TILDEN LECTURE*

Electrophilic *C*-Nitroso-compounds

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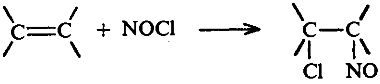
1 Introduction

A century has elapsed since Baeyer's first preparation[1] of nitrosobenzene (1) and Tilden's investigation[2] of the olefin nitrosochlorides (2). The extensive body of chemistry stemming from these early studies is a reflection of the high, reactivity of *C*-nitroso-compounds towards reagents of diverse electronic type. The nitroso-group, like nitro-group, is powerfully electrophilic and can, for example, activate benzene rings towards nucleophilic attack and stabilize α-carbanions. However, *C*-nitroso-compounds generally are more readily reduced, to hydroxylamines, oxidized, to nitro-compounds, attacked by radicals to give nitroxyls, and by nucleophiles, to give adducts,[3] than are their nitro-analogues (Scheme 1).

$$Ph_2Hg + NOBr \longrightarrow \underset{(1)}{PhNO} + PhHgBr$$



(2)

C-Nitroso-compounds are deoxygenated[4] by phosphines and phosphites much more rapidly than are nitro-compounds, and they readily undergo condensation reactions, for example with amines to give azo-compounds. Two characteristic properties of *C*-nitroso-compounds were recognized early. The blue or blue-green monomers readily give colourless dimers which may exist in *cis*- or *trans*-forms (3). Dimerization is usually freely reversible in solution, the

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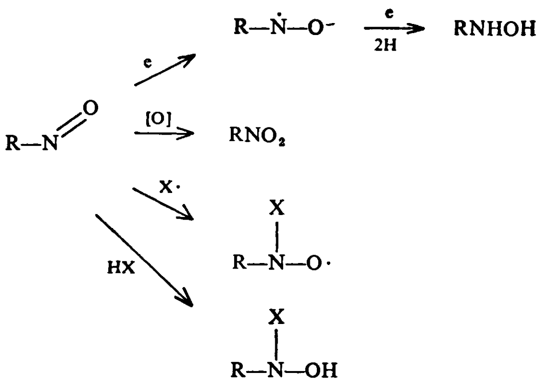
*An amplified version of the Tilden Lecture delivered on various occasions during 1974—75.

[1] A. Baeyer, *Ber.*, 1874, 7, 1638.

[2] W. A. Tilden, *Chem. Soc. J.*, 1875, 514.

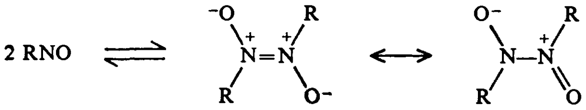
[3] For recent examples see J. C. Trisler, P. H. Deland, and M. M. Goodgame, *Tetrahedron Letters*, 1975, 3125; A. Darchen and C. Moinet, *J.C.S. Chem. Comm.*, 1976, 820.

[4] J. I. G. Cadogan and R. K. Mackie, *Chem. Soc. Rev.*, 1974, 3, 87.



Scheme 1

position of the equilibrium depending critically upon the nature of the group R. Primary and secondary alkyl derivatives are readily prepared and stored as their crystalline dimers but, in solution, irreversible tautomerization of the monomer may occur, with acid–base catalysis, to yield the related oxime (4). For this



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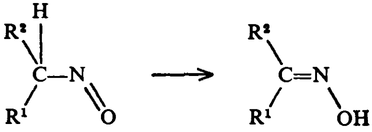

(4)

reason, aryl and tertiary alkyl nitroso-compounds are often preferred as reagents in organic chemistry, although both conjugation and steric effects may diminish the reactivity of the nitroso-group.

A full account of the preparation and properties of *C*-nitroso-compounds is beyond the scope of this article, and the reader is directed to authoritative reviews[5] for further information. Here, attention will be given to new classes

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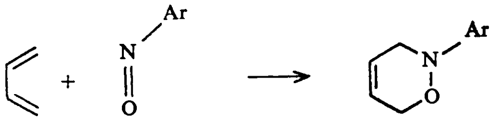
[5] G. Gowenlock and W. Lüttke, *Quart. Rev.*, 1958, **12**, 321; P. A. S. Smith, 'The Chemistry of Open-Chain Organic Nitrogen Compounds', Vol. 2, W. A. Benjamin, New York, 1966, Chapter 13; S. R. Sandler and W. Karo, 'Organic Functional Group Preparations', Vol. 2, Academic Press, New York, 1971, Chapter 16; 'The Chemistry of Nitro and Nitroso Groups', Part 1, ed. H. Feuer, Interscience, New York, 1969.

of *C*-nitroso-compounds showing enhanced electrophilic character, with particular emphasis on their reactions with conjugated dienes.

2 *C*-Nitroso-compounds as Dienophiles

The Diels–Alder reaction of *C*-nitroso-compounds with conjugated dienes was first reported[6] by Wichterle and Arbuzov; later work[7] has confirmed and greatly extended their early findings. Nitrosoarenes generally react with simple dienes, for example buta-1,3-diene, to give 1,2-oxazine derivatives (5) in good yield.



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Hamer *et al.*[8] and Kresze *et al.*[9] have studied kinetically the second-order reactions of cyclohexa-1,3-diene and 2,3-dimethylbuta-1,3-diene with various *para*-substituted nitrosobenzenes. Electron-withdrawing substituents strongly accelerate the cycloaddition. For example, *p*-nitronitrosobenzene reacts 3500 times faster than *p*-methoxynitrosobenzene with the cyclic diene.[9] Thus, *C*-nitroso-compounds fall into the familiar class of electron-demanding dienophiles. This appears to be borne out by the properties of *gem*-cyanonitroso- and *gem*-chloronitroso-compounds which, unlike most tertiary nitrosoalkanes, form adducts with a variety of conjugated dienes. Although the reaction of 1-chloronitrosocyclohexane (6) (or 2-chloro-2-nitrosopropane) with dienes is sluggish, and the equilibrium may be unfavourable, it has preparative value when carried out in alcoholic solvents.[10] The adduct is solvolysed irreversibly and good yields of 3,6-dihydro-1,2-oxazines [*e.g.* (7)] may be obtained. The procedure has limitations[11] in that adduct formation may be slow relative to competing processes. For example, the low yield of adduct obtained from isoprene was attributed[12] to competing attack ['ene' reaction (I)] of the nitroso-group on the allylic methyl group of the olefin. Nevertheless, the synthetic value of this approach

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[6] O. Wichterle, *Coll. Czech. Chem. Comm.*, 1947, **12**, 292; Y. A. Arbuzov, *Doklady Akad. Nauk S.S.S.R.*, 1948, **60**, 993.

[7] J. Hamer and M. Ahmad, '1,4-Cycloaddition Reactions', ed. J. Hamer, Academic Press, New York, 1967, Chapter 12.

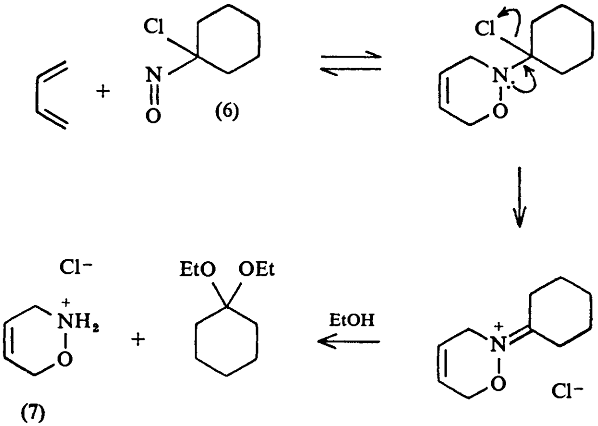
[8] J. Hamer, A. Ahmad, and R. E. Holliday, *J. Org. Chem.*, 1963, **28**, 3034.

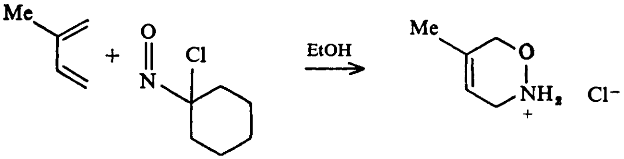
[9] G. Kresze, J. Firl, H. Zimmer, and U. Wollnik, *Tetrahedron*, 1964, **20**, 1605.

