~~SOME~~ SYNTHETIC AND BIOSYNTHETIC STUDIES OF ERYTHRINA ALKALOIDS

A Thesis presented by

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To my Parents, Brother and Malkanthi

CONTENTS

ABSTRACT

This thesis consists of three main parts.

The first part describes the isolation and identification of some alkaloids from Erythrina abyssinica. The presence of orientaline and isoboldine in this plant is of some biosynthetic interest. A possible biosynthetic route to isoboldine from orientaline involving dienone-phenol rearrangement of orientalinone is suggested.

The second part constitutes a facile and convenient synthesis of diphenylethyl amine precursor of erysodienone. The overall process involved five steps from O-benzylisovanillin with an overall yield of 43%. A nitroso directed specific alkylation of nitrosamines was discovered.

The third part is a discussion of some experiments performed towards the synthesis of novel 2-azaallenium cations by a hydride abstraction process.

ACKNOWLEDGEMENTS

I am thankful to Professor Sir Derek H.R. Barton, F.R.S., for the provision of facilities and for his interest, guidance and encouragement, and to Dr. D.A. Widdowson for his constant guidance throughout this work.

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PART I

Alkaloids of *Erythrina abyssinica*: Structures and Biosynthesis

'Before we can begin to challenge Nature we have to understand how, in fact, she does her remarkable synthetic work'

Derek H.R. Barton

'Not infrequently Nature is more knowledgeable and artful than the chemist, and devises combinations between, or transformations of, reacting molecules which the designer had not anticipated at all'

Robert B. Woodward

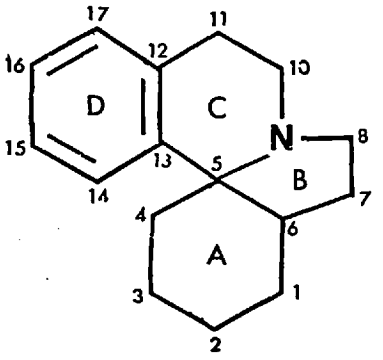
INTRODUCTION

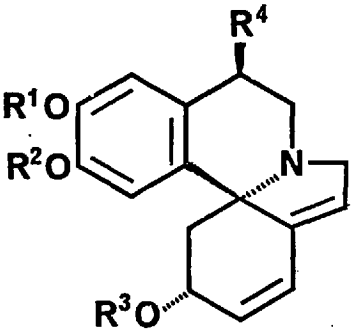
During the past three and a half decades *Erythrina* alkaloids have attracted special interest from both biochemists and organic chemists, because of their physiological activity and because they appear to contain a structural type not previously encountered among the alkaloids.

Botanically, the genus *Erythrina* belongs to the subfamily Papilionaceae of the legume family . Alkaloids occur in the seeds and various plant organs of *Erythrina* species which grow in the tropic and subtropic zones of all parts of the world[1]. Alkaloids of various species of *Erythrina* have attracted biochemists' interest because they are curarizing agents of high potency[2].

Isolation and characterisation of a wide variety of *Erythrina* alkaloids gave organic chemists the opportunity to elucidate their structure, synthesis and biosynthesis. The structure proved to be highly complex but the problem was resolved when, in 1951, Prelog and his group postulated a novel spiroamine system, Erythrinane 1 for the basic skeleton of these alkaloids[3]. The absolute stereochemistries at C-3 and C-5 positions were subsequently determined by X-ray diffraction[4-6] and spectroscopic[7] studies. Commendable and extensive efforts by Mondon and his collaborators[8] have culminated in a total synthesis of this spiroamine skeleton as exemplified by erysotrine 2. A biogenetic-like approach starting from erysodienone 8 by the same group had recently led to the synthesis of dihydroerysodine 9 and erythratidine

10[9]. Ingenious biosynthetic proposals by Barton and his coworkers[10-15] involving oxidative coupling of phenolate radicals have contributed a great deal to the understanding of the origin of this somewhat complicated skeleton in nature.





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2 $R^1 = R^2 = R^3 = Me$ $R^4 = H$

3 $R^1 = R^2 = R^4 = H$ $R^3 = Me$

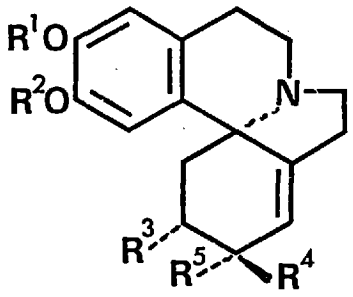
4 $R^1 = R^4 = H$ $R^2 = R^3 = Me$

5 $R^1 = R^2 = CH_2$ $R^3 = Me$ $R^4 = H$

6 R^1 = 1-β-glucosyl

$R^2 = R^3 = Me$ $R^4 = H$

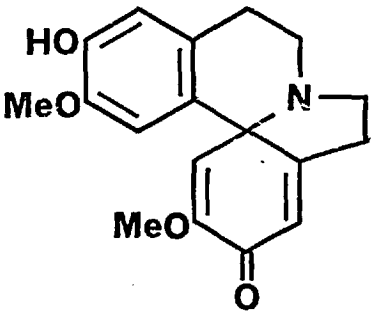
7 $R^1 = R^2 = R^3 = Me$ $R^4 = OMe$



9 $R^1 = R^4 = R^5 = H$ $R^2 = Me$ $R^3 = OMe$

10 $R^1 = R^2 = Me$ $R^3 = OMe$ $R^4 = H$ $R^5 = OH$

11 $R^1, R^2 = CH_2$ $R^3 = OMe$ $R^4 = OH$ $R^5 = H$



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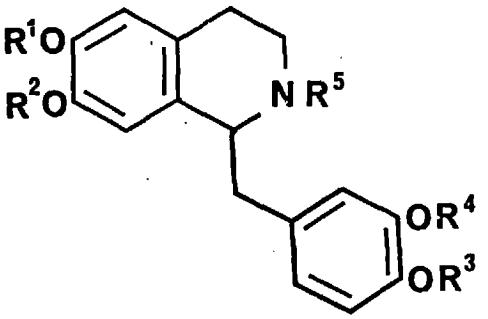
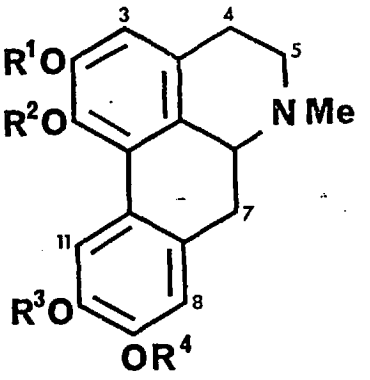




12 $R^1 = R^4 = R^5 =$ Me $R^2 = R^3 =$ H

13 $R^1 = R^3 = R^5 =$ Me $R^2 = R^4 =$ H

14 $R^1 = R^4 =$ H $R^2 = R^3 = R^5 =$ Me

15 $R^1 = R^3 =$ H $R^2 = R^4 = R^5 =$ Me

16 $R^1 = R^4 =$ Me $R^2 = R^3 = R^5 =$ H

17 $R^1 = R^2 = R^3 = R^4 = R^5 =$ Me

18 $R^1 = R^4 =$ Me $R^2 = R^3 =$ H

19 $R^1 = R^4 =$ H $R^2 = R^3 =$ Me

20 $R^1 = R^2 = R^3 = R^4 =$ Me

DISCUSSION

Some years ago Folkers and Konuiszy, the pioneers of *Erythrina* alkaloid field, reported the isolation of erysopine 3, erysodine 4 and glucoerysodine 6 from the seeds of *E. abyssinica*[17,18]. In 1949 Prelog and his group reinvestigated these seeds and reported[19] the presence of erysodine 4 and erythraline 5 in their extracts. The leaves however were not examined.

Extraction of the macerated leaves with 0.02 N hydrochloric acid gave a crude basic fraction, the t.l.c. of which indicated the presence of at least five compounds. These were separated by column chromatography over alumina.

First, elution with 10% ethyl acetate in benzene gave erythraline 5 in 0.00023% yield. It was characterised as the hydrobromide, m.p. 241-245°, $[\alpha]_D$ + 219°, identical (m.m.p., t.l.c.) with the authentic material.

Further elution with the same solvent system afforded erythristemine 7 in 0.00013% yield, m.p. 126-128°, $[\alpha]_D$ + 183°, indistinguishable (m.m.p., t.l.c.) from the material obtained from *E. lysistemon*, the structure of which had been deduced by X-ray crystallographic and n.m.r. (INDOR) studies[20].

Elution with pure ethyl acetate gave erythratine 11 in 0.00025% yield, m.p. 176-178°, identical (m.m.p., t.l.c. and mass spectrum) with the available authentic alkaloid.

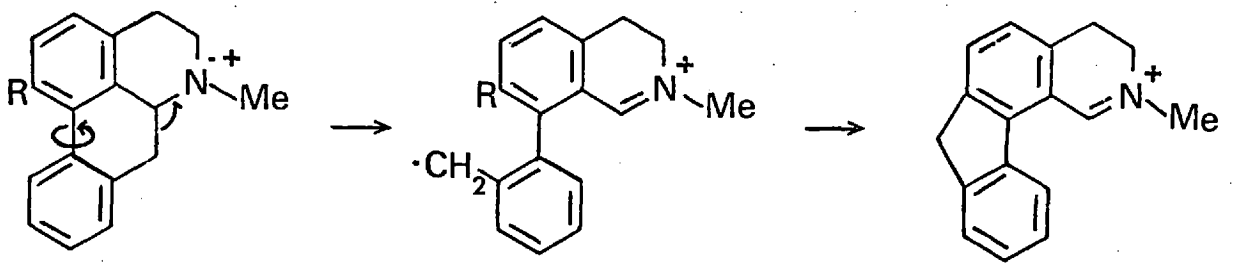
Finally, elution with ethanol-ethyl acetate afforded a mixture of two bases, chromatographically different to any available *Erythrina* alkaloid. These were separated by

preparative t.l.c. The faster running (R_F 0.5) component, obtained in 0.0008% yield had m.p. 118-120° and analysed for $C_{19}H_{21}NO_4$ by mass spectrometry and via the crystalline picrate, m.p. 197-198°. The free base had a u.v. spectrum characteristic of an aporphine alkaloid[21]. The n.m.r. spectrum showed only three protons in the aromatic region, consistent with the tetraoxygenated aporphine system. Methylation of the free base with diazomethane gave (+)-glaucine 20, m.p. 120-123°, $[\alpha]_D$ + 120°, having spectral characteristics (u.v., n.m.r. and mass spectrum) identical to those reported (see Experimental section). The hydrochloride had m.p. 240-242° which was undepressed on admixture with authentic natural glaucine hydrochloride.

The difference of 24 mass units between the parent peaks in the mass spectra of the methylated product (glaucine) and the parent alkaloid indicated the latter to be one of the two natural aporphines, boldine 19 or isoboldine 18. Careful analysis of n.m.r. and mass spectra, as described below, suggested it to be isoboldine.

In the n.m.r. of aporphine alkaloids the methoxy protons resonate in a very close range at τ, 6.09 ± 0.07 except those in the C-1 or C-11 positions, which occur at τ, 6.30 ± 0.06[22]. The two methoxyl groups of the compound isolated were found to occur at a low field (τ, 6.17) showing that none of them is attached to C-1. The mass spectra of aporphines lacking a C-1 methoxy group show a relatively small peak at $M^+ - 31$, due to loss of methoxyl group[23d]. This is claimed to be of some diagnostic utility in determining the substitution pattern of an unknown aporphine alkaloid.[23a] In the mass spectrum of the isolated

alkaloid the M^+- 31 peak (at m/e 296) was found to be very weak. An intense peak was found at M^+-17 (m/e 310), which implied the presence of a hydroxy function at C-1 (Scheme 1). A base catalysed deuterium exchange experiment[24] (exchange of *one* proton confirmed by mass spectrometry) also eliminated the possibility of the hydroxylation pattern being similar to that in boldine. Finally, the isolated alkaloid was identified as isoboldine 18 by spectroscopic and chromatographic comparison with synthetic racemic material. A plausible biosynthetic scheme for the origin of isoboldine in E. abyssinica is discussed elsewhere in this thesis (p. 18).



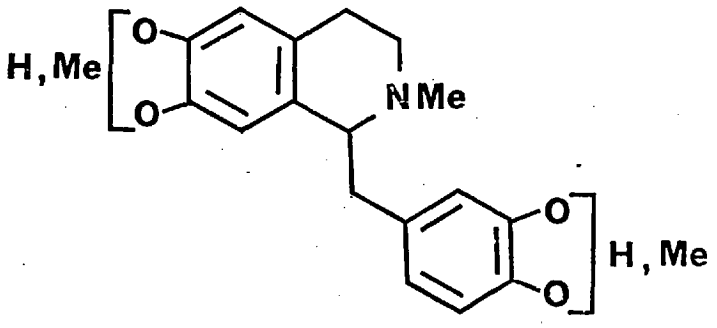
M^+ – 17 (R = OH)

M^+ – 31 (R = OMe)

Scheme I

The slower running component (R_F 0.3) was purified as the amorphous methiodide, and corresponded to a 0.001% yield of the free base. The u.v. spectrum (λ_{max} 283 nm.) was consistent with the presence of dioxygenated aromatic rings[25],

and a reversible base induced red shift of 30 nm. indicated the presence of free phenolic groups[26]. The high resolution mass spectrum suggested a molecular formula of $C_{20}H_{25}NO_4$ for the thermal Hofmann elimination product[27] and a base peak at m/e 192 was indicative of a 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid with one methoxy and one hydroxy group on each aromatic ring[23b]. The n.m.r. spectrum was assignable to a 3',4',6,7-tetraoxygenated system (see Experimental section) with two methoxy and one N-methyl groups (as in 21)[28]. A small sample of the free base was purified by column chromatography on alumina and crystallisation of the



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perchlorate salt. This had a m.p. identical to that reported for orientaline perchlorate[29]. (±)-Orientaline 12 was prepared from the available (±)-N-nororietaline 16 and found to be chromatographically identical with the natural material. This was chromatographically [alumina/chloroform-methanol (20:1); silica/benzene-ethyl acetate-diethylamine (5:4:1), double development; silica/chloroform-acetone-diethylamine (5:4:1)] distinct from the other three isomers with one methoxy-and one hydroxy- group in each aromatic ring

With the oxygenation pattern as in 21, viz reticuline 13, protosinomenine 14, and the wholly synthetic compound 15.

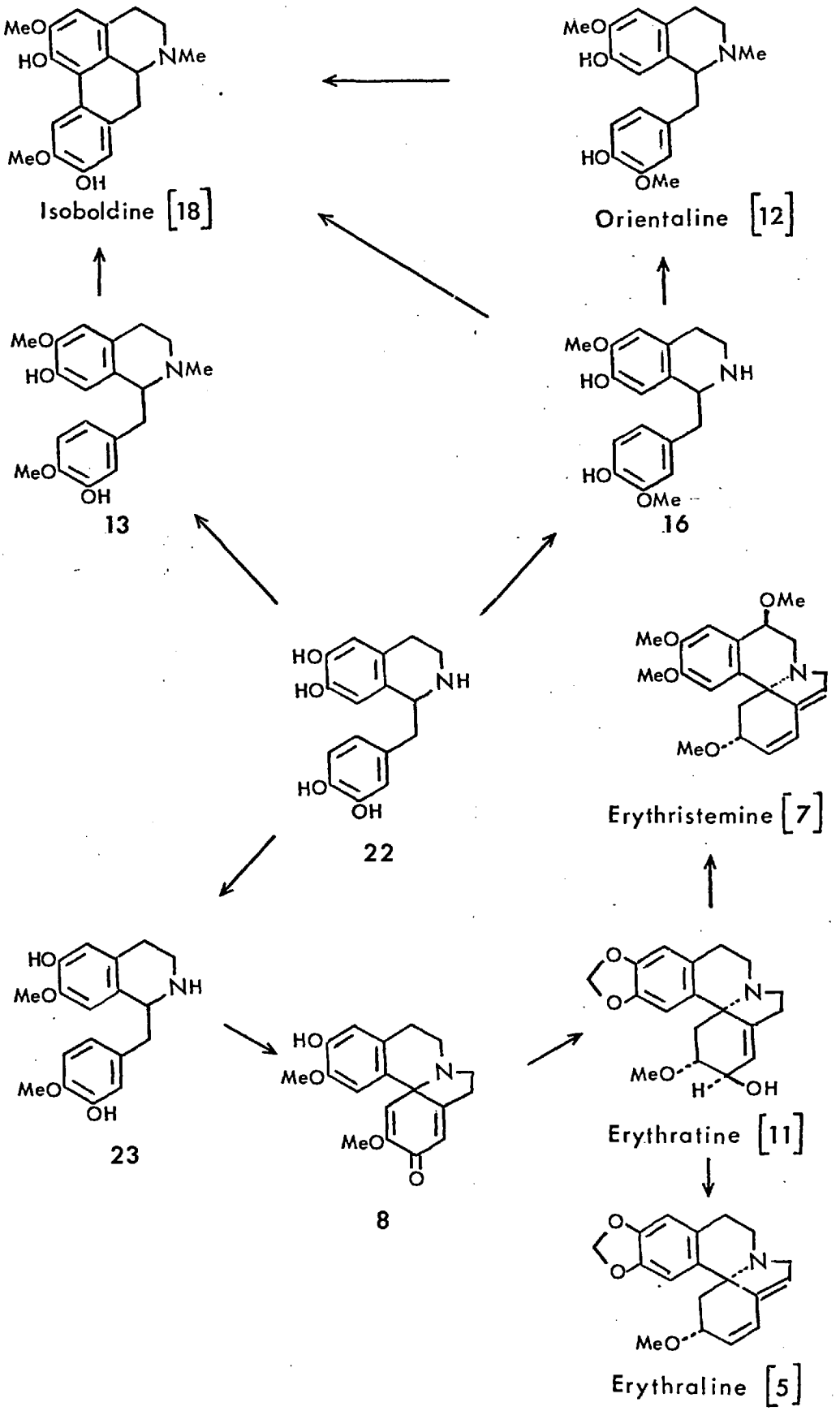
Finally, the oxygenation pattern was confirmed and the absolute stereochemistry assigned by O-methylation of the natural base with diazomethane to give partially racemic (-)-laudanosine 17, and N-methylation to the methiodide, m.p. 219-220°. This established the orientaline 12 to be of the 1 R configuration. The origin of the partial racemisation was not determined here, but the biological interconversion of 1-benzyl-1,2,3,4-tetrahydroisoquinoline enantiomers via the imine intermediate is well authenticated in other species[30].

Some plausible routes for the biosynthetic origin of the five alkaloids isolated from E. abyssinica are depicted in Scheme 2.

The biosynthesis of erythratine 11 from norprotosinomenine 23 via erysodienone 8 and the biosynthetic conversion of erythratine to erythraline 5 are well established in E. crista-galli[10-15]. The occurrence of the C-11 substituted, erythristemine 7 suggests a late stage benzylic hydroxylation. Other C-11 oxygenated Erythrina alkaloids are also known[31,32] and in all cases, the alkaloids are of the 'biogenetically complete' 1,6-diene types.

Although the 'obvious' biosynthetic origin of orientaline 12 from N-norlaudanosoline 22 had not yet been confirmed, it was found to act as an efficient precursor in the biosynthesis of the aporphine alkaloid, isothebaine (30, Scheme 4), in Papaver orientale (Family Papaveraceae)[33].

Barton and Cohen, in their paper[34] on oxidative coupling of phenols, proposed two biosynthetic pathways by


Isoboldine [18]
Orientaline [12]
13
16
22
Erythristemine [7]
23
8
Erythratine [11]
Erythraline [5]

Scheme 2

which suitable phenolic tetrahydroisoquinolines may be converted to aporphines either by a direct coupling or indirectly *via* an intermediate dienone (as 28) which, in turn, could undergo rearrangements to a variety of aporphines. Although the elucidation of biosynthetic pathways leading to aporphine alkaloids are far from complete, there is now considerable evidence in support of both the direct coupling and the mechanisms that require an intermediate dienone. *In vitro* experiments have shown that isoboldine 18 could be obtained from reticuline 13 by the action of one electron oxidising agents.[35,36] Co-occurrence of reticuline with isoboldine in *Papaver somniferum* (Family Papaveraceae) had prompted Brochmann-Hanssen and his coworkers to examine the possibility of the biosynthetic conversion of (±)-reticuline into isoboldine[37]. When labelled (±)-reticuline was administered to opium poppies, it was incorporated into isoboldine to an extent of about 0.08%. Leete has pointed out[38] 'however, that in this case only reticuline was tested as a precursor, and additional studies with other methyl ethers of laudanosoline and norlaudanosoline are warranted'.

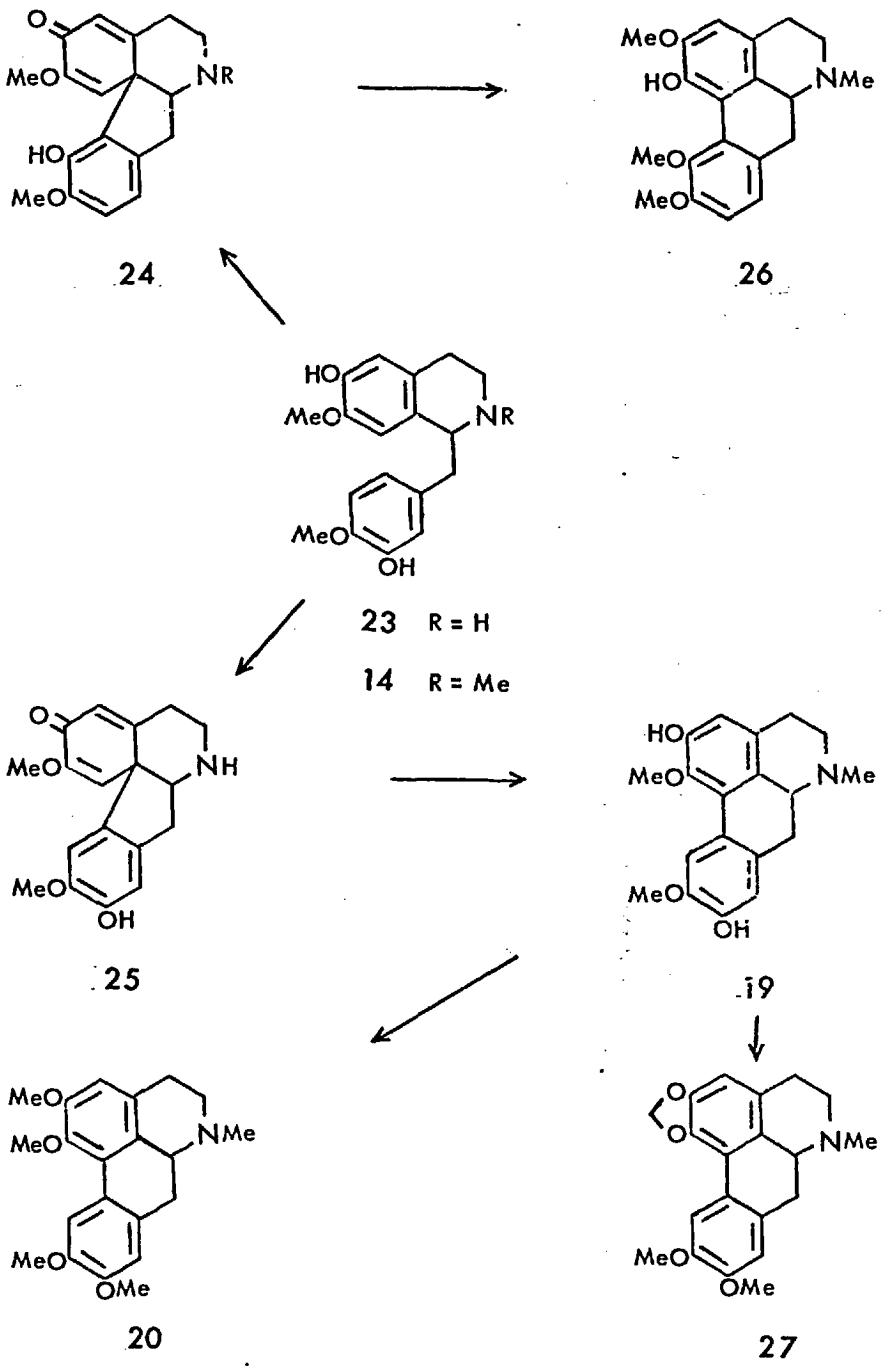
Battersby and his group have recently elucidated a surprising biogenetic route to the apparently 'directly coupled' aporphine alkaloids, corydine 26, glaucine 20 and dicentrine 27 in *Dicentra eximia* (Family Papaveraceae)[39]. All these three alkaloids were found to be derived from N-norprotosinomenine 23 *via* the dienones 24 and 25 (Scheme 3). As the possible intermediacy of proerythrinadienone 25 in the biosynthesis of *Erythrina* alkaloids had already been suggested[12,15], Battersby states[39] that 'the differing uses made of this skeleton in *Erythrina* (Family

Leguminosae) and Dicentra (Family Papaveraceae) species is of biosynthetic and taxonomic interest'.

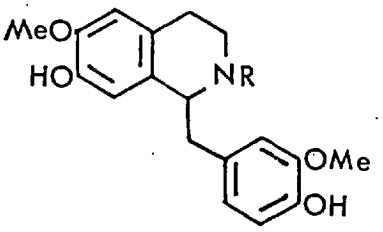
Aporphines have also been obtained in vitro by oxidative coupling to a dienone, reduction to the corresponding dienol, and rearrangement to the aporphine. The synthesis of isothebaine 30 from orientaline 12 via the dienone, orientalinone 28 and the dienol, orientalinol 29 was performed by Battersby et. al [29,40]. Rearrangement of orientalinone without prior reduction would give rise to either isoboldine 18 isocorytuberine 31 and the compound 32 or 33 (Scheme 4). Although the latter three have not yet been found in nature, isocorytuberine has been obtained as a result of the acid catalysed rearrangement of orientalinone[41]. Similar 'biogenetic-type' syntheses of aporphines by dienone-phenol rearrangement were reported by several investigators[42-45]. Aporphine producing dienones related to orientalinone are found in nature and are generally referred to as proaporphines. Experimental evidence for the in vivo conversion of proaporphines to aporphines was furnished by Barton et. al.[45,46] and Battersby et. al[33,47,48]. Co-occurrence of isoboldine with orientaline in E.abyssinica is noteworthy. Dienone-phenol rearrangement of orientalinone 28 derived from orientaline would lead to isoboldine as discussed earlier (Scheme 4). But the final confirmation of the route proposed should emerge as a result of appropriate feeding experiments.

