

PEDLER LECTURE

Spirodiene Rearrangements

By D. H. Hey, F.R.S.

KING'S COLLEGE, LONDON WC2R 2LS

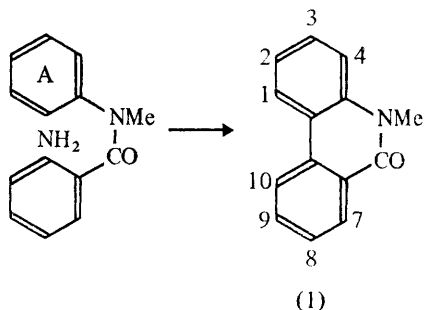
In the presentation of an up-to-date review of the results of an experimental investigation which extends over a period of many years it is frequently difficult to know where to start. In the development of the topic chosen for this Pedler Lecture it is possible to detect a common thread which can be traced back over a period of more than forty years but it is not my intention to inflict all this upon you. I will take as my starting point the years around 1950, although my main emphasis will naturally fall on advances which have been made in the last five years or so and on topics which are still under active investigation today. There is a point of special interest in going back twenty years because the period 1950—1970 has seen a major revolution in the methods of experimental organic chemistry mainly, but not exclusively, as the result of developments in the applications of spectroscopy and chromatography. A re-reading of the papers of twenty years ago frequently gives a picture of blind men fumbling in the dark. By modern standards progress was painfully slow and tedious but, as in other branches of chemistry, this was the way in which so many of the basic foundations were laid, upon which it has become possible to build the more spectacular developments of today.

Our main interests about twenty years ago were centred upon the problem of intramolecular free-radical substitution, and the reaction which pre-eminently suggested itself for the study of this problem was the Pschorr reaction for the synthesis of the phenanthrene ring system. This interest arose from our earlier work on intermolecular free-radical substitution as exemplified in what has become known as the Gomberg reaction. This was a reaction which, nearly forty years ago, gave clear evidence of a homolytic mechanism involving free-radical intermediates and it has always seemed to me to be quite remarkable that of all people, Gomberg, the father of free-radical chemistry, should have been handling these reactions and yet had himself apparently failed to recognise, or at any rate had made no comment on, their free-radical character. It is of interest to record, however, that in a letter I received from Gomberg over thirty years ago, he fully agreed with our free-radical interpretation of his reaction and considered that our evidence for the participation of radicals was fully as valid as anything that had been published by Wieland and others with regard to the reactions of radicals in solution at that time.

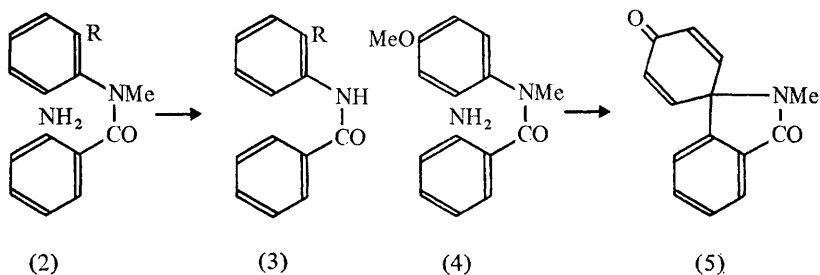
In our work on intramolecular free-radical substitution our attention, for various reasons, became directed not to the classical Pschorr Reaction itself but

Spirodienone Rearrangements

to the closely related reactions leading to the formation of *N*-alkyl-phenanthridones. The basic reaction for the preparation of *N*-methyl-phenanthridone (1) from diazotised 2-amino-*N*-methylbenzanilide was first



reported in 1897 by Pictet and Gonset¹ but in the succeeding fifty years it seems to have been almost completely forgotten. By a curious coincidence an interest in this reaction was developed simultaneously and independently by ourselves in London and by Govindachari in Madras. In our work we found that the reaction provided a useful general method for the preparation of *N*-alkyl-phenanthridones but that it failed (*a*) when ring A contained an *ortho*-substituent,² and (*b*) when ring A contained a methoxy-group in the *para*-position.³ In the former case the reaction resulted in demethylation and deamination [*e.g.* (2) → (3)], whereas in the latter case a new spirodienone system was formed [(4) → (5)]. These anomalous results were not reported by Govindachari but his later work confirmed them.⁴



With regard to the demethylation–deamination reaction, it was at first considered that this anomalous reaction was restricted solely to compounds in which there was a substituent atom or group at the *ortho*-position with respect

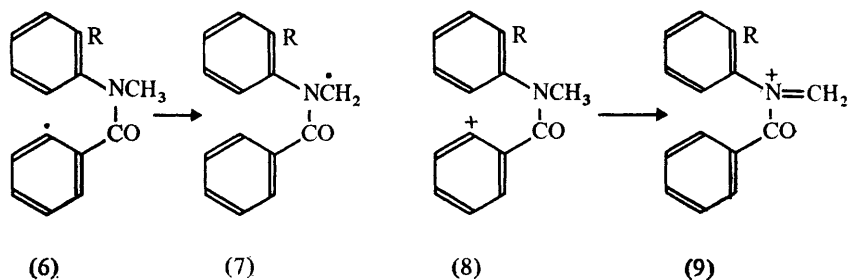
¹ A. Pictet and A. Gonset, *Arch. Sci. phys. nat. Genève*, 1897, 3, 37.

² D. H. Hey and D. G. Turpin, *J. Chem. Soc.*, 1954, 2471.

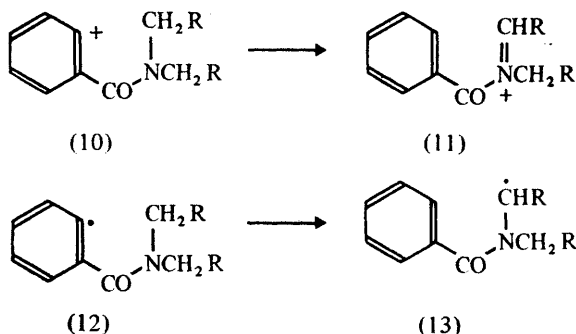
³ D. H. Hey, J. A. Leonard, T. M. Moynehan, and C. W. Rees, *J. Chem. Soc.*, 1961, 232.

