NEW APPROACHES TO HETEROCYCLES VIA NITRENES

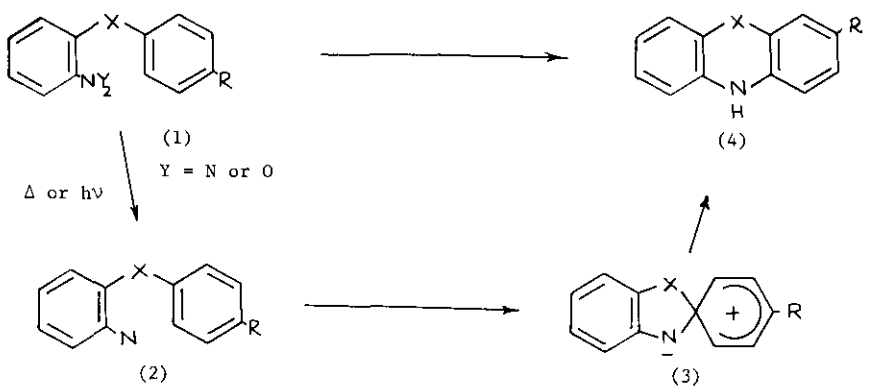
Otto Meth-Cohn

Department of Chemistry & Applied Chemistry, The Ramage Laboratories,

University of Salford, Salford M5 4WT, England

Nitrenes derived from 2-azidophenyl aryl sulphides, 2-azidophenyl aryl ketones, aryl 2-azidobenzoyl esters and aryl or arylalkyl azidoformates have been cyclised to yield a wide variety of novel heterocycles.

In 1968, two classical and important nitrene-mediated cyclisations[1,2] were shown to involve a novel rearrangement which pointed to a spirodiene intermediate such as (3; Scheme 1).[3,4]



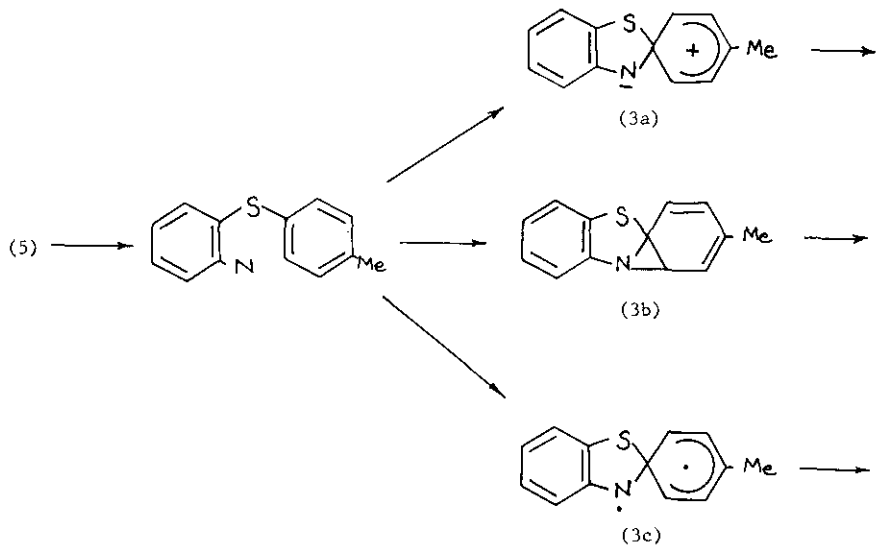
Scheme 1

The formation of phenothiazines (4; X=S) was thoroughly studied, particularly by Cadogan's group, who noted some fascinating substituent effects leading to a variety of heterocycles.[5]

As part of our extended studies on the chemistry of singlet and triplet arylnitrenes[6] we examined this reaction under various conditions (Scheme 2). Surprisingly, both singlet- and triplet-promoting conditions favoured the reaction suggesting a unique equilibrium in the intermediate spirodiene (Scheme 2). Indeed using hot photolysis conditions gave twice the best yield previously observed for this reaction. Applying the same methods to the corresponding

(5) (6)

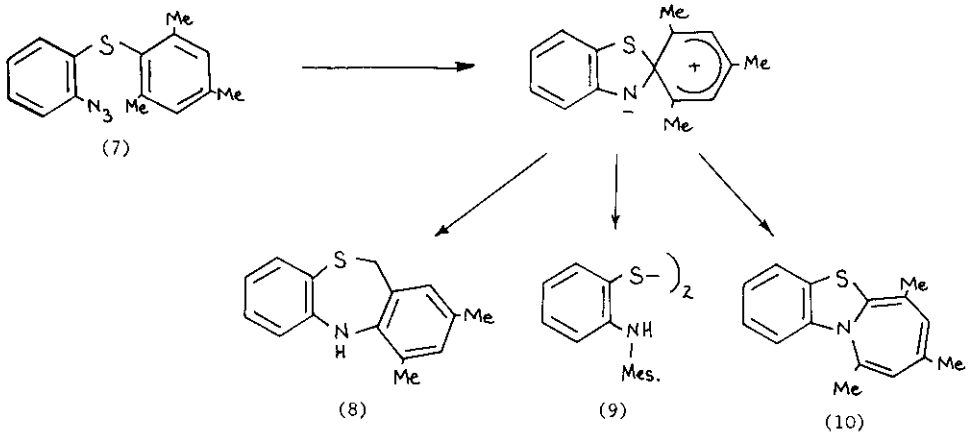
Method	%
Δ, decalin	33 (Cadogan et al.[5])
Δ, PhBr	34
hν, CH_2Cl_2	7
hν, CH_2Cl_2, pyrene	15
hν, PhAc, 20°	0
hν, PhAc, 107°	69



(3a) (3b) (3c)

Scheme 2

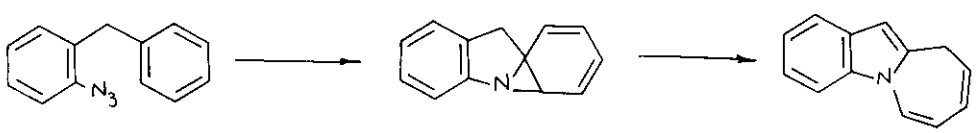
mesitylsulphide (7) revealed related trends in that both singlet and triplet nitrenes gave similar products (Scheme 3). However as well as the products noted by Cadogan (8 and 9) the interesting azepinobenzothiazole (10) was also isolated, reasonably derived from an intermediate of the (3b) type by electrocyclic ring expansion. Other workers have noted a related process with 2-azido-diphenylmethanes (Scheme 4).[7] We have found that a chloro group para to the azide function often optimises the yield of reactions involving either singlet and triplet nitrenes. This proved to hold true in this reaction also (Scheme 5).



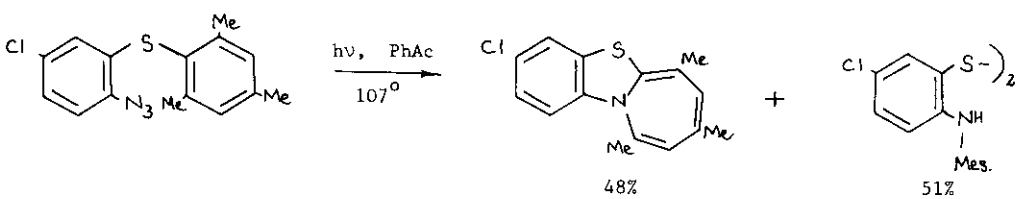
(7) (8) (9) (10)

Method	%	%	%
Δ, decalin, 180°	45	33	-
Δ, PhBr, 154°	50	17	6
hν, PhAc, 15°	0	28	20
hν, PhAc, 107°	14	45	20
hν, CH_2Cl_2 + pyrene, 15°	2	17	11

