gave two porphyrin bis(methyl esters) after chromatography on silica gel (activity IV, chloroform–acetone, 20:1 v/v). The more mobile porphyrin proved to be a di-*p*-cresol adduct (vide supra). The less mobile porphyrin was chromatographed three times and still streaked ahead of and behind the main band after the third column. As a consequence, the yield was only 6 mg. The acetylated derivative again ran as a single compact spot, but it was necessary to chromatograph this compound on silica gel thin-layer plates (chloroform–acetone, 40:1) to remove a small amount of contaminating material. The mass spectra of the less mobile porphyrin dimethyl ester from hemin band III and its acetylated derivative again indicated C-alkylation of *p*-cresol by a single vinyl group of protoporphyrin had occurred; the other vinyl group had been lost: mass spectrum, *m/e* 672 (100), 599 (41), 538 (96), 465 (90); λ_{max} ($CHCl_3$) (ϵ mM) 402 nm (163), 498.5 (11.2), 533.5 (7.66), 568 (5.70), 621.5 (3.36). The acetylated derivative was prepared as above:[7] mass spectrum, *m/e* 714 (100), 672 (20), 538 (29). Anal. Calcd for $C_{43}H_{46}N_4O_6$: C, 72.25; H, 6.49; N, 7.84. Found: C, 71.87; H, 6.59; N, 7.99.

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Registry No. 4, 553-12-8; **6a**, 77745-05-2; **6a** diacetate, 77745-06-3; **6b**, 77745-07-4; **6b** diacetate, 77773-67-2; **9**, 77773-68-3; **9** tetraacetate, 77745-09-6; **10** (isomer 1), 77745-08-5; **10** (isomer 1) diacetate, 77745-10-9; **10** (isomer 2), 77745-11-0; **10** (isomer 2) diacetate, 77773-69-4; 2-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin bis(methyl ester), 77745-14-3; 4-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin bis(methyl ester), 77745-15-4; 2-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin, 77745-16-5; 4-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin, 77745-17-6; 2,4-bis[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin bis(methyl ester), 77745-18-7; 2-[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester), 77745-12-1; 4-[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester), 77773-70-7; protohemin, 15489-47-1; deuterohemin, 21007-21-6; resorcinol, 108-46-3; *p*-cresol, 106-44-5.

Dipolar Cycloaddition on the Transient Thiophene Sulfone: Isoxazoline and Isoxazolidine Derivatives

Armand Bened, Robert Durand, Daniel Pioch, and Patrick Geneste*

Laboratoire de Chimie Organique Physique Appliquée, Ecole Nationale Supérieure de Chimie de Montpellier, 34075 Montpellier, France

Jean Paul Declercq and Gabriel Germain

Laboratoire de Chimie Physique et Cristallographie, Université de Louvain-la-Neuve, Louvain-la-Neuve, Belgium

Joëlle Rambaud and Raymond Roques

Laboratoire de Cristallographie de l'Université Nationale de Côte d'Ivoire, Abidjan 04, Ivory Coast

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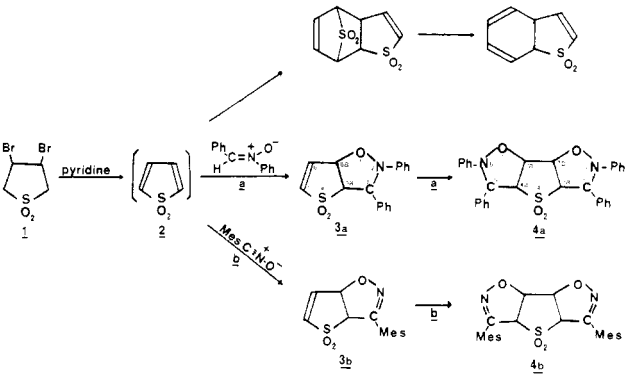
From the 3,4-dibromotetrahydrothiophene 1,1-dioxide under basic conditions and in the presence of 1,3 dipoles such as *N*,α-diphenylnitrone and/or mesitonitrile oxide are obtained isoxazoline and isoxazolidine derivatives of the transient thiophene sulfone as mono- or diadducts. Kinetic studies of the nitrone cycloaddition show a consecutive kinetic scheme of the addition and show that the monoadduct formation is 10^3 faster than that of the diadduct. NMR analysis (^1H and ^{13}C) and crystallographic studies show the formation of the adduct where the regioselectivity corresponds to the oxygen atom of the dipoles bonded to the carbon atom β to the sulfone group, the "endo" nature of the addition, and the anti situation of the two rings in the diadduct.

