Evidence for a Stereospecific 1,2-Elimination Reaction in a 1,1-Diazene. Synthesis and Decomposition of [*N*-Phenyl(*threo*- (and *erythro*)-2-deuterio-1-methylpropyl)amino]nitrene†[1]

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The mechanism of the formal 1,2-elimination reaction of 1,1-diazenes to alkenes is examined. The syntheses and decompositions of [*N*-phenyl(1-methylpropyl)amino]nitrene (**6**), [*N*-phenyl(*erythro*-2-deuterio-1-methylpropyl)amino]nitrene (**7**), and [*N*-phenyl(*threo*-2-deuterio-1-methylpropyl)amino]nitrene (**8**) are reported. Oxidation of 1-(1-methylpropyl)-1-phenylhydrazine (**9**) with nickel peroxide at 100 °C affords 1-butene, *trans*-2-butene, *cis*-2-butene, butane, and benzene in ratios of 0.59:0.30:0.097:0.005:1.00. Reaction of the corresponding benzenesulfonamide **10** with base at 100 °C affords similar ratios. Oxidation of 1-(*erythro*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (**14**) at 100 °C affords 1-butene, *trans*-2-butene (100 ± 2% d_1), *cis*-2-butene (2.8 ± 2% d_1), and butane in ratios of 0.67:0.30:0.03:0.004. Oxidation of 1-(*threo*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (**20**) at 100 °C affords 1-butene, *trans*-2-butene (1.8 ± 2% d_1), *cis*-2-butene (97.9 ± 2% d_1), and butane in ratios of 0.77:0.11:0.11:0.009. Reaction of the corresponding benzenesulfonamides **15** and **21** with base at 100 °C affords similar results. Primary kinetic isotope effects for 2-butene formation from the *erythro*- and *threo*-1,1-diazene diastereomers were 3.5 and 3.4, respectively. The 1,1-diazene 1,2-elimination reaction studied here is a stereospecific cis-elimination process.

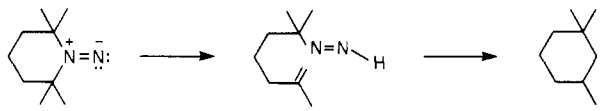
1,1-Diazenes (aminonitrenes, *N*-nitrenes) **1** unlike their

1 **2**

more stable 1,2-diazene isomers **2** are usually not isolated or detected by spectroscopic methods but rather are assumed intermediates on the basis of a substantial body of chemical evidence.[4,5] Recently the syntheses and characterization of persistent 1,1-diazenes have allowed direct studies on this reactive species.[6]

There are several methods reported for the generation of 1,1-diazenes, those most versatile being the oxidation of 1,1-disubstituted hydrazines, the reduction of *N*-nitrosamines, and the base-induced decomposition of 1,1-disubstituted 2-sulfonylhydrazines (Scheme I).[4]

Recent work from our laboratories raised the possibility that in certain cases 1,1-diazenes may undergo a 1,2-elimination reaction to alkene and monosubstituted 1,2-diazene.[6f] Small amounts of 1,1,3-trimethylcyclohexane (**3**)

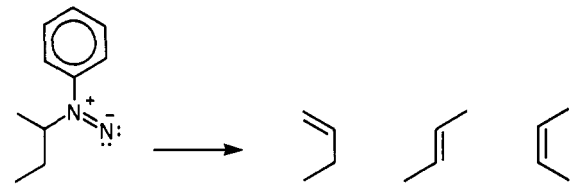


4 **5** **3**

product were observed from the thermal decomposition of *N*-(2,2,6,6-tetramethylpiperidyl)nitrene (**4**). One mechanistic scheme considered was the radical-chain decomposition[7] of a monosubstituted 1,2-diazene **5** derived from a formal 1,2-elimination of 1,1-diazene **4**.[6f]

The presumed 1,2-elimination reaction of 1,1-diazenes to alkene could occur stepwise by single-bond rupture to an intermediate diazenyl radical or by a one-step concerted process similar to amine oxides (Scheme II).[8]

In this paper we report the stereochemical consequences of a 1,1-diazene, 1,2-elimination reaction. The test system chosen was [*N*-phenyl(1-methylpropyl)amino]nitrene (**6**). Generation of this 1,1-diazene by two different routes



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affords a high yield of butenes, products of formal 1,2-elimination reactions. We describe here the stereospecific syntheses of precursors for the generation of [*N*-phenyl(*erythro*-2-deuterio-1-methylpropyl)amino]nitrene (**7**, Scheme III) and [*N*-phenyl(*threo*-2-deuterio-1-methylpropyl)amino]nitrene (**8**). Examination of the deuterium label in the *trans*- and *cis*-2-butene products should dis-

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(3) Camille and Henry Dreyfus Teacher-Scholar, 1978-1983.

