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STUDIES ON HETEROCYCLIC CHEMISTRY—V[1]

A NOVEL SYNTHESIS OF 1-AZIRINES HAVING AN ESTER FUNCTION AND OBSERVATION OF THEIR MASS SPECTRA

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Abstract—It has been revealed that 1-azirines having an ester function at C can be synthesized by the thermally induced skeletal rearrangement of 5-alkoxyisoxazoles and 5-alkylmercaptoisoxazoles. Characterization of the azirines obtained was made by chemical reactions as well as by spectrometry. A further thermal transformation of azirine esters into oxazole derivatives could not be found. Mass spectra of representative 1-azirines are discussed with the aid of high resolution mass spectrometry and their behaviour under electron impact is correlated with that of 5-alkoxyisoxazoles which are their valence isomers.

RECENTLY we studied mass spectrometry of 5-alkoxyisoxazoles and reported several mechanistically interesting observations,[2] some of which could be rationalized by postulating an electron-impact-induced cleavage of an N—O linkage. In parallel with this study we felt it necessary to know the thermal behaviour of isoxazoles since, as mass spectra are usually determined by vaporizing the sample in a heated inlet system. the observed scission of an N—O bond may not be necessarily triggered solely by the electron-impact process. The result was published in a preliminary form,[3] which could reveal that 3-phenyl-5-alkoxyisoxazoles (VI, VII, VIII) undergo a serious change on heating at high temperature and transform into alkyl 2-phenyl-1-azirine-3-carboxylates (XIII, XIV, XV) in moderate yield. Thermally induced skeletal rearrangement of isoxazoles into a highly strained ring is a surprise,† but it appears to offer a potential synthetic method of 1-azirines. These reactions are described in detail.

Further, as an extention of this study, we desired to know the effect of a substituent on the benzene ring at C$_5$ to the reaction course in order to gain mechanistical insight, and to study the thermal behaviour of other isoxazoles having a substituent at C$_3$ with the hope to obtain other 1-azirines having a carbonyl function, because they are rather difficult to prepare by the known methods discussed later. Our additional object was to compare the mass spectra of 1-azirine esters with those of their isomeric isoxazoles and, if possible, to find the correlation between their electron-impact-induced fragmentations.

Preparation of isoxazoles. For the present study we required many 5-alkoxyisoxazoles in large quantity. Although 5-methoxyisoxazoles can be obtained by the action of diazomethane on appropriate isoxazol-5-one in moderate yield,[5,6] application of the diazoalkane procedure to the preparation of higher 5-alkoxyisoxazoles appears to be less convenient. We examined the action of alcohol and sulfuric

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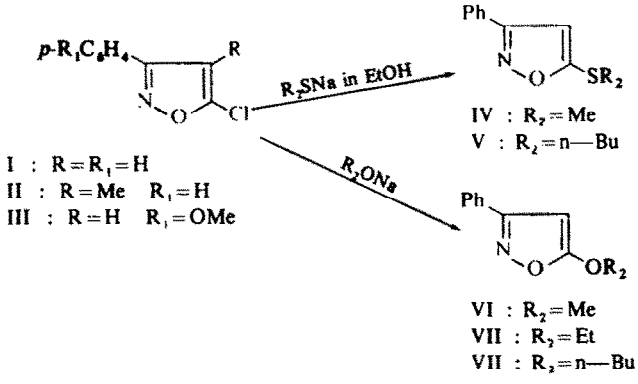
† Related observations on 4-isoxazolines have been made recently.[4]

acid on isoxazol-5-ones.[7] but the yield was very small. Consequently, we studied nucleophilic displacement of 5-haloisoxazoles with alkoxide. Adembri and Tedeschi reported the preparation of 3-phenyl-5-chloroisoxazole (I) by the action of phosphorus oxychloride on 3-phenylisoxazol-5-one in the presence of triethylamine molar-equivalent to the isoxazol-5-one.[8] Our detailed study reveals that use of the amine in less than one equivalent can give I in a consistent yield (60–63%). But in our experiences the rate of the addition of the amine appears to be very critical to the yield of I, rapid addition resulting in a poor yield. Similar observations were made for the preparation of 3-phenyl-4-methyl-5-chloro-isoxazole (II)[8] and 3-*p*-anisyl-5-chloro-isoxazole (III), but their yields were small. The reaction of I and III with sodium alkoxide proceeds satisfactorily. 3-Phenyl-5-alkylmercaptoisoxazoles (IV, V) were obtained by a similar procedure.



I : R=R$_1$=H
II : R=Me R$_1$=H
III : R=H R$_1$=OMe

IV : R$_2$=Me
V : R$_2$=n—Bu

VI : R$_2$=Me
VII : R$_2$=Et
VII : R$_2$=n—Bu

Skeletal rearrangement. It was reported that isomerization of VI, VII, and VIII takes place at 200° and the azirines (XIII, XIV, XV) can be isolated in moderate yield.[3] However, as is supposed, the azirines cannot always be isolated in a reproducible yield, because the reaction depends greatly on heating conditions. We used to take IR spectra at intervals in every run and stop heating when an absorption at 1600 cm^{-1}, which is very strong for isoxazoles, diminishes in intensity relative to a developing $\nu_{C=O}$ band. The 1600 cm^{-1} band is weak to medium for the azirines. Continued heating after this stage causes an appreciable decrease in yield and a tarry and intractable material increases. By observing this precaution we could obtain 50–70% yield.