[10] *E.g.* O. Wichterle and J. Novak, *Coll. Czech. Chem. Comm.*, 1950, **15**, 309.

[11] See ref. 7 for a discussion.

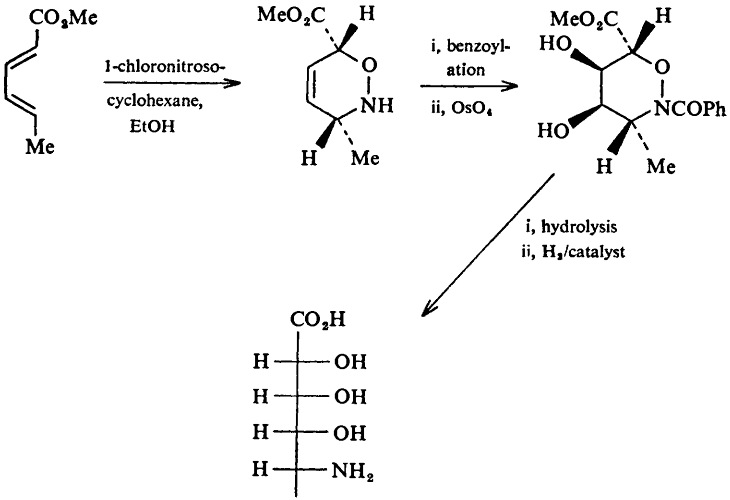
[12] N. J. Leonard, A. J. Playtis, F. Skoog, and R. Y. Schmitz, *J. Amer. Chem. Soc.*, 1971, **93**, 3056.





(I)

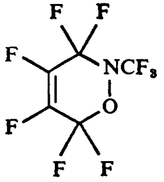
to the functionalization of dienes is considerable; an elegant example[13] is provided by the synthesis of (±)-5-amino-5,6-dideoxyallonic acid from methyl *trans-trans*-sorbate (Scheme 2).



Scheme 2

[13] B. Belleau and Yum-Kin Au-Young, *J. Amer. Chem. Soc.*, 1963, **85**, 64.

The influence of electron-withdrawing substituents on the reactivity of nitrosoalkanes is well illustrated by the chemistry of trifluoronitrosomethane (CF_3NO), which has been extensively studied by Haszeldine and his colleagues. They found[14] that CF_3NO rapidly undergoes a Diels–Alder reaction with buta-1,3-diene at −78 °C. Even perfluorobutadiene, which is unreactive towards conventional dienophiles, reacted, though more slowly, with CF_3NO to give (8) together with a 1 :1 alternating copolymer.



(8)

With the foregoing findings in mind, we considered the design of highly dienophilic *C*-nitroso-compounds based on two criteria: in the system C—N=O, the carbon atom (i) should be trigonal or digonal rather than tetrahedral, thereby reducing steric effects, and (ii) should form part of an electron-withdrawing functional group. The extent to which these criteria have been met in practice will be described in the sequel. It was realized, of course, that the reactivity of 'electrophilic *C*-nitroso-compounds' of this type would be fully displayed only in reactions with electron-rich dienes or other nucleophilic coreactants.

3 Nitrosyl Cyanide

In nitrosyl cyanide, O=N—C≡N, the nitroso-group is attached to a digonal carbon atom forming part of a powerfully electron-withdrawing [$\sigma_I(CN) = 0.56$; *cf.* $\sigma_I(CF_3) = 0.41$, $\sigma_I(NO_2) = 0.63$] cyano-group. Both criteria for a good, electrophilic dienophile are met. Curiously, nitrosyl cyanide, the cyanogen ('pseudo-halogen') analogue of the familiar nitrosyl halides, was not a well-characterized substance at the outset of our studies. Norrish and Smith[15] postulated the formation of nitrosyl cyanide in the photolysis of mixtures containing cyanogen and nitric oxide, and later, flash-photolysis experiments[16] supported this view. Further, mass spectrometric evidence for the formation of nitrosyl cyanide by photolysis of cyanogen iodide and nitric oxide had been reported.[17] However, conclusive evidence for the existence and structure of nitrosyl cyanide and information on its reactions with other molecules were lacking.

We elected to study the reaction of nitrosyl chloride with silver cyanide at low temperatures in the expectation that nitrosyl cyanide, if formed, could be

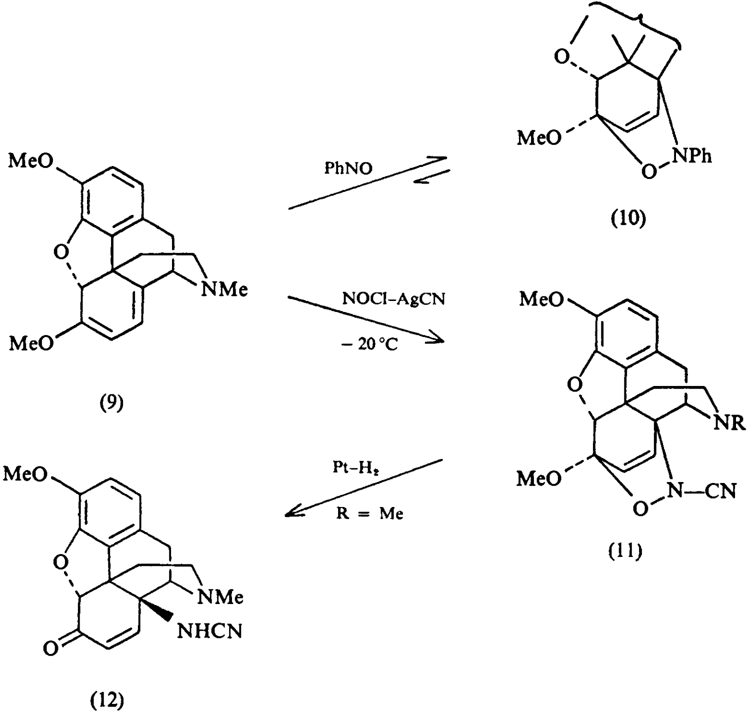
[14] R. E. Banks, M. G. Barlow, and R. N. Haszeldine, *J. Chem. Soc.*, 1965, 4714, 6149.

[15] R. G. W. Norrish and F. F. P. Smith, *Trans. Faraday Soc.*, 1928, **24**, 620.

[16] N. Basco, J. E. Nicholas, R. G. W. Norrish, and W. H. J. Vickers, *Proc. Roy. Soc.*, 1963, **A272**, 147; N. Basco and R. G. W. Norrish, *ibid.*, 1965, **A283**, 291.

[17] J. P. Galvin and H. O. Pritchard, *J. Phys. Chem.*, 1964, **68**, 1035.

readily trapped by a suitable conjugated diene. The alkaloid thebaine (9) was selected for this purpose. This somewhat esoteric choice was made in the knowledge that thebaine reacts with nitrosobenzene to give a single, crystalline adduct (10) in high yield.[18] Silver cyanide and nitrosyl chloride were found to react,[19] with formation of silver chloride, heterogeneously in chloroform at −20 °C. Addition of thebaine to the reaction mixture, at the same temperature, led to the formation of two adducts (11; R = Me or CH_2CN) of the expected type. The structure of (11; R = Me) was confirmed by catalytic hydrogenation to produce the cyanamido-ketone (12), presumably *via* the methyl hemiacetal arising from hydrogenolysis of the N—O bond. The other adduct (11; R = CH_2CN) became the major product when 'nitrosyl cyanide' was used in excess; it is still not clear whether this unusual cyanation of an *N*-methyl group was effected by nitrosyl cyanide itself or by other components of the reaction mixture. The adducts (11) were stable crystalline compounds which did not dissociate detectably in solution at room temperature. In contrast, the nitrosobenzene–thebaine adduct (10) exists, under these conditions, in mobile equilibrium with its components.[18] The rapid formation of (11) at low temperatures and this lack of dissociation both suggested that nitrosyl cyanide was, as predicted, powerfully dienophilic.



