REACTIONS OF NITRONES WITH KETENES

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Abstract - A survey of the reactions of nitrones with ketenes is presented. Possible mechanisms for the reported reactions are discussed.

INTRODUCTION

Nitrones (azomethine oxides) are well known 1,3-dipolar species which readily undergo cycloadditions with many unsaturated systems.[1] The reactions of nitrones with alkenes and alkynes, for example, have been extensively studied and documented.[1] The corresponding addition reactions with ketenes, however, have not been similarly exploited and are much less understood. To stimulate research in this area, a review of the available literature is herein presented. The presentation is divided into three sections, each dealing with the type of nitrone investigated.

I. REACTIONS OF HETEROAROMATIC N-OXIDES WITH KETENES

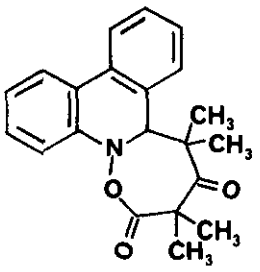
Although heteroaromatic N-oxides are not usually classified as nitrones, they do contain a nitrone function and are in principle capable of undergoing the same reactions. The similarity between N-oxides and azomethine oxides becomes apparent when their reactions with ketenes are compared. Early investigations of the reactions of ketenes with heteroaromatic N-oxides have contributed much to our understanding of later work carried out with nitrones and therefore serve as a good starting point in this discussion.

The reactions of heteroaromatic N-oxides with ketenes resulted in deoxygenation of the N-oxides. Several other products formed concurrently, but in very low yields. Although much effort was spent in the identification of the various secondary products, this phase of the investigations will not be discussed extensively, as it is beyond the scope of our review.

The reactions of pyridine N-oxides with both diphenylketene[2] and dimethylketene[3] have been examined. With diphenylketene, the main products were benzophenone (45% yield) and carbon dioxide. Dimethylketene failed to react with pyridine N-oxide in ethyl acetate. In benzene, however, a mixture of products was obtained including pyridine and 4-isopropylpyridine, which were isolated and characterized as their picrates, and acetone which was identified as its 2,4-dinitrophenylhydrazone. In addition, a very low yield (2.7%) of another product was isolated. This product had a composition corresponding to an adduct of one mole of pyridine N-oxide and two moles of

dimethylketene with one extra atom of oxygen. Purification of this material proved to be difficult and it was not possible to assign an unequivocal structure to this product.

The reaction of phenanthridine N-oxide with excess dimethylketene in ethyl acetate afforded an adduct corresponding to the addition of two moles of ketene to one mole of the N-oxide.[4] The infrared spectrum of this adduct exhibited strong absorptions at 1791 cm^{-1} and 1752 cm^{-1} indicating the presence of two carbonyl groups, one of which was consistent with an O-acylhydroxylamine, thereby suggesting 1 as a possible structure. The reduction of 1 with lithium aluminum hydride afforded 2, further supporting the postulated structure (1).



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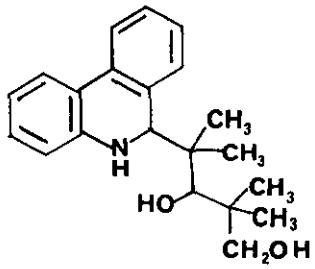
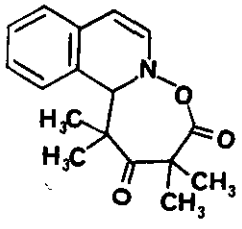


2

Deoxygenation was also observed when dimethylketene was treated with phenanthridine N-oxide in chloroform.

