

A stirred mixture of crude 2-amino-4',4"-bis(dimethylamino)-triphenylmethane (23.3 g, 83 mmole) in concentrated hydrochloric acid (42 ml) was maintained at 0° to -5° during treatment with a solution of sodium nitrite (6.3 g, 91 mmole) in water (84 ml). The resulting mixture was filtered into a stirred solution of sodium azide (6.3 g, 97 mmole) and sodium acetate (126.4 g, 1.5 mole) in water (420 ml), which was maintained at 0° for 30 min after the addition was complete, and then extracted with chloroform. The chloroform extract was dried ($MgSO_4$), concentrated, and then chromatographed on an alumina column (activity IV, eluent 10% benzene : 90% petrol) to obtain the pure azide (9.5 g, 25.6 mmole, 31%) m.p. 109-111° (60-80° petrol). (Found: C, 74.7; H, 6.65; N, 18.9. $C_{23}H_{25}N_5$ requires C, 74.35; H, 6.8; N, 18.85%), m/e 371 ($M^{+\cdot}$, 22%), 344 (16), 343 (64), 342 (84), 341 (100), 326 (18), 299 (12), 283 (18), 282 (72), 240 (18), 239 (62), 224 (18), 223 (80), 207 (12), 271.5 (12), 270.5 (20), 269.5 (12), 149 (30), 148 (38), 121 (32), 120 (20), δ ($CDCl_3$) 2.95 (12H, s, $-CH_3$), 5.60 (1H, s, -CH), 6.5-7.15 (12H, cplx m, aromatic), $\bar{\nu}$ ($CDCl_3$) 2120 cm^{-1} ($-N_3$ stretch).

Thermolysis of 2-azido-4',4"-bis(dimethylamino)triphenylmethane -

A solution of the azide (9.5 g, 25.6 mmole) in 1,2,4-trichlorobenzene (100 ml) was added dropwise during 1 h to 1,2,4-trichlorobenzene (1000 ml) which was being vigorously stirred and purged with nitrogen. The temperature in the reaction flask was maintained between 180° and 200° throughout the addition of azide and for four hours after

it was complete. The solution was then allowed to cool and the solvent was removed on a rotary evaporator (1 mm pressure). Column chromatography (activity IV alumina) and P.L.C. of the residue yielded 3-dimethylamino-9-(4'-dimethylaminophenyl)acridine (0.99 g, 10%) m.p. 222-227°. (Found: M^+, 341.1892. $C_{23}H_{23}N_3$ requires M, 341.1892), m/e 341 (M^+, 45%), 150 (100), 71 (30), 69 (25), 57 (45), 55 (30), 43 (50), δ ($CDCl_3$) 3.06 (6H, s, $-N(CH_3)_2$), 3.12 (6H, s, $-N(CH_3)_2$), 6.88 (2H, d, J9, -2'H and -6'H), 7.29 (2H, d, J9, -3'H, 5'H), 7.05-7.34 (3H, m), 7.57 - 7.79 (3H, m), 8.11 (1H,br d, $J_{5,6}$ 8, -5H), λ_{max} 241 (log ε 4.19), 283 (4.26), 455 nm (3.37), λ_{max} (0.2% conc. HCl added) 241 (log ε 4.31), 296 (4.28), 360 (3.62), 378 (3.69), 492 nm (3.99), and 2-dimethylamino-9-(4'-dimethylaminophenyl)acridine (0.55 g, 6%), m.p. 220-222°. (Found: M^+, 341.1896. $C_{23}H_{23}N_3$ requires M, 341.1892), m/e 342 (27%), 341 (100), 325 (10), 170.5 (11), 170 (10), 169.5 (11), δ ($CDCl_3$) 2.96 (6H, s, $-2N(CH_3)_2$), 3.08 (6H, s, $-4'N(CH_3)_2$), 6.75 (1H, d, $J_{1,3}$ 2.5, -1H); 6.9 (2H, d, J9.5, -2'H and -6'H); 7.32 (2H, d, J9.5, -3'H and -5'H), 7.25-7.39 (1H, m, -7H), 7.55 (1H, q, $J_{1,3}$ 2.5 and $J_{3,4}$ 9.5, -3H), 7.51 - 7.67 (1H, m, -6H), 7.72 (1H,br d, $J_{7,8}$ 9.5, -8H), 8.12 (1H, d, $J_{3,4}$ 9.5, -4H), 8.16 (1H,br d, $J_{5,6}$ 8.5, -5H), λ_{max} 244 (log ε 4.53), 281 (4.68), 464 nm (3.66), λ_{max} (0.2% conc HCl added) 240 (log ε 4.44), 300 (4.59), 392 (3.66) and 576 nm (3.83).

