Thermal and Photochemical Valence Isomerizations of 4-Carbonyl-Substituted Isoxazoles[1]

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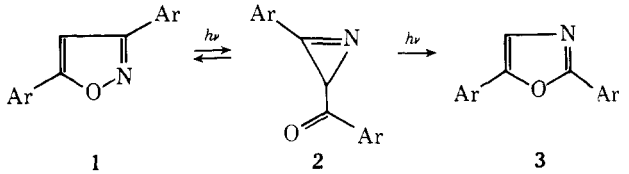
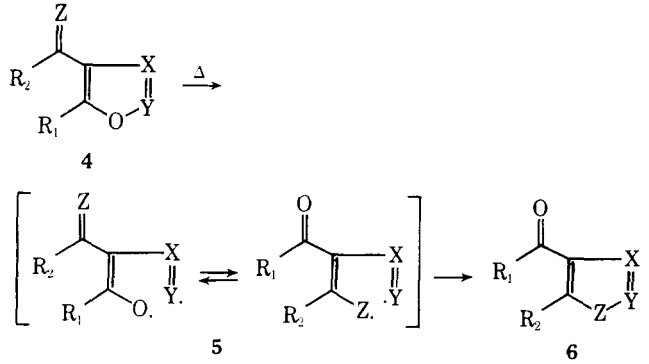
Abstract: A number of 3-phenyl-4-acyl-5-alkylisoxazoles have been found to undergo thermal rearrangement to 2-phenyl-4-acyl-5-alkyloxazoles. Thermolysis of 3-phenyl-4-benzoyl-5-methylisoxazole (**21**) at 230° gave a mixture of 3,5-diphenyl-4-acetylisoxazole (**22**), 2,5-diphenyl-4-acetyloxazole (**23**), and 2-phenyl-4-benzoyl-5-methyloxazole (**24**). A similar set of products was obtained on heating 3,5-diphenyl-4-acetylisoxazole (**22**). The thermal interconversion of the two isoxazoles was rationalized by cleavage of the O–N bond to produce a reactive acyclic intermediate which undergoes bond rotation and subsequent reclosure to the isomeric isoxazole. A 2*H*-azirine is suggested as an intermediate in the thermal formation of the oxazoles from the isoxazoles. The photochemistry of the 4-acylisoxazole system was also studied. In contrast to the thermal results, photolysis of 3,5-diphenyl-4-acetylisoxazole (**22**) produced 3-phenyl-4-benzoyl-5-methylisoxazole (**21**) as the only primary photoproduct. On further irradiation, this material rearranged to 2,5-diphenyl-4-acetyloxazole (**23**). The exclusive formation of **21** from **22** was rationalized by considering the differences in the free energy of activation for ring closure of the acyclic diradical intermediates formed on thermolysis or photolysis. The mechanism for the formation of oxazole **23** from isoxazole **21** does not proceed via an azirine intermediate. A possible reaction path which explains the results is postulated.

Studies of the photochemical and thermal isomerizations of five-membered heterocyclic ring compounds have received considerable attention in recent years.[2] Photoisomerization involving interchange of the positions of two ring atoms has been demonstrated for many of these systems. A ring contraction–ring expansion process in these reactions was first demonstrated by Ullman and Singh for the photorearrangement of 3,5-diarylisoxazoles (**1**) to 2,5-diaryloxazoles (**3**).[3] An analogous path nicely rationalizes the major



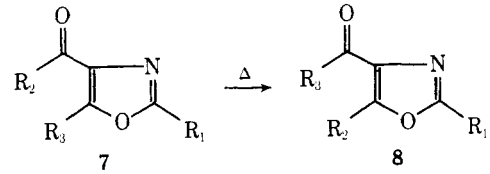
products produced in the photoisomerization of other five-membered heterocyclic rings.[4-7]

There are also a number of reports in the literature describing the thermally induced isomerizations of five-membered heterocyclic rings.[8-15] In each case, the thermal product obtained can be rationalized by a sequence involving homolytic cleavage of the O–Y bond of **4** to produce a reactive acyclic intermediate (**5**) which recloses to produce the rearranged heteroaromatic compound **6**. An example of this

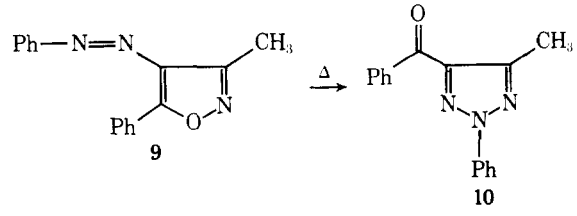


X = N, C; Z = N, O; Y = N, C

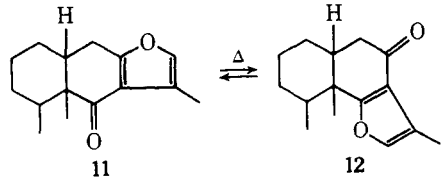
type of reaction involves the thermal rearrangement of 4-carbonyl-substituted oxazoles.[8-13] The reaction was first observed by Cornforth and coworkers who found that substituted 4-acyloxazoles (**7**) rearrange thermally to the isomeric oxazoles **8** in high yield.[8] A reaction similar to the Cornforth rearrangement was reported by Wittig and co-



workers in 1928.[14] These authors found that 3-methyl-4-phenylazo-5-phenylisoxazole (**9**) was converted to 2-phenyl-4-benzoyl-5-methyl-1,2,3-triazole (**10**) on heating. This



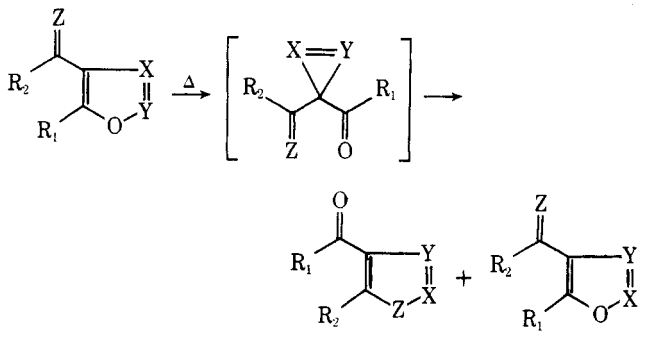
transformation can be explained by a mechanism similar to that suggested by Dewar to account for the interconversion of oxazole derivatives in the Cornforth rearrangement.[12,13] A related rearrangement, recently reported by Tada and Takahashi, involves the thermal interconversion of ligularone (**11**) and isoligularone (**12**).[15] This equilibration was ra-



tionalized by a C–O bond cleavage followed by rotation about the C_7–C_{11} bond of the intermediate diradical and recyclization.