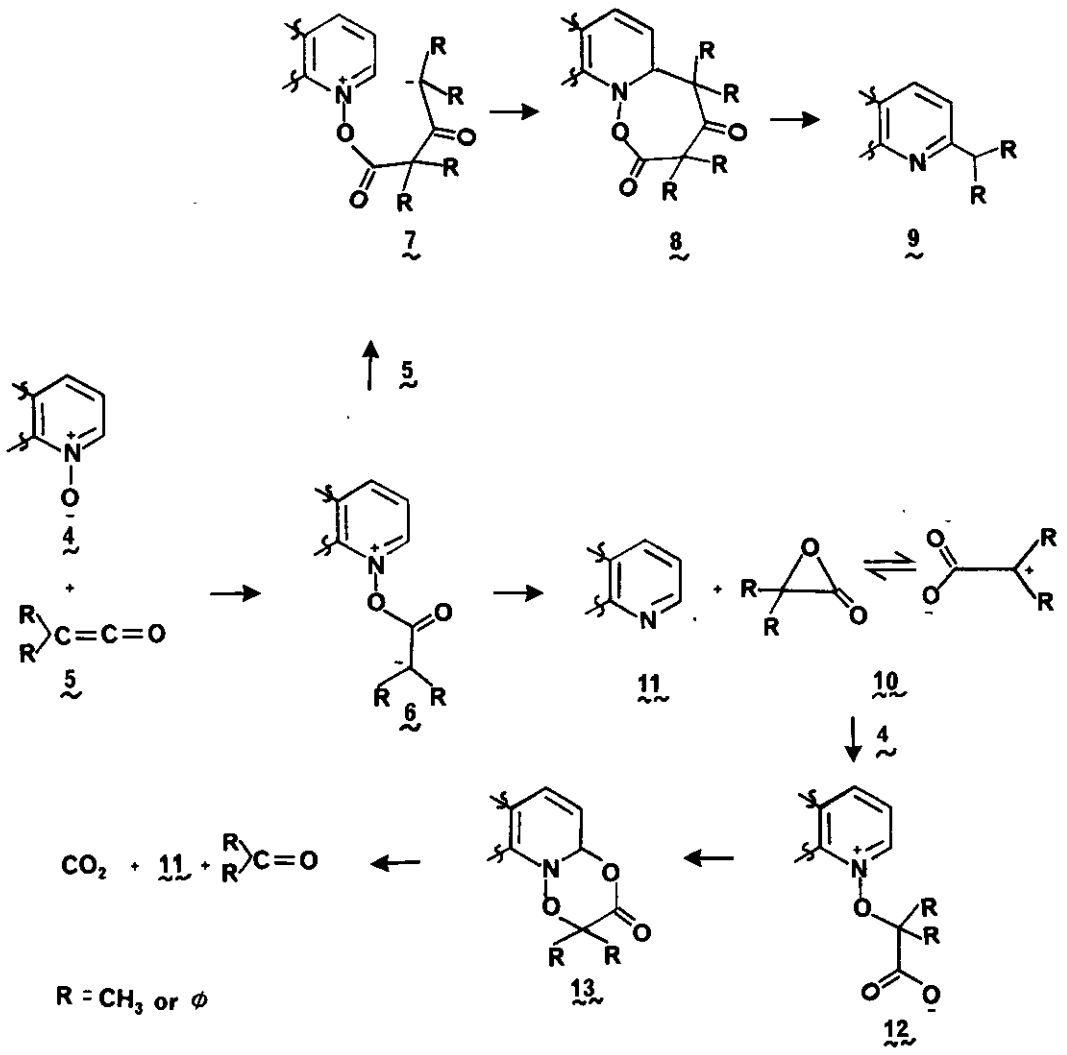
In addition to deoxygenation, the reaction of an excess of dimethylketene with isoquinoline N-oxide either as a solution in ethyl acetate or as a suspension in benzene or ether also afforded a low yield of an unstable 2:1 adduct.[4] All attempts to degrade this product by chemical means resulted in red tars. Spectroscopic data were consistent with structure 3.



3

Attempts to prepare a similar adduct from quinoline N-oxide were inconclusive, although quinoline and 2-isopropylquinoline were identified after attempted distillation of the reaction mixture.[4] The latter compound could conceivably arise from the thermal decomposition of an unstable cyclic adduct.

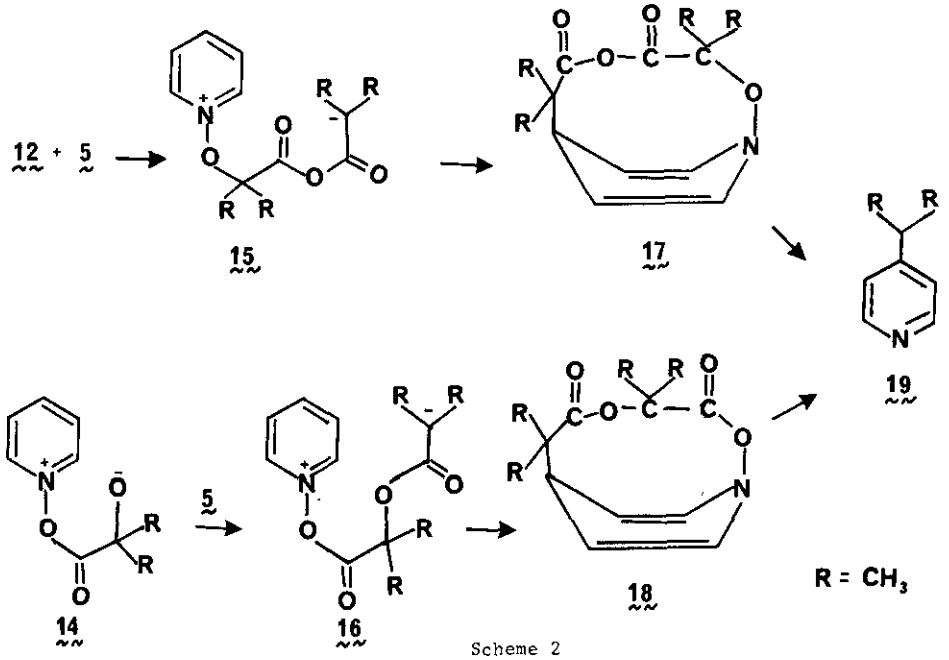
Koenig was the first to postulate an mechanism for the deoxygenation of pyridine N-oxide by diphenylketene *via* the intermediacy of an α-lactone[2] but his attempts to trap this α-lactone were unsuccessful.[2] Taylor and co-workers extended this mechanism to the reactions of other N-heteroaromatic N-oxides.[3,4] The essential features of the suggested mechanisms[2,4] for the reactions of heteroaromatic N-oxides and ketenes are summarized in Scheme 1.