3-*p*-Tolyl-5-methoxyisoxazole (IX) and 3-*p*-chlorophenyl-5-methoxy-isoxazole (X)

IX : R=R$_1$=Me
X : R=Cl R$_1$=Me
XI : R=OMe R$_1$=Me
XII : R=NO$_2$ R$_1$=Me

XIII : R=H R$_1$=Me
XIV : R=H R$_1$=Et
XV : R=H R$_1$=n—Bu
XVI : R=R$_1$=Me
XVII : R=Cl R$_1$=Me
XVIII : R=OMe R$_1$=Me
XIX : R=NO$_2$ R$_1$=Me

behave similarly, but the above-stated IR spectral change cannot be a reliable criterion for IX, because the 1600 cm^{-1} band is moderately strong for the rearranged product and thus the intensity of two developing $\nu_{C=O}$ and $\nu_{C=N}$ bands only provides an internal check for the change, Isomerization of IX and X is completed within *ca.* 30 min heating at 200° and an oil obtained from IX and a crystalline material from X can be characterized as the azirines XVI and XVII, respectively.

The reaction of 3-*p*-anisyl-5-methoxyisoxazole (XI) proceeds differently. When 0·015 mole of the compound was immersed in a heating bath (200°), an explosive reaction took place immediately after melting and a tarry and intractable material resulted. Several runs were attempted under similar conditions without success. Consequently, the temperature was lowered to 130° and the compound was slowly heated up to 180°. IR spectral change suggested that the transformation was negligible below 170°. However, when the temperature reached 180°, an explosive reaction ensued in two out of three runs. From a successful run a pale yellow slightly viscous oil was obtained in 33% yield, the analyses and spectral data of which establish its structure as the azirine (XVIII).

We also examined the rearrangement of 3-*p*-nitrophenyl-5-methoxy-isoxazole (XII). When the compound was heated at 200° for about 10 min, effervescence took place with concomitant evolution of a nitrile-like odour, suggesting the operation of competing reactions. Heating was stopped when this was observed and we were able to isolate an 18% yield of a crystalline material which was identified as the azirine (XIX).

It is of great interest that the thermal rearrangement of 4-isoxazolines into aroylaziridines proceeds at a much lower temperature than the condition reported herein[4] and the difference in chemical reactivity of isoxazoles apd isoxazolines[9] will also prevail here.

In the light of the thermally induced ready isomerization of acylaziridines into 4-oxazolines[4] and/or 2,5-diaryloxazoles[10] and of 2-phenyl-3-benzoyl-1-azirine into 2-phenyl-5-aryloxazole[11] we studied the thermal rearrangement of methyl 2-*p*-chlorophenyl-1-azirine-3-carboxylate (XVII) in diglyme, but we were unable to obtain isoxazole or oxazole derivatives in a detectable amount. Such an event would have produced an appreciable amount of 5-alkoxyoxazoles during the rearrangement process of 5-alkoxyisoxazoles, the formation of which could not be confirmed. It is considered that most of the azirine esters are fairly stable to the thermally induced ring enlargement reaction and this is one of the most noteworthy features of the present synthetical method.

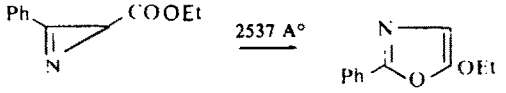
IR and UV spectral characteristics of the obtained azirines are indicated in Table 1, which reveals that introduction of a carboalkoxy function brings $\nu_{C=N}$ band to a higher frequency than that of 2-phenyl-1-azirine (1742 cm^{-1}).[12] UV spectra of 2-phenyl-5-alkoxyoxazoles, other valence tautomers of 3-phenyl-5-alkoxyisoxazoles, have λ_{max} 287 mμ and, thus, the oxazole structure for the present product can be convincingly eliminated.

Additional support for the proposed structures is provided by chemical reactions. Irradiation of ethyl 2-phenyl-1-azirine-3-carboxylate (XIV) with 2537 A° light afforded 2-phenyl-5-ethoxyoxazole (XX) in 48% yield. Excitation at a ketimine group must be responsible for this rearrangement, since $n \rightarrow \pi^*$ excitation of a CO_2Et moeity is unlikely.

TABLE 1. IR AND UV ABSORPTIONS OF THE AZIRINE ESTERS (XIII, XIV, XV, XVI, XVII, XVIII, AND XIX)

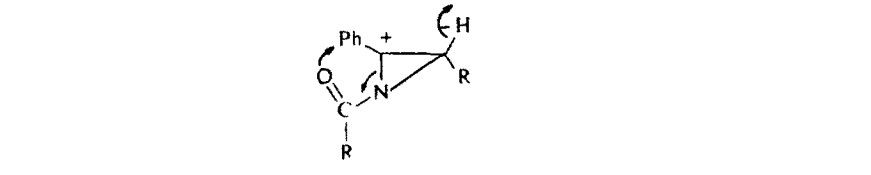
Azirine	IR Spectra (cm^{-1})			UV Spectra (mμ, log ε) (EtOH)
	$\nu_{C=O}$	ν_{C-O-C}	$\nu_{C=N}$	λ_{max}
XIII	1742[a]	1202	1778	243 (3·96), 288 (sh) (2·69)
XIV	1730[b]	1196	1773	243 (4·02), 288 (sh) (2·91)
XV	1732[b]	1195	1774	243 (3·96), 288 (sh) (2·82)
XVI	1731[b]	1205	1770	251 (4·21)
XVII	1736[a]	1200	1773	254 (4·06)
XVIII	1733[b]	1203	1770	214 (3·92), 270 (4·10)
XIX[d]	1732[c]	1200	1770	270 (4·05)

[a] CCl_4; [b] Neat; [c] $CHCl_3$; [d] ν_{NO_2} 1533 and 1350 cm^{-1}; [e] dioxan



XIV XX

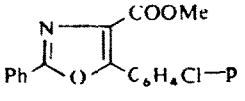
Ring expansion of 1-azirines on treatment with acid chloride has been well studied by Sato, *et al.*[13] and Fowler, *et al.*[14] Sato, *et al.* observed that treatment of 2-phenyl-1-azirine (XXI) with acid chloride in hot benzene yields 2-substituted-5-phenyloxazole (XXII), while Fowler, *et al.* isolated 4-methyl-2,5-diphenyloxazole (XXIV) from the reaction of 2-phenyl-3-methyl-1-azirine (XXIII) with benzoyl chloride in cold acetone, or N-benzoyl-2-phenyl-2-chloro-3-methylaziridine (XXV) by the reaction in hot benzene. Oxazole formation can be rationalized by postulating 1,2-scission of the intermediate aziridine ring.