(9)

(10)

(11)

(12)

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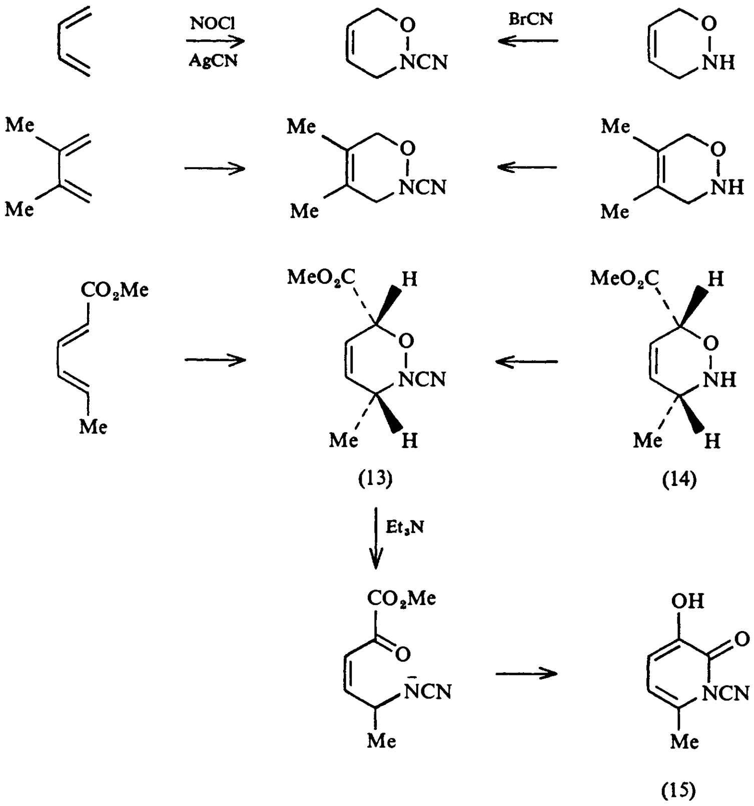
[18] K. W. Bentley, P. Horsewood, G. W. Kirby, and Serjinder Singh, *Chem. Comm.*, 1969, 1411.

[19] P. Horsewood and G. W. Kirby, *Chem. Comm*. 1971, 1139, and unpublished work.

The reactions of various simple butadiene derivatives with the NOCl–AgCN system were explored. In several instances it was possible to confirm the structures of the products by alternative syntheses from known oxazines. Examples are provided in Scheme 3. The formation of (13) in high yield (70%) from methyl *trans-trans*-sorbate is notable since the structure and stereochemistry of the parent oxazine (14) had been established earlier[13] (see above). Thus, at least in this case, nitrosyl cyanide behaved like other *C*-nitroso-compounds adding *cis* to the diene system with the preferred orientation[20] shown (13). Treatment of (13) with triethylamine caused rapid cleavage of the weak N—O bond and led, ultimately, to the *N*-cyanopyridone (15) in high yield.[20]



Scheme 3

The foregoing experiments, taken alone, did not provide conclusive evidence for the formation of nitrosyl cyanide. In principle, the *N*-cyanodihydro-oxazines might have been produced by consecutive reactions involving other components

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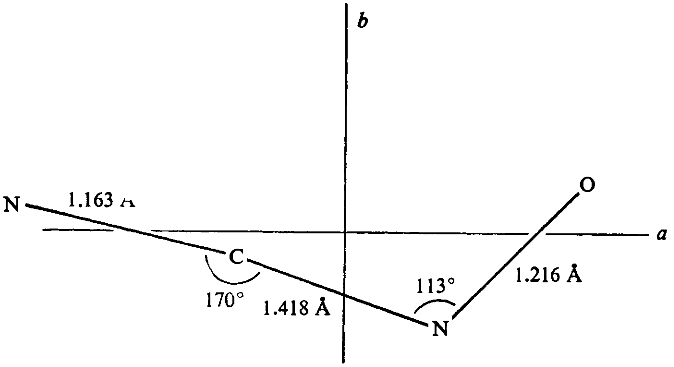
[20] *Cf.* J. Firl and G. Kresze, *Chem. Ber.*, 1966, **99**, 3695.

of the AgCN–NOCl system. More direct evidence was therefore sought. Nitrosyl chloride was condensed (preferably on a vacuum line) on to an excess of finely powdered, dry silver cyanide at −60°C. The mixture was vigorously stirred and the temperature allowed to rise slowly. At *ca.* −40°C a blue-green gas was detected above the reaction mixture and by −20°C this gas had filled the reaction vessel. Introduction of various dienes in suitable solvents, *e.g.* dichloromethane, to the vessel caused immediate discharge of the blue-green colour and led to the formation of the corresponding nitrosyl cyanide adducts. The colour of the gas (λ_{max} 738 nm) was indicative of a *C*-nitroso-compound, *i.e.* ONCN rather than ONNC, and a detailed spectroscopic study established its structure (see Figure) unequivocally. Samples of ONCN and the labelled species $O^{15}NCN$, $ONC^{15}N$, $ON^{13}CN$, and $^{18}ONCN$ were examined by microwave spectroscopy in a copper-waveguide Stark cell cooled with solid CO_2. The molecule was found[21] to be planar, within experimental error, with an OCN angle close to structural angle of ONCl. A surprising feature of the structure was the distinct bend about the carbon atom, although a similar effect had been observed[22] earlier in F_2NCN. The i.r. spectrum[23] of nitrosyl cyanide was entirely consistent with the microwave data; for example, bands at ν_{max} 2175, 1500, and 821 cm^{-1} could be attributed to the C≡N, N═O, and C—N stretching modes, respectively. So far, there is no evidence that nitrosyl cyanide dimerizes appreciably in the gas phase, and the characteristic colour of the monomer persists even in the liquid and solid states.



Figure

Nitrosyl cyanide, as prepared routinely from silver cyanide and nitrosyl

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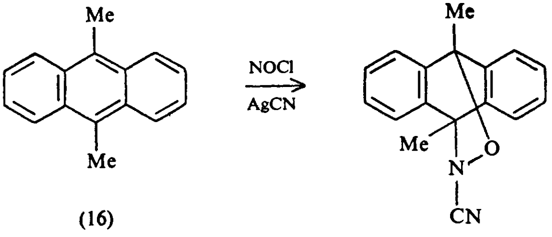
[21] R. Dickinson, G. W. Kirby, J. G. Sweeny, and J. K. Tyler, *J.C.S. Chem. Comm.*, 1973, 241.

[22] P. L. Lee, K. Cohn, and R. H. Schwendeman, *Inorg. Chem.*, 1972, **11**, 1920.

[23] J. A. Campbell and J. K. Tyler, unpublished work; E. A. Dorko and L. Buelow, *J. Chem. Phys.*, 1975, **62**, 1869.

chloride, is contaminated with NOCl, NO, NO_2, HCN, and ClCN. Purification on a small scale, for spectroscopic studies, can be carried out readily by vacuum-line techniques. However, this is inconvenient for preparative (1 g) work and may be hazardous.* The impure gas is suitable for many preparative purposes (see above) but the reactive impurities, especially NOCl and NO_2, may lead to the formation of troublesome by-products. An alternative method of generating nitrosyl cyanide was therefore devised.[24] Treatment of 9,10-dimethylanthracene (DMA) (16) with the impure gas gave the expected adduct (17). This was readily



(16) (17)

purified by chromatography and crystallization, and samples have been stored at room temperature for extended periods without decomposition. However, reversal of the Diels–Alder reaction with regeneration of the aromatic anthracene system was achieved under mild conditions. Thus when (17) was heated in benzene at 80°C with thebaine (9), rapid and quantitative intermolecular transfer of nitrosyl cyanide was observed with the formation of the thebaine adduct (11; R = Me) and the liberation of DMA. This transfer reaction with thebaine was followed kinetically in benzene at 40°C by observing the formation of DMA (absorption at 385 nm). First-order kinetics were observed with a rate constant, $k = 7.1 \times 10^{-5}\ s^{-1}$, insensitive to the initial concentration of thebaine. It appears therefore that, under these conditions, the adduct (17) dissociates (rate-determining step) into DMA and nitrosyl cyanide and the latter is captured rapidly, and effectively irreversibly, by the reactive diene, thebaine. This conclusion was reinforced by an experiment[25] with an efficient trapping agent of a different kind. When (17) was heated with triphenylphosphine (2 equivalents), first-order decomposition was again observed with a similar rate constant, $k = 6.8 \times 10^{-5}\ s^{-1}$ (40 °C in benzene); the products from the reaction are shown in Scheme 4. Deoxygenation of nitrosyl cyanide by triphenylphosphine has

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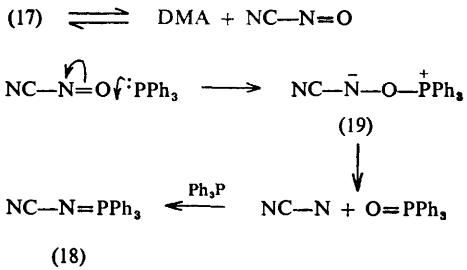
*We have observed rapid decomposition of impure nitrosyl cyanide in the condensed state and explosions may occur (Professor R. N. Haszeldine, personal communication; see also ref. 23). Also ONCN reacts with NO to give an explosive product (Professor B. G. Gowenlock, personal communication). Impure ONCN appears to be stable at −20 °C in the gas phase but clearly precautions should be taken in its preparation.