Scheme 1

These reactions are believed to involve nucleophilic attack by the heteroaromatic N-oxide (4) on the ketene (5) to afford a zwitterion (6) which may react with an excess of ketene to afford a new zwitterion (7) or its cyclized form (8). Since nucleophilic attack at the 2-position of a N-substituted heteroaromatic is a well known reaction, the formation of a cyclic 2:1 adduct such

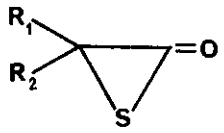
as 8 is plausible. Alternatively, 6 may undergo internal nucleophilic displacement to afford a labile α-lactone (10) and a deoxygenated product (11). The α-lactone could conceivably exist in equilibrium with a 1,3-dipole which would be capable of reacting with additional N-oxide to yield 12 or its cyclized form, 13. Nucleophiles are known to attack α-lactones at the 3-position,[5] therefore further attack on lactone 10 by 4 would also afford 12. Both 12 and 13 could fragment to acetone, carbon dioxide and pyridine. The formation of a 2-isopropyl derivative (9) isolated in some reactions could result from the decomposition of either 7 or 8. The presence of phenanthridone in the reaction of phenanthridine N-oxide and dimethylketene could be accounted for by nucleophilic attack of adventitious water at the 2-position of an intermediate similar to 12 or 13. It will be remembered, however, that the reaction of pyridine N-oxide with dimethylketene has afforded the 4- rather than the 2-isopropyl derivative and that the 2:1 adduct isolated contained an extra oxygen. Nucleophilic attack at the 4- rather than the 2-position of pyridine N-oxides is well known; therefore such a reaction is entirely plausible. The formation of an adduct containing an extra oxygen was explained by again invoking an intermediate α-lactone which, as shown in Scheme 1, could react with 4 to afford 12. However, if nucleophilic attack occurred at the carbonyl group instead of the adjacent carbon atom.[6] a different zwitterion (14) would be obtained. Both 12 and 14 could then react with another mole of ketene to afford zwitterions 15 and 16 which, in turn, can cyclize by attack at the 4-position to afford either 17 or 18. Although the authors could not distinguish between 17 or 18 either product could be hydrolized (perhaps during workup) and aromatized to 4-isopropylpyridine (19), as shown in Scheme 2.



Scheme 2

The very low yield of adduct (17 or 18) has been ascribed to the ease of decomposition of 12 and 14 to pyridine, acetone, and carbon dioxide.

The most interesting aspect of these mechanistic considerations is the existence of the α-lactone. Taylor[3] also attempted to trap this intermediate by treating pyridine N-oxide with dimethylketene in methanol, but only the N-oxide was recovered since the reaction of this ketene with methanol is catalyzed by the starting material.[7] Therefore, trapping or isolation of an α-lactone intermediate still remains a challenge. Properly substituted ketenes could conceivably afford less labile α-lactones. Some support for this assumption and also for the existence of an α-lactone intermediate in the reactions described, may be found in the work of Schaumann and Behrens.[8] These investigators have identified several α-thiolactones (20a-c) obtained from the oxidation of the corresponding thioketenes with nitrones of the 1-pyrroline1-oxide type.



20

(a) $R_1 = CHMe_2$, $R_2 = CMe_3$

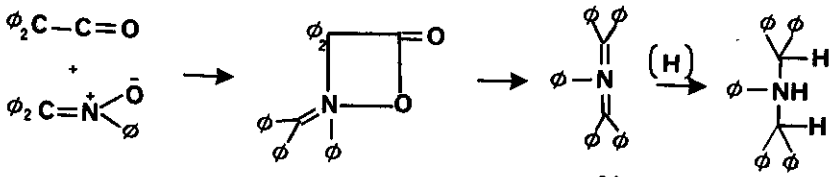
(b) $R_1, R_2 = CMe_3$

(c) $-CMe_2(CH_2)_3CMe_2-$

These compounds undergo decarbonylation to the corresponding thioketones on heating. They are relatively stable to hydrolysis and solvolysis when bulky groups are present. Methanol and benzylamine afford the corresponding α-mercapto carboxylic acid derivatives. Thus, α-thiolactones react via 1,2-ring cleavage whereas α-lactams[9] and the corresponding α-lactones are attacked preferentially at the 1,3-bond by protic reagents.[10]

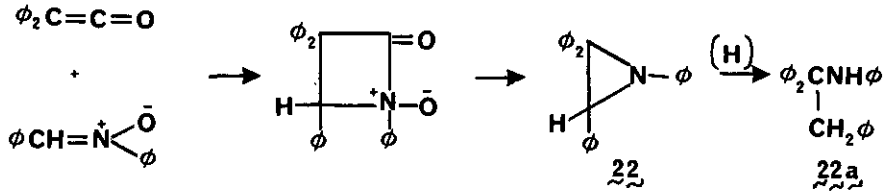
II. REACTIONS OF N-ARYL NITRONES WITH KETENES

The reactions of ketenes with N-aryl nitrones were first investigated by Staudinger and Miescher in 1919.[11] These authors reported that the reactions of N-phenyl nitrones and diphenylketene afforded an adduct which decomposed to carbon dioxide and a novel product (21) termed "nitrene". The proposed course of the reaction is shown in Scheme 3.