2-Bromothiazole -

Concentrated nitric acid (65%, 75 ml) was added, at a rate which maintained the reaction temperature at -5°, to the bottom of a stirred mixture of 2-aminothiazole (50 g, 0.5 mole) and phosphoric acid (80%, d = 1.71, 167 ml). The temperature in the reaction flask was maintained between -10° and 0° for 1 h while a solution of sodium nitrite (38 g, 0.55 mole) in water (42 ml) was added to it. The resulting dark

brown sludge was stirred at -5° for 1 h. A saturated solution of sodium bromide (83 g, 0.81 mole; 72 ml water) and the dark brown reaction mixture were added simultaneously to a 5 l beaker containing a copper sulfate solution (83 g, 0.52 mole; 250 ml water). After the evolution of nitrogen had ceased, the solution was neutralized (pH 7) with sodium hydroxide solution, and steam distilled. The distillate was extracted with ether, dried ($CaCl_2$) and the ether removed on a rotary evaporator. Distillation (69-70°/20 mm) of the crude product yielded 2-bromothiazole (40.8 g, 0.25 mole, 50%) which had m/e 165 ($M^{+\cdot}$, 32%), 163 ($M^{+\cdot}$, 36), 58 (100), δ ($CDCl_3$) 7.15, 7.2, 7.45, 7.5 (AA'BB', aromatic).

2-Nitrophenyl-2-thiazolylmethanol -

A vigorously stirred solution of 2-bromothiazole (40 g, 0.24 mole) in dry ether (610 ml) at -70° was treated with n-butyllithium (1.6 M in hexane, 152.5 ml, 0.24 mole) over a period of 1 h and then stirred, at -70°, for a further 1 h. The resulting mixture was then maintained at -65° to -60° during the addition, over 1 h, of a solution of 2-nitrobenzaldehyde (29.5 g, 0.20 mole) in dry tetrahydrofuran (122 ml). After being stirred at -65° to -60° for a further 1.5 h and then at -55° for 30 min, the reaction mixture was added to water (500 ml) containing ammonium chloride (50 g), and methylene chloride (500 ml). The methylene chloride layer was separated from the aqueous phase which was then extracted with methylene chloride (4 x 100 ml). The combined organic phases were then dried (Na_2SO_4) and concentrated. The concentrate was then slurried in ether and filtered to give the product, a tan coloured solid (32.1 g, 0.14 mole, 68%) which had δ ($CDCl_3$, D_6 DMSO) 3.25 (1H, s, -OH), 6.7 (1H, s, -CH), 7.2 - 7.9 (6H, cplx m, aromatic).

2-Aminophenyl-2-thiazolylmethanol -

Palladium on charcoal (10%, 8.5 g) was added to a solution of 2-nitrophenyl-2-thiazolylmethanol (17.0 g, 0.072 mole) in ethanol (95%, 510 ml), and the resulting mixture was stirred in a hydrogen atmosphere for 17 h (0.21 mole hydrogen absorbed). The mixture was then filtered and the solvent removed on a rotary evaporator to yield a yellow solid (14.6 g, 0.071 mole, 98%) which had m.p. 97.5 - 98° (ethylacetate). (Found: C, 58.15; H, 4.8; N, 13.6. $C_{10}H_{10}N_2OS$ requires C, 58.25; H, 4.85; N, 13.6%), m/e 206 ($M^{+\cdot}$, 58%), 188 (18), 187 (33), 173 (15), 129 (15), 122 (15), 121 (25), 120 (18), 94 (23), 93 (48), 92 (18), 86 (100), 77 (30), 75 (15), 66 (13), 65 (23), 59 (23), 58 (18), 51 (18), 39 (18), and δ ($CDCl_3/D_6$ acetone) 4.7 (3H,br s, -OH and $-NH_2$), 6.0 (1H, s, -CH), 6.4 - 7.5 (6H, cplx m, aromatic).

2-Aminophenyl-2-thiazolylmethane -

Palladium on charcoal (10%, 3.0 g) was added to a solution of 2-aminophenyl-2-thiazolylmethanol (7.2 g, 35 mmole) and concentrated hydrochloric acid (3 ml) in ethanol (95%, 400 ml), and the resulting mixture was stirred in a hydrogen atmosphere for one week. After another quantity of palladium on charcoal (10%, 3.0 g) had been added to the mixture it was stirred under hydrogen for a further week and then filtered. The filtrate was concentrated, neutralized with saturated sodium bicarbonate solution, extracted with methylene chloride, and the extract dried (Na_2SO_4) and concentrated to give a brown oil (5.9 g). The oil was triturated with a mixture of ethyl acetate (25%) and hexane (75%) and the solid 2-aminophenyl-2-thiazolylmethanol (2.96 g, 14 mmole) so obtained, was filtered off. The filtrate was concentrated and then purified by medium pressure column chromatography (70% hexane : 30% ethyl acetate) to yield 2-amino-2-thiazolylmethane (1.5 g, 7.9 mmole,