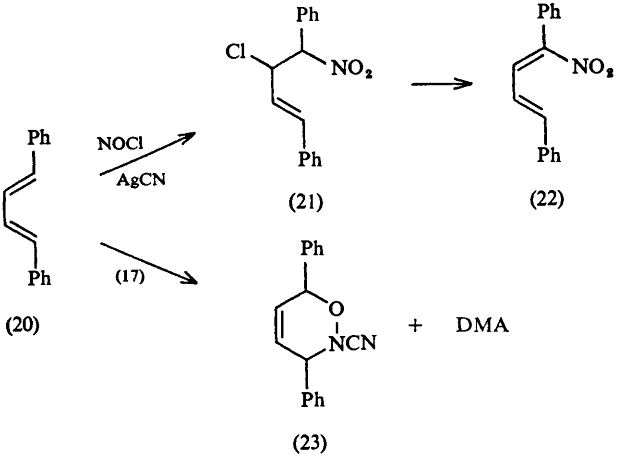
[24] P. Horsewood, G. W. Kirby, and J. G. Sweeny, unpublished work.

[25] J. E. T. Corrie, G. W. Kirby, and R. P. Sharma, *J.C.S. Chem. Comm.*, 1975, 915.



Scheme 4

ample analogy,[4] and formation of the known[26] phosphinimine (18) could occur by capture of cyanonitrene (as shown) or *via* direct attack by triphenylphosphine on the cyano-nitrogen of (19). The DMA,ONCN adduct (17) is stable for prolonged periods in benzene at 40°C in the absence of dienes or phosphines. Presumably, the adduct dissociates reversibly under these conditions but the equilibrium must lie heavily on the side of (17); the stationary concentration of ONCN is therefore very low and irreversible loss from the system inappreciable. The DMA,ONCN adduct provides therefore a convenient, clean source of ONCN for further studies. The following examples illustrate its use.[24]



Treatment of the diene (20) with impure ONCN gave a complex mixture from which the chloronitro-compound (21) was isolated and identified by conversion into the known[27] derivative (22). In contrast, the reaction of (20) with (17) proceeded cleanly to give the expected adduct (23). Similarly, norbornadiene

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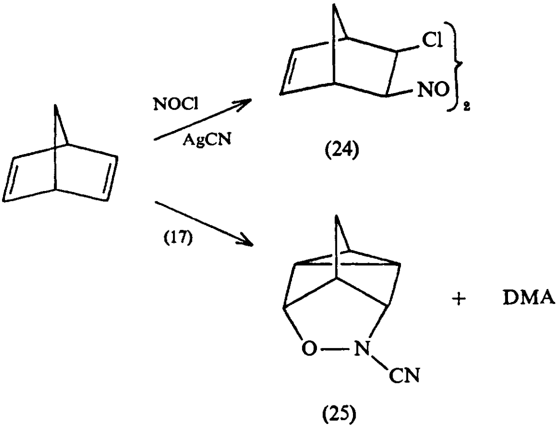
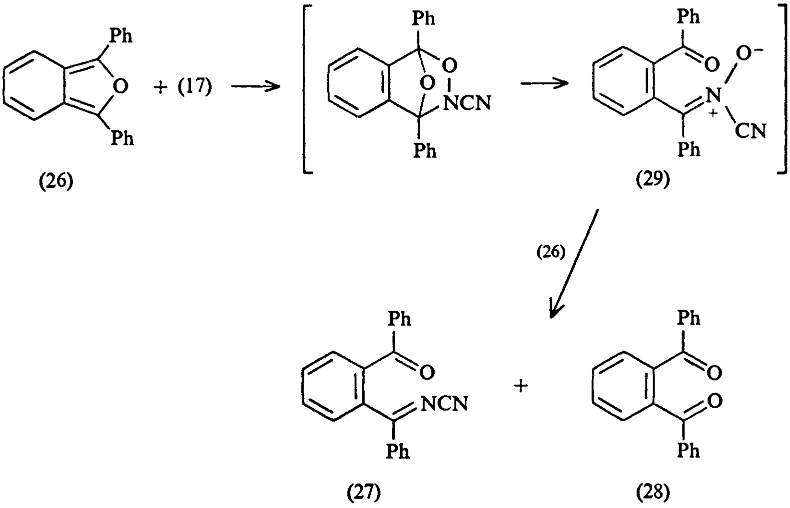
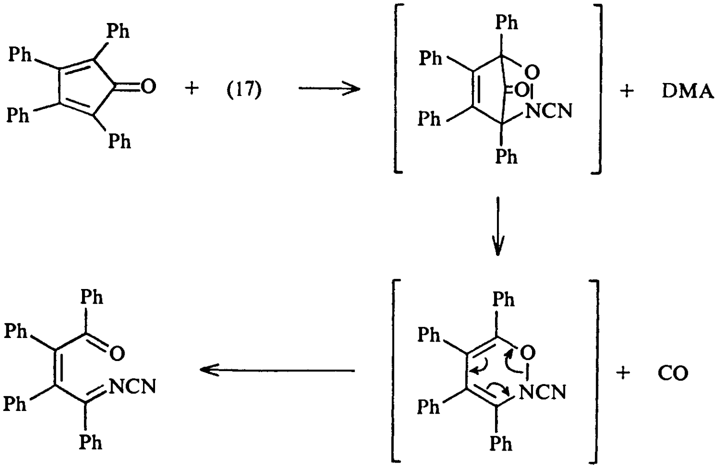
[26] F. D. Marsh and M. E. Hermes, *J. Amer. Chem. Soc.*, 1964, **86**, 4506.
[27] H. Wieland and H. Stenzl, *Ber.*, 1907, **40**, 4825.





reacted with impure ONCN to form the nitrosochloride dimer (24) as the only characterized product, but with (17) formation of the homodiene adduct (25) was observed. The reaction of (17) with 1,3-diphenylisobenzfuran (26) in benzene or dichloromethane was interesting in that two products, (27) and (28), were formed in approximately equal amounts, the latter being produced even with exclusion of moisture and oxygen. A speculation reaction scheme involving an *N*-cyanonitrone (29) has been considered but not proven. The reaction of (17) with tetraphenylcyclopentadienone was more straightforward (Scheme 5) and followed a path analogous to that observed[28] with nitrosobenzene.

[28] J. Rigaudy, G. Cauquis, and J. Baranne-Lafont, *Bull. Soc. chim. France*, 1969, 2756.



Scheme 5

4 *C*-Nitrosocarbonyl Compounds

The chemistry of nitrosyl cyanide suggested that compounds of the type RCONO (30) might likewise exhibit enhanced dienophilic or, more generally, electrophilic properties. Moreover, the group R might profitably be varied to control reactivity and to facilitate chemical modification of the reaction products. In this section the chemistry of the *C*-nitrosocarbonyl compounds (30; R = alkyl or aryl) will be considered.