We recently reported that the thermolysis of 4-carbonyl-substituted isoxazoles resulted in a rearrangement to both a 4-acyloxazole as well as a 4-acylisoxazole.[16] Our initial observations indicated that this system differed from heretofore observed thermal reactions of five-membered rings, in

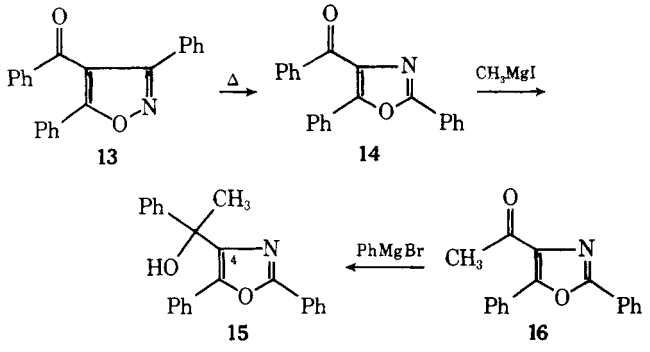
that part of the reaction followed a ring contraction–ring expansion sequence:



The present publication describes our findings in detail and delineates the significant role played by 2*H*-azirines in the overall thermal chemistry of this ring system. In addition, we have studied the photochemistry of several 4-carbonyl-substituted isoxazoles and have found the product distributions to be significantly different from those for the thermal reactions.

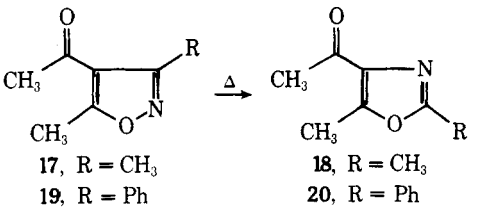
Results and Discussion

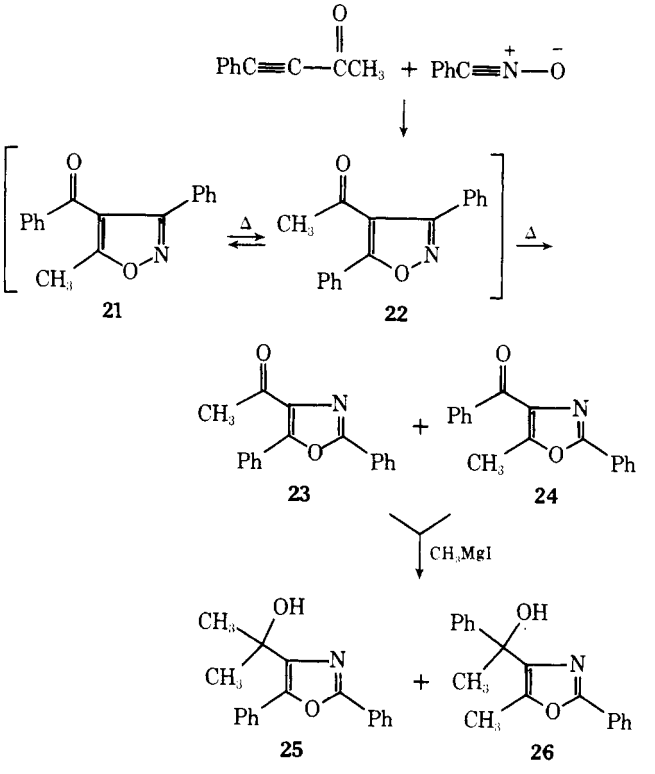
Thermal Chemistry of 4-Carbonyl-Substituted Isoxazoles. It is well known that, when two heteroatoms of higher electronegativity than carbon (e.g., nitrogen and oxygen) are linked together through a single bond, the bond dissociation energy of such a linkage is considerably lower than that of a C–C single bond.[17,18] The origins of this effect are not at present clear, but repulsion between the necessarily higher nuclear charges and/or the nonbonded electron pairs may be responsible. Whatever its source, this effect was considered to be a potential driving force for the cleavage of the isoxazole ring. Taking this into consideration, we decided to examine the thermal behavior of 3,5-diphenyl-4-benzoylisoxazole (**13**). Thermolysis of isoxazole **13** at 240° under a nitrogen atmosphere for 18 hr afforded 2,5-diphenyl-4-benzoyloxazole (**14**) in 80% yield. The structure of the rearranged product was established by treating it with methylmagnesium iodide and comparing the resulting alcohol (**15**) with an authentic sample of methylphenyl(2,5-diphenyloxazol-4-yl)carbinol (**15**) prepared from the reaction of 2,5-diphenyl-4-acetyloxazole with phenylmagnesium bromide.



The thermal rearrangement of 3,5-dimethyl-4-acetylisoxazole (**17**) was also investigated. Thermolysis of isoxazole **17** at 230° for 24 hr afforded the known 2,5-dimethyl-4-acetyloxazole (**18**), mp 46–47°, in 82% yield. Similarly, thermolysis of 3-phenyl-4-acetyl-5-methylisoxazole (**19**) afforded 2-phenyl-4-acetyl-5-methyloxazole (**20**), mp 78–79°, in quantitative yield. The structure of the rearranged product **20** was established by comparison with an authentic sample.[19]

To probe for the possibility of a degenerate Cornforth-type rearrangement in the above systems, the thermal behavior of an unsymmetrical 4-acylisoxazole was also investigated. When 3-phenyl-4-benzoyl-5-methylisoxazole (**21**) was subjected to thermolysis (230°, 5 hr), a mixture of three new compounds was produced. Analysis of the crude reaction mixture by NMR showed that it contained 3,5-diphenyl-4-acetylisoxazole (**22**, 8%), 2,5-diphenyl-4-acetyloxazole (**23**, 29%), and 2-phenyl-4-benzoyl-5-methyloxazole (**24**, 39%), as well as unreacted starting material. Chromatography of the crude reaction mixture on a silica gel column separated isoxazole **22** from the mixture of oxazoles and starting material. Confirmation of the structure of isoxazole **22**, mp 92–94° [NMR ($CDCl_3$) τ 7.8 (3 H)], was obtained by comparison with an authentic sample prepared by treating 4-phenyl-3-butyn-2-one with benzonitrile oxide. Attempts to separate the mixture of oxazoles into its component parts failed. To overcome this difficulty, the mixture of oxazoles was converted into carbinols **25** and **26** by treating the mixture with methylmagnesium iodide. The two carbinols were readily separated by silica gel chromatography. The first fraction contained material identified as dimethyl(2,5-diphenyloxazol-4-yl)carbinol (**25**), mp 114–115°, on the basis of its spectral data and by comparison with an authentic sample prepared by treating a pure sample of 2,5-diphenyl-4-acetyloxazole (**23**)[19] with methylmagnesium iodide. The second compound isolated from the chromatography column was identified as methylphenyl(2-phenyl-5-methyloxazol-4-yl)carbinol (**26**), mp 79–80°, by comparison with an authentic sample prepared from the reaction of phenylmagnesium bromide with 2-phenyl-4-benzoyl-5-methyloxazole (**24**) (mp 61–62°, see Experimental Section).

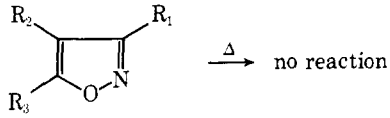




A study of the product distribution vs. extent of thermolysis showed that isoxazole **22** was a major product during the early phase of the reaction. At longer periods of time, the amount of **22** decreased, and oxazoles **23** and **24** increased in concentration. This was independently verified by studying the thermolysis of isoxazole **22.** Heating a sample of **22** at 230° for 5 hr gave a mixture of **21** (8%), **23** (30%), **24** (38%), and recovered starting material. Again, at short periods of time, isoxazole **21** was a major thermal product. These observations suggest that the thermal isomerization of the two isoxazoles occurs rapidly and is followed by rearrangement to the 4-acyloxazole system. A complete equilibration between isoxazoles **21** and **22** was never established because of the competing oxazole rearrangement path.