XXV

XXI : R = H
XXIII : R = Me
XIII : R = COOMe

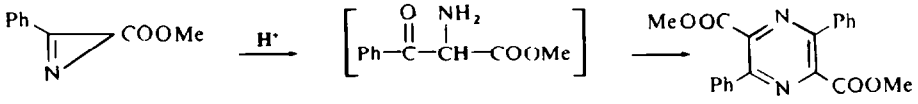
XXII : R = H
XXIV : R = Me
XXVI : R = COOMe R = Ph



XXVII

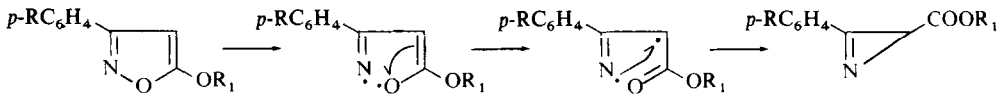
Reaction of methyl 2-phenyl-1-azirine-3-carboxylate (XIII) with benzoyl chloride in hot benzene afforded a compound $C_{17}H_{13}NO_3$, the UV spectrum of which exhibits λ_{max}^{EtOH} 298 mμ (log ε, 4·26), resembling that of 2,5-diphenyloxazole-4-carboxylic acid (λ_{max}^{EtOH} 303 mμ).[15] It has $\nu_{C=O}^{CCl_4}$ 1731 cm^{-1} in IR spectrum. The reports of previous workers[13,14] and these spectral data can formulate this compound as methyl 2,5-diphenyloxazole-4-carboxylate (XXVI). However, the azirine ring is generally stable to the action of acid chloride if there is a carboalkoxy function on the ring. When this reaction was applied to other azirine esters, the starting material was recovered almost quantitatively in most cases. Prolonged heating of the methyl ester (XVII) with benzoyl chloride in toluene gave a small amount of the oxazole ester (XXVII) as well as a large amount of the recovered azirine ester. Electron drawing carboalkoxy group will probably diminish electron density at ring nitrogen, which will make an electrophilic attack by aroyl chloride difficult.

The other reaction which was examined is the hydrolysis of the methyl ester XIII. The reaction was repeated several times, but in many cases a tarry material resulted, amount of a crystalline material as well as a large amount of tar. Insufficient quantity precluded its final characterization, but analysis and spectral data ($\nu_{C=O}^{Nujol}$ 1740 cm^{-1}, λ_{max}^{EtOH} 289 mμ (log ε, 3·99) suggest that dimethyl 2,5-diphenylpyrazine-3,6-dicarboxylate (XXIX) is one of the acceptable structures. The presence of three functions in the amino ketone (XXVIII), which must be a direct hydrolysis product of XIII, make the reaction complicated. Dimerization of 2-phenyl-1-azirine (XXI) into 2,5-diphenylpyrazine is known.[12,16,17]



XIII XXVIII XXIX

Initial step for the formation of 1-azirine would be a scission of an N—O linkage of the isoxazole to give the diradical, and subsequent rehybrization and electron pairing would lead to the azirine ring. Close values of electronegativities for nitrogen and oxygen (Pauling scale, 3·0 and 3·5, respectively) suggest that there will be a repulsion between the two heteroatoms of the isoxazole and the scission will be easy at high temperature. If a homolytic mechanism should operate, a substituent on the benzene ring will play an additional role in this cleavage. This is because a homolytic cleavage between electronegative atoms is generally facilitated by an electron releasing substituent and retarded by an electron drawing one, as has been observed for the unimolecular dissociation of benzoyl peroxide.[18] Although our results on the transformation of 3-*p*-substituted-phenyl-5-methoxyisoxazoles are less revealing in this respect, one observation pertinent to this prediction could be cited: namely, an explosively rapid reaction of 3-*p*-anisyl-5-methoxyisoxazole (XI) could be accounted for in terms of a substituent effect. In this isoxazole repulsion between the two heteroatoms must be large due to the presence of an electron-donating substiuent at para-position and the thermally induced scission must be quite rapid. This effect, coupled



with a relatively unstable nature of the azirine ester (XVIII), which was most unstable even at ambient temperature among the azirines reported here, must be responsible for the failure we often encountered in isolating XVIII.