Substituted thiophene sulfones are reasonably well-characterized substances,[1,2] but the parent thiophene 1,1-dioxide is highly reactive and hence cannot be isolated.[3] In fact, the oxidations of thiophene by any reagents do not lead to specific products unless it is possible to form a dimer[4] or the sesquioxide.[5]

In continuation of our studies on oxidation[6] and 1,3-cycloaddition reactions[7] in the benzo[*b*]thiophene series,

Scheme I



we now report the intermediate formation of the transient sulfone of the thiophene by using different 1,3-dipoles under conditions that prevent the formation of other compounds. Oxidation of the thiophene molecule in the presence of a diene such as a quinone may lead to a

(1) W. L. Mock, *J. Am. Chem. Soc.*, **92**, 7610 (1970).
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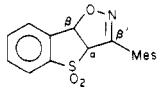
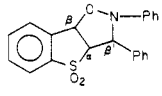
Table I. ^{13}C Chemical Shifts of the Tertiary Carbons Located on the Thiophen (C_α and C_β according to the SO_2 Group)

	C_α	C_β	$C_{\beta'}$	C_β-C_α
3a	71.88	79.96	69.45	8.08
4a	75.92	78.70	70.68	2.78
3b	70.41	82.42	151.38	12.01
4b	74.37	85.52	152.79	11.15
4ab	74.10	84.56	152.93	10.46[a]
	76.14	79.83	70.23	3.69[b]
 5	73.23	81.31	151.76	8.08
 6	75.00	78.24	70.41	3.24

[a] According to the isoxazoline ring. [b] According to the isoxazolidine ring.

Diels–Alder-type cycloadduct,[8] but under the same conditions and in the presence of 1,3-dipole there was no reaction. It was therefore necessary to start with a stable precursor of this sulfone in order to perform the cycloaddition in a nonoxidative reaction. The best precursor is the 3,4-dibromotetrahydrothiophene 1,1-dioxide, as previously used.[9] The transient sulfone **2** was obtained in basic medium, according to Scheme I and then reacted with two 1,3-dipoles [*N*,α-diphenylnitrone (a) and mesitonitrile oxide (b)]. The reaction leads to the corresponding mono- or diisoxazolidine and -isoxazoline adducts.

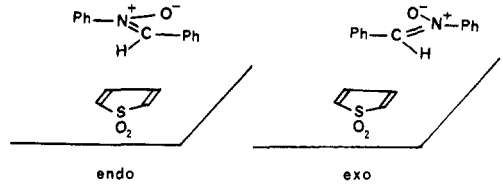
Results and Discussion

The possible reaction pathways outlined in Scheme I involve all the allowed cycloadducts and include the dimerization of the thiophene sulfone.

Cycloaddition Reactions of 2 with a (Isoxazolidine Derivatives). Heating a mixture of **1** and **a** in the presence of pyridine or triethylamine in refluxing benzene (or chloroform) for 48 h resulted in the formation of only two crystalline products. The cycloadduct **3a** (mp 148 °C; yield 70%) was assigned the formula $C_{17}H_{15}NO_3S$. The diadduct **4a** (mp 193 °C; yield 70%), which was assigned the formula $C_{30}H_{26}N_2O_4S$, was obtained only with a large excess (5 equiv) of nitrone.

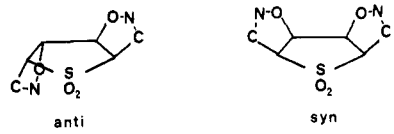
The ^1H NMR spectra of **3a** exhibited complex absorption bands for the aromatic and ethylenic protons in the range of δ 6.65–7.5. The high-field quartet at δ 4.13 corresponds to H_{3a} in an α-position with respect to the SO_2 group.[10] H_{6a} gives a signal at δ 5.43 and is coupled with H_{3a} ($J_{H_{3a}H_{6a}}$ = 5 Hz); H_3 gives a doublet at δ 5.65 ($J_{H_3H_{3a}}$ = 2 Hz). The results are consistent with a cis addition reaction where H_{6a} and H_{3a} are cis and correspond to the regioisomer where O_1 is bonded to C_{6a}.[11]

The ^{13}C NMR results confirm this structure. From (i) chemical shift values of the thiophenic tertiary carbon atoms (Table I),[10] (ii) the structure of the corresponding benzo[*b*]thiophene adduct **5**, which has been established by the ring opening of the isoxazoline,[7] and (iii) the X-ray stereostructure of the benzo[*b*]thiophene adduct **6**,[12] it is evident that in this series the carbon atom signal at higher fields is due to the one located at the position α to the SO_2 group. This signal at higher fields is due to the effect of the heterocyclic oxygen atom as shown from the results of the substituent increments observed in the tetrahydrothiophene series.[13] However, none of these NMR results give any information about the stereochemical position of the protons H_{3a} and H_3, i.e., whether the attack of the 1,3-dipole was "endo" or "exo".