(4) For reviews of 1,1-diazene behavior see: (a) Lemal, D. M. In "Nitrenes"; Lwowski, W., Ed.; Interscience: New York, 1970; Chapter 10. (b) Ioffe, B. V.; Kuznetsov, M. A. *Russ. Chem. Rev.* (*Engl. Transl.*) **1972**, *41*, 131.

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(7) Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193.

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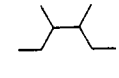
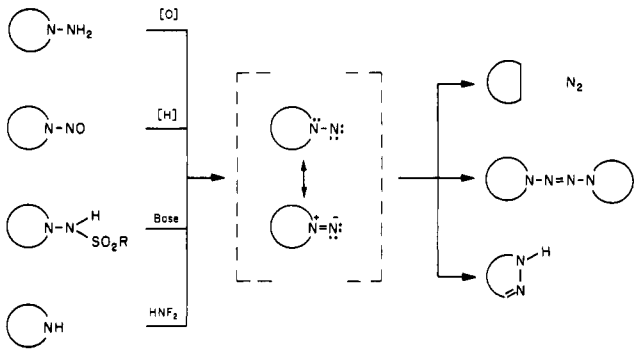
Table I. Hydrocarbon Product Ratios[a] from Generation and Thermolysis of 6 at 100 °C[b]

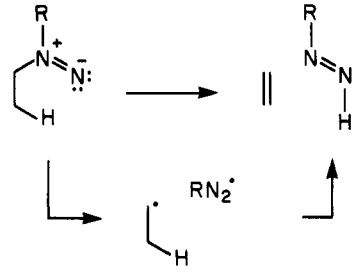
precursor							
9	59.3	30.4	9.7	0.5	100	<0.5	<0.3
10	58.8	30.6	9.6	1.1	75	<0.5	<0.3

[a] Molar ratios. [b] Absolute yield of C_4 hydrocarbon was typically 60% by the benzenesulfonamide/base route and 13% by the hydrazone/peroxide route.

Scheme I



Scheme II



tinguish between a stereospecific cis-1,2-elimination process (path a) and a stepwise pathway via a common 1-methylpropyl radical intermediate (path b).

For a stereospecific cis-1,2-elimination process (path a) the erythro diastereomer should afford *trans*-2-butene-d_1 and *cis*-2-butene-d_0. Similarly, the threo diastereomer should afford *trans*-2-butene-d_0 and *cis*-2-butene-d_1. The stepwise mechanism (path b) destroys one of the chiral centers that distinguish **7** and **8** and therefore each diastereomeric 1,1-diazene should afford similar ratios of partially deuterated *trans*- and *cis*-2-butenes.

Results

Synthesis of 1-(1-Methylpropyl)-1-phenylhydrazine (9) and the Benzenesulfonamide (10). In this study 1,1-diazenes **6–8** were not observed as persistent species but are presumed transient intermediates. Because the 1,1-diazenes were not directly observed and characterized, they were generated by two different routes in all cases. Product analyses were carried out for comparison from the oxidation reaction of 1-(1-methylpropyl)-1-phenylhydrazine (**9**) (Scheme IV) with nickel peroxide (diglyme, 100 °C) and decomposition of 2-benzenesulfonamido-1-(1-methylpropyl)-1-phenylhydrazine (**10**) with sodium 2-(2-ethoxyethoxy)ethoxide (diglyme, 100 °C). 1-(1-Methylpropyl)-1-phenylhydrazine (**9**) and its benzenesulfonamide derivative (**10**) were prepared as outlined in Scheme V. Reaction of *N*-(1-methylpropyl)aniline with freshly prepared *O*-mesitylenesulfonylhydroxylamine afforded 1-(1-methylpropyl)-1-phenylhydrazine (**9**). Subsequent treatment of the alkylphenylhydrazine **9** with benzenesulfonyl chloride affords the white crystalline 2-benzenesulfonamido-1-(1-methylpropyl)-1-phenylhydrazine (**10**).

Table II. Hydrocarbon Ratios from Decomposition of 7 and 8 at 100 °C[a]

precursor				
erythro				
14	66.8	29.8	3.0	0.4
15	65.5	30.1	3.1	1.2
threo				
20	76.6	11.3	11.1	0.9
21	75.7	11.6	11.3	1.4

[a] Molar ratios.

Synthesis of 1-(*erythro*- (and *threo*)-2-Deuterio-1-methylpropyl)-1-phenylhydrazine (14 and 20) and Their Benzensulfonamides (15 and 21). 1-(*erythro*-2-Deuterio-1-methylpropyl)-1-phenylhydrazine (**14**) and its benzenesulfonamide derivative (**15**) were prepared from *trans*-2-butene by known synthetic methodology as outlined in Scheme VI. Similarly, 1-(*threo*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (**20**) and its benzenesulfonamide derivative (**21**) were prepared from *trans*-2-butene oxide as outlined in Scheme VII. The diastereomeric purities of the materials from Schemes VI and VII were shown to be >98% from proton-decoupled high-field (76.7 MHz) ^2H NMR of the diastereomeric amines **13** and **19**.[9] The erythro and threo amine diastereomers, **13** and **19**, give singlets at 1.49 and 1.62 ppm, respectively (Figure 1).