To obtain other 1-azirines having a carbonyl function, thermal transformation of 3-phenyl-5-alkylmercaptoisoxazoles (IV, V) was investigated. Preliminary experiments indicated that the isoxazole V is more stable to heat than 5-alkoxyisoxazoles, which was shown from the intensity of a developing ν_{C-O} band, and therefore the reaction was undertaken at 230°. The product obtained in 17% yield was an orange oil, the analyses of which are indicative of, but not fully satisfactory for, the composition $C_{13}H_{15}NOS$ corresponding to methyl 2-phenyl-1-azirine-3-thiolcarboxylate (XXX). The most characteristic IR band was at 1673 cm^{-1}, which falls in the region assignable to the $\nu_{C=O}$ band of thiolesters.[19] An IR band at 1763 cm^{-1} of medium intensity can be attributable to the $\nu_{C=N}$ band of the 1-azirine ring (Fig. 1). Its high resolution mass spectrum has an *m/e* 233·083 ion as an apparent molecular ion, which agrees with $C_{13}H_{15}NOS$. It has also a peak at *m/e* 116·053 $(M—COSBu)^+$. Its UV spectrum has λ_{max}^{EtOH} 282 mμ (log ε, 4·11) and 250 mμ (log ε, 3·84) (sh). Based on these spectral observations, the structure of the azirine thiolester (XXX) can be proposed for the oil obtained. The reaction of 3-phenyl-5-methylmercaptoisoxazole (IV) was carried out at 200°, because the reaction product at higher temperature was very difficult to

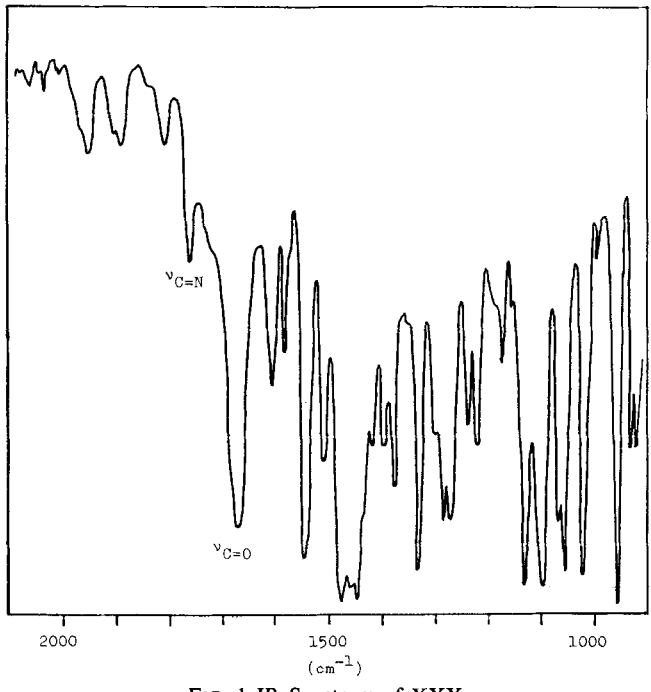
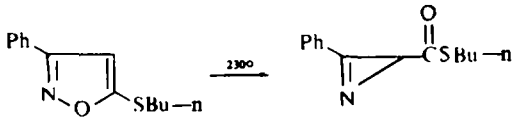


FIG. 1 IR Spectrum of XXX.



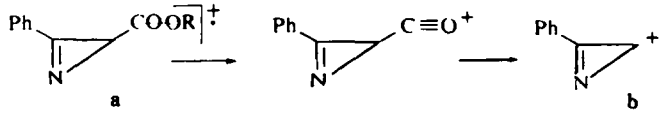
V XXX

work up. But in this case only a few drops of an orange oil appeared on the walls of the flask, the remainder being an intractable tar, and a further detailed study on this compound was given up. It is noted, however, that the UV spectrum of this oil is essentially similar to that of XXX. We consider the photochemical method[11] to be more promising for the isomerization of 5-alkylmercaptoisoxazoles into azirine thiolesters, which is in study.

The identity of 2-(2,4-dinitrophenyl)-3-methyl-1-azirine was confirmed for the first time by Cram, *et al.*[20] Since then several methods have been devised for the construction of 1-azirine ring. Pyrolysis of vinyl azides was developed,[12,21] but this procedure was limited in that vinyl azides were relatively unavailable until recently, when a convenient preparation of them was reported.[22] Photolysis of vinyl azides also gives 1-azirines.[23] Base-catalysed rearrangement of quaternary hydrazones has been employed as another standard method for the synthesis of 1-azirines.[24,25] Other less studied methods are the reactions of nitrile oxide with phosphorus ylide,[26,27] or of nitrile with sulfur ylide,[28] and addition of nitrene to an acetylenic compound.[29] However, only one 1-azirine ester has been obtained by these methods.[23] Preparation of conjugate vinyl azides from allenic esters and subsequent photolysis could produce two azirine esters,[30] but obviously this method is limited to 2-methyl-1-azirines.

Two 3-aroyl-2-aryl-1-azirines have been isolated as intermediates of photoinduced isoxazole ·oxazole rearrangement.[11] As is evident from the present work and the reports of Ullman, *et al.*[11] and Baldwin, *et al.*,[4] that the isoxazole derivative will provide a useful route for the preparation of 1-azirines having a carbonyl function, if an adequate isomerization method (thermal or photochemical*) is employed. With respect to yield of the azirine esters and convenience the 5-alkoxyisoxazole thermolysis will compare favourably with the vinyl azide photolysis procedure.[23]

Mass spectra. Partial mass spectra of ethyl 2-methyl-1-azirine-3-carboxylate and ethyl 2,3-dimethyl-1-azirine-3-carboxylate have been given.[30] We determined the spectra of the azirine esters XIII and XIV (Figs 2 and 3) and could find the $(M-59)^+$ and $(M-73)^+$ ions, respectively, associated with the cleavage of the ester group, as substantiated by exact mass determinations of XIII (Table 2). The resulting ions may be formulated as an azirinyl ion (b) if the decomposition takes place through an intact azirine molecular ion (a). However, it must be noted that this ester function is not ejected in one step, observation of metastable ions apparently indicating the operation of two-step fragmentation.



a b

* The photo-chemical preparation of 1-azirine amide from 5-aminoisoxazole, for example, depends very much on the kind of solvent.[31]