Scheme 3



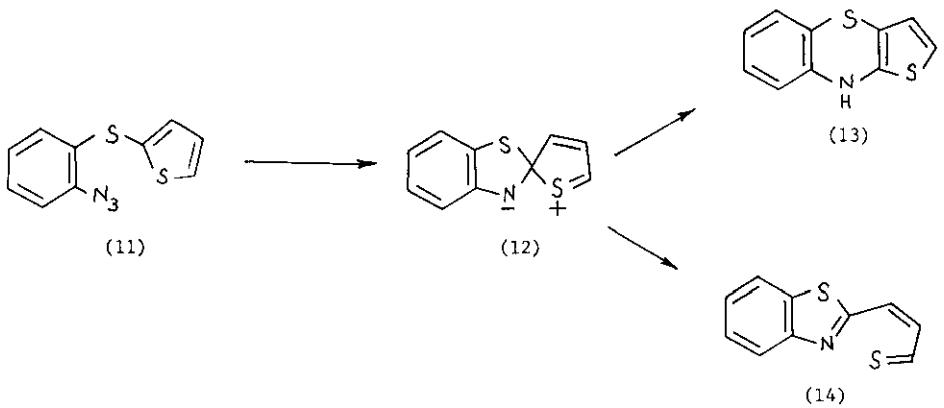
Scheme 4



48% 51%

Scheme 5

It is evident that if such spiro-intermediates as (3) are involved in these rearrangements, their further chemistry could be dramatically altered by use of hetero-substituted analogues (Scheme 6). Thus, the thienyl sulphide (11) would give rise to a spiro-ortho-ester (12) which



(11) (12) (13) (14)

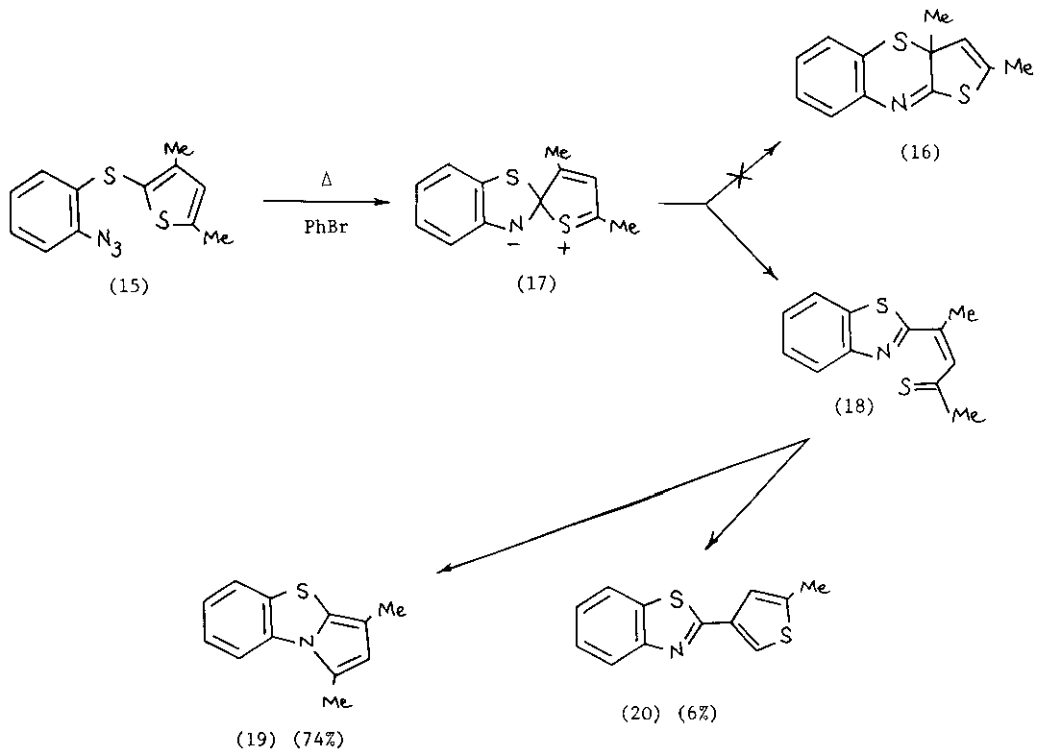
Scheme 6

could potentially yield a thio-aldehyde (14) alternative to the thienobenzothiazine (13). The thieno-sulphides indeed revealed some interesting new chemistry,[8] which is best exemplified by the dimethyl derivative (15).

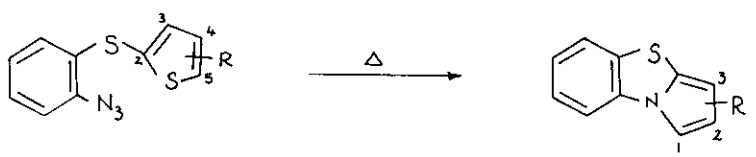
Thienothiazine (16) formation was totally supressed in favour of two benzothiazoles (19 and 20) derived by further cyclisation of the thioketone (18), which in turn was formed by the ring-opening of the spirodiene (17) (Scheme 7). (Recently Jones has isolated a thioketone from a related type of reaction.[9]) Once again both singlet and triplet nitrene pathways gave the same products though in varying ratio. The formation of pyrrolobenzothiazoles is a general reaction which proceeds the more effectively the greater the number of methyl substituents on the thiophen ring (Scheme 8). The parent 2-azidophenyl 2-thienyl sulphide as well as its 3-thienyl analogue gave mainly a purple polymer under these conditions which possibly arose from an o-quinonoid intermediate.

Rather surprisingly, the 3-thienyl sulphide (21) did not yield the expected thienothiazine (22) but 2-methylbenzothiazole (30%) together with hydrogen sulphide and considerable tar formation, for which a rationalisation is presented in Scheme 9.

We next examined the corresponding benzothiophens[10] wherein ring-fusion could influence the balance between thiazine and thiazole formation significantly, since a quinonoidal spiro-intermediate would be involved (Scheme 10). Indeed the 2-azidophenyl 2-benzothienyl sulphide (23) gave almost equal quantities of the two products (Scheme 10), the latter product being isolated as

