3aH-INDENES AND THEIR HETEROCYCLIC ANALOGUES

C.W. Rees

Department of Organic Chemistry, University of Liverpool, England

Abstract - Whilst studying the use of sulphimides, $RN=SMe_2$, in heterocyclic synthesis
we found that N-arylamidinosulphimides can be cleaved photolytically to give
imidoylnitrenes which then cyclise to benzimidazoles. When both ortho positions
of the N-aryl group are substituted, cyclisation still occurs to give a variety of products
derived by rearrangement of the initially formed 3aH-benzimidazole; skeletal
rearrangements, [1,5] -, and the rare [1,9]-sigmatropic shifts are proposed. When
only one ortho position of the N-aryl group is substituted cyclisation sometimes occurs
at this position, as well as at the unsubstituted position, and indeed this unusual
process can predominate.
        Since the proposed 3aH-benzimidazole intermediates could not be isolated,
we have undertaken a more general study of their synthesis and of the parent
carbocyclic 3aH-indene system; they are still elusive.

The sulphur nitrogen ylides, sulphimides $R\bar{N}—\overset{+}{S}R_2^{\bullet}$, in which a nucleophilic nitrogen bears a good
leaving group, have considerable potential in organic synthesis. [1] They have an obvious relationship
with the sulphonium ylides, $R_2\bar{C}—\overset{+}{S}R_2$, on the one hand, and with organic azides, $R\bar{N}—N_2^{+}$, on the
other. We have developed the former analogy by studying their reactions with various electrophilic
substrates, [2] and have considered the latter where, by nitrogen-sulphur bond cleavage, they could
provide a source of nitrenes. This latter could be especially useful when the corresponding azide
is not available or does not have suitable reactivity. We have shown, for example, that photolysis
of the readily prepared N-(N-arylimidoyl)sulphimides provides a good method of synthesising
benzimidazoles. A possible mechanism involves nitrogen-sulphur bond cleavage to the imidoylnitrene,
which cyclises to a 3aH-benzimidazole and thence to a 1H-benzimidazole (Scheme 1). [3]

SCHEME 1
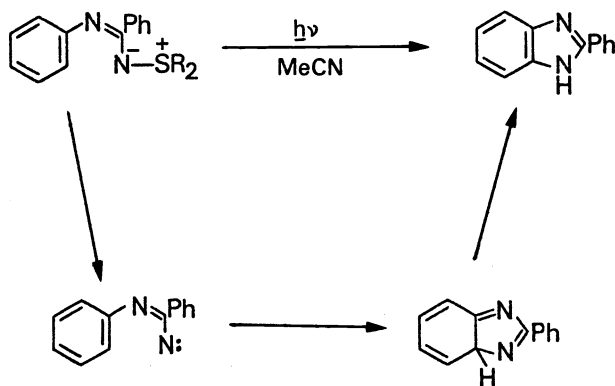
A number of other photochemical and thermal reactions which give benzimidazoles [4] can be rationalised
in the same way. In keeping with the participation of an electron deficient nitrogen species, the
analogous sulphimide with an adjacent nucleophilic nitrogen (Scheme 2) gave the pyridotriazole very

readily on photolysis, and on mild thermolysis; ring closure was exclusively to nitrogen rather than carbon.
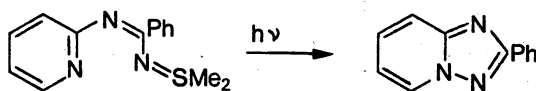
SCHEME 2

We wished to discover more about the mechanism of these reactions and, in particular, to obtain evidence for the intermediacy of 3aH-benzimidazoles. We had previously found that with only one ortho methyl or chloro group present, the cyclisation went exclusively to the other, unoccupied ortho position, to give benzimidazoles in the usual way. [3] With both positions occupied, however, if cyclisation of the nitrene still occurred, the resulting 3aH-benzimidazole seemed less likely to aromatise.