Nitrosocarbonyl-alkanes and -arenes (30) had been proposed as transient intermediates in the oxidative cleavage of hydroxamic acids (31)[29] and the pyrolysis of alkyl nitrites in the presence of aldehydes.[30] However, there was no direct evidence for the existence of the species (30), the reaction products being, typically, acyl derivatives of various nucleophiles present in the reaction mixtures (Scheme 6). We reasoned that *C*-nitrosocarbonyl compounds, though short-lived, might be trapped in Diels–Alder reactions. Accordingly, the oxidation of hydroxamic acids (31) in the presence of conjugated dienes was investigated.[31] Addition of benzo- or aceto-hydroxamic acid at 0 °C to a solution containing thebaine (9) and tetraethylammonium periodate gave the corresponding adducts (32; R = Ph or Me) in high yield. The structure (32; R = Me) was confirmed by hydrolysis with hydrochloric acid to the enone (33) which by treatment with base followed by acetylation, afforded the compound (34). Curiously, similar hydrolysis of (32; R = Ph) proceeded with loss of the benzoyl

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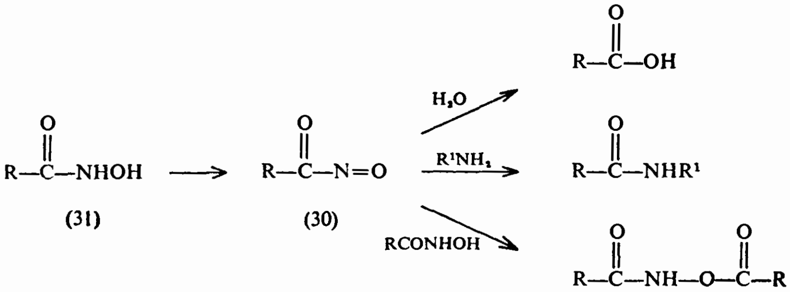
[29] B. Sklarz and A. F. Al-Sayyab, *J. Chem. Soc.*, 1964, 1318; J. E. Rowe and A. D. Ward, *Austral. J. Chem.*, 1968, **21**, 2761; U. Lerch and J. G. Moffat, *J. Org. Chem.*, 1971, **36**, 3391.

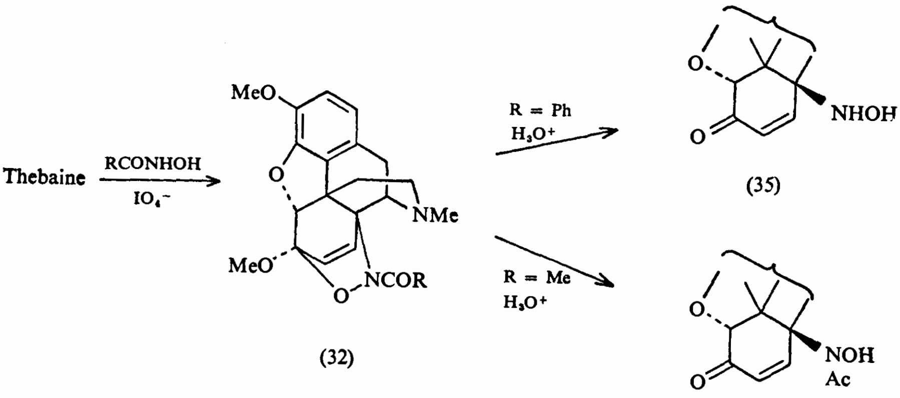
[30] A. L. J. Beckwith and G. W. Evans, *J. Chem. Soc.*, 1962, 130.

[31] G. W. Kirby and J. G. Sweeny, *J.C.S. Chem. Comm.*, 1973, 704, and unpublished work.



Scheme 6

group to give (35). This latter reaction has more recently been studied in some detail (Scheme 7).[32] Under milder conditions, (32; R = Ph) was converted into (36) which, upon further hydrolysis, produced (35). It appears that the intermediate (37), formed by acid-catalysed opening of the cyclic acetal (32; R = Ph), cyclizes to the labile compound (38), which is hydrolysed to (36). Support



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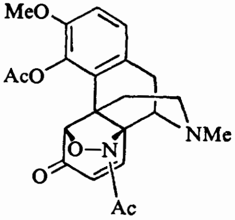

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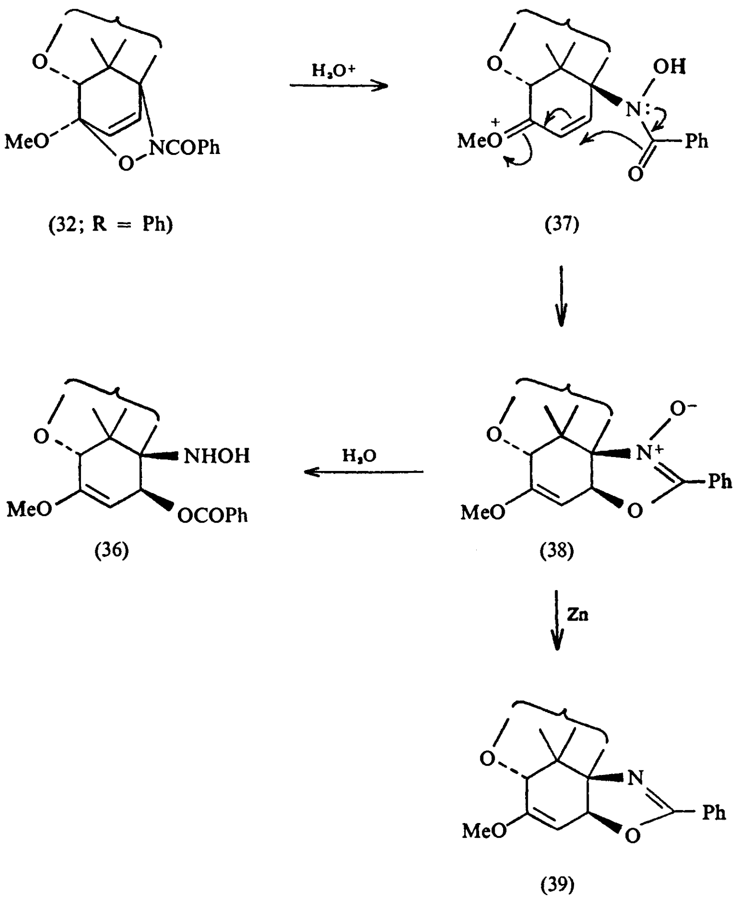
[32] G. W. Kirby and D. J. McDougall, unpublished work.

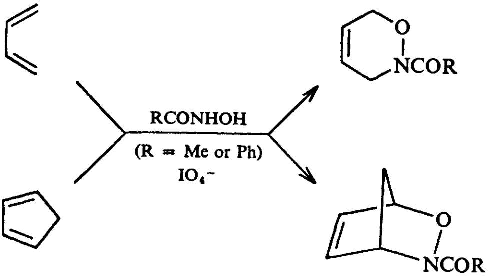


Scheme 7

for this mechanistic scheme came from the formation of (39) by treatment of (32; R = Ph) with zinc in acetic acid. As expected, simple conjugated dienes such as butadiene and cyclopentadiene also trapped the transient nitrosocarbonyl compounds efficiently [see reaction (II)].[33]

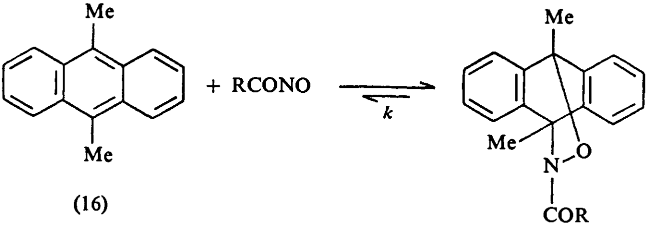
The foregoing syntheses of *N*-acyldihydro-oxazines are preparatively simple, proceed in high yield, and appear generally applicable for conjugated dienes lacking electron-withdrawing substituents. However, the postulated intermediates, RCONO, have, so far, not been detected by physical methods. Indirect evidence for the free existence of *C*-nitrosocarbonyl compounds was

[33] G. W. Kirby and J. W. M. Mackinnon, unpublished work.



