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(18) In all cases, the percent conversion of caffeine to its 2-propanol photoproduct (I) was approximately the same in the presence or absence of DMU. The low conversion of caffeine to product at 80 °C results from the slow decomposition of $(t\text{-BuO})_2$ at this temperature.
(19) Though stable under VPC conditions (injector at 280 °C), under the reaction condition, II slowly decomposes back to starting material at the same rate at all concentrations, more slowly in the presence of caffeine and more rapidly as the temperature is raised. Hence, the values of R_M/R_B plotted in Figure 3 are lower limits.
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Fragmentation Reaction of Ylide. 5.[1] A New Metabolic Reaction of Aziridine Derivatives

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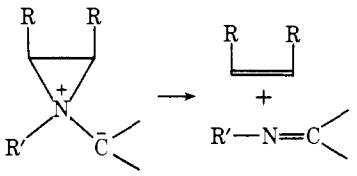
Abstract: Reactions of a number of substituted aziridines with rat liver microsomes under in vitro condition were carried out. Most of the aziridines employed gave olefin and nitrosoalkane as the fragmentation reaction products of the aziridine ring. This is a new metabolic reaction of aziridine, which has been discussed as an alkylating reagent or a precursor of amino alcohol formation in vivo. The fragmentation reaction of aziridine with enzyme(s) should be important in discussions on the biological character of aziridines hereafter.

In studies of the chemical properties of aziridine derivatives, known as strong carcinogenic substances, we found that aziridinium ylide, prepared by addition of carbene onto aziridine[2] or by abstraction of a proton from the N-substituent group of aziridine,[3] decomposed immediately after formation into fragments of olefin and heterounsaturated product.



The olefin formation reaction of the aziridinium ylide usually proceeded with stereospecific retention of the configuration and no other typical ylide reaction, for example, Stevens rearrangement, was observed.

Under the assumption that the metabolic course of aziridines might proceed through the formation of ylide by hepatic enzyme, we examined the in vitro biotransformation of aziridines by hepatic microsomes obtained from normal rats. Here we wish to report a new fragmentation reaction of aziridines by microsomal enzymes and the possibility of this hitherto unknown process of decomposing aziridines in vivo as a characteristic biological property.

The metabolic reactions of aziridines by liver microsomes were carried out in 50 mM Tris–HCl buffer (pH 7.4) containing 150 mM KCl, 10 mM $MgCl_2$, 1 mM nicotinamide, 1 mM pyrophosphate, 30 mg of protein of microsomes, 0.01 mM of aziridines, and NADPH-generating system (0.9 mM NADP, 10 mM glucose 6-phosphate, and 2.5 units of glucose-6-phosphate dehydrogenase) in a final volume of 5 ml. Unless otherwise stated, incubations were carried out aerobically at 37 °C for 60 min with moderate shaking.

After the reaction time was over, 2 N NaOH solution was added and the mixture was extracted with an appropriate amount of CH_2Cl_2 for VPC analysis. For the substrate, aziridine derivatives were converted into their tartarate immediately before use. In the case of compound **10**, we used the HCl salt of 2-chloro-*N*-isopropyl-2-(β-naphthyl)ethylamine instead of aziridine. This chloroamine was a precursor of aziridine **10** and was converted immediately into aziridine in the reaction solution.

In a preliminary experiment without introduction of the enzymatic system, aziridines were stable under the reaction conditions. First, tartarate of *cis*-2,3-diphenylaziridine (**1**) was used as a substrate. Fortunately, in the reaction mixture we found the formation of *cis*-stilbene by VPC analysis, although the yield was poor.

In our experiments, immediately after mixing the aziridines into the microsome solution, extraction with CH_2Cl_2 gave only 80–90% recovery of the aziridines. Thus, we calculated the reaction rate constant on the basis of the amount of aziridine recovered as the initial concentration and obtained 2×10^{-4} s^{-1} as the pseudo-first-order rate for the disappearance of *cis*-2,3-diphenylaziridine. The yield of *cis*-stilbene from compound **1** was approximately 4% at the half-life of the reaction.[4] We had expected a better yield, however, under the reaction conditions; olefin also smoothly disappeared from the mixture by another metabolic reaction.

Table I. Formation of *cis*-Stilbene from *cis*-2,3-Diphenylaziridine (1) by Rat Liver Microsomes

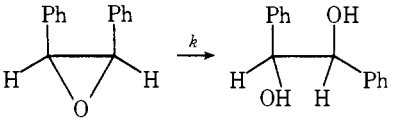
Expt no.[a]	Rxn mixture	Gas phase	*cis*-Stilbene formation
I, II	Complete system	Air	4%
III	Without NADPH-generating system	Air	No
IV	Without microsomes	Air	No
V	Complete system	Argon	No

[a] Experiments numbered II and V were performed in Thunberg tubes. The complete system contained all components required for microsomal drug metabolism, as described in the text. Concentration of substrate 1 was 2 mM.