Generation and Decomposition of 1,1-Diazenes 6 and 7. The hydrocarbon products from the generation and decomposition of 1,1-diazene **6** by two routes were analyzed by analytical VPC against an internal standard and are shown in Table I. It can be seen that the formal 1,2-elimination reaction is the major pathway for the decomposition of **6**. The presence of small amounts of butane indicates that the stepwise process is probably occurring to some extent. The mechanism for the generation of the butenes cannot, however, be determined from these data. The presence of a high yield of benzene is consistent with either mechanism.

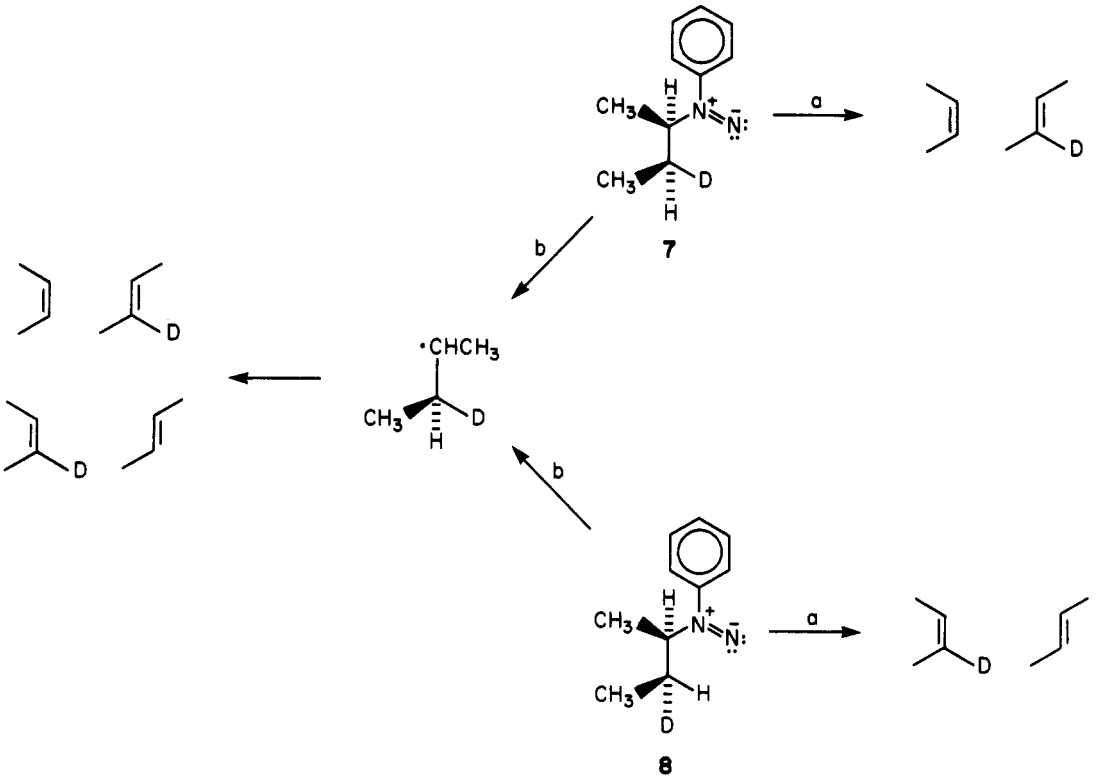
The relative C_4 hydrocarbon ratios and the deuterium content for the butenes resulting from the thermolysis of **7** and **8** are presented in Tables II and III. The hydrocarbon ratios were measured by analytical VPC against an internal standard. The hydrocarbon products were separated and isolated by preparative VPC for analysis of deuterium content by ion cyclotron resonance spectroscopy (ICR).[10] Oxidation of 1-(*erythro*-2-deuterio-1-methyl-

(9) Bruker WM-500 spectrometer.[1] We thank William Croasmun for his assistance.

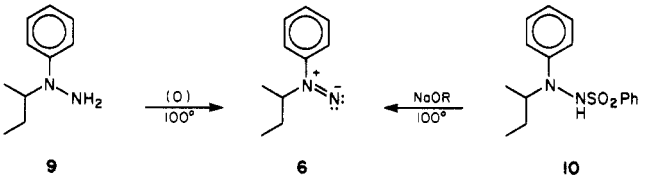
(10) We are grateful to Charles Wight and Mary Mandich in Professor J. L. Beauchamp's group at the California Institute of Technology for their generous assistance with the ion cyclotron resonance spectroscopy (ICR) experiments.[11]

(11) For a discussion of ion cyclotron resonance spectroscopy, see: Beauchamp, J. L. *Annu. Rev. Phys. Chem.* **1971**, *22*, 527.

