

STUDIES ON HETEROCYCLIC CHEMISTRY. III.<sup>1</sup> THERMALLY INDUCED SKELETAL  
REARRANGEMENT OF 5-ALKOXYISOXAZOLES INTO ALKYL 1-AZIRINE-3-CARBOXYLATES

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1-AZIRINES are the compounds of recent history. Since the first confirmation of 2-(2,4-dinitrophenyl)-3-methyl-1-azirine as a Neber rearrangement product of oxime tosylate by Cram, et al.,<sup>2</sup> several methods have been devised for their preparation, among which pyrolysis<sup>3</sup> and photolysis<sup>4</sup> of vinyl azides and the base-catalyzed rearrangement of quaternary hydrazones<sup>5</sup> are worthy of attention. It is reported here that 5-alkoxyisoxazoles undergo a facile thermally induced skeletal rearrangement into alkyl 1-azirine-3-carboxylates in moderate yield.<sup>6</sup> This result, coupled with a recent publication<sup>7</sup> that 3,5-diphenylisoxazole undergoes a photochemical transformation into 2-phenyl-3-benzoyl-1-azirine, demonstrates that isoxazoles are potential starting materials for the syntheses of functionally substituted 1-azirines, which otherwise are rather difficult to obtain.

5-Alkoxyisoxazoles are very stable to heat under reduced pressure, being recovered almost quantitatively on vacuum distillation. However, they undergo a serious change on heating at atmospheric pressure at high temperature. IR spectrum of 3-phenyl-5-methoxyisoxazole (0.025 mole) (I) heated at 200° for 5 minutes has already displayed very weak, but distinct absorptions at 1700-1800 cm<sup>-1</sup> region. The intensity of these absorptions gradually becomes strong

on continued heating and after 20-25 minutes of heating the spectrum becomes almost identical with that of the compound described below. This change was not observed even after heating at 160° for 30 minutes.

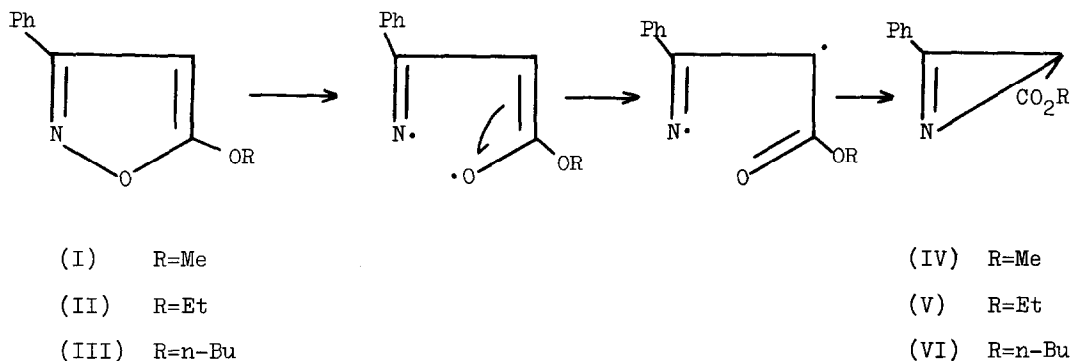
Distillation gave a liquid (b.p. 98-102°/1 mm, 60-66 %), which on standing for a long time solidified (m.p. 50-51°, colourless plates from petroleum ether). This compound is isomeric<sup>8</sup> with the starting isoxazole (I) and has  $\nu_{C=O}$  1742  $\text{cm}^{-1}$ ,  $\nu_{C=N}$  1778  $\text{cm}^{-1}$  characteristic<sup>4</sup> of 1-azirines, and an absorption at 1601  $\text{cm}^{-1}$  (IR spectrum,  $\text{CCl}_4$ ), and  $\lambda_{\text{max}}$  204  $\mu$  ( $\log \epsilon$ , 4.22), 243  $\mu$  ( $\log \epsilon$ , 3.96), and a shoulder at 288  $\mu$  ( $\log \epsilon$ , 2.69) (UV spectrum (EtOH)), which closely resemble those of (I) ( $\lambda_{\text{max}}$  204  $\mu$  ( $\log \epsilon$ , 4.27), 238  $\mu$  ( $\log \epsilon$ , 3.89) (EtOH)) indicating the presence of a similar chromophore in this molecule. It has an  $M^+$  at  $m/e$  175 (Found: 175.066.  $\text{C}_{10}\text{H}_9\text{NO}_2$  requires: 175.063) and an  $(M-\text{CO}_2\text{Me})^+$  at  $m/e$  116 (Found: 116.051.  $\text{C}_8\text{H}_6\text{N}$  requires: 116.050) in its mass spectrum,<sup>9</sup> the gross feature of which is however very akin to that of (I),<sup>10</sup> having skeletal rearrangement ions.