The present work was undertaken in an attempt to detect the presence of any intermediates of biosynthetic interest[58]. Although no such biointermediates were found to occur in the alkaloidal fraction of the E. abyssinica leaves investigated, the presence of the biogenetically interesting

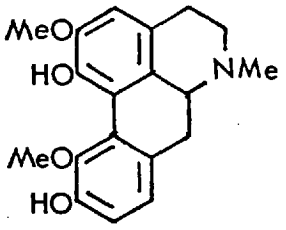
1,2,3,4-tetrahydroisoquinoline alkaloid, orientaline 12 and the aporphine alkaloid, isoboldine 17 was confirmed by means of extensive physical data. Orientaline was only recently detected in E. arborescens[16]. This is the first instance of an aporphine alkaloid in an Erythrina species.



Scheme 3



R = H or Me (12)



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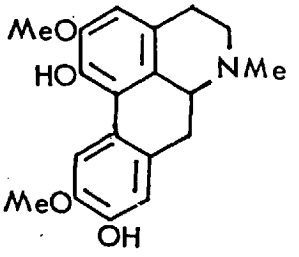

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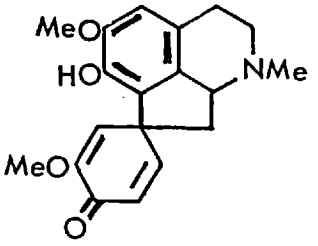

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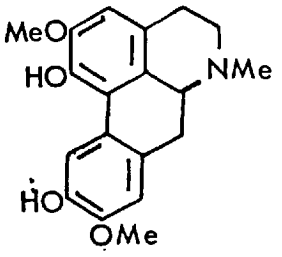

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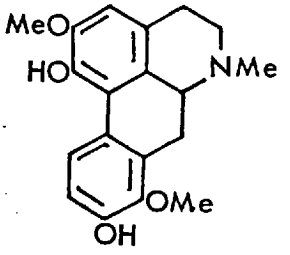

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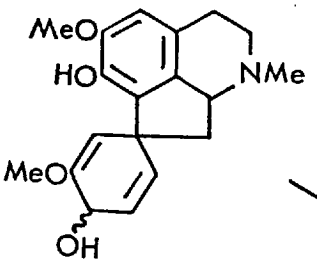

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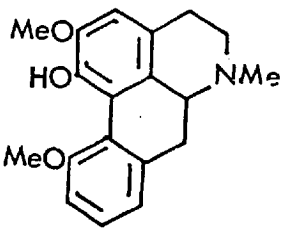

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Scheme 4

EXPERIMENTAL

Unless otherwise stated the following data apply to experiments described in this thesis. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. I.r. spectra were recorded for chloroform, on a Unicam SP 200 or a Perkin Elmer 257 spectrometer. Nuclear magnetic resonance (n.m.r.) spectra were taken in deuteriochloroform with a tetramethylsilane (TMS) internal standard on a Varian T 60 or HA 100 spectrometer. Signals are reported in the order of chemical shift designated on the τ scale, and within parentheses intensity, multiplicity, coupling constant in Hz, and assignment, with the aid of the following abbreviations:- s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; e, envelope; b, broad. Ultraviolet spectra (u.v.) were recorded in ethanol on a Unicam SP 800 B spectrometer. Mass spectra were recorded with a Perkin Elmer 270 low-resolution or A.E.I. MS 9 high-resolution spectrometer. Rotations were measured on a Perkin Elmer 141 polarimeter. All solvents used were purified according to standard procedures. T.l.c. was carried out on alumina GF or silica plates. For preparative work these were 1 mm. thick.

Extraction of E. abyssinica.—

Powdered dried leaves of E. abyssinica (10.0 kg) were stirred for three days in 0.02 N-hydrochloric acid (120 l). The acidic solution was filtered through Celite and washed with light petroleum (b.p. 40-60°, 6 x 4 l). The acidic extract was basified ($NaHCO_3$) to pH 9 and repeatedly extracted with chloroform (8 x4.8 l). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure,

and the alkaloidal residue (11.25 g , 0.1125%) chromatographed on alumina (Grade III).

Erythraline (5).— Elution with 10% ethyl acetate in benzene gave erythraline, isolated as hydrobromide salt (23 mg , 0.00023%), m.p. 241-245° (decomp.) (from ethanol), $[\alpha]_D$ 219° (c 0.1 in H_2O) (lit.[49] , m.p. 243°(decomp.), $[\alpha]_D$ 217° (H_2O)). The free base had M^+ 297 and a fragmentation pattern identical with that of authentic material[50].

Erythristemine (7).— Further elution of the column with the same solvent gave a crude alkaloid which was purified by preparative t.l.c. (alumina) to yield erythristemine (12.5 mg. , 0.00013%), m.p. 126-128° (from light petroleum), mixed m.p. 124-127° with an authentic specimen (lit.[20] , m.p. 127-129°), $[\alpha]_D$ 183°(c 0.13 in $CHCl_3$) (lit.[20] , $[\alpha]_D$ 189°($CHCl_3$)).

Erythratine (11).— Fractions eluted with ethyl acetate, after purification by preparative t.l.c. (alumina), gave erythratine (25.0 mg , 0.00025%), m.p. 176-178° (from ethyl acetate), mixed m.p. 173-175° with an authentic specimen (lit.[51] , m.p. 172-174°). The mass spectrum, with M^+ 315, was identical with that of authentic material[50].

Elution with an increasing concentration of ethanol in ethyl acetate gave a mixture of two alkaloids which were separated by preparative t.l.c. (5% methanol in chloroform) and were identified as isoboldine 18, R_F 0.5, and orientaline 12, R_F 0.3 (see below).

Isoboldine (18).— This was isolated as the hydrochloride (83 mg , 0.0008%), m.p. > 300° (from methanol-ether) (lit.[52] , m.p. > 300°). The free base had m.p. 118-120° (from $CHCl_3$), (lit.[52] , m.p. 118-120°), $\nu_{max.}$ 3500, 3250, 1605 and 1485 cm^{-1},

$\lambda_{max.}$ 303.5 (log ϵ 3.99), and 280.0 nm (4.05), τ 2.06 (1H, s, 11-H), 3.28 (1H, s, 8-H), 3.55 (1H, s, 3-H), 6.17 (6H, split s, OMe), 7.53 (3H, s, NMe), and 6.40-7.80 (7H, complex, aliphatics), m/e 327 (M^+), 326 (100%), 310, 296, 284, 269, and 253 (Found: M^+, 327.1437, $C_{19}H_{21}NO_4$ requires M^+, 327.1444). These u.v.[36], n.m.r.[52], and mass[41] spectra were identical with those reported for isoboldine.

Isoboldine Picrate.— Treatment of isoboldine (16 mg) with recrystallised picric acid (10 mg) in ethanol (2 ml) yielded on cooling a brown solid which was treated with animal-charcoal and recrystallised to give orange needles (10 mg), m.p. 197-198° (from ethanol-methanol) [Found: C, 52.18; H, 4.19; N, 9.61. $C_{25}H_{24}N_4O_{12} \cdot H_2O$ requires C, 52.26; H, 4.56; N, 9.75%].

Deuterium Exchange of Aromatic Protons of Isoboldine[24].— Isoboldine (5 mg) in D_2O (0.5 ml) containing dimethyl acetamide (2 ml) was heated in a sealed tube under nitrogen for 65 h at 100°. The solvents were removed in vacuo, and the product purified by t.l.c. to obtain a brown gum (3 mg), the mass spectrum of which confirmed exchange of only one proton, m/e 328 (M^+), 327 (100%), 313, 300, 298, 293, and 284.

(±)-Glaucine (20).— Natural isoboldine (30 mg) in absolute methanol (5 ml) was methylated with excess of ethereal diazomethane during 16 h at room temperature. Purification of the product by t.l.c. gave (±)-glaucine (22 mg), m.p. 120-123° (from ether), $[\alpha]_D$ 102° (c 0.7 in $CHCl_3$) (lit.[53], m.p. 119-120°, $[\alpha]_D$ 120° ($CHCl_3$)). The product had u.v.[54], n.m.r.[35], and mass[55] spectra identical with those reported for glaucine.

Orientaline (12).— This was isolated as the methiodide, an amorphous solid (102 mg , 0.001%), $[\alpha]_D$ -35.5° (c 0.2 in Me_2CO), $\lambda_{max.}$ 283 (ε 5400) and 225 infl nm (17,000), $\lambda_{max.}$ (NaOH-EtOH) 310 (ε 6,900) and 252 nm (14,800), τ (($^2H_6$)-acetone) 3.17 br (2H, s, 2- and 5-H), 3.39 (1H, d, J 8.0 Hz, 5'-H), 3.52 (1H, dd, J_1 8.0, J_2 2.0 Hz, 6'-H), 3.89 (1H, s, 8-H), 4.90 (1H, dd, J_1 9.0, J_2 4.0 Hz, 1-H), 6.22 (3H, s, OMe), 6.27 (3H, s, OMe), 6.93 br (3H, s, NMe), 6.67 br (3H, s, NMe), and 6.10-6.90 (6H, complex, aliphatics), m/e 343 (M^+), 312, 206, 192 (100%), 177, 149, and 137 (Found: M^+, 343.1775, $C_{20}H_{25}NO_4$ (Hofmann elimination product)[27] requires M^+, 343.1783) .

The free base was obtained as a gum from a sample of crude alkaloid by column chromatography on alumina. It had identical chromatographic properties with those of a sample of orientaline obtained by N-methylation of authentic N-nor-orientaline with methyl iodide. The natural base was purified as orientaline perchlorate, m.p. 123-126° (from methanol-ether) (lit.[29] , m.p. 127°).

Laudanosine (17).— Orientaline (40 mg) in absolute methanol (7.5 ml) was methylated with excess of ethereal diazomethane, during 16 h at room temperature. The product was purified by t.l.c. to yield partially racemic laudanosine as a gum (33 mg), $[\alpha]_D$ - 11.5° (c 0.2 in $CHCl_3$) (lit.[56] , $[\alpha]_D$ - 52° ($CHCl_3$)) .

Laudanosine Methiodide.— Laudanosine (15 mg) was refluxed with excess methyl iodide in absolute methanol (2 ml) to obtain laudanosine methiodide, m.p. 219-220° (from acetone) (lit.[57] , m.p. 218-221), m/e 371 (M^+), 340, 220, 206 (100%),

191, 162, and 151. (Found: $\underline{M}^+$, 371.2098, $C_{22}H_{29}NO_4$ (Hofmann elimination product)[27] requires $\underline{M}^+$, 371.2106) [Found: C, 53.70; H, 6.26; N, 2.77. $C_{22}H_{30}INO_4 \cdot C_2H_6O$ requires C, 53.86; H, 6.51; N, 2.51%].

REFERENCES

1 S.W. Pelletier, ' Chemistry of the Alkaloids', Van Nostrand Reinhold Company, New York, 1970, p 173.

2 R.H.F. Manske, 'The Alkaloids', Vol V, Academic Press, London, 1955, p 281.

3 M. Carmack, B.C. McKusick, and V. Prelog, Helv. Chim. Acta, 1951, 34, 1601.

4 W. Nowacki and G.F. Bonsma, Z. Krist., 1958, 110, 89.

5 A.W. Hanson, Proc. Chem. Soc. 1963, 52.

6 A.W. Hanson, Acta. Cryst., 1963, 16, 939.

7 D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, Chem. Comm., 1966, 294.

8 A. Mondon and H.J. Nestler, Angew. Chem. internat. Edit., 1964, 3, 588.

9 A. Mondon and M. Ehrhardt, Tetrahedron Letters, 1966, 2557.

10 D.H.R. Barton, Chem. in Britain, 1967, 330.

11 D.H.R. Barton, R. James, G.W. Kirby and D.A. Widdowson, Chem. Comm., 1967, 267.

12 D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, J. Chem. Soc. (c), 1968, 1529.

13 D.H.R. Barton, and D.A. Widdowson, Abhandl. Deut. Akad. Wiss. Berlin, 4 internationales Symposium, Biochemie und physiologie der Alkaloide, Halle, Juin 1967, p 18.

14 D.H.R. Barton, R.B.Boar, and D.A. Widdowson, J. Chem. Soc. (c), 1970. 1208.

15 D.H.R. Barton, R.B. Boar, and D.A. Widdowson, J. Chem. Soc. (c), 1970, 1213.

16 S. Ghosal, A. Chakraborti, and R.S. Srivastava, Phytochemistry, 1972, 11, 2101.

17 K. Folkers and F. Konuiszy, J. Amer. Chem. Soc., 1940, 62, 1677.

18 K. Folkers and F. Konuiszy, Chem. Abs., 1946, 40, 1283.

19 V. Prelog, K. Wiasner, H.G. Khorana, and G.W. Kenner, Helv. Chim. Acta, 1949, 32, 453.

20 D.H.R. Barton, P.N. Jenkins, R. Letcher, D.A. Widdowson, E. Hough, and D. Rogers, Chem. Comm., 1970, 391.

21 A.W. Sangster and K.L. Stuart, Chem. Revs., 1965, 65, 69.

22 W.H. Baarshers, R.R. Arndt, K. Pachler, J.A. Weisbach, and B. Douglas, J. Chem. Soc., 1964, 4778.

23a H. Budzikiewicz, C. Djerassi, and D.H. Williams, 'Structure Elucidation of Natural Products by Mass Spectrometry', Holden-day, San Francisco, 1964, Vol. 1, p 174.

23b ibid., p 173.

24 G.W. Kirby, and L. Ogunkoya, J. Chem. Soc., 1965, 6914.

25 L. Doub and J.M. Vanderbelt, J. Amer. Chem. Soc., 1949, 71, 2414.

26 A.I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products', Pergamon Press, Oxford, 1964, p 95.

27 H. Budzikiewicz, C. Djerassi and D.H. Williams, 'Mass Spectrometry of Organic Compounds', Holden-day inc., London, 1967, p 330.

28 D.H.R. Barton, R.H. Hesse, and G.W. Kirby, J. Chem. Soc., 1965, 6379.

29 A.R. Battersby, T.H. Brown, and J.H. Clements, J. Chem. Soc., 1965, 4550.

30 A.R. Battersby, D.M. Foulkes, and R. Binks, J. Chem. Soc., 1965, 3323.

31 K. Ito, H. Furukawa, and H. Tanaka, Chem. Comm., 1970,1076.

32 R.H. Letcher, J. Chem. Soc. (C), 1971, 652.

33 A.R. Battersby, R.T. Brown, J.H. Clements, and G.G. Iverach, Chem. Comm., 1965, 230.

34 D.H.R. Barton and T. Cohen, 'Festschrift Arthur Stoll', Birkhauser, Basel, Switzerland, 1957, p 117.

35 A.H. Jackson and J.A. Martin, J. Chem. Soc. (C), 1966, 2061.

36 W. Chan and P. Maitland, J. Chem. Soc. (C), 1966, 753.

37 E. Brochmann-Hanssen, C-C Fu, and L.Y. Misconi, J. Pharm. Sci., 1971, 60, 1880.

38 E. Leete, in 'Biosynthesis' Vol 1, The Chemical Society, London, 1972, p 171.

39 A.R. Battersby, J.L. McHugh, J. Staunton, and M. Todd, Chem. Comm., 1971, 985.

40 A.R. Battersby, and T.H. Brown, Proc. Chem. Soc., 1964, 85.

41 A.H. Jackson, and J.A. Martin, J. Chem. Soc. (C), 1966,2222.

42 J. Slavik and L. Slavikova, Collect. Czech. Chem. Comm., 1963, 28, 1720.

43 M. Shamma, and W.A. Slusarcbyk, Chem. Comm., 1965, 528.

44 L.J. Haynes, K.L. Stuart, D.H.R. Barton, and G.W. Kirby, J. Chem. Soc. (C), 1966, 1676.

45 D.H.R. Barton, D.S. Bhakuni, G.M. Chapman, and G.W. Kirby, J. Chem. Soc. (C), 1967, 2134.

46 L.J. Haynes, K.L. Stuart, D.H.R. Barton, D.S. Bhakuni, and G.W. Kirby, Chem. Comm., 1965, 141.

47 A. R. Battersby, and T.H. Brown, Chem. Comm., 1966, 170.

48 A.R. Battersby, T.J. Brocksom, and R. Ramage, Chem. Comm., 1969, 464.

49 V. Boekelheide, and G.R. Wenzinger, J. Org. Chem., 1964, 29, 1307.

50 R.B. Boar, and D.A. Widdowson, J. Chem. Soc. (B), 1970, 1591.

51 K. Folkers, and F. Konuiszy, J. Amer. Chem. Soc., 1940, 62, 436.

52 P.S. Clezy, E. Gellert, D.Y.K. Lau, and A.W. Nichol, Austra. J. Chem., 1966, 19, 135.

53 R.H.F. Manske, Canad. J. Res., 1938, 8, 592.

54 M. Shamma, Experientia, 1960, 16, 484.

55 A.H. Jackson, and J.A. Martin, J. Chem. Soc. (C), 1966, 2181

56 M. Tomita, and J. Kunitomo, Yakugaku Zasshi, 1962, 82,734.

57 von H. Corrodi, and E. Hardegger, Helv. Chim. Acta , 1956, 39, 889.

58 D.H.R. Barton, A.A.L. Gunatilaka, R.M. Letcher, A.M.F.T. Lobo, and D.A. Widdowson, J. Chem. Soc. Perkin 1, 1973,874.

PART II

A Facile Synthesis of Erysodienone

'There is an additional dimension in organic synthesis as soon as one considers economics. To synthesise a given structure in an elegant and a novel manner is one thing; to do it more cheaply than by all other possible ways is a challenge of another order'

Derek H.R. Barton

'The arithmetic demon dictates one of the major axioms of synthesis. Get the most done in the fewest steps and in the highest yield'

Robert E. Ireland

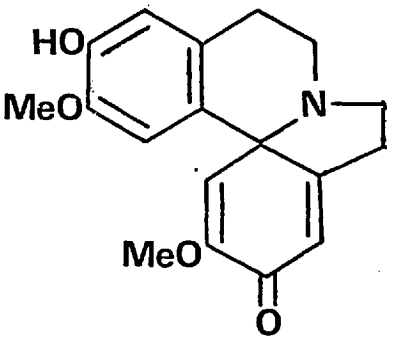
INTRODUCTION

Erythrina alkaloids have been shown to arise in nature *via* a spirodienone intermediate, erysodienone *1*, and its progenitor, 5,6,8,9-tetrahydro-2,12-dimethoxy-7 *H*-dibenz [d,f] -azonine-3,11 diol *2*. This is itself derived from the tetrahydrobenzyl isoquinoline alkaloid, *N*-norprotosinomenine *3*[1,4]. During this sequence the asymmetry of the system is apparently inverted[2]. In order to determine the means by which this inversion occurs, it was necessary to synthesise erysodienone and the dibenzazonine *2* intermediates in optically active form. Ready conversion of erysodienone into the dibenzazonine *2* by the action of reducing agents is well known[3], as is its *in vitro* conversion to various *Erythrina* alkaloids[4]. It occupies, therefore, a key position in both the biosynthesis and in the synthesis of *Erythrina* alkaloids.

The oxidative conversion of di-[2-(3-hydroxy-4-methoxy phenyl)ethyl] -amine *4* into erysodienone *1* was acheived by several groups[3-5] in 35% yield. The synthesis of *4* is lengthy and the mechanism of the oxidative cyclisation is not yet fully understood. A detail study of the whole process was therefore undertaken.

An efficient synthesis of di-2-phenylethylamine was the first requirement. Di-2-phenylethylamines have been synthesised by somewhat laborious methods[3,4,6]. A recent report from this laboratory described[7] an elegant 6-step route (overall yield 27%) for the synthesis of *4*. But, for above purposes a shorter and more efficient synthetic procedure was required.

Recognition of the symmetrical nature of the molecule



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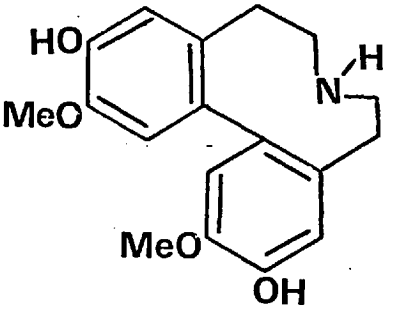

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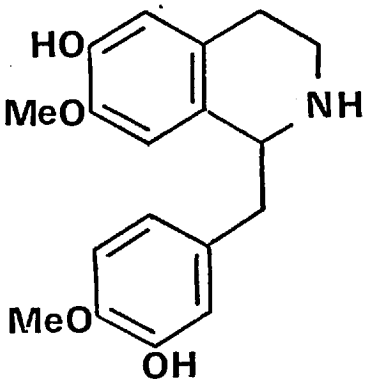

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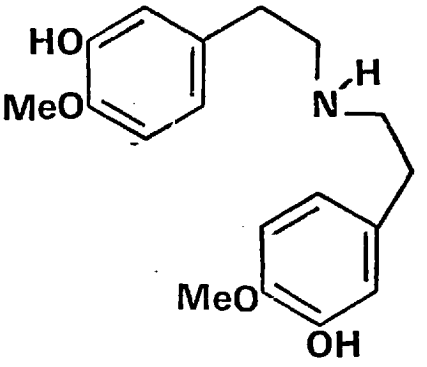
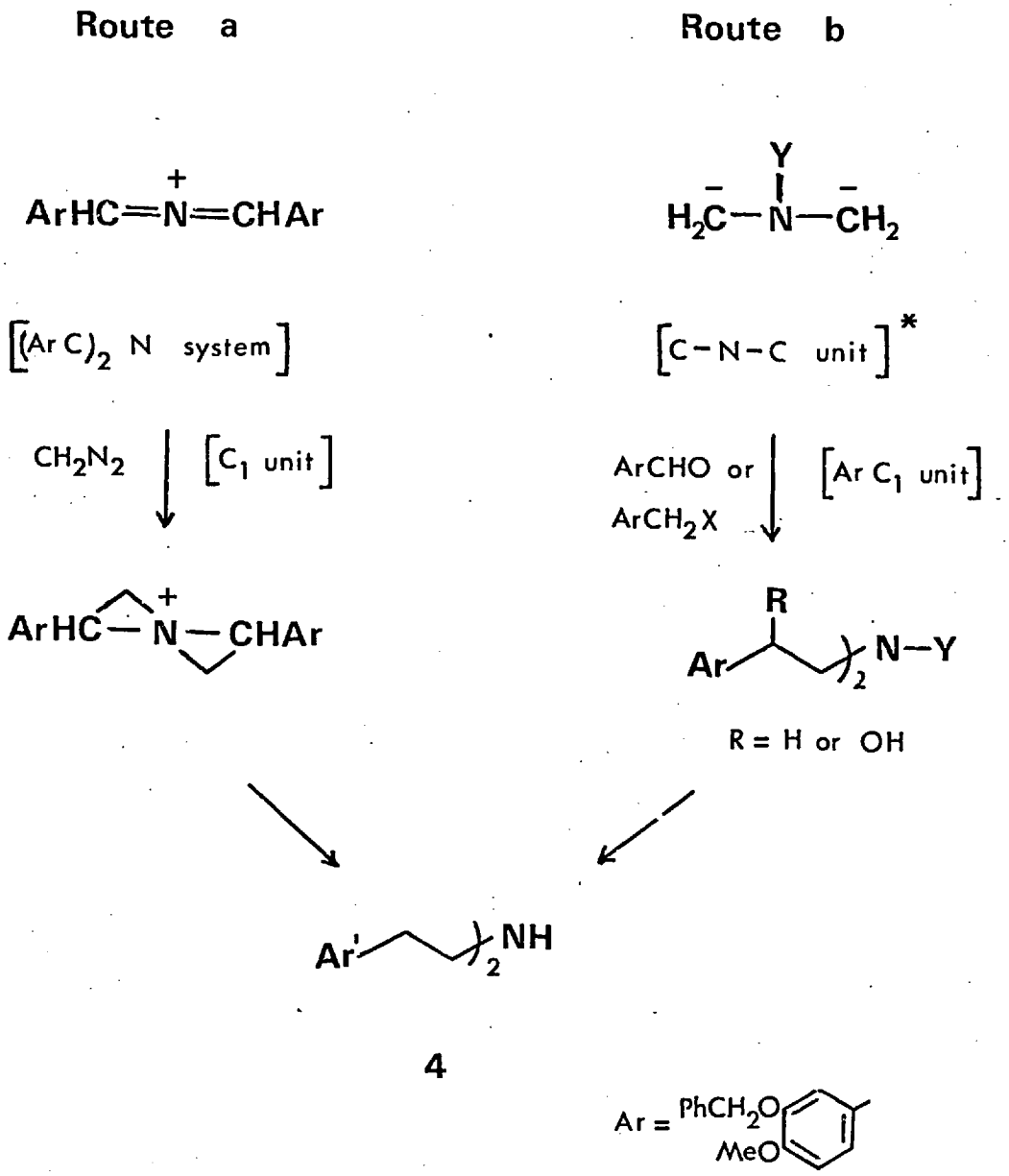


4

4 during early planning of the synthesis led to the development of two routes based on (a) carbon insertion reaction of $(Ar\text{-}C)_2N$ systems, and (b) C-C bond formation between an aryl-C_1 unit an a C-N-C unit (Scheme 1).

Insertion of carbenoid C_1 units into 2-azaallenium cations, was the principle approach to type (a) synthesis. Although considerable evidence for the existence of 2-azaallenium cation was obtained, insertion of carbenoid C_1 units (e.g. diazomethane) into this system was not possible. Experiments on these novel cations constitute the third part of this thesis.

Dimethylnitrosamine 5 was selected as the C-N-C unit for the second type of approach, as it is known[9] to metalate at the α-position. The aryl-C_1 unit chosen, was either O-benzyl isovanillin 7 or the 3-benzyloxy-4-methoxybenzyl halide 19 or 20. Using this approach, the synthesis of di-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-amine 4 was achieved by an efficient convergent route (Scheme 6). The overall process involved 5 steps with an overall yield of 43%. This approach also offers a new synthetic procedure of general applicability in addition to the specific usage cited.