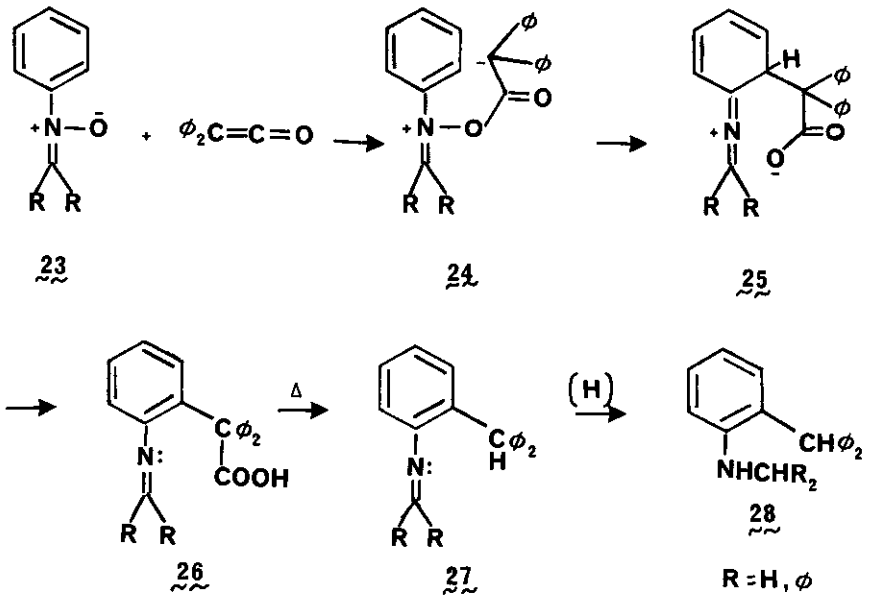
Scheme 3 21

Staudinger suggested that structure 21 accounted for the yellow color and chemical properties of "nitrene" (notably its addition reactions with halogens, halogen acids, and hydrogen). The dihydro derivative obtained on reduction of 21 was believed to be identical with a product obtained in low yield by heating N-diphenylmethylaniline with diphenylmethyl bromide. As the pentavalent formulation of 21 was obviously untenable, additional studies were subsequently undertaken. Taylor and co-workers[12] postulated an ethyleneimine structure (22) for the adduct, the reduction product of which with aluminum amalgam (22a) gave a nitroso derivative on nitrosation.[12] The proposed structural assignments are shown in Scheme 4.



Scheme 4

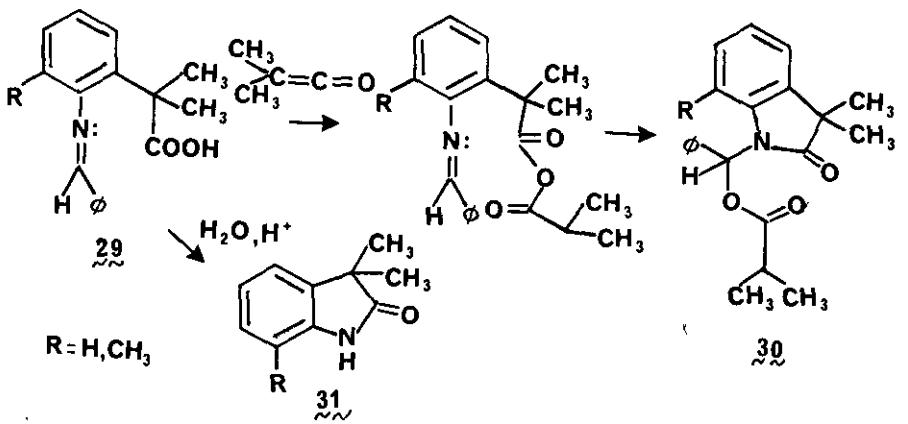
Further studies of the reactions of diphenylketene and N-phenyl nitrones refuted Taylor's ethyleneimine formulation and established by degradation and synthesis that "nitrenes" should be formulated as ortho-diphenylmethylphenylimino derivatives (27).[13] Hassall and Lippman[13] proposed a new mechanism for the reactions of diphenylketene and N-aryl nitrones as shown in Scheme 5.



Scheme 5

The reaction was believed to involve nucleophilic attack by the nitrone (23) on diphenylketene to afford a zwitterion (24) which could then undergo a sigmatropic rearrangement to give the corresponding 1,2-dihydro derivative (25). Aromatization of 25 and thermal decarboxylation of the resultant product (26) yielded 27. Catalytic hydrogenation of 27 gave 28. Hassall and Lippmann[13] assigned structure 27 to Staudinger's compound and structure 28 to its hydrogenation product.