(II)

nevertheless obtained in the following way.[31] Periodate oxidation of benzo- or aceto-hydroxamic acid in the presence of DMA (16) gave the expected adducts (40) which, like the nitrosyl cyanide adduct, were easily purified and stored. Each adduct (40) decomposed in hot benzene in the presence of thebaine to yield the corresponding adduct (32) of thebaine with release of DMA. As



(16)

(40)

before, the intermolecular transfer of RCONO was followed kinetically. First-order kinetics were observed (60°C in benzene) for the formation of DMA, with $k(\mathrm{R = Me}) = 4.4 \times 10^{-5}\,\mathrm{s}^{-1}$ and $k(\mathrm{R = Ph}) = 5.1 \times 10^{-5}\,\mathrm{s}^{-1}$. The analogy with the behaviour of DMA,ONCN (17) was therefore complete. Once again, these results are most simply explained if slow dissociation of the adducts (40) is followed by rapid capture of free RCONO by thebaine. However, unlike (17), the nitrosocarbonyl adducts (40) decomposed slowly in benzene at 60 °C in the absence of thebaine. It appears, therefore, that the species RCONO do not survive for long in the free state even at low concentration and in the absence of nucleophiles. On a preparative scale, the decomposition of (40; R = Ph) in benzene at 80°C gave[34] benzoic anhydride (73%) with evolution of N_2O (detected mass spectrometrically). The mechanism for this reaction is still not clear but it may involve dimerization of nitrosocarbonylbenzene as the first step.

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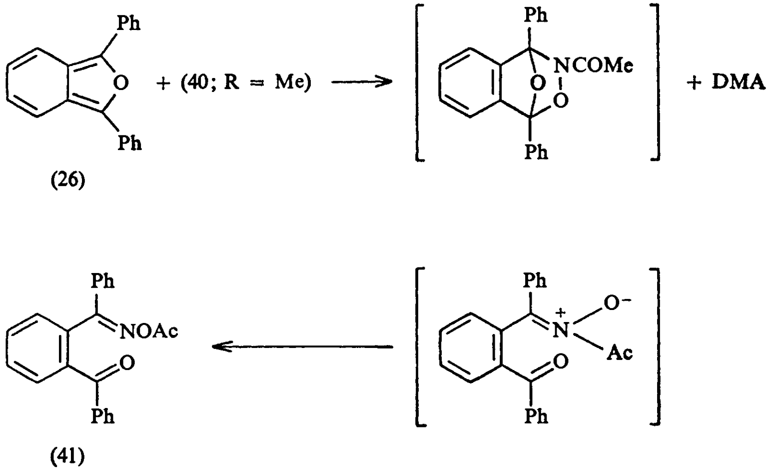
[34] J. E. T. Corrie and G. W. Kirby, unpublished work.

With supplies of various adducts (40) available it was possible to explore more generally the reactivity of *C*-nitrosocarbonyl compounds. In particular, co-reactants which would not survive the oxidative conditions used in the direct preparation of RCONO could be tested. The reaction of 1,3-diphenylisobenzfuran (26) (Scheme 8) with nitrosocarbonylmethane was investigated[31] in the hope of clarifying the corresponding reaction with nitrosyl cyanide. The major product, the oxime acetate (41), was that expected from the rearrangement of an *N*-acetylnitrone intermediate. This observation lends some support



Scheme 8

to the idea (see above) that an *N*-cyanonitrone (29) may be involved in the reaction of (26) with (17). The adducts of DMA with various nitrosocarbonylarenes (40; R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, and 4-$NO_2C_6H_4$) reacted in hot benzene with triphenylphosphine at rates closely similar to those with thebaine.[25] Aryl isocyanates were formed in high yield together with triphenylphosphine oxide and DMA. The overall transformation may be represented as shown [reaction (III)] with dissociation of the adducts as the rate-limiting step.

Nitrosoarenes are known[35] to react with certain mono-olefins by an 'ene' process leading to allylic hydroxylamines (42). *C*-Nitrocarbonyl compounds. released thermally from their DMA adducts, were likewise found to react with mono-olefins to form *N*-allylhydroxamic acids (Scheme 9).[33,34] However, the 'ene' reactions of *C*-nitrosocarbonyl compounds are generally slow relative to their Diels–Alder additions to conjugated dienes. An interesting exception

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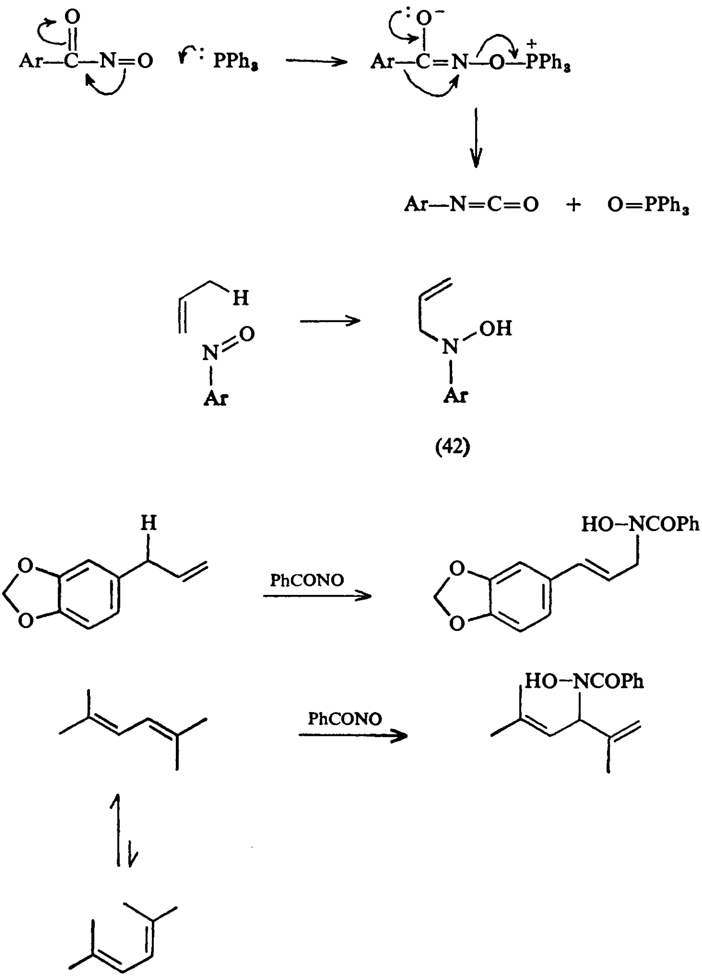
[35] G. T. Knight and B. Pepper, *Tetrahedron*, 1971, **27**, 6201; M. E. Cain, G. T. Knight, P. M. Lewis, and B. Saville, *Rubber J.*, 1968, **150**, 10; M. E. Cain, G. T. Knight, and P. M. Lewis, *Chem. and Ind.*, 1970, 126.

$$(40;\ R = Ar) \rightleftharpoons ArCONO + DMA$$



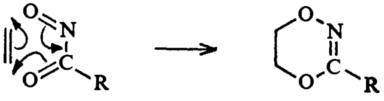
(III)

(42)

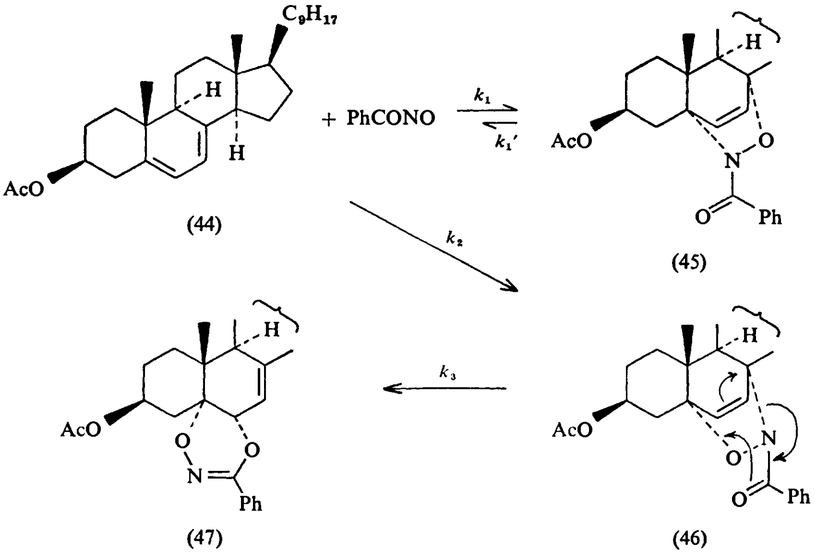
Scheme 9

to this rule is provided by 2,5-dimethylhexa-2,4-diene (Scheme 9), which cannot readily adopt the *cisoid* conformation required for the Diels–Alder reaction: this diene was found to react slowly with nitrosocarbonylbenzene [from (40; R = Ph)] to yield only the 'ene' reaction product.[33]