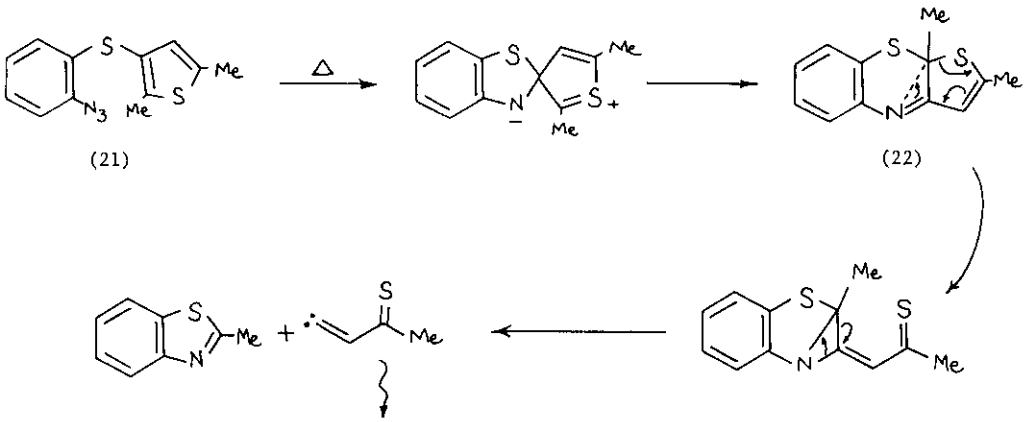


Scheme 7



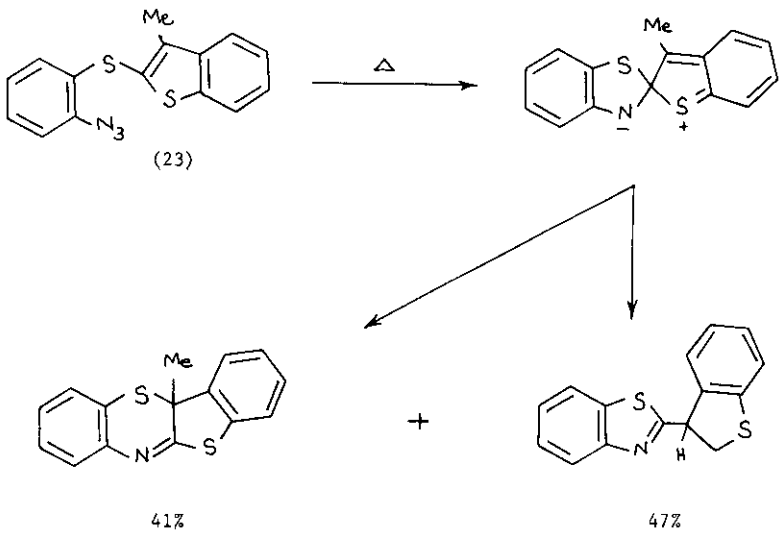
		%
R=H	R=H	23
R=3-Me	R=3-Me	65
R=5-Me	R=1-Me	65
R=3,5-Me_2	R=1,3-Me_2	74

Scheme 8



(21) (22)

Scheme 9



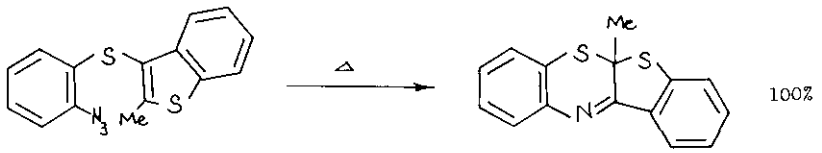
(23)

41% 47%

Scheme 10

its dihydro-derivative. Dihydrothiophens aromatise much more readily than their benzo-fused analogues (cf. Scheme 7). On the other hand the isomeric azide (24) gave solely a thiazine in quantitative yield (Scheme 11).

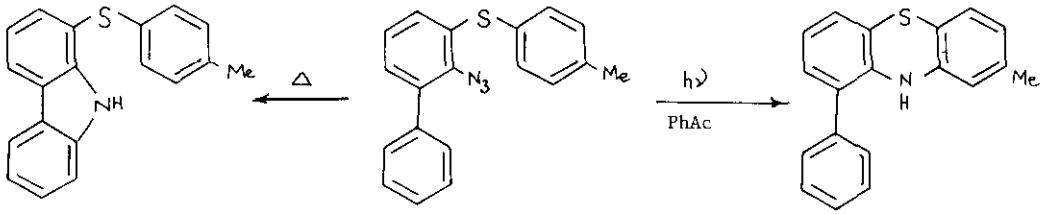
The formation of carbazoles from 2-azidobiphenyls and of phenothiazines from 2-azidophenyl phenyl sulphides probably constitute the most important and synthetically most useful syntheses



(24)

Scheme 11

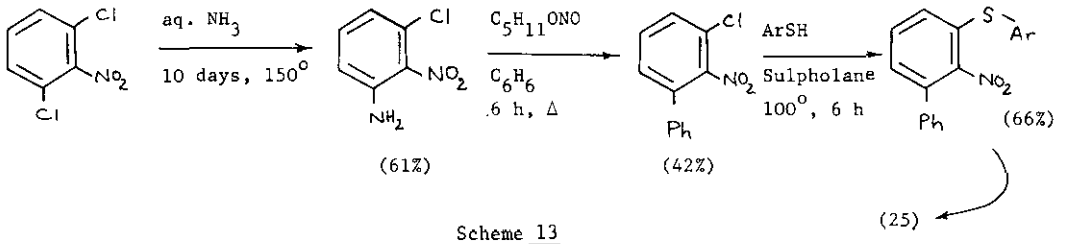
from aryl azides.[11] We next chose to examine a system in which choice between carbazole and phenothiazine formation was presented (Scheme 12).



(26) (25) (27)

Scheme 12

The required azide was synthesised by standard means (Scheme 13) and on thermolysis gave solely the carbazole (26). This was unequivocally demonstrated by desulphurisation of this



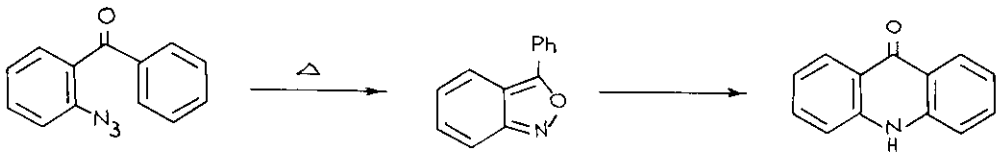
(61%) (42%) (25)

Scheme 13

product with Raney nickel, when carbazole was isolated. We have proved elsewhere that carbazole formation is exclusively a singlet nitrene pathway. Thus photolysis in acetophenone at 95° allowed the alternative route to be followed giving the phenothiazine (27). In this case desulphurisation was not helpful, giving only polymeric material, but spectroscopic data (m.s., i.r., n.m.r.) strongly supported this structure.

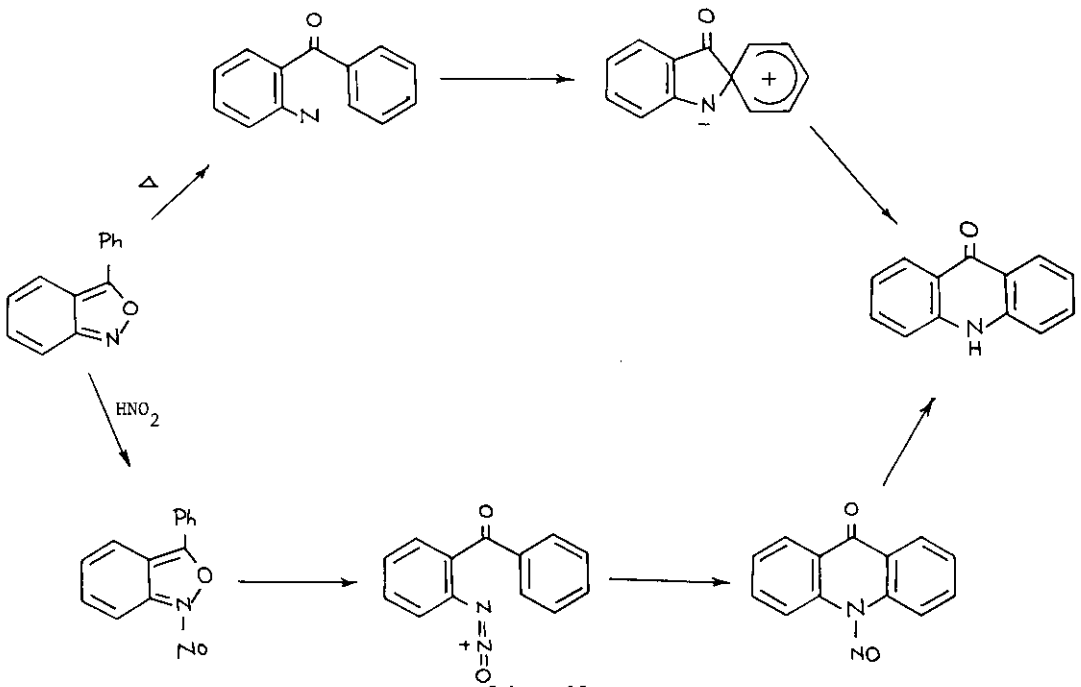
Our next study constituted one of the oldest arylnitrene-mediated cyclisations known,[1]

the conversion of 2-azidobenzophenones successively into benzisoxazoles ('anthranils') and acridones (Scheme 14). The first step does not involve a nitrene[12] but the second thermally