Taylor and co-workers[14] further investigated the reactions of dimethylketene and diaryl nitrones. The reaction of (N-phenyl)phenylmethyleneamine N-oxide with dimethylketene in ethyl acetate afforded both 1:1 and 2:1 adducts which were identified as an imino acid (29) similar to 26 and an oxindole (30). The reaction pathway leading to 29 is the same as shown for 26 (Scheme 5). The formation of 30 is illustrated in Scheme 6. Strongly acidic conditions converted the imino acid (29) to the corresponding 3,3-dimethyloxindole (31).

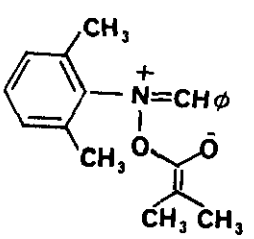


Scheme 6

Similar results were obtained in the reaction of dimethylketene with (N-o-tolyl)phenylmethyleneamine N-oxide in ethyl acetate, although, compared with the N-phenyl analog, the relative proportions of the adducts differed considerably. It was presumed that the steric effect of the extra methyl group was insignificant in the transition state leading to 29 but important in that leading to 30. The migration of the acyloxy group requires close approach of the lone pair on nitrogen to the carbonyl group and therefore the near coplanarity of the azomethine and N-phenyl groups. The methyl substituent interferes with the hydrogen of the azomethine group and inhibits the necessary coplanarity of the transition state. It is noteworthy that deoxygenation of the nitrones was not observed in these reactions.

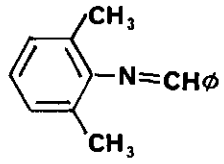
In the light of their results, Taylor and co-workers also supported Hassal and Lippman's assignment for Staudinger's compound.

The reaction of N-(2,6-xylyl)phenylmethyleneamine N-oxide with dimethylketene in ethyl acetate was also investigated by Taylor[15] in the hope of observing a para-Claisen rearrangement from zwitterion 32.



32

The expected rearrangement did not occur, but three other products were identified: N-benzylidene-2,6-dimethylaniline (33), 3,3-dimethyl-4-phenyl-1-(2,6-xylyl)azetidin-2-one (34), and a 1:1 ketene-nitrone adduct characterized as bicyclic lactone 35.



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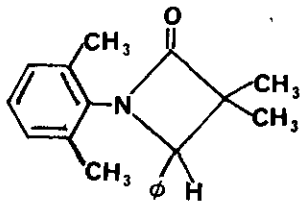

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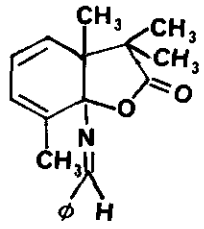
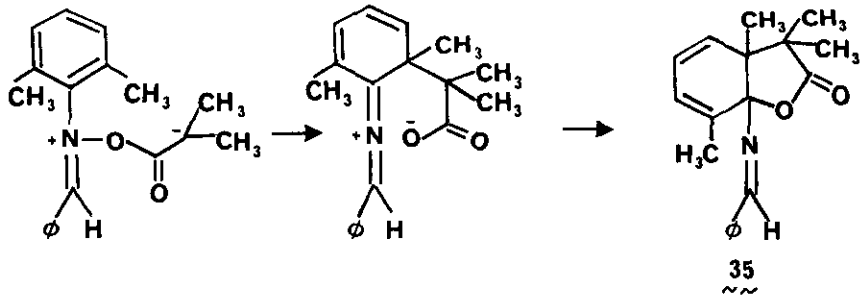


35

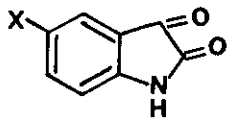
The first two products (33) and (34) resulted from the deoxygenation of N-(2,6-xylyl)nitrone, a reaction which was not observed with dimethylketene and N-phenyl-or N-(2-tolyl) nitrone.[14] Compound 34 was formed via the reaction of dimethylketene with 33. It was previously observed[14] that in the presence of an ortho-methyl group, nucleophilic attack on aryl nitrones occurred exclusively at the other unsubstituted ortho position. When both positions are substituted, nucleophilic attack at these sites could be retarded to such an extent that deoxygenation becomes a competing reaction pathway. Although the formation of an oxindole analogous to 30 was not observed since aromatization is not possible in this system, a similar reaction process involving a sigmatropic rearrangement did, in fact, occur leading to the formation of lactone 35. (Scheme 7).



35

Scheme 7

As part of a study on the use of *N-aryl nitrones, some investigators* examined the reactions of these compounds with dichloroketene.[16] The reactions led to oxindoles similar to 30 which were subsequently hydrolyzed with boiling water or aqueous acids to the corresponding substituted isatins (36a-d).