⁴ T. R. Govindachari and N. Arumugam, *J. Sci. Ind. Res., India*, 1954, 13B, 694; 1955, 14B, 250.

to the *N*-methyl group. Later work with the aid of improved chromatographic techniques showed that this behaviour was more general and could in fact be observed even in the absence of any substituent but in such cases, of course, the yield of the demethylation–deamination product could be very small. With an *ortho*-substituent it formed the main identified product. The reasons for the occurrence of this abnormal reaction are primarily steric in origin and the reaction can involve either a 1,5-hydrogen atom shift [(6) → (7)] or a 1,5-hydride ion shift [(8) → (9)] depending upon experimental conditions.



Numerous examples of such shifts are known. For example, Cohen and his co-workers⁵ have studied the thermal and catalytic decomposition of diazonium salts derived from *o*-amino-*NN*-disubstituted benzamides and the nature of the products formed indicated that the thermal reaction involves a 1,5-hydride ion transfer [(10) → (11)], whereas the copper-catalysed reaction in the cold involves a 1,5-hydrogen atom transfer [(12) → (13)].



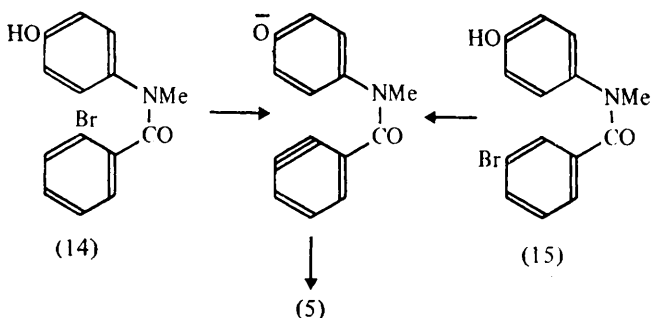
With regard to the abnormal reaction with diazotised 2-amino-*N*-methyl-4'-methoxybenzanilide (4), the identification of the product as a spirodienone was made by Dr. T. M. Moynihan⁶ in 1956, as a result of ultimate analysis (which

⁵ A. H. Lewin, A. H. Dinwoodie, and T. H. Cohen, *Tetrahedron*, 1966, **22**, 1527.

⁶ T. M. Moynihan, Ph.D. Thesis, London, 1956.

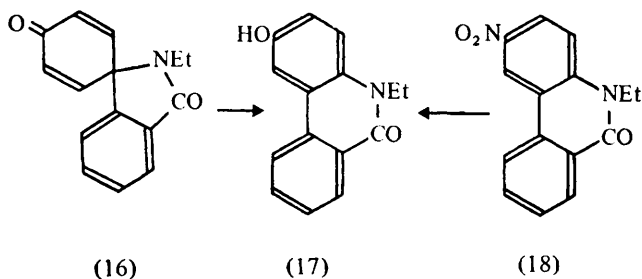
Spirodiene Rearrangements

confirmed loss of one carbon atom and two hydrogen atoms), the preparation of carbonyl derivatives, and i.r. and u.v. spectroscopy. The structure of the spirodienone (5) was subsequently confirmed by synthesis from both 2- and 3-bromo-*N*-methyl-4'-hydroxybenzanilide (14) and (15) involving a benzyne intermediate.⁷



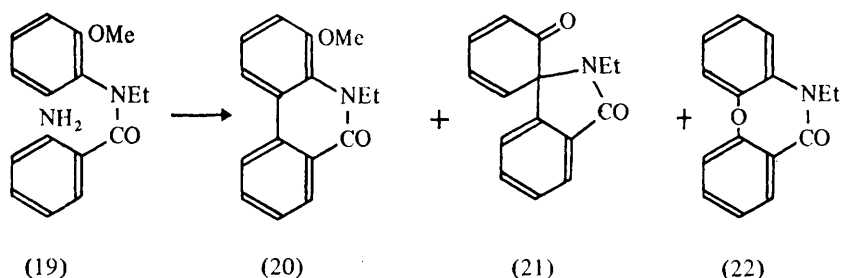
This spirodienone was recognised to have a structure of considerable interest and since that time many examples have been published in which compounds of this type have figured in synthetic processes and in biogenetic pathways. The spirodienone is susceptible to an acid-catalysed dienone-phenol rearrangement which, to the best of our knowledge, provided the first reaction of this type involving a heterocyclic ring. Unexpectedly vigorous conditions are required for this reaction. For example, the dienone (16) (prepared from 2-amino-*N*-ethyl-4'-methoxybenzanilide) required 100% phosphoric acid at 170 °C to bring about rearrangement to 2-hydroxy-*N*-ethylphenanthridone (17), the formation of which involves a carbon-carbon shift and not a nitrogen-carbon shift in the intermediate spirodienyl cation.³ The structure of the hydroxyphenanthridone was confirmed by independent synthesis from 2-nitro-*N*-ethylphenanthridone (18).

In many of the reactions of diazotised amines it has long been recognised that the nature of the products formed can depend to a large extent upon experi-

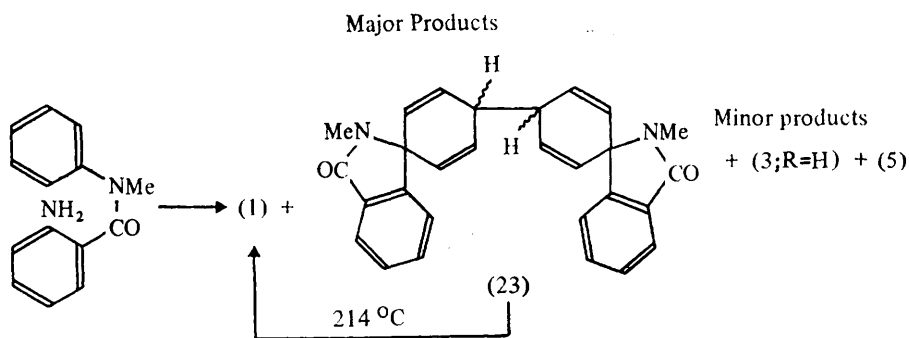


⁷ D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1963, 5266.