Scheme 14

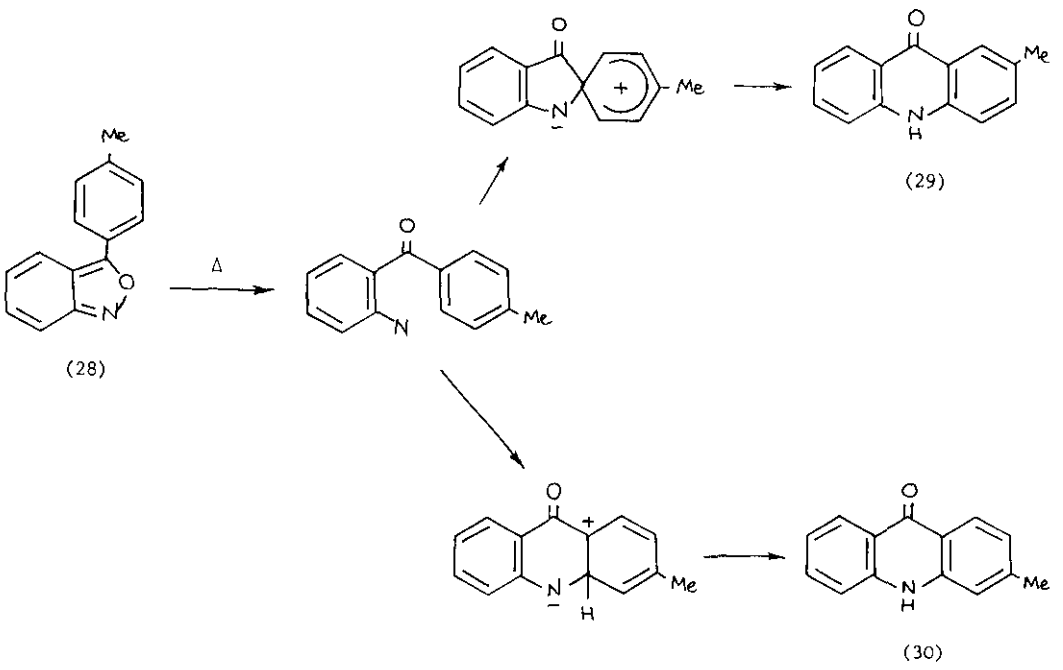
induced rearrangement step does.[13] Within a few months in 1909 the conversion of anthranils into acridones by the action of either heat[1] or nitrous acid[14] was demonstrated. The former process was later shown to involve rearrangement analogous to the phenothiazine formation, implicating a spirodiene intermediate again (Scheme 15), although some 'unrearranged' acridone was also noted in one case.[4]



Scheme 15

We first checked the possible role of a spirodiene in both of these reactions, using 3-(p-tolyl) anthranil (28). While 2- and 3-methyl acridone (29 and 30, respectively) are difficult to separate or analyse when admixed, the corresponding N-methyl derivatives readily separate on

column chromatography. We found that while with the thermal reaction a mixture of pathways was followed (Scheme 16) with nitrous acid solely the 'unrearranged' product (30) was formed.[15] The



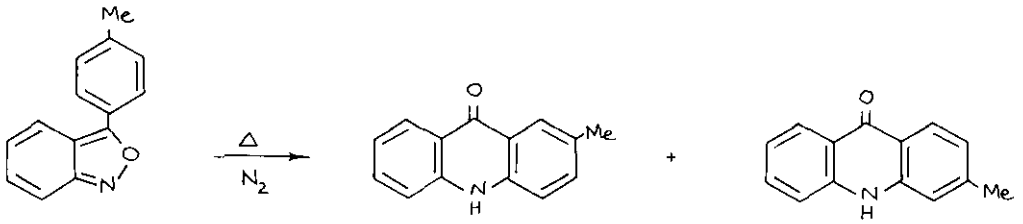
Scheme 16

ratio of acridone isomers in the thermal process was dependent upon both temperature and substituent. Moreover a fascinating sensitivity of the reaction to catalysts was also discovered.

The influence of temperature on the ratio of 2- and 3-methyl acridones formed by thermolysis of the anthranil (28) is shown in Scheme 17. It is evident that 'direct' substitution dominates at higher temperature (i.e. is thermodynamically favoured) while spiro attack is the kinetically preferred pathway. Catalysts have little influence on this ratio.

Unlike the 4-methylphenyl anthranil (28) the 2,4-dimethyl- and 2,4,6-trimethyl-derivatives showed no evidence of 'direct' substitution by the nitrene (Schemes 18 and 19). Clearly ipso attack is more attractive in these more electron-rich analogues. However, they reveal some fascinating reactivity. 2,4-Dimethylacridone (31) was unambiguously synthesised by a classical Ullmann synthesis to verify the structure of the spiro-derived products in Schemes 18 and 19. Also the 2,4,10-trimethylacridone (34) [derived probably by intermolecular methylation of the collapsed intermediate from (36)] was also synthesised by N-methylation of the 2,4-dimethyl-acridone. 2,4,5-Trimethylacridone is best considered to form by two consecutive [1,5] methyl

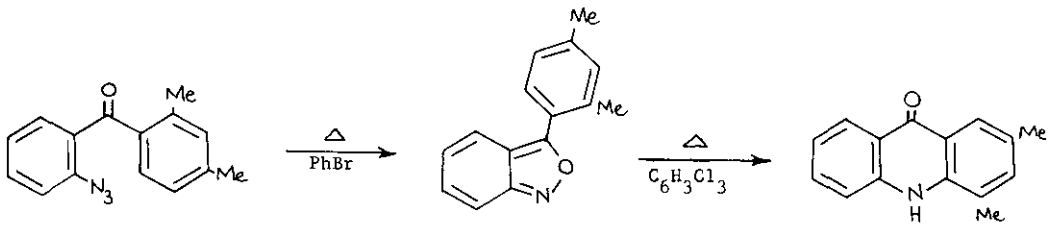
shifts (Scheme 20).



(28) (via 'spiro') (29) (via 'direct') (30)

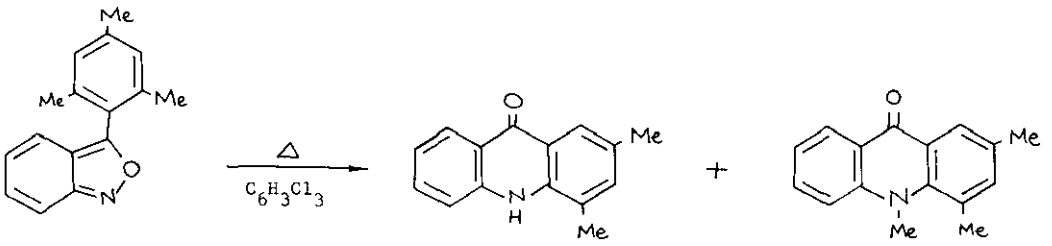
Conditions*	Total Yield Acridone (%)	Ratio (29)/(30)	Other Products
214°, neat, 24 h	55	2.14	amine 30%
280°, neat, 0.5 h	48	2.06	amine 9%
350°, neat, 5 min	53	4.715	amine 12%
214°, TCB, 24 h	71	0.57	amine 16%
214°, TCB, 4 h, Fe	84	0.695	amine 14%

Scheme 17

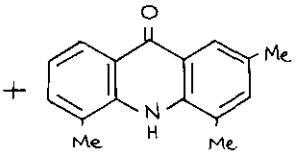


(84%) (31) (64%)

