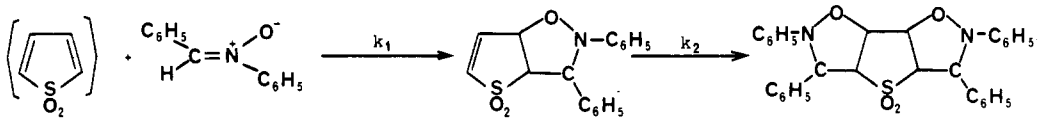
Scheme III



2 a 3a 4a

concentrated, and a chromatographic separation under the same conditions as above gave **4b**: 75% yield; mp 229–230 °C; mass spectrum, *m/e* 438; ^{1}H NMR ($CDCl_3$) 6.67–6.92 (s, 4 H), 5.7 (d, 1 H, J = 8 Hz ($H_{7b}H_{3a}$)), 4.95 (d, 1 H, J = 8 Hz ($H_{3a}H_{7b}$)), 2.33 (s, 6 H), 2.25 (s, 3 H). Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.91; H, 5.89; N, 6.28. This compound can be also prepared by refluxing (3 days) a mixture of 1 (0.5 g, 1.79 mmol), pyridine (0.425 g, 5.80 mmol), and mesonitrile oxide (3 g, 18 mmol) in chloroform and separated by column chromatography in 60% yield.

Preparation of 4,4-Dioxo-3-(2,4,6-trimethylphenyl)-5,6-diphenyl-3a,4a,7a,7b-tetrahydroisoxazolidino[2,3-*d*]thieno-[5,6-*d*']isoxazoline (4ab). This compound can be prepared in the following two ways.

(A) A solution of **3a** (0.5 g, 1.59 mmol) and mesonitrile oxide (0.805 g, 5 mmol) was refluxed in chloroform (20 mL) for 3 days. The solid material (furazan *N*-oxide) was eliminated by filtration, and the filtered solution was concentrated. The residue was chromatographed by the standard procedure to give **4ab**: 0.50 g (80% yield); mp 205–206 °C; mass spectrum, *m/e* 474; ^{1}H NMR ($CDCl_3$) 6.77, 8.30 (m, 12 H), 5.56 (d, 1 H, J = 6.3 Hz ($H_{7a}H_{4a}$)), 5.20 (d, 1 H, J = 2.4 Hz (H_5H_{4a})), 5.0 (d, 1 H, J = 9 Hz, ($H_{3a}H_{7b}$)), 4.06 (dd, 1 H, J = 6.3 Hz ($H_{4a}H_{7a'}$), J = 2.4 Hz ($H_{4a}H_5$)). Anal. Calcd for $C_{27}H_{26}N_2O_4S$: C, 68.24; H, 5.52; N, 5.90. Found: C, 68.50; H, 5.62; N, 5.98.

(B) A solution of **3b** (0.5 g, 1.80 mmol) and *N*,α-diphenylnitrone (0.79 g, 4 mmol) was refluxed under in the same condition as in part A. The solution was evaporated and the residue chromatographed to give the diadduct **4ab**, 0.56 g, (75% yield).

Kinetic Conditions. Under batch conditions, in refluxing chloroform, solutions of dipole (0.3 M), triethylamine, the precursor of the dipolarophile, i.e., 3,4-dibromotetrahydrothiophene 1,1-dioxide (2×10^{-2} M), and an internal standard, i.e., phenol (2×10^{-2} M), were prepared.

The reaction kinetics are carried out by analyzing aliquots by HPLC, with a UV detector at 260 nm.

The pseudo-first-order kinetic constants were determined by least-squares analysis, and the given values are the means of at least three runs with a precision of about 5%. For the monoadduct formation the column we used was a Porasil Waters type with a dichloromethane/cyclohexane mixture (75/25 v/v) as eluent. For the diadduct formation, the column was a Bondapak CN Waters type, and the eluent was a cyclohexane/ethylacetate mixture (97.5/2.5 v/v).