We first photolysed sulphimides where the ortho substituents were simple alkyl groups, such as the mesityl compound shown in Scheme 3. Together with much dark coloured, polar material, the carbodiimide, Mesityl N=C=NPh, and the cyclopentapyrimidine shown were
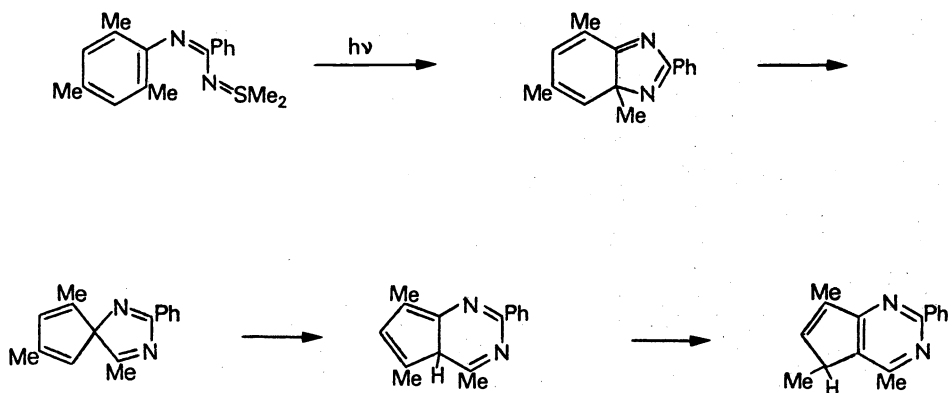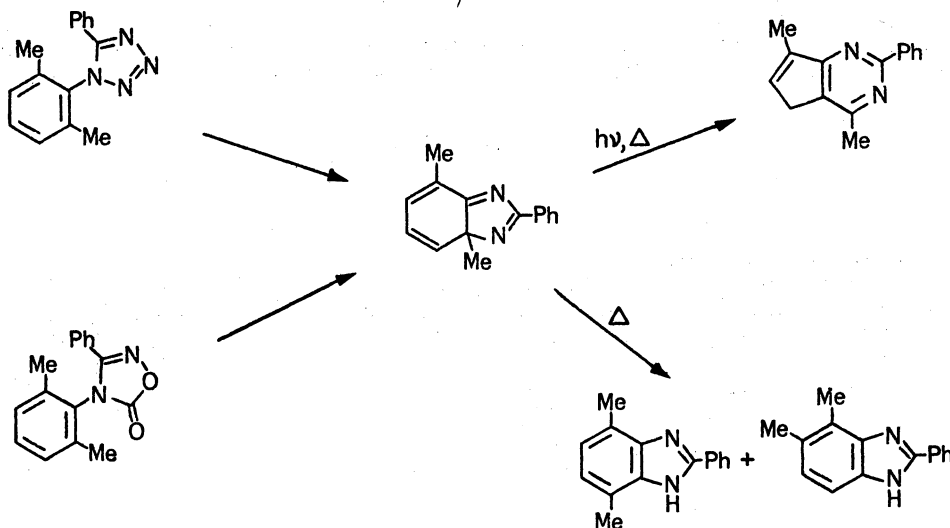
SCHEME 3

produced in modest amounts. The carbodiimide was the expected product of a Curtius-type 1,2-phenyl shift, possibly concerted with loss of the dimethyl sulphide, but the cyclopentapyrimidine was unexpected. We consider that the most economical explanation for its formation, and the one with the best literature precedents, is that illustrated in Scheme 3. Cyclisation of the imidoylnitrene leads to a 3aH-benzimidazole with a bridgehead methyl group. Although this could aromatise by a [1,5] methyl shift to nitrogen, there is an alternative, lower-energy pathway i.e. [1,5] vinyl shift to the spiro compound shown. The cyclopentapyrimidine can then be

derived by successive [1,5] imidoyl and hydrogen shifts. Circumstantial evidence which support our mechanism includes the following.

(i)   [1,5] Vinyl shifts occur in preference to [1,5]Me shifts both in five-membered carbocyclic [5] and heterocyclic systems.[6]

(ii)   A [1,5] imidoyl shift has also been found to occur with great facility, and in preference to a [1,5]Me shift. [7]

(iii) [1,5] Rearrangement of spiro [4,4] nonatetraene to 3aH-indene itself takes place with a low activation energy, [8] and heterocyclic counterparts of this rearrangement also occur with great facility.[9]

On the basis of these analogies it seems reasonable to assume that all the steps in the rearrangement of 3aH-benzimidazoles to cyclopentapyrimidines are low energy thermal processes; attempts to intercept the intermediates as Diels-Alder adducts with dimethyl acetylenedicarboxylate or cyclohexene were unsuccessful. We decided, therefore, to generate the initial imidoyl nitrene from alternative precursors, which could be decomposed thermally, as well as photochemically. The tetrazole and oxadiazolone shown in Scheme 4 were chosen since, by analogy with the literature, [10,11] extrusion of nitrogen and carbon dioxide should give the required nitrene.