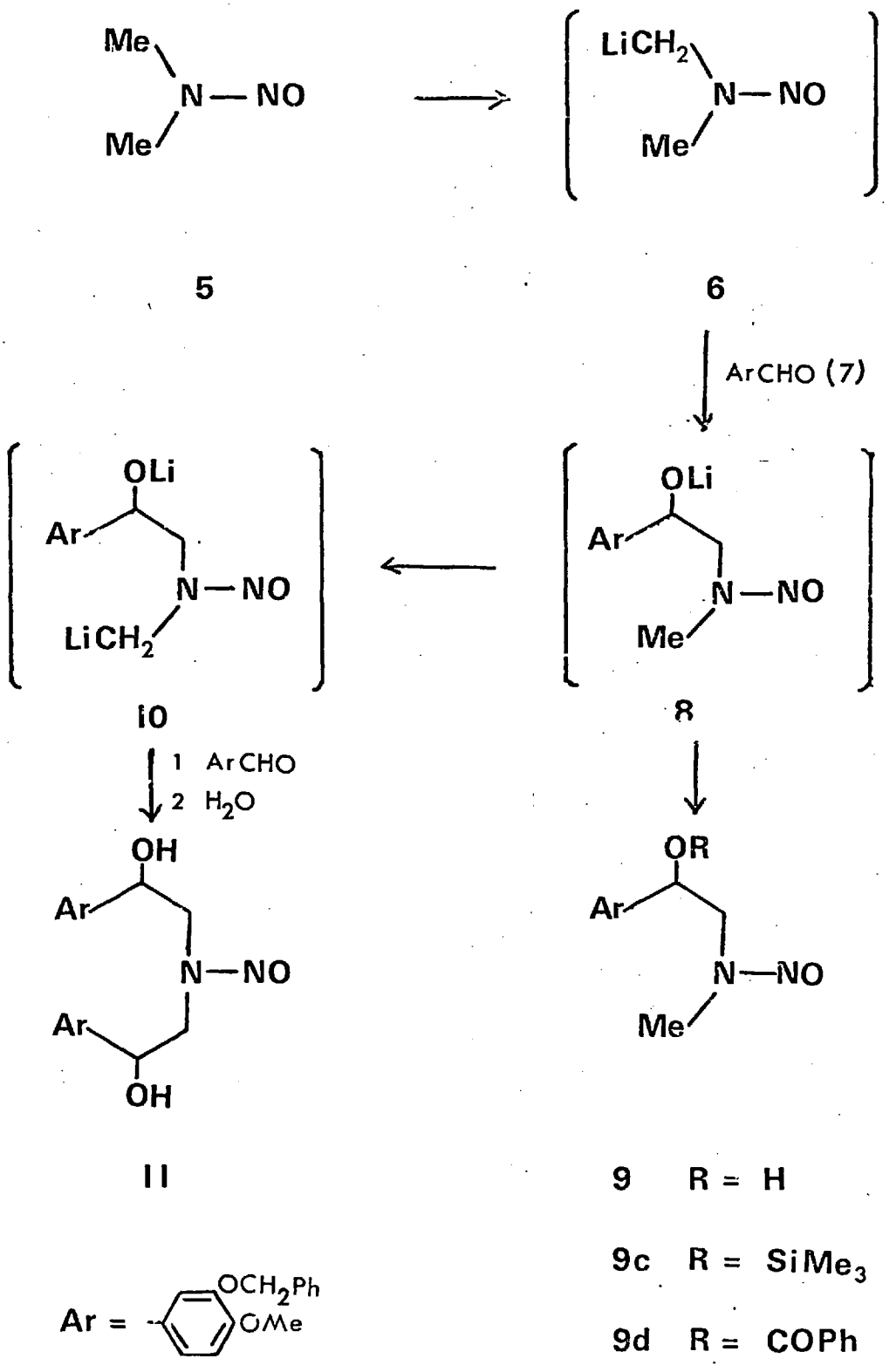
Scheme I

* A similar C-N-C unit would be the Wittig reagent $Ph_3\overset{+}{P}\text{-}\overset{-}{C}H\text{-}N(R)\text{-}\overset{-}{C}H\text{-}\overset{+}{P}Ph_3$. A number of attempts made in this laboratory to produce such a reagent were unsuccessful[8].

DISCUSSION

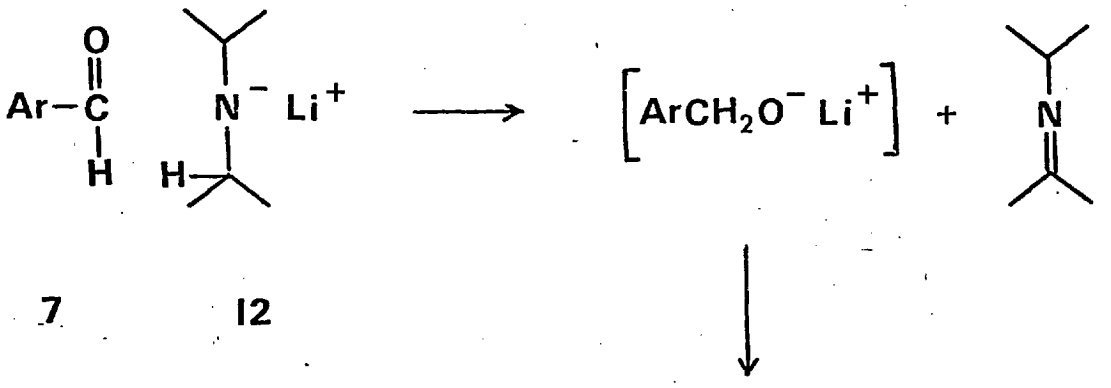
In 1972 Seebach and Enders published their successful α-alkylation of dimethylnitrosamine 5 via its α-lithio derivative 6[9]. As the original planning of the synthesis of di-2-phenylethylamine 4 had envisaged the formation of C-C bond between an aryl C_1 unit and a C-N-C unit, it was decided to test the feasibility of this available method.

In a preliminary experiment, the α-lithioderivative 6, obtained by the reaction of dimetylnitrosamine with lithium di-isopropylamide 12, was reacted with O-benzylisovanillin 7 in a manner similar to that reported by Seebach and Enders[9]. The crude product when examined by n.m.r. spectroscopy was shown to contain the desired nitrosamine 9 as the sole product. This was isolated as a yellow gum in 94% yield. In a second experiment, the product was further alkylated by the same procedure without isolation of the intermediate. Examination of the crude double alkylation product by n.m.r. spectroscopy indicated only 10-15% reaction. The rest of the mixture consisted of about 50% of the unreacted 9 and about 35% of 3-benzyloxy-4-methoxybenzyl alcohol 18. This product distribution was confirmed by isolation of N-nitroso-di [2-hydroxy-2-(3-benzyloxy-4-methoxyphenyl)ethyl] amine 11 and the benzyl alcohol 18 in yields of 12 and 35%, respectively. Consistent results were obtained when the reaction was repeated under identical conditions, with the rigorous exclusion of moisture. Formation of 18 could be explained by a hydride ion transfer from lithium diisopropylamide to O-benzylisovanillin. Such α-hydride ion transfer to substrates containing actual or latent Lewis acid sites was found to be a main side reaction in syntheses with $LiN(CHR_2)_2$[10] bases.

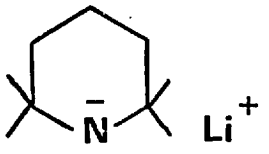

Me
N — NO
Me
LiCH2
N — NO
Me
5
6
ArCHO (7)
OLi
Ar
N — NO
LiCH2
OLi
Ar
N — NO
Me
10
8
1 ArCHO
2 H2O
OH
Ar
N — NO
Ar
OH
OR
Ar
N — NO
Me
11
9 R = H
9c R = SiMe3
9d R = COPh
Ar =
OCH2Ph
OMe

Scheme 2

In order to avoid this 12 was replaced by lithium 2,2,6,6-tetramethylpiperidide 13. Although the use of the latter as a base had not been reported previously, a more recent communication[11] describes its advantages as a non-hydride transferring base. When the two substitutions on 5 were carried out as above but using 13, only a trace of the side



7 12



13

ArCH₂OH

18

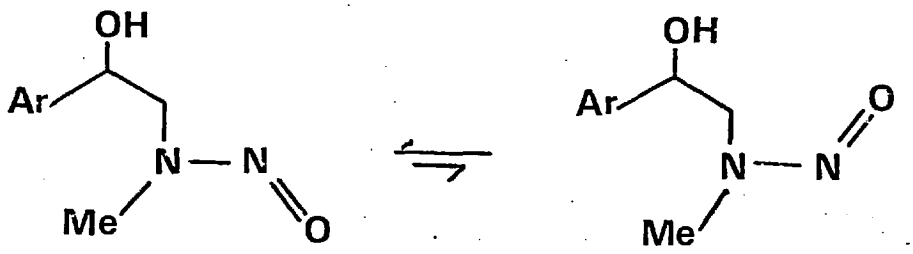
product 18 was observed along with about 15% of the desired nitrosamine 11. Most of the crude reaction mixture constituted the unchanged starting materials. Formation of 18 in this case may be attributed to the base catalysed Cannizaro reaction[12].

Ready monosubstitution and the difficulty encountered during the second substitution on 5 was thought, at this stage

to be due to either the decreased solubility of the dianion 10 in THF and/or the lesser reactivity of the second methyl group of the substituted dimethylnitrosamine. Hexamethylphosphoramide (HMPT) was found to have excellent co-solvent properties in the reactions involving intermediate dianions[13,14]. The reaction was therefore repeated under identical conditions using 13 as the base and with added HMPT during the second substitution. No significant improvement of the yield was observed.

N.m.r. spectra of 5 and related nitrosamines had shown[15] that the protons of the methyl group anti to nitroso oxygen resonate at lower field than those of the syn methyl group. Correlation of the chemical shift with the relative acidity of protons[16] would imply that the protons of the anti methyl group should exhibit a higher acidity than those of the syn methyl group. Although the presence of 72% (by n.m.r.) of the syn conformer 9 a does not support the above argument, it is possible that the product would have undergone an equilibration during the 'work up'. This conformer distribution is in agreement with that observed for related nitrosamines at room temperature[15]. However, the 9 a → 9 b conversion at -80°, the temperature at which the reaction was performed would be expected to be slow or non-existent. Therefore the reaction involving the second substitution was repeated at -20°, 0° and 25°. T.l.c. examination of the reaction mixtures indicated the presence of unidentified polar decomposition product(s), in addition to unreacted benzylisovanillin. This is in accord with the observation of Seebach and Enders, on the short half-life (2 h at -80°), of α-lithiodimethylnitrosamine[9]. Subsequently they isolated and identified the

decomposition products of metalated nitrosamines as tetrahydro-*ν*-tetrazine-*N*-oxides[17].

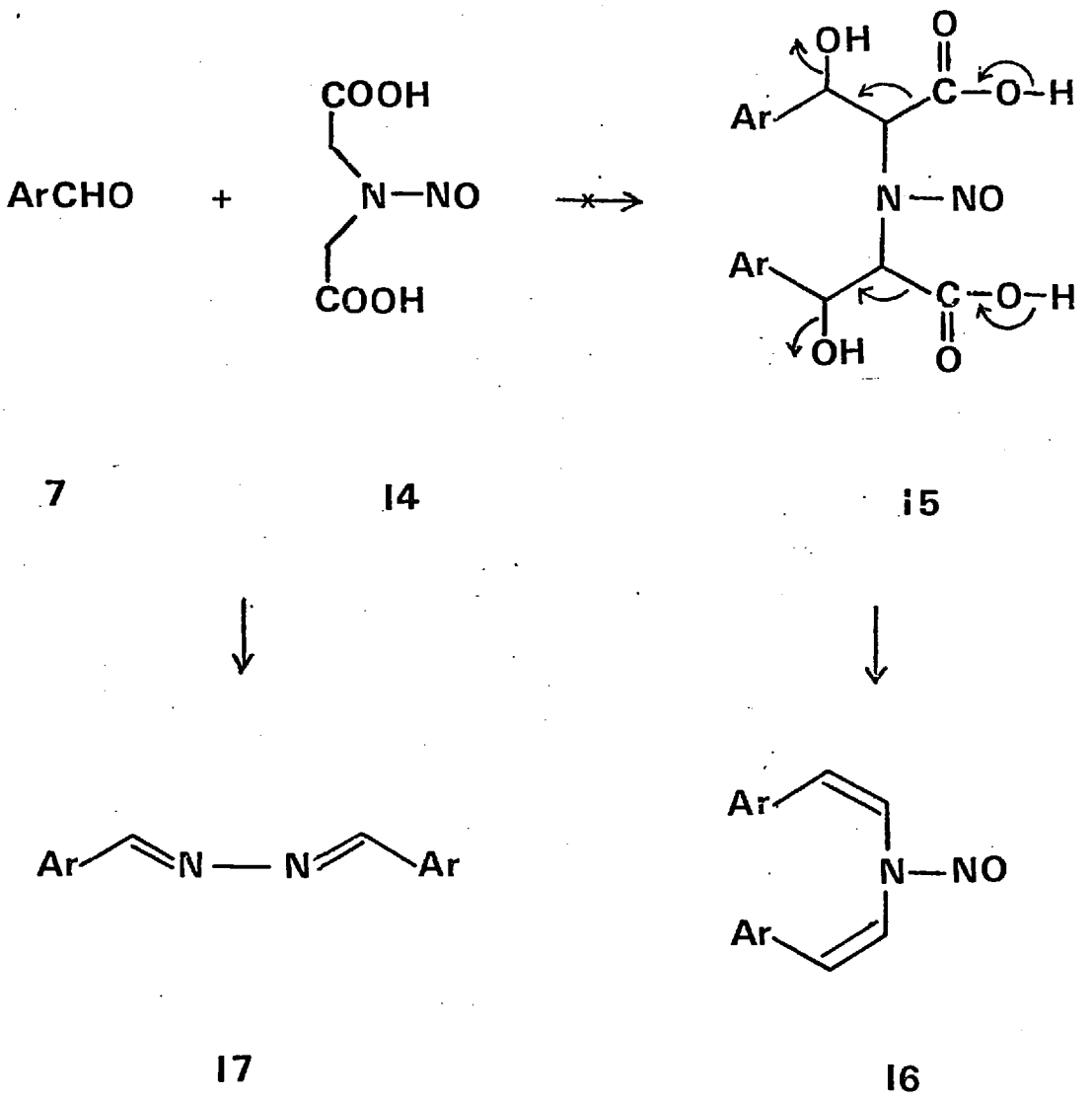


9 a **9 b**

One possibility to circumvent the problem was to enhance the acidity of the protons of the two methyl groups of dimethylnitrosamine by replacing one H from each of these, with an electron attracting, but readily removable group. *N*-Nitrosoiminodiacetic acid 14 was selected to serve this purpose with the expectation that the *N*-nitrosodienamine 16 would result from the decarboxylative dehydration of the intermediate aldol condensation product 15 (Scheme 3).

N-Nitrosoiminodiacetic acid 14 was prepared from the commercially available disodium salt of iminodiacetic acid by a modified (see Experimental) literature procedure[18]. When 14 was mixed with two equimolar proportions of *O*-benzylisovanillin in pyridine solvent which contained piperidine as catalyst[19,20] no change was observed at room temperature. On warming the reaction mixture over a steam bath, the starting

materials slowly changed into a new compound, which was isolated in 25% yield as pale yellow needles, m.p. 210-212°. The i.r. spectrum of this compound showed no characteristic



7 14 15

17 16

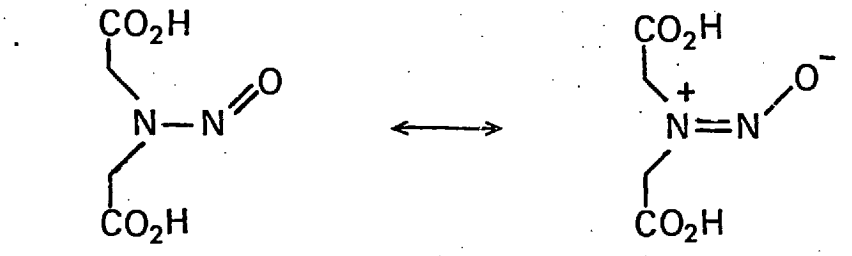
Scheme 3

absorptions due to N-NO function[21], and the n.m.r. spectrum lacked the expected styrene proton signals. Microanalysis and mass spectrum assigned to it the molecular formula

$C_{30}H_{28}N_2O_4$, which indicated that the product was formed from two O-benzylisovanillin units by the substitution of two nitrogen atoms in place of the two oxygens. This suggested that the product was the azine derived from O-benzylisovanillin. I.r.[22], and u.v.[23], spectra also supported the azine structure. Di(3-benzyloxy-4-methoxybenzylidene)azine 17 was prepared as pale yellow needles, m.p. 215-217°, by the condensation of hydrazine with O-benzylisovanillin[24a]. Comparison (t.l.c., mixed m.p., i.r., u.v., m.s., and n.m.r.) of the previous product with the authentic material confirmed the identity.

The origin of the azine 17 in the above reaction (Scheme 3) is obscure. A possible scheme for the formation of 17 is given in Scheme 4. Although the replacement of the nitroso function in 14 by a cyano group could possibly have led to the desired dienamine similar to 16 by a reaction sequence analogous to that depicted in Scheme 3, the preparation of N-cyanoiminodiacetic acid was found to be rather troublesome. Therefore this route was abandoned.

A report appeared at this point which clearly indicated the possibility of preferential substitution at the methyl group of N-alkyl-N-methylnitrosamines[25]. N.m.r. studies have shown[15] that in N-alkyl-N-methylnitrosamines the syn conformer predominates over the anti conformer at room temperature. Therefore, the previous assumption of substitution only at the methyl group anti to nitroso oxygen was untenable. The difficulty encountered during the second substitution of 5 with O-benzylisovanillin 7 above could have been due simply to the solubility problem. The use of the benzylic halide derived from O-benzylisovanillin as the



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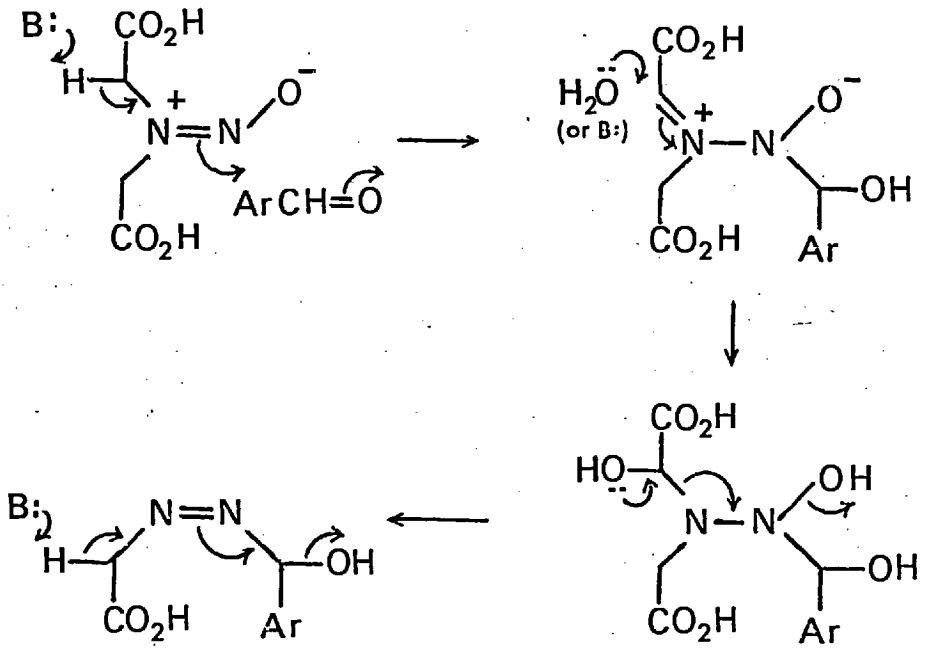
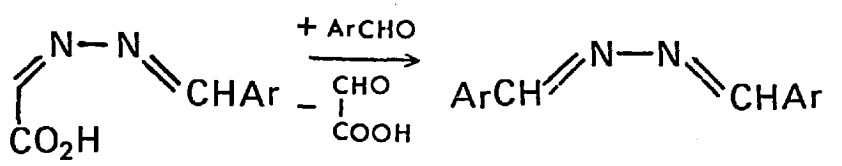




17

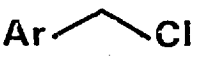
Scheme 4

electrophile would avoid the problem and would also avoid the complication due to α-hydride transfer from the base (see above).

Sodium borohydride reduction of O-benzylisovanillin afforded a quantitative yield of 3-benzyloxy-4-methoxybenzyl alcohol 18.[26] Latter was converted to its chloride 19 with

7

18

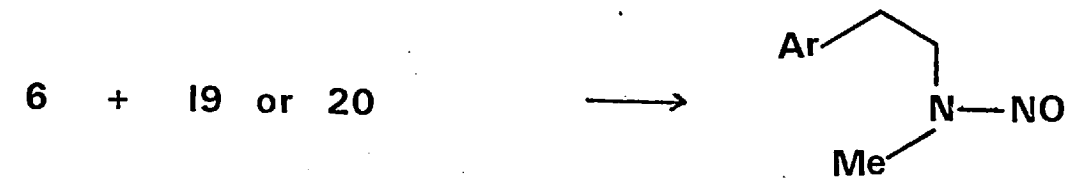


19

20

thionyl chloride by the standard procedure[26] in 96% yield. Alkylation of α-lithiodimethylnitrosamine 6 produced using 12 as the base, with the above chloride 19 was found to be rather sluggish. The overnight reaction yielded only 30-35% of the isolated N-methyl-N-nitroso-2-(3-benzyloxy-4-methoxy phenyl)ethylamine 21. The use of HMPT as a co-solvent, or a

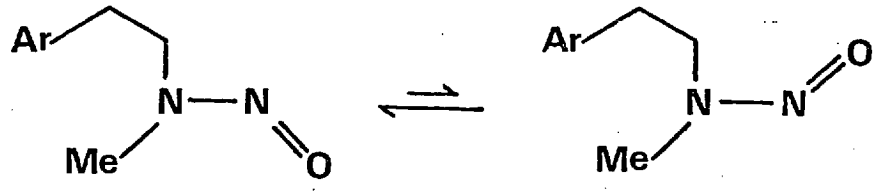
change of solvent (THF) to the more polar diglyme did not cause any significant increase in the yield. Addition of silver tetrafluoroborate to assist ionisation[27], resulted in the formation of an intractable tar.



21

The more reactive halide[28], 3-benzyloxy-4-methoxy benzyl bromide 20 was prepared in 90-93% yield from 18 by the recent method of allylic and benzylic bromination[29]. A facile reaction was observed between this bromide 20 and 6 in THF at -80°. The product was isolated in 84% yield. Microanalysis and spectral data (see Experimental section) were consistent with the N-methyl-N-nitroso-2(3-benzyloxy-4-methoxyphenyl)ethylamine 21 structure. The mass spectrum showed, in addition to the molecular ion peak, a prominent ion at m/e 240, which may be due to a McLafferty rearrangement (Table 1). In other cases (see below) this has been

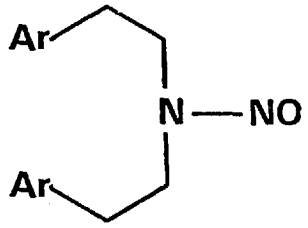
substantiated by accurate mass measurements of the corresponding ions. Although the reported mass spectrometric studies[30] of alkyl nitrosamines do not refer to such a process, McLafferty rearrangements of analogous compounds are well documented[31]. The n.m.r. spectrum of 21 indicated that it is a mixture of syn 21 a and anti 21 b conformers in the ratio 76:24.



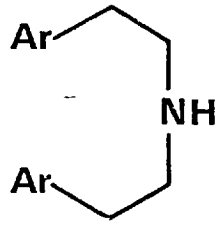
21 a 21 b

Sequential addition to metalated dimethylnitrosoamine of the bromide 20 and, after 1 h at -80°, two molar equivalents of base (to ensure complete metalation) and a second molar equivalent of the bromide, gave a new non-crystalline compound. Accurate mass measurements of the molecular ion gave the molecular formula, $C_{32}H_{34}N_2O_5$. This would arise from the addition of two aralkyl units to dimethylnitrosamine. Surprisingly, it was found to be different from the

anticipated N-nitroso-di [2-(3-benzyloxy-4-methoxyphenyl) ethyl]-amine 22, prepared by the nitrosation[32] of the corresponding amine 23[33]. The mass spectrum of the product had a base peak at m/e, 466 due to the ion formed through a McLafferty rearrangement (Table 1), the constitution of which was confirmed by an accurate mass measurement. Additional evidence came from the metastable peak at m/e, 413 due to the

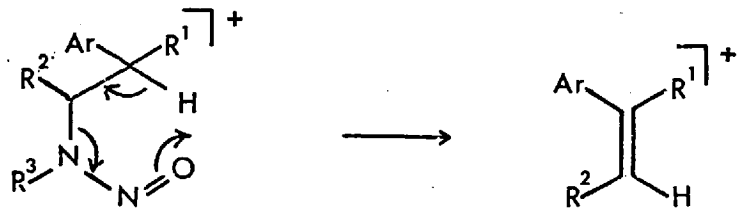


22



23

$M^+ \longrightarrow$ base peak fragmentation, (calc. M* 413). In contrast, the mass spectrum of the symmetrical nitrosamine 22 had the base peak at m/e 240. The n.m.r. spectrum of the product was also found to be different from the desired nitrosamine 22, and indicated the presence of an N-methyl group. These data suggested the product to be the unsymmetrical nitrosamine 24. The proportion of syn 24 a to anti conformer 24 b was in the ratio 86:14 by n.m.r., which is in agreement with the conformer distribution observed[15] for related nitrosamines.