In the same way, the ^1H NMR spectrum for the diadduct **4a** shows a multiplet at δ 6.65–7.62 corresponding to the aromatic protons and three signals at δ 4.12 (quartet), 5.20 (doublet), and 5.27 (doublet). The last three signals correspond to the proton pairs H_{3_a} and H_{4a}, H_3 and H_5, and H_{7a} and H_{7b}, respectively. These results in conjunction with the coupling constant values $J_{H_{7a}H_{4a}} = J_{H_{7b}H_{3a}}$ = 5.7 Hz and $J_{H3aH3} = J_{H4aH5}$ = 3 Hz suggest a symmetrical structure for the diadduct **4a**.

The ^{13}C NMR (Table I) results confirm that the regioselectivities of the two consecutive cycloadditions leading to the compound **4a** are identical; i.e., the oxygen atom is in the position β to the SO_2 group. Again neither the exo or the endo approach of the 1,3-dipole nor the stereoselectivity (syn or anti) could be determined from



the NMR results. For the elucidation of the complete stereostructure of these adducts, the crystal structure analysis has been carried out; the results are reported in a later section.

Cycloaddition Reactions of 2 with b (Isoxazoline Derivatives). Heating a mixture of **1** and **b** in the presence of pyridine or triethylamine in refluxing benzene (or chloroform) for 48 h resulted in the formation of two crystalline products, **3b** and **4b**. The cycloadduct **3b** (mp 170–171 °C, yield 65%) was assigned the formula $C_{14}H_{15}NO_3S$. The diadduct **4b** (mp 229–230 °C, yield 75%), which was assigned the formula $C_{24}H_{26}N_2O_4S$, was obtained only with an excess (5 equiv) of mesitonitrile oxide.

The ^1H NMR spectra of **3b** exhibited a multiplet at δ 6.25–6.90 for the aromatic and ethylenic protons, a signal at δ 2.3 for the CH_3 group and two signals at δ 6.08 and δ 5.0 for the protons H_{6a} and H_{3a}, respectively, with a coupling constant $J_{H_{6a}H_{3a}}$ = 9 Hz. In the same way for the diadduct, the ^1H NMR revealed two signals at δ 4.95 and 5.7 for the proton pairs H_{7a}, H_{7b} and H_{3a}, H_{4a} with a symmetrical structure. By analogy with the preceding reactions and according to the ^{13}C NMR results (Table I), the oxygen atom is bonded to carbon 6a, and the two protons H_{3a} and H_{6a} are cis to each other with a dihedral angle very near to 0°. Here again no answer could be given to the

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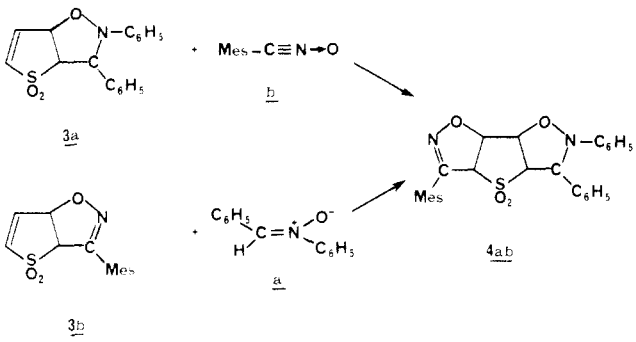
Scheme II