X-ray Analysis and Structure Determination of 3a. The following crystal data were obtained: $C_{30}H_{26}N_2SO_4$, orthorhombic, a = 33.834 (20) Å, b = 13.457 (5) Å, c = 11.307 (4) Å, space group, *Pccn*, Z = 8.

The crystal was mounted on a Syntex $P2_I$ diffractometer which used Cu Kα radiation (λ = 1.54179 Å) to a maximum 2θ value of 114°; 3477 reflections were measured, and only 2153 of them have $I > 2.5\sigma(I)$. The intensities were corrected for Lorentz and polarization factors but not for absorption.

The structure was solved with the MULTAN 78 program.[18] Then the structure was refined with the SHELX 76 program.[19] After three cycles of isotropic full-matrix least-squares refinement, R fell to 11%, and after two cycles of anisotropic refinement R was 8%. The H atom positions were assumed, and their corresponding parameters were inserted but not allowed to vary in the last cycle of anisotropic refinement (final R = 5.8%).

Registry No. 1, 15091-30-2; **3a**, 77965-73-2; **3b**, 77965-74-3; **4a**, 77965-75-4; **4b**, 77965-76-5; **4ab**, 77965-77-6; **2**, 1137-96-8; **b**, 2904-57-6.

Supplementary Material Available: Tables of atomic coordinates and thermal parameters and a figure showing the structure of the crystal of **4a** (4 pages). Ordering information is given on any current masthead page.

(18) P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. Woolfson, "MULTAN 78 (1978): A System of Computer Programs for the Automatic Solution of Crystal Structure from X-ray Diffraction Data", University of York, York, England, and University of Louvain, Louvain, Belgium, 1978.

(19) G. M. Sheldrick, "SHELX-76: Program for Crystal Structure Determination", University of Cambridge, Cambridge, England, 1976.

Gas-Phase Thermal Isomerization of Some Aminomethylisoxazoles

Jorge D. Pérez,* Rosario G. de Díaz, and Gloria I. Yranzo[1]

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Estafeta 32, 5000 Córdoba, Argentina

Received October 24, 1980

The kinetic results from the gas-phase thermal isomerization of 5-amino-3,4-dimethylisoxazole (1), 3,5-dimethylisoxazole (2), and 3-amino-5-methylisoxazole (3) are reported. Compound 1 afforded quantitatively 3-carbamoyl-2,3-dimethyl-1-azirine (4). On the other hand, 2 and 3 gave the isomeric oxazoles 5 and 7, respectively. Different reaction pathways are discussed according to the activation parameters.

Thermal and photochemical isomerization of isoxazole derivatives to give 1-azirines and oxazoles has been largely studied during the last decade.[2] Most of the reactions have been carried out in solution, focussing on product composition as a major criterion of mechanism.

(1) Grateful recipient of a fellowship from the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

(2) (a) Nishiwaki, T.; Kitimura, T.; Nakano, A. *Tetrahedron* **1970**, *26*, 453. (b) Nishiwaki, T.; Saito, T.; Onomura, S.; Kondo, K. *J. Chem. Soc. C* **1971**, 2644. (c) Fowler, F. W. *Adv. Heterocycl. Chem.* **1971**, *13*, 45. (d) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123.

0022-3263/81/1946-3505$01.25/0

Table I. Reactions of 5-Amino-3,4-dimethylisoxazole

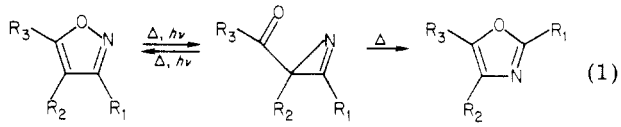
temp, °C	carrier	k, s^{-1} [a]
423	toluene	7.59
433	toluene	9.66
448	toluene	13.5
463	toluene	18.7
473	toluene	27.9
503	toluene	49.8
503	nitrogen	51.0
503	dry air	51.8

[a] Averaged over at least three determinations; contact times ranged from 10^{-1} to 10^{-2} s and pressures from 0.5 to 1.8 mm.