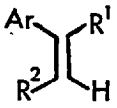
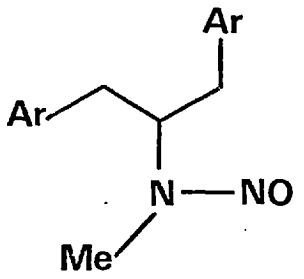
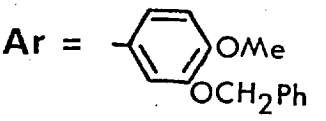
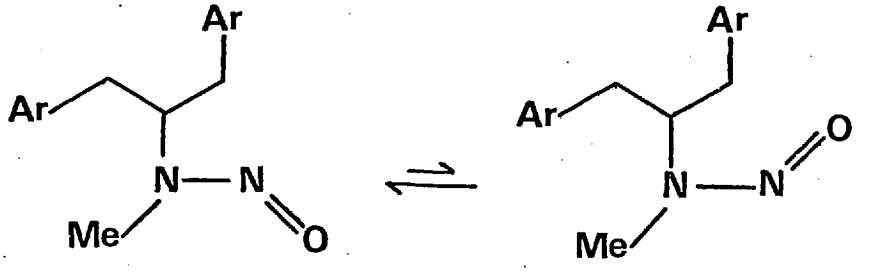
NITROSAMINE	R^1	R^2	R^3	 m/e
9	OH	H	Me	256
9d	OCOPh	H	Me	360
21	H	H	Me	240
22	H	H	$ArCH_2CH_2$	240
24	H	$ArCH_2$	Me	466

Table 1





24



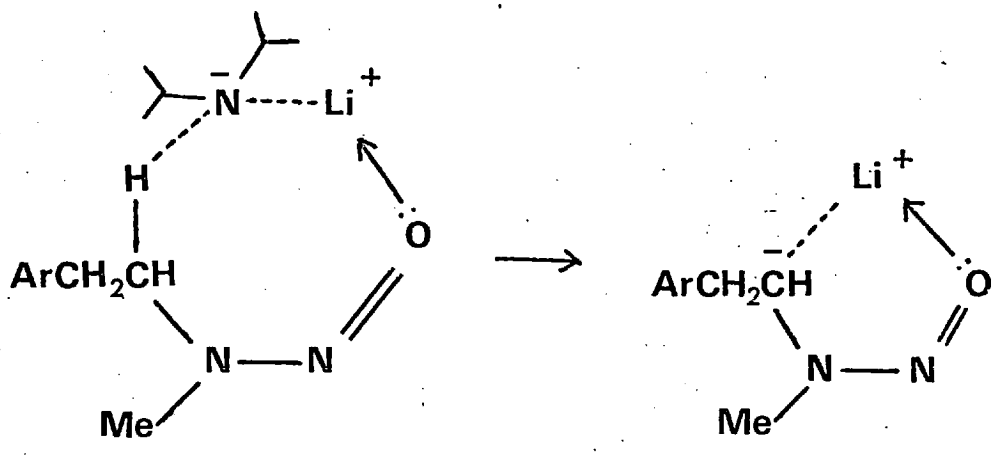
24 a 24 b

At this stage it was felt that the addition of two equivalents of base during the second substitution could have produced the dianion of 21 and the secondary anion been more reactive would have given rise to the above unsymmetrically dialkylated compound 24. In order to check this the sequential dialkylation of 5 was carried out under identical conditions to those above, but using only one equivalent of base during the second step. The product obtained was found

to have an i.r. and mass spectra superimposable with the previously obtained unsymmetrical nitrosamine 24. The n.m.r. spectrum of the compound, obtained with one equivalent of base, indicated that it was predominantly the unstable anti conformer 24 b. Its conversion to the equilibrium mixture containing 84% of the more stable syn conformer 24 a could be followed by n.m.r. spectroscopy at room temperature. This equilibration could also be followed by t.l.c. (SiO_2/ 25% ethyl acetate in benzene) and the two conformers separated accordingly. Separation of nitrosamines containing bulky groups such as benzyl and 2,6-dimethylphenyl attached to the nitrogen atom had only been achieved previously by two dimensional chromatography [34].

The products obtained in the above two reactions were not in agreement with the observations of Seebach and Enders[25]. However, the isolation of the less stable isomer 24 b in one of the above reactions implies a kinetically controlled reaction of the more nucleophilic secondary carbanion. Clearly the base strength is sufficient to generate this species. Steric factors would appear to be of little importance in the displacement process. Deprotonation at the secondary carbon atom may have been facilitated by complexation of the lithium counterion of the base with the oxygen atom of the syn nitroso function (as in 25). A similar phenomenon would stabilise the anion 26 after formation. Addition of N,N,N',N'-tetramethylethylenediamine (TMED) which is an excellent chelating agent[35], to the reaction mixture prior to the introduction of the base did not alter the position of metalation as shown by the isolation of 24 as the only product of alkylation. The chelation

of lithium ion by the nitroso-anion, if real, is clearly very strong. The yields obtained by Seebach and Enders in their alkylation reactions of various alkylmethylnitrosamines[25] are also in accordance with this nitroso directed metalation theory (see Table 2). A similar theory had been proposed to explain the observed faster rate of deuterium exchange[36]



25 26

and the sole methylation[37] at H_4 of the conformationally rigid nitrosamine 27, but had been discounted[38] in the deuterium exchange studies of N-nitrosomethylcyclohexylamine 28.

If above theory is correct, in dimethylnitrosamine the syn methyl group should be metalated preferentially

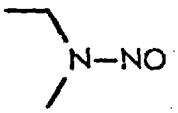
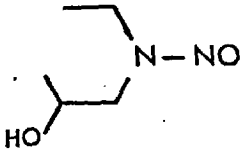
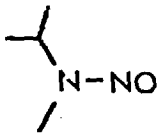
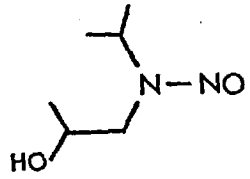
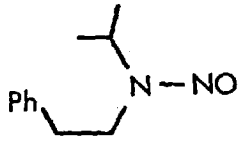
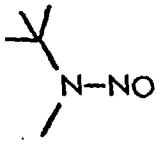
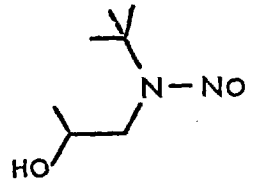
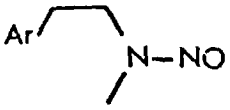
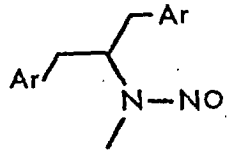
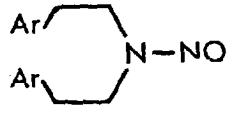
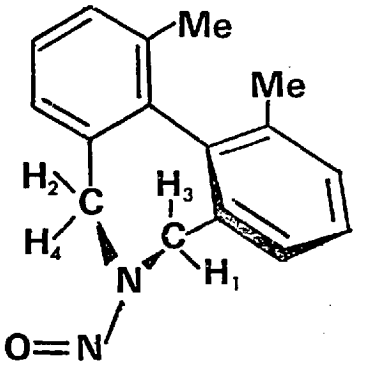
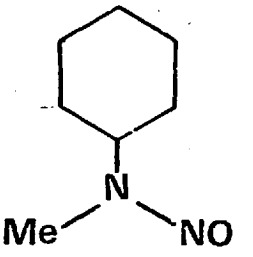
NITROSAMINE	ELECTROPHILE	PRODUCT	YIELD (%)[25]	Syn-ISOMER BY NMR (%)[15]
	CH_3CHO		75	73 - 78
	CH_3CHO		85	84 - 88
	$PhCH_2Br$		90	
	CH_3CHO		95	100
	$ArCH_2Br$		93	00
			75	76
			94	100

Table 2

giving an intermediate similar to 26, and therefore causing alkylation to occur at this position in preference to the anti oriented methyl group. This was tested by carrying out the metalation and subsequent alkylation of 5 at -80° for one hour. The product ratios were checked by low temperature n.m.r. spectroscopy before thermal equilibration was established. Using both 3-benzyloxy-4-methoxybenzyl



27

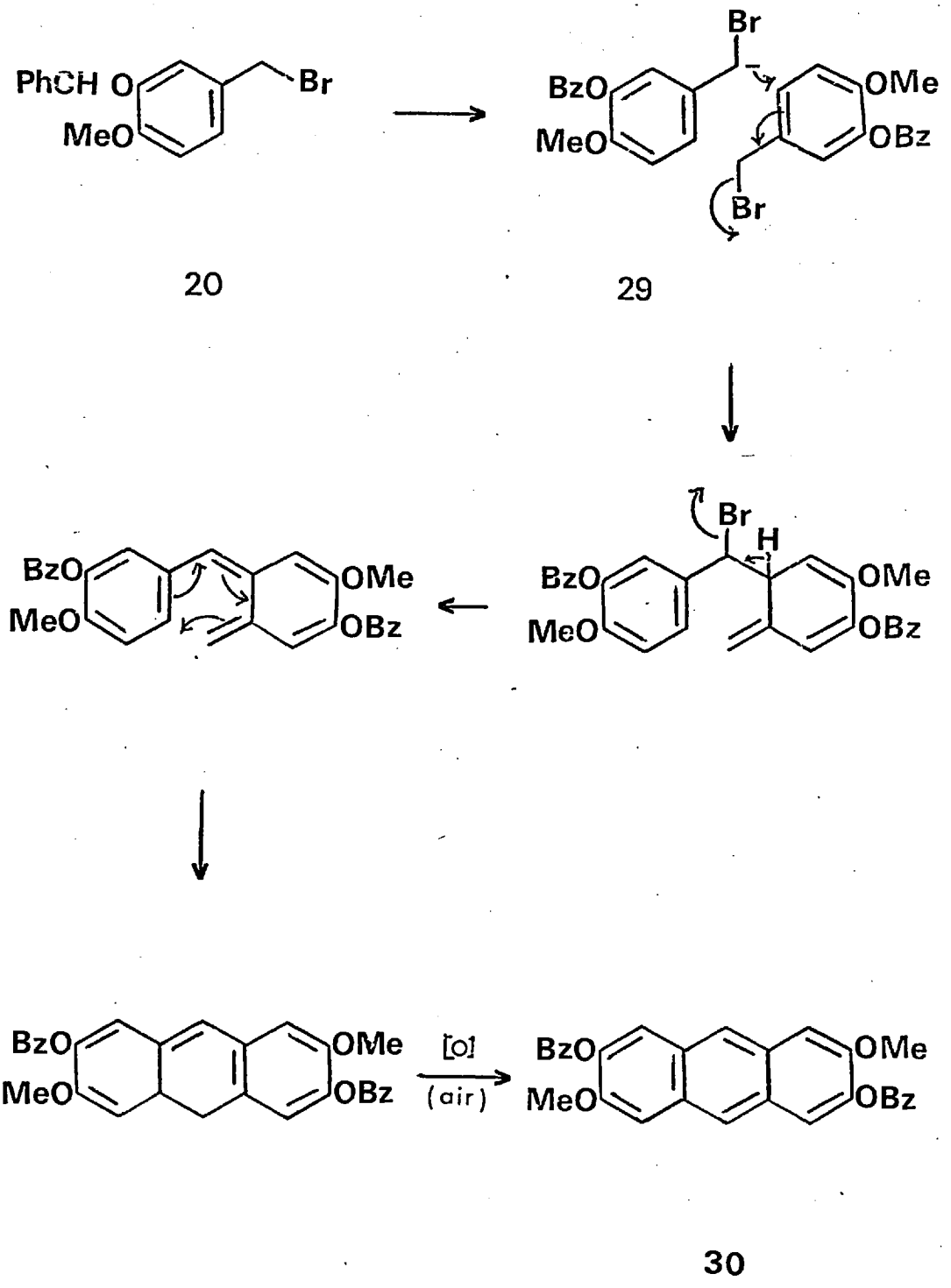


28

bromide 20 and O-benzylisovanillin 7 as the alkylating agents, it was demonstrated accordingly that the products formed were the anti conformers 21 b and 9 b respectively. Equilibration of these less stable conformers to produce equilibrium mixtures of syn and anti conformers could also be followed by n.m.r. spectroscopy at room temperature. If the second alkylation is carried out after equilibration of the monoalkylated product 21, it should result in alkylation of the methyl group to yield the desired nitrosamine 22. An especially gratifying result was achieved this way.

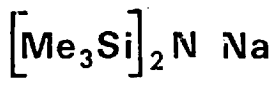
When the nitrosamine 21 (containing 76% of the syn conformer 21 a by n.m.r.) was metalated with one molar equivalent of lithium diisopropylamide, and then reacted with the bromide 20 at -80° the desired nitrosamine 22 was obtained as a yellow gum in about 60% yield. The rest of the product mixture contained unreacted starting materials. With 1.5 equivalents of the base, in addition to about 75% of the desired nitrosamine, a non-nitrogen compound was isolated in about 10% yield. The latter compound obtained as colourless needles, m.p. 183-184° (from ethyl acetate), had a featureless mass spectrum with M^+, at m/e 450 and a base peak at m/e 91 (benzyl or tropilium cation). Microanalysis, combined with above M^+ suggested a molecular formula $C_{30}H_{26}O_4$. The n.m.r. spectrum showed aromatic protons and the aliphatic protons of the OMe and the OCH_2 of benzyl substituents as the only assignable resonances. The u.v. spectrum[39] was characteristic of a 2,3,6,7-tetraoxygenated anthracene. A base mediated reaction of two molecules of the bromide 20 explained the product, assigned the structure 30. Although the reaction of benzyl halides with proton-specific bases were found to produce carbanions of the type 29[40], reaction of the latter with another molecule of halide to give an anthracene constitutes a novel type of reaction. A reasonable mechanism for the formation of 2,6-dibenzyloxy-3,7-dimethoxyanthracene 30 from 20 is depicted in Scheme 5.

With a reasonable route to the nitrosamine 22 and hence diphenethylamine 23 now defined, optimisation of the steps was attempted to enable a large scale process to be developed. Because of the hazardous nature of using large quantities of methyl lithium a search for an alternative base was made.

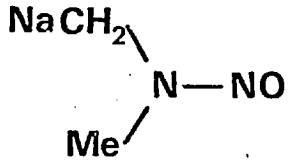

PhCH O
MeO
Br
20
Br
BzO
MeO
OMe
OBz
Br
29
Br
H
BzO
MeO
OMe
OBz
BzO
MeO
OMe
OBz
BzO
MeO
OMe
OBz
[o]
(air)
BzO
MeO
OMe
OBz
30

Scheme 5

Bases which selectively abstract protons from substrates containing intrinsically more reactive sites toward nucleophilic attack (i.e. strong base, weak nucleophile) are few in number. Most of the bases belonging to this category are metal alkyls or sterically hindered alkoxides. Although the use of sodium hydride as a base in the α-alkylation of nitrosamines had been recognised earlier, the reported low yields[38] were discouraging. Sodium di-trimethyl silylamide 31[41] is known to have very strong basic properties[42-44]. It shows nucleophilic reactivity only in the absence of acidic protons[45]. Thus, it was decided to investigate its use in metalating dimethylnitrosamine 5. It offers following advantages: a) large quantities of it could be prepared[41] without having to handle hazardous alkyl lithium reagents; b) its solid nature presents no difficulty in transferring large amounts into reaction vessels; c) there is no need to store the reagent under an inert gas atmosphere, the base may be kept for an extended period prior to its use without decomposition or deterioration[46] and d) its solubility in THF[41] would be advantageous.



31



32

Sodium di-trimethylsilylamide 31 was prepared by the method of Wannagat and Niederprum[41]. Metalation of dimethylnitrosamine with this at -80°, in THF and alkylation of the resulting α-sodio derivative 32 with the bromide 20 produced the desired N-methyl-N-nitroso-2-(3 benzyloxy-4-methoxyphenyl)ethyl amine 21 in 97% yield. The crude crystalline product obtained this way proved to be pure enough to carry on to the second alkylation. Using 1.5 molar equivalents of the same base 31 for the second step two rather gratifying results were achieved. Firstly, the desired nitrosamine 22 was obtained in 75% yield, after recrystallisation of the crude crystalline product. This is in contrast to the yellow gum produced using lithium diisopropylamide. Secondly, the product was found to be devoid of any of the anthracene 30 obtained as a byproduct using excess lithium diisopropylamide for the second metalation (see above). According to the previously observed nitroso directed metalation, the maximum yield expected in the second alkylation step using 21 would not exceed 76%, unless the pure conformer 21 a was used in the reaction.

A considerable enrichment of the conformers of benzylisopropylnitrosamine had been achieved by Mannschreck by a crystallisation technique[47]. It was thought that if 21 was recrystallised from a dilute solution in a suitable solvent at low temperature over a long period of time the enrichment of the more stable conformer 21 a would ensue. When 21 dissolved in the minimum volume of light petroleum was allowed to stand at 0°, 21 a was precipitated as a colourless amorphous solid. Standing for three weeks at this temperature led to the almost total recovery of 21 as 21 a. The n.m.r.

spectrum of this solid at -50° confirmed it to be purely the syn conformer 21 a . After allowing the solution to equilibrate at room temperature for 24 h the n.m.r. spectrum indicated the usual conformer mixture. Not surprisingly, when 21 a was used for the second alkylation step, 22 was obtained in 94% yield.

The final step of the projected synthesis required an efficient removal of the nitroso function from the nitrosoamine 22. Numerous methods[25,37,48-51] for the cleavage of the nitroso group of nitrosoamines have been described in literature. All methods but one[51] required the participation of strong acids. Because of the complication of concommitant debenzylation by such reagents, a non-acidic denitrosation was sought.

Diphenylnitrosoamine was known to react with phenylhydrazine, but the conditions for this reaction were not reported[51]. When the model compound, N-nitrosomorpholine was subjected to the reaction with phenylhydrazine under variety of conditions only the starting nitrosoamine was recovered. Reaction of this model nitrosoamine with hydroxylamine under both mild and vigorous conditions gave the same result. When the nitrosoamine 22 was refluxed with ammonium chloride in dimethylformamide (DMF) no reaction was observed even after three days.

A number of reactions were attempted in acidic media using glacial acetic acid as the solvent. Sodium azide (effectively hydrazoic acid) or ammonium chloride did not cause any denitrosation even under vigorous conditions (80°, 3 days). Aliphatic nitrosoamines were known to undergo transnitrosation reactions with active methylene compounds, such as 1,2,3,4-

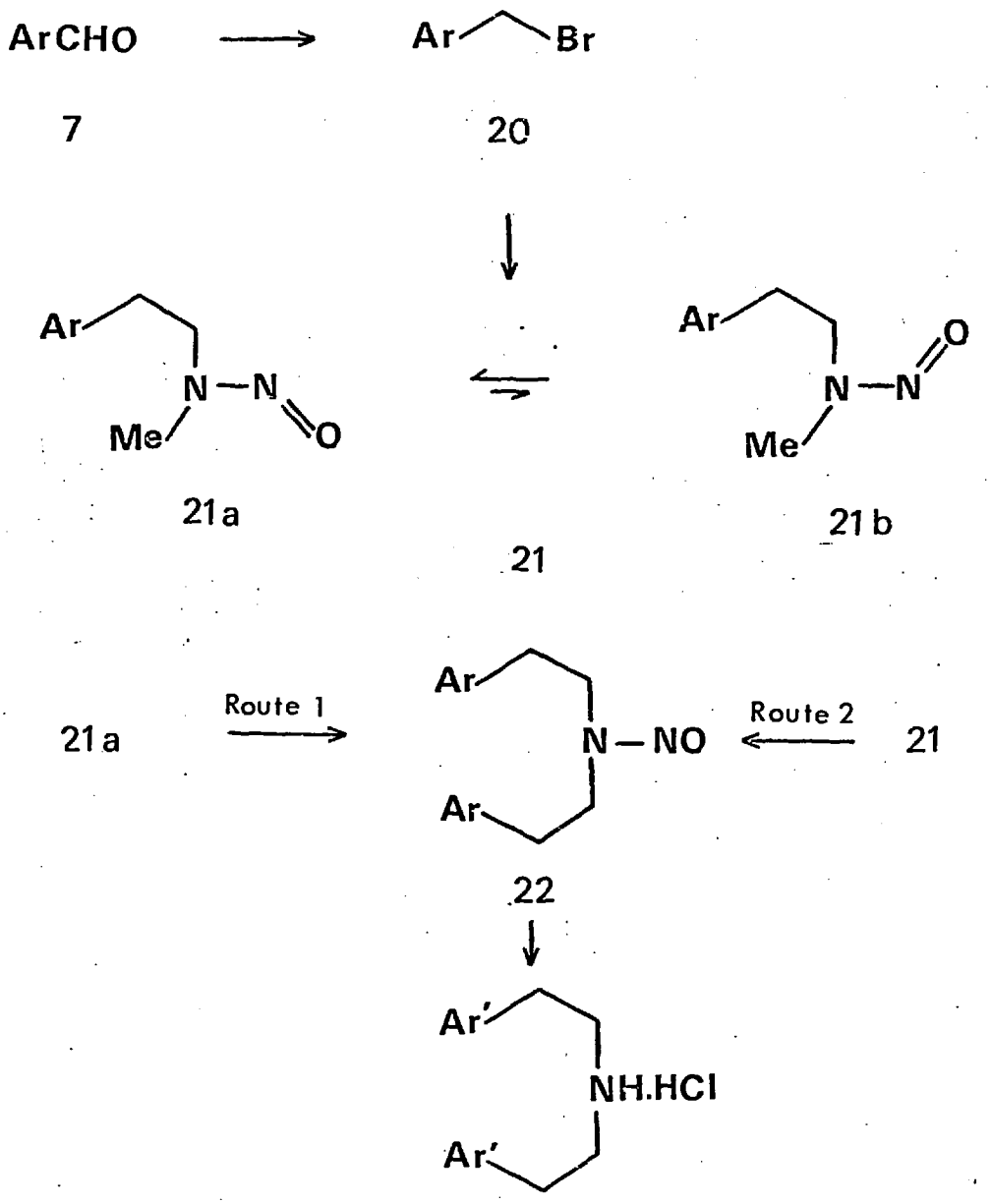
tetrachlorocyclopentadiene or malononitrile, when heated in acetic acid solvent with mineral acid catalysis[50]. However, when 22 was mixed with diethylmalonate in glacial acetic acid containing a drop of conc. HCl at 100° no product corresponding to the desired amine 23 was detected (t.l.c.), although the starting material 22 was found to disappear slowly. Examination of the product mixture by t.l.c. indicated it to be a complex mixture and, therefore, it was not further investigated.

All the successful denitrosations accomplished involved the use of strong mineral acids. The reaction of nitrosoamine 22 with a 7% solution of HBr in glacial acetic acid[25] saturated with cuprous chloride[48] gave highly coloured product mixtures containing the desired amine 23 hydrobromide. But the attempted crystallisation of this hydrobromide salt from the product mixture was unsuccessful. When denitrosation was carried out with gaseous HCl in dry benzene by the method of Stewart[37,49] but using urea to capture the nitrosyl chloride formed, the amine 23 hydrochloride was isolated as a colourless crystalline solid in 51% yield. This was hydrogenolysed[3] to give 95% yield of the bisdiphenolic amine 4 hydrochloride. Use of acetylacetone to capture nitrosylchloride under similar conditions afforded only 42% of the amine 23 hydrochloride. In ethanolic medium more vigorous conditions were needed for denitrosation, and urea was found to be unstable in this medium. Simultaneous debenzylation was found to occur under these conditions and as a result the bisdiphenolic amine 4 hydrochloride was obtained in 45% yield directly. However, replacement of urea with resorcinol gave no improved yields. Use of hydrogen iodide under

variety of conditions gave rather complex product mixtures.

The low yields and the coloured products observed in above reactions may have been due to the participation of nitrosyl halide (or nitrous acid) in side reactions. One such possibility is the Fischer-Hepp rearrangement [52,53]. The starting nitrosamine 22 as well as the products 22 and 4 in these reactions contain two dioxygenated aromatic rings activated towards electrophilic attack. Although the nitrosation of phenolic ethers under these conditions is virtually unknown [54], N,N-dimethylaniline is known to undergo nitrosation with nitrous acid under very mild conditions [55]. Complete intervention of urea to destroy nitrosyl chloride in benzene is unlikely [56] because of its insolubility. Unfortunately, the use of resorcinol did not lead to any improved yields, but its participation in a reaction with nitrosyl chloride was indicated by the resulting green solution.

Scheme 6 summarises the successful synthetic routes that have been pursued to obtain the di-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-amine 4 with their respective yields. Although the method suffers from the disadvantage of the low yield obtained in the denitrosation step, it provides facile and convenient routes to the precursor 4 of erysodienone 1, which has been established as the key intermediate, both in synthesis and biosynthesis of Erythrina alkaloids.



Route 1

overall yield

43 %

Route 2

overall yield

34 %

Scheme 6

EXPERIMENTAL

General directions are as for Part I. Solvents were purified by the standard procedures[57], THF was distilled from LAH prior to use.

Dimethylnitrosamine (DMNA).- Nitrosation of dimethylamine hydrochloride by the method of Vogel[24b], drying the product (benzene solution, CaH_2 soxhlet) and distillation from anhydrous K_2CO_3 afforded 5 as a yellow oil, b.p. 150° at 760 mm Hg (lit.[24b], b.p. 150-151° at 760 mm Hg).

O-Benzyl Isovanillin (7).— This was prepared from isovanillin according to the procedure of Robinson and Sugasawa[58].

α- Lithio- Derivatives of Nitrosamines. General Method of Preparation and Reaction with Electrophiles.— A serum stoppered 3-necked flask containing a magnetic stirrer bar was fitted with a 3 way tap for making connections either to a dry N_2 source or to a vacuum pump. The system was thereby repeatedly flushed with nitrogen, after which the tube leading to the pump was disconnected and attached to a mercury bubbler. Nitrogen was passed through the system at a rate sufficient to maintain a positive pressure. All reagents were introduced by use of syringe techniques. First, diisopropylamine in THF was added. The flask was surrounded by a cardice-ether bath (at -80°) and standardised[59] methyl lithium in ether was introduced into the stirred solution. Approximately 30 min later the nitrosamine in THF was added to the lithium diisopropylamide thus prepared. After being stirred for 10-15 min the electrophile (7, 19 or 20) dissolved in THF was added, and the mixture stirred at -80° for the required length of time (t.l.c. control). The reaction mixture

was either worked up (see below for the general work up procedure) or transferred to another flask containing lithium diisopropylamide prepared *in situ* as above, followed after 10-15 min by a second batch of the electrophile in THF. After stirring for a while (t.l.c. control), the reaction mixture was worked up by the general procedure described below.

The reaction mixture was poured into a separatory funnel containing ether and a saturated brine solution. The aqueous layer was washed several times with ether and chloroform. The combined organic phase was dried (K_2CO_3) and evaporated under reduced pressure to give the crude product.