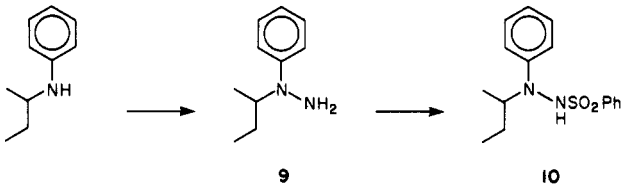
Scheme III



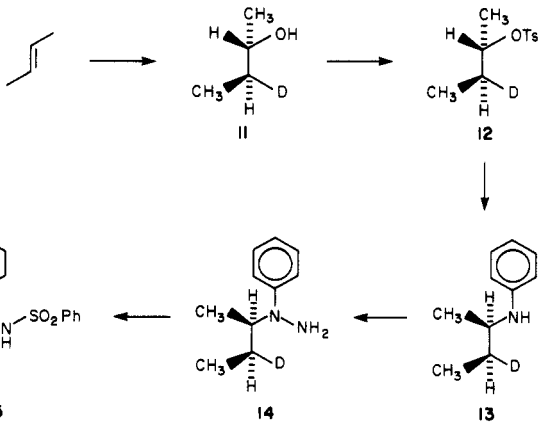
Scheme IV



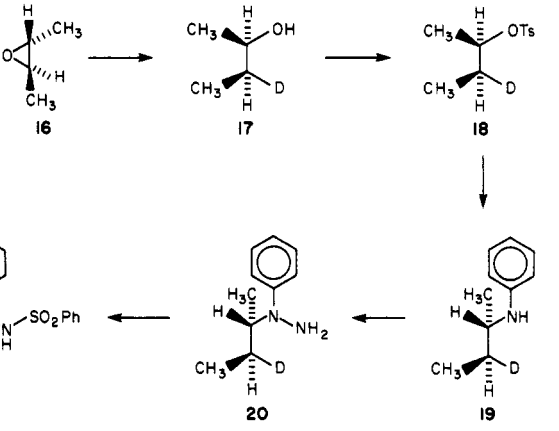
Scheme V



Scheme VI



Scheme VII



propyl)-1-phenylhydrazine (14) at 100 °C affords *trans*-2-butene (100 ± 2% d_1) and *cis*-2-butene (2.8 ± 2% d_1). Oxidation of 1-(*threo*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (20) at 100 °C affords *trans*-2-butene (1.8 ± 2% d_1) and *cis*-2-butene (97.9 ± 2% d_1). Reaction of the corresponding benzenesulfonamides 15 and 21 with base at 100 °C affords similar results (Table III).

Table III. Deuterium Content of 2-Butenes from Decomposition of 7 and 8 at 100 °C[a]

precursor	trans	cis
erythro		
14	100 ± 2	2.8 ± 2
15	99.9 ± 1	3.9 ± 1
threo		
20	1.8 ± 2	97.9 ± 2
21	1.9 ± 2	98.7 ± 2

[a] See Experimental Section.

Discussion

The fact that the butene ratios and deuterium content for the oxidative and benzenesulfonamide decomposition routes match so closely supports the notion that both routes are going through a common intermediate, presumably the 1,1-diazene. From the data presented in

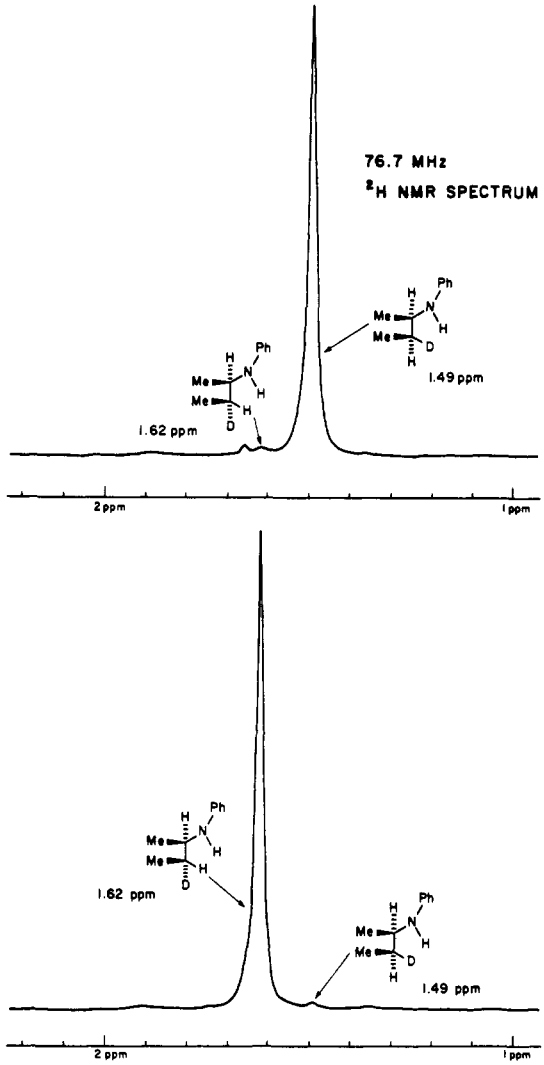
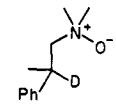
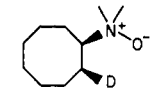
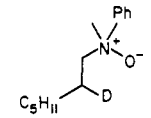