TABLE 2. EXACT MASS DETERMINATIONS OF XIII

m/e	Composition	Found	Calcd.	*m/e*	Composition	Found	Calcd.
175	$C_{10}H_9NO$	175·066	175·063	132	C_8H_6NO	132·044	132·045
160	C_9H_6NO	160·043	160·040	120	C_8H_8O	120·058	120·058
147	C_9H_9NO	147·069	147·069	116	C_8H_6N	116·051	116·050
144	C_9H_6NO	144·046	144·045	105	C_7H_5O	105·035	105·034

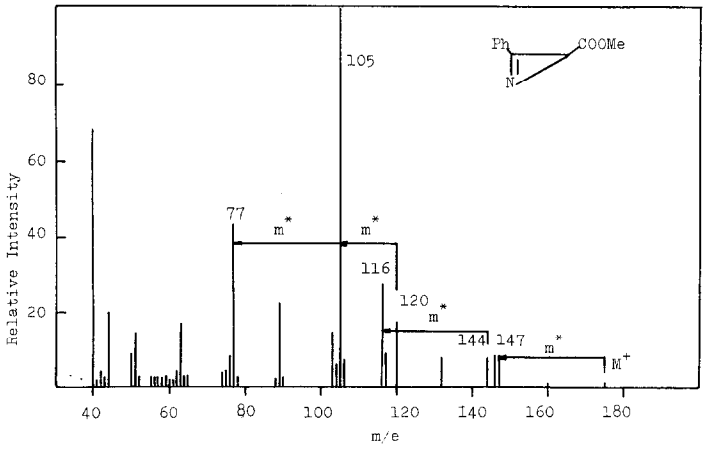


FIG. 2 Mass Spectrum of XIII.

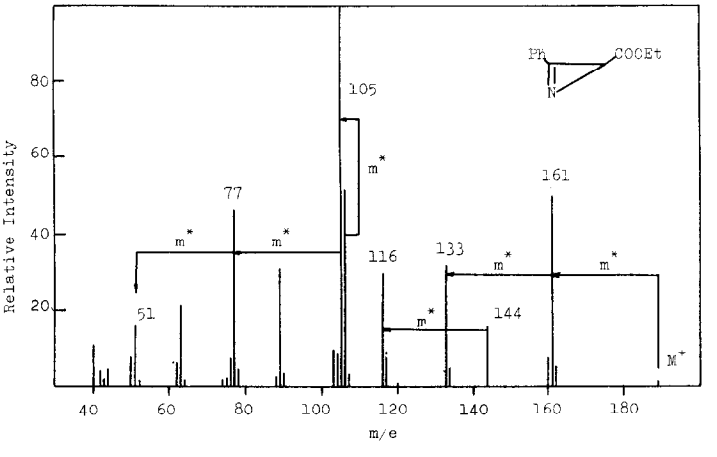
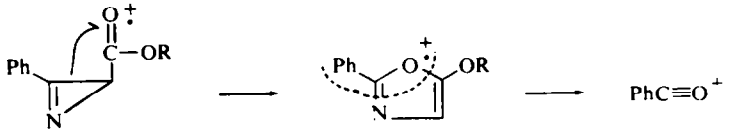


FIG. 3 Mass Spectrum of XIV.

The most characteristic feature in the spectra of the present azirine esters is that an *m/e* 105 ion (C_7H_5O solely for XIII) is the base peak, the formation of which can not be rationalized unless a skeletal rearrangement of the molecular ion operates. One of the likely precursors could be 2-phenyl-5-alkoxyoxazole radical ion (c), which may be generated by an electron-impact-induced ring expansion of the azirine esters. Scission at a dotted line could produce a benzoyl ion. If this is true, a metastable ion for the process $M^+ \rightarrow m/e$ 105 might be present, which, however, was not found. Bowie, *et al.* determined a number of the mass spectra of 2-phenyl-5-substituted-oxazoles and found that the benzoyl ion occupies a minor proportion of the total ion currents,[32] but of course these facts do not necessarily disprove the supposed generation of the



a c

benzoyl ion from (c). A process *m/e* 120 (C_8H_8O solely for XIII)→*m/e* 105 and other route leading to the *m/e* 105 ion depicted in Figs. 2 and 3 are strongly supported by the presence of metastable ions. But again the genesis of the precursors cannot be accounted for in terms of an intact azirine skeleton and it is suggested that this type of compound undergoes an extensive skeletal rearrangement on electron impact.

Comparison of the spectra of the present azirine esters with those of 3-phenyl-5-alkoxyisoxazoles[2] reveals that the spectra of both isomers are similar not only in precise ion compositions* but also in metastable transitions. The spectra of the azirine esters were not determined under the same experimental conditions employed previously,[2] but their striking similarity will suggest a tentative conclusion that the behaviour of azirine esters under electron bombardment is closely associated with that of their isomeric 5-alkoxyisoxazoles, as is often pointed out.[2,33,34] However, in the light of the chemical observations reported herein, it must be emphasized that the thermally induced formation of azirines must not be neglected in the interpretation of the spectra of isoxazoles determined through a heated inlet system, although this must be a function of the time the compound stays there and of the temperature employed.

EXPERIMENTAL

M.ps were determined on a Yamagimoto hot stage and uncorrected. UV and IR spectra were obtained with Hitachi–124 and JASCO–IR–G spectrophotometers, respectively. Mass spectra were determined with a Hitachi RMU 6D single focussing spectrometer with the following condition: ionization energy, 70 eV; total emission, 100 μA; inlet system temperature, 100°; ion source temp, 200°. Exact mass determinations were carried out with a CEC–110–B mass spectrometer at 70 eV by inserting the sample directly in an ion source (80°). Pet ether had b.p. 30–70°. Elemental analyses were performed at Department of Pharmacy, Kyoto University.