Reaction of α-Lithiodimethylnitrosamine (6) with O-Benzyl Isovanillin (7). — To a solution of 6 [2 mmoles, prepared from diisopropylamine (0.3 ml), methyl lithium (1.4 ml of 1.42 M solution) and DMNA (0.15 g) in THF, total volume 4 ml] was added a solution of O-benzyl isovanillin 7 (0.48 g, 2 mmole) in THF (2 ml) according to the general method. After 2.5 h at -80° it was quenched either with i) water, ii) trimethyl silyl chloride or iii) benzoic anhydride and worked up as above.

i) Quenching with water afforded the isomeric mixture of *syn* and *anti* N-methyl-N-nitroso-2-hydroxy-2-(3-benzyloxy-4-methoxyphenyl) ethylamine 9 as a pale yellow non distillable oil (0.58 g, 94%), ν_{max} (neat) 3405 (OH), 3025,2965 and 2865 (C-H), 1607, and 1590 (Ar), 1467, 1463, 1450, and 1430 (N-NO)[59] cm^{-1}, τ ($CDCl_3$) 2.40-2.90 (5H, m, ArH), 2.90 - 3.30 (3H, m, ArH), 4.90 (2H, s, O-CH_2-), 5.13 (1H, t J 6 Hz, ArCH(O)-C), 5.80 (72% of 2H, d J 6Hz, CH_2-N), 6.17 (3H, S, OMe), 6.47 (28% of 3H, s, NMe), 5.00-6.50 (1H + 28% of 2H, m, 1H exchangeable with D_2O, OH and CH_2-N), and 7.03 (72%

of 3H, s, NMe), m/e 316 [M^+ (Found: 316.1418 $C_{17}H_{20}N_2O_4$ requires 316.1423)], 256 [cf. Table 1 (Found: 256.1096 $C_{16}H_{16}O_3$ requires 256.1099)], 243, and 91(100%).

ii) When quenched with trimethyl silyl chloride, N-methyl-N-nitroso-2-trimethyl silyloxy-2-(3-benzyloxy-4-methoxy phenyl)ethylamine 9c was obtained as a yellow gum, ν_{max} ($CHCl_3$) 1600 (Ar), and 1450 br. (N-NO) cm^{-1}, m/e 388 (M^+), 373, 343, 328, 315 (100%), 299, 243, 224 and 91.

iii) Quenching the reaction mixture with benzoic anhydride afforded after the usual work up, the isomeric mixture of syn- and anti- N-methyl-N-nitroso-2-benzoyloxy-2-(3-benzyloxy-4-methoxy phenyl) ethylamine 9d as a thick yellow oil, ν_{max} (neat) 1720 (ester CO), 1600 (Ar), and 1460 br (N-NO) cm^{-1}, τ ($CDCl_3$) 1.80-2.20 (2H, m, ArH), 2.40-2.80 (8H, m, ArH), 2.90-3.20 (3H, m, ArH), 3.73 (1H, q J 4 Hz, ArCH(O)C), 4.83 (2H, s, OCH_2), 5.50 (75% of 2H, t J 4 Hz, NCH_2), 5.83 (25% of 2H, t J 4 Hz, NCH_2), 6.17 (3H, s, OMe), 6.40 (25% of 3H, s, NMe), and 7.03 (75% of 3H, s, NMe), m/e 420 [M^+ (Found: 420.1678 $C_{24}H_{24}N_2O_5$ requires 420.1685)], 360 [cf. Table 1 (Found: 360.1373, $C_{23}H_{20}O_4$ requires 360.1362)], 348, 326, and 91 (100%).

Sequential Reaction of Dimethylnitrosamine with O-Benzyl Isovanillin. — i) The monosubstitution product 8 (10 mmole, in 30 ml) after being prepared and stirred at -80° for 2.5 h was transferred to a freshly prepared solution of lithium diisopropylamide (11 mmole, 15 ml). After ca. 15 min the solution was treated with O-benzyl isovanillin (2.40 g, 10 mmole) in THF (5 ml). Stirring was continued at -80° for 5 h and overnight at room temperature. Work up by the general method afforded a brown gum (5.37 g) the t.l.c. of which

showed the presence of 3 compounds. These were separated by p.l.c. (SiO_2 - 5% methanol in chloroform) to give a) 3-benzyloxy-4-methoxy benzyl alcohol 18 (1.4 g, 35%) as colourless needles, m.p. and mixed m.p. 70-71° (from ether-light petroleum) (lit.[26], m.p. 72°), m/e 244 (M^+), 227, 214, 153, 136, and 91 (100%), b) unreacted 9 (2.1 g, 53%) obtained as a yellow oil the identity of which was confirmed by direct comparison (i.r., n.m.r., and m.s.) with an authentic sample, and c) the desired N-nitroso di-[2-hydroxy-2-(3-benzyloxy-4-methoxy phenyl)ethyl]amine 11 (0.5 g, 12%) as a yellow gum, ν_{max} (neat) 3400 (OH), 3020, 2965 and 2860 (CH), 1605, and 1590 (Ar), 1450 br (N-NO) cm^{-1}, τ ($CDCl_3$) 2.40-2.90 (10H, m, ArH), 2.90-3.30 (6H, m, ArH), 4.93 (4H, s, OCH_2), 6.20 (6H, s, OMe), and 4.80-7.00 (8H, complex m, 2H exchangeable with D_2O, aliphatic + OH), m/e 558(M^+), 540, 528, 492, 480, 333, 286, 268, 257, 243, 227, and 91 (100%).

ii) This reaction was conducted using 2,2,6,6-tetramethyl piperidine in place of diisopropylamine, otherwise following a procedure identical to that above. The n.m.r. spectrum of the product mixture indicated the presence of ca.15% of the desired nitrosamine 11, unreacted O-benzyl isovanillin and the nitrosamine 9. T.l.c. examination revealed the presence of the benzyl alcohol 18 (a trace) in addition to the above 3 compounds.

When hexamethyl phosphoramide (2 ml) was introduced prior to the second lithiation (see Discussion) no marked improvement in the yield of the nitrosamine 11 was observed as indicated by the n.m.r. spectrum of the crude product.

N-Nitrosoiminodiacetic Acid (14).— Iminodiacetic acid di-sodium salt monohydrate (10.0 g) was nitrosated with excess

nitrous acid[24b] at 0°. After overnight reaction, water was removed *in vacuo* and the resulting solid was exhaustively extracted with hot chloroform. This was dried ($MgSO_4$) and evaporated to yield N-nitrosoiminodiacetic acid 14 (4.0 g, 40%) as a pale yellow powder, m.p. 149-150° (from ether) (lit.[18], m.p. 146-148°), ν_{max} (nujol) 3500-2500 (COOH), 1720 and 1700 (CO) cm^{-1}, τ (D_2O) 4.67 (2H, s, CH_2) and 5.43 (2H, s, CH_2), m/e 162 (M^+), 132, 117, and 88 (100%).

Reaction of N-Nitroso Iminodiacetic acid with O-Benzyl Isovanillin.— i) N-Nitrosoiminodiacetic acid (0.40 g, 2.0 mmoles) was dissolved in dry pyridine (5 ml) and to this was added O-benzyl isovanillin (1.30 g, 4.1 mmole) followed by 2 drops of dry piperidine. The mixture was stirred at room temperature for 24 h but no reaction was observable (t.l.c.). Therefore, the reaction was heated to 100° for 12 h (t.l.c. control), cooled, poured into water and extracted with chloroform. The organic layer was washed with 2% HCl and water, dried ($MgSO_4$) and solvent evaporated under reduced pressure to give di-(3-benzyloxy-4-methoxy benzylidene) hydrazine 17 (0.65 g, 25%) as pale yellow needles, m.p. 215-217° (from benzene- light petroleum), ν_{max} (nujol) 1624 (C=N) cm^{-1}, λ_{max} (EtOH) 213 (ϵ 36,960), 238 (16,320), and 346 nm (35,050), τ ($CDCl_3$) 1.50 (2H, s, CH=N), 2.40-3.20 (16H, m, ArH), 4.80 (4H, s, OCH_2), and 6.07 (6H, s, OMe), m/e 480 (M^+), 389, and 91 (100%) [Found: C, 74.75; H, 5.89; N, 5.39 . $C_{30}H_{28}N_2O_4$ requires C, 75.00; H, 5.82; N, 5.82%]. This was shown to be identical (m.p., m.m.p., i.r., n.m.r., u.v. and t.l.c.) with the authentic azine prepared from hydrazine hydrate and O-benzyl isovanillin by the conventional procedure[24a].

ii) When the reaction was carried out as above but with the use of 2 drops of pyrrolidine instead of piperidine, no

reaction was observed at room temperature (t.l.c.), but at 100°, the azine 17 was formed in 2 h as before.

3-Benzyloxy-4-methoxybenzyl Alcohol (18). — Sodium borohydride reduction of O-benzylisovanillin by the conventional method[26] afforded 3-benzyloxy-4-methoxybenzyl alcohol 18 in quantitative yield, m.p. 71-72° (from ether-light petroleum) (lit.[26], m.p. 72°), ν_{max} (nujol) 3245 (OH) cm^{-1}, τ ($CDCl_3$) 2.40-2.70 (5H, m, ArH), 2.93-3.13 (3H, m, ArH), 4.83 (2H, s, OCH_2Ph), 5.43 (2H, s, OCH_2Ar), 6.13 (3H, s, OMe), and 8.30 (1H, s, exchangeable with D_2O, OH), m/e 244 (M^+), 227, 153, 136, and 91 (100%).

3-Benzyloxy-4-methoxybenzyl Chloride (19). — The foregoing alcohol 18 (8.0 g) in benzene (80 ml) was added slowly to a solution of thionyl chloride (40 ml) in boiling benzene (80 ml) containing pyridine (0.8 ml). The solution was refluxed for 2 h, cooled and treated with cold water. The benzene layer was washed successively with $NaHCO_3$ (1N, 1.2 l) and water, dried ($MgSO_4$) and evaporated under reduced pressure to yield 3-benzyloxy-4-methoxybenzyl chloride 19 (8.6 g, 96%) as colourless needles, m.p. 78-79° (from ether-light petroleum) (lit.[26], m.p. 77°), $\nu_{max.}$ (nujol) 1611 and 1595 (Ar) cm^{-1}, m/e 264, 262 (M^+) 227, and 91 (100%).

Monoalkylation of α-Lithiodimethylnitrosamine (6) with 3-Benzyloxy-4-methoxybenzyl Chloride. — To a solution of 6 (0.01 moles, prepared by the general method) was added after 10 min the above chloride 19 (2.6 g, 0.01 mole) in THF (2.5 ml). After being stirred at -80° for 5 h and overnight at room temperature it was worked up by the usual procedure to yield a yellow oil, the n.m.r. spectrum of which indicated

ca. 35% of the anticipated nitrosamine 21, together with ca. 65% of the unreacted chloride. Purification by p.l.c. (SiO_2 - chloroform) gave N-methyl-N-nitroso-2-(3-benzyloxy-4-methoxyphenyl)ethyl amine 21 (0.9 g, 30%) as a pale yellow gum, $\nu_{max.}$ (neat) 3025, 2965 and 2880 (C-H), 1605 and 1592 (Ar), 1464, 1458, 1448, and 1436 (N-NO),[59] τ ($CDCl_3$) 2.73 (5H, m, ArH), 3.13 3.37 (3H, m, ArH), 5.00 (2H, s, OCH_2), 5.87 (2H, t J 8Hz, $ArCH_2$), 6.27 (3H, s, OMe), 6.70 (24% of 3H, s, NMe), 6.00-7.00 (2H, m, CH_2N), and 7.23 (76% of 3H, s, NMe), m/e 300 (M^+), 240 (cf. Table I), 91 (100%).

3-Benzyloxy-4-methoxybenzyl Bromide (20). — N-Bromosuccinimide (32.4 g, 0.18 mole, recrystallised and dried) in dry dichloromethane (600 ml) was cooled to 0° and dimethyl sulphide (15.75 ml, 0.22 mole) in dichloromethane (30 ml) was added dropwise (this addition was controlled in order to avoid coagulation). The reaction mixture was cooled to -20°, stirred for ca. 30 min and the benzyl alcohol 18 (29.28 g, 0.12 mole) in dichloromethane (60 ml) was added dropwise over a period of 1 h, after which it was allowed to warm to room temperature and the stirring continued until a clear solution was obtained. This was poured into a separatory funnel containing saturated brine and light petroleum. The organic layer was washed 3 times with brine, dried ($MgSO_4$) and evaporated to yield 3-benzyloxy-4-methoxy benzyl bromide 20 (34.5 g, 93%) as colourless needles, m.p. 94-95° (from chloroform-light petroleum), $\nu_{max.}$ (nujol) 1607 and 1595 (Ar) cm^{-1}, τ ($CDCl_3$) 2.60-2.80 (5H, m, ArH), 3.00-3.33 (3H, m, ArH), 4.90 (2H, s, OCH_2), 5.60 (2H, s, CH_2Br), and 6.17 (3H, s, OMe), m/e 308, 306 (M^+), 227, and 91 (100%) [Found: C, 59.01 ; H, 5.12; Br, 25.92 $C_{15}H_{15}BrO_2$ requires C, 58.65; H, 4.92; Br, 26.02%].

Monoalkylation of (6) with 3-Benzyloxy-4-methoxybenzyl Bromide.— α-Lithiodimethylnitrosamine 6 (0.012 mole) prepared by the general method was treated with the above benzyl bromide 20 (2.25 g, 0.0075 mole) in THF (10 ml). After stirring for 2 h at -80° (t.l.c. control) the reaction mixture was worked by the usual procedure to afford N-methyl-N-nitroso-2-(3-benzyloxy-4-methoxyphenyl)ethyl amine 21 (1.88 g, 84%) as pale yellow needles, m.p. 87-90° (from methanol-light petroleum). This had spectral characteristics (i.r., n.m.r. and m.s.) identical to those of the product obtained from 6 and the benzyl chloride 19 (see above) [Found: C, 68.04, H, 6.68, N, 9.10, $C_{17}H_{20}N_2O_3$ requires C, 67.98; H, 6.71; N, 9.33%].

Sequential Dialkylation of Dimethylnitrosamine with the Benzyl Bromide (20).— i) α-Lithiodimethylnitrosamine (0.01 mole, total volume 15 ml) obtained from lithium diisopropylamide 12 (0.01 mole) and dimethylnitrosamine (0.75 g, 0.01 mole) was treated with the benzyl bromide 20 (1.50 g, 0.005 mole) in THF (5 ml) in the usual manner. The reaction mixture was stirred at -80° for 3 h after which it was transferred to a freshly prepared solution of 12 (0.01 mole, 10ml), stirred for ca. 15 min at -80° and treated with the bromide 20 (1.40 g, 0.004 mole) in THF (5 ml). The reaction was worked up after 30 min (t.l.c. control) to obtain the isomeric mixture of N-methyl-N-nitroso-1-(3-benzyloxy-4-methoxybenzyl)-2-(3-benzyloxy-4-methoxyphenyl)ethylamine 24 (2.45 g, ca 93%) as a yellow gum, $\nu_{max.}$ (neat) 3025, 2965, and 2880 (C-H), 1608, and 1592 (Ar), and 1460-1430 br (N-NO)[39] cm^{-1}, τ ($CDCl_3$) 2.50-2.90 (10H, m, ArH), 3.12-3.50 (6H, m, ArH), 4.98 (4H, s, OCH_2), 6.24 (6H, s, OMe), 6.82 (14% of 3H, s, NMe), 7.12 (ca. 86% of 4H, d J 8Hz, CH_2Ar) 7.36 (ca. 14% of 4H, d J

8 Hz, CH_2Ar), and 7.48 (86% of 3H, s, NMe), m/e 526 [M^+ (Found: 526.2449, $C_{32}H_{34}N_2O_5$ requires 526.2449)], 496, 470, 466 [100%, cf. Table 1 (Found: 466.2135 $C_{31}H_{30}O_4$ requires 466.2144)], 452, 413 (m*, 526 → 466), 270, 240, 227, and 91.

ii) The reaction was repeated under conditions identical to above reaction and using the same amounts of reagents except for the amount of 12 (0.005 moles) in the second α-lithiation. The product was obtained as a yellow gum, which had i.r. and mass spectra superimposable with the above unsymmetrical nitrosamine 24. The n.m.r. spectrum, however showed a different isomer distribution, τ ($CDCl_3$) 2.50-2.90 (10H, m, ArH), 3.12-3.50 (6H, m, ArH), 4.98 (4H, d, OCH_2), 6.26 (6H, s, OMe), 6.84 (ca. 60% of 3H, s, NMe), 7.14 (ca. 40% of 4H, d J 8 Hz, CH_2Ar), 7.36 (ca. 60% of 4H, d J 8 Hz, CH_2Ar), and 7.48 (ca. 40% of 3H, s, NMe). The n.m.r. spectrum, after one week at room temperature, was found to be superimposable with that of the previous product which represents the equilibrium distribution of isomers.

N-Nitroso-di[2-(3-benzyloxy-4-methoxyphenyl)ethyl]amine (22).— A suspension of di-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]amine 23[33] hydrochloride (33 mg) in dry pyridine (3 ml) was cooled to 0° and gaseous nitrosyl chloride was passed slowly[32] until the solution turned brown. The mixture was stirred at 0° for 30 min (t.l.c. control), treated with dil. HCl and extracted with ether. The ether layer was dried (Na_2CO_3) and evaporated to yield N-nitroso-di[2-(3-benzyloxy-4-methoxyphenyl)ethyl]amine 22 (36 mg, 100%) as pale yellow needles, m.p. 63-66° (decomp.) (from chloroform-light petroleum), $\nu_{max.}$ ($CHCl_3$) 3025, 2965, and 2880 (CH), 1605, and 1590 (Ar), 1464, 1458,

1448, and 1432 (N-NO)[60] cm^{-1}, τ ($CDCl_3$) 2.50-2.90 (10H, m, ArH), 3.10-3.50 (6H, m, ArH), 4.98 (4H, s, OCH_2), 6.10 (2H, m, CH_2N), 6.24 (6H, s, OMe), 6.48 (2H, m, CH_2N), and 7.34 (4H, m, CH_2Ar), m/e 526 [M^+ (Found: 526.2444, $C_{32}H_{34}N_2O_5$ requires 526.2449)], 496, 404, 330, 286, 270, 240 [100%, cf. Table 1 (Found: 240.1165, $C_{16}H_{16}O_2$ requires 240.1150)], 227, and 91.

Alkylation of the Nitrosamine (21) with the Benzyl Bromide (20).— i) A solution of 12 (0.005 mole, 7.5 ml) was prepared from diisopropylamine and methyl lithium at -80° as described above. After ca. 30 min the nitrosamine 21 (1.50 g, 0.005 mole) in THF (6 ml) was added while stirring, followed after 10 min by the bromide 20 (1.50 g, 0.005 mole) in THF (4 ml). After 1.5 h at -80°, it was worked up by the general procedure to obtain a brown semi-solid. The n.m.r. spectrum (and t.l.c.) of this indicated the presence of ca. 40% unreacted nitrosamine 21.

ii) The reaction was carried out with excess of 12 (0.008 mole) otherwise following a method similar to the above reaction, and using identical amounts of reagents. The product was obtained as a brown semi-solid (2.77 g). T.l.c. of this showed the presence of 2 compounds in addition to polar decomposition products. Purification by p.l.c. (SiO_2-20% ethylacetate in benzene) afforded 2,6-dibenzyloxy-3,7-dimethoxyanthracene 30 (0.20 g, ca. 10%) as colourless needles, m.p. 183-184°(from ethyl acetate), $\nu_{max.}$ 1600 cm^{-1}, $\lambda_{max.}$ (log ε) 215 (4.44), 235 (4.24), 295 (4.26), 305 (4.33), 320 (4.45), 334 (4.51), 345 (4.35 τ($CDCl_3$) 2.50-2.73 (10H, m, ArH), 2.90-3.20 (6H, m, ArH), 4.80 (4H, s, OCH_2), and 6.10 (6H, s, OMe), m/e 450 (M^+), 237, and 91 (100%) [Found: C, 77.53; H, 6.08 . $C_{30}H_{26}O_4$ 0.5 EtOAc requires C, 77.71; H, 6.11%]. N-Nitroso di-[2-(3-benzyloxy-

-4-methoxyphenyl)ethyl]amine 22 (2.0 g, 75%) was obtained as a yellow gum, and was shown to be identical (t.l.c., i.r., n.m.r., and m.s.) with an authentic sample.

Sodium Di-trimethylsilylamide (31). — Reaction of hexamethyl disilazane (66.5 g) with sodium amide (16.0 g, prepared from sodium and liquid ammonia[60]) in dry benzene (500 ml) by the method of Wannagat and Niederprum[41] afforded 31 (48.5 g, 71%) as a colourless amorphous solid, m.p. 163-166° (cap.) (lit.[41], m.p. 165-167°).

Alkylation of α-Sodiodimethylnitrosamine (32) with the Benzyl Bromide (20). — Sodium dimethylsilylamide 29 (13.5 g, 0.075 mole) in THF (125 ml) at -80° was treated (under N_2) with dimethylnitrosamine (5.0 g, 0.065 mole) in THF (30 ml) followed, after ca. 10 min, by a solution of the bromide 20 (14.0 g, 0.045 mole) in THF (45 ml). After stirring for 3 h at -80° the reaction was worked up in the usual way to obtain N-methyl-N-nitroso-2-(3-benzyloxy-4-methoxyphenyl)ethylamine 21 (13.6 g, 97%) as a pale yellow solid which was shown to be identical (m.p., i.r., n.m.r., and t.l.c.) with the previously obtained sample.

Alkylation of the Nitrosamine (21) with the Benzyl Bromide (20) via its α-Sodio Derivative. — To a solution of sodium di-trimethylsilylamide 31 (3.83 g, 0.021 mole) in THF (40 ml) was added a solution of the nitrosamine 21 (3.75 g, 0.012 mole) in THF (30 ml) with stirring at -80°. The resulting α-sodio derivative 32 was treated after 10 min with a solution of the bromide 20 (3.40 g, 0.012 mole) in THF (30 ml). The reaction mixture was stirred for 5 h at -80° and worked up by the usual method to obtain N-nitroso di-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]amine 22 (4.65 g, 75%) as

a pale yellow amorphous solid, which was identical (i.r., n.m.r., m.s. and t.l.c.) with an authentic sample.

syn-N-Methyl-N-nitroso-2-(3-benzyloxy-4-methoxyphenyl)ethyl amine (21a). — The equilibrium conformer mixture of the nitrosamine 21 (1.00 g, syn : anti, 76: 24% by n.m.r.) was dissolved in the minimum volume of hot light petroleum (b.p. 60-80°). The colourless solution thus obtained was filtered and allowed to stand at 0° for 3 weeks, whereby the syn-nitrosamine 21a was obtained as a pale yellow amorphous solid (0.91 g, 91% recovery), τ ($CDCl_3$) 2.50-2.80 (5H, m, ArH), 3.14-3.40 (3H, m, ArH) 4.84 (2H, s, OCH_2), 5.72 (2H, t J 6 Hz, CH_2-N), 6.14 (5H, s br at the base, OMe and $ArCH_2$) and 7.10 (3H, s, NMe).

Alkylation of the syn-Nitrosamine (21a) with the Benzyl Bromide (20) via its α-Sodio derivative. — This was carried out in a manner similar to above alkylation reaction, but using 21a instead of the equilibrium mixture. The nitrosamine 22 was obtained in 94% yield.

Denitrosation of the Nitrosamine (22). —

i) Urea (1.50 g) was suspended in a solution of 22 (1.40 g) in dry benzene (60 ml), and into this was passed dry HCl gas with stirring at room temperature for 1 h (t.l.c. control). The solution was filtered and the filtrate swept with N_2 to remove excess HCl gas. Evaporation of benzene and trituration with ether afforded di-[2-(3-benzyloxy-4-methoxyphenyl)ethyl] amine 23 hydrochloride (0.72 g, 51.4%) as colourless needles, m.p. 173-174° (from methanol), τ ($CDCl_3$+D_2O) 2.50-2.83 (10H, m, ArH), 3.30 (6H, br s, ArH), 5.00 (4H, s, OCH_2), 5.37 (2H, s, HOD), 6.23 (6H, s, OMe), and 6.90 (8H, br s, Ar CH_2CH_2N), m/e

497 ($\underline{M}^+$), 406, 270 [100% ($ArCH_2CH_2\overset{+}{N}=CH_2$ due to α-cleavage[61])], 241,228, 215 (m*, 270 → 241), and 91. [Found: C, 71.68; H, 6.67; N, 2.32 $C_{32}H_{35}NO_4$.HCl requires C, 71.96; H, 6.79; N, 2.62%].

Hydrogenolysis of this amine 23 hydrochloride (0.40 g) in ethanol (15 ml) and 2 drops of conc. HCl by the conventional method[3] using 10% Pd-C catalyst afforded di-[2-(3-hydroxy-4-methoxyphenyl)ethyl] amine 4 hydrochloride (0.25 g, 95%) as colourless plates, m.p. 225-227° (decomp.) (from ethanol) (lit.[3], m.p. 228-233°), τ (D_2O + NaOH) 3.33 (2H, d J 8 Hz, H-5 of Ar), 3.60 (2H, d J 2 Hz, H-2 of Ar), 3.83 (2H, dd J 8 and 2 Hz, H-6 of Ar), 6.30 (6H, s, OMe), and 7.43 (8H, br t J 6 Hz, $ArC\underline{H}_2C\underline{H}_2N$), m/e 317 ($\underline{M}^+$), 180 [100% ($ArCH_2CH_2\overset{+}{N}=CH_2$, due to α-cleavage[61])], 151, 137, and 127 (m*, 180 → 151).

ii) A solution of the nitrosamine 22 (75 mg) in 5% acetyl acetone in benzene (10 ml) was treated with gaseous HCl at room temperature for 1 h (t.l.c. control) after which N_2 was passed through the solution to remove excess HCl. Evaporation of the solution to dryness and trituration with methanol and ether afforded the amine 23 hydrochloride (32 mg, 42%) which was identical (m.p., m.m.p., t.l.c.) with an authentic sample.

iii) A solution of the nitrosamine 22 (86 mg) and urea (100 mg) in ethanol (10 ml) was treated with gaseous HCl for 1 h with stirring at room temperature. The denitrosation was found to be sluggish at this temperature (as indicated by t.l.c.). Therefore the mixture was refluxed on a steam bath for 1.5 h after which it was flushed with N_2, and the solution concentrated and cooled to yield di-[2-(3-hydroxy-4-methoxyphenyl)ethyl] amine 4 hydrochloride (26 mg, ca. 45%)

as colourless plates, m.p. and mixed m.p. 225-227° (decomp.) (from ethanol) (lit.[3], m.p. 228-233°).

iv) A solution of nitrosamine 22 (0.375 g) and resorcinol (0.5 g) in ethanol (40 ml) was saturated with gaseous HCl and the solution was refluxed for 8 h (t.l.c. control). The deep green solution thus obtained was concentrated and cooled to afford the bisdiphenolic amine 4 hydrochloride (0.115 g, 45%) which was identical (m.p., m.m.p.) with an authentic sample.