mental conditions. This fact is brought out very clearly in the reactions of diazotised *o*-aminobenzanilides. For example, in the thermal decomposition at 80 °C in aqueous solution of the diazonium sulphate prepared from 2-amino-2'-methoxy-*N*-ethylbenzanilide (19), the product consists of a mixture of 4-methoxy-*N*-ethylphenanthridone (20), the *ortho*-spirodienone (21), and the oxazepinone (22).⁸ These are conditions which favour a heterolytic mechanism. In the



catalytic decomposition of a diazotised amine in the form of its fluoroborate in acetone at 20 °C by the addition of copper powder, conditions which favour a homolytic mechanism, a very different result can be obtained. For example, the catalytic decomposition of the diazonium fluoroborate from 2-amino-*N*-methylbenzanilide gives a product which contains mainly *N*-methylphenanthridone (1) and the dimer (23), together with small quantities of benzanilide (3; R = H) as the result of demethylation and deamination and, surprisingly, the spirodienone (5).⁹

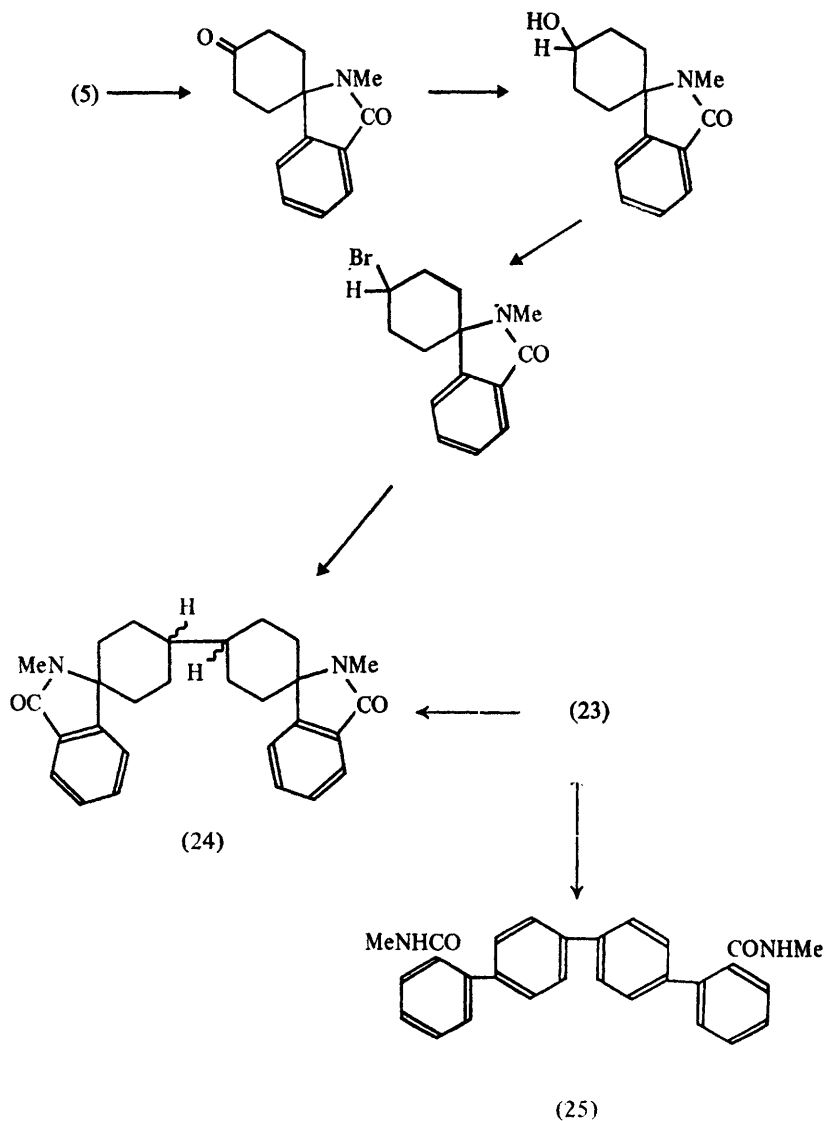


This latter result is one of particular interest because in the formation of the spirodienone (5) an additional oxygen atom is incorporated into the molecule. This must occur by the action of air on an intermediate radical. The spirodienone

⁸ D. H. Hey, J. A. Leonard, C. W. Rees, and A. R. Todd, *J. Chem. Soc. (C)*, 1967, 1513.

⁹ D. H. Hey, C. W. Rees, and A. R. Todd, *J. Chem. Soc. (C)*, 1967, 1518.

Spirodiene Rearrangements



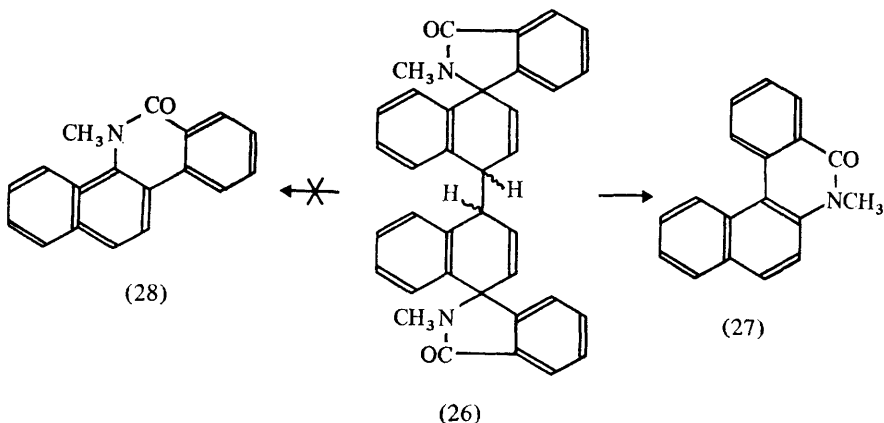
was not formed when the reaction was carried out under nitrogen, and the non-participation of water in the process was confirmed by carrying out the experiment with acetone diluted with $H_2^{18}O$; there was no incorporation of isotopic oxygen into the product. The formation of the dimer of an intermediate radical further confirms the free-radical character of this reaction, which in fact proves

to be a very close replication of Gomberg's original work with triphenylmethyl, which also reacted with air and also formed a dimer.