Figure 1. ^2H NMR spectra of amines **13** and **19**.

Tables II and III the thermal decomposition of [*N*-phenyl(*erythro*-2-deuterio-1-methylpropyl)amino]nitrene (**7**) and [*N*-phenyl(*threo*-2-deuterio-1-methylpropyl)-amino]nitrene (**8**) to 2-butene is predominantly a stereospecific cis-1,2-elimination reaction. The crossover deuterium content in *cis*-2-butene from *erythro*-**7** and in *trans*-2-butene from *threo*-**8** may simply be a reflection of the diastereomeric purities of the starting materials (>98%). Importantly, the crossover deuterium content sets an upper limit of a few percent for the stepwise 1,2-elimination process.

The data in Tables I and II permit the calculation of deuterium isotope effects for the elimination reactions of **7** and **8**. From the undeuterated benzensulfonamide **10**, the ratios of 1-butene:*trans*-2-butene:*cis*-2-butene products are 1.00:0.520:0.163 (Table I). From the erythro series **15**, these ratios change to 1.00:0.460:0.047. Assuming the rate of 1-butene formation does not change, the major observation is that for the erythro deuterated diastereomer **7** there is a decrease in *cis*-2-butene formation by a factor of 3.5, a primary deuterium isotope effect. In addition, a small decrease in *trans*-2-butene formation occurs, which allows calculation of a secondary deuterium isotope effect for the 1,2-elimination reaction, $k_H/k_D = 1.13$. Similarly, from the threo precursor **21**, the ratios of 1-butene:*trans*-2-butene:*cis*-2-butene products are 1.00:0.153:0.149 (Table I). In this case the major observation from the threo deuterated diastereomer **8** is a decrease in *trans*-2-butene formation by a factor of 3.4, a primary deuterium isotope effect, and a small decrease in *cis*-2-butene production, affording the secondary deuterium isotope effect, $k_H/k_D = 1.09$. The primary deuterium kinetic isotope effects for several Cope elimination reactions believed to be concerted are in the same range and are shown for comparison in Table IV.[8]

Table IV. Primary Kinetic Isotope Effects for 1,2-Elimination Reactions of 1,1-Diazenes 7 and 8 and Selected Amine Oxides

precursor	temp, °C	k_H/k_D	ref
diazene **7**	100	3.5	*a, b*
diazene **8**	100	3.4	*a, b*
 **23**	52	3.0	8d
 **24**	110–120	3.5	8c
 **25**	90/110	2.2	8e

[a] This work. [b] These numbers were calculated from the benzenesulfonamide data by assuming that the rate constants for formation of 1-butene are the same for 1,1-diazenes **6–8** at 100 °C.

Amine oxide 1,2-eliminations are believed to occur via bent cyclic transition states.[8] The similarity of the primary deuterium isotope effects for the 1,1-diazene and Cope elimination reactions suggest that the 1,1-diazene may be undergoing a similar process.

Summary

The stereochemistry and deuterium isotope effects of the formal 1,2-elimination reaction of a 1,1-diazene have been examined. The thermal decomposition of [*N*-phenyl(*threo*- (and *erythro*)-2-deuterio-1-methylpropyl)-amino]nitrenes to 2-butenes occur via a stereospecific (>98%) syn elimination with a primary deuterium isotope effect of 3.5. Taken together the stereochemical and isotope data are consistent with a concerted elimination reaction via a five-membered cyclic transition state.

Experimental Section

Melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 infrared spectrophotometer. Proton NMR spectra were obtained on a Varian Associates EM-390 spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane in δ units, and coupling constants are in hertz (Hz). NMR data are reported in this order: chemical shift; multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet); number of protons; coupling constants. Deuterium NMR spectra were run on a Bruker WM-500 spectrometer. Peak positions are given in ppm units. $CDCl_3$ was used as internal standard and assigned the value of 7.25 ppm. Carbon NMR spectra were run on a JEOL FX-90Q. For capillary vapor-phase chromatography (VPC) a Hewlett-Packard 5700A gas chromatograph equipped with a Hewlett-Packard 18704A inlet splitter and a flame ionization detector was used. Hydrogen was employed as the carrier gas, and the makeup gas was nitrogen. Packed column analytical VPC was done with a Hewlett-Packard 5720A gas chromatograph equipped with a flame ionization detector and nitrogen carrier gas. This instrument was used with 0.125-in.