REFERENCES

1 D.H.R. Barton, Chem. in Britain, 1967, 330.

2 D.H.R. Barton, R.B. Boar, and D.A. Widdowson, J. Chem. Soc. (c), 1970, 1213.

3 D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, J. Chem. Soc. (c), 1968, 1529.

4 A. Mondon and M. Ehrhardt, Tetrahedron Letters, 1966,2557.

5 J.E. Gervay, F. McCapra, T. Money, G.M. Sharma, and A.I. Scott, Chem. Comm., 1966, 142.

6 G.M. Chapman, Ph. D. Thesis, University of London, 1966, p. 126. See also ref. 4.

7 D.H.R. Barton, R.D. Bracho, and D.A. Widdowson, Chem. Comm., 1973, 781.

8 R.D. Bracho, Ph. D. Thesis, University of London, 1974.

9 D. Seebach, and D. Enders, Angew. Chem. internat. Edit., 1972, 11, 301.

10 R.W. Hoffmann, 'Dehydrobenzene and Cycloalkynes', Academic Press, New York. N.Y., 1967, p. 101.

11 R.A. Olofson, and C.M. Dougherty, J. Amer. Chem. Soc., 1973, 95, 582.

12 O.H. Wheeler, 'The Chemistry of the Carbonyl Group', Ed. by S. Patai, Interscience, London, 1966, p. 537.

13 H. Normant, Angew. Chem. internat. Edit., 1967, 6, 1046.

14 P.E. Pfeffer, and L.S. Silbert, Tetrahedron Letters, 1970, 699.

15 G.J. Karabastsos, and R.A. Taller, J. Amer. Chem. Soc., 1964, 86, 4373.

16 L.M. Jackman, and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry', 2 nd Ed., Pergamon Press, Oxford, 1969, p. 61.

17 D. Seebach, D. Enders, B. Renger, and W. Brügel, Angew. Chem. internat. Edit., 1973, 12, 495.

18 J.V. Dubsky, and M. Spritzmann, J. Prakt. Chem., 1917, 96, 106.

19 A. Mustafa, and M. Kamel, J. Amer. Chem. Soc., 1955, 77, 1828.

20 A. Mustafa, M. Kamel, and M.A. Allam, J. Amer. Chem. Soc., 1956, 78, 4693.

21 C.E. Looney, W.D. Phillips, and E.L. Reilly, J. Amer. Chem. Soc., 1957, 79, 6136.

22 L.J. Bellamy, 'The Infra-red Spectra of Complex Molecules, Methuen & Co Ltd., London, 2 nd Edit., 1958, p. 270.

23 K. Hirayama, 'Handbook of Ultraviolet and Visible Absorption Spectra of Organic Compounds', Plenum Press Data Division, New York, 1967, p. 148.

24a A.I. Vogel, 'A Text-book of Practical Organic Chemistry', Longmans Green & Co., London, 1948, p. 649.

24b ibid. p. 417.

25 D. Seebach, and D. Enders, Angew. Chem. internat. Edit., 1972, 11, 1101.

26 I. Baxter, L.T. Allan, and G.A. Swan, J. Chem. Soc., 1965. 3645.

27 K. Fukui, K. Ohkubo, and T. Yamabe, Bull. Chem. Soc. Japan, 1969, 42, 312.

28 R. Breslow, 'Organic Reaction Mechanisms', W.A. Benjamin, Inc., New York, 1965, p. 79.

29 E.J. Corey, C.V. Kim, and M. Takeda, Tetrahedron Letters, 1972, 4339.

30 H. Budzikiewicz, C. Djerassi, and D.H. Williams, 'Mass Spectrometry of Organic Compounds', Holden-day, Inc., London, 1967, p. 329.

31 K. Biemann, 'Mass Spectrometry- Organic Chemical Applications', McGraw-Hill, New York, 1962, p. 119.

32 M.S. Newman, and A. Kutner, J. Amer. Chem. Soc., 1951, 73, 4199.

33 Prepared by Professor P.W. Jeffs in this laboratory via the usual route[3].

34 A. Mannschrek, H. Munsch, and A. Matheus, Angew. Chem. internat. Edit., 1966, 5, 728.

35 C. Agami, Bull. Soc. Chim. France, 1970, 1619.

36 R.R. Fraser, and Y.Y. Wigfield, Tetrahedron Letters, 1971, 2515.

37 R.R. Fraser, G. Boussard, I.D. Postescu, J.J. Whiting, and Y.Y. Wigfield, Canad. J. Chem., 1973, 51, 1109.

38 L.K. Keefer, and C.H. Fodor, J. Amer. Chem. Soc., 1970, 92, 5747.

39 'Organic Electronic Spectral Data - vol III' Eds. O.H. Wheeler and L.A. Kaplan, Interscience, 1956-57, p. 694.

40 R.A. Olofson, and C.M. Dougherty, J. Amer. Chem. Soc., 1973, 95, 581.

41 V. Wannagat, and H. Niederprum, Chem. Ber., 1961, 94, 1540.

42 C. Kruger, and E.G. Rochow, Angew. Chem. internat. Edit., 1963, 2, 617.

43 D.H.R. Barton, R.H. Hesse, G. Tarzia, and M.M. Pechet, Chem. Comm., 1969, 1497.

44 M.W. Rathke, J. Amer. Chem. Soc., 1970, 92, 3222.

45 C. Kruger, E.G. Rochow, and V. Wannagat, Chem. Ber., 1963, 96, 2132.

46 C.R. Kruger, and E.G. Rochow, J. Organometal. Chem., 1964, 1, 476.

47 A. Mannschreck, Angew. Chem. internat. Edit., 1965, 4, 985.

48 E.C.S. Jones, and J. Kenner, J. Chem. Soc, 1932, 711.

49 F.W.C. Stewart, Austr. J. Chem., 1969, 22, 2451.

50 C.H. Schmidt, Angew. Chem. internat. Edit., 1963, 2, 101.

51 C.G. Overberger, J.P. Anselme, and J.G. Lombardino, 'Organic Compounds with Nitrogen-Nitrogen Bonds', The Ronald Press Co., N.Y., 1966, p. 83.

52 O. Fischer, and E. Hepp, Chem. Ber., 1886, 19, 2291.

53 B.T. Balinga, J. Org. Chem., 1970, 35, 2031.

54 J.H. Boyer, in 'The Chemistry of the Nitro and Nitroso groups, Part I', Ed. by H. Feuer, Interscience Publishers, New York, 1969, p. 226.

55 R. Adams, and G.H. Coleman, Org. Syntheses, Coll. Vol. I, 1941, 214.

56 B.C. Challis, and M.R. Osborne, J.C.S. Perkin II, 1973, 1526.

57 D.D. Perrin, W.L.F. Armarego, and D.R. Perrin, 'Purification of Laboratory Chemicals', Pergamon Press, Oxford, 1966.

58 R. Robinson, and S. Sugasawa, J. Chem. Soc., 1931, 3163. Also cf. p. 103 of this Thesis.

59 C.E. Looney, W.D. Phillips, and E.L. Reilly, J. Amer. Chem. Soc., 1957, 79, 6136.

60 J.A. Elvidge, and P.G. Sammes, 'A Course in Modern Techniques of Organic Chemistry', Butterworths, 1966, p. 168.

61 D.H. Williams, and I. Flemming, 'Spectroscopic Methods in Organic Chemistry', McGraw Hill, London, 1966, p. 152.

PART III

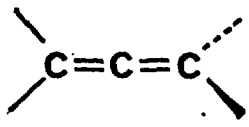
Novel Aza-allenium Cations

'Chemical synthesis is essentially entirely a creative activity in which art, design, imagination, and inspiration play a predominant role'

Robert B. Woodward

INTRODUCTION

The azaallenium cation is an isoelectronic nitrogen analogue of an allene 1. Two basic types of azaallenium cation could exist depending on the position of the nitrogen atom in the allene system. The 1-azaallenium cations (keteniminium cations) 2, have not been reported. The 2-azaallenium cations 3, which contain a linear quaternary nitrogen atom have, to date, been reported only as reactive intermediates (See below). Other analogous isoelectronic systems containing a nitrogen atom that have been extensively studied are ketenimines 4[1,2], and nitrile ylids 5[3,4].



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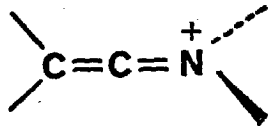

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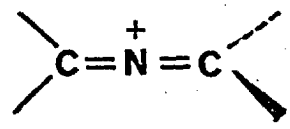

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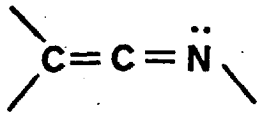

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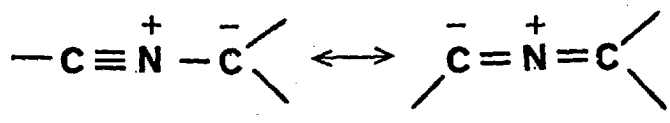
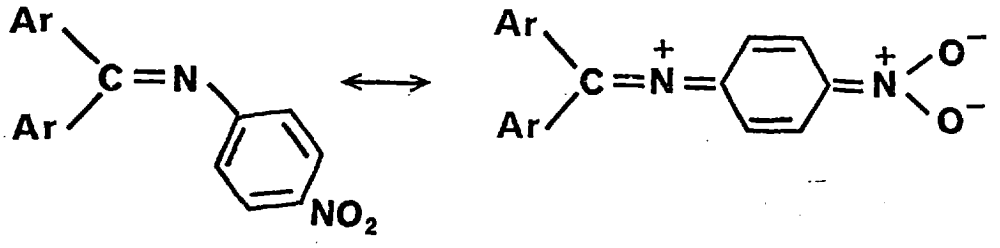


5

The contribution of the dipolar resonance structure 7 to the linear transition state has been envisaged in the syn-anti isomerisation of the N-aryl ketemine 6[5,6]. Similarly, the

cause for the surprisingly low barrier to syn-anti isomerisation of the N-perfluoroimines such as 8 was explained by the special stabilisation of a linear transition state having the 2-azaallenium structure 9[4,7]. More recently, another isomerisation of an imine 10 was suggested to occur via the enamine and 2-azaallenium structures (Scheme 1)[8].



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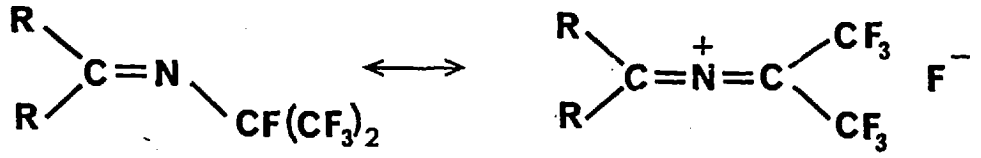
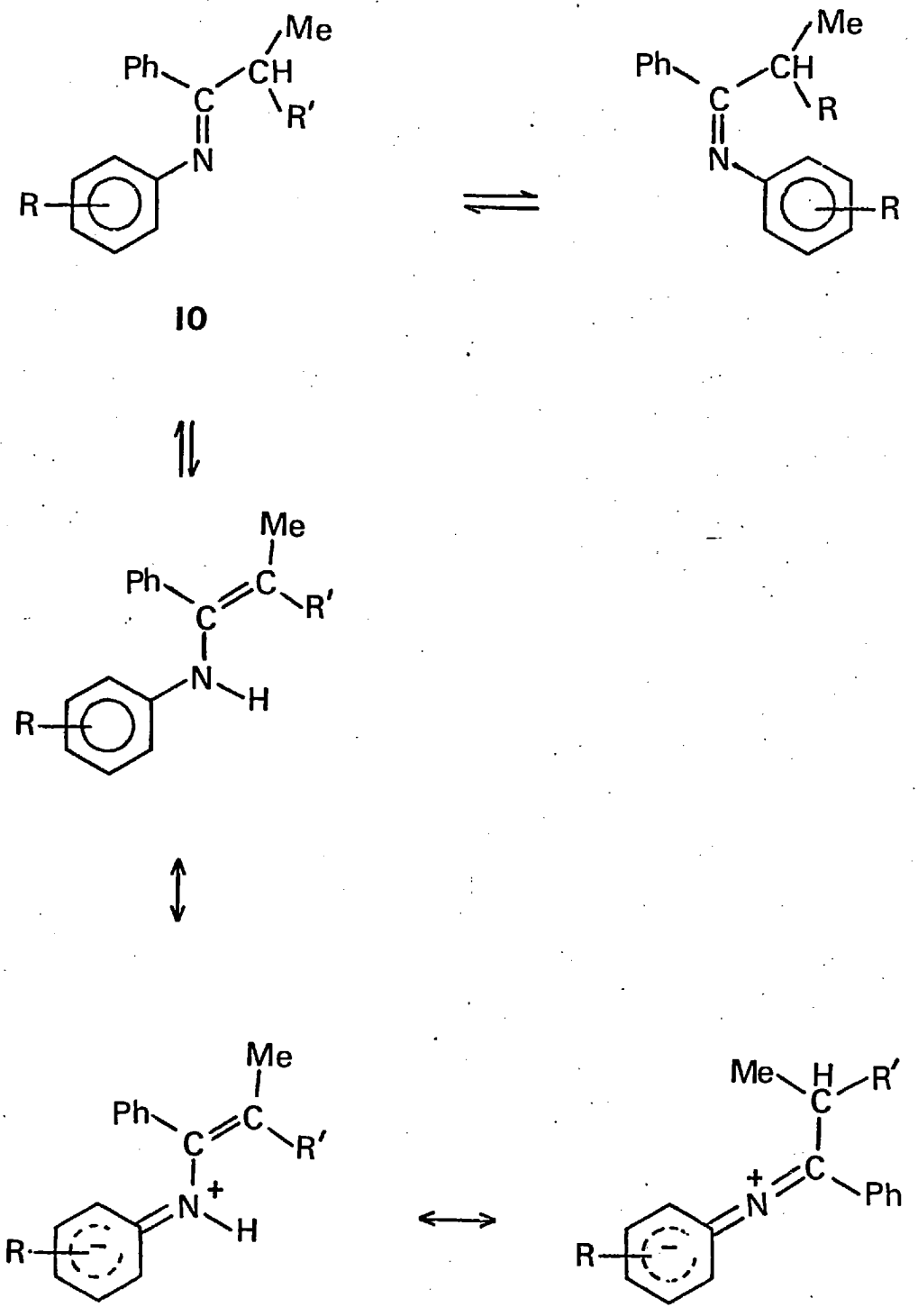


8 9

In a synthesis of 7α-methylthiocephalosporin 13 by the acid catalysed methylthiolation of the fluoro Schiff base 11, the intermediacy of the 2-azaallenium cation 12 has been suggested[9]. More recently, Cama and Christensen assumed the



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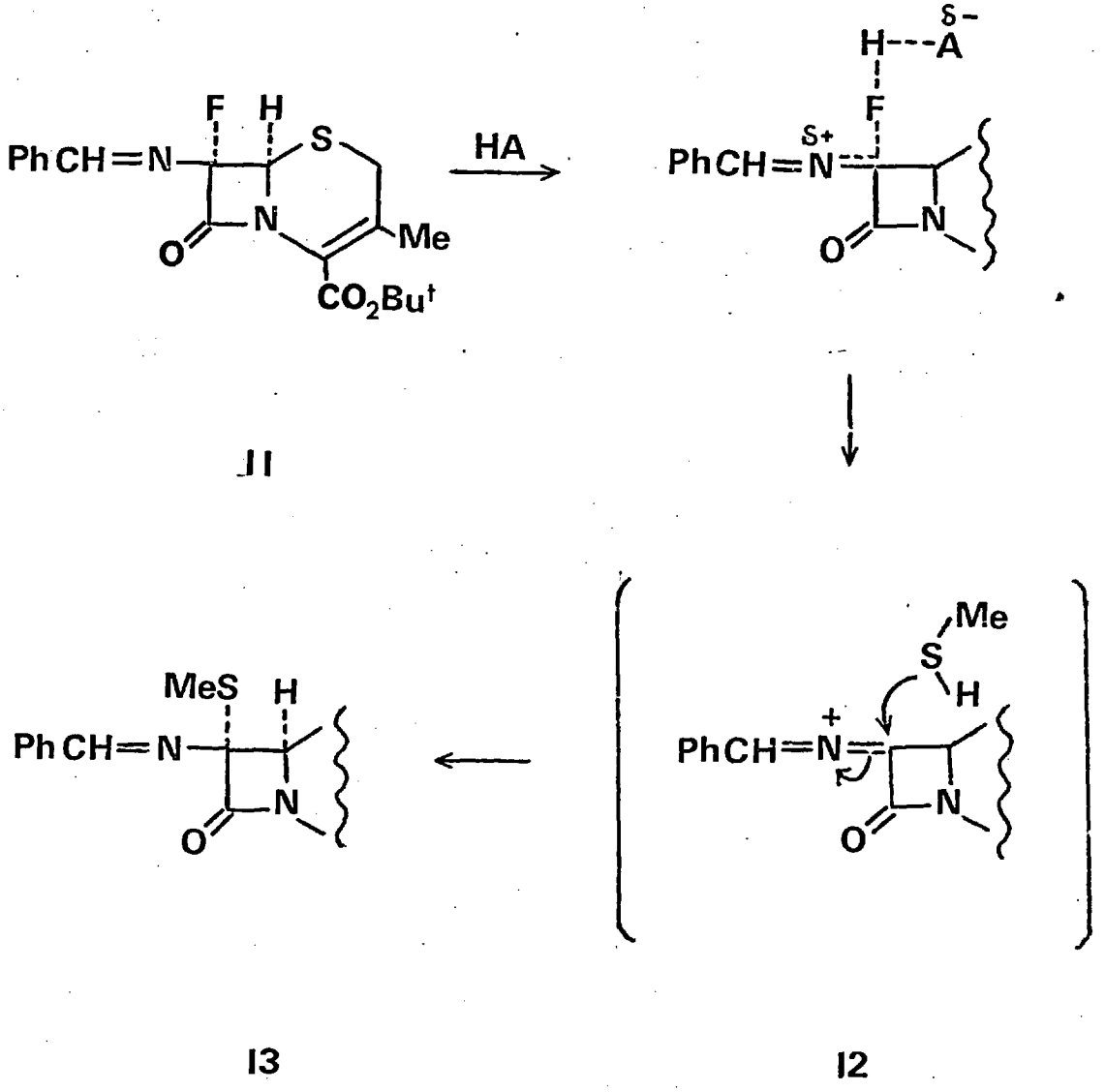
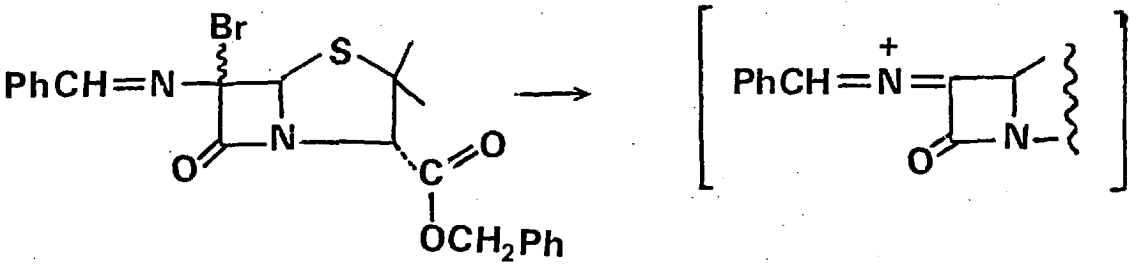
Scheme I

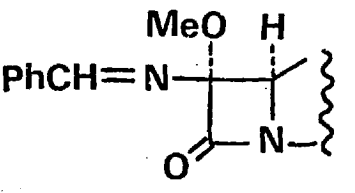
formation of a similar intermediate 15 to account for the stereospecific formation of 6α-methoxypenicillin 16 by the methanolysis of the corresponding 6-bromocompound 14 (Scheme 2).[10]



The possibility that the 2-azaallenium cation 17 exists either as a discrete intermediate or as a point along the reaction pathway (not necessarily the transition state) during the solvolysis of 1-chloroaziridines was suggested by Gassman and coworkers (Scheme 3)[11].

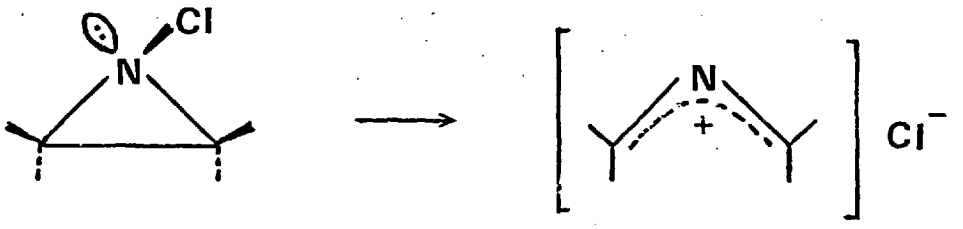


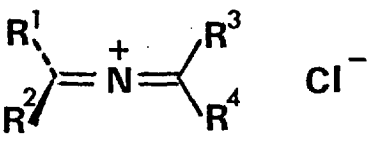
I4 I5



I6

Scheme 2





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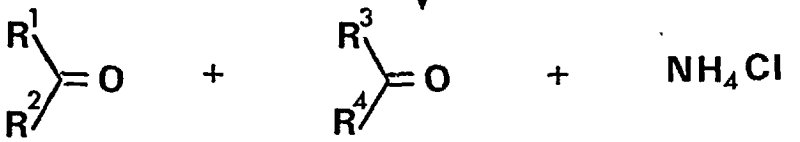
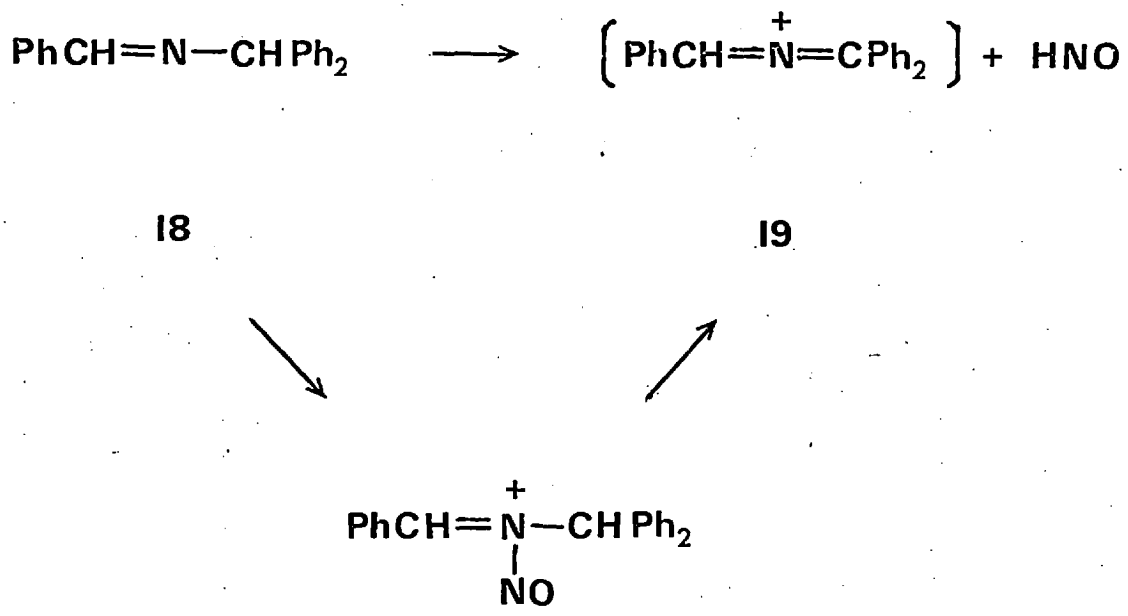


Scheme 3

Another possible intermediacy of a 2-azaallenium cation came from the cleavage of the carbon-nitrogen double bond of N-benzylidenebenzhydrylamine 18 by NO^+ [12].

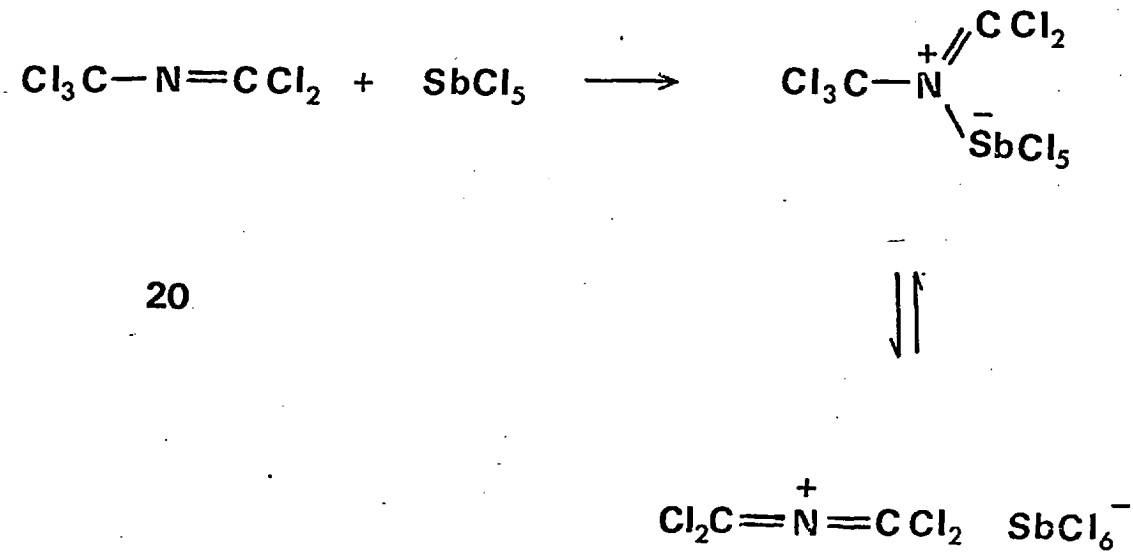


Scheme 4

The production of benzophenone, nitrous oxide, and nitric oxide in this reaction required hydrogen transfer to give the 2-azaallenium intermediate 19. No evidence for the independent existence of the latter was obtained. Attempts to generate 19 from the imine 18 by the use of trityl salts in acetonitrile at 65° proved to be unsuccessful (Scheme 4)[12].