As illustrated in Table I, the formation of *cis*-stilbene was observed in the reaction mixture containing every component required for microsomal drug-metabolizing reactions,[5] and lack of either microsomes, NADPH-generating system, or molecular oxygen gave only aziridine and not stilbene. This result indicates clearly that the olefin-forming fragmentation of aziridine is an enzymatic reaction, supposedly associated with either cytochrome P-450 containing monooxygenase system[6] or mixed function amine oxidase.[7] The *cis*-stilbene forming reaction also proceeded stereospecifically and the product did not contain trans isomer according to the limits of VPC analysis.

The results obtained from the enzymatic reactions of several aziridines are shown in Table II.

As shown in Table II, *cis*-aziridines have higher reactivity and better olefin formation yields than *trans*-aziridines. A similar tendency was observed by Watabe et al. recently in the enzymatic hydrolysis of stilbene oxide.[8] They found that *cis*-stilbene oxide in microsomes has 800 times the reactivity of the



$k_{cis}/k_{trans} = 800$

trans isomer. Both these results indicate the importance of the steric factor in the reaction of aziridines on the enzyme surface.

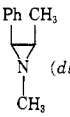
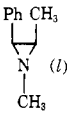
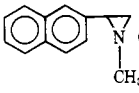
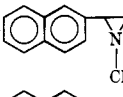
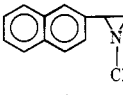
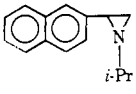
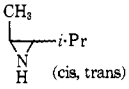
The methyl group on the nitrogen of aziridine seems to raise the reactivity of the olefin-forming reaction. Among the optically active aziridines, different amounts of olefin formation were also observed although their configurations were not clear.

The alkyl substituent group of positions 2 and 3 tends to decrease the reactivity of the aziridines. Dialkylaziridines **11** and **12** were practically inert under our reaction conditions. This is very similar to the tendency found with the sterilization ability of the aziridines in which the alkyl group also very effectively removes the special character of chemical sterilants.[9]

In our experiment, highest olefin formation was observed in the reaction of *N*-methyl-β-naphthylaziridines **7–9** as shown in Table II. The olefin, vinylnaphthalene, was also found in the extract obtained from fresh blood of rat injected with compound **8** under independent work of Dr. Amano.[10] In relation to the olefin formation ability of *N*-methyl-β-naphthylaziridine, it is very interesting that compound **8** has a very strong carcinogenicity when applied to the skin of rat.[11]

The configuration of olefin obtained from the reaction of **1** or **4** completely retained that of the starting materials. However, *cis*-phenylmethyl derivatives **3, 5,** or **6** gave the by-product, trans olefin. The composition of cis,trans olefin largely depended on the character of the microsomes; trans was varied from less than 1% to about 40%. We supposed that the cis olefin formed initially in the stereospecific reaction was converted to trans olefin by some unknown property of the microsomal suspension.

Table II. Reaction of Aziridines in the Complete Reaction System (37 °C, 60-min Incubation)[a]

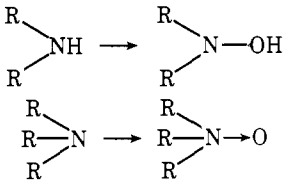
No.	Aziridine	Recovered aziridine, %	Olefin formed	Yield of olefin, %[b,c]
1		50	*cis*-Stilbene	4
2		Rxn too slow >90		
3		88	1-Phenylpropene[e] (cis + trans)	1.0
4		92	1-Phenylpropene[e] (only trans)	0.1
5		87	1-Phenylpropene[e] (cis + trans)	5
6		85	1-Phenylpropene[e] (cis + trans)	6.4
7		21	β-Vinylnaphthalene	4.5
8		19	β-Vinylnaphthalene	7.3
9		20	β-Vinylnaphthalene	8.3
10		19	β-Vinylnaphthalene	<0.1
11 12		Rxn too slow >90		

[a] The reactions were carried out under the conditions described for the complete system in Table I. The data obtained largely depended on the character of the microsomes and were variable. In this table, we chose the value obtained from a single experiment which corresponded to the approximate average for comparison convenience. [b] Poor agreement of material balance for the reactions attributed the absorption of aziridines on microsomes, the consumption of olefin by further reaction, and the formation of amino alcohol. [c] Calculated on the basis of the amount of aziridines consumed at the end of the reaction. [d] Instead of aziridine, 2-chloro-*N*-isopropyl-2-(β-naphthyl) ethylamine hydrochloride was used. This compound was converted immediately into aziridine upon mixing with the incubation mixture. [e] The trans percent was changed from <1 to 40% which largely depended on the character on the microsomes employed in the reaction.