The dimer (23) showed a further property of special interest, to which reference will be made later, in that when heated at 214 °C it was converted into *N*-methylphenanthridone in about 90% yield, by symmetrical fission, a 1,2-shift, and loss of a hydrogen atom.¹⁰ This then is a spirodiene rearrangement involving a spirodienyl radical and is different from the dienone-phenol rearrangement previously discussed, which involves a spirodienyl cation. This new rearrangement involves the breaking of three bonds in the dimer, namely the central C-C bond and either a C-C bond or a C-N bond in both of the heterocyclic rings. In the particular example cited, it is not possible to arrive at any decision on this point because the same product would be obtained in both cases.

The structure of the dimer (23) was established on classical lines by degradation and by synthesis of its product of hydrogenation. The octahydro-derivative (24) of the dimer was synthesised as shown above from the spirodienone (5), which had itself already been synthesised.¹¹ In addition, treatment of the dimer (23) with base resulted in the unfolding of the molecule to give the methylamide of a dicarboxylic acid of *p*-quaterphenyl (25), which on hydrolysis and decarboxylation gave *p*-quaterphenyl.⁹

A decision between C-C fission (*i.e.* aryl migration) and C-N fission (*i.e.* nitrogen migration) in the rearrangement of the spirodienyl radical mentioned above can be made from a study of suitably substituted spirodienyl radicals obtained by heating an appropriate dimer. For example, the dimer (26), prepared from the diazonium fluoroborate of 2-amino-*N*-methyl-*N*-(1-naphthyl)benzamide, gave on heating the benzo-*N*-methylphenanthridone (27)¹² and not

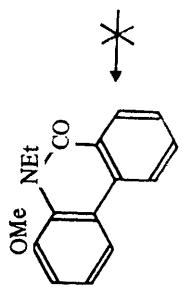
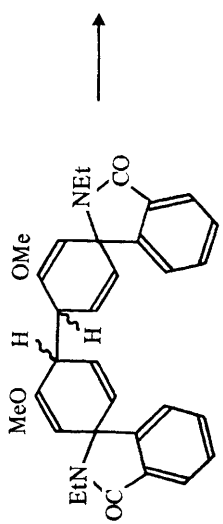
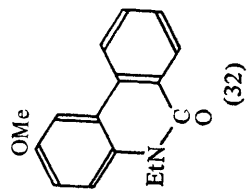
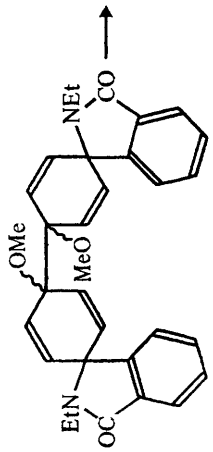
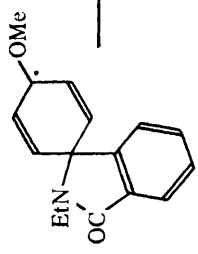
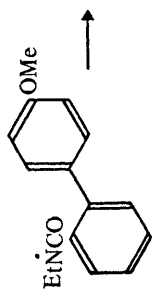
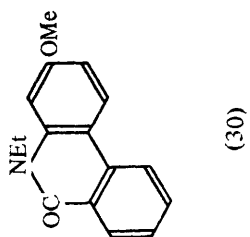


¹⁰ D. M. Collington, D. H. Hey, and C. W. Rees, *J. Chem. Soc. (C)*, 1968, 1026.

¹¹ D. M. Collington, D. H. Hey, and C. W. Rees, *J. Chem. Soc. (C)*, 1968, 1017.

¹² G. H. Jones, Ph.D. Thesis, London, 1971.

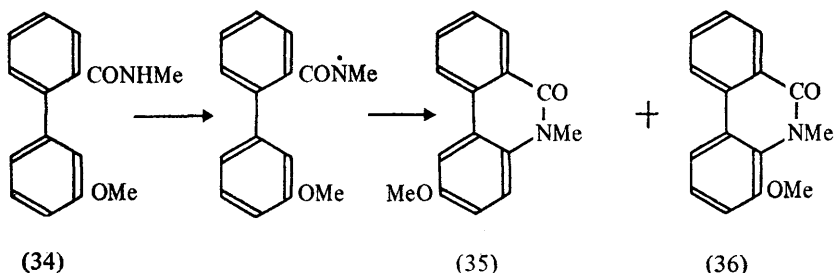
Spirodiene Rearrangements



(28).^{*} This is clearly an example of C–N fission or nitrogen migration in contrast to the C–C fission or aryl migration found for the spirodienyl cation.

A further example of nitrogen migration is provided by the observation that pyrolysis of a pure stereoisomer of (29) gave the methoxy-*N*-ethyl-phenanthridone (30).¹² This rearrangement can be envisaged as a process involving an intermediate amido radical of a type proposed by Thomson in his work on the persulphate oxidation of amides.¹³

Pyrolysis of the dimer (31) gave the methoxy-*N*-ethylphenanthridone (32) in 80% yield and not (33), although both isomers are possible by nitrogen migration.¹² This example again shows nitrogen migration, but the movement seems to be exclusively to the position *para* to the methoxy-group. On the other hand the related persulphate oxidation of the methoxybiphenylcarboxymethylamide (34), gave the two isomeric products (35) and (36), the former predominating.¹² This result suggests that similar open amido radicals may not be involved in both reactions, unless the effect of altering the *N*-alkyl group is unexpectedly large.