Analyses of the preliminary reported azirines (XIII, XIV, XV)[3] given: XIII (Found: C, 68·56; H, 5·09; N, 7·94. $C_{10}H_9NO_2$ requires: C, 68·56; H, 5·18; N, 8·00%: XIV (Found: C, 69·54; H, 5·88; N, 7·41. $C_{11}H_{11}NO_2$ requires: C, 69·82; H, 5·86; N, 7·40%): XV (Found: C, 71·58; H, 7·08; N, 6·58. $C_{13}H_{13}NO_2$ requires: C, 71·86; H, 7·00; N, 6.45%).

* Ion compositions of all fragment ions of XIII were determined by a computer technique. Similar spectra were also obtained by inserting the sample directly in an ion source.

3-Phenyl-5-chloroisoxazole (I). Et_3N (8·0 g, 0·08 mole) was slowly added over 30 min to an ice-cooled and stirred mixture of 3-phenylisoxazol-5-one (16·0 g, 0·1 mole) in $POCl_3$ (90 ml) and the mixture was refluxed for 1·5 hr, a clear soln having resulted after *ca.* 30 min of heating. Excess of $POCl_3$ was removed *in vacuo*, the residue was poured into ice, and the soln was made alkaline to litmus. Ppts were extracted with ether, the extracts were dried (Na_2SO_4), and distilled (b.p. 84–92°/0·4 mm) to give a solid, 11·4 g (63%), m.p. 46–47° (lit. m.p. 51–52°[8]). Recrystallization from light petroleum gave the compound as colourless needles, m.p. 46–47°. (Found: C, 60·00; H 3·28. C_9H_6ClNO requires: C, 60·18; H, 3.37%). However, this compound was used for the subsequent reactions without recrystallization throughout this study.

By essentially similar procedure II (b.p. 97–99°/1 mm, n_D^{27} 1·5631 (lit. b.p. 85°/0·5 mm, m.p. (28–30°[8])). (Found: C, 61·82; H, 4·43. $C_{10}H_8ClNO$ requires: C, 62·06; H, 4·17%) was obtained in 22% yield.

3-Phenyl-5-n-butoxyisoxazole (VIII). 3-Phenyl-5-chloroisoxazole (0·9 g) was added to the soln prepared from Na (0·15 g) and n-BuOH (10 ml) and the mixture was heated for 30 min on a steam bath. The solvent was removed *in vacuo* and a solid (0·9 g) was recrystallized from light petroleum as colourless needles, m.p. 61–63°. (Found: C, 71·56; H, 6·92; N, 6·34. $C_{13}H_{15}NO_2$ requires: C, 71·86; H, 7·00; N, 6·45%).

By a similar procedure VII, m.p. 75–77° (from light petroleum), was derived.

3-Phenyl-5-methylmercaptoisoxazole (IV). A soln of 3-phenyl-5-chloroisoxazole (7·2 g) in EtOH (30 ml) was mixed with 20% aqueous sodium methyl mercaptide (14·4 g) and refluxed for 2 hr. Crystals separated on cooling, which were filtered off. The filtrate was concentrated in a rotary evaporator and extracted with ether, from which an additional crop was obtained. Combined materials (8·1 g) were distilled at 134–136°/2 mm and the solidified distillate (4·4 g, m.p. 39–40°) was recrystallized from light petroleum as colourless needles, m.p. 42–43°. (Found: C, 62·89; H, 4·68; N, 7·30. $C_{10}H_9NOS$ requires: C, 62·80; H, 4·74; N, 7·33%); λ_{max}^{EtOH} 225 mμ (log ε, 4·10), 238 mμ (log ε, 4·11), and 264 mμ (sh).

3-Phenyl-5-n-butylmercaptoisoxazole (V). 3-Phenyl-5-chloroisoxazole (9·0 g) was added in small portions to the soln of n-butyl mercaptan (4·5 g), NaOH (2·5 g), water (25 ml), EtOH (75 ml) and the mixture was refluxed for 2 hr. Low boiling materials were removed in a rotary evaporator and the residue was extracted with ether. Dried (Na_2SO_4) extracts were distilled to give the compound as yellow oil (b.p. 149–152°/0·7 mm), 8·1 g, $n_D^{21.7}$ 1·5762. (Found: C, 66·95; H, 6·68; N, 5·99. $C_{13}H_{15}NOS$ requires: C, 66·91; H, 6·48; H, 6·00%); λ_{max}^{EtOH} 226 mμ (log ε, 4·20), 238 mμ (log ε, 4·23), 264 mμ (sh).

3-p-Tolylisoxazol-5-one. Ethyl *p*-toluoylacetate (b.p. 119–124°/0·7 mm $\nu_{C=O}$ 1738, 1680 cm^{-1}) (44·0 g), hydroxylamine hydrochloride (22·2 g), NaOH (21·3 g), and water (80 ml) were heated for 30 min at 100°. The resulting soln was acidified and ppts were dissolved in boiling water. The product (17·6 g) obtained on cooling the soln was twice recrystallized from CCl_4 as colourless rods, m.p. 135–137°. (Found: C, 68·60; H, 5·24; N, 7·81. $C_{10}H_9NO_2$ requires: C, 68·56; H, 5·18; N, 8·00%).

3-p-Tolyl-5-methoxyisoxazole (IX). 3-*p*-Tolylisoxazol-5-one (7·9 g) was treated with ethereal diazomethane and the resulting soln was washed with 2% NaOH aq. Evaporation of the dried (Na_2SO_4) soln gave a product, which was repeatedly recrystallized from light petroleum as colourless rods, 4·3 g, m.p. 78–79°. (Found: C, 69·85; H, 5·79; N, 7·35. $C_{11}H_{11}NO_2$ requires: C, 69·82; H, 5·86; N, 7·40%); λ_{max}^{EtOH} 243 mμ (log ε, 4·25).