SCHEME 4

Photolysis did indeed follow a very similar course to that of the corresponding sulphimide, to give the same cyclopentapyrimidine as well as carbodiimide. The thermal decompositions were best carried out in the vapour phase under unimolecular conditions, as flash vacuum pyrolyses at 600°/0.01mm. Again the tetrazole and oxadiazolone gave a similar pattern of products. The carbodiimide now proved to be the major product, but the cyclopentapyrimidine was again formed, together with a small amount (10%) of a 1:1-mixture of 4,5- and 4,7-dimethyl-2-phenylbenzimidazole. These isomers could not be separated but were identified by comparison with a mixture of the independently synthesised benzimidazoles.

The formation of these dimethylbenzimidazoles, observed only in the pyrolyses, can also be logically rationalised in terms of the key 3aH-benzimidazole intermediate (Scheme 5) where the bridgehead methyl group has migrated to the 5- and 7- positions only. They could arise, as outlined in the Scheme by a simple sequence of symmetry-allowed
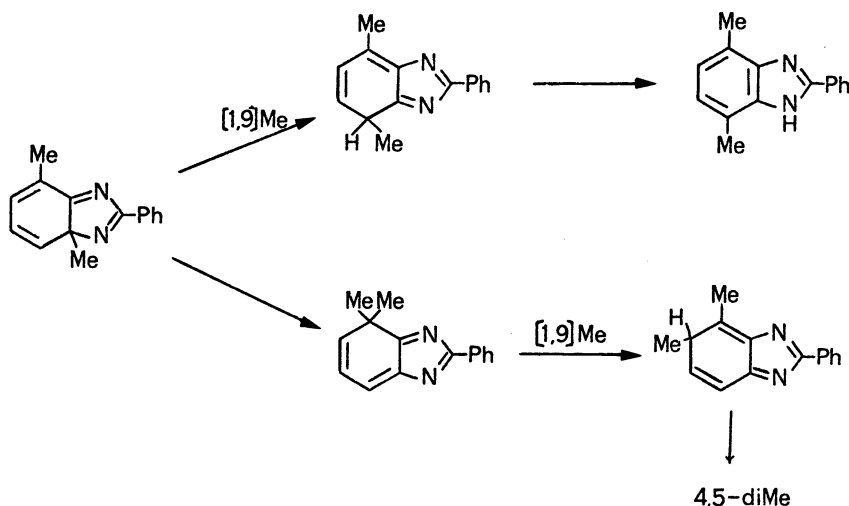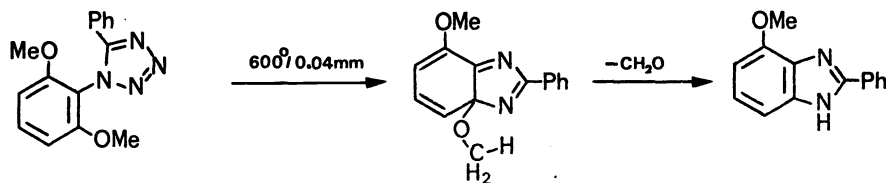

SCHEME 5

sigmatropic shifts of methyl, followed by hydrogen. The most favourable of these involve migration to an adjacent atom, thus allowing a favourable overlap in the transition state. In addition to the well known [1,5] shifts, we also propose [1,9] shifts involving the whole of the peripheral π-electron system. The 4,7-dimethyl product could arise by one [1,9] Me migration only, whilst the 4,5-dimethyl isomer could most simply arise from the gem-dimethyl compound shown; this could be formed by a [1,5] and a [1,9] shift to adjacent atoms, or by one [1,5] shift across the six membered ring.

[1,9] Sigmatropic alkyl shifts, though thermally allowed, had not been reported when this work was carried out, [12] though a [1,9] inter-oxygen alkyl migration has recently been proposed in the thermal rearrangement of tropolone ethers. [13] The 3aH-benzimidazoles and related systems described here provide a favourable bond arrangement (cf Figures 1 and 2 below) for such shifts to take place, especially at the high temperatures of the flash pyrolyses where activation energy differences between the alkyl and vinyl shifts become less significant.

Further evidence for 3aH-benzimidazole intermediates was sought by flash vacuum pyrolysis of 1-(2,6-dimethyoxyphenyl)-5-phenyltetrazole (Scheme 6). If such an intermediate was involved, the bridgehead methoxyl group might well be lost, as formaldehyde, in a retro-ene

process faster than any of the possible sigmatropic shifts. A similar loss of methoxyl in just

SCHEME 6

cf.
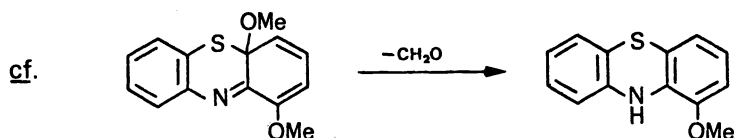
SCHEME 7

this way (Scheme 7) has been reported previously. [14] In our case this would result in the formation of 4-methoxy-2-phenylbenzimidazole, and this was indeed the isolated product, to the exclusion of the dimethyoxybenzimidazole or the corresponding cyclopentapyrimidine.