About three years ago a new turn was taken in our work in this field when it was decided to follow up some of the experimental results reported by Norman Kharasch in California on the production of radicals by the photolysis of aromatic iodides. Bryce-Smith and his colleagues had already shown in 1959 that the photolysis of iodobenzene in cumene gives a mixture of the three isomeric isopropylbiphenyls in the same ratio as is found in the decomposition of benzoyl peroxide in cumene, together with the dimer 2,3-dimethyl-2,3-diphenylbutane.¹⁴ The development of this reaction was further explored by Kharasch and his co-workers who, in 1967, reported that the photolysis of 2-iodobenzanilide in benzene gives phenanthridone.¹⁵

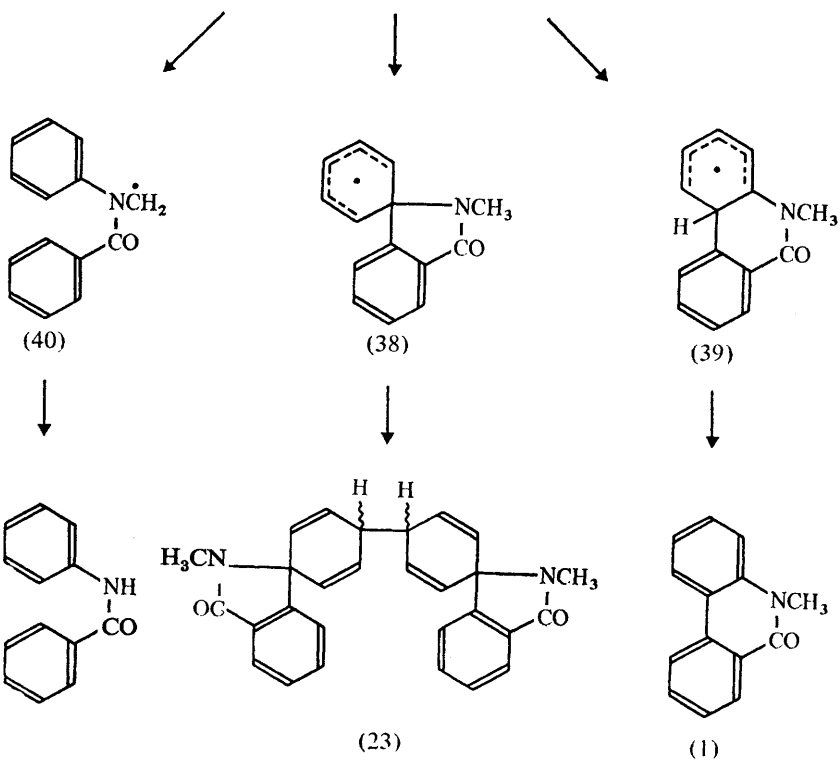
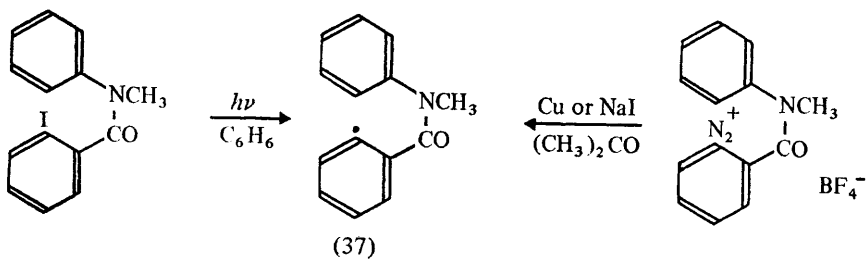
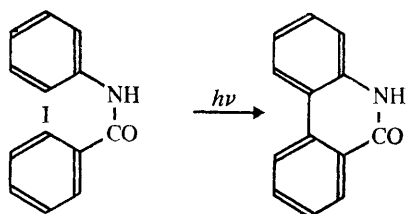
^{*} The product from the thermal decomposition of the dimer (26) has been previously but incorrectly reported to be (28).¹⁰ (See also D. H. Hey, *Intra-Science Chemistry Reports*, 1969, 3, 167.)

¹² P. M. Brown, P. S. Dewar, A. R. Forrester, A. S. Ingram, and R. H. Thomson, *Chem. Comm.*, 1970, 849.

¹⁴ J. M. Blair, D. Bryce-Smith, and B. W. Pengilly, *J. Chem. Soc.*, 1959, 3174.

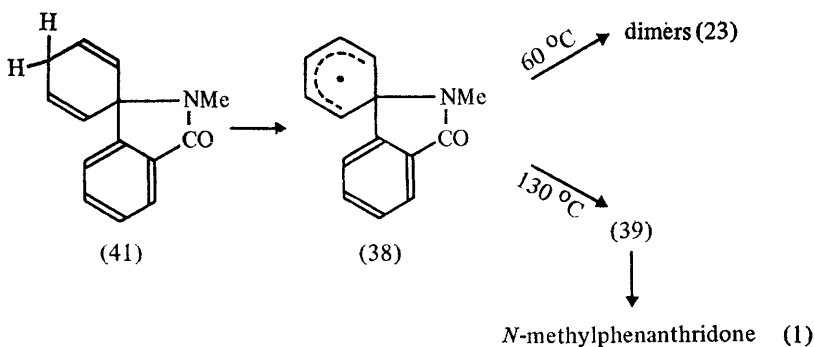
¹⁵ B. S. Thyagarajan, N. Kharasch, H. B. Lewis, and W. Wolf, *Chem. Comm.*, 1967, 614.

Spirodiene Rearrangements



We extended this reaction to include a number of *N*-alkyl-2-iodobenzanilides primarily to find out to what extent these photochemical reactions followed the pattern already established in the catalytic decomposition of the corresponding diazonium fluoroborates in acetone. There proved in fact to be a close resemblance between the two reactions and such differences as were brought to light can be attributed to differences in solvent, to photoreactions of primary products, and to the presence in the photochemical reaction of iodine and hydrogen iodide. The general overall reaction scheme may be represented as shown opposite.

The initially-formed radical (37) undergoes cyclisation to give the intermediates (38) and (39), which lead to the dimer (23) and *N*-methylphenanthridone (1) respectively. The dimer (23) resulting from (38) was shown to be a mixture of three stereoisomers, each of which can be converted into the same derivative of quaterphenyl on treatment with base. A 1,5-hydrogen atom shift in the radical (37) leads to (40) and then to benzanilide, the product of demethylation and deamination. In addition, a monomeric diene (41) is formed but *only* in the photochemical reaction or, and in better yield, when dry hydrogen iodide is employed to promote decomposition of the diazonium fluoroborate in methylene chloride. The hydrogen iodide acts as an efficient hydrogen donor.¹⁶ Hydrogen abstraction from the diene (41) with *t*-butoxyl radicals (derived from di-*t*-butyl peroxyoxalate at 60 °C) led to the radical (38), which was converted into a mixture of dimer isomers (23). At a higher temperature with *t*-butoxyl radicals (derived from di-*t*-butyl peroxide at 130 °C) hydrogen abstraction from the diene gave *N*-methylphenanthridone (1) directly as a major product.¹² The phenanthridone is not formed at this temperature from the dimers. Only at the higher temperature, therefore, does the rearrangement of the spiro-dienyl radical (38) compete effectively with the dimerisation.