Table II. Arrhenius Parameters for 1-3

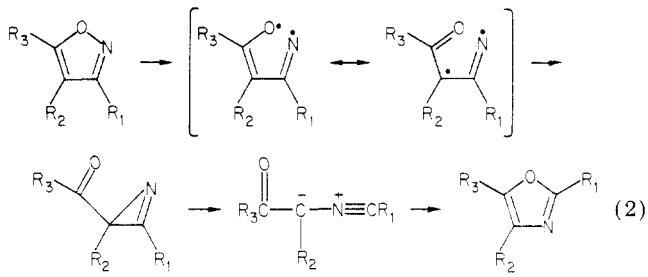
compd	log A	E_a (kcal/mol
1	9.0 ± 0.5	25.8 ± 0.3
2	11.2 ± 0.4	41.1 ± 0.5
3	11.1 ± 0.5	40.2 ± 0.5

It has been clearly shown that isoxazoles led to oxazoles through the intermediacy of 1-azirines[3,4] (eq 1)



(1)

The mechanism generally accepted is depicted in eq 2.



(2)

The reaction begins with a homolytic cleavage of the N–O bond and a subsequent ring closure leading to 1-azirine. Then, after the C–C bond scission of the azirine ring, a nitrile ylide is formed,[5] which in a second step undergoes cyclization to the oxazole derivative.

As far as we know, the activation parameters for these reactions are scarcely known. The activation parameters in solution for the isomerization of 5-methoxy-3-phenylisoxazole have been reported.[6]

Here we report the kinetic results from the thermal isomerization of 5-amino-3,4-dimethylisoxazole (**1**), 3,5-dimethylisoxazole (**2**), and 3-amino-5-methylisoxazole (**3**) in the gas phase.

Results

Reactions were carried out in the gas phase by using a flow system and the specific rate constants were calculated according to: eq 3, where C_0 is the value at 100%, u is the

$$k = u/V_0 \ln C_0/C \quad (3)$$

flow rate and V_0 is the reactor volume.

5-Amino-3,4-dimethylisoxazole. Results are shown in Table I. In all runs the only product formed was 3-carbamoyl-2,3-dimethyl-1-azirine (**4**). No meaningful changes in the reaction rates resulted when the surface–volume ratio was substantially modified (1:20) by packing the reaction vessel. Therefore the reaction is homogeneous. The specific rate constants remained unchanged (within ±5%) when dry air or nitrogen was used as the carrier; therefore a radical chain can be rejected under these reaction conditions. When **4** was heated under the same conditions as those used with **1**, no reaction was observed; this led us to reject an equilibrium under these conditions.

Arrhenius parameters calculated by the least-squares method are shown in Table II.

Table III. Reactions of 3,5-Dimethylisoxazole

temp, °C	carrier	k, s^{-1} [a]
540	nitrogen	1.45
560	nitrogen	2.48
580	nitrogen	4.16
600	nitrogen	8.61
600	dry air	8.95
600	toluene	8.20

[a] Averaged over at least three determinations; contact times ranged between 8 and 20 s and pressures from 0.5 to 1.0 mm.

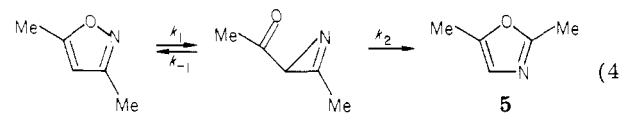
Table IV. Reactions of 3-Amino-5-methylisoxazole

temp, °C	carrier	k, s^{-1} [a]
560	nitrogen	3.95
580	nitrogen	6.40
600	nitrogen	12.5
620	nitrogen	20.4
620	dry air	21.2

[a] Averaged over at least three determinations; contact times ranged from 10^{-1} to 10^{-2} s and pressures from 5×10^{-2} to 10^{-1} mm.