We are also interested in determining whether oxazoles **23** and **24** were interconverted during the thermolysis since this interconversion would represent another example of the Cornforth reaction and seemed quite plausible. We found, however, that, when oxazole **23** was subjected to thermolysis at 230° for 5 hr, a very low yield (ca. 4%) of oxazole **24** was obtained. Similarly, oxazole **24** produced an insignificant amount (ca. 5%) of **23** under identical thermal conditions. The lack of significant thermal interconversion of oxazoles **23** and **24** under the reaction conditions used for the isoxazole thermolysis indicates that the ratio of oxazoles obtained from the thermolysis of the isoxazole system is not the result of a subsequent thermal reaction. This result rules out any regiospecific mechanism for the thermal rearrangement of isoxazoles **21** and/or **22.** A thermal equilibration of the two oxazoles could be established, however, by heating **23** under a nitrogen atmosphere at 230° for 12 days. This ratio (**23**/**24** = 0.67) was also obtained when **24** was subjected to the same thermolysis conditions.

In order to determine the role of the 4-acyl group in the thermal rearrangement of these isoxazoles, a number of isoxazoles (**27a–e**) which were devoid of this functionality

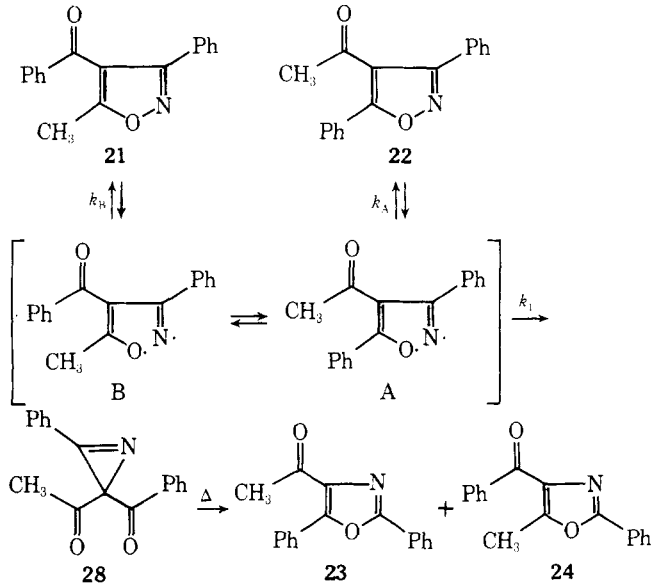


27a, $R_1 = R_3 = Ph$; $R_2 = CH_3$
b, $R_1 = Ph$; $R_2 = R_3 = CH_3$
c, $R_1 = R_3 = Ph$; $R_2 = H$
d, $R_1 = Ph$; $R_2 = H$; $R_3 = Ph$
e, $R_1 = R_2 = Ph$; $R_3 = CH_3C{=}O$

were prepared and subjected to thermolysis using more stringent conditions than those previously employed (i.e., 280°, 10 days). We found, however, that these molecules were perfectly stable to the thermal conditions. This was true even when a carbonyl group was present in the 5-position of the isoxazole ring (i.e., **27e**). This observation would tend to indicate that the dissociation energy of the O–N bond is significantly diminished when the isoxazole ring is in conjugation with a carbonyl group.

The formation of the rearranged oxazole from the 4-carbonyl-substituted isoxazole requires bonding, at some point in the reaction, between C-3 of the isoxazole ring and the oxygen of the carbonyl group. We believe that the experiments reported here require the intermediacy of a 2*H*-azirine (i.e., **28**) to rationalize the transposition of the two ring atoms. The most reasonable pathway for the formation of **28** involves homolytic cleavage of the relatively weak O–N bond of the isoxazole ring to form an acyclic intermediate which can either recyclize to generate rearranged isoxazole or close to give a 3,3-diacyl-2-phenyl-2*H*-azirine (**28**) intermediate (Scheme I). The second step, **28** → **23** + **24**, most likely involves C–C bond rupture of the 2*H*-azirine ring followed by cyclization to the observed products. Although the products formed on thermal decomposition of 2*H*-azirines generally appear to involve C–N rather than C–C bond cleavage,[20-30] Wendling and Bergman have recently reported that the thermolysis of certain 2*H*-azirines proceeds by way of C–C bond cleavage.[31] Each of the steps of the above mechanism are thermally induced, and the rates and products were not influenced by oxygen, radical inhibitors, or small amounts of acids and bases. It is interesting to note that 5-alkoxyisoxazoles have been reported to undergo a facile thermally induced skeletal rearrangement to alkyl-1-azirine-3-carboxylates.[32] This rearrangement provides good analogy for the ring contraction step of the proposed sequence. The literature also contains several references dealing with the thermal rearrangement of 4-isoxazolines.[33-37] Most of the rearrangements observed with these systems can also be attributed to a ring contraction–ring expansion sequence.

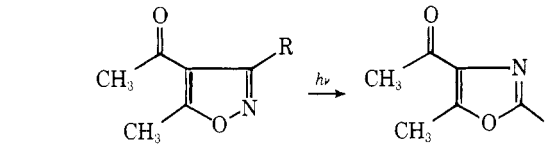
Scheme I



In earlier papers, we have shown that arylazirines undergo ring opening reactions to produce nitrile ylides.[38] The initially generated nitrile ylide could be intercepted with a number of dipolarophiles to give cycloadducts.[39,40] In an attempt to document the existence of azirine **28** in the thermal rearrangement of the 4-acylisoxazole system, we have tried to trap a nitrile ylide by carrying out the thermolysis of **21** (and/or **22**) in the presence of dimethyl fumarate. Unfortunately, no cycloaddition product could be isolated in these experiments. The failure to trap such a species does not necessarily eliminate the azirine as a reaction intermediate since the bimolecular trapping might be too slow to compete with a rapid unimolecular rearrangement of the 1,3-dipole.

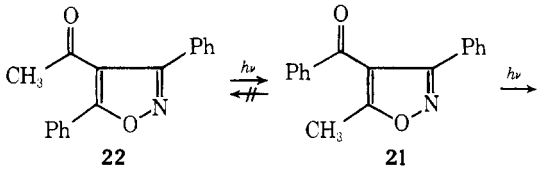
Photochemistry of 4-Carbonyl-Substituted Isoxazoles. As was pointed out earlier, the photochemistry of five-membered heterocyclic rings has been the object of a considerable amount of study since the first irradiation induced isomerization was reported in 1967.[3-5] To date, there has been no attempt to correlate the photo and thermal valence isomerizations of these molecules. As part of a broad study concerned with heterocyclic photochemistry, we have examined the photochemical behavior of several 4-carbonyl-substituted isoxazoles. The results obtained are of particular interest in view of the differences from product distributions of the thermal reactions.