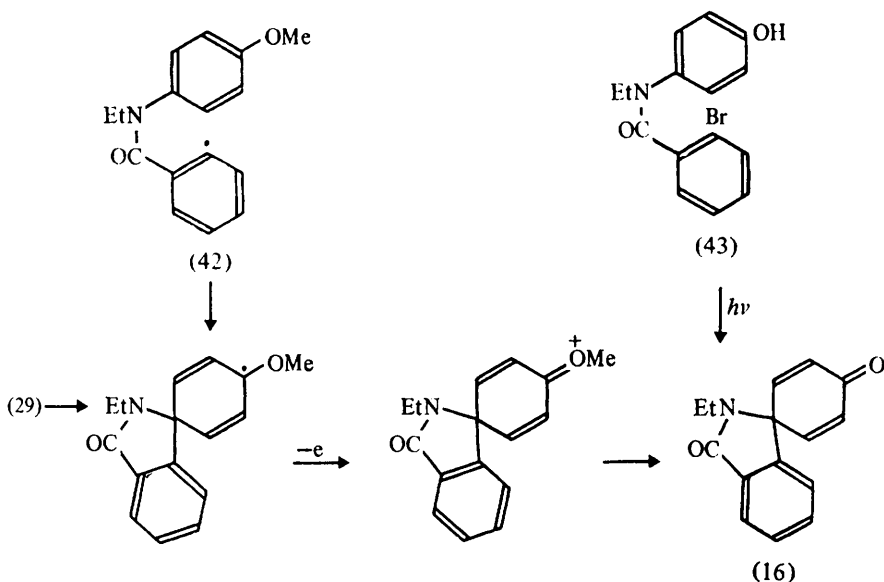


A further point of interest arises from the pyrolysis of the dimer (29), which gives no dienone except in the presence of iodine, when it is formed in high yield, whereas the dienone (16) is a significant product from the radical (42) (prepared

¹⁶ D. H. Hey, G. H. Jones, and M. J. Perkins, *Chem. Comm.*, 1969, 1375.

Spirodiene Rearrangements

from the diazonium salt) because it is invariably produced in the presence of an oxidising agent.¹² This dienone (16) has recently been reported to be formed in the irradiation of 2-bromo-*N*-ethyl-4'-hydroxybenzanilide (43) in aqueous



alkali.¹⁷ We have found that the methyl analogue (5) is itself subject to a photo-induced rearrangement in which it is converted into an isomeric dienone (44) in high yield. Irradiation in benzene solution in the presence of iodine gives instead two isomeric cyclopentenones (45) and (46).¹⁸ Evidence for formation of the expected intermediate lumiketone (47) could not be found.

The n.m.r. spectra of the isomeric cyclopentenones both showed pairs of doublets, which straddle that part of the spectrum due to the aromatic protons. This unusual pattern (see Figure) is readily understandable in terms of the electron distribution in the vinylogous amide structures assigned to these molecules.¹²

Closely related to the dienone-phenol rearrangement, exemplified here by the acid-catalysed conversion of the spirodienone (5) into a hydroxyphenanthridone, is the dienol-benzene rearrangement. Borohydride reduction of the dienone (5) gives a mixture of the two stereoisomeric spirocyclohexadienols (48). These, on heating with acid, undergo the dienol-benzene rearrangement to give *N*-methylphenanthridone (1). However, brief exposure of these dienols to aqueous ethanolic hydrochloric acid brings about their interconversion, as well as ether formation to give (49).¹² Evidently, nucleophilic capture by solvent of the inter-

¹⁷ Z. Horii, C. Iwata, S. Wakawa, and Y. Nakashita, *Chem. Comm.*, 1970, 1039.

¹⁸ D. H. Hey, G. H. Jones, and M. J. Perkins, *Chem. Comm.*, 1971, 47.