Table V. VPC Columns

designation	description
Carbowax 20M capillary	50-m 0.31 mm i.d. fused silica Carbowax 20M capillary
Pennwalt	6 ft × 1/4 in. glass; 20% Pennwalt 223 80/100 Chrom R 20 ft × 1/8 in. stainless steel; 15%
β,β	β,β'-oxydipropionitrile on 100/120 Chrom P-NAW
DMS	20 ft × 3/8 in. aluminum; 25% 2,4-dimethylsulfolane on 80/100 Chrom P-NAW
Carbowax 20M	10 ft × 3/8 in. aluminum; 25% Carbowax 20M on 60/80 Chrom W-AW-DMCS

packed stainless steel columns. All quantitative VPC analysis was accomplished with a Hewlett-Packard 3390A electronic integrator. VPC response factors for normal aliphatic hydrocarbons were assumed to be 1.00 relative to butadiene. Quantitative analyses of other compounds were corrected for detector response. For preparative VPC a Varian 920 instrument equipped with a thermal conductivity detector and helium carrier gas was used. This instrument was used with 0.25-in. glass or 0.375-in. aluminum-packed columns. VPC columns used are listed in Table V. The identities of butane and benzene were verified by coinjection techniques. Isotope compositions of the butenes were determined with an ion cyclotron resonance spectrometer operated with an electron impact energy of 9 or 10 eV to provide ionization with negligible fragmentation. Gas pressures were measured with an MKS type 221 capacitance manometer. UV spectra were recorded with a Beckman Model 25 spectrophotometer. Dichloromethane was dried by distillation from calcium hydride. Triethylamine and pyridine were dried over 4A molecular sieves. Benzenesulfonyl chloride was distilled under an argon atmosphere. The procedure described by Pelletier was used for the purification of *p*-toluenesulfonyl chloride.[12] Aniline was distilled from zinc dust at reduced pressure and then dried over 4A molecular sieves. *N*-(1-methylpropyl)aniline was distilled from zinc dust at reduced pressure. Diglyme was fractionally distilled at reduced pressure and then distilled from calcium hydride at reduced pressure just prior to use. Nickel peroxide was prepared and then activated with sodium hypochlorite according to the procedure of Nakagawa et al.[13] Sodium 2-(2-ethoxyethoxy)ethoxide was prepared by dissolving sodium metal in 2-(2-ethoxyethoxy)ethanol. 3,4-Dimethylhexane was obtained from Albany Int. and shown to be about an equal mixture of the two diastereomers by ^{13}C NMR.[14] Butadiene used as a VPC standard was purified by preparative VPC (DMS room temperature). The *p*-xylene used as a VPC standard was also purified by preparative VPC (Carbowax 20M). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Reactions were carried out under a positive pressure of argon.

***O*-Mesitylenesulfonylhydroxylamine.** This reagent was prepared fresh for each amination by using the procedure described by Tamura et al.;[15] ^1H NMR ($CDCl_3$) 7.0 (s, 2 H), 4.7 variable (br s, 2–3), 2.6 (s, 6 H), 2.2 (s, 3 H).

1-(1-Methylpropyl)-1-phenylhydrazine (9). A 500-mL round-bottom flask was charged with 13.3 g (0.089 mol) of *N*-(1-methylpropyl)aniline and 120 mL of dichloromethane. This mixture was cooled to 0 °C and then a solution of 19.8 g (0.092 mol) of *O*-mesitylenesulfonylhydroxylamine in 120 mL of dichloromethane was added dropwise with stirring. After addition was complete, stirring was continued for 3 min. The cooling bath was then removed, and stirring was continued for 20 minutes. The reaction mixture was combined with 25% aqueous sodium hydroxide and ether and then filtered through Celite. The organic phase was extracted several times with 3 N HCl. The acidic aqueous phase was cooled with ice and made strongly basic by adding 25% sodium hydroxide solution. This was then extracted several times with ether. The organic phase was dried (Na_2SO_4), and the ether was removed by distillation. Fractional distillation at reduced pressure yielded 2.7 g (18%) of 1-(1-methylpropyl)-1-phenylhydrazine (**9**), bp 69–77 °C (0.3 torr). This was further purified by preparative VPC (Pennwalt, 180 °C); IR (film) 3360, 2980, 1605, 1500, 1460, 1385, 1290, 1260, 1160, 1000, 875, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.6–7.4 (m, 5), 3.5–3.9 (m, 1), 3.2 (br s, 2), 1.2–1.9 (m, 2), 0.8–1.1 (m, 6). Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; N, 17.05. Found: C, 72.97; H, 10.00; N, 16.92.