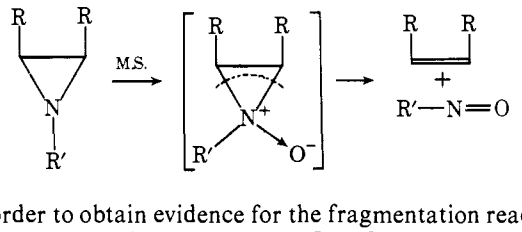
Discussion

Recently, the flavoprotein oxidase isolated from pig hepatic microsomes was reported to catalyze the N-oxidation of a

variety of secondary and tertiary amines.[12,13] The product of the oxidation was hydroxylamine from secondary amine and *N*-oxide from tertiary amine. Hydroxylamine should be formed by the hydrogen migration from nitrogen atom after



formation of *N*-oxide from the secondary amine. Ziegler and Mitchell showed clearly that the oxidation reaction of amine is essential as a first step in the metabolism of amino compounds.[13] The aziridines used in our experiment were probably converted to *N*-oxide at an initial stage of the reaction in the microsomal suspension. Aziridine *N*-oxides are already known as being very unstable intermediates which decompose immediately after formation into olefin and nitrosoalkane derivatives.[14,15] In order to confirm the steric course of aziridine *N*-oxide decomposition, we examined the oxidation of 2,3-diphenyl- and 2,3-methylphenylaziridines using *m*-chloroperbenzoic acid and obtained a good yield of olefins with retention of the configuration. This oxidative fragmentation reaction proceeded rapidly even at 0 °C. The result indicates that the aziridinium *N*-oxide (a kind of ylide) has the same character as the aziridinium ylide cited in the introduction of this paper. The aziridines introduced into the microsomal suspension probably gave *N*-oxide as an unstable intermediate which then decomposed into olefin and nitrosoalkane as shown below.

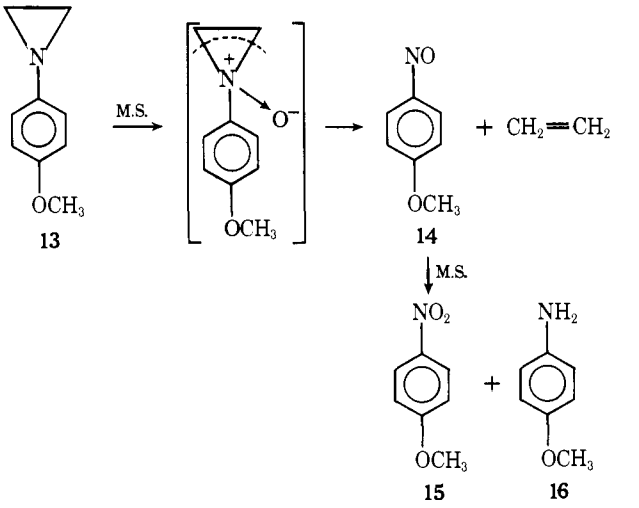


In order to obtain evidence for the fragmentation reaction of aziridines, we tried to detect HNO or CH_3NO, which was supposed to exist in the incubation mixture, but failed. These products are too unstable to be detected in the usual manner.

Nitrosoaromatic compounds are generally known as being more stable than aliphatic derivatives. Therefore, in the next experiment, we tried the metabolism of *N*-*p*-anisylaziridine (**13**) by microsomal enzymes. After 1 h of incubation of **13** under the complete system described in Table I, we observed only the formation of few percent of *p*-nitroanisole **15** and *p*-anisidine **16** and recovered the starting aziridine but not *p*-nitrosoanisole. In the control experiment, however, we found that nitrosoanisole prepared independently was also converted into *p*-nitroanisole and *p*-anisidine. The ratio of both products was completely identical with the result obtained in the enzymatic reaction of aziridines **7–9**. The nitroso substituent was converted smoothly to nitro and amino compound by the enzymatic action of microsomes.

The *p*-nitroanisole and *p*-anisidine obtained from *N*-*p*-anisylaziridine (**13**) came from *p*-nitrosoanisole formed in the fragmentation reaction by further conversion in microsomal suspension as shown in the reaction formula.