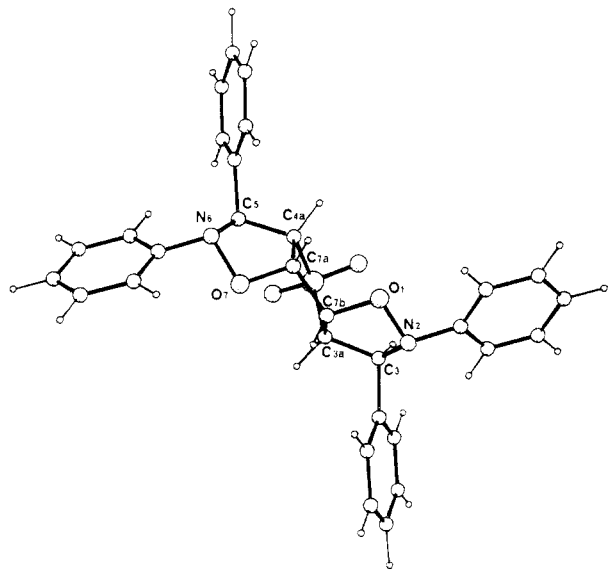


Figure 1. Perspective drawing and numbering scheme of **4a**.

question of the stereoselectivity of the reaction from the NMR results.

Cycloaddition Reactions of 3a with b and 3b with a. Heating a mixture of **3a** or **3b** with **b** and **a** under the same experimental conditions as previously described led only to one compound, **4ab** (Scheme II); (mp 205–206 °C; yield 80%; $C_{27}H_{26}N_2O_4S$). ^1H NMR results give H_3 at δ 5.20, H_{3a} at δ 4.06 and H_{6a} at δ 5.4 for the isoxazolidine part of the structure with $J_{H_3H_{3a}}$ = 2.4 Hz and $J_{H_{3a}H_{6a}}$ = 6.3 Hz. For the isoxazoline part, H_{3a} presents a doublet at δ 5.0 and H_{6a} at δ 5.6 with $J_{H_{3a}H_{6a}}$ = 9 Hz as in the case of **4b**. ^{13}C NMR (Table I) confirms the cis nature of the cycloaddition reaction and also its regioselectivity (oxygen atoms bonded to the carbons **7a** and **7b**).

Crystallographic Study. As described above, the ^1H NMR and ^{13}C NMR spectra do not give any precise information about the stereoselectivity (syn or anti) of the reaction. In order to elucidate the complete stereostructure of the cycloadducts and to account for the spectroscopic data, we carried out the crystallographic analysis of the cycloadduct **4a**.

As shown in the computer generated drawing (Figure 1), the molecular structure of **4a** was confirmed as an anti diadduct with the oxygen atoms bonded to the carbon atoms C_{7a} and C_{7b}, in positions β to the SO_2 group. The dihedral angles are $H_3C_3C_{3a}H_{3a}$ = 104.8°, i.e., H_3 and H_{3a} trans to each other ($J_{H_3H_{3a}}$ = 3 Hz), $H_{3a}C_{3a}C_{7b}H_{7b}$ = 28.1°, i.e., H_{3a} and H_{7b} cis ($J_{H_{3a}H_{7b}}$ = 5–6 Hz), and $H_{7a}C_{7a}C_{7b}H_{7b}$ = 82.5° ($J_{H_{7a}H_{7b}}$ = 0 Hz). The last value indicates that the two isoxazolidine rings are anti to each other.

The fact that the protons H_3 and H_{3a} are trans to each other proves the "endo" nature of the addition as is illustrated in the endo and exo structures; i.e., the nitrogen atom is above the thiophene ring during the approach.[14,15]

Kinetic Studies. The kinetic studies of the nitrone cycloaddition, by HPLC analysis, show the rapid first-order disappearance of the dibromo precursor **1** before the cycloaddition starts from sulfone **2**. Then, the kinetic scheme is consecutive (Scheme III), and the dimer formation is not observed. The formation of the first cycloadduct is 3 orders of magnitude faster than that of the diadduct probably due to some steric factor: $k_1 = 10^{-2}$ L mol^{-1} s^{-1}; $k_2 = 10^{-5}$ L mol^{-1} s^{-1}.

Experimental Section

General Methods. All melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian EM 390 for ^1H and on a Bruker WP 80 for ^{13}C. The spectra are given as δ values in parts per million from Me_4Si. Mass spectra were determined on a CEC 21-110 C.

Starting Materials. 3,4-Dibromotetrahydrothiophene 1,1-dioxide (1),[1] *N*,α-diphenylnitrone (a),[16] and mesitonitrile oxide (b)[17] were prepared according to standard procedures.