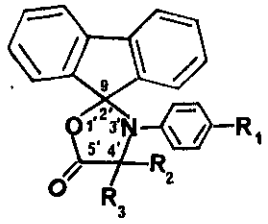
36

(a) X = H (c) X = Cl

(b) X = Me (d) X = Br

This reaction constitutes a new isatin synthesis noteworthy for its brevity, simplicity, and good yields.[16]

As part of an investigation of the 1,3-dipolar cycloadditions of ketenes, Abou-Gharbia and Joullie[17] examined the reactions of several N-fluorenylidenearylamine N-oxides with cyclopentamethyleneketene, tert-butylcarbethoxyketene, and tert- butylcyanoketene in toluene.[17] In all cases, only spirooxazolidinones (37a-f) were obtained.



37

(a) R_1=Me, R_2, R_3 = - $(CH_2)_5$-

(b) R_1=Me, R_2=CMe_3 R_3=CO_2Et

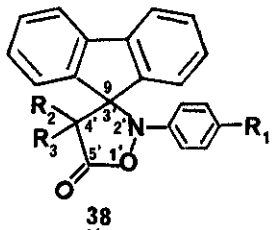
(c) R_1=Me, R_2=CMe_3 R_3=CN

(d) R_1=OMe, R_2=CMe_3, R_3=CN

(e) R_1=F, R_2=CMe_3, R_3=CN

(f) R_1=CF_3, R_2=CMe_3, R_3=CN

The unequivocal assignment of a spirooxazolidinone structure rather than the expected 1,3-cycloaddition product, spiroisoxazolidinone 38, was based on spectral data principally ^{13}C- and ^1HNMR.[18]



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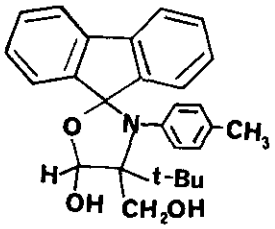
Chemical evidence, although consistent with structure 37, was inconclusive in distinguishing between the isomers. The lithium aluminum hydride reduction of 37a afforded 9-fluorenol in quantitative yield. This product could be explained by assuming the intermediacy of an unstable dihydro derivative which would decompose to fluorenone, the latter species then being

reduced to 9-fluorenol. The intermediacy of a dihydro derivative was supported by the isolation of a stable cis diol 39 from the lithium aluminum hydride reduction of 37b.



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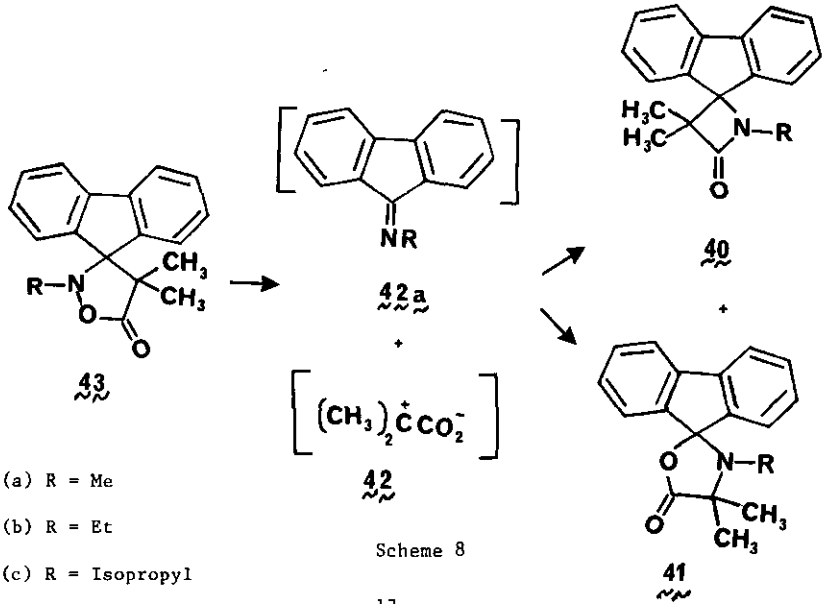
III. REACTIONS OF N-ALKYL NITRONES WITH KETENES

The reactions of diphenylketene with N-fluorenylidenealkylamine N-oxides in benzene was reported by Taylor [18] to afford spiro-β-lactams (40) and spirooxazolidinones (41). Similar results were obtained with dimethylketene and the same nitrones in ethyl acetate.[19] N-Methyl nitrone afforded five compounds: fluorenone azine (1%), a spiroazetidinone (19%), a spirooxazolidinone (8%) and two additional products which were not further identified. N-Ethyl nitrone also afforded a spiroazetidinone (60%) and spirooxazolidinone (12%) but N-isopropyl nitrone gave only the latter product (91%). Structural assignments were based on mass spectral fragmentation data and chemical evidence. To explain these results, Taylor proposed a mechanism (Scheme 8) involving a zwitterion (42) and an imine (42a) believed to result from the decomposition of the expected 1,3-cycloaddition product, spiroisoxazolidinone 43.