Generally, two fundamental processes are recognized as important biological reactions of aziridines. One of them is hydrolysis of three-membered rings to form amino alcohols and the other is alkylation with protein or DNA. We suggest a new process, fragmentation, which should be considered in dealing



with the carcinogenicity or chemical mutagenicity of aziridine derivatives.

Experimental Section

Materials. *cis,trans*-2,3-Diphenylaziridine (**1** and **2**),[16] *trans*-2-methyl-3-phenylaziridine (**4**),[16] *dl*- and *l*-1,2-dimethyl-3-phenylaziridine (**5** and **6**),[17] and *p*-nitrosoanisole[18] were prepared according to the literature. *cis*-2-Methyl-3-phenylaziridine (**3**) and *cis,trans*-2-methyl-3-isopropylaziridine (**11** and **12**) were prepared by the method of Hassner et al.[16] from corresponding olefins, respectively.

cis-2-Methyl-3-phenylaziridine (**3**): bp 95.5–96 °C (12 mm); NMR ($CDCl_3$) τ 2.63 (s, 5), 6.65 (m, 1), 7.55 (m, 1), 9.1 (d, 3). Anal. Calcd for C_9Hc11N: C, 81.16; H, 8.33; N, 10.52. Found: C, 80.90; H, 8.36; N, 10.29.

cis-2-Methyl-3-isopropylaziridine (**11**): bp 120 °C; NMR ($CDCl_3$) τ 7.9 (m, 1), 8.4 (t, 1), 8.9 (m, 10). Anal. Calcd for $C_6H_{13}N$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.37; H, 13.19; N, 14.17.

trans-2-Methyl-3-isopropylaziridine (**12**): bp 112–114 °C; NMR ($CDCl_3$) τ 8.2 (m, 1), 8.55 (m, 1), 8.9 (m, 10). Anal. Calcd for $C_6H_{13}N$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.78; H, 13.17; N, 14.30.

N-Methyl-2-β-naphthylaziridines (**7–9**) and 2-chloro-*N*-isopropyl-2-β-naphthylethylamine hydrochloride (**10**) were prepared according to the Kanao method[19] from β-naphthylaldehyde by Mr. T. Okada, Dr. Y. Nishitani, and Dr. K. Kotera of Shionogi laboratory. **7**: mp 74–75 °C; $[\alpha]^{25}D$ +157.1 ± 1.9° (CH_3OH). **8**: mp 50–51 °C. **9**: mp 75.5–76.5 °C; $[\alpha]^{25}D$ −160.0 ± 2.1° (CH_3OH). **10**: mp 196–197 °C. The detail of the preparation will be published in the near future.

Washed liver microsomes were prepared from normal Wistar strain male rats, weighing about 300 g, by the differential centrifugation method.[20] Protein concentration of microsomes was determined by the biuret reaction[21] using bovine serum albumin as standard.

General Procedure of Transformation of Aziridines in Microsomal Suspension. The reactions were carried out as described in the report. After the reaction time was over, 2 ml of 2 N NaOH solution, 2 ml of CH_2Cl_2, and suitable amount of internal reference compound were added. Vigorous shaking for 15 min at room temperature and 1 h of centrifuge gave a clear solution of CH_2Cl_2 for VPC analysis. As the internal reference, n-$C_{19}H_{40}$ for reaction 1 and 2, n-$C_{11}H_{24}$ for reaction 3–6, and n-$C_{16}H_{34}$ for reaction 7–10 (cf. Table **II**) were used. 5% OV-17 on Chromosorb W, 4 mm × 1.5 m glass column, 1% Apiezon L on Chromosorb W, 4 mm × 1.5 m glass column, and 5% KF-54 on Chromosorb W, 4 mm × 1.5 m glass column and 0.25 mm × 45 m Golay column coated with Apiezon L, were used for the analysis of the recovered aziridines and the products.

Reaction of *p*-Nitrosoanisole in Microsomal Suspension. The solution of *p*-nitrosoanisole in ethanol (20 μl, 0.003 mmol) was added in the complete system described in this paper. After 60 min of incubation at 37 °C with moderate shaking, 2 ml of 2 N NaOH, 2 ml of CH_2Cl_2, and n-$C_{18}H_{38}$ as an internal reference were added. After vigorous shaking and 60 min of centrifuge, CH_2Cl_2 solution separated and was supplied to VPC analysis. *p*-Nitrosoanisole disappeared

completely and *p*-nitroanisole and *p*-anisidine were obtained as an equimolar mixture. The yield of both compounds was 80%.