The only reported evidence for the independent existance of a 2-azaallenium cation emerged from the recent

vibrational spectral studies made by Schmidt on the adduct 21 obtained from trichloromethylisocyanide dichloride 20 and antimony pentachloride (Scheme 5)[13].



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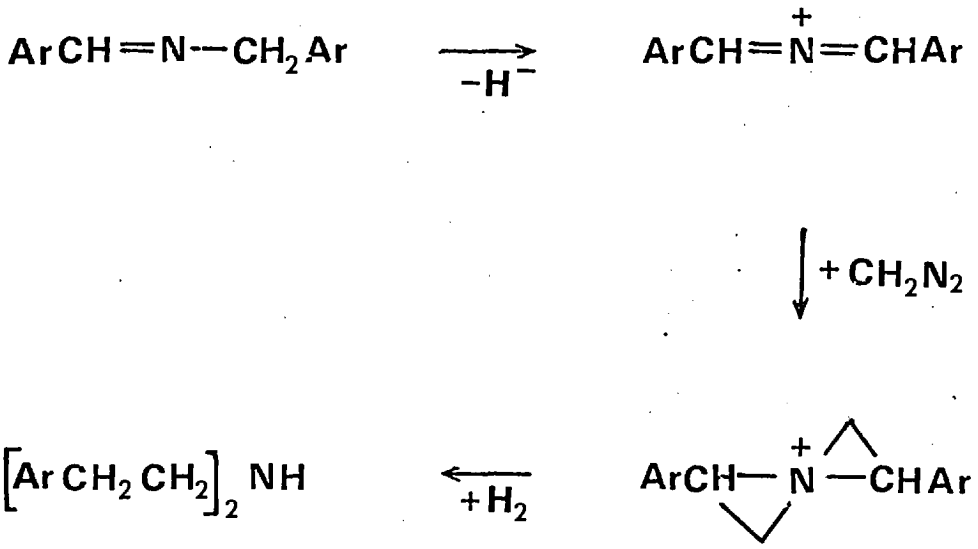
21

Scheme 5

DISCUSSION

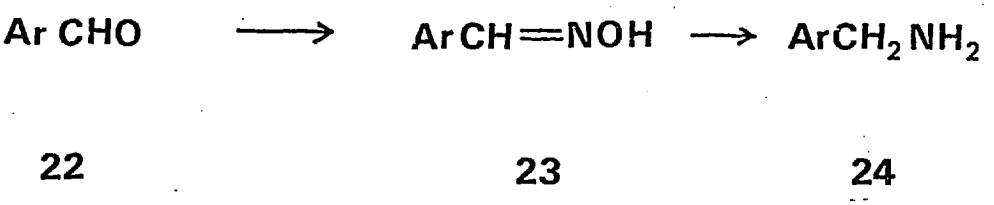
During the past two decades trityl cation has been utilized to abstract hydride ions from a variety of olefinic and oxygen-containing compounds[14-18]. The facile hydride transfer from oxygen compounds can be attributed to stabilisation of the carbonium ions by resonance contributions of nonbonding electrons on oxygen. It is surprising therefore that there is little reported work on the use of trityl salts to abstract hydride ions from the isoelectronic nitrogen compounds.

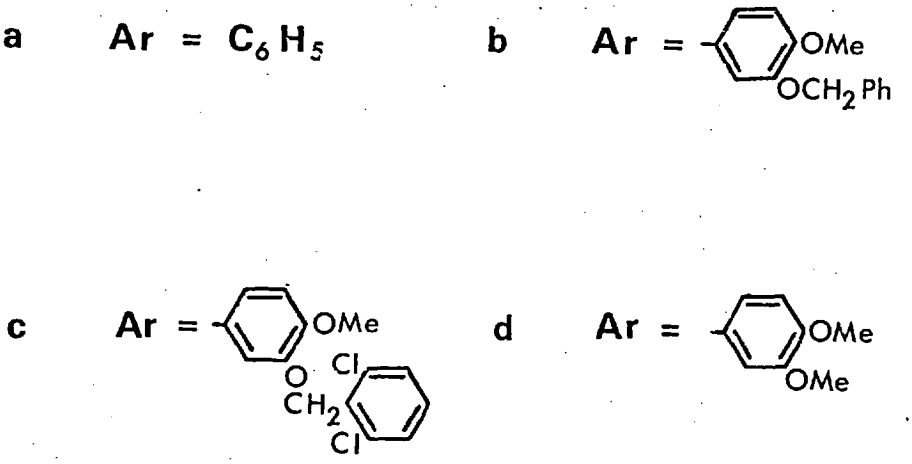
Although few in number, there are reports of trityl salts as oxidants of tertiary amines to their corresponding iminium salts[17,19,20]. However successful extention of this reaction to tertiary imines has not been reported (but see ref. 12). It was envisaged that such a process would generate the 2-azaallenium ion which could be utilised by a double insertion of 1-carbon units in a diphenethylamine synthesis (see Scheme 6)



Scheme 6

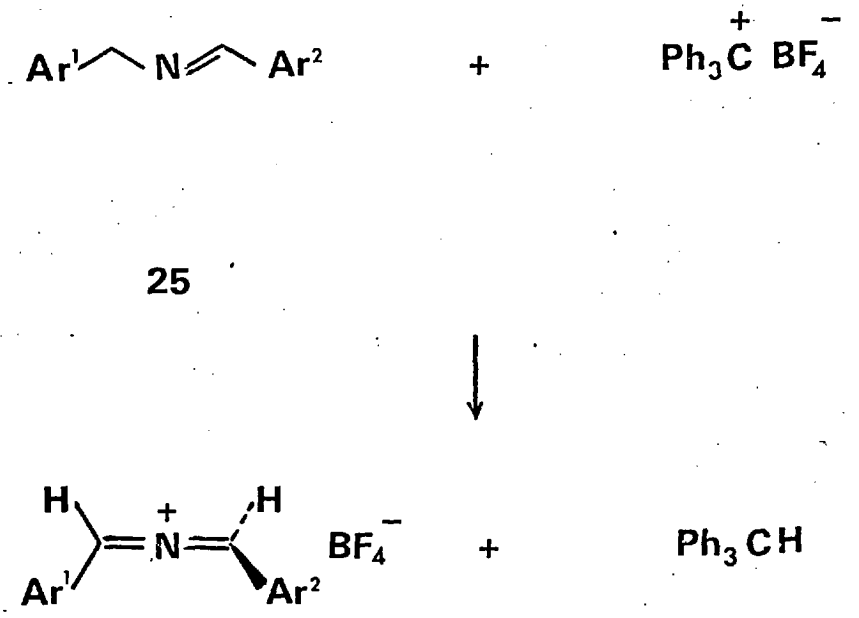
Accordingly, a series of imines 25 a-d was prepared by the standard procedure[21] of the condensation of the corresponding aldehydes 22 a-d with amines 24 a-c. In an attempt to prepare the 1,3-diphenyl-2-azaallenium cation 26 a by hydride abstraction, the imine 25 a was treated with trityl tetrafluoroborate (Scheme 8). The n.m.r. spectrum of the



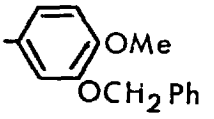


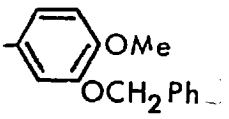
Scheme 7

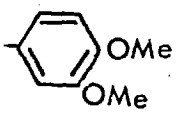
reaction mixture indicated that only quaternization of the nitrogen atom to provide the iminium salt 27 has occured.[25,37] No hydride abstraction was observed, even over an extended period at room temperature. This was confirmed by the absence of

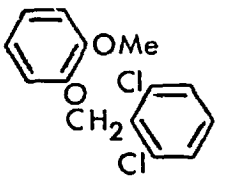


a $Ar^1 = Ar^2 = C_6H_5$

b $Ar^1 = Ar^2 =$ 

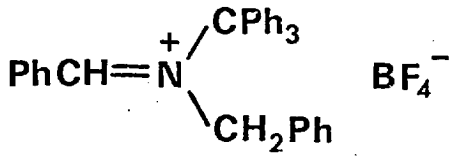
c $Ar^1 =$ 

$Ar^2 =$ 

d $Ar^1 = Ar^2 =$ 

Scheme 8

triphenyl methane among the products. However,the reaction of N-(3-benzyloxy-4-methoxybenzylidene)-3-benzyloxy-4-methoxy benzylamine 25 b with the same trityl salt, monitored by n.m.r. spectroscopy, gave an initial quaternization followed by the loss of a hydride ion from the methylene group. The



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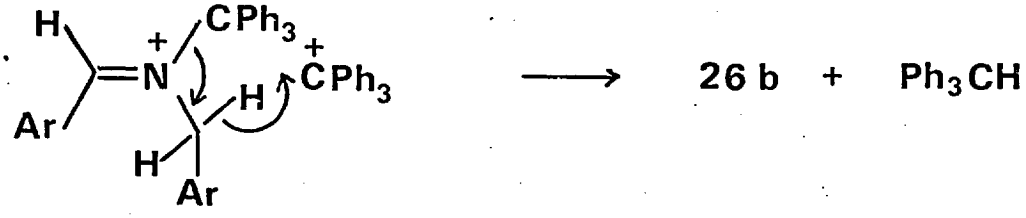
five fold increase in the rate of reaction (determined by the appearance of Ph_3CH) with 1.2 molar equivalents of the trityl salt compared to the reaction using 1 molar equivalent suggested a catalytic requirement for a second trityl cation for the abstraction of the hydride ion (Scheme 9).

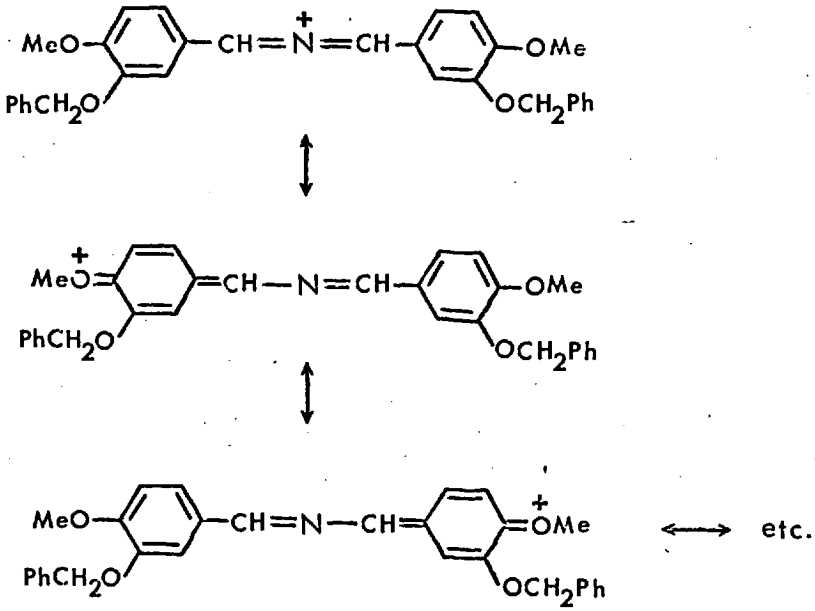


Scheme 9

However, when excess trityl cation was used, in addition to the desired process a hydride ion was also extracted from one of the O- benzyl groups. This was implied by the detection of benzaldehyde in the product mixture after

hydrolysis. Such reactions of trityl salts with ethers are authenticated in the literature [22,24].

Hydride abstraction from the imine 25 b would be facilitated by the p-methoxy groups. These substituents in addition to increasing the hydride character of the hydrogens to be abstracted, would participate in the resonance stabilization of the resulting cation 26 b as shown below.

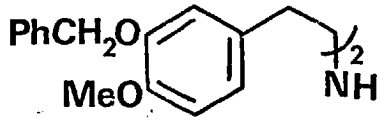


26 b

Isolation of the 2-azaallenium salt 26 b in a crystalline form was not possible. However, its presence was confirmed by the isolation of triphenyl methane and the hydrolysis product, benzylisovanillin 22 b in ca. 60% yield.

The projected synthesis of di-[2(3 benzyloxy-4-methoxyphenyl) ethyl] amine 28 from the above azaallenium salt 26 b required the addition of diazomethane to produce the diaziridinium salt and the subsequent ring opening of this (see

Scheme 6). However the addition of excess ethereal diazomethane to the crude 2-azaallenium tetrafluoroborate 26 b by the method of Leonard and coworker[23] gave an array of unidentified products and catalytic decomposition of diazomethane. The decomposition of diazomethane by trityl cation is not unknown[24]. Recently Leonard and coworkers reported[25] the instability of the aziridinium salt 29 even at low temperature. This was ascribed to the electron donating effect of the 4-methoxy group.



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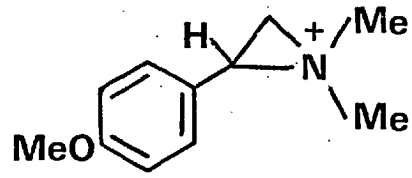
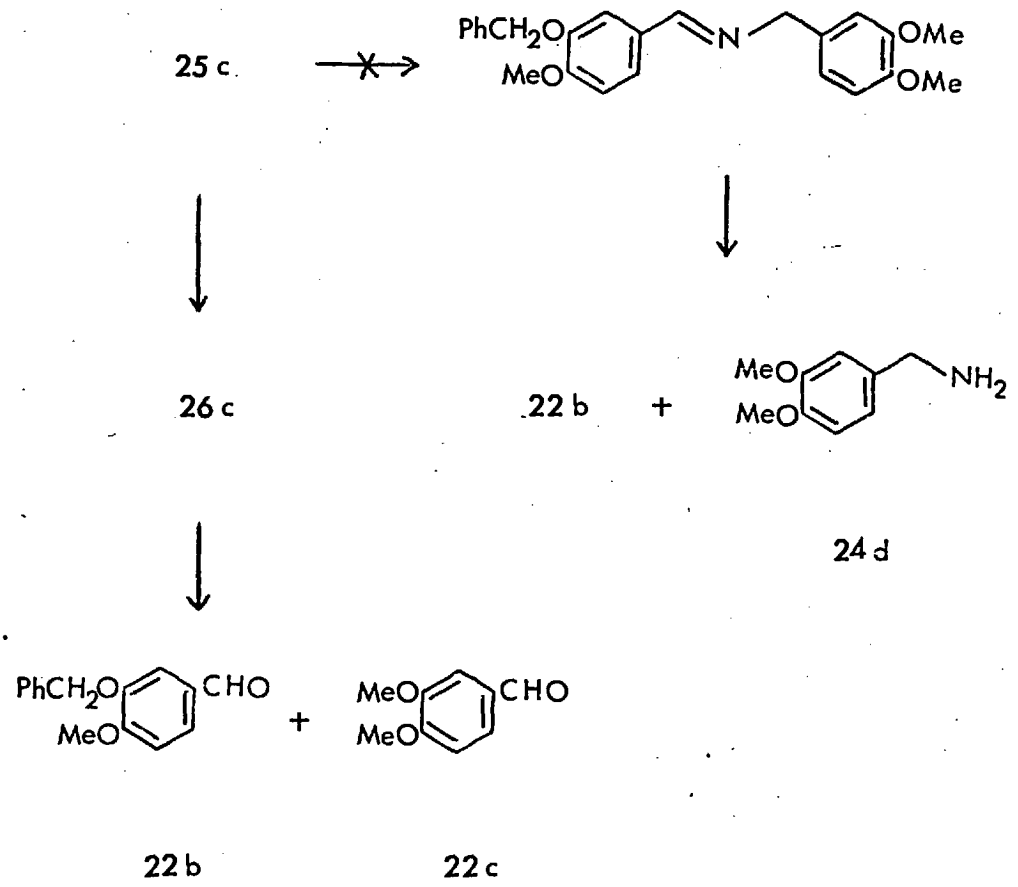


29

Hydrolytic cleavage of an unsymmetrical 2-azaallenium cation should liberate two different carbonyl compounds, provided that the starting imine has not undergone a double bond isomerisation[26]. For this reason N-(3,4-dimethoxybenzylidene)-3-benzyloxy-4-methoxybenzylamine 25 c was treated with trityl tetraflouroborate. After ca.70% hydride abstraction has occured (by n.m.r.), the crude product was treated with D_2O. The n.m.r. spectrum had two singlets in the low field region (τ, 0.18 and 0.22). Isolation of O-benzylisovanillin

22 b, veratraldehyde 22 d and triphenyl methane confirmed the existance of the 2-azaallenium cation 26 c. The absence of any veratrylamine 24 d in the product mixture led to the conclusion that double bond isomerisation had not occurred (Scheme 10).



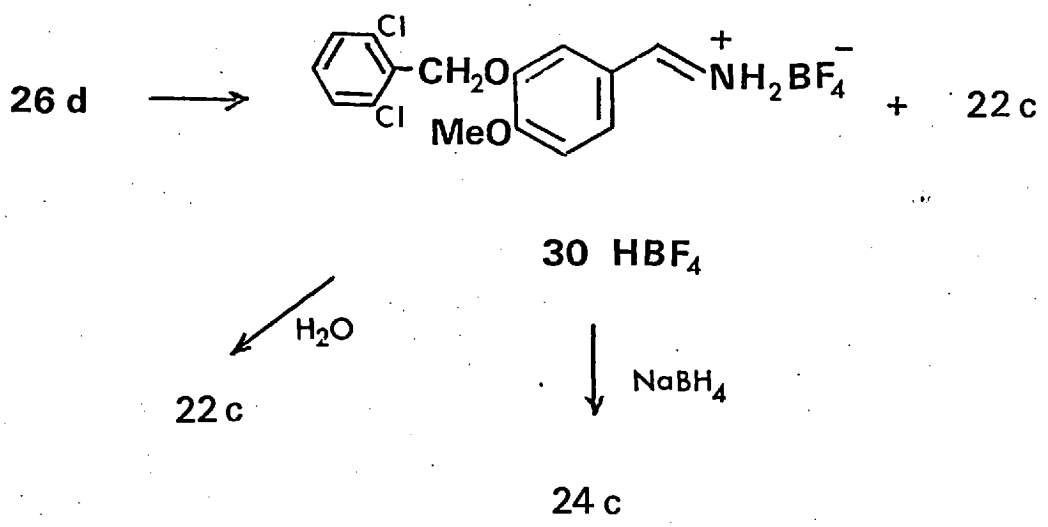
Scheme 10

To circumvent reaction at the O-benzylic position (see above), N-[3-(2,6-dichlorobenzyloxy)-4-methoxybenzylidene]- 3-(2,6-dichlorobenzyloxy)-4-methoxybenzylamine 25 d was prepared by an analogous method to 25 b. Treatment of

this imine 25 d with trityl tetrafluoroborate in dichloromethane at room temperature deposited after two days (70% reaction by n.m.r.) a bright red crystalline solid which was washed several times with dichloromethane to yield a pale yellow solid, m.p. 173-178°(sintering and turning red at 130°), $\nu_{max.}$ (nujol) 1910 and 1600 cm^{-1}.

T.l.c. examination of this solid indicated the presence of triphenyl methane, O-2,6-dichlorobenzylisovanillin 22 c and a another component. Attempted isolation of this unknown band from the t.l.c. (silica- dichloromethane) always gave a mixture of the compound with the aldehyde 22 c. The n.m.r. spectrum of the isolated mixture showed the ratio of aldehyde to the unknown compound to be 3:1. Acid treatment of the mixture converted it to the pure aldehyde. The second compound was suspected therefore, to be the aldimine 30 which would arise from a partial hydrolysis of the 2-azaallenium cation 26 d. The crude 3:1 mixture of aldehyde and aldimine tetrafluoroborate 30 was reduced with methanolic $NaBH_4$. Acid extraction provided an amine isolated as the hydrochloride which was identified to be 3-(2,6-dichlorobenzyloxy)-4-methoxy benzylamine 24 c (Scheme 11).

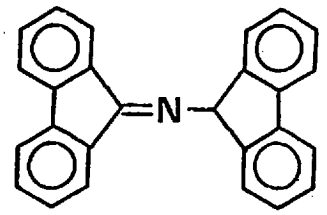
Preparation of the difluorenyliden-ammonium tetrafluoroborate 32 by the standard method (Scheme 12), gave after evaporation of the solvent a bright red solid mixture. The i.r. spectrum of this had a strong broad absorption at 1880 cm^{-1}. Attempted purification of this by fractional crystallisation afforded an orange solid which lacked the absorption at 1880 cm^{-1} in its i.r. spectrum. This was shown to be 9-fluoreniminium tetrafluoroborate 33 by hydrolysis to fluorenone 34 and by $NaBH_4$ reduction to 9-fluorenylamine 35.



Scheme II

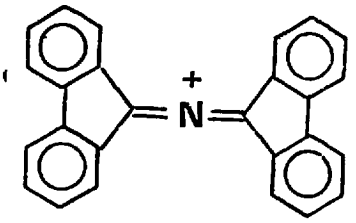
The strong i.r. absorptions exhibited by the 2-aza-allenium cations 26d and 32 at 1910 and 1880 cm^{-1} respectively could be attributed to a linear skeletal stretching vibration $\nu_{asymmetric}$ $(C=\overset{+}{N}=C)$ [13]. The loss of the absorptions between 1600-1650 cm^{-1}, indicate that the imine unit $\diagdown C=N-CH\diagup$ is indeed the point of attack by the oxidant. The weak absorptions above 1660 cm^{-1} may be due to the $\nu(C=O)$ arising from hydrolysis products. The aldehyde 22 c and fluorenone have $\nu_{(C=O)}$ at 1679 and 1710 cm^{-1} respectively.

The asymmetric skeletal stretching frequencies $\nu(C=\overset{+}{N}=C)$ exhibited by 2-azaallenium cations are lower than the stretching frequencies $\nu(X=Y=Z)$ of analogous linear isoelectronic systems such as allenes [27,28], azides [29], carbodiimides [30], diazoalkanes [31], isocyanates [32], isothiocyanates [33],



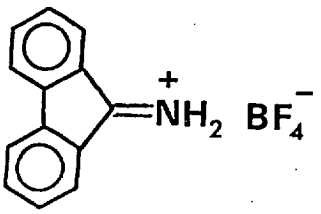
+ $Ph_3C^+ BF_4^-$

31

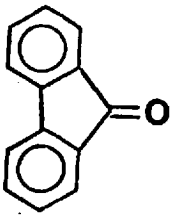


BF_4^-

32

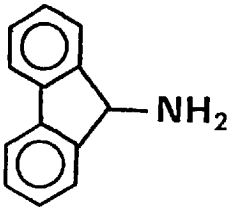


+



33

34



35

Scheme 12

and ketenimines [34]. Nevertheless, they are in the anticipated region. The following Table summerises skeletal stretching frequencies of some allenic (X=Y=Z) compounds.

Compound	X=Y=Z	$\nu_{(X=Y=Z)}$ [cm^{-1}]	Ref.
$Ph_2C=C=CPh_2$	C=C=C	1938	27
		1900	28
$Ph-N=N=N$	N=N=N	2114	29
$ArN=C=NAr$	N=C=N	2120 , 2142	30
$PhCH_2CH=\overset{+}{N}=NPh$	C=N=N	2020	31
$PhN=C=O$	N=C=O	2262 , 2278	32
$PhN=C=S$	N=C=S	2060	33
$Ph_2C=C=NMe$	C=C=N	1998	34
$Cl_2C=\overset{+}{N}=CCl_2\ \ SbCl_6^-$	C=N=C	1855	13
26d		1910	
32		1880	

Table

From the foregoing it is considered that the 2-azaallenium structure is proven despite the lack of accurate microanalytical data. Although the synthetic exploitation of the system envisaged here was not realizable compounds remain attractive intermediates for other synthetic applications.

EXPERIMENTAL

General details are the same as for Part 1. Dichloromethane was purified prior to use by the following procedure. Commercial solvent was stirred with conc. H_2SO_4 for 2 days, the organic layer was separated, washed with water, a saturated solution of $NaHCO_3$, and again with water until the washings were neutral. It was dried with $CaCl_2$, distilled from P_2O_5, and stored over anhydrous BaO. Chloroform-d used in n.m.r. monitered reactions was dried over anhydrous BaO.

Trityl Tetrafluoroborate.— Trityl chloride (50.0 g) was refluxed with water (250 ml) for 3.5 hr (t.l.c. control). The resulting pale yellow solid was filtered, dried, and was chromatographed over a column of alumina (Grade III). Elution with 25% benzene-light petroleum (b.p. 40-60°) gave pure trityl carbinol as colourless crystals (46.0 g, 98%), m.p. 163-164° (from benzene) (lit.[35], m.p. 162.5°).

Trityl carbinol (45.0 g) was converted to trityl tetrafluoroborate by the method of Deuben and coworkers[35]. It was washed 10 times with dry ether (50 ml aliquots) and dried for 3 days under vacuum in the dark to give the yellow crystalline salt (52.0 g, 91%), m.p.(sealed tube) 198-200° (decomp) [lit.[35], m.p. ca. 200° (decomp)].

N-Benzylidenebenzylamine (25 a).— Azeotropic removal of water from a benzene solution of benzaldehyde (1.0 g, 10 mmole) and benzylamine (1.0 g, 10 mmole) using a Dean-Stark apparatus[21] resulted in a clear liquid. After evaporation of the benzene, this was distilled to give pure N-benzylidenebenzylamine 25 a (1.83 g, 94%), b.p. 115-117° /0.1 mm., n_D^{22} 1.5981

(lit.[36], b.p. 116-117°/0.1 mm., n_D^{20} 1.6017), $\nu_{max.}$(liq.) 1645 (C=N) cm^{-1}, τ ($CDCl_3$) 1.67 (1H,s, -CH=N), 2.07-2.43 (2H,m, ArH), 2.60-2.80 (8H,m,ArH) and 5.23 (2H,s,CH_2-N=).