3,5-Dimethylisoxazole. Results are shown in Table III. We have previously reported[3] that **2** afforded 2,5-dimethyloxazole (**5**; up to 90%) at temperatures higher than 500 °C. At 480 °C the only detectable reaction product was 3-acetyl-2-methyl-1-azirine (**6**; less than 4%). The specific rate constants remained unaffected when both the surface–volume ratio and the carrier gas were changed, leading to the same conclusions as stated above for **1**. activation parameters obtained by the least-squares method are shown in Table II.

According to the experimental evidence previously reported,[3] we are able to suggest the following reaction scheme (eq 4).



(4)

A quantitative conversion of **6** into **5** (45%) and **2** (55%) was determined by pyrolysis at 450 °C. Under the same conditions, **2** was quantitatively recovered. Then, the equilibrium assumption shown in eq 5 was considered.

$$-\frac{d[2]}{dt} = \frac{k_1 k_2}{k_{-1}}[2] = k_\psi[2] \quad (5)$$

Since $k_2 \approx k_{-1}$, we conclude that $k_\psi \approx k_1$. Thus the determined activation parameters refer essentially to the first step.

3-Amino-5-methylisoxazole. Results are shown in Table IV. The only product formed was identified as 2-amino-5-methyloxazole (**7**). The same results as those reported for **1** and **2** were obtained by changing the carrier

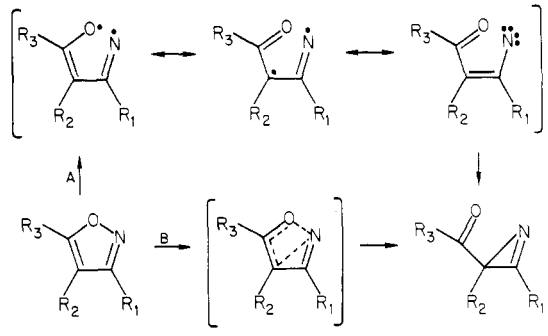
(3) Murature, D.; Pérez, J. D.; de Bertorello, M. M.; Bertorello, H. E. *An. Asoc. Quim. Argent.* **1976**, *64*, 337.
(4) Dietliker, K.; Gilgen, P.; Heingartner, H.; Schmid, H. *Helv. Chim. Acta* **1976**, *59*, 2074.
(5) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181 and references cited therein.
(6) Komendantov, M. I.; Bekmukhametov, R. R.; Kostikov, R. R. *Khim. Gterotsikl. Soedin.* **1978**, *8*, 1053.

Table V. Calculated $\Delta\Delta H_f^\circ$ and Experimental E_a Values

isoxazole	1-azirine	isolated product	E_a, kcal/mol	$\Delta\Delta H_f^\circ$,[a] kcal/mol
1	4	4	25.8	−10.0
2	6	5	41.1	3.6
3	8	7	40.2	1.9

[a] From ref 6.

Scheme I



gas and the surface–volume ratio; hence the simplest conclusion is the absence of a radical chain and surface catalysis. Arrhenius parameters calculated by the least-squares method are shown in Table II. It was not possible to isolate the corresponding 2-amino-3-acetyl-1-azirine (8); however, considering both the similar activation parameters and a structure similar to that of **2**, we assume for **3** the same kinetic law as that was stated above for **2**.

Discussion

Komendantov and co-workers[6] reported the $\Delta\Delta H_f^\circ$ of several pairs of isoxazoles and 1-azirines, calculated by using the additivity rules of Benson.[7] We can see from Table V that the E_a values here reported parallel the estimated $\Delta\Delta H_f^\circ$ for **1–3**, which can be attributed to the fact that the transition state of the rate-limiting step resembles the 1-azirine isomer. Besides, this fact reinforces the assumption $k_\psi \simeq k_1$ for **2** and **3**, since this parallelism would be unlikely for another kinetic law.

According to the kinetic results we suggest two alternative reaction pathways (Scheme I). The path A involves a β-oxovinyl nitrene analogue to that proposed[8] in thermal reactions of β-azidovinyl ketones. Chemical evidence of the intermediacy of nitrenes often comes from the observation of rearrangement products generated by 1,2 hydride or 1,2 alkyl shifts.[9] However, in our reactions it was not possible to find a ketenimine derivative.

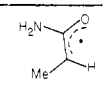
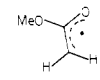
Looking at the diradical involved in route A, one can see that the π moiety is isoelectronic with pentadienyl radical. Then, R_1 and R_3 are attached to atoms which belong to quasi-nodal points in the π HOMO of the diradical; therefore, the net effect of substituents at C_3 and C_5 on the diradical stability should be small. This statement is reinforced by the results of the calculation of the π bonding energy (Table VI), which is essentially constant for the three isoxazoles under study. On the other hand, it can be seen that the E_a is essentially unaffected when we change an amino group to a methyl group at position 3 (**2** and **3**). Then the E_a difference (~14 kcal/mol) between **1** and **3** can hardly be attributed to the effect of a methyl group linked to C_4 in **1**.

Table VI. π Bonding Energy ($E_{\pi b}$) of Diradicals

compd	diradical $E_{\pi b}(\beta)$[a]	compd	diradical $E_{\pi b}(\beta)$[a]
1	6.769	3	6.669
2	6.568		

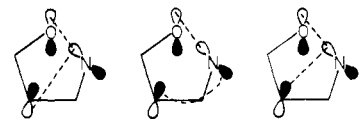
[a] Calculated as $E_{\pi b} - E_p$. HMO calculations were carried out by using h_X and k_{CX} parameters from ref 17. The methyl group was calculated as heteroatom.

Table VII. Energy of the HOMO of the Model MF and E_a Values

compd	MF HOMO[a]	E_a, kcal/mol	model MF
1	$\alpha + 0.222\beta$	25.8	
2	$\alpha + 0.413\beta$	41.1	
3	$\alpha + 0.413\beta$	40.2	
5-methoxy-3-phenylisoxazole[b]	$\alpha + 0.403\beta$	38.9	

[a] HMO values. [b] From ref 6.

Route B involves a concerted [1,3] sigmatropic shift. According to the Woodward–Hoffmann rules[10] there are two "allowed" reaction modes, namely, supra (migrating group)–antara (migrating framework) (SA) and antara (MG)–supra (MF) (AS).



SA AS SS

Both reaction modes involve a strong steric hindrance which leads them to be seldom considered as the preferred reaction course vis a vis the radical pathway. However, there is a third possible reaction mode, i.e., supra (MG)–supra (MF) (SS), which has lower steric requirements but is formally "forbidden" because of a phase dislocation. This "forbidding" can be overcompensated if the MG and the MF differ in their electron releasing–electron withdrawing ability.[11] The difference, $I_D - A_A$ (I_D = ionization potential of the donor pattern; A_A = electron affinity of the acceptor pattern), affords an index of the activation energy of a sigmatropic shift with the reaction barrier becoming lower as $I_D - A_A$ decreases.[12] The MG electron affinity is constant throughout the different isoxazoles. On the other hand, the ionization potential of the MF can be estimated through the energy of the π HOMO of the model MF. Looking at the values shown in Table VII, one can see that they parallel the reported E_a values. Besides, the concerted pathway can easily explain the differences in behavior of compounds **1–3** since the transition state should be less affected by substituents at C_3 than at C_5 which is directly involved in the cyclobutadiene-like transition state. The small size of the *A* factors makes unlikely a simple ring opening for the rate-determining step. The difference between **1** and **2** or **3** can be attributed either to a change in the transition state or to the isokinetic consequence of the low activation

(7) Benson, S. "Thermochemical Kinetics"; Wiley-Interscience: New York, 1976.
(8) Nesmeyarov, A. N.; Rybinskaya, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1962**, 816.
(9) Lwowski, W. "Nitrenes"; Wiley: New York, 1970.
(10) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinhein/Bergstr., Germany, 1970.
(11) (a) Epiotis, N. D. *J. Am. Chem. Soc.* **1972**, *94*, 1924. (b) *Ibid.* **1973**, *95*, 1191.
(12) Epiotis, N. D. "Theory of Organic Reactions"; Springer-Verlag: New York, 1978.

Table VIII. Kinetic Results of the Pyrolysis of 1-Phenylethyl Acetate

temp, °C	k, s^{-1}	E_a, kcal/mol	$\Delta S^{\ddagger}$,[a] eu
528	7.22	44.8 ± 0.4 (44.9)[a]	−0.6 (+0.4)[a]
500	1.93		
480	1.29		

[a] Reference 20.

energy of 1. On the basis of these considerations, we suggest that compounds 1–3 belong to case III AX of Epiotis' classification[11] and react according to mechanism B.

Experimental Section

^1H nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer, and chemical shifts are quoted in δ (parts per million) downfield from tetramethylsilane. Ultraviolet spectra were run on a Beckman DBG or Model 24 spectrophotometers. Infrared spectra were obtained with a Beckman IR 8 or IR 12 spectrometer. Elemental analysis were carried out on a Hewlett-Packard F&M 185 elemental analyzer. Mass spectra were obtained from a Varian CH 7A Mat. Vapor-phase chromatography was performed on a Varian Aerograph, Series 2400. Melting points are uncorrected and were determined by the capillary method. Solvents were analytical reagents or otherwise purified by standard methods.

5-Amino-3,4-dimethylisoxazole (1) was obtained by hydrolysis from the commercially available 5-sulfanilamido-3,4-dimethylisoxazole by using a previously described method.[13] 3,5-Dimethylisoxazole (2) was obtained according to the literature,[14] and its purity was checked by boiling point, NMR,[15] and UV.[16] 3-Amino-5-methylisoxazole (3) was obtained by hydrolysis from the commercially available 3-sulfanilamido-5-methylisoxazole by using a previously described method.[13]

Gas-phase reactions were carried out in a Vycor glass reactor (30-cm length and 1.2-cm internal diameter). The reactor was "seasoned" by the thermal decomposition of *n*-butyl bromide at 500 °C. Heating was performed in a Lindberg heavi duty Model 55035 tube furnace equipped with a thermocouple and pyrometer. The products were obtained from the trap after the reaction tube at the liquid air temperature. In all runs the mass balance between the weight of sample used and the quantitative analysis of the reaction products was higher than 97%.

In a typical run, 1 mmol of the purified isoxazole (previously degassed) was placed 10 cm before the oven inlet; then the system was evacuated to 10^{-3} torr. A stream of carrier gas was allowed to pass through the reactor. The sample was introduced into the carrier stream by heating with an external resistance. The carrier gas flow rate was determined by a flow meter calibrated at room temperature and pressure and then corrected to the temperature and pressure of the reaction tube. Contact time was determined by neglecting the sample contribution to the overall flow rate provided that $u(\text{carrier})/u(\text{sample}) \geq 50$.

Standardization of the Flow System. The pyrolysis flow system was checked by pyrolyzing 1-phenylethyl acetate which was obtained from acetophenone by reduction with BH_4Na and further acetylation with acetic anhydride in pyridine according to the literature.[19] The ester pyrolysis was studied between 480 and 528 °C. Quantitative analysis of the reaction mixtures was performed by two alternative methods, i.e., GLC (OV-101, 1.5% on Chromosorb G) and potentiometric titration of the acetic acid formed, which gave equivalent results. The values here reported agree quite well with those previously informed[20] (Table VIII), even considering that the values previously reported were obtained in a static system using a stainless-steel reactor. It was necessary to perform the study at temperatures higher than those employed by Taylor[20] because our time scale differs with the one of a static system.

5-Amino-3,4-dimethylisoxazole. The reaction products were eluted with ether, and after the solvent was evaporated in vacuo, the products were chromatographed on silica gel with ether and then with ethyl acetate. From the latter eluate was obtained an oil which crystallized from *n*-hexane as a white crystalline product (needles, mp 60–61.5 °C) and was identified as 3-carbamoyl-2,3-dimethyl-1-azirine (4): IR (KBr) 1740 (C=N), 1625 (C=O) cm^{-1}; NMR (chloroform-*d*) 1.45 (s, 3 H), 2.50 (s, 3 H), 5.60 (br s, 2 H, removed on addition of D_2O, NH); UV max (MeOH) 228 nm (log ϵ 2.60), 205 (3.92). Anal. Calcd for $C_5H_8N_2O$: C, 53.55; H, 7.19; N, 25.00. Found: C, 53.41; H, 7.43; N, 24.92.

3,5-Dimethylisoxazole. The products trapped were dissolved with carbon tetrachloride and submitted to NMR analysis. Compounds 5 and 4 were identified by comparison with authentic samples obtained photochemically by a previously described method.[3]

3-Amino-5-methylisoxazole. The products trapped were eluted with methanol. After the solvent was evaporated, the reaction mixture was submitted to GLC (SE-30 4% on Chromosorb G), affording two signals, one of them with the same retention time than 3. The combined GLC/MS analysis of the mixture gave a fragmentation pattern coincident with the one reported for 3[18] and afforded the following result for the reaction product: mass spectrum, m/e 98 ($M^{+\cdot}$, 99.28), 97 (M − 1, 29.47), 83 (M − CH_3, 2.64), 71 (M − CNH, 1.36), 56 (M − 1 − CN_2H, 6.74), 55 (M − C_2H_3O, M − 1 − CHNO, 100); IR (KBr) 3000, 2500, 1700, 1690, 1400, 1280, 1220, 1110 cm^{-1}; NMR (Me_2SO-d_6) 6.2 (s, 1 H), 6.2 (br s, 2 H, removed on addition of D_2O, NH), 2.1 (s, 3 H); UV max (MeOH) 225 nm. These results agree with the structure of 2-amino-5-methyloxazole (7).

Acknowledgment. This research was supported in part by the Secretaría de Estado de Ciencia y Tecnología, Argentina. We thank Dr. Domingo Murature for the photochemical synthesis of compound 6.

Registry No. 1, 19947-75-2; 2, 300-87-8; 3, 1072-67-9; 4, 68289-83-8; 5, 23012-11-5; 6, 55393-93-6; 7, 33124-04-8.

(13) Manzo, R. H.; de Bertorello, M. M. *J. Pharm. Sci.* **1973**, *62*, 152.
(14) Morgan, G. T.; Burgess, H. *J. Chem. Soc.* **1921**, 697.
(15) Sokolov, S. D.; Yudintseva, M.; Petrovskii, P. V. *Zh. Org. Khim.* **1970**, *6*, 2584.
(16) *Chem. Abstr.* **1958**, *49*, 12960*f*.
(17) Streitweiser, A., Jr. "Molecular Orbital Theory for Organic Chemists"; Wiley: New York, 1961.
(18) Mamoru, O.; Hajime, K.; Hisoro, N. *Tetrahedron Lett.* **1968**, 379.
(19) Taylor, R.; Smith, G. G.; Wetzel, W. H. *J. Am. Chem. Soc.* **1962**, *84*, 4817.
(20) Taylor, R. *J. Chem. Soc. B* **1968**, 1397.