We hoped to shed further light on the mechanism of these reactions by designing an imidoylnitrene which could close either onto a blocked conjugated position or an unblocked unconjugated position, and the naphthalene system of Scheme 8 was chosen. Photolysis of this naphthyltetrazole gave the diazafluorene, together with its oxidation product, the fluorenone, in
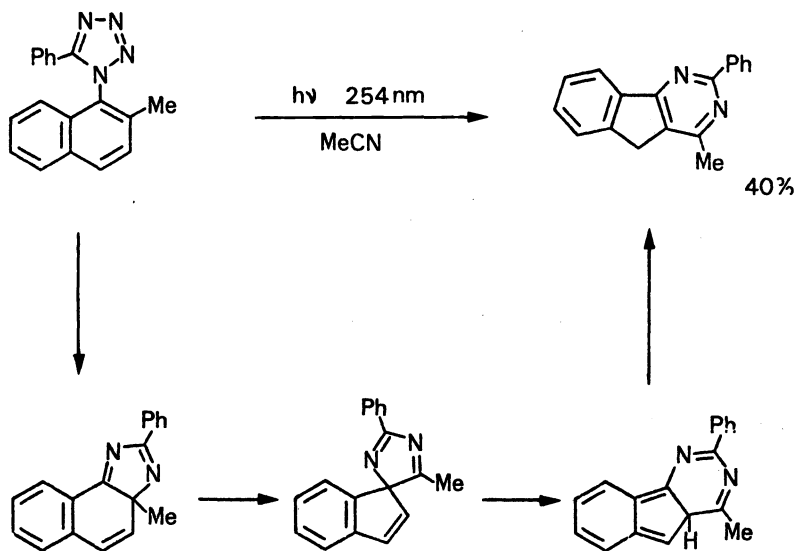

SCHEME 8

substantial yield, to the exclusion of any product of closure of the nitrene onto the 8-position of the naphthalene ring. This result indicates that the ring closure is an electrocyclic process and is not primarily directed by the electrophilicity of the nitrene; if the nitrene was acting simply as an electrophile, some attack at the 8-position, to give a very stable perimidine, would be expected.

In view of the molecular rearrangements undergone by these proposed 3aH-benzimidazole intermediates it seemed interesting to vary the ortho blocking substituents. Groups which migrate more readily than vinyl should favour the formation of benzimidazoles at the expense of cyclopentapyrimidines. The presence of different ortho substituents in the same molecule should lead, competitively, to two 3aH-benzimidazoles, and hopefully provide further mechanistic information.

The first such system that we investigated had a methyl and an ester as the ortho blocking groups (Scheme 9). Photolysis of this tetrazole gave the two products shown, in
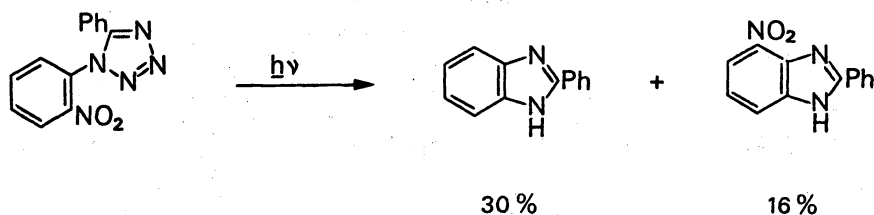

SCHEME 9
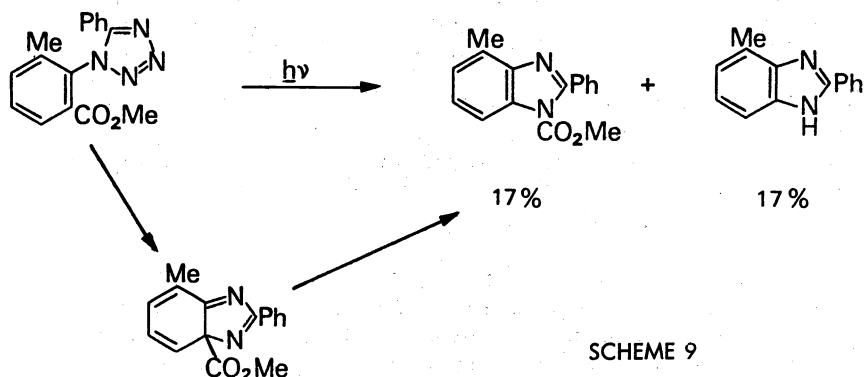
reasonable combined yield, the second product being formed from the first by hydrolysis. These products have presumably arisen from the 3aH-benzimidazole with a bridgehead ester group, which has undergone the expected [1,5] ester shift to nitrogen.[15] From our earlier results with the 2,6-dimethyl compound we could anticipate what products would result from closure of the nitrene onto the methyl-bearing carbon, and none of these were detected. If our general mechanistic scheme is correct, the nitrene is thus closing selectively to the ring carbon bearing the ester rather than the methyl group. In view of this unexpected selectivity, we photolysed the tetrazole with the methyl blocking group removed, where competition for cyclisation would be between an unsubstituted position and the ester substituted position (Scheme 10). We wondered whether there might now be some attack at the