Irradiation of 4-acylisoxazole **17** in benzene with Corex filtered light produced oxazole **18** as the only photoproduct. Similarly, irradiation of 3-phenyl-4-acetyl-5-methylisoxazole (**19**) afforded 2-phenyl-4-acetyl-5-methyloxazole (**20**) in quantitative yield. These results are identical with those previously found on thermolysis of these systems. When the irradiation of 3,5-diphenyl-4-acetylisoxazole (**22**) was carried out in benzene, however, the only product formed was 3-phenyl-4-benzoyl-5-methylisoxazole (**21**). This product was isolated by preparative thick layer chromatography and compared directly with an authentic sample. The chemical yield of **21** was 60–90%, as the material formed rapidly at first, but then decreased as photolysis was continued owning to formation of a secondary photoproduct. This secondary

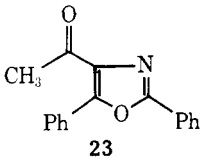


17, R = CH_3
19, R = Ph

18, R = CH_3
20, R = Ph



22 **21**



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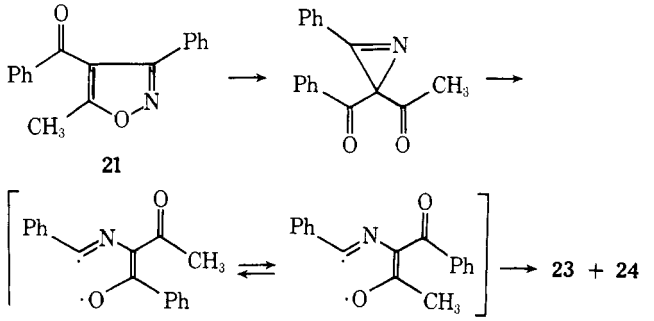
photoproduct was formed in good yield when a pure sample of isoxazole **21** was irradiated in benzene. The structure of this compound was identified as 2,5-diphenyl-4-acetyloxazole (**23**) by comparison with an authentic sample. Most importantly, the isomeric 2-phenyl-4-benzoyl-5-methyloxazole (**24**) was completely absent in the photolysis mixture. Control experiments showed that **24** was not converted to **23** under the irradiation conditions employed. We also found that isoxazole **22** was not formed on photolysis of **21** in benzene, nor was **21** or **22** formed on photolysis of **23**.[41] Thus, isoxazole **21** is the primary photoproduct of isoxazole **22**, and oxazole **23** is the only product produced from the irradiation of **21**. The exclusive formation of **21** from **22** and the absence of a photolytic interconversion of **21** → **22** is in *marked contrast* to the results previously encountered on thermolysis of these systems.

The most striking aspect of the photochemical studies is the product specificity. The simplest interpretation of the photochemical results encountered with isoxazole **22** is that electronic excitation results in O–N cleavage of the isoxazole ring to generate diradical intermediate A which can isomerize to diradical intermediate B (see Scheme I). According to this argument, the same intermediates (A and B) are involved in the thermal and photochemical equilibration of the 4-carbonyl-substituted isoxazole system. Since benzoylisoxazole **21** is formed in high yield from **22** and since the irradiation of **21** does not produce **22**, it may be concluded that the overall rate of formation of **21** from B is greater than the overall rate of formation of **22** from A (i.e., $k_B > k_A$) (Scheme I). Since the product selectivity obtained from the photochemical reaction derives from the lower free energy of transition state **21** relative to **22**, it is instructive to examine the factors which may influence the free energy of the transition states and lead to the lower energy of **21**.[42] Inspection of molecular models show that diradicals A and B cannot attain a planar conformation. Thus, the acetyl group in diradical A and the phenyl portion of the benzoyl group in B are tipped out of the molecular plane. The net effect of tipping the acetyl group out of conjugation is to raise the transition state energy for ring closure. The transition state associated with closure of diradical B, on the other hand, suffers less steric inhibition of resonance and consequently is of lower energy.[43] It should be pointed out that isoxazoles **21** and **22** are readily interconverted at 230°. This observation indicates that the activation energy differential for closure of diradicals A and B is not important at 230° but is significant at the temperature employed in the photolysis reaction (i.e., 25°).

The photochemical reaction of benzoylisoxazole **21** was found to afford only oxazole **23**; the isomeric oxazole **24** was not detected in the reaction mixture (NMR analysis). One possible explanation to account for this result is to assume that irradiation of **21** leads to azirine **28** which preferentially rearranges to oxazole **23**. This explanation would require a significant difference in the activation energy of closure of the diradicals produced from the azirine intermediate.



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There is a major flaw in this interpretation, however. As was mentioned earlier, oxazoles **23** and **24** do not interconvert appreciably in 5 hr at 230° (<5%). Thus, the distribution of the oxazoles obtained from the thermolysis of isoxazoles **21** and/or **22** (i.e., **23**/**24** = 0.75) is the result of a kinetic controlled process. This ratio is essentially the same as the ratio of oxazoles obtained from a 12-day equilibration study at 230° (**23**/**24** = 0.67). This observation indicates that the activation energy difference for the closure of the diradicals produced from the azirine is essentially the same as the internal energy difference for oxazoles **23** vs. **24** (i.e., kinetic and thermodynamic control give the same product distribution). The Boltzmann energy differential ($N/N_0 = e^{-\Delta E_a/RT}$) for the formation of oxazoles **23** and **24** from a common intermediate (**28**) at 230° indicates that the activation energy difference for oxazole formation is approximately 0.3 kcal/mol:

$$N/N_0 = \mathbf{23/24} = 0.75 = e^{-0.288} = e^{-\Delta E_a/2(503)};$$

$$E_a = 290 \text{ cal/mol}$$

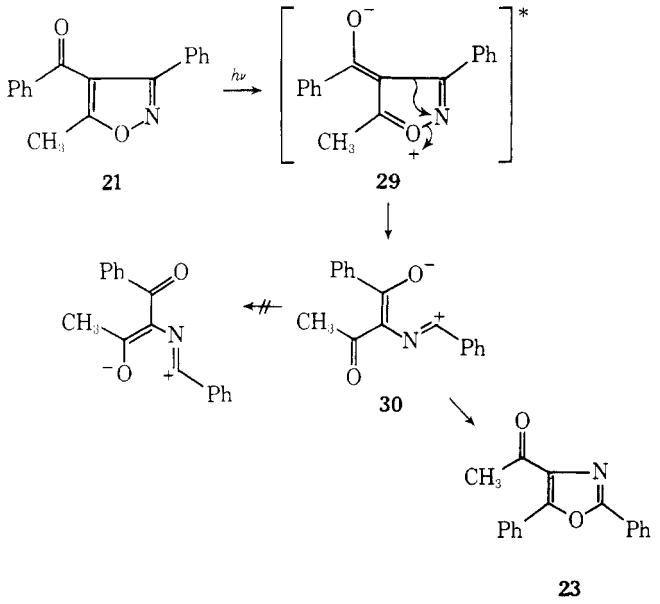
If it is assumed that a yield of **24** of 3% or less would have escaped detection in the irradiation of **21**, the product distribution of the oxazoles would be **23**/**24** = 97:3. If the room temperature photolysis proceeded through the same pathway as did the thermolysis, then a product distribution of **23**/**24** = 38:62 rather than the observed (minimum) **23**/**24** = 97:3 would be expected.

$$N/N_0 = \mathbf{23/24} = e^{(-290/2(298))} = e^{-0.48} = 0.618 = 38{:}62$$

These simple calculations clearly show that the expected ratio of oxazoles at 25° is significantly different from that actually determined. We must conclude, therefore, that the mechanism for the photolysis of **21** leading to **23** does not