2-Benzenesulfonamido-1-(1-methylpropyl)-1-phenylhydrazine (10). A flask was charged with 8 mL of dry dichloromethane, 652 mg (4.0 m mol) of 1-(1-methylpropyl)-1-phenylhydrazine (**9**), and 436 mg (4.3 m mol) of dry triethylamine. This mixture was cooled to −20 °C, and 700 mg (4.0 m mol) of freshly distilled benzenesulfonyl chloride was added dropwise with stirring. Stirring was continued for 15 min, and then the mixture was warmed to 0 °C and stored at this temperature for 2 days. The mixture was then diluted with 25 mL of dichloromethane and washed three times with water, once with 10% HCl and then once with saturated sodium bicarbonate. The organic phase was then dried (Na_2SO_4) and concentrated, affording a brown oil. This was then purified by preparative thin-layer chromatography (silica gel/dichloromethane). The resulting product was dissolved in dichloromethane/petroleum ether, treated with Norit SG, and then filtered. This solution was then concentrated and the resulting oil allowed to solidify at −20 °C and then recrystallized from petroleum ether to yield 325 mg (27%) of white crystalline benzensulfonamide **10**: mp 81–81.5 °C; IR (CCl_4) 3250, 2980, 1600, 1495, 1450, 1345, 1170, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) 6.7–7.9 (m, 10), 6.5 variable (s, 1), 3.2–3.5 (m, 1), 1.1–1.8 (m, 2), 0.75–1.05 (m, 6). Anal. Calcd for $C_{16}H_{20}N_2SO_2$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.38; H, 6.80; N, 9.25.

***threo*-2-Butanol-3-d_1.** This compound was prepared from *trans*-2-butene by using the procedure of Kabalka and Bowman;[16] ^1H NMR ($CDCl_3$) 3.5–3.85 (br m, 1), 2.0 (br s, 1), 1.2–1.6 (m, 1), 1.15 (d, 3, J = 7 Hz), 0.9 (d, 3, J = 7 Hz).

***threo*-2-Butanol-3-d_1 Tosylate.** A 1-L flask was charged with 27.3 g (0.36 mol) of *threo*-2-butanol-3-d_1 and 525 mL of dry pyridine. This mixture was cooled to 0 °C, and 137 g (0.72 mol) of *p*-toluenesulfonyl chloride was added with stirring. Stirring was continued until all material had dissolved. The mixture was allowed to stand at 0 °C for 2 days, then poured into 3.3 L of ice water, and extracted several times with ether. The combined organic phase was washed successively with cold 1:1 hydrochloric acid and water. The solution was dried (K_2CO_3/Na_2SO_4), concentrated, taken up in a minimum volume of petroleum ether, treated with Norit SG, filtered, and then slowly cooled to −78 °C. The petroleum ether was then transferred from the product. Warming to room temperature yielded 63.5 g (77%) of a colorless oil: IR (film) 2995, 1367, 1193, 1180, 910 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (d, 2, J = 8 Hz), 7.3 (d, 2, J = 8 Hz), 4.35–4.7 (m, 1), 2.4 (s, 3), 1.3–1.65 (m, 1), 1.2 (d, 3, J = 6 Hz), 0.8 (d, 3, J = 7 Hz).

***N*-(*erythro*-2-Deuterio-1-methylpropyl)aniline (13).** A flask was charged with 350 mL of dry ether and 15.6 g (0.17 mol) of aniline. This mixture was cooled to −78 °C, and then 0.17 mol of methyllithium–lithium bromide complex in ether was added dropwise with stirring. After 0.5 h the cold bath was removed and stirring was continued for 1 h. The mixture was cooled to 0 °C, and 24.0 g (0.11 mol) of *threo*-2-butanol-3-d_1 tosylate was added dropwise with stirring. The mixture was warmed to room temperature and stirred for 2 days. Water and dichloromethane were added, and the mixture was filtered through Celite and extracted three times with 3 N hydrochloric acid. The combined aqueous phase was made strongly basic with 25% sodium hydroxide solution and then extracted with ether. The organic solution was dried (Na_2SO_4) and concentrated. The product was isolated by fractional distillation at reduced pressure yielding 8.9 g (56%) of **13**: IR (film) 3420, 2980, 1610, 1510, 1320, 755, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.25 (m, 2), 6.45–6.7 (m, 3), 3.15–3.5 (br m, 2), 1.35–1.7 (m, 1), 1.1 (d, 3, J = 7 Hz), 0.9 (d, 3, J = 8 Hz);

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(13) Nakagawa, K.; Konaka, R.; Nakata, T. *J. Org. Chem.* **1962**, *27*, 1597.
(14) Lindeman, L. P.; Adams, J. Q. *Anal. Chem.* **1971**, *43*, 1245.
(15) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
(16) Kabalka, G. W.; Bowman, N. S. *J. Org. Chem.* **1973**, *38*, 1607.

deuterium NMR ($CHCl_3$) δ 1.49 (s).