In principle, a mono-olefin might undergo Diels–Alder, $(4\pi + 2\pi)$ cycloaddition to a nitrosocarbonyl compound with the latter providing the 4π-component. A favourable feature of this process, energetically, would be the conversion of a nitroso-group into an oximino-group (see above). So far, no reaction of this kind is known but the formation of dioxazines [as (43)] has been observed in an unexpected way.[36] Nitrosocarbonylbenzene was generated, by periodate oxidation of benzohydroxamic acid, in the presence of ergosteryl acetate (44). Examination of the reaction mixture by n.m.r. spectroscopy revealed the presence of the two expected adducts, (45) and (46), in a ratio of *ca.* 1:1.6. When the reaction mixture was warmed (to *ca.* 60 °C) (45) remained unchanged but (46) was converted into the dioxazine (47) (Scheme 10). Similar results were observed with other nitrosocarbonylarenes. The conversion of (46) into (47) is thought to occur by an intramolecular, [3,3] sigmatropic rearrangement rather than *via*



(43)

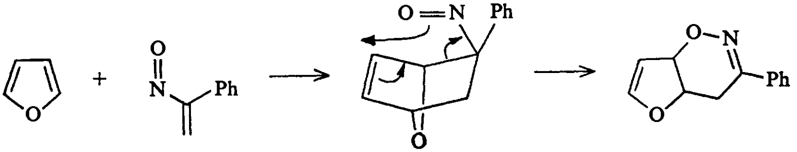


$k_2 > k_1 \gg k_3 \gg k_1'$

Scheme 10

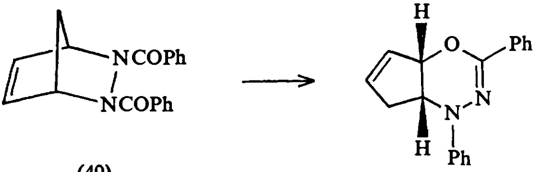
[36] G. W. Kirby and J. W. M. Mackinnon. *J.C.S. Chem. Comm.*, 1977, in press (Com. 1268).

dissociation (retro-Diels–Alder reaction) followed by recombination in the alternative mode. If dissociation occurred, then the liberated PhCONO should be trappable[25] with triphenylphosphine. However, the isomerization of (46) to (47) took place cleanly even in the presence of excess triphenylphosphine. In contrast, when (45) was heated (111 °C) with triphenylphosphine, slow but efficient formation of ergosteryl acetate (44) was observed. In the absence of triphenylphosphine, (45) isomerized slowly at 111 °C to give the thermodynamically stable adduct (47), presumably *via* (46). The isomerization, (46) → (47), appears to represent a new type of sigmatropic rearrangement, although two interesting and close analogies had been reported previously. α-Nitrososostyrene reacts with furan (and other cyclic dienes) to afford the product (48) apparently



(48)

via rearrangement of a transient adduct of the conventional type.[37] Also, the relatively stable cyclopentadiene adduct (49) rearranges upon heating to the oxadiazine derivative (50).[38]



(49)

(50)

5 *O*-Nitrosocarbonyl Compounds

The *O*-nitrosocarbonyl compounds or nitrosoformates, ROCONO, were investigated in the expectation that they too would behave as reactive dienophiles. This was found to be so.[39] Thus, oxidation of *N*-benzyloxycarbonylhydroxylamine (51; R = $PhCH_2$)[40] or *N*-t-butoxycarbonylhydroxylamine (51; R = Bu^t)[41] with periodate in the presence of thebaine (9) gave the expected adducts (52) in high yield. The adducts of benzyl nitrosoformate with 9,10-dimethylanthracene

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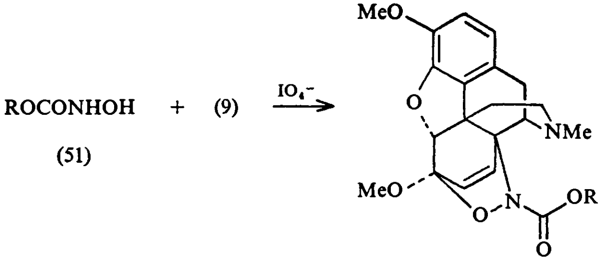
[37] R. Faragher and T. L. Gilchrist, *J.C.S. Chem. Comm.*, 1976, 581.

[38] D. Mackay, J. A. Campbell, and C. P. R. Jennison, *Canad. J. Chem.*, 1970, **48**, 81; J. A. Campbell, D. Mackay, and T. D. Sauer, *ibid.*, 1972, **50**, 371.

[39] G. W. Kirby, J. W. M. Mackinnon, and R. P. Sharma, *Tetrahedron Letters*, 1977, 215.

[40] E. Boyland and R. Nery, *J. Chem. Soc.* (*C*), 1966, 354.

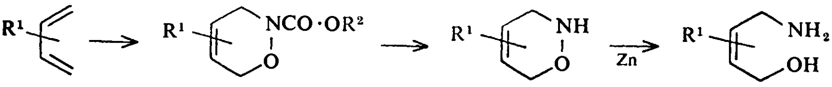
[41] L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Amer. Chem. Soc.*, 1959, **81**, 955.



(51)

(52)

(DMA) and simpler conjugated dienes were likewise prepared without difficulty. It appeared, therefore, that the dienophilic properties of the nitrosoformates generally resembled those of the *C*-nitrosocarbonyl compounds. This correspondence between the two series was reinforced by observing the transfer of benzyl nitrosoformate from its DMA-adduct to thebaine, to yield (52; R = $PhCH_2$) essentially quantitatively. The first-order rate constant, *k*(60 °C in benzene) = 4.3×10^{-4} s^{-1}, for the release of DMA, was *ca.* 10 times greater than that measured for DMA, MeCONO (40; R = Me). The use of dihydro-oxazines in the synthesis of 4-amino-alcohols from conjugated dienes has been referred to earlier. The *N*-alkoxycarbonyl derivatives (53) should be well suited for this

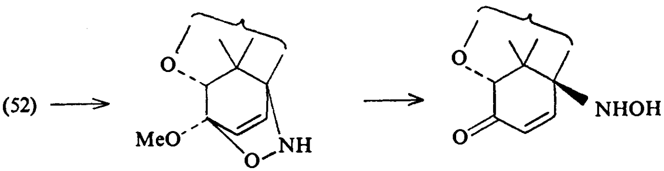


(53)

(54)

Scheme 11

purpose (Scheme 11) since they are readily prepared and, with appropriate choice of R^2, de-acylated. For example, the butadiene adduct (53; R^1 = H, R^2 = $PhCH_2$) was cleaved by hydrogen bromide in acetic acid to yield the parent dihydro-oxazine (54; R^1 = H) as the hydrobromide.[33] Also, the thebaine adduct (52; R = Bu^t) gave 14-hydroxyaminocodeinone (35), presumably *via* (55), in high



(55)

(35)

yield when treated with methanolic hydrogen chloride.[39] The use of other alkoxycarbonyl, 'protecting' groups removable under basic or reductive conditions is currently being explored.