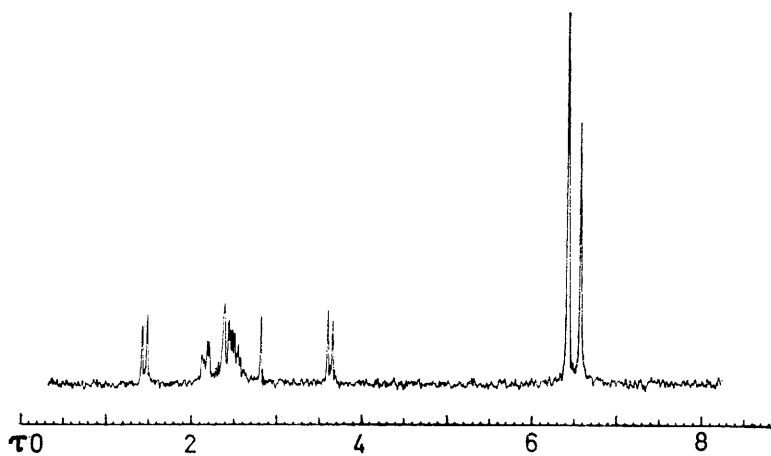
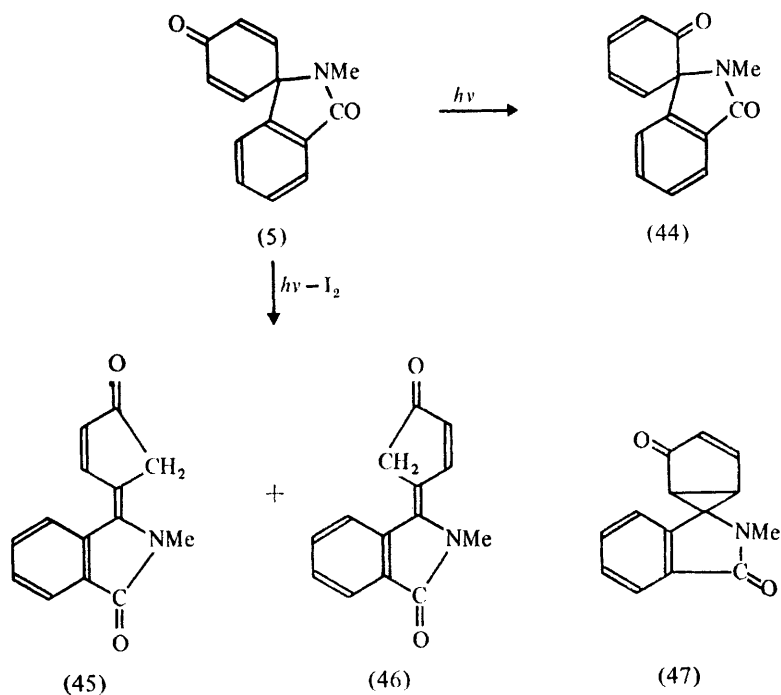
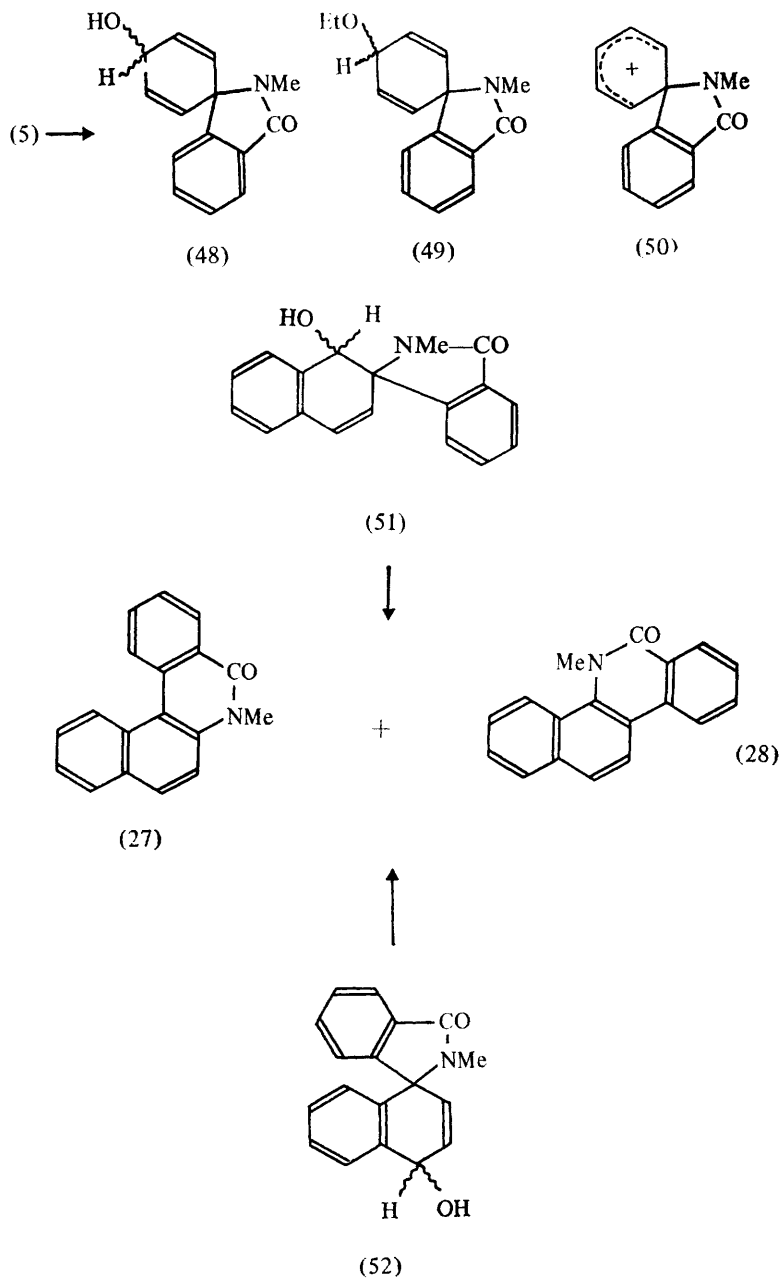


Figure The 100 MHz proton n.m.r. spectrum of one of the isomeric cyclopentenones [(45) and (46)], showing two vinyl doublets at τ 1.45 and 3.61.

Spirodiene Rearrangements

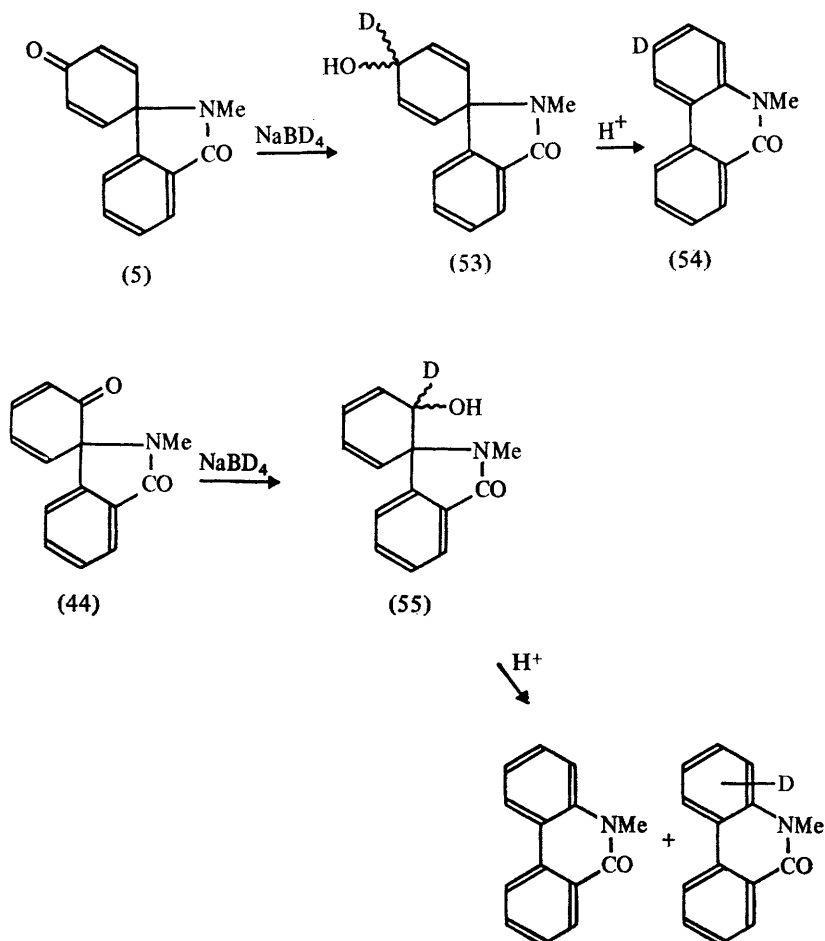
mediate cyclohexadienyl cation (50) is considerably more rapid than rearrangement to the phenanthridone.