38%), m.p. 49 - 49.5° (cyclohexane). (Found: C, 63.15; H, 5.3; N, 14.85. $C_{10}H_{10}N_2S$ requires C, 63.15; H, 5.25; N, 14.75%), m/e 191 (18%), 190 ($M^{+\cdot}$, 100), 189 (12), 157 (44), 131 (18), 130 (38), 118 (15), 117 (35), 106 (26), 104 (15), 78 (15), 77 (26), 58 (18), 51 (15), 39 (18), δ ($CDCl_3$) 4.05 (2H, br s, $-NH_2$), 4.1 (2H, s, $-CH_2$), 6.4 - 7.5 (6H, cplx m, aromatic).

2-Azidophenyl-2-thiazolylmethane -

A solution of sodium nitrite (0.9 g, 0.013 mole) in water (20.3 ml) at 0° was added slowly to a stirred mixture of 2-aminophenyl-2-thiazolylmethane (2.24 g, 0.012 mole) water (5.5 ml), concentrated hydrochloric acid (5.5 ml), and dioxan (14.5 ml) which was maintained at 0° to -5°. The resulting red solution, containing a yellow precipitate, was added slowly to a solution of sodium azide (0.9 g, 0.014 mole) and sodium acetate (9.1 g) in water (40.6 ml) which was maintained at 0° to -5° during the addition, and then allowed to warm to room temperature over 30 min. The methylene chloride extract of this aqueous mixture was dried (Na_2SO_4), concentrated (below 35°), taken up in a mixture of methylene chloride and toluene and rapidly chromatographed on an alumina column (activity IV, 70 g, eluent 20% benzene : 80% petrol). Fraction 1 (100 ml) contained 2-azidophenyl-2-thiazolylmethane (0.9 g, 0.004 mole, 35%). (Found: C, 55.4; H, 3.6; N, 25.75. $C_{10}H_8N_4S$ requires C, 55.55; H, 3.7; N, 25.95%), δ ($CDCl_3$) 4.25 (2H, s, $-CH_2$), 7.0 - 7.6 (6H, cplx m, aromatic), ν (liq. film) 2120 cm^{-1} ($-N_3$ stretch). Fractions 4 and 5 (eluent methylene chloride) contained thiazolo-[1,2-c]benzo[f]-1,2,3-triazepine (0.5 g, 0.0025 mole, 21%), m.p. 176-177.5°. (Found: C, 59.55; H, 3.5; N, 20.85. $C_{10}H_7N_3S$ requires C, 59.7, H, 3.5; N, 20.9%), m/e 201 ($M^{+\cdot}$, 33%), 160 (35), 159 (28), 145 (10), 144 (17), 129 (26), 128 (13), 127 (10), 107 (10), 105 (38), 91 (14), 61 (14),

58 (22), 51 (10), 45 (13), 44 (100), 43 (85), 39 (10), ($CDCl_3$) 7.3 - 8.7 (cplx m, aromatic), λ_{max} 219 (log ε 2.28), 255 (1.90), and 325 nm (2.20), λ_{max} (0.2% conc. HCl added) 214 (log ε 2.26), 259 (1.94), 327 (2.11), and 340 nm (2.08).

Thermolysis of 2-azidophenyl-2-thiazolylmethane -

A solution of the azide (0.9 g, 4.2 mmole) in 1,2,4-trichlorobenzene (10 ml) was added dropwise during 30 min to 1,2,4-trichlorobenzene (100 ml) which was being vigorously stirred and purged with nitrogen. The temperature in the reaction flask was maintained at 188° throughout the addition of azide and for a further 4 h after the addition was complete. Removal of the solvent with a rotary evaporator (0.5 mm pressure) yielded a black tar. Treatment of the tar with ethyl acetate caused a black solid to precipitate (0.23 g). P.L.C. (50% toluene : 50% ethyl acetate) of the filtrate (0.35 g) yielded 2-aminophenyl-2-thiazolylmethane (0.08 g, 9%) m/e 191 (16%), 190 (M^+, 100), 189 (10), 157 (50), 131 (18), 130 (50), 118 (10), 117 (36), 106 (30), 104 (16), 78 (16), 77 (26), 58 (18), 51 (16), 39 (16) and $\delta(CDCl_3)$ 4.1 (2H, br s, $-NH_2$), 4.2 (2H, s, $-CH_2$), 6.5 - 7.6 (6H, cplx m, aromatic).

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