Scheme 18

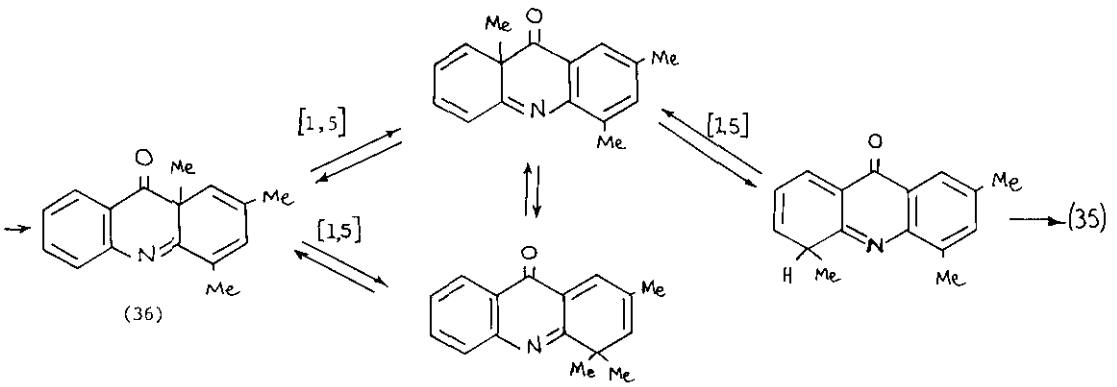


(32) (33) (68%) (34) (7%)



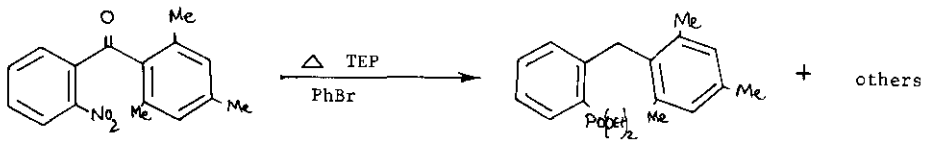
(35) (21%)

Scheme 19



Scheme 20

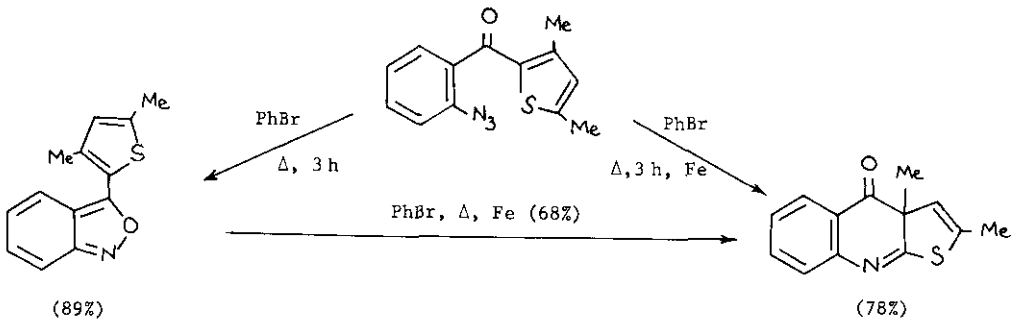
Interestingly, deoxygenation of 2-nitrophenyl mesityl ketone (37) gave the phosphonate (38) as the major product as well as the anthranil (32; 26%), the 2,4-dimethylacridone (31; 6%) and 2-aminophenyl mesityl ketone (8%) (Scheme 21). A nucleophilic substitution of the nitro group by



Scheme 21

phosphite is evident.[16]

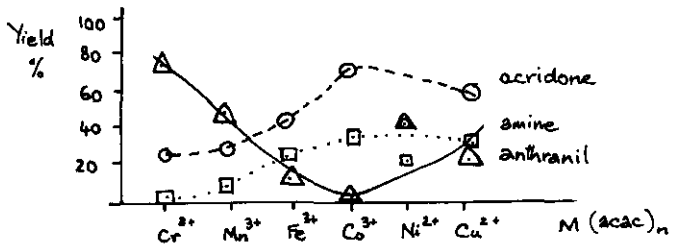
However, the most interesting feature of these anthranil→acridone rearrangements lay in their sensitivity to metal catalysis, found accidentally during some puzzling attempts to repeat an anthranil synthesis (Scheme 22). Adventitious traces of iron (from a previous reduction in the



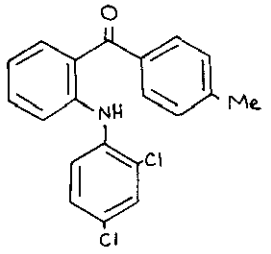
Scheme 22

same flask) totally altered the course of an anthranil synthesis whereby the thienoquinolone was exclusively formed, evidently by way of the anthranil.

We have tested numerous catalysts and find a remarkable diversity of results in the conversion of anthranils to acridones. Taking 4-methylphenylanthranil (28) as our test case (heating for 4 h in refluxing trichlorobenzene) aluminium acetylacetonate proves the most clean and efficient catalyst, giving an 84% yield of acridone admixed with some aminobenzophenone (a probable triplet nitrene derived product). Without catalyst only a 13% yield of acridone resulted the rest of the anthranil being recovered. Transition metals were of variable effect, an interesting trend being noted in the first transition series (Graph) with cobalt tris-(acetylacetonate) giving the best results. Catalytic efficiency would seem to be related to complex

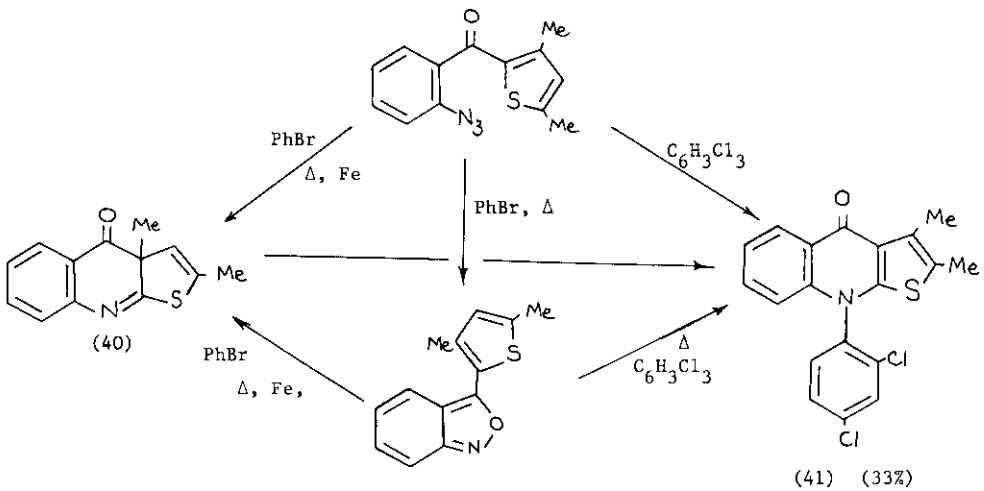


stability since the iron and cobalt complexes are known to eliminate acetylacetone below 200° giving coordinately unsaturated metal derivatives. The yield of amine would likely reflect the strength of the nitrene-metal bond since the stronger the bond the more likely the nitrene would be to drop into its triplet state rather than cyclise to an acridone. Heavy metal catalysts [$Rh_2(OAc)_4$, $UO_2(OAc)_2$, $Th(OAc)_4$, $Eu(fod)_3$] were generally less efficient. Coordinately unsaturated metals, and metal powders were however powerful catalysts, but again gave lower acridone yields at the expense of amine formation. Copper powder and nitrato bis(triphenylphosphine) copper (a coordinately unsaturated copper (I) derivative bearing an easily removed nitro group) also yielded a third product (39) apparently an 'Ullmann product' since blank experiments with the amine in trichlorobenzene gave the same compound in low yield.