Preparation of 4,4-Dioxo-2,3-diphenyl-3a,6a-dihydrothieno[2,3-*d*]isoxazolidine (3a). A solution of compound 1 (0.5 g, 1.79 mmol), pyridine (0.425 g, 5.79 mmol), and *N*,α-diphenylnitrone **a** (0.390 g, 2.0 mmol) was refluxed in chloroform (15 mL) for 4 h. After removing the solid salt (pyridine bromohydrate) by filtration, the solution was evaporated. Compound **3a** was separated by chromatography on a silica column eluted with 90% petroleum ether and 10% methylene chloride: yield 70%; mp 147–148 °C; mass spectrum, *m/e* 313; ^1H NMR ($CDCl_3$) 6.65–7.50 (m, 12 H), 5.65 (dd, 1 H, *J* = 5 Hz ($H_{6a}H_{3a}$), *J* = 0.7 Hz ($H_{6a}H_6$)), 5.43 (d, 1 H, *J* = 2 Hz (H_3H_{3a})), 4.13 (dd, 1 H, *J* = 5 Hz ($H_{3a}H_{6a}$), *J* = 2 Hz ($H_{3a}H_3$)). Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.17; H, 4.82; N, 4.47. Found: C, 64.82; H, 4.71; N, 4.46.

Preparation of 4,4-Dioxo-2,3,5,6-tetraphenyl-3a,4a,7a,7b-tetrahydrothieno[2,3-*d*:5,4-*d*]diisoxazolidine (4a). A solution of compound **3a** (0.44 g, 1.4 mmol) and *N*,α-diphenylnitrone was refluxed in chloroform (15 mL). Compound **4a** was obtained in a 70% yield by chromatography on a silica column with 90% petroleum ether and 10% methylene chloride as eluent: mp 192–193 °C; mass spectrum, *m/e* 510; ^1H NMR ($CDCl_3$) 6.65–7.62 (m, 10 H), 5.27 (d, 1 H, *J* = 5.7 Hz ($H_{6a}H_{3a}$)), 5.20 (d, 1 H, *J* = 3 Hz (H_3H_{3a})), 4.12 (dd, 1 H, *J* = 5.7 Hz ($H_{3a}H_3$)). Anal. Calcd for $C_{30}H_{26}N_2O_4S$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.44; H, 5.11; N, 5.41. Compound **4a** can also be synthesized by refluxing for 2 days a mixture of 1 (0.5 g, 1.79 mmol) and *N*,α-diphenylnitrone (2 g, 10 mmol) with pyridine (0.425 g, 5.80 mmol) in chloroform (20 mL). By use of the procedure described above, the yield was found to be 33%.

Preparation of 4,4-Dioxo-3-(2,4,6-trimethylphenyl)-3a,6a-dihydrothieno[2,3-*d*]isoxazoline (3b). Compound 1 (0.5 g, 1.79 mmol), pyridine (0.425 g, 5.79 mmol), and mesitonitrile oxide **b** (0.40 g, 2.5 mmol) were refluxed in chloroform (15 mL) for 3 h. The solid salt and the furazan *N*-oxide (dipole dimer) were removed by filtration. The filtered solution was evaporated, and compound **3b** was obtained by column chromatography in the same way as described above: yield 67%; mp 170–171 °C; mass spectrum, *m/e* 277; ^1H NMR ($CDCl_3$) 6.75–6.90 (m, 4 H), 6.0 (dd, 1 H, *J* = 0.4 Hz ($H_{6a}H_6$)), 5.02 (d, 1 H, *J* = 9 Hz ($H_{3a}H_{6a}$)), 2.3 (s, 9 H). Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.40; H, 5.25; N, 5.01.

Preparation of 4,4-Dioxo-3,5-bis(2,4,6-trimethylphenyl)-3a,4a,7a,7b-tetrahydrothieno[2,3-*d*:4,5-*d*']diisoxazoline (4b). Compound **3a** (0.41 g, 1.48 mmol) and mesitonitrile oxide (0.35 g, 2.2 mmol) were refluxed in chloroform (15 mL) for 2 days. After the furazan *N*-oxide was removed by filtration, the solution was

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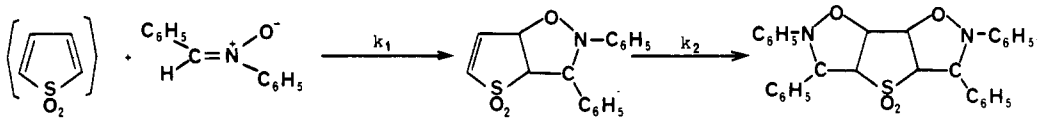
(17) O. H. Wheeler and D. H. Gore, *J. Am. Chem. Soc.*, **78**, 3363 (1956).

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.

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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

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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.

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