Reaction of N-benzylidenebenzylamine with Trityl tetrafluoroborate. — To a solution of N-benzylidenebenzylamine 25 a (80 mg, 0.4 mmole), in chloroform-d (1 ml) was added trityl tetrafluoroborate (165 mg, 0.5 mmole). The reaction was monitored by n.m.r. for 24 hr but no triphenyl methane was produced. This was confirmed by t.l.c. The n.m.r. spectrum indicated quaternisation of the nitrogen atom [25,37], τ ($CDCl_3$) 1.05(CH=N) and 5.07 (CH_2-N).

O-Benzylisovanillin (22 b). — This was obtained from isovanillin by the method of Robinson and Sugasawa [38], as pale yellow cubes, m.p. 62-63° (from methanol-ether) (lit.[39], 63.5°), $\nu_{max.}$ (nujol) 1675 (C=O) cm^{-1}, τ (D^6-Me_2CO) 0.12 (1H,s,CHO), 2.34-2.90 (8H,m,ArH), 4.80 (2H,s, -CH_2-O), and 6.07 (3H,s,OMe).

O-Benzylisovanillin Oxime (23 b). — A mixture of O-benzylisovanillin (8.0 g) and hydroxylamine hydrochloride (8.0 g) in ethanol (160 ml) and pyridine (40 ml) was refluxed on a water bath[40] for 14 h (t.l.c. control). Evaporation of the solvents under reduced pressure and trituration of the resulting oil with cold water yielded colourless needles of O-benzylisovanillin oxime (7.30 g, 86%), m.p. 90-92° (from alcohol-water), $\nu_{max.}$(nujol) 1529 (C=N) cm^{-1}, m/e 257 (M^+), 240,166, and 91 (100%), [Found: C, 70.28 ; H, 6.04 ; N, 5.32 $C_{15}H_{15}NO_3$ requires C, 70.02 ; H, 5.88 ; N, 5.44%].

3-Benzyloxy-4-methoxybenzylamine (24 b) Hydrobromide. — To a stirred solution of O-benzylisovanillin oxime (7.0 g) in absolute ether (150 ml) was added a suspension of $LiAlH_4$

(7.0 g) in absolute ether (150 ml) under dry nitrogen . After 72 h at 60° (t.l.c. control) the reaction mixture was cooled and water (300 ml) was added dropwise under a nitrogen [41] atmosphere, followed by a solution of NaOH (10%, 100 ml). The aquous phase was extracted with ether (5 x 500 ml), and the collected ether extracts were dried (Na_2SO_4) and evaporated to yield the crude amine as a yellow oil. A solution of this in methanol was saturated with gaseous hydrogen bromide. Trituration with ether gave 3-benzyloxy-4-methoxy benzylamine 24 b hydrobromide as colourless needles (6.0 g, 67%), m.p. 215-217° (decomp) (from methanol), $\nu_{max.}$ (nujol) 1593 cm^{-1}, τ (CD_3OD + D_2O) 2.50-2.75 (5H, m, ArH), 2.80-3.00 (3H, m, ArH), 4.80 (2H,s,-CH_2-O), 5.93 (2H,s,-CH_2-N), and 6.13 (3H,s,OMe) [Found: C, 55.53; H, 5.78; N, 4.29, $C_{15}H_{18}BrNO_2$ requires C, 55.60; H, 5.60; N, 4.32%].

N-(3-Benzyloxy-4-methoxybenzylidene)-3-benzyloxy-4-methoxy benzylamine (25 b).— 3-Benzyloxy-4-methoxybenzylamine (1.56 g, 6.4 mmole, liberated from the above salt with aq. $NaHCO_3$) was condensed with O-benzylisovanillin (1.56 g, 6.4 mmole) by the general procedure (see above) to obtain the imine 25 b as colourless needles (2.84 g, 94%), m.p. 115-118° (from benzene- light petroleum), $\nu_{max.}$ (nujol) 1643 (C=N) cm^{-1}, $\lambda_{max.}$ 212 (ϵ 22,400), 227 (18,000), 246 (11,000), and 302 nm (7,400), τ ($CDCl_3$) 1.80 (1H,s,CH=N), 2.40-2.80 (13H,m,ArH), 2.97-3.20 (3H,m,ArH), 4.85 (2H,s,-CH_2-O), 4.88 (2H,s,-CH_2-O), 5.33 (2H,s,-CH_2N), 6.13 (3H,s,OMe), and6.17 (3H,s,OMe), m/e 467 (M^+), 376,332,242,227 (100%), and 91. [Found: C, 76.91; H, 6.45; N, 2.90. $C_{30}H_{29}NO_4$ requires C, 77.07; H, 6.25; N, 3.00%].

Reaction of the imine (25 b) with Trityl Tetrafluoroborate.

i). Using 1 molar equivalent of trityl tetrafluoroborate.

The imine 25 b (93 mg, o.2 mmole) in chloroform-d (1 ml) was treated with trityl tetrafluoroborate (66 mg, 0.20 mmole). The reaction was monitored by n.m.r. which showed slow disappearance of $ArCH_2N$ protons and a corresponding appearance of a singlet at τ 4.47. The n.m.r. spectrum after 36 h indicated ca.62% reaction. Addition of D_2O caused a rapid appearance of a low field proton at τ 0.23. The peaks at τ 4.47 and 0.23 were shown to be due to triphenyl methane (methyne proton)[42] and O-benzylisovanillin (aldehyde proton) respectively by the peak enhancement method. Integration of these peaks soon after hydrolysis indicated that they are in the ratio of 1:2.

ii). Using 1.2 molar equivalents of trityl tetrafluoroborate.

The imine 25 b (47 mg, 0.1 mmole) was treated with trityl tetrafluoroborate (40 mg, o.12 mmole) in chloroform-d (0.5 ml). The reaction was monitored by a procedure identical to that above and showed ca. 60% hydride abstraction in 7 h.

The imine 25 b (1.17 g, 2.5 mmole) in dry CH_2Cl_2 (15 ml) was treated (in a dry box) with trityl tetrafluoroborate (1.00 g, 3.0 mmole) to obtain a clear red solution. After 14 h (ca.65% reaction by n.m.r.), it was treated with water (10ml) and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to yield a yellow gum. This was separated by p.l.c. (alumina-benzene solvent) to give triphenyl methane, (o.365 g, 60%), m.p. 92-94° (from light petroleum), m.m.p. with an authentic sample 90-92° (lit.[43], m.p. 92°), benzaldehyde(trace, isolated as the 2,4-dinitrophenyl hydrozone, m.p. and mixed m.p.[44] 237-238°), O-benzylisovanillin 22 b (0.70 g,

58%), m.p. 61° (from ether), mixed m.p. with an authentic sample 60-63°.

Reaction of the 2-Azaallenium salt (26 b) with Diazomethane [25]. — The imine 25 b (0.60 g, 1.25 mmole) in dry CH_2Cl_2 (7.5 ml) was treated (in a dry box) with trityl tetrafluoroborate (0.50 g, 1.5 mmole). After ca. 67% reaction (15 h, n.m.r. control), the solvent was evaporated and the resulting crude solid was suspended in dry THF (10 ml) and stirred at 0° under nitrogen, while dry ethereal diazomethane [45] was slowly added. After the addition was complete (30 min) the mixture was stirred for 1 h. The solvents were evaporated under reduced pressure to obtain a brown oil, the n.m.r. spectrum of which showed a complex mixture of products. There were no peaks in the region (τ 6.40-7.00) expected for the $C\underline{H}_2$ of the aziridinium salts [25].

N-(3,4-Dimethoxybenzylidene)-3-benzyloxy-4-methoxybenzyl amine (25 c). — Condensation of 3-benzyloxy-4-methoxybenzyl amine 24 b (0.522 g, 2.1 mmole) with veratraldehyde 22 d (0.356 g, 2.1 mmole) by the general method (see above), afforded the imine 25 c as colourless needles (0.740 g, 90%), m.p. 80-81° (from benzene-light petroleum), $\nu_{max.}$ (nujol) 1653 (C=N) cm^{-1}, τ ($CDCl_3$) 1.90 (1H,s,C<u>H</u>=N), 2.63-3.30 (11H,m,Ar<u>H</u>), 4.93 (2H,s,-$C\underline{H}_2O$), 5.33 (2H,s,-$C\underline{H}_2N$), 6.13 (6H,s,O<u>Me</u>), and 6.20 (3H,s,O<u>Me</u>), m/e 391 ($\underline{M}^+$), 300,256,227, and 91 (100%). [Found: C,73.85; H,6.29; N,3.49 . $C_{23}H_{25}NO_4$ requires C,73.64; H,6.44; N,3.58%].

Reaction of the imine (25 c) with Trityl Tetrafluoroborate. — In a pilot experiment the imine 25 c (78 mg, 0.2 mmole) in chloroform-d (1 ml) was treated with 1.2 molar equivalents

of trityl tetrafluoroborate (80 mg). The reaction was monitored by the n.m.r. method for the triphenyl methane (see above). Hydrolysis (D_2O) after ca.70% reaction produced two low field singlets in the n.m.r. spectrum, at τ 0.18 and 0.22. These were shown to be due to O-benzylisovanillin and veratraldehyde 22 d respectively by the peak enhancement technique. The ratio of these two aldehydes to triphenyl methane was also shown by n.m.r. to be 2:1.

The imine 25 c (0.39 g, 1 mmole) in dry CH_2Cl_2 (5 ml) was treated with trityl tetrafluoroborate (0.40 g, 1.2 mmole). After 20 h (ca.70% reaction by n.m.r.), aqueous $NaHCO_3$ solution was added and the mixture extracted with dichloromethane. The organic extracts were dried ($MgSO_4$) and evaporated to yield a yellow gum. This was separated by p.l.c. (SiO_2- CH_2Cl_2 solvent) into, (indicated in the order of increasing polarity) triphenyl methane (0.16 g, 66%), benzaldehyde (a trace, obtained as 2,4-dinitrophenyl hydrazone, m.p. 237-239°), O-benzylisovanillin 22 b (0.14 g, 60%, 2,4-dinitrophenyl hydrazone,[44] m.p. 200-201°), and veratraldehyde 22 d (0.11 g, 66%, 2,4-dinitrophenyl hydrazone, m.p. and mixed m.p.[44] 263-265°). T.l.c. [alumina/ chloroform-methanol (20:1)] of the crude mixture after hydrolysis showed the absence of any veratrylamine 24 d .

2,6-Dichlorobenzyl Bromide.— This was prepared in 80% yield by the method of Chapman and Williams[46], m.p. 54-56° (from light petroleum) (lit.[47], m.p. 55°), τ ($CDCl_3$) 2.57-3.00 (3H, m,ArH), and 5.27 (2H,s,-CH_2-Br).

O-(2,6-Dichlorobenzyl)-Isovanillin (22 c).— Isovanillin (4.0 g) was benzylated with 2,6-dichlorobenzyl bromide as above[38] to give the ether as colourless cubes (6.0 g, 73%),

m.p. 168-170° (from benzene), $\nu_{max.}$(nujol) 1679 (C=O) cm^{-1}, $\tau(CDCl_3)$ 0.08 (1H,s,CHO), 2.50-3.20 (6H,m,ArH), 4.67 (2H,s, $-OCH_2-$), and 6.13 (3H,s,OMe), m/e 312,310 (M^+), 161,159 (100%). [Found: C,57.88; H,3.80 . $C_{15}H_{12}Cl_2O_3$ requires C,57.90; H,3.89%] .

O-(2,6-Dichlorobenzyl)-Isovanillin Oxime (23 c).— A mixture of the above aldehyde 22 c (5.0 g) and hydroxylamine hydrochloride (5.0 g) in ethanol (70 ml), pyridine (20 ml) and benzene (10 ml) was refluxed on a water bath for 3 h (t.l.c. control) under nitrogen. Solvents were removed under reduced pressure and the residue triturated with cold water to yield the oxime 23 c as colourless plates (5.28 g, 100%), m.p. 182-184° (from alcohol-water), $\nu_{max.}$(nujol) 3300 (N-OH), and 1568 (C=N) cm^{-1}, m/e 327,325 (M^+), and 161,159 (100%). [Found: C,55.34; H,3.85; N,4.39; $C_{15}H_{13}Cl_2NO_3$ requires C,55.23; H,4.02; N,4.30%] .

3-(2,6-Dichlorobenzyloxy)-4-Methoxybenzylamine (24 c) Hydrochloride.— The above oxime 23 c (1.63 g) was reduced with $LiAlH_4$ (1.00 g) by the usual method[41] to obtain the amine 24 c as a yellow oil, which when treated with methanolic HCl afforded the hydrochloride as colourless needles (0.87 g, 50%), m.p. 232-234° (from methanol-ether), $\nu_{max.}$(nujol) 3400 (NH), 1599, 1591 and 1573 cm^{-1}, τ ($CDCl_3$+ D_2O + NaOH) 2.60-3.17 (6H,m,ArH), 4.70 (2H,s,$-OCH_2-$), 6.20 (3H,s,OMe), and 6.23 (2H,s,CH_2N), m/e 313,311 (M^+), 161,159, and 152 (100%). [Found: C,51.82; H, 4.83; N,3.95; Cl^- ,10.06. $C_{15}H_{15}Cl_2NO_2$.HCl requires C,51.68; H,4.63; N,4.02; Cl^- ,10.24%] .

N-[3-(2,6-Dichlorobenzyloxy)-4-methoxybenzylidene] -3-(2,6-dichlorobenzyloxy)-4- methoxybenzylamine (25 d).— Condensation of the amine 24 c (0.60 g, 1.9 mmole, liberated from above salt)

with O-(2,6-dichlorobenzyl) isovanillin 22 c (0.59 g, 1.9 mmole) by the general method (see above) afforded the imine 25 d as colourless rosettes (1.04 g, 90%), m.p. 154-156° (from benzene-light petroleum), $\nu_{max.}$ (nujol) 1640 (C=N), 1590 and 1580 cm^{-1}, τ ($CDCl_3$) 1.70 (1H,s,CH=N), 2.27-3.17 (12H,m,ArH), 4.63 (4H,s,-OCH_2-), 5.27 (2H,s,-CH_2N-), and 6.17 (6H,s,OMe), m/e 605 (M^+), 571 and 569, 470, 446 and 444, 297 and 295 (100%), 261, 180, 161 and 159, [Found; C, 59.45; H, 4.33; N, 2.32; Cl, 22.85. $C_{30}H_{25}Cl_4NO_4$ requires C, 59.53; H, 4.16; N, 2.31; Cl, 22.42%].

1,3-Di-[3-(2,6-dichlorobenzyloxy)-4-methoxyphenyl]-2-azaallenium Tetrafluoroborate (26 d).— A pilot reaction of the imine 25 d (121 mg, 0.2 mmole) with trityl tetrafluoroborate (80 mg, 0.24 mmole) in chloroform-d (0.5 ml) by the usual n.m.r. method (see above) indicated ca. 70% hydride abstraction in 13 h.

The imine 25 d (0.48 g, 0.8 mmole) in dry CH_2Cl_2 (2 ml) was treated (in a dry box) with trityl tetrafluoroborate (0.32 g, 0.96 mmole) to obtain a greenish yellow solution. This, on standing for 3 days, deposited a bright yellow solid which was washed with dry dichloromethane to afford a pale yellow crystalline solid (0.15 g, 28%), m.p. 173-178° (decomp.), $\nu_{max.}$ (nujol) 1910 (C=$\overset{+}{N}$=C), 1665 (C=O, hydrolysis product), and 1600 cm^{-1}. [Found: C, 48.65; H, 3.67; N, 1.61. $C_{30}H_{24}Cl_4NO_4BF_4\frac{1}{2}CH_2Cl_2$ requires C, 49.94; H, 3.44; N, 1.91%]. The supernatant liquid was chromatographed over a small alumina (Grade III) column to obtain triphenyl methane as a colourless solid (120 mg, 61%). T.l.c. of the supernatant liquid also showed the aldehyde 22 c and traces of the amine 24 c and

triphenyl carbinol and also the absence of any 2,6-dichlorobenzaldehyde. The solid 26 d (120 mg) was dissolved in CH_2Cl_2-MeOH. T.l.c. of this showed two compounds, which were separated by p.l.c. (SiO_2-CH_2Cl_2 solvent). The faster running compound was identified (m.p., t.l.c., and n.m.r.) as O-(2,6-dichlorobenzyl)isovanillin 27 c (58 mg, 54%). The lower band was obtained as a pale yellow amorphous solid (56 mg, 52%). On t.l.c. this was found to undergo partial hydrolysis to give a spot corresponding to above aldehyde. Hence it was suspected to be the aldemine 36 . A portion (ca. 10 mg) of this was boiled briefly with methanolic aqueous HCl (6 N) basified ($NaHCO_3$) and extracted with CH_2Cl_2. Evaporation of the dried ($MgSO_4$) organic phase yielded O-(2,6-dichlorobenzyl)-isovanillin (identified by t.l.c. and mass spectrum). The second portion (40 mg) in MeOH (1.5 ml) was treated with $NaBH_4$ (50 mg). After 14 h the methanol was evaporated, water was added and the solution extracted with ether. The organic layer was dried ($MgSO_4$), and evaporated to yield a yellow gum. Addition of methanolic HCl followed by ether, precipitated the amine 29 c hydrochloride as colourless needles (8 mg), m.p. and mixed m.p. 230-231°.

Fluorenone Oxime. — This was prepared by the conventional procedure[40] from fluorenone (4.0 g), hydroxylamine hydrochloride (4.0 g) in ethanol (65 ml) and pyridine (16 ml). Fluorenone oxime was obtained as yellow needles (3.9 g, 90%), m.p. 195-196° (from benzene) (lit.[48a], m.p. 195°), m/e 195 (M^+, 100%), 178, 165 and 151.

9-Fluorenylamine (41) Hydrochloride. —The foregoing oxime (2.0 g) was reduced with $LiAlH_4$ (1.0 g) in THF (40 ml) by

the reported method[41] to obtain the crude amine 35 as an orange oil. Treatment with methanolic HCl and trituration with ether afforded the title compound as pale yellow needles (2.3 g, 100%), m.p. 250-253° (from methanol-ether) (lit.[48c], m.p. 255°).

9- Fluorenylidenaminofluorene (31).— 9-Fluorenylamine (1.8 g, 10 mmole, liberated from above HCl salt with aq. NaOH) was condensed with fluorenone (1.8 g, 10 mmole) by the general method. After 3 days (t.l.c. control) the benzene was evaporated and the resulting gum was triturated with light petroleum to afford 31 as a pale yellow powder (1.84 g, 54%), m.p. 190-191° (from benzene-light petroleum) (lit.[48c], m.p. 179-182°), ν_{max} (nujol) 1630 (C=N) and 1600 cm^{-1}, m/e 343($M^{+\cdot}$), 180 and 165 (100%).

Difluorenylideneammonium Tetrafluoroborate (32).— 9-Fluorenylidenaminofluorene 31 (186 mg, 0.54 mmole) in dry dichloromethane (1 ml) was treated (in a dry-box) with trityl tetrafluoroborate (360 mg, 1.1 mmole). After 3 days the solvent was evaporated to yield a red crystalline mass, ν_{max} (nujol) 1880 ($C=\overset{+}{N}=C$). Attempted recrystallisation from CH_2Cl_2 - Et_2O afforded orange needles of crude fluoren-9-iminium tetrafluoroborate 33 (70 mg, 48%), m.p. 230-240° (decomp.). Treatment of a portion of this with aq. $NaHCO_3$ gave fluoren-9-imine 35 as a pale yellow amorphous solid, m.p. 120-124° (lit.[49], m.p. 123-124°). The above orange solid 33 (30 mg) was dissolved in absolute MeOH (1 ml) and treated with $NaBH_4$ (50 mg) for 15 h, after which the solvent was evaporated. The pale yellow solid thus obtained was treated with water and extracted into ether. Ether extracts were dried ($MgSO_4$) and evaporated to

yield a yellow oil, which when treated with methanolic HCl afforded pale yellow needles (10 mg) of 9-fluorenylamine 35 HCl, m.p. and mixed m.p. 248-253°, (lit.[49b], m.p. 255°). Brief acid (aq. HCl) treatment of above crude fluoren-9-iminium tetrafluoroborate (27 mg) in MeOH yielded fluorenone 34 (11 mg, 61%). The mother liquors from above recrystallisation afforded triphenylmethane (61 mg, 46%) and 34 (44 mg).

REFERENCES

1 C.L. Stevens, and J.C. French, J. Amer. Chem. Soc., 1954, 76, 4398.

2 C.L. Stevens, R.C. Freeman, and K. Noll, J. Org. Chem., 1965, 30, 3718.

3 A.I. Meyers, and J.C. Sircar in ' The Chemistry of the Cyano group', Ed. by Zvi Rappoport, Interscience, London, 1970, p. 350.

4 A. Padwa, and J. Smolanoff, Chem. Comm., 1973, 342.

5 C.G. McCarty in ' The Chemistry of the Carbon-nitrogen double bond' Ed. by S. Patai, Interscience, London, 1970, p. 406.

6 D.Y. Curtin, E.J. Grubbs, and C.G. McCarty , J. Amer. Chem. Soc., 1966, 88, 2775.

7 J. Hine, J. Amer. Chem. Soc., 1963, 85, 3239.

8 H. Ahlbrect, and S. Fischer, Tetrahedron, 1973, 29, 659.

9 W.A. Slusarchyk, H.E. Applegate, P. Funke, W. Coster, M.S. Puar, M. Young, and J.E. Dolfini, J. Org. Chem., 1973, 38, 943.

10 L.D. Cama, and B.G. Christensen, Tetrahedron Letters, 1973, 3505.

11 P.G. Gassman, D.K. Dygos, and J.E. Trent, J. Amer. Chem. Soc., 1970, 92, 2084.

12 M.P. Doyle, M.A. Zaleta, J.E. De Boer, and W. Wierenga, J. Org. Chem., 1973, 38, 1663.

13 A. Schmidt, Chem. Ber., 1972, 105, 3050.

14 C.D. Nenitzescu, in ' Carbonium Ions', Eds., G.A. Olah and P.V.R. Schleyer, Wiley-Interscience Publishers, 1970, Vol. 2, p. 484.

15 H.J. Dauben Jr., F.A. Gadecki, K.M. Harmon, and D.L. Pearson, J. Amer. Chem. Soc., 1957, 79, 4557.

16 P.D. Bartlett, and J.D. McCollum , J. Amer. Chem. Soc., 1956, 78, 1441.

17 H. Meerwein, V. Henerick, H. Morshel, and K. Wunderlich, Ann., 1960, 635,1.

18 D.H.R. Barton, P.D. Magnus, G. Smith, and D. Zurr, Chem. Comm., 1971, 861.

19 R. Damico, and C.D. Broaddus, J. Org. Chem., 1966, 31, 1607.

20 H. Volz, and H.H. Kiltz, Tetrahedron Letters, 1970, 1917.

21 R.B. Moffett, Org. Synth., Coll. Vol. 4, 1963, 605.

22 M. Gomberg, J. Amer. Chem. Soc., 1913, 35, 200.

23 N.J. Leonard, and J.A. Klainer, J. Heterocycl. Chem., 1971, 8, 215.

24 H.W. Whitlock Jr., J. Amer. Chem. Soc., 1962, 84, 2807.

25 T.R. Keenan, and N.J. Leonard, J. Amer. Chem. Soc., 1971, 93, 6567.

26 R.L. Reeves, in 'The Chemistry of the Carbonyl group' Ed. S. Patai, Wiley Interscience Publishers, London, 1966, p. 610.

27 J.H. Wotoz, and D.E. Mancuso, J. Org. Chem., 1957, 22, 207.

28 L.J. Bellamy, 'The Infrared Spectra of Complex Molecules', Methuen & Co. Ltd., London, 1958, p. 61.

29 E. Lieber, C.N.R. Rao, T.S. Chao, and C.W.W. Hoffman, Analyt. Chem., 1957, 29, 916.

30 G.D. Meakins, and R.J. Moss, J. Chem. Soc., 1957, 993.

31 L.J. Bellamy, 'Advances in Infrared Group Frequencies', Methuen & Co. Ltd., London, 1968, p. 64.

32 H. Hoyer, Chem. Ber., 1956, 89, 2677.

33 P. Kristiān, S. Kovāč, and K. Antoš, Coll. Czech. Chem. Comm., 1964, 29, 2509.

34 S. Otsuka, A. Nakamura, and T. Yoshida, J. Organometallic. Chem., 1967, 7, 339.

35 H.J. Deuben, Jr., L.R. Honnen, and K.M. Harmon, J. Org. Chem., 1960, 25, 1442.

36 R.E. Jorday, and H. Adkins, J. Amer. Chem. Soc., 1955, 77, 4559.

37 G. Olah, and P. Krüenbühl, J. Amer. Chem. Soc., 1967, 89, 4756.

38 R. Robinson, and S. Sugasawa, J. Chem. Soc., 1931, 3163.

39 K.W. Merz, and J. Fink, Arch. Pharm., 1956, 289, 347.

40 D.J. Pasto, and C.R. Johnson, 'Organic Structure Determination', Prentice-Hall, 1969, p. 391.

41 M.E. Rafelson, Jr., G. Ehrensvard, M. Bashford, E. Saluste, and C.G. Heden, J. Biol. Chem., 1954, 211, 725.

42 H.A. Szymanski, and R.E. Yelin, 'NMR Band Hand-Book', IFI/Plenum, N.Y., 1968, p. 244.

43 L.C. Anderson, J. Amer. Chem. Soc., 1928, 50, 208.

44 D. Johnson, J. Amer. Chem. Soc., 1953, 75, 2720.

45 F. Arndt, 'Organic Syntheses', Collect. Vol. II, Wiley, New York, N.Y., 1943, p. 165.

46 N.B. Chapman, and J.F.A. Williams, J. Chem. Soc., 1952, 5044.

47 V.F. Krohnke, and K. Ellegast, Ann. Chim. (France), 1956, 600, 176.

48a I. Heilbron, 'Dictionary of Organic Compounds'. Vol. 3, 1965, p. 1441.

b ibid. Vol. I, 1965, p. 133.

c Chem. Abs., 1965 , 62, 14593c.

49 J.P. Anselme, Org. Prep. Proced., 1969, 1, 201.