Prosser *et al.*[42] had earlier made the interesting suggestion that nitrosoformates might be generated by transfer of oxygen to alkoxycarbonylnitrenes. They studied the thermal decomposition of octadecyl azidoformate in dimethyl sulphoxide (DMSO) at 120°C and proposed the reaction sequence shown to

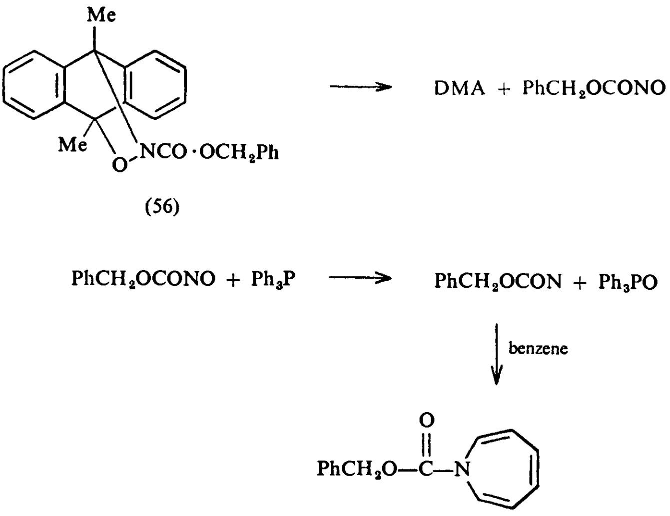
$$\mathrm{ROCON_3} \longrightarrow \mathrm{ROCON} + \mathrm{N_2}$$

$$\mathrm{ROCON} + \mathrm{Me_2SO} \longrightarrow \mathrm{ROCONO} + \mathrm{Me_2S}$$

$$\mathrm{ROCONO} \longrightarrow \mathrm{R}\cdot + \mathrm{CO_2} + \mathrm{NO}$$

account for the formation of dimethyl sulphide, carbon dioxide, and nitric oxide. A solid product of the reaction was assumed to be the sulphoximine, $\mathrm{ROCON{=}SOMe_2}$, formed by competitive attack of the nitrene on the sulphur, rather than the oxygen, atom of DMSO. There was no direct evidence for the formation of octadecyl nitrosoformate, but we considered that a trapping experiment might be revealing.[39] Accordingly, thebaine was heated in DMSO with an excess of benzyl or t-butyl azidoformate until decomposition of the azide was complete. The adducts (52; R = $\mathrm{PhCH_2}$ or $\mathrm{Bu^t}$) were then isolated from the reaction mixture in good yield (based on thebaine). Decomposition of the azides in DMSO in the absence of thebaine gave the corresponding sulphoximines as the major products. These experiments suggested that nitrenes, at least those of the non-rearranging, 'starre' type, may indeed be oxidizable to nitrosoformates. This conclusion prompted a search for the converse process, namely, the de-oxygenation of nitrosoformates to produce alkoxycarbonyl nitrenes. The oxidizing conditions used for the direct production of nitrosoformates from hydroxamic acids were, of course, inappropriate. Instead, the adduct (56) was employed.[43] When (56) was heated in benzene in the presence of one or two equivalents of triphenylphosphine a mixture was obtained from which the azepine (57) was isolated in 20—30% yield. The structure of the labile product (57) was first recognized from the n.m.r. spectrum and then confirmed by the isolation of identical material from the thermolysis of benzyl azidoformate in benzene at 120°C. *N*-Acylazepines of the type (57) are characteristic products from the reactions of alkoxycarbonylnitrenes with benzene.[44] The formation of (57) from (56) is therefore most simply, though not uniquely, explained by the reaction sequence shown (Scheme 12).

[42] T. J. Prosser, A. F. Marcantonio, and D. S. Breslow, *Tetrahedron Letters*, 1964, 2479.
[43] G. W. Kirby and R. P. Sharma, unpublished work.
[44] 'Nitrenes', ed. W. Lwowski, Interscience, New York, 1970.



(56)

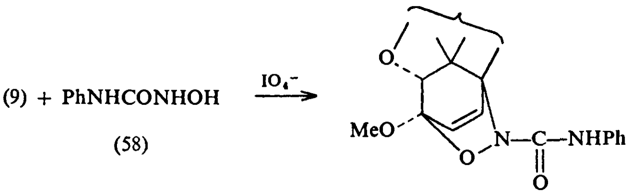
(57)

Scheme 12

6 Other Electrophilic *C*-Nitroso-Compounds

The *C*-nitrosocarbonyl compounds and nitrosoformates exemplify a more general class of substances, XC(=Y)NO, where X may be, *inter alia*, H, C, N, O, S, or halogen, and Y may be an electronegative element, *e.g.* N, O, or S. Many representatives of this class have yet to be prepared but two recent examples will be described here to illustrate the directions further research might take.

The *C*-nitrosoformamides (X = N and Y = O) appear to be experimentally accessible by the standard methods described in earlier sections of this review. Thus, periodate oxidation of the *N*-hydroxyurea (58) in the presence of thebaine (9) gave an adduct which was assigned, on spectroscopic grounds, the structure (59).[33] It remains to be seen whether electron donation from the amido-nitrogen

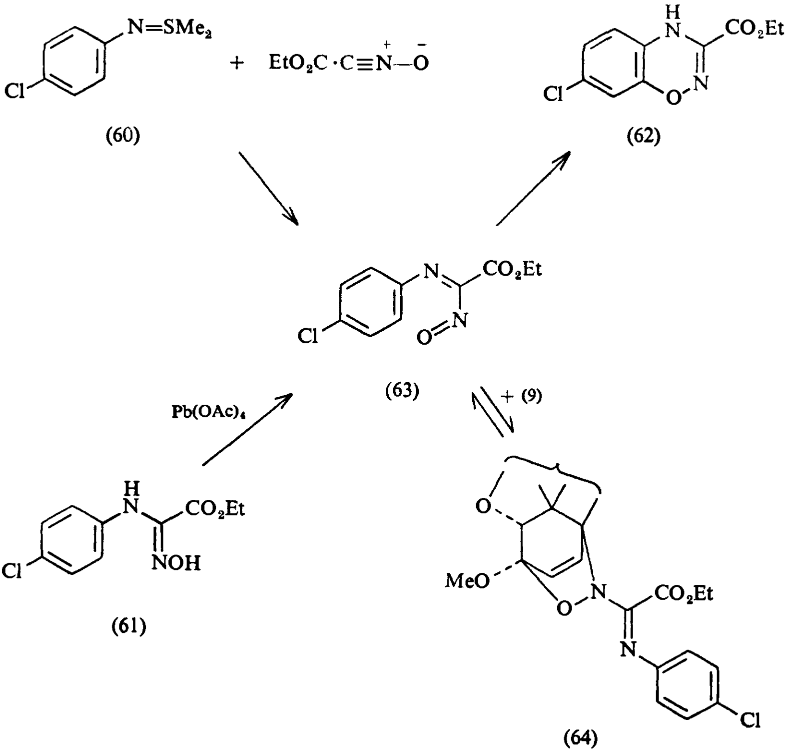


(58)

(59)

of the transient species, PhNHCONO, will modify significantly its dienophilic character and stability.

Clear evidence for the transient existence of *C*-nitrosoimines (X = C, Y = N) has emerged from the work of Rees *et al.* on the formation of 1,2,4-benzoxadiazines (Scheme 13).[45] Treatment of the sulphimide (60) with ethyl cyanoformate *N*-oxide or oxidation of the amidoxime (61) with lead tetra-acetate gave the same benzoxadiazine (62). They reasoned that the *C*-nitrosoimine (63) might be



Scheme 13

a common intermediate and, in support of this, found that both reactions, when conducted in the presence of thebaine (9), gave an adduct (64) of the expected type. This adduct dissociated in hot benzene to yield thebaine and (62). An interesting illustration of the electrophilic properties of the nitroso-group was provided by the oxidation of (65) to give the *N*-oxide (66); again, the intermediate *C*-nitrosoimine was trapped efficiently by thebaine.

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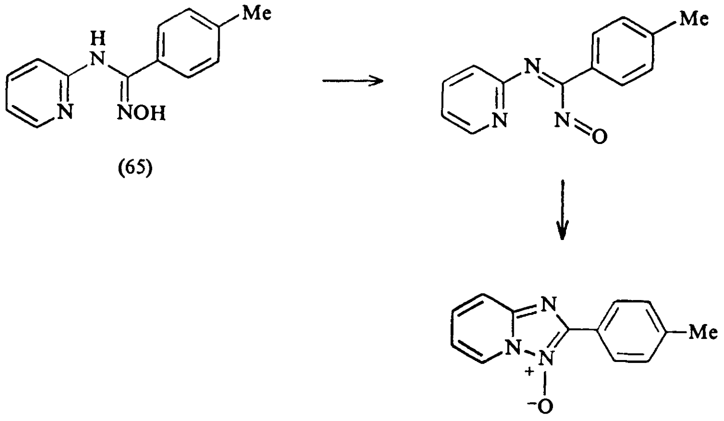
[45] T. L. Gilchrist, M. E. Peck, and C. W. Rees, *J.C.S. Chem. Comm.*, 1975, 913, 914.



(65)

(66)