43 %

29 %

10 %

SCHEME 10
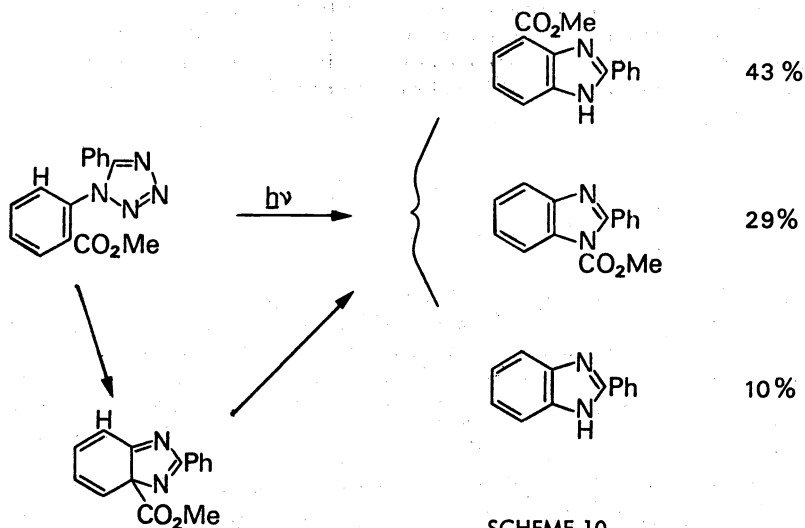
substituted position. The reaction was particularly clean, yielding the three benzimidazoles shown in high combined yield (82%). 2-Phenylbenzimidazole was shown, by control experiments, to be formed from its N-methoxycarbonyl derivative under the reaction conditions, and thus the two primary products, the 1- and 4- methoxycarbonyl compounds, are formed in about equal amounts.   The 4-CO$_2$Me product most simply derives from nitrene closure onto the free ortho position, as observed before, [3] but we believe that the N-CO$_2$Me compound cannot be derived from the same intermediate. It is, however, the expected product of [1,5] ester shift to nitrogen in the 3aH-benzimidazole intermediate shown. Thus we conclude that, in this example at least, cyclisation to the substituted position is competitive with cyclisation to the unsubstituted position. This is a sufficiently rare occurrence, for which convincing explanations are lacking, to justify further investigation. We are now exploring the decomposition of related tetrazoles with the ester group replaced by other groups with representative electronic and steric features.

The mononitro compound (Scheme 11) gave 2-phenyl- and 4-nitro-2-phenylbenzimidazole

30 %   16 %

SCHEME 11

in the yields shown. The latter product could most simply be formed by nitrene cyclisation to the open position, but the former, higher-yield product cannot. Since the nitro group has been lost from this product we must assume that the nitrene has closed onto the nitro-bearing carbon to give the 3a-nitrobenzimidazole. This could now conceivably lose the nitro group directly by hydrolysis, but [1,5] NO$_2$ shift to ring nitrogen followed by hydrolysis of the N-nitrobenzimidazole seems more reasonable. Control experiments show that 4-nitro-2-phenylbenzimidazole was not converted into 2-phenylbenzimidazole under the photolysis conditions. Thus again nitrene closure appears to occur at the substituted, as well as the unsubstituted position, and in this case it predominates. Indeed, since the 4-nitro product could also have been formed from the 3a-nitro intermediate by a [1,9] NO$_2$ shift to carbon, it is just possible that here cyclisation could be exclusively to the substituted position. However in preliminary experiments where the ortho substituent is cyano, aminocarbonyl, and pyrrolidinocarbonyl, cyclisation appears to be largely or exclusively to the unblocked position, unless again the bridgehead substituent is undergoing a [1,9] shift to adjacent carbon. This possibility will be tested by further labelling of the ring positions.