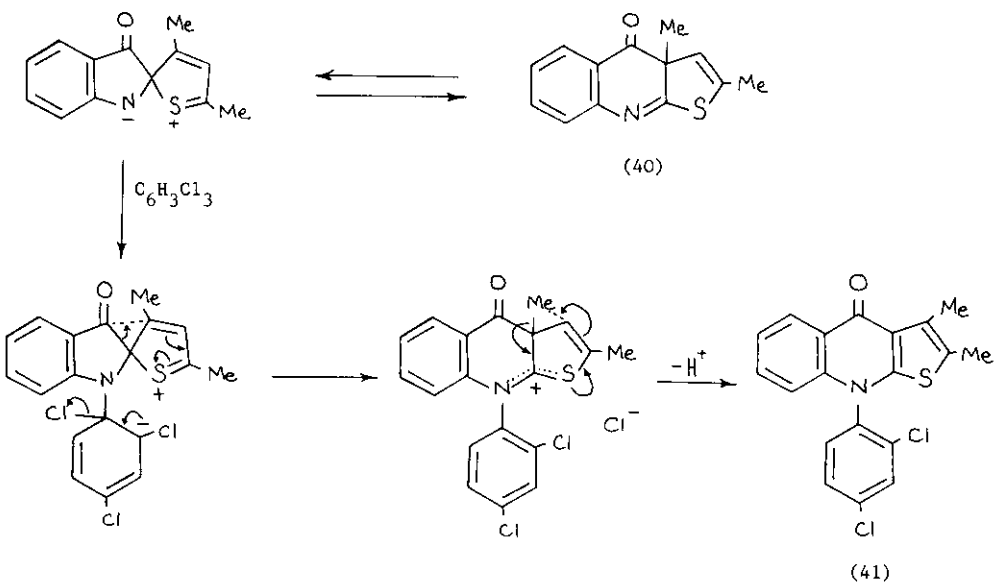
(39)

The thienylanthranils were also of some interest as briefly noted earlier (Scheme 22). Unlike decompositions in bromobenzene, those in trichlorobenzene took an unexpected turn, the primary product (41) being derived by further solvent attack (Scheme 23). This product was formed even more efficiently from the precursor azide (47%) and less so from the thienoquinolone (40; 18%). Thus from the one azide under slightly variable conditions of thermal decomposition, three totally



Scheme 23

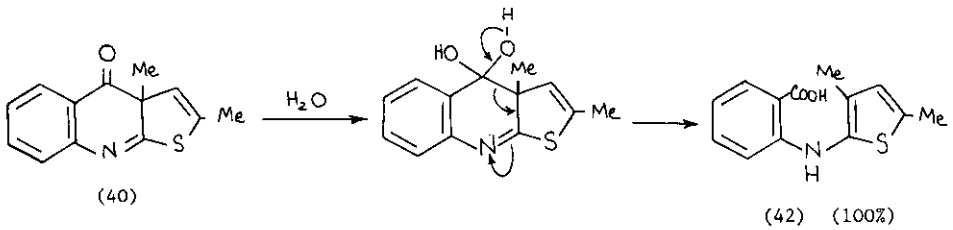
different products ensued! We explain these results as in Scheme 24 in which the unstable thienoquinolone is in thermal equilibrium with a spiro-intermediate, which, we believe



Scheme 24

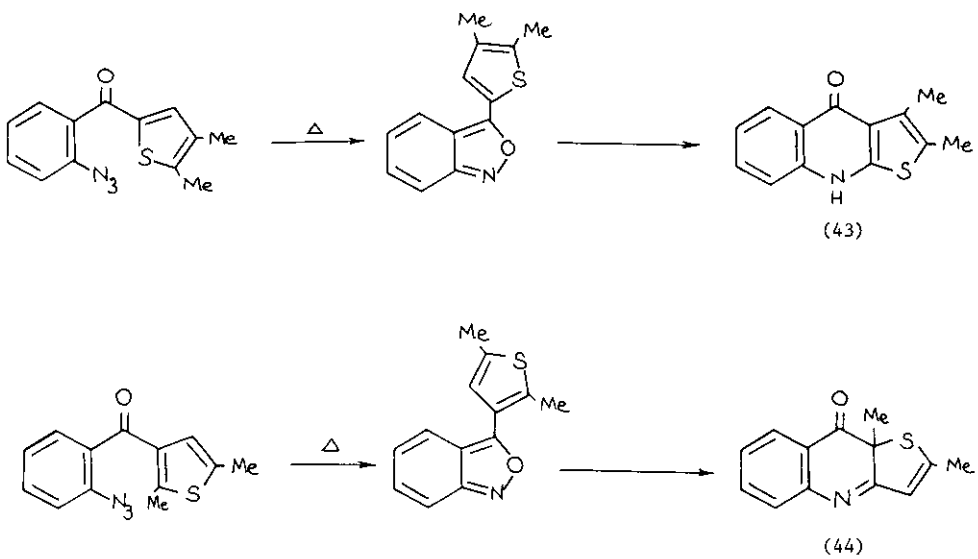
nucleophilically substitutes the solvent. That the electrophilic nitrene is not the active principle is revealed by the lack of substitution of dimethylaniline or p-dimethoxybenzene, both known to undergo such attack.[17] However, neither 1,2-dichlorobenzene or p-fluoronitrobenzene underwent substitution either. The instability of the thienoquinolone is further underlined by

its ready hydrolysis in moist air (or more efficiently in aqueous ethanolic alkali to the anthranilic acid (42; Scheme 25).



Scheme 25

Two other analogous azides were similarly examined (Scheme 26). The first gave a thienoquinolone (43) which we hoped would allow an unambiguous synthesis of the corresponding

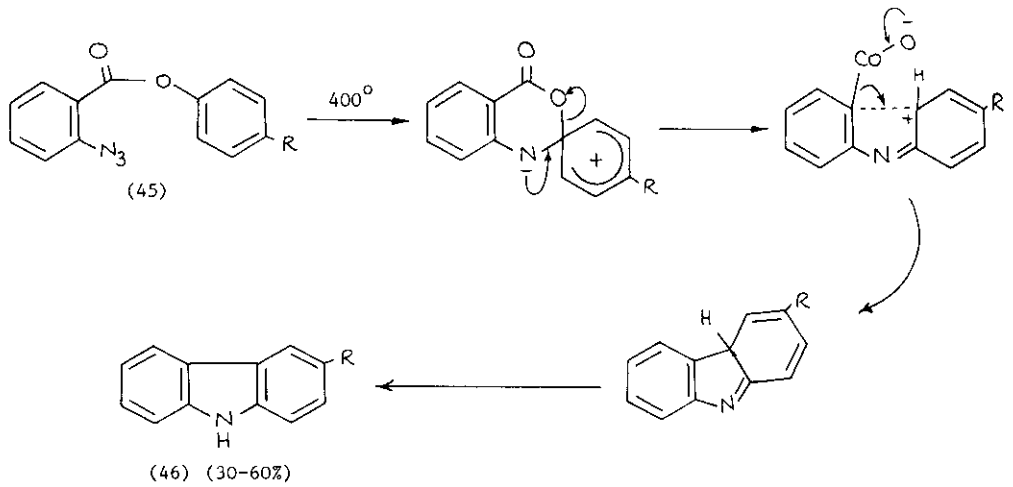


Scheme 26

N-(dichlorophenyl) derivative (41) by an Ullmann reaction with 2,4-dichloroiodobenzene - not realised even using the new powerful Rieke copper.[18] The second was of note in that the product indicated that rearrangement from the spiro-intermediate preferably proceeded to a blocked thiophen α-position than an unblocked β-position! Once again no 'direct' attack was noted.

Finally to add cream to an already overich cake, two new areas of development must be briefly noted. All the chemistry to date involving spiro-intermediates has involved 5-membered ring formation. We have commenced a study of analogues with potential 6-membered

spiro-rings as intermediates. Although first attempts at thermal decomposition in solution proved abortive, vapour phase thermolysis of the readily available azido-esters (45) gave carbazoles (46) in reasonable yields. Not only is this a valuable ready source of carbazoles which obviates the need for inaccessible biphenyls and diphenylamines, but it is fascinating from a mechanistic viewpoint since once more a rearrangement involving a spiro-intermediate is again evident. Of several explanations possible we currently favour that shown in Scheme 27.