(a) R = Me

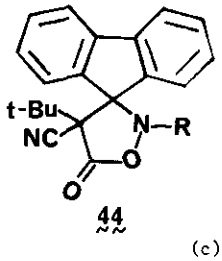
(b) R = Et

(c) R = Isopropyl

Scheme 8

Results obtained by Abou-Gharbia and Joullie[17] on the reactions of tert-butylcyanoketene with

N-alkyl nitrones in toluene, however, contrasted sharply with those of Taylor. The only products isolated were spiroisoxazolidinones (44a-c).



44

(a) R = Me (c) R = ϕCH_2

(b) R = Et

Abou-Gharbia and Joullie were unable to detect β-lactams or any other products under a variety of experimental conditions including low temperatures and the presence of radical inhibitor. Evidence for structure 44 was provided by both ^{13}C- and $^{1}HNMR$. The ^{13}C chemical shifts of the spiro carbons in compounds 44a-c for example were found to occur at more shielded field positions than those of 37a-f. This technique provides the most reliable method of distinguishing between isomeric spirooxazolidinones and spiroisoxazolidinones. The $^{13}CNMR$ chemical shifts of the spiro carbon (C-9), carbonyl carbons (C-5'), and quarternary carbons C-4') for compounds 37a-f and 44a-c are shown in Table I. The infrared frequencies of the carbonyl carbons (C-5') of compounds 37a-f, 41a-c, and 44a-c are also shown in Table I. The $^{1}HNMR$ spectra of spiroisoxazolidinones having a tert-butyl group also provide a means of identifying these compounds. The resonance of a tert-butyl geminal to an electron-withdrawing group usually appears at approximately 1.25 ppm. In compounds 44a-c, the chemical shifts of this group are seen at approximately 0.8 ppm. This divergence may be ascribed to the proximity of the tert-butyl substituent to the fluorene nucleus in the spirooxazolidinones and the resulting effect of the fluorene ring current.

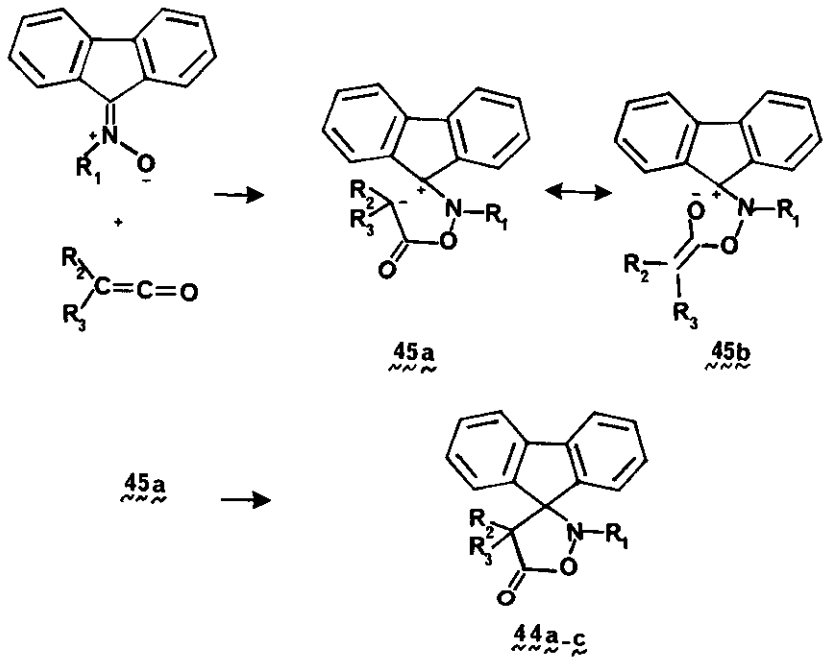
An important consideration in examining the cycloadditions of ketenes and nitrones is the purity of the nitrone especially when these compounds are synthesized by the oxidation of imines. Syntheses of this type are known to afford oxaziridines,[20] however, when the products are unstable as for example N-phenyl or 2,3-diaryloxaziridines,[21,22] nitrones are isolated instead. Since oxaziridines, in contrast to nitrones, oxidize iodide ion quantitatively,[23] iodometric titrations allow the detection of even trace quantities of oxaziridines and must be used to establish the purity of the starting materials.