Methyl 2-p-tolyl-1-azirine-3-carboxylate (XVI). 3-*p*-Tolyl-5-methoxyisoxazole (3·2 g) was charged in a distillation flask and heated in an oil bath (200°) for 30 min. Distillation (b.p. 95–105°/0·3 mm) gave the azirine, 1·6 g, 50%. A further fractional distillation gave an analytically pure sample as colourless oil, b.p. 100–105°/0·6 mm, n_D^{25} 1·5492, which next day turned into yellow even on standing in the dark. (Found: C, 70·02; H, 5·96; N, 7·17. $C_{11}H_{11}NO_2$ requires: C, 69·82; H, 5·86; H, 7·40%).

3-p-Chlorophenylisoxazol-5-one. This compound was prepared from ethyl *p*-chlorobenzoylacetate and hydroxylamine hydrochloride and recrystallized from MeOH as colourless rods, m.p. 153–156° (dec). (Found: C, 55·51; H, 3·31. $C_9H_6ClNO_2$ requires: C, 55·26; H, 3·09%); $\nu_{C=O}^{CHCl_3}$ 1807 cm^{-1}. Grünanger, *et al.* recorded m.p. 152–153° for this compound.[35] but it was found that the decomposition point of this compound is a function of the time of heating and we often noted the decomposition point higher than 160° for the same specimen.

3-p-Chlorophenyl-5-methoxyisoxazole (X). This compound was prepared as described before and recrystallized from MeOH as colourless needles, m.p. 107–108°. (Found: C, 57·38; H, 4·15; N, 6·69. $C_{10}H_8ClNO$ requires: C, 57·29; H, 3·85; N, 6·68%); λ_{max}^{EtOH} 246 mμ (log ε, 4·20).

Methyl 2-p-chlorophenyl-1-azirine-3-carboxylate (XVII). 3-*p*-Chlorophenyl-5-methoxyisoxazole (4·2 g) was charged in a distillation flask and immersed in an oil bath (200°). After 30 min of heating the flask

was evacuated and a colourless distillate was obtained at b.p. 108–113°/0·9 mm, which immediately solidified in a condenser. 2·6 g (62%), m.p. 70–73°. Two recrystallizations from ligroin gave the compound as colourless needles, m.p. 72–73°. (Found: C, 57·16; H, 3.74; N, 6·45. $C_{10}H_7ClNO$ requires: C, 57·29; H, 3·85; N, 6·68%).

3-p-Anisyl-5-methoxyisoxazole (XI). (a). 3-*p*-Anisylisoxazol-5-one (6·0 g) was treated with ethereal diazomethane and the mixture was treated as before. The product was twice recrystallized from MeOH as colourless rods, 2·5 g, m.p. 97–98°. (Found: C, 64·17; H, 5.54; N, 6·82. $C_{11}H_{11}NO$ requires: C, 64·38; H, 5·40; N, 6·83%); λ_{max}^{EtOH} 255 mμ (log ε 4.20). (b) Compound III prepared in 29% yield from 3-*p*-anisylisoxazol-5-one in the same way as I and II (b.p. 123°/2 mm, m.p. 81–83° (from light petroleum) (Found: C, 57·16; H, 3.83; N, 6·65. $C_{10}H_8ClNO_2$ requires: C, 57·29; H, 3·85; N, 6·68%) (1.4 g) was added to a soln of Na (0·2 g) in MeOH (5 ml) and the mixture was refluxed for 1 hr. The solvent was removed and addition of water to the residue gave crystals, 1·2 g, which were recrystallized from MeOH, m.p. 97°.

Methyl 2-p-anisyl-1-azirine-3-carboxylate (XVIII). 3-*p*-Anisyl-5-methoxyisoxazole (3·6 g) was charged in a distillation flask and immersed in an oil bath (130°). Temp was slowly raised to 190° during 1 hr 20 min and then maintained at that temp for 15 min. Distillation gave a colourless oil (b.p. 128–134°/0·7 mm, 1.2 g), which turned into yellow during distillation. This distillate was fractionated to give the compound as pale yellow oil, b.p. 108–112°/0·5 mm, n_D^{25} 1·5638. (Found: C, 64·18; H, 5·52; N, 6·76. $C_{11}H_{11}NO_3$ requires: C, 64·38; H, 5·40; N, 6·83%). On standing this compound turned into a viscous oil.

3-p-Nitrophenyl-5-methoxyisoxazole (XII). 3-*p*-Nitrophenylisoxazol-5-one[6] (7·4 g) was treated with ethereal diazomethane. Pale yellow needles separated immediately, which were filtered off, washed well with 2% NaOH aq and dried, 6·1 g. The filtrate was concentrated to give a solid, 1·3 g. Combined crystals were recrystallized from EtOH as pale yellow needles, m.p. 173–174°. (Found: C, 54·51; H, 3·73; N, 12·74. $C_{10}H_8N_2O_4$ requires: C, 54·55; H, 3.66; N, 12·72%); λ_{max}^{EtOH} 213 mμ (log ε, 3·92), 275 mμ (log ε, 4·00); $\nu_{NO_2}^{CHCl_3}$ 1530 and 1352 cm^{-1}.