Reaction of *N*-*p*-Anisylaziridine (13) in Microsomal Suspension. The solution of *N*-*p*-anisylaziridine in ethanol (20 μl, 0.01 mmol) was added in the complete system and incubated for 60 min at 37 °C with moderate shaking. NaOH (2 N, 2 ml), 2 ml of CH_2Cl_2, and *n*-$C_{14}H_{30}$ and *n*-$C_{18}H_{38}$ as internal references were added. After vigorous shaking and centrifuge, CH_2Cl_2 solution was supplied to VPC analysis. The recovered aziridine (71%), 0.7% of *p*-nitroanisole, and 0.7% of *p*-anisidine were observed.

Reactions of Aziridines and *m*-Chloroperbenzoic Acid. Aziridine (1 mmol) in 10 ml of CH_2Cl_2 was cooled at 0 °C and 2 mmol of *m*-chloroperbenzoic acid was added. After 1 h, the reaction mixture poured on 30 g of Merck standard Al_2O_3 column was eluted with pentane to obtain the olefin fraction. VPC analysis showed that the reactions proceeded with retention of the configuration and the yields of olefins were usually 30–40%.

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Communications to the Editor

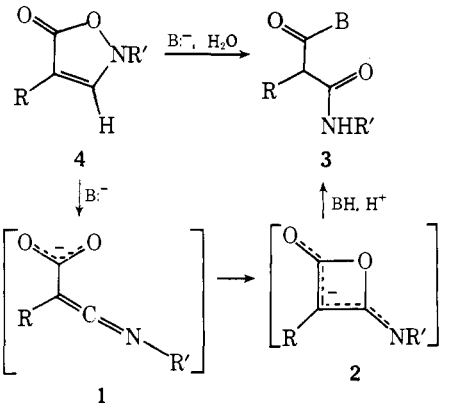
Observation of Ketenimine Carboxylates and Their Conversion to Four-Membered Heterocycles

Sir:

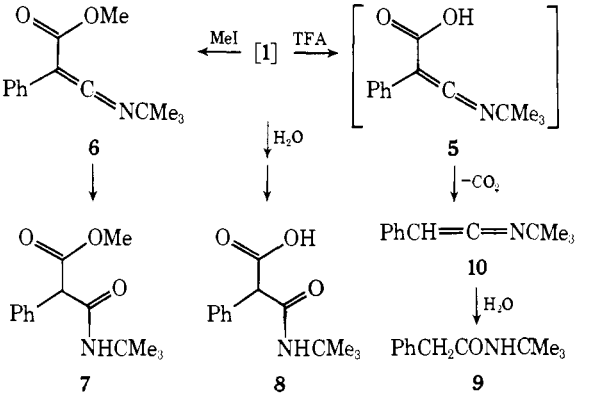
Monoimino derivatives of cyclic malonic anhydrides previously have been proposed as unstable intermediates in heterocumulene cycloadditions.[1] We have now established that ring closure of ketenimine carboxylates (**1**) provides a new, anionic entry to this reactive heterocyclic system. Elimination with ring cleavage, followed by cyclization to give the four-membered ring **2** (Scheme I), was suggested earlier to account for the formation of products of type **3** from isoxazolones having the substitution pattern **4**.[2] The present results confirm the essential mechanistic features of Scheme I and bring to light an additional rearrangement leading to malonimides.

To demonstrate that the postulated intermediates **1** can be generated by an elimination about the C–N bond of **4**, ring opening studies were conducted with 4-phenyl substituted compounds (**4**, R = Ph) and strong bases in nonnucleophilic media. Definitive infrared spectral evidence for **1** (R′ = CMe_3, Ph, or Me; absorptions at 4.95, –C=C=N–, and 6.3 μ, $-CO_2^-$) was obtained when the respective starting materials were treated with BuLi or hexamethyldisilazane anion in THF. In the case of the *N*-*tert*-butyl compound, further characterization included the transformations of Scheme II.[3] Consistent with Scheme I, the anions **1** were found to undergo conversion to type **3** products. In the reaction of **4** with methoxide, in one case (R = Ph, R′ = CMe_3) **1** was detected (ir) as a transient species during the formation of **3** (–B = –OMe). Moreover, when THF solutions of **1** were added to aqueous solutions of diethylamine, the corresponding diamides were obtained in 70–80% yield. However, clean diamide formation did not take place upon addition of amines or amine salts to THF solutions of **1**, apparently because of competing decarboxylation in that solvent.

Scheme I



Scheme II



Attempts to utilize nonnucleophilic solvents more polar than THF, in the hope of favoring the pathway of Scheme I over