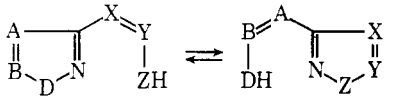
go through the same intermediate(s) as that involved in the thermolysis of **21.** We have previously argued that the thermal isomerization of the 4-carbonyl-substituted isoxazole system proceeds through a 2*H*-azirine intermediate (i.e., **28**). Consequently, this intermediate and the diradical(s) derived from it must not be involved in the photoisomerization of **21** to **23.**

As the photochemical formation of oxazole **23** could not be reconciled with a 2*H*-azirine intermediate, it was necessary to consider other intermediates which might be the logical precursors to **23.** The data can be rationalized in terms of a mechanism involving O–N bond cleavage followed by a 1,2-carbon–nitrogen shift. In the π–π^* excited state, the isoxazole chromophore will have considerable charge transfer character as is represented by the valence bond structure **29.** Cleavage of the O–N bond from this excited state will result in an electron deficient nitrogen atom. A 1,2-carbon–nitrogen shift is the most obvious low-energy path available to the π–π^* state, and this will result in the formation of zwitterion **30.** Recombination of the two reactive centers in **30** affords oxazole **23.** Zwitterion **30** has the proper cisoid

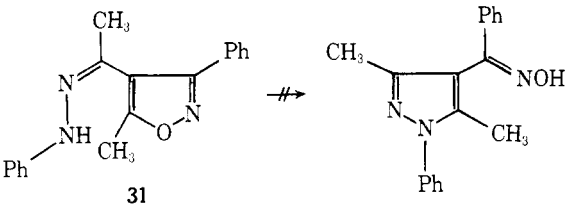


conformation of the oxygen atom and the electron deficient carbon center to close to oxazole **23.** The above mechanism avoids the necessity of having a symmetrical intermediate (i.e., **28**) and can accommodate the product specificity since the dipolar species formed (**30**) on bond migration can readily collapse to the observed product before isomerization occurs. In order to form the isomeric oxazole **24,** it is necessary to rotate about the C–N bond of **30.** This would require disruption of the coplanarity of the system and would have a significant activation energy barrier. Further studies on related 4-carbonyl-substituted heterocycles are presently being made to test this mechanism.

There have been a number of reports in the literature which describe the thermal valence isomerization of isoxazoles which contain a suitable side chain in the 3-position of the ring.[44-48] Katritzky and coworkers have proposed the following scheme in order to rationalize the mononuclear rearrangement of a large number of 3-substituted azole derivatives:[45]



These authors have pointed out that a large number of transformations are available for different ABD and XYZ combinations. In an effort to uncover further reactions of this type, our attention was directed toward the thermal and photochemical behavior of the phenylhydrazone (**31**) and oxime (**32**) derivatives of 3-phenyl-4-acetyl-5-methylisoxazole (**19**).



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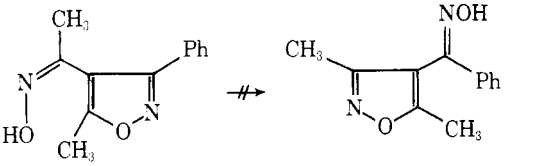

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Unfortunately, all attempts to induce rearrangement of these two systems failed. The initial phenylhydrazone synthesized from the reaction of **19** with phenylhydrazine, mp 133–135°, was thermally (and photochemically) transformed into a geometrical isomer, mp 156–158°, rather than the pyrazole oxime. Similarly, thermolysis (or photolysis) of the related oxime **32** resulted in syn-anti isomerization rather than rearrangement. The lack of success with these systems suggests that the XYZ side chain must be located in the 3-position of the azole ring in order for the mononuclear heterocyclic rearrangement to occur.

Experimental Section

All melting points are corrected and boiling points uncorrected. Elemental analysis were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Jeol-MH-100 spectrometer. Mass spectra were determined on a Hitachi Perkin-Elmer mass spectrometer Model RMU-6, using a standard ionizing potential of 70 eV.

Thermolysis of 3,5-Diphenyl-4-benzoylisoxazole. A 0.5-g sample of 3,5-diphenyl-4-benzoylisoxazole (**13**)[49] was heated at 240° in a Curtius tube under a nitrogen atmosphere for 18 hr. The crude black mixture was then chromatographed on a silica gel column using a 8% ethyl acetate–hexane mixture as the eluent. The first fraction obtained was a crystalline solid which was recrystallized from methanol to give 2,5-diphenyl-4-benzoyloxazole (**14**), mp 80–81° (0.4 g, 80%): ir (KBr) 6.05, 6.28, 6.45, 6.75, 6.94, 7.40, 7.56, 8.18, 9.36, 9.77, 11.20, 12.90, 13.64, 13.93, 14.23, and 14.65 μ; NMR ($CDCl_3$) δ 7.20–8.35 (15 H, m); uv (methanol) 290 nm (ϵ 20,000) and a shoulder at 267 (17,000); *m/e* 325 (M^+), 105 (base), 77, 57.

Anal. Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 81.32; H, 4.61; N, 4.24.

The structure of the rearranged oxazole was unambigously established by conversion to the carbinol by treating it with methylmagnesium iodide. A solution containing 0.65 g of 2,5-diphenyl-4-benzoyloxazole in 10 ml of anhydrous ether was added dropwise to a methylmagnesium iodide solution prepared from 0.56 g of methyl iodide and 0.097 g of magnesium turnings in 2 ml of anhydrous ether. The mixture was stirred at room temperature for 1 hr and was then decomposed with 10 ml of a 20% sulfuric acid solution. The reaction mixture was extracted with ether which was then washed with a 5% sodium bicarbonate solution and dried over magnesium sulfate. Concentration of the solution under reduced pressure left a yellow solid which was recrystallized from chloroform–hexane (10%) to give methylphenyl(2,5-diphenyloxazol-4-yl)carbinol (**15**) as a white solid, mp 120–121°C; ir (KBr) 2.90,

6.42, 6.70, 6.90, 7.12, 8.35, 8.60, 9.32, 10.02, 10.82, 10.96, 12.00, 13.10, 14.14, and 14.40 μ; NMR ($CDCl_3$) 1.90 (s, 3 H), 3.30 (s, 1 H), 7.0–7.80 (m, 13 H), 7.90–8.30 (m, 2 H); uv (methanol) 235 nm (ϵ 16,800); *m/e* 323 (M^+) 220, 192, 165, 105, and 77.

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.17; H, 5.48; N, 4.31.

An authentic sample of the above carbinol was independently prepared by treating 0.26 g of 2,5-diphenyl-4-acetyloxazole (**16**)[19] with phenylmagnesium bromide (prepared from 0.63 g of bromobenzene and 0.09 g of magnesium turnings in 5 ml of anhydrous ether). The two carbinols were identical in every detail.