All the above results have been explained on the basis of 3aH-benzimidazole intermediates, but these could not be isolated or intercepted, even under the mild photochemical conditions. Furthermore, there are surprisingly few references in the literature to these structures, the parent carbocyclic system, 3aH-indenes, its tricyclic valence tautomer (Scheme 12), and
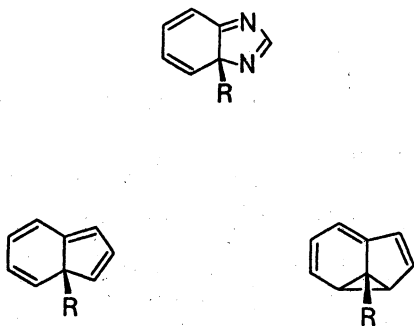
SCHEME 12

other aza analogues. 3aH-Indene has itself been proposed by Semmelhack as an intermediate in the thermal isomerisation of spiro[4.4]nonatetraene to indene, though it was too transient to be detected.[8] An earlier report of the same isomerisation of tetraalkyltetrachloro derivatives of this spiro compound was also thought to involve the analogous intermediate in which a bridgehead alkyl group has to migrate.[16] The only examples of isolable compounds of this type that we have located are heavily substituted; these are tetrachloroindazoles with strongly electron-withdrawing substituents at the 3- and 3a- positions,[9] and a benzo fused derivative of a triphenyl 3a-methylindene.[17]

It was not immediately obvious why this system should be so reactive, except that it is indeed very well set up for the sigmatropic shifts widely invoked above. This is clearly shown in the computer drawn representations of 3aH-indene, based on the MNDO method (Figure 1), and
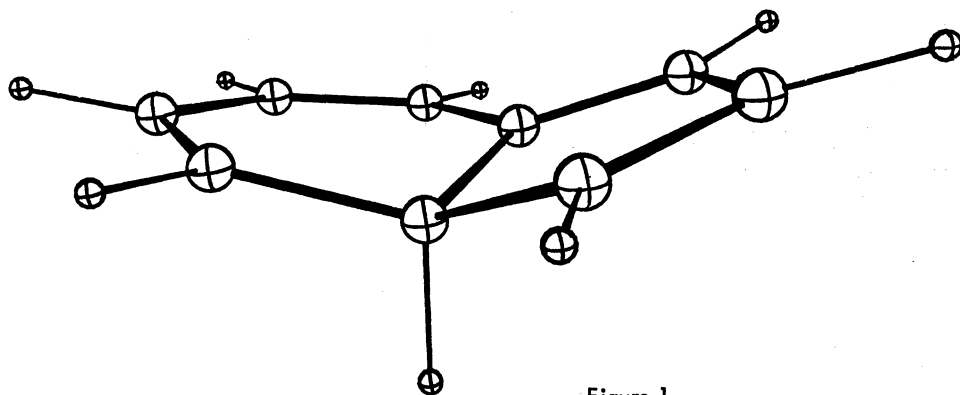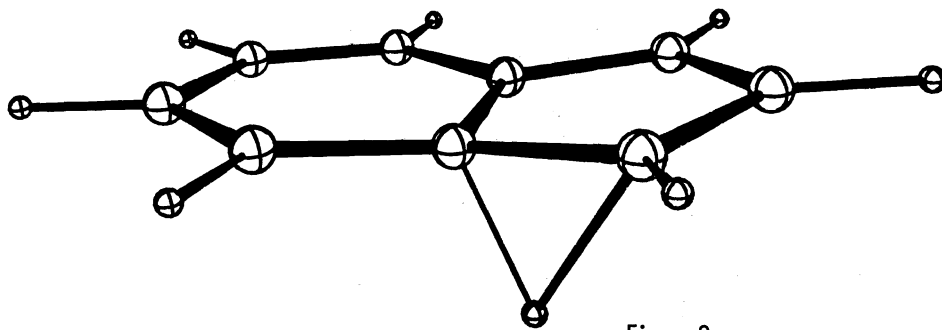
Figure 1.

Figure 2.

of the transition state for [1,5] shift of the 3aH-hydrogen (Figure 2).[18] The bridgehead substituent is almost perpendicular to the approximate plane of the 8 peripheral sp^2 carbon atoms.