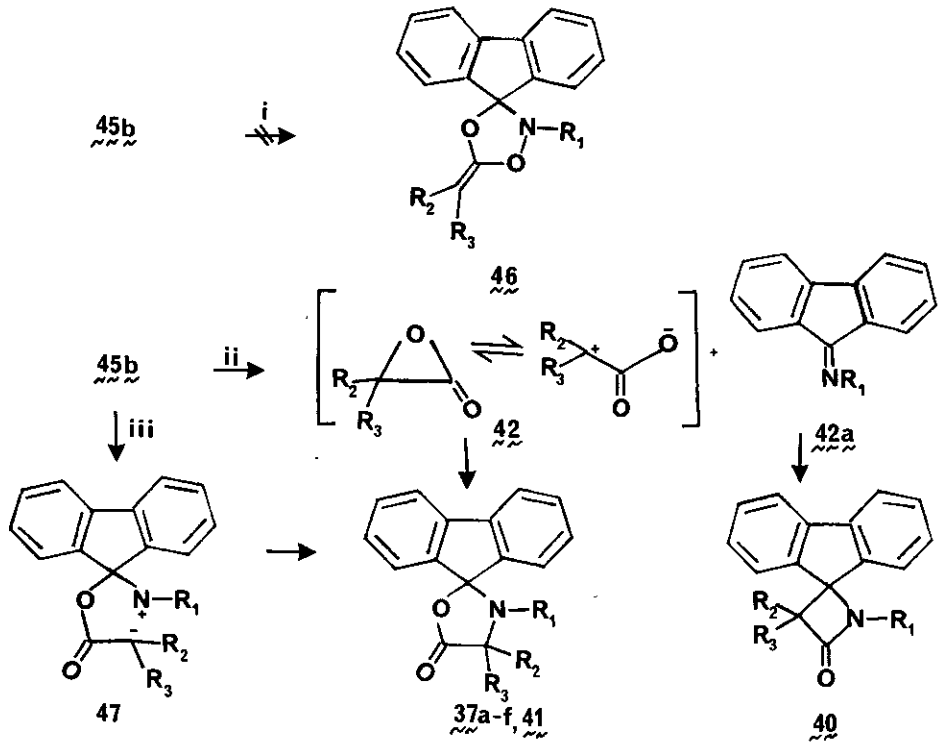
Preliminary observations by Joullié and co-workers have shown that oxaziridines derived from N-fluorenylidenealkyl amines afford the corresponding spiroxazolidinones.[24]

The divergent results of Taylor and Joullié are easier to explain if one assumes that imine 42a and zwitterion 42 were more likely formed via the deoxygenation reaction first observed in the

reactions of dimethyl- and diphenylketene with heteroaromatic N-oxides (Scheme 1). The presumed α-lactone intermediate could exist in equilibrium with a 1,3-zwitterion such as 42.

A plausible mechanism encompassing the formation of all products reported by both Taylor and Joullié is shown in Scheme 9.





Scheme 9

The reactions are believed to involve nucleophilic attack of the nitrones on the ketenes to afford a delocalized zwitterion whose major contributing forms may be represented by 45a or 45b depending on substituents (R_1, R_2, and R_3). Zwitterion 45 a can undergo ring closure to compounds 44a-c as observed with tert-butylcyanoketene. Cyclization in this case involves nucleophilic attack on a very stable benzylic cation. Steric effects should be important in this cyclization since formation of a spiroisoxazolidinone produces significant steric interactions between the C-4' substituents and the fluorene ring. For the same reason, the nature of the N-substituent must influence the ease of ring closure to an appreciable extent. When a less stabilized electron-deficient center is generated in the presence of an N-aryl substituent, a sigmatropic rearrangement is the preferred pathway as observed with diphenylketene and N-aryl nitrones (Scheme 5)

When substituents R_2 and R_3 are methyl groups, less effective stabilization of carbanion 45a results, therefore the negative charge might be expected to reside predominantly on oxygen rather than carbon. The resulting zwitterion 45b should not cyclize readily to 46 because such a process (path i) would entail a hard-soft interaction. Several attempts by Abou-Gharbia and Joullié were made to isolate a product such as 46, but all were unsuccessful.[24] Other reaction paths, however, are possible. Elimination to imine 42a and zwitterion 42 (or the corresponding α-lactone), as postulated by Taylor may occur (path ii). Alternatively, cleavage of the nitrogen-oxygen bond would harden the benzylic center and allow attack by oxygen at this position, affording a new zwitterion (47) with an electropositive nitrogen atom (path iii) This nitrenium ion should be better stabilized by aromatic than aliphatic groups when N-aryl nitrones are used as substrates. The cleavage of a nitrogen-oxygen bond has a precedent in the sigmatropic rearrangement shown in Scheme 5, and is therefore not unexpected. The stabilization of the carbanion center in 47 is important. When cyano or carbethoxy groups are present, cyclization to spirooxazolidinones, 37a-f occurs exclusively. With dimethyl or diphenyl groups elimination becomes a competing path since these groups can better stabilize zwitterion 42 than 47. Clearly further investigations should be carried out to increase our understanding of the reactions of nitrones with ketenes. It is hoped that this article, having brought forth the salient features of these interesting reactions, will stimulate such research.

TABLE I. ^{13}C NMR AND IR DATA OF ISOXAZOLIDINONES AND OXAZOLIDINONES

Compound No.	^{13}C Chemical Shifts, ppm			νC=O, cm^{-1}	Ref.
	C-9	C-5'	C-4'		
37a	101.8	175.8	60.7	1775	17
37b	102.4	170.5	61.9	1775	17
37c	102.7	166.7	61.8	1775	17
37d	102.7	166.4	68.3	1770	17
37e	102.7	166.1	68.1	1800	17
37f	102.8	166.1	67.9	1800	17
41a	-	-	-	1782	19
41b	-	-	-	1782	19
41c	-	-	-	1780	19
44a	83.7	166.9	62.3	1775	17
44b	82.7	166.5	61.8	1770	17
44c	82.9	166.8	61.8	1770	17

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