1-(*erythro*-2-Deuterio-1-methylpropyl)-1-phenylhydrazine (14). This compound was prepared from *N*-(erythro-2-deuterio-1-methylpropyl)aniline (**13**) by using the procedure described for 1-(1-methylpropyl)-1-phenylhydrazine (**9**); ^1H NMR ($CDCl_3$) δ 6.6–7.3 (m, 5), 3.5–3.85 (m, 1), 3.1 (br s, 2), 1.4–1.8 (m, 1), 1.05 (d, 3, J = 6 Hz), 0.9 (d, 3, J = 7 Hz).

2-Benzenesulfonamido-1-(*erythro*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (15). This compound was prepared from 1-(*erythro*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (**14**) by using the procedure described for the preparation of 2-benzenesulfonamido-1-(1-methylpropyl)-1-phenylhydrazine (**10**); ^1H NMR ($CDCl_3$) 6.6–7.9 (m, 10), 6.5 (s, 1), 3.15–3.5 (m, 1), 1.4–1.8 (m, 1), 1.0 (d, 3, J = 7 Hz), 0.9 (d, 3, J = 8 Hz).

***erythro*-2-Butanol-3-d_1.** This compound was prepared from *trans*-2-butene by using the procedure of Jackman and Bowman;[17] ^1H NMR ($CDCl_3$) 3.45–3.85 (br m, 1), 2.4 (br d, 1 J = 3 Hz), 1.25–1.65 (m, 1), 1.15 (d, 3, J = 6 Hz), 0.9 (d, 3, J = 7 Hz).

***erythro*-2-Butanol-3-d_1 Tosylate.** This compound was prepared from *erythro*-2-butanol-3-d_1 by using the procedure described for *threo*-2-butanol-3-d_1 tosylate; IR (film) 2990, 1360, 1190, 1180, 910 cm^{-1}; ^1H NMR ($CDCl_3$) 7.75 (d, 2, J = 8 Hz), 7.3 (d, 2, J = 8 Hz), 4.35–4.7 (m, 1), 2.4 (s, 3), 1.4–1.75 (m, 1), 1.2 (d, 3, J = 6 Hz), 0.8 (d, 3, J = 8 Hz).

***N*-(*threo*-2-Deuterio-1-methylpropyl)aniline (19).** This compound was prepared from *erythro*-2-butanol-3-d_1 tosylate by using the procedure described for *N*-(*erythro*-2-deuterio-1-methylpropyl)aniline (**13**); IR (film) 3410, 2980, 1610, 1510, 1320, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$) 7.0–7.3 (m, 2), 6.4–6.75 (m, 3), 3.15–3.5 (m, 2), 1.2–1.6 (m, 1), 1.1 (d, 3, J = 6 Hz), 0.9 (d, 3, J = 8 Hz); deuterium NMR ($CHCl_3$) δ 1.62 (s).

1-(*threo*-2-Deuterio-1-methylpropyl)-1-phenylhydrazine (20). This compound was prepared from *N*-(*threo*-2-deuterio-1-methylpropyl)aniline (**19**) by using the procedure described for 1-(1-methylpropyl)-1-phenylhydrazine (**9**); ^1H NMR ($CDCl_3$) 6.5–7.3 (m, 5), 3.5–3.9 (m, 1), 3.1 (br s, 2), 1.2–1.55 (m, 1), 1.05 (d, 3, J = 6 Hz), 0.85 (d, 3, J = 8 Hz).

2-Benzenesulfonamido-1-(*threo*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (21). This compound was prepared from 1-(*threo*-2-deuterio-1-methylpropyl)-1-phenylhydrazine (**20**) by using the procedure described for 2-benzenesulfonamido-1-(1-methylpropyl)-1-phenylhydrazine (**10**); ^1H NMR ($CDCl_3$) δ 6.6–7.8 (m, 10), 6.3 (s, 1), 3.1–3.5 (m, 1), 1.05–1.4 (m, 1), 1.0 (d, 3, J = 7 Hz), 0.9 (d, 3, J = 8 Hz).

1,4-Bis(1-methylpropyl)-1,4-diphenyl-2-tetrazene (22). A round-bottom flask was charged with 25 mL of diethyl ether and 1.8 g of nickel peroxide (equivalent to 15 mmol of OH). The mixture was cooled to 0 °C with stirring, and a solution of 318 mg (1.9 m mol) of 1-(1-methylpropyl)-1-phenylhydrazine (**9**) in 2 mL of diethyl ether was added over about 15 s. Stirring was continued for 1 h at 0 °C and then 1 h at room temperature. The mixture was filtered and the solvent removed at reduced pressure to yield a brown oil. This was crystallized by dissolving in a small volume of ethanol and then cooling to −78 °C. This yielded 50 mg (16%) of