We therefore decided to try to synthese and isolate a few simple 3aH-indenes, though these have proved to be particularly elusive. One attempt is shown in Scheme 13. The starting tosylate was readily prepared in high yield from the alcohol. Many attempts at dehydration of this alcohol and of elimination of tosic acid from the tosylate under standard conditions failed to give useful amounts of product. Treatment of the tosylate with the borane complex of sodium phenylselenide gave the corresponding phenylselenide in good yield, however, and oxidation of this with hydrogen peroxide at room temperature effected elimination in high yield. The starting tosylate of Scheme 13 was then dehydrogenated, again most efficiently by the selenoxide route, the product was converted into the phenylselenide shown, and oxidation with hydrogen peroxide
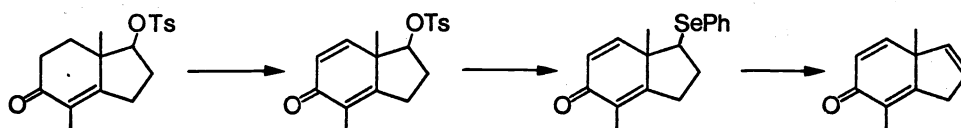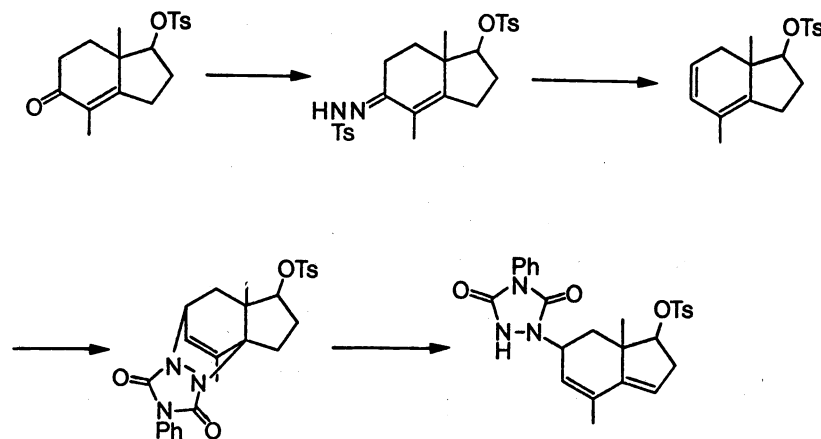
SCHEME 13

finally gave a high yield of the trienone, a colourless liquid with a characteristic smell of apples.
Simple conversion of this trienone into its enol derivatives would produce the required
3aH-indene system, but all our attempts to isolate such derivatives have failed. With strong bases
such as lithium diisopropylamide in THF at -78°, the trienone gives a deep red colour, presumably
of its anion, which persists at low temperatures. Treatment of this solution with acetic anhydride,
methyl fluorosulphonate, or trimethyloxonium tetrafluoroborate at -78°, which rapidly discharged
the colour, gave complex mixtures from which only two products could be isolated. One was the
trienone isomeric with starting material, where the isolated double bond had been brought into
conjugation, presumably by protonation of the anion. The other, more interesting product, from the
magic methyl reaction, has not yet been purified but it is clearly an O-methyl compound (NMR) and
has molecular weight (MS) indicative of a dimeric species. Since enolisation as the final step was
not very successful, we decided to reverse the order of the last two conversions, to end up with a
mild selenoxide elimination. Thus the dienone selenide (Scheme 14) was converted into its
O-acetyl derivative with lithium diisopropylamide at -78°, followed by acetic anhydride.
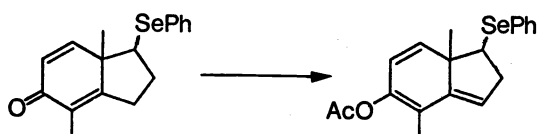
SCHEME 14

This enol acetate was a rather unstable pale yellow oil which was therefore freshly prepared for
attempted selenoxide elimination with hydrogen peroxide; a complex and unresolvable mixture of
products always resulted in this last step however.

        In parallel with these attempts we explored another route (Scheme 15) starting from the
same enone tosylate as before. Treatment of the tosylhydrazone with lithium diisopropylamide

SCHEME 15

gave the cyclohexadiene shown. We intended to convert this diene into a triene using the
technique of cycloaddition of 4-phenyl-1,2,4-triazolin-3,5-dione followed by (double)
elimination of this as its dihydro derivative, under the catalytic influence of $BF_3 \cdot Et_2O$.
This sequence has recently been used effectively by Whalley in the steroid field.[19] Addition of
triazolindione to our dien gave the Diels-Alder adduct quantitatively, but the $BF_3 \cdot Et_2O$ reaction
introduced only one new double bond, leaving the reagent still bonded to the cyclohexane ring.
Attempts to effect complete elimination of the triazolindione, either directly from the Diels-Alder
adduct or from the isolated half-way intermediate, with boron trifluoride or other Lewis acids have
so far failed.