Preparation of 3,5-Dimethyl-4-acetylisoxazole. A solution of sodium ethoxide in ethanol was prepared by adding 0.55 g of freshly cut sodium metal to 40 ml of absolute ethanol. To this mixture was added 2.40 g of acetylacetone, and then 2.15 g of acetohydroxamoyl chloride in 40 ml of ethanol was added rapidly at room temperature. The mixture was heated at reflux for 12 hr. The precipitated salts were removed by filtration, and the mixture was concentrated under reduced pressure to give a light yellow residue. The residue was sublimed at 25° (0.03 mm) and recrystallized from hexane to give 0.92 g (40%) of 3,5-dimethyl-4-acetylisoxazole (**17**) as a white solid: mp 47–48°; ir (KBr) 5.95, 6.30, 7.10, 7.70, 9.21, and 10.50 μ; uv (methanol) 230 nm (ϵ 8450); *m/e* 139 (M^+), 124, 82, and 43; NMR ($CDCl_3$) δ 2.41, (6 H, s), 2.61 (3 H, s)

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.76; H, 6.56; N, 9.99.

Thermolysis of 3,5-Dimethyl-4-acetylisoxazole. A 0.1-g sample of 3,5-dimethyl-4-acetylisoxazole (**17**) was heated at 230° in an evacuated Pyrex test tube for 24 hr. The crude mixture obtained was subjected to column chromatography using a 7% ethyl acetate–hexane mixture as the eluent. The yellow solid obtained from the column was recrystallized from hexane to give 0.082 g (82%) of 2,5-dimethyl-4-acetyloxazole (**18**): mp 46–47°; ir (KBr) 3.15, 5.90, 6.18, 7.15, 8.30, 9.30, 10.50, and 13.00 μ; NMR ($CDCl_3$) δ 2.41 (s, 3 H), 2.48 (s, 3 H), and 2.57 (s, 3 H); uv (methanol) 250 nm (ϵ 38,400); *m/e* 139 (M^+), 124 (base), 82, 54, 43. An authentic sample of the above oxazole was independently prepared by treating a mixture of 3.87 g of hydroximino acetylacetone, 10 ml of acetic anhydride, 15 ml of glacial acetic acid, 0.15 g of sodium acetate, and 0.2 g of mercuric chloride with 8.2 g of zinc dust. The mixture was heated at reflux for 30 min and then filtered. The resulting solution was concentrated under reduced pressure to give a yellow oil which was sublimed at room temperature (0.03 mm) to give 1.9 g (45%) of 2,5-dimethyl-4-acetyloxazole as white crystals, mp 46–47° (lit.[50] 48–49°). A mixture melting point of the two oxazoles was undepressed at 46–47°, and the spectral properties of the two oxazoles were identical.

Thermolysis and Photolysis of 3-Phenyl-4-acetyl-5-methylisoxazole. A 1.3-g sample of 3-phenyl-4-acetyl-5-methylisoxazole (**19**)[51] was heated at 230° in a Curtius tube under a nitrogen atmosphere for 2 hr. The crude mixture obtained was subjected to column chromatography using a 7% ethylacetate–hexane mixture as the eluent. The crystalline solid obtained amounted to 1.21 g (96%) and was identified as 2-phenyl-4-acetyl-5-methyloxazole (**20**): mp 78–79°; NMR ($CDCl_3$) δ 2.60 (s, 3 H), 2.71 (s, 3 H), 7.3–7.6 (m, 3 H), and 7.9–8.2 (m, 2 H) by comparison with an authentic material.[19]

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.86; H, 5.57; N, 7.02. Found: C, 71.62; H, 5.51; n, 6.96.

Irradiation of a 1.0-g sample of 3-phenyl-4-acetyl-5-methylisoxazole (**19**) in 500 ml of benzene for 3.5 hr with a 450-W medium-pressure mercury arc (Vycor filter) gave 2-phenyl-4-acetyl-5-methyloxazole (**20**), mp 78–79° (85%), as the only identifiable photoproduct.

Thermolysis of 3-Phenyl-4-benzoyl-5-methylisoxazole. A 1.0-g sample of 3-phenyl-4-benzoyl-5-methylisoxazole (**21**)[52] was heated at 230° in a Curtius tube under a nitrogen atmosphere for 5 hr. The NMR of the crude reaction mixture showed the presence of unreacted starting material (24%), 3,5-diphenyl-4-acetylisoxazole (**22**) (8%), 2-phenyl-4-benzoyl-5-methyloxazole (**24**) (39%), and 2,5-diphenyl-4-acetyloxazole (**23**) (29%). A mixture of the two oxazoles (1:1) was isolated from the crude reaction mixture by column chromatography using a 7% ethylacetate–hexane mixture as the eluent. All attempts to separate the mixture of oxazoles into its component parts failed. To overcome the difficulty of isomer separation, the above mixture of oxazoles was treated with methylmagnesium iodide.

A mixture of the two oxazoles (0.67 g) in 10 ml of anhydrous ether was added dropwise to a solution of methylmagnesium iodide (prepared by treating 0.072 g of magnesium turnings with 9.4 g of methyl iodide in 20 ml of ether). The mixture was allowed to stir overnight at room temperature. At the end of this time, the Grignard reaction was decomposed with 20 ml of a 20% sulfuric acid solution and was extracted with ether. The ether layer was washed with a 5% sodium bicarbonate solution and then dried over anhydrous magnesium sulfate. Evaporation of the solvent left a yellow residue which was subjected to column chromatography using a 7% ethylacetate–hexane mixture as the eluent. The first fraction collected contained 0.6 g (86%) of a white solid whose structure was assigned as dimethyl(2,5-diphenyloxazol-4-yl)carbinol (**25**), mp 114–115°, on the basis of the following data: ir (KBr) 2.88, 6.70, 6.90, 7.32, 7.50, 8.60, 8.90, 9.06, 9.40, 10.40, 12.82, 13.06, 14.30, and 14.60 μ; NMR ($CDCl_3$) δ 1.62 (s, 6 H), 2.70 (s, 1 H, exchanged with D_2O), 7.20–8.20 (m, 10 H); *m/e* 261 (M^+), 158, 143, 120, 129, 115, 105, and 77 (base); uv (methanol) 297 nm (ϵ 19,700).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.13; H, 6.10; N, 4.93.

An authentic sample of the above carbinol was independently prepared by treating 0.67 g of 2,5-diphenyl-4-acetyloxazole (**23**)[19] with methylmagnesium iodide (prepared from 0.43 g of methyl iodide and 0.075 g magnesium turnings in 20 ml of anhydrous ether). A mixture melting point of the two carbinols was undepressed at 114–115°. The second compound isolated from the chromatography column amounted to 0.08 g (11%) and was identified as methylphenyl(2-phenyl-5-methyloxazol-4-yl)carbinol (**26**), mp 79–80°, on the basis of the following data: ir (KBr) 3.00, 6.17, 6.40, 6.70, 6.89, 7.20, 7.28, 7.45, 7.73, 8.17, 8.62, 8.92, 9.30, 9.50, 9.72, 10.80, 10.97, 11.85, 12.78, 13.08, 13.55, and 14.33 μ; NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.10 (s, 3 H), 3.38 (s, 1 H, exchanged with D_2O), 7.10–7.70 (m, 8 H), 7.80–8.10 (2 H, m); *m/e* 261 (M^+), 260, 244, 219, 218, 191, 184, 158, 129, 115, 105, and 77; uv (methanol) 278 nm (ϵ 26,300).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.34; H, 6.14; N, 4.99.