Scheme 27

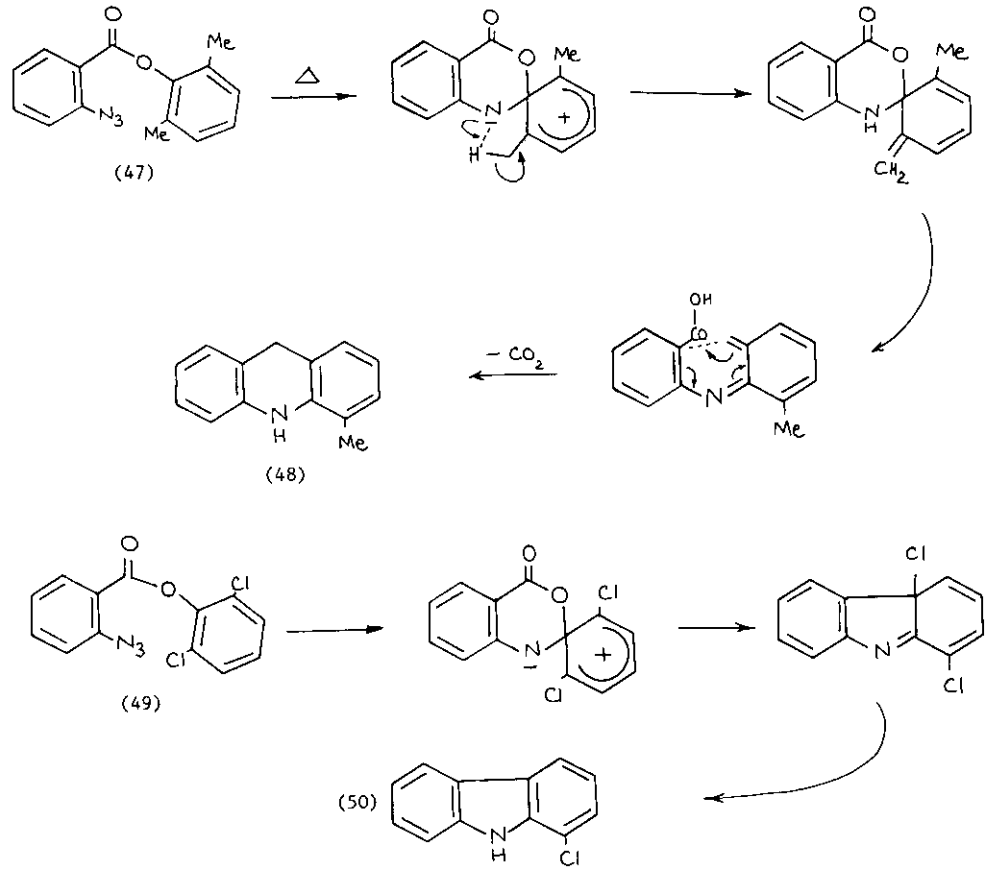
Interestingly, the ortho-blocked esters (47 and 49) also react analogously giving an acridan (48) (oxidised to the acridine on work-up) and a further rearranged 1-chloro-carbazole (50) respectively (Scheme 28).

The last examples deviate slightly from the pattern since they involve carbonyl azides rather than aryl azides. It is known that azidoformates readily attack aliphatic and aromatic solvents by insertion and azepine formation respectively.[19] Furthermore, in the vapour phase intramolecular insertion has been noted (Scheme 29).[20] We have observed three types of insertion during vapour phase pyrolysis of azidoformates.

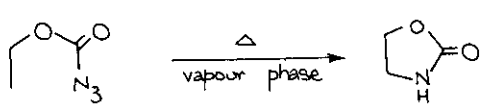
(a) Aryl azidoformates

Aryl azidoformates yield benzoxazolones without rearrangement and in good yield, i.e. no 4-membered spiro-intermediate interposes (Scheme 30). Not only is this a valuable o-amino-phenol synthesis but it has some novel and valuable features. Thus α-naphthyl azidoformate (51) is potentially capable of giving a 1,2- (53) or 1,8-substitution product (52) (Scheme 31). It is evident considering the intermediates that 1,8-attack should be preferred and this is indeed the case! We are currently developing this intriguing peri-substitution.

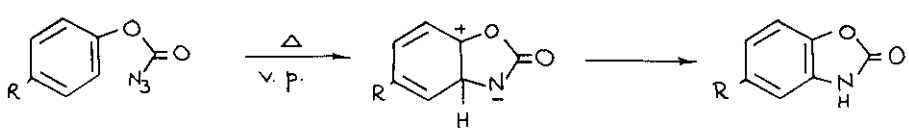
Ortho-blocked aryl azidoformates also produce fascinating chemistry (Scheme 32).