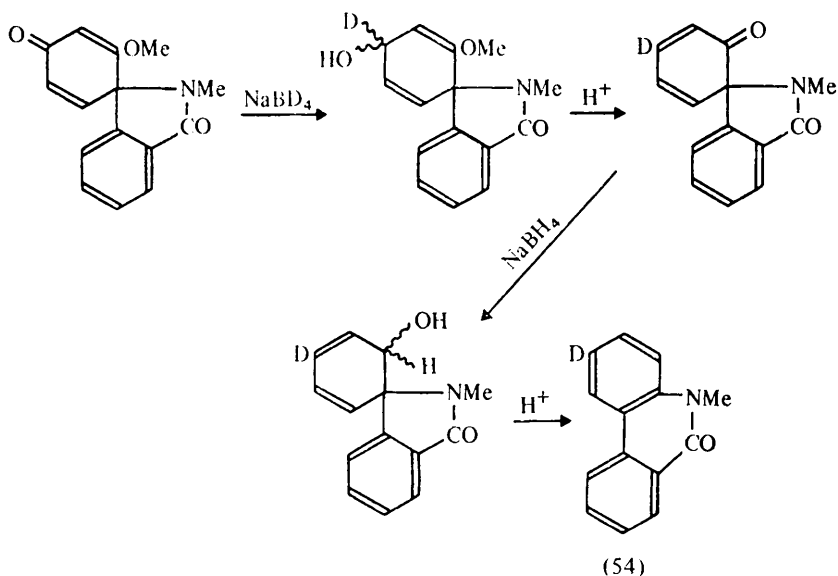
Similar dienol-benzene rearrangements in the naphthalene series give benzo-phenanthridones, the identities of which have revealed the occurrence of nitrogen migration in addition to the expected aryl migration. Thus the dienols (51) and (52) both give mixtures of the *N*-methylbenzophenanthridones (27) and (28),¹² although in different proportions.

These unexpected results prompted an investigation of the migration pattern in the case of the unsubstituted dienols (48). The deuteriated analogues (53), obtained from the dienone (5) by reduction with sodium borodeuteride, gave the deuteriated *N*-methylphenanthridone (54), the substitution pattern of which clearly establishes aryl migration in this case.¹²

Similar reduction of the *ortho*-dienone (44) gave a mixture of deuteriated dienols (55) together with other reduction products. Acid-catalysed rearrange-



ment then produced a mixture of *N*-methylphenanthridone and a deuteriated *N*-methylphenanthridone.¹² The predominant formation of the deuterium-free product could indicate that at least part of the rearrangement occurs in concert with loss of water, thus circumventing the formation of an intermediate cyclohexadienyl cation, which would be expected to give 50% deuterium retention. Unfortunately, experimental difficulties have so far precluded any definite decision on this interesting point. However, the migrating group in the rearrangement of the *ortho*-dienols is clearly identified as aryl by the substitution pattern found in the deuteriated phenanthridone (54), which results from the sequence of reactions set out below.¹²



The chemistry of the acid-catalysed rearrangements in the spirodienol series appears so far to be quite complex. In entering this field we are at present only on the threshold of a new chapter which has yet to be written.

In the present state of our knowledge the rearrangements involving spirocyclohexadienyl radicals in the systems studied lead in every case to the shift of the nitrogen atom rather than the carbon atom, whereas in the acid-catalysed spirodienone-phenol rearrangements, which appear to involve spirodienyl cations, only carbon shifts have come to light, although work in the naphthalene series is still incomplete. In the related spirodienol-benzene rearrangements the position is much less clear. Examples of both nitrogen and carbon shifts have been encountered and the evidence so far available appears to differentiate between spirodienyl cation intermediates in the *para*-dienols and a more complicated situation with *ortho*-dienols, in which there is the possibility of a concerted mechanism rather than one involving a spirodienyl cation.

There remain to me two obligations which I am required to discharge. The Pedler Lecturer is specifically required to devote his lecture, as far as is practicable, to the description of new knowledge. This has been done. He is also asked to point out the directions in which further research is desirable. In the broadest sense it can be said that it is in the unfolding of the detailed mechanisms of organic reactions, for which task the organic chemist is now equipped as never before, that there is to be found a most fascinating, productive, and rewarding preoccupation. The exploration of the properties and behaviour of the atoms within a molecule is no less a challenge to man than the exploration of the universe itself. It is only the scale which is different.

In conclusion, I must express my indebtedness to those who have worked with me on the problems which have formed the subject matter of this lecture. There are a large number extending over many years but I should like to pay particular tribute to T. M. Moynehan, J. A. Leonard, A. R. Todd, and D. M. Collington and also to G. H. Jones, who is still active in this field. This in fact is the cause of a little embarrassment because the Pedler Lecture has been given five times over a period of nearly six months and some material included in my earlier lectures has been replaced by more recent developments in my final version. I am also very conscious that I have been exceedingly fortunate in having enjoyed collaboration in this work firstly with Professor C. W. Rees and subsequently with Dr. M. J. Perkins, both of whom have been in their time major contributors, not merely in the day-to-day supervision of experimental detail but also in the development of new ideas and in the insight which they have provided in the interpretation of experimental observations. I am glad to have this opportunity of expressing in public the great debt I owe to them.