An authentic sample of the above carbinol was independently prepared by treating 2.0 g of 2-phenyl-4-acetyl-5-methyloxazole (**20**)[19] with phenylmagnesium bromide (prepared from 2.04-g of bromobenzene and 0.288 g magnesium turnings in 50 ml of anhydrous ether). A mixture melting point of the two carbinols obtained was undepressed at 79–80°, and the spectral properties were identical.

Preparation of 2-Phenyl-4-benzoyl-5-methyloxazole. An authentic sample of 2-phenyl-4-benzoyl-5-methyloxazole (**24**) could be independently prepared by treating 5-methyl-2-phenyl-oxazole-4-carboxylic acid chloride with diphenylcadmium. The corresponding carboxylic acid was prepared by treating a 2.01-g sample of 2-phenyl-5-methyl-4-acetyloxazole in 60 ml of dioxane at 15° with an aqueous sodium hypobromite solution prepared by adding 5.4 g of bromine to 25 ml of 2 *N* sodium hydroxide solution at 10°. The resulting solution was allowed to stir for 12 hr at room temperature. After this time, the solution was extracted with ether and then acidified with concentrated hydrochloric acid. The crude acid which precipitated was extracted with chloroform which was subsequently dried over anhydrous magnesium sulfate. Removal of the solvent left a yellow solid which was recrystallized from benzene to give 2.0 g (98%) of 2-phenyl-5-methyloxazole-4-carboxylic acid: mp 185–186° (lit.[19] 185–186°); ir (KBr) 3.45, 3.76, 5.87, 6.20, 6.40, 6.75, 6.92, 7.47, 7.57, 7.96, 8.36, 8.95, 9.46, 9.76, 10.85, 12.66, 14.11, and 14.51; NMR ($CDCl_3$) δ 2.78 (*s*, 3 H), 7.30–7.68 (*m*, 3 H), 7.90–8.23 (*m*, 2 H), 11.01 (*s*, 1 H).

A mixture containing 2.0 g of the above carboxylic acid, 5.0 g of thionyl chloride, and 0.5 ml of dimethylformamide was heated on a steam bath for 1 hr and was then allowed to stand at room temperature for an additional 12 hr. The excess thionyl chloride was removed under reduced pressure, and the resulting solid was recrystallized from benzene to give 2.14 g (97%) of 2-phenyl-5-methyloxazole-4-carboxylic acid chloride: mp 135–136°; ir (KBr) 5.62, 6.27, 6.86, 7.40, 8.15, 8.50, 9.43, 9.70, 10.57, 11.90, 12.76, 13.52, and 14.28; NMR ($CDCl_3$) δ 2.70 (3 H, s), 7.20–7.40 (3 H, m), 7.90–8.10 (2 H, m).

A solution containing 1.0 g of the above acid chloride in 40 ml of

dry benzene was added to a benzene solution of diphenylcadmium. The diphenylcadmium reagent was prepared by adding 0.55 g of anhydrous cadmium chloride to phenyl Grignard (prepared from 0.78 g bromobenzene and 0.12 g of magnesium turnings in 20 ml ether). After all of the cadmium had been added, the mixture was heated to reflux for 1 hr, and the ether was distilled out of the flask. To the dark residue was added 3 ml of dry benzene, and the mixture was heated at reflux for 5 min in order to break up the cake in the flask and disperse it through the solvent. The solution was then cooled at 0° and the acid chloride (1.0 g) in 40 ml of benzene was added to the diphenylcadmium reagent. After heating for 10 hr, the mixture was decomposed by adding 2 ml of a 20% sulfuric acid solution. The organic layer was diluted with ether, and the combined extracts were washed with a 5%-sodium bicarbonate solution followed by water. The ether layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The yellow solid obtained was chromatographed on a silica gel column using a 5%-ethyl acetate–hexane mixture as the eluent. The initial fractions contained 0.12 g (10%) of 2-phenyl-4-benzoyl-5-methyloxazole (**24**): mp 61–62°; ir (KBr) 3.28, 6.06, 6.25, 6.35, 6.75, 6.93, 7.30, 7.43, 8.06, 8.35, 8.84, 9.45, 9.76, 10.55, 11.00, 12.90, 13.72, 14.16, and 14.56; NMR ($CDCl_3$) δ 2.70 (s, 3 H), 7.10–7.50 (m, 6 H), 7.8–8.0 (m, 2 H), 8.10–8.35 (m, 2 H); uv (methanol) 260 and 272 nm (ϵ 22,800 and 21,800); *m/e* 263 (M^+), 262, 248, 220, 193, 165, 105 (base), and 77.

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.68; H, 5.25; N, 5.28.

Preparation of 3,5-Diphenyl-4-acetylisoxazole. Confirmation of the structure of 3,5-diphenyl-4-acetylisoxazole (**22**) was obtained by comparison with an authentic sample synthesized by the method described below. To a solution containing 1.44 g of 4-phenyl-3-butyn-2-one and 1.55 g of benzhydroxamoyl chloride in 50 ml of carbon tetrachloride was added, at −10°, a solution containing 1.5 g of triethylamine in 20 ml of carbon tetrachloride over 10 min. The solution was allowed to stir at 5° for 30 hr and at room temperature for an additional 12 hr. The mixture was then filtered and washed with water and then dried over anhydrous magnesium sulfate. Removal of the solvent left a dark orange oil which was chromatographed on a thick layer plate using a 15% ethyl acetate–hexane mixture as the eluent. In addition to 0.8 g (55%) of recovered starting material, a new compound was isolated (0.3 g, 13%) which was identified as 3,5-diphenyl-4-acetylisoxazole (**22**): mp 94–95°; ir (KBr) 5.95, 6.40, 7.12, 9.10, 9.30, 10.30, 10.60, 12.72, 13.00, 13.61, and 14.40 μ; NMR ($CDCl_3$) δ 2.20 (s, 3 H), 7.34–7.98 (m, 10 H); *m/e* 263 (M^+), 248, 235, 234, 221, 220, 193, 105 (base), and 77; uv (methanol) 267 nm (ϵ 16,400).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.42; H, 5.14; N, 5.16.

Thermal Equilibration of 2,5-Diphenyl-4-acetyloxazole with 2-Phenyl-4-benzoyl-5-methyloxazole. A 0.1-g sample of 2,5-diphenyl-4-acetyloxazole (**23**) was heated at 230° in a Curtius tube under a nitrogen atmosphere for 12 days. At the end of this time, the NMR spectrum showed the presence of both 2-phenyl-4-benzoyl-5-methyloxazole (**24**) (60%) and 2,5-diphenyl-4-acetyloxazole (**23**) (40%). The same ratio was obtained when 2-phenyl-4-benzoyl-5-methyloxazole (**24**) was heated at 230° for 12 days. Attempts to trap the transient azirine by heating 2,5-diphenyl-4-acetyloxazole in the presence of excess dimethyl fumarate (10 mole excess) failed. The only products present in the crude reaction mixture were recovered starting material and 2-phenyl-4-benzoyl-5-methyloxazole.