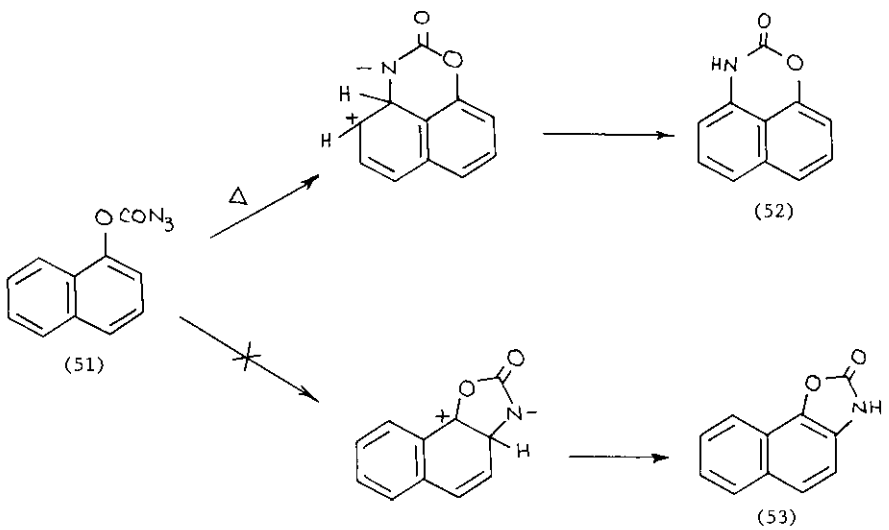
Scheme 28



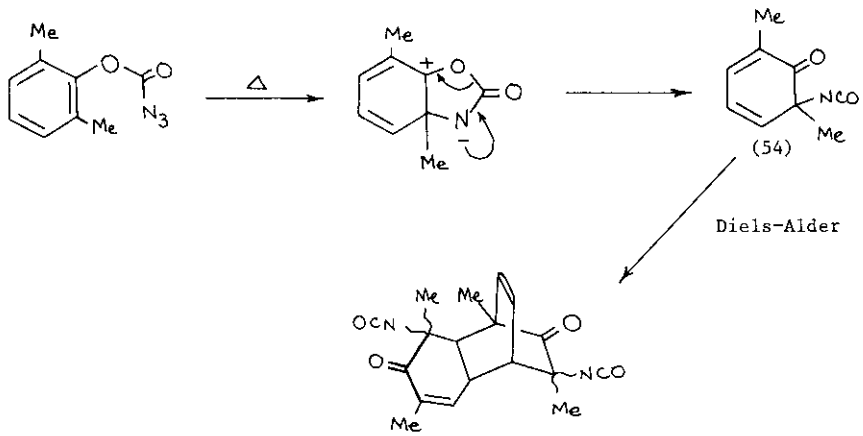
Scheme 29



Scheme 30



Scheme 31

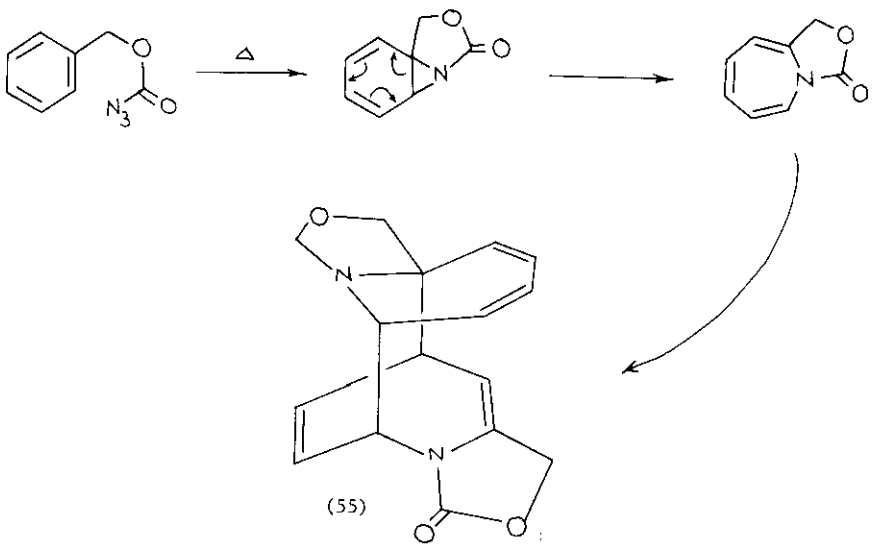


Scheme 32

The dipolar intermediate from nitrene attack of the ring, prefers to ring-open to give a cyclohexadienone (54) which spontaneously dimerises under the reaction conditions. We are avidly exploring this further.

(b) Benzyl azidoformates

These azides behave quite differently giving the first example of an intramolecular azepine formation (Scheme 33). The derived azepines, because of the constraints of the fused 5-membered ring are almost planar and thus antiaromatic and therefore also spontaneously dimerise. We believe that, as with simple azepines, studied by Paquette, the dimers form by

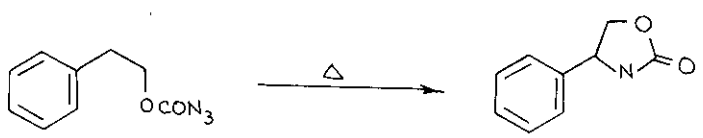


Scheme 33

[6+4] cycloaddition and, of the numerous possible isomers we favour that shown in the Scheme on the basis of extensive decoupling of the 300 MHz p.m.r. spectrum. The parent azide, its 4-chloro, 2,4-dichloro, and 2,4,6-trichloro-analogue all gave dimers with definitive spectral data (Diagram).

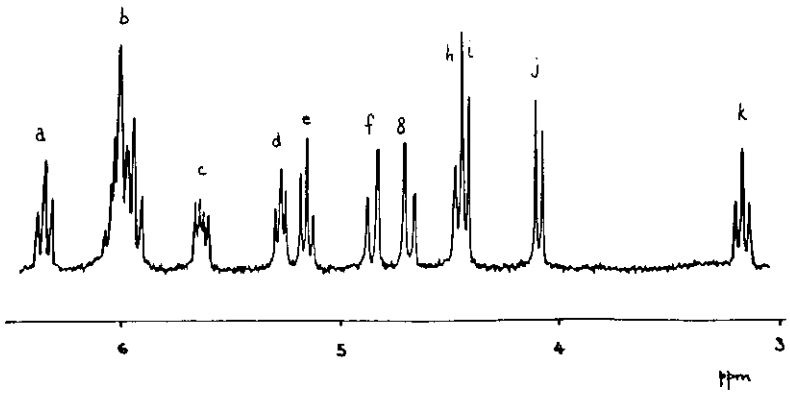
(c) Phenethyl azidoformate

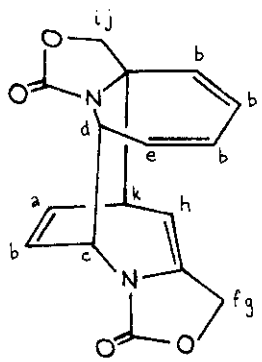
Lastly the phenethyl azidoformates behave as the aliphatic analogues giving the CH-insertion product (Scheme 34). This method for β-amino-alcohol formation has considerable potential.



Scheme 34

^{1}H N.m.r. Spectrum of Compound (55) in $CDCl_3$ at 300 MHz





(55)

I wish to acknowledge the hard work of my co-workers, Dr. I.M. McRobbie, Dr. J.M. Lindley, Mr. D.G. Hawkins, Mr. S. Rhouati, Dr. M. Hesabi and Mr. M. Clancy, and the interest of my friends and colleagues especially Professor H. Suschitzky.

References

1. A. Kliegl, Chem. Ber., 1909, 42, 591.
2. P.A.S. Smith in 'Nitrenes', Ed. W. Lwowski, Wiley, New York, N.Y., 1970, p.99.
3. (a) J.I.G. Cadogan, S. Kulik and M.J. Todd, J.C.S. Chem. Comm., 1968, 736
   (b) M. Messer and D. Farge, Bull. Soc. Chim. France, 1968, 2832.
4. R. Kwok and P. Pranc, J. Org. Chem., 1968, 33, 2880.
5. J.I.G. Cadogan, Accounts Chem. Res., 1972, 5, 303; J.I.G. Cadogan, J.N. Done, G. Lunn and P.K.K. Lim, J.C.S. Perkin I, 1976, 1749; J.I.G. Cadogan and B.S. Tait, J.C.S. Perkin I, 1975, 2396; J.I.G. Cadogan, D.S.B. Grace, P.K.K. Lim and B.S. Tait, J.C.S. Perkin I, 1975, 2376.
6. B. Iddon, O. Meth-Cohn, E.F.V. Scriven, H. Suschitzky, and P.T. Gallagher, Angew. Chem. Internat. Edn., 1979, 18, 900 and refs. therein.
7. L. Krebchek and N. Takimoto, J. Org. Chem., 1968, 33, 4286; and G.R. Cliff, E.W. Collington, and G. Jones, J. Chem. Soc. (C), 1970, 1490.
8. J.M. Lindley, O. Meth-Cohn, and H. Suschitzky, J.C.S. Perkin I, 1978, 1198.
9. G. Jones, C. Keates, I. Kladko, and P. Radley, Tetrahedron Letters, 1979, 1445.
10. D.G. Hawkins, O. Meth-Cohn, and H. Suschitzky, J.C.S. Perkin I, 1979, 3207.
11. Ref. 2, p.129.
12. L.K. Dyall, Australian J. Chem., 1977, 30, 2669.
13. P.L. Coe, A.T. Jukes, and J.C. Tatlow, J. Chem. Soc. (C), 1966, 2020; and R. Kwok and P. Pranc, J. Org. Chem., 1968, 33, 2880.
14. E. Bamberger, Chem. Ber., 1909, 42.
15. cf. I. Tanasescu, C. Anghel, and A. Popescu, Stud. Univ. Babes-Bolyai, Ser. 1, 1963, 8, 141 (Chem. Abs., 1964, 61, 13279d).
16. J.I.G. Cadogan, D.J. Sears, and D.M. Smith, J. Chem. Soc. (C), 1969, 1314.
17. R.A. Abramovitch and E.F.V. Scriven, J.C.S. Chem. Comm., 1970, 787; and R.A. Abramovitch, S.R. Challand, and E.F.V. Scriven, J. Amer. Chem. Soc., 1972, 95, 1374; J. Org. Chem., 1972, 37, 2705.
18. R.D. Rieke and L.D. Rhyne, J. Org. Chem., 1979, 44, 3445.
19. W. Lwowski, in 'Nitrenes', Ed. W. Lwowski, Wiley, New York, N.Y. 1970, p.185.
20. R. Kreher and D. Kuhling, Angew. Chem., 1965, 77, 43.
21. L.A. Paquette, J.H. Barrett, and D.E. Kuhla, J. Amer. Chem. Soc., 1969, 91, 3616.