3-Phenyl-5-ethoxyisoxazole (0.022 mole) (II) behaves similarly, isomerization of which completes within 25-30 minutes of heating at 200°. Distillation gave a slightly yellow liquid (b.p. 92-95°/0.5 mm,  $n_D^{23}$  1.5370 after two fractionations, 68-72 %). This compound is also isomeric<sup>8</sup> with the compound (II) and has  $\nu_{C=O}$  1730  $\text{cm}^{-1}$ ,  $\nu_{C=N}$  1773  $\text{cm}^{-1}$ , and an absorption at 1600  $\text{cm}^{-1}$  in IR spectrum (neat). Its UV absorptions are  $\lambda_{\text{max}}$  204  $\mu$  ( $\log \epsilon$ , 4.24), 243  $\mu$  ( $\log \epsilon$ , 4.02), and a shoulder at 288  $\mu$  ( $\log \epsilon$ , 2.91) (EtOH), again resembling those of (II) ( $\lambda_{\text{max}}$  204  $\mu$  ( $\log \epsilon$ , 4.14), 238  $\mu$  ( $\log \epsilon$ , 3.81) (EtOH)).

However, complete isomerization of 3-phenyl-5-n-butoxyisoxazole (m.p. 61-63°) (0.034 mole) (III) takes about 1 hour of heating at 200°, new bands at 1700-1800  $\text{cm}^{-1}$  beginning to appear after heating for about 10 minutes. The obtained compound<sup>11</sup> (b.p. 100-103°/0.5 mm,  $n_D^{23}$  1.5244 after two fractionations, 56 %) is isomeric<sup>8</sup> with (III) and has  $\nu_{C=O}$  1732  $\text{cm}^{-1}$ ,  $\nu_{C=N}$  1774  $\text{cm}^{-1}$ , and an absorption at 1606  $\text{cm}^{-1}$  (IR spectrum, neat), and  $\lambda_{\text{max}}$  203  $\mu$  ( $\log \epsilon$ , 4.22), 243  $\mu$  ( $\log \epsilon$ , 3.96), and a shoulder at 288  $\mu$  ( $\log \epsilon$ , 2.82) (UV spectrum (EtOH)) ( $\lambda_{\text{max}}$  of (III), 204  $\mu$  ( $\log \epsilon$ , 4.09), 238  $\mu$  ( $\log \epsilon$ , 3.79) (EtOH)).

These facts firmly establish the compounds to be alkyl 1-azirine-3-carbo-

ylates (IV, V, VI) and the following rationalization is suggested, where the homologous cleavage of a labile N-O linkage of isoxazoles<sup>12</sup> is postulated to be an initial step. Thermally induced transformation into a highly strained ring is surprising, but it parallels with the behaviour of 2,3-dihydrofuran,<sup>13</sup> which isomerizes to cyclopropane aldehyde on heating at above 375°. Extention to other isoxazoles and the chemical reactions of alkyl 1-azirine-3-carboxylates are now under exploration.

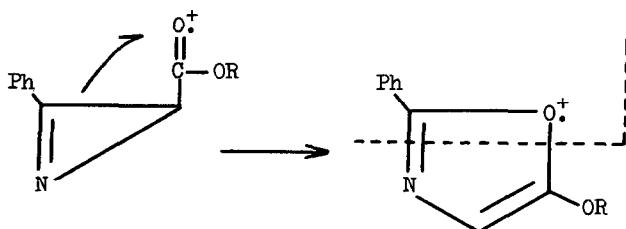


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#### References

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2. D. J. Cram and M. J. Hatch, *J. Am. Chem. Soc.*, 75, 33 (1953).
3. G. Smolinsky, *J. Org. Chem.*, 27, 3557 (1962).
4. A. Hassner and F. W. Fowler, *J. Am. Chem. Soc.*, 90, 2869 (1968).
5. S. Sato, *Bull. Chem. Soc. (Japan)*, 41, 1440 (1968).
6. It was reported<sup>10</sup> that 5-alkoxyisoxazoles undergo extensive skeletal rearrangements on electron impact. Their mass spectra have benzoyl ion ( $\text{PhC}\equiv\text{O}^+$ ) as a base peak. If the molecule transforms into alkyl 1-azirine-3-carboxylate during evaporation procedure, the latter may rearrange into 5-alkoxyoxazole radical ion on electron impact and can generate a benzoyl ion by the scission

at a dotted line. The present observation can not necessarily rule out this possibility. However, the spectrum (I) taken by a direct insertion into an ion source ( $80^\circ$ ) (CEC-110-B spectrometer) shows the benzoyl ion still carries a large ion current and it will be concluded that most of the observed benzoyl ion is generated by electron-impact-induced-decomposition of 5-alkoxyisoxazoles themselves.



7. E. F. Ullman and B. Singh, J. Am. Chem. Soc., 88, 1844 (1966).
8. Sufficient carbon, hydrogen, and nitrogen analyses have been obtained for the new compounds (III, IV, V, VI) at Department of Pharmacy, Kyoto University.
9. Exact mass measurements were carried out on a photographic plate with a CEC-110-B spectrometer at  $70^\circ$ .
10. T. Nishiwaki, Tetrahedron, 25, 747 (1969).
11. This liquid was colourless at the initial stage of distillation, but gradual colouration in yellow during fractionations was noted. This will suggest that this compound is less thermally stable than (IV) and (V). The present 1-azirines can be stored open to air, but they cause irritation to the skin.
12. M. K. Kochetkov and S. D. Sokolov, Advances in Heterocyclic Chemistry, 2, 365 (1963).
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