Methyl 2-p-nitrophenyl-1-azirine-3-carboxylate (XIX). 3-*p*-Nitro-phenyl-5-methoxyisoxazole (0·8 g) in a test tube was heated in an oil bath (200°) until a little effervescence began, which took about 10 min. After cooling the tube was destroyed and the content was repeatedly extracted with ether. The extracts were evaporated and the residue was chromatographed on SiO_2 with light petroleum-EtOAc (1:1). An initially eluted product was orange crystals, which were repeatedly recrystallized from ligroin as pale yellow prisms, m.p. 100°, 0·15 g. (Found: C, 54·72; H, 3·90; N, 12·76. $C_{10}H_8N_2O_4$ requires: C, 54·55; H, 3·66; N, 12·72%). The next eluted material and a product remained on the column were a brown tar, which never crystallized.

Photochemical reaction of ethyl 2-phenyl-1-azirine-3-carboxylate (XIV). A soln of XIV (0·50 g) in ether (300 ml) was irradiated over 3 hr 45 min with a Riko low-pressure Hg lamp (30 W) in a quartz immersion well. The solvent was evaporated and the residue was chromatographed on SiO_2 with ether. An initially eluted product was the starting azirine (0·11 g, λ_{max}^{EtOH} 243 mμ) and the next eluted product (0·24 g) was a pale yellow oil, the IR spectrum of which was identical with that of XX prepared according to Karrer, *et al.*[36] Its UV spectrum had λ_{max}^{EtOH} 287 mμ.

Thermal behaviour of methyl 2-p-chlorophenyl-1-azirine-3-carboxylate (XVII). The azirine XVII (0·082 g) was heated in refluxing diglyme (3 ml) for 8 hr and the reaction was monitored by UV specra. An absorption max remained at 254 mμ after 8 hr of refluxing. Evaporation of the solvent *in vacuo* and chromatography of the residue on SiO_2 with ether gave a pale yellow oil, 0·05 g, which did not crystallize but had an almost identical IR spectrum with that of XVII.

Methyl 2,5-diphenyloxazole-4-carboxylate (XXVI). To a mixture of methyl 2-phenyl-1-azirine-3-carboxylate (0·42 g), Et_3N (0·25 g), and anhyd benzene (5 ml) a soln of benzoyl chloride (0·34 g) in anhyd benzene (5 ml) was added, the soln was refluxed for 2 hr and then washed with Na_2CO_3 aq. The solvent was removed in a rotary evaporator and a gummy residue was dried on a porous plate to give a solid. This was twice recrystallized from aqueous EtOH as colourless needles, 0·04 g, m.p. 85·5–86°. (Found: C, 73·38; H, 4·81; N, 5·14. $C_{16}H_{11}NO_3$ requires: C, 73·11; H, 4·69; N, 5·02%).

Methyl 2-phenyl-5-p-chlorophenyloxazole-4-carboxylate (XVII). A soln of methyl 2-*p*-chlorophenyl-1-azirine-3-carboxylate (0·42 g), Et N (0·2 ml), and toluene (5 ml) was mixed with a soln of benzoyl chloride (0·3 g) in toluene (5 ml) and refluxed for 4 hr. The mixture was washed with Na_2CO_3 aq, the solvent was removed in a rotary evaporator, and the residue solidified on standing, which was filtered off and recrystallized from light petroleum, 0·25 g, m.p. 72–73°. This was identified as XVII by a mixed

m.p. The filtrate gave crystals on refrigeration for about a week, which were twice recrystallized from EtOH as colourless needles, 30 mg, m.p. 137–138·5°. (Found: C, 64·95; H, 3·73; N, 4·52. $C_{17}H_{12}ClNO_3$ requires: C, 65·08; H, 3·86; N, 4·47%); λ_{max}^{EtOH} 306 mμ (log ε, 4·05). $\nu_{C=O}^{CCl_4}$ 1726 cm^{-1}. When this reaction was carried out in hot benzene, the starting azirine was recovered quantitatively.

Attempted hydrolysis of methyl 2-phenyl-1-azirine-3-carboxylate (XIII). The azirine XIII (0·50 g) was heated in MeOH (10 ml) containing HCl (0·1 ml) for 7 hr. The yellow soln was evaporated and a residual oil was refluxed in MeOH (5 ml) containing NH_4OH (0·1 ml) for 1·5 hr. The solvent was removed, a residual gummy material yielded a small amount of crystals on trituration with ether, which were filtered off, washed with ether, and recrystallized from EtOH as pale yellow needles, m.p. 192–194°, 11 mg. (Found: N, 8·26. $C_{20}H_{16}N_2O_4$ requires: N, 8·04%).

n-Butyl 2-phenyl-1-azirine-3-thiolcarboxylate (XXX). 3-Phenyl-5-n-butylmercaptoisoxazole (4·7 g) in a distillation flask was immersed in an oil bath (230°) and heated for 1 hr 10 min. IR spectrum of black-brown tarry material showed a strong, but broad absorption at 1660 cm^{-1}. Distillation gave a pale orange oil, b.p. 117–123°/0·7 mm, 0·7 g. This procedure was repeated once more by heating the isoxazole (4·7 g) for 1 hr and an oil, 1·2 g, was obtained. A portion (1·6 g) of the combined distillates was fractionally distilled and a pale orange oil (b.p. 104–109°/1 mm, n_D^{25} 1·5723), 1·1 g, was analyzed. (Found: C, 65·92; H, 7·03; N, 5·42. $C_{13}H_{15}NOS$ requires: C, 66·91; H, 6·48; N, 6·00%). Other major mass spectral peaks other than those noted in the text are at *m/e* 105·036 (C_7H_5O), *m/e* 121·016 (C_7H_5S), *m/e* 144·047 (C_9H NO) (M—SBu)$^+$, and *m/e* 177·021 (C_9H NOS) (M—C_4H_9)$^+$.

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