A highly attractive entry into the 3aH-indene system is provided by the conversion of
cyclooctatetraene dianion into the bicyclic chloride shown (Scheme 16). Dehydrochlorination
under sufficiently mild conditions should generate 3a-phenylindene itself, though [1,5] phenyl shift,

SCHEME 16

A.S. Kende and T.L. Bogard,
Tetrahedron Letters, 3383 (1967)
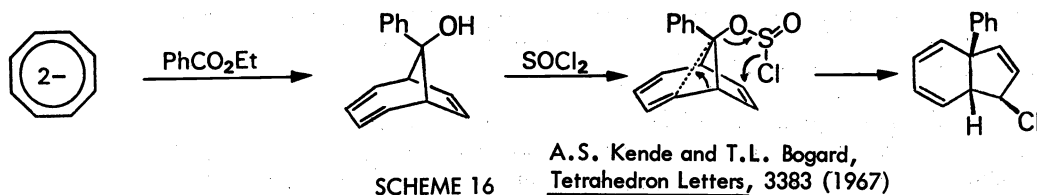
with aromatisation of the six-membered ring, is expected to be a highly favoured process. In the
event dehydrochlorination with lithium dialkylamides in ether or THF from -78^0 to 0^0 did not give
3-phenylindene but a good yield of a colourless mixture of solids with molecular weight 384, i.e.
dimers of the dehydrochlorinated species. Again the 3a-substituted indene appears to have been
produced but is too reactive, towards cycloaddition, to be isolated. Curiously, all our attempts to
intercept the indene with reactive dienophiles, added before or immediately after addition of
base, have failed.

To supplement base catalysed dehydrochlorination, the chloro compound was converted, via
the alcohol, into the o-nitrophenylselenide shown in Scheme 17 (Ar=o-$O_2N \cdot C_6H_4$) by the
selenocyanide - tributylphosphine reaction. Selenoxide elimination with hydrogen peroxide and

SCHEME 17
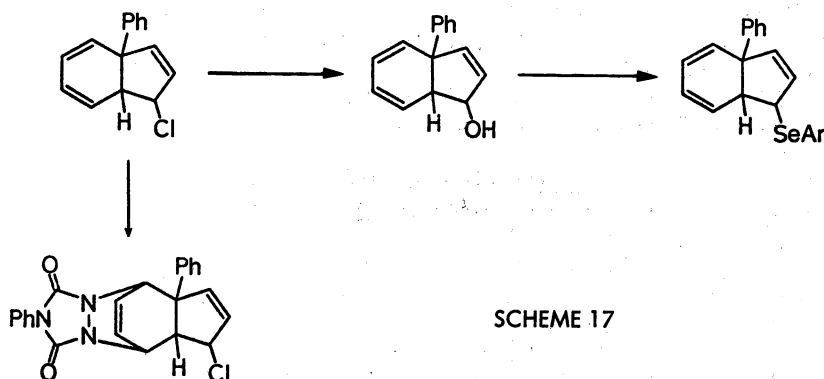
triethylamine gave a mixture of five components. These include the starting alcohol, the isomeric
allylic alcohol, presumably derived by a [2,3] - sigmatropic shift of the selenoxide across the allylic
group, and ketones derived from these alcohols by oxidation. 3-Phenylindene was also isolated as a
minor product but no dimers were detected. Oxidation of the selenide with m-chloroperbenzoic acid
in non-aqueous conditions gave four products, all retaining the arylselenium residue. The alcohol
of Scheme 17 could not be cleanly dehydrated but flash vacuum pyrolysis of its O-acetyl derivative
gave a mixture of 1- and 3-phenylindene in good yield, again with no dimeric products.

Similar experiments have been performed with the more readily available tetraphenyl compounds (Scheme 18). For example, the ketone can be converted into its deep purple lithium
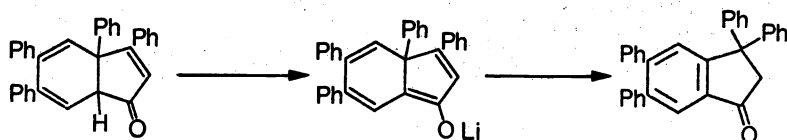
SCHEME 18

enolate, particularly with the lithium diisopropylamide - butyl lithium combination,[20] but attempted methylation of this with magic methyl gave only the rearranged tetraphenylindanone, which is known to be the product of thermal rearrangement and of acid and base catalysed rearrangement at elevated temperatures.[21]

Our efforts to generate 3aH-indenes have thus met with relatively little success. Clearly the system is highly reactive, in agreement with our earlier observations on 3aH-benzimidazoles, but the structural factors which control the rates of rearrangement and dimerisation have yet to be unravelled.

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