Photolysis of 3,5-Diphenyl-4-acetylisoxazole. A solution containing 100 mg of 3,5-diphenyl-4-acetylisoxazole in 150 ml of benzene was irradiated for 2 hr using a 450-W Hanovia lamp equipped with a Vycor filter. Removal of the solvent under reduced pressure left a yellow oil which was purified by thick layer chromatography. The only material that was isolated from the thick layer band was identified as 3-phenyl-4-benzoyl-5-methylisoxazole (**21**) (85%) by comparison with an authentic sample.[52] If the irradiation was continued for an additional 8 hr, a new component was detected in the crude photolysate. Thick layer chromatography of the reaction mixture afforded 2,5-diphenyl-4-acetyloxazole (**23**) as the only oxazole. Irradiation of a pure sample of 3-phenyl-4-benzoyl-5-methylisoxazole (**21**) (100 mg) in 150 ml of benzene for 12 hr using a 450-W Hanovia lamp equipped with a Vycor filter was found to give 2,5-diphenyl-4-acetyloxazole as the major photoproduct. The photoreaction was carefully monitored as a function of time, and no detectable quantities of 3,5-diphenyl-4-acetylisoxazole (**22**) or 2-phenyl-4-benzoyl-5-methyloxazole (**24**) were present in the crude photolysate as evidenced by NMR analysis.

Preparation and Thermolysis of the Phenylhyrazone of 3-Phenyl-4-acetyl-5-methylisoxazole. A solution containing 1.01 g of 3-phenyl-4-acetyl-5-methylisoxazole, 0.16 g of phenylhydrazine, and two drops of acetic acid in 20 ml of absolute ethanol was heated at reflux for 10 hr. At the end of this time, 50 ml of water was added, and the solid that precipitated was collected and recrystallized from ethanol to give a phenylhydrazone derivative of 3-phenyl-4-acetyl-5-methylisoxazole (**31**): mp 133–135°; ir (KBr) 3.10, 6.30, 6.65, 6.75, 7.35, 8.50, 9.40, 10.41, 13.70, 14.50 μ; uv (methanol) 283 nm (ϵ 25,300); NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.60 (s, 3 H), and a multiplet between δ 6.8 and 7.4 (11 H).

A 0.2-g sample of the above hydrazone was heated at 185° under a nitrogen atmosphere for 2 hr. The NMR spectrum of the crude mixture showed the presence of unreacted starting material as well as new singlets at δ 2.3–2.1. The crude mixtuure was chromatographed on a thick layer plate, and the new thermal product was isolated as a crystalline solid: mp 156–158°; ir (KBr) 3.05, 6.20, 6.60, 6.90, 7.08, 7.95, 8.00, 8.80, 9.20, 9.30, 9.95, 10.22, 10.91, 11.25, 12.73, 13.35, 13.70, and 14.40 μ; uv (methanol) 275 nm (ϵ 18,300); NMR ($CDCl_3$) δ 6.9–7.5 (m, 11 H), 2.3 (s, 3 H), 2.1 (s, 3 H).

Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.08; H, 5.96; N, 14.37.

This same material was also formed when the initial hydrazone **29** was heated in refluxing benzene which contained a trace of iodine. Thermolysis of the 156–158° isomer at 185° or in benzene which contained a trace of iodine gave a mixture of unreacted starting material as well as the original 133–135° geometrical isomer.

Preparation and Thermolysis of the Oxime of 3-Phenyl-4-acetyl-5-methylisoxazole. A solution containing 1.05 g of 3-phenyl-4-acetyl-5-methylisoxazole, 0.69 g of hydroxylamine hydrochloride, and 0.4 g of sodium hydroxide in 9 ml of a 90% ethanol solution was heated at reflux for 10 hr. The solvent was removed under reduced pressure, and 5 ml of water was added to the residue. The aqueous suspension was extracted with ether and the ethereal layer was dried over magnesium sulfate. Removal of the solvent left a white solid which was recrystallized from aqueous ethanol to give 1.07 g of the oxime of 3-phenyl-5-methyl-4-acetylisoxazole (**32**): mp 121–122°; ir (KBr) 3.00, 6.20, 6.80, 7.00, 7.60, 7.95, 8.70, 9.25, 9.65, 9.81, 10.95, 12.70, 13.25, 13.65, and 14.20 μ; NMR ($CDCl_3$) δ 10.4 (broad s, 1 H), 7.3–7.5 (m, 5 H), 2.50 (s, 3 H), 1.90 (s, 3 H).

A 0.4-g sample of the above oxime was heated at 190° under a nitrogen atmosphere for 7 hr. The NMR spectrum of the crude mixture showed that syn–anti isomerization of the oxime had occurred. Chromatography of the mixture on silica gel gave 3-phenyl-5-methyl-4-acetylisoxazole.

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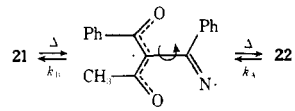
(42) It should be pointed out that no direct information is available concerning the relative energies of diradicals A and B or isoxazoles **21** and **22**.
(43) The difference in the relative rates of cyclization ($k_B > k_A$) could also be attributed to a difference in the electron density on the oxygen atoms of a delocalized diradical



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Electrochemical Reactions of Organic Compounds in Liquid Ammonia. III. Reductive Alkylation of Quinoline

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Abstract: The electrochemical behavior of quinoline in anhydrous liquid ammonia was investigated by cyclic voltammetry and controlled potential coulometry. In the absence of added alkylating agent, quinoline is reduced in two steps to yield the radical anion and dianion both of which undergo further chemical reaction. The radical anion species dimerizes to form the dimeric dianion which is stable in the medium and can be reversibly reoxidized back to parent compound. The second-order rate constant for this dimerization reaction was found to be 1.5×10^2 l./mol sec at −40°C. In the presence of ethyl bromide or *n*-butyl bromide, reductive alkylation proceeds via an ECEC mechanism to yield approximately equal quantities of the 1,2-dihydro-1,2-dialkyl and 1,4-dihydro-1,4-dialkyl derivatives. Differences in product composition between chemical reduction with lithium and electrochemical reduction are explained.

Recently there has been an upsurge of interest in the study of reductive alkylation reactions in nonaqueous solvents because of their possible applications to organic synthesis. Previously, this technique has been used to prepare a variety of mono- and dialkyl derivatives by chemically reducing an unsaturated hydrocarbon with an alkali metal in liquid ammonia, followed by quenching of the reaction mixture with an alkyl halide.[1-4] In more recent work, these reactions have been performed in the nonaqueous solvents dimethylformamide (DMF) and acetonitrile (AN) with electrochemical reduction of the parent compound.[5-7] An advantage in this procedure over alkali metal reduction is that both reactants can be present in solution simultaneously since selective reduction of the unsaturated compound can be obtained by proper adjustment of the electrode potential. With the electrochemical procedure, the scope of the reaction has been broadened to include reduction of unsaturated carbon–oxygen, carbon–nitrogen, and nitrogen–oxygen bonds, while the use of acid chlorides or acid anhydrides as electrophiles has led to the preparation of certain acyl derivatives in addition to the alkyl derivatives available from reaction with alkyl halides.

A competing protonation reaction frequently accompanies the alkylation reaction in DMF and AN, producing a product mixture consisting of diprotonated, monoalkylated, and dialkylated derivatives, with the dialkyl derivative often occurring in very low yield. A higher yield of the alkyl derivatives as well as a better understanding of the alkylation reaction would be obtained if protonation could be eliminated. For this reason, a study of this reaction with