Phototransposition Chemistry of Methylisothiazoles and Methylthiazoles

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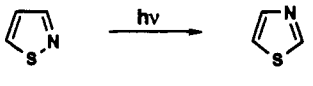
Methylisothiazoles undergo phototransposition in neutral solution to methylthiazoles by a single permutation process. Methylisothiazole → methylisothiazole transpositions, previously reported to occur, were not detected in these reactions. In trifluoroacetic acid solvent, protonated methylisothiazoles and methylthiazoles phototranspose by P_4 and P_5 permutation pathways, respectively, resulting in a unique phototransposition cycle.

Introduction

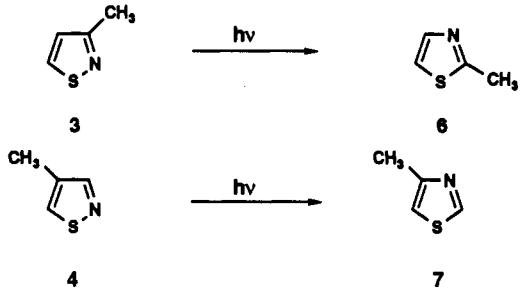
The photoisomerization of isothiazole (1) to thiazole (2) was the first reported phototransposition in the isothiazole–thiazole heterocyclic system.[1] Although the isothiazole to thiazole transposition was observed to occur



1 2

upon photolysis in a variety of solvents, the reverse transposition of thiazole to isothiazole was reported not to take place.

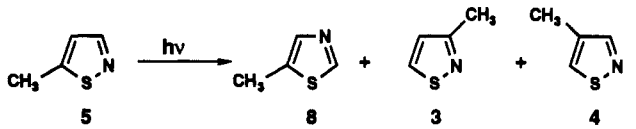
Methylisothiazoles have also been shown to undergo transposition. In neutral solvents, Lablache-Combier and co-workers reported that whereas 3-methylisothiazole (3) and 4-methylisothiazole (4) each transpose to a single



3 6

4 7

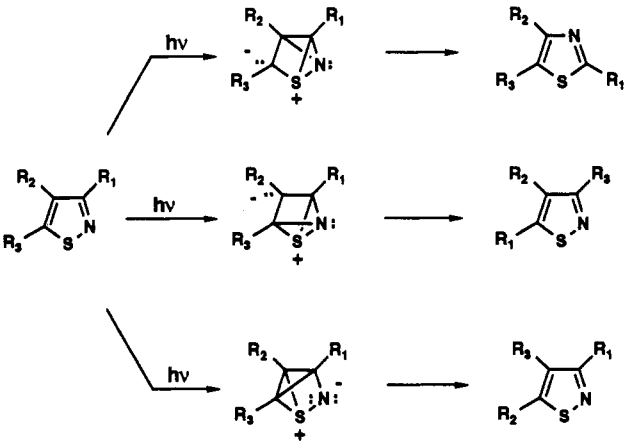
product, 2-methylthiazole (6) and 4-methylthiazole (7), respectively, 5-methylisothiazole (5) transposes, to three products, 5-methylthiazole (8), 3-methylisothiazole (3) and



5 8 3 4

4-methylisothiazole (4).[2] Methylisothiazoles 3, 4, and 5, were suggested to phototranspose *via* tricyclic zwitterionic intermediates (Scheme I) analogous to the intermediates

Scheme I



invoked to rationalize the phototransposition reactions of 2-phenylthiophene.[3]

Although the tricyclic zwitterion mechanism accounts for the isothiazole → thiazole and isothiazole → isothiazole phototranspositions reported for 5-methylisothiazole (5), it also predicts that in addition to the isothiazole → thiazole transpositions reported for 3- and 4-methylisothiazole (3 and 4), these isothiazoles should also phototranspose to other isothiazole isomers. In the latter two cases, no isothiazole → isothiazole phototranspositions were reported to occur. Because of this ambiguity, a reinvestigation of the phototransposition chemistry of methylisothiazoles and methylthiazoles was undertaken.

Results and Discussion

Each methylisothiazole (3–5), 1.0×10^{-2} M in absolute ethanol, was irradiated at 254 nm under nitrogen at ambient temperature. Product formation was monitored as a function of irradiation time using quantitative capillary GLC under conditions that allowed clear separation of all six isomeric methylisothiazoles and methylthiazoles. Products were identified by coinjection of the observed photoproducts with authentic samples.

The primary phototransposition products observed in these irradiations are shown in Scheme II. In this scheme the numbers in parentheses represent the absolute quantity of reactant consumed during the given irradiation

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(1) Catteau, J. P.; LaBlache-Combier, A.; Pollet, A. *J. Chem. Soc., Chem. Commun.* **1969**, 1018.
(2) Lablache-Combier, A.; Pollet, A. *Tetrahedron* **1972**, *28*, 3141.
(3) Wynberg, H.; van Driel, H.; Kellogg, R. M.; Buter, J. *J. Am. Chem. Soc.* **1967**, *89*, 3487.

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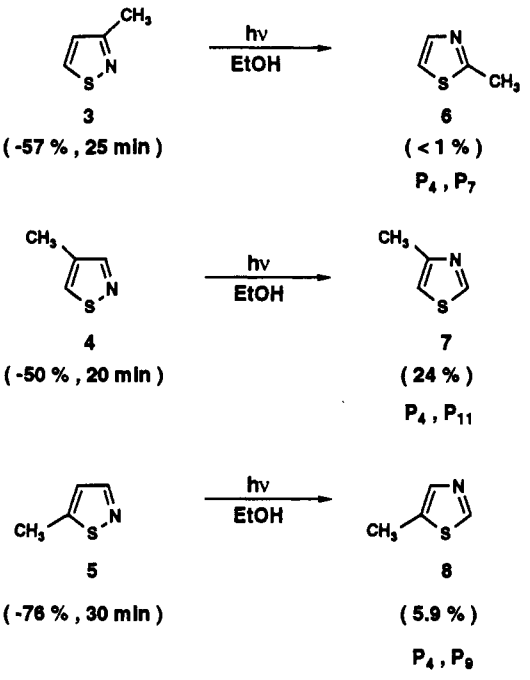
Scheme II



time or the percent yield[4] of the phototransposition product formed. As Scheme II shows, although in all cases greater than 50% of the reactant was consumed, we observed that methylisothiazoles **3–5** each transposed to a single product, methylthiazoles **6–8**, respectively.

Although in the case of 3-methylisothiazole (**3**) and 4-methylisothiazole (**4**) our results agree qualitatively with the observations reported by Lablache-Combier,[2] in the case of 5-methylisothiazole (**5**) there is substantial difference in our results. Thus, despite numerous attempts to reproduce their findings, we were unable to detect the formation of 3-methylisothiazole (**3**) or 4-methylisothiazole (**4**) as photoproducts in this reaction. Spiking of our irradiated solutions with authentic samples of **3** and **4** showed that these compounds would have easily been detected at well below 1% yield. Accordingly, although we are unable to explain the difference between these results, our experimental results shows that 5-methylisothiazole (**5**) transposes to a single photoproduct, 5-methylthiazole (**8**).

Considering the positions of the methyl-substituted carbon atom, the methylthiazole phototransposition products were formed by either P_4 or P_7, P_4 or P_{11}, or P_4 or P_9 permutation pattern processes respectively.[5-7] Since it is reasonable to assume that the three isomeric methylisothiazoles isomerize *via* the same transposition mechanism, the simplest inference is that the mechanistic pathway is consistent with the P_4 permutation pattern since this is the only pattern common to all cases.

Methylthiazoles have been reported not to undergo transposition upon irradiation in a variety of neutral solvents. Although work in our laboratory confirms these earlier reports, we have observed that methylthiazoles **6–8** do undergo transposition upon irradiation in trifluoroacetic acid (TFA) solvent.

Methylthiazoles **6–8**, which have pK_a values ranging from 3.12 to 3.43,[8] are sufficiently basic to be protonated in TFA solvent. As expected, chemical shifts in the ^1H NMR spectra of methylthiazoles **6–8** show that ring protons and methyl substituents are substantially deshielded upon changing from $CDCl_3$ to TFA solvent. Furthermore, the magnitude of the changes in the position of the methyl resonances are consistent with protonation of the heterocycle on nitrogen. This change is largest for the 2-methyl isomer (δ TFA − δ $CDCl_3$ = 0.41) as would be predicted from resonance delocalization in the resulting N-protonated thiazolium ions. By comparison, when the methyl group is located in position 4 or 5, the methyl resonance is shifted downfield by only 0.20 or 0.36 ppm upon changing from $CDCl_3$ to TFA solvent.

Although methylisothiazoles **3–5** are considerably less basic, with pK_a values ranging from 0.02 to 0.48,[9] their ^1H NMR spectra exhibit identical behavior upon changing from $CDCl_3$ to TFA solvent. Thus, the methyl group in either the 3 or 5 position is deshielded by 0.40 or 0.46 ppm, respectively, as compared to only 0.25 ppm when it is located in position 4. In addition, the chemical shifts of the ring protons and methyl substituents of **3–5** in TFA are identical to their absorption positions in concd H_2SO_4, in which the heterocycles have been shown to be N-protonated.[10]

Each methylthiazole **6–8**, 1.0×10^{-1} M in TFA,[11] was irradiated at 254 nm under nitrogen at ambient temperature. Aliquots of the solutions were removed at various irradiation times and neutralized by dropwise addition to a rapidly stirred aqueous suspension of sodium bicarbonate. The resulting solutions were extracted with ether and the concentrated ether extracts were analyzed by quantitative capillary GLC. Scheme III shows the primary products observed and reveals that in TFA solvent methylthiazolium ions $\mathbf{6H^+}$, $\mathbf{7H^+}$, and $\mathbf{8H^+}$ each transpose to yield (after neutralization) single methylisothiazole products **5**, **3**, and **4**, respectively. Permutation pattern analysis indicates that these products arise by a P_5 permutation process. In the case of $\mathbf{7H^+}$, after more prolonged photolysis, 2-methylthiazole (**6**) and 5-methylisothiazole (**5**) could also be detected in the ether extract indicating that 2-methylthiazolium ion ($\mathbf{6H^+}$) and 5-methylisothiazolium ion ($\mathbf{5H^+}$) were also formed in the photoreaction. The concentration vs irradiation time profile indicated, however, that $\mathbf{6H^+}$ and $\mathbf{5H^+}$ were formed in two sequential secondary photoreactions, i.e., $\mathbf{7H^+} \rightarrow \mathbf{3H^+} \rightarrow \mathbf{6H^+} \rightarrow \mathbf{5H^+}$, rather than directly from $\mathbf{7H^+}$.

In view of the effect of TFA solvent on the photochemical behavior of methylthiazoles, and the observed secondary phototransposition of 3-methylisothiazolium ion ($\mathbf{3H^+}$) to 2-methylthiazolium ion ($\mathbf{6H^+}$), the phototransposition chemistry of methylisothiazoles **3–5** were also investigated in TFA solvent under conditions identical to those employed for the methylthiazole isomers. In this case,

(4) All product yields reported in this paper are based on the actual number of moles of reactant consumed.

(5) For a discussion of permutation pattern analysis in aromatic phototransposition chemistry and in five-membered heteroaromatic phototransposition chemistry see: Barltrop, J. A.; Day, A. C. *J. Chem. Soc., Chem. Commun.* **1975**, 177 and Barltrop, J. A.; Day, A. C.; Moxon, P. D.; Ward, R. W. *J. Chem. Soc., Chem. Commun.* **1975**, 786.

(6) For five-membered heterocycles containing two heteroatoms there are 12 different ways of transposition of the five ring atoms resulting in 12 permutation patterns. For a tabulation of the 12 patterns see ref 7.

(7) Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313.

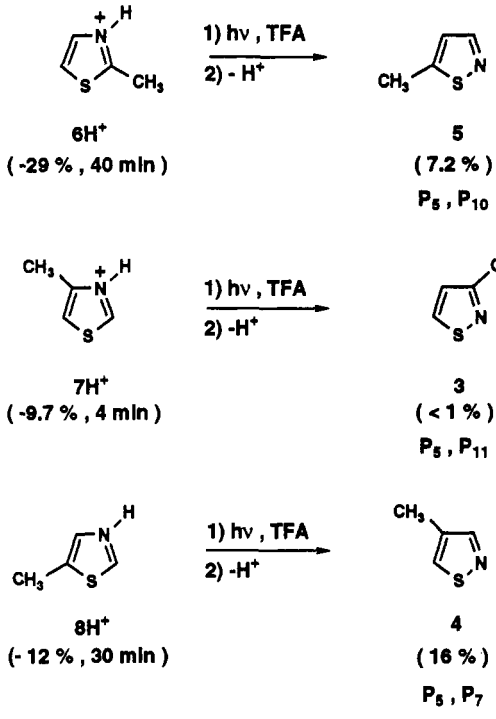
(8) Phan-Tan-Luu, R.; Surzur, J. M.; Metzger, J.; Aune, J. P.; Dupuy, C. *Bull. Soc. Chim. Fr.* **1967**, *9*, 3274.

(9) Clementi, S.; Forsythe, P. P.; Johnson, C. D.; Katritzky, A. R.; Terem, B., *J. Chem. Soc. Perkin Trans. 2* **1974**, 399.

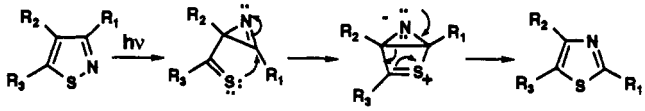
(10) Staff, H. A.; Mannschreck, A. *Chem. Ber.* **1965**, *98*, 1111.

(11) At this concentration in TFA methylisothiazoles and methylthiazoles absorb from 12–16% of the incident light at 254 nm.

Scheme III



Scheme IV



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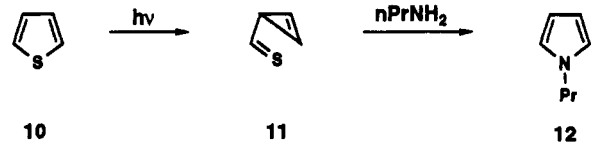
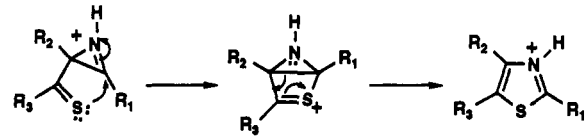
GLC analysis of the ether extracts obtained after irradiation of isothiazoles **3**, **4**, and **5** in TFA solvent revealed the formation of methylthiazoles **6**, **7**, and **8**, respectively, in yields comparable to those observed in absolute ethanol (Scheme II). Again, as in the phototransposition of **5** to **8**, photolysis of $\mathbf{5H^+}$ yielded $\mathbf{8H^+}$ as the exclusive phototransposition product and no other methylisothiazole or methylthiazole isomers could be detected. Thus, as is the case in absolute ethanol solvent, in TFA solvent methylisothiazolium ions phototranspose to methylthiazolium ions *via* a P_4 permutation process.

In neutral solution, the 2,3-interchange demanded by the P_4 permutation pattern can be rationalized by the ring contraction–ring expansion mechanism (Scheme IV) and the intermediacy of thioacylazirine **9**. Previous workers have demonstrated the involvement of acylazirines in the analogous isoxazole → oxazole P_4 phototransposition[12] and iminoazirines have been suggested[13] as intermediates in the P_4 process by which *N*-methylpyrazoles transpose to *N*-methylimidazoles. Although thioacylcyclopropene **11** generated by irradiation of thiophene (**10**) has been trapped by *n*-propylamine and converted to *N*-(*n*-propyl)pyrrole (**12**),[14] similar attempts to trap thioacylazirines **9** by photolysis of isothiazoles in *n*-propylamine has not been successful.[2] In the latter case, however, intramolecular attack of sulfur on the C=N of the azirine should be faster than attack of sulfur on the C=C of **11**. Furthermore, when the irradiation is carried out in TFA this intramolecular attack of sulfur on the azirine should be enhanced by N-protonation. It should be emphasized



10 11 12



that unlike the tricyclic zwitterion mechanism proposed by Lablache-Combier,[2] this mechanistic pathway predicts the formation of only those products experimentally observed.

The 3,5-interchange demanded by the P_5 permutation observed for the methylthiazole → methylisothiazole phototransposition in TFA solvent is consistent with a mechanism (Scheme V) involving initial electrocyclic ring closure, 1,3-sigmatropic shift of sulfur toward the positively charged nitrogen (path A) and rearomatization.

It is of interest to note that in the initially formed bicyclic species, sulfur could walk (path B) in the opposite direction—away from nitrogen—resulting, after rearomatization, in a 1,5-interchange and a thiazole → thiazole transposition *via* a P_6 permutation process. Since we were unable to detect any thiazoles as primary products in these reactions, we conclude that sulfur walks only toward nitrogen. This is in marked contrast to previous studies that show that in neutral solution *N*-methylimidazoles undergo only P_6 imidazole → imidazole transposition.[7,15] Thus, whereas nitrogen walks only away from nitrogen in this system, in the thiazole to isothiazole transposition sulfur walks only toward nitrogen.

In view of the well-established effects of protonation on the relative energies of n,π^* and π,π^* states in nitrogen heteroaromatics,[16] it is tempting to suggest that in TFA solvent protonated methylthiazoles phototranspose *via* their π,π^* excited states whereas in neutral solvent, excitation leads to the population of n,π^* states which have different reactivity. The spectroscopic properties of methylthiazoles are not consistent with this explanation. The UV spectrum of these compounds in solvents of widely ranging polarity exhibit only absorption bands characteristic of $\pi \rightarrow \pi^*$ transitions. Furthermore, the lowest energy transition in the photoelectron spectrum of these compounds is reported to exhibit fine structure characteristic of the removal of an electron from a π rather than an n-orbital.[17] Thus, it appears that S_1 is π,π^* in neutral as well as in acidic media. Protonation of the various

(12) a) Kurtz, D. W.; Schechter, H. *J. Chem. Soc., Chem. Commun.* **1966**, 686. b) Ullman, E. F.; Singh, B. *J. Am. Chem. Soc.* **1966**, *88*, 1844. *Ibid.* **1967**, *89*, 6911. c) Singh, A.; Zweig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199. d) Nishiwaki, T.; Nakano, A.; Matsuoka, H. *J. Chem. Soc. C.* **1970** 1825. e) Nishiwaki, T.; Fujiyama, F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1456. f) Wamhoff, H. *Chem. Ber.* **1972**, *105*, 748. g) Good, R. H., Jones, G. *J. Chem. Soc. C* **1971**, 196. h) Goth, H.; Gagneux, A. R.; Eugster, C. H.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 137. i) Padwa, A.; Chen, E.; Kua, A. *J. Am. Chem. Soc.* **1975**, *97*, 6484. j) Kietliker, K.; Gilgen, P.; Heimgartner, H.; Schmind, H. *Helv. Chim. Acta* **1976**, *59*, 2074.

(13) Tiefenthaler, H.; Dörscheln, W.; Göth, H.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 224.

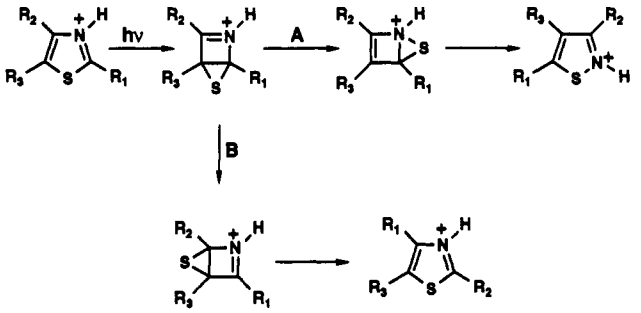
(14) Couture, A.; Lablache-Combier, A. *Tetrahedron* **1971**, *27*, 1059.

(15) Beak, P.; Messer, W. R. *Tetrahedron* **1969**, *25*, 3287.

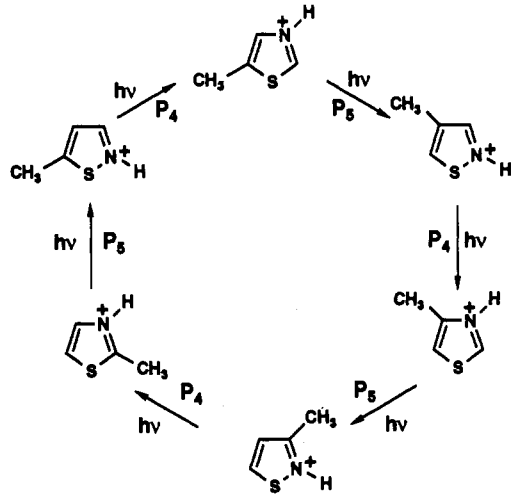
(16) Compare for example the difference in photoreactivity of pyridine and pyridinium cations; Wilzback, K. E.; Rausch, D. J. *J. Am. Chem. Soc.* **1970**, *90*, 2178; Kaplan, L.; Pavlik, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283.

(17) Salmona, G.; Faure, R.; Vincent, E.-J.; Guimon, C.; Pfister-Guillouzo, G. *J. Mol. Struct.* **1978**, *48*, 205.

Scheme V



Scheme VI



species on the thiazole → isothiazole transposition coordinate would be expected to alter the relative heights of the energy barriers. Presumably, this results in an energetically more feasible transposition pathway.

Conclusion

These results show that in neutral solution, methylisothiazoles undergo phototransposition to methylthiazoles by a single permutation process. Methylisothiazole → methylisothiazole transpositions, previously reported to occur, were not observed in these reactions. In TFA solvent, protonated methylisothiazoles and methylthiazoles phototranspose by P_4 and P_5 permutation pathways, respectively, resulting in a unique phototransposition cycle. As shown in Scheme VI, sulfur first walks toward nitrogen as 5-methylthiazole undergoes P_5 transposition to 4-methylisothiazole. Upon further photoexcitation, nitrogen moves back away from sulfur as 4-methylisothiazole undergoes P_4 transposition to 4-methylthiazole. Thus, in TFA solvent, sulfur follows nitrogen around the ring as methylthiazoles and methylisothiazoles undergo alternating P_5 and P_4 transpositions.

Experimental Section

General Procedures. ^1H NMR were recorded at 60 MHz on a PE R-24B system. Infrared spectra were recorded on a PE-683 spectrometer. UV spectra were recorded on a Shimadzu 2100 fast-scan spectrophotometer. GLC was performed on a PE-8500 FID instrument equipped with a 30 m × 0.25 mm i.d. fused silica column coated with 0.25 μm Supelcowax 10 bonded phase (column A) or on a Gow-Mac Series 350 instrument using an 8 ft × 1/4 in. column packed with 20% carbowax 20M on Chromosorb (column B) for preparative work. Mass spectra were obtained using a HP 5970 mass-selective detector interfaced to an HP 5880 capillary gas chromatograph equipped with a 12 m × 0.2 mm i.d. cross-linked methylsilicone column. Column chromatography was performed with Merck-EM type (70–230 mesh) silica absorbants. Preparative TLC was performed on 20 × 20 cm plates precoated with a 2-mm layer of Merck-EM Type 60 GH-254 silica gel.

Starting Materials and Products. 4-Methylthiazole (**7**) and 5-methylisothiazole (**5**) were obtained from Aldrich Chemical Co. and purified by distillation. Compounds previously described in the literature were prepared as follows: 2-Methylthiazole (**6**)[18] from thioacetamide and chloroacetaldehyde diethyl acetal and purified by distillation; 5-methylthiazole (**8**)[18] by diazotization and reduction of 2-amino-5-methylthiazole[19] and purified by distillation; 3-methylisothiazole (**3**)[20] from 4-chlorobutenone[21] and ammonium thiocyanate and purified by preparative GLC (column B); 4-methylisothiazole (**4**)[22] from 3-chloro-2-methylpropenal[22] and ammonium thiocyanate and purified by preparative TLC.

Irradiation and Analysis Procedures. Photolyses were carried out in a Rayonet RPR-100 photochemical reactor fitted with 16 low-pressure Hg lamps. The formation of photoproducts was monitored by irradiating the appropriate reactants while removing aliquots at various time intervals for GLC analysis on column A. The retention times of all products are given relative to the appropriate reactants at 80 °C.

Quantitative GLC analysis of reactant consumption and product formation was accomplished using calibration curves constructed for each reactant and product by plotting detector response vs a minimum of four standards of known concentration. Correlation coefficients ranged from 0.987 to 0.999.

Irradiations in Absolute Ethanol. To monitor methylisothiazole to methylthiazole photoconversions in absolute ethanol on an analytical scale, solutions of the appropriate methylisothiazoles (2.0 mL, 1.0×10^{-2} M) were placed in quartz tubes (7 mm i.d. × 13 cm long), sealed with rubber septa, and purged with nitrogen for 5 min prior to irradiation.

3-Methylisothiazole (3). GLC analysis of the irradiated solution at 80 °C showed the formation of 2-methylthiazole (**6**) with a relative retention of 1.16.

4-Methylisothiazole (4). GLC analysis of the irradiated solution showed the formation of 4-methylthiazole (**7**) with a relative retention of 1.25.

5-Methylisothiazole (5). GLC analysis of the irradiated solution showed the formation of 5-methylthiazole (**8**) with a relative retention of 1.13. Upon GLC analysis of the concentrated photosylate, no additional transposition products were detected.

Irradiations in TFA Solvent. To monitor methylthiazole and methylisothiazole photoconversions in TFA solvent on an analytical scale, a solution of the appropriate compound (1.0 mL or 2.0 mL, 1.0×10^{-1} M) was placed in quartz tubes, sealed with rubber septa, and irradiated. The irradiated solutions were neutralized by dropwise addition to a rapidly stirred aqueous suspension of sodium bicarbonate and extracted with diethyl ether. The extracts were dried over anhydrous sodium sulfate, diluted to 10.0 mL with diethyl ether, and analyzed. Photolysis of methylisothiazoles **3–5**, respectively, in TFA solvent resulted in the formation of methylthiazoles **6–8**, respectively, as the sole transposition products, with relative retention times as described previously.

2-Methylthiazole (6). GLC analysis of the ether extract showed the formation of **5** with a relative retention of 1.28.

4-Methylthiazole (7). GLC analysis of the ether extract showed the formation of **3** with a relative retention of 1.02.

5-Methylthiazole (8). GLC analysis of the ether extract showed the formation of **4** with a relative retention of 0.98.

(18) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1889**, *250*, 270.
(19) Nagazawa, H. J. *J. Pharm. Soc. Jpn.* **1940**, *60*, 433.
(20) Willie, F.; Capeller, L.; Steiner, A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 335.
(21) Price, C. C.; Pappalardo, J. A. *J. Am. Chem. Soc.* **1950**, *72*, 2613.
(22) Arnold, Z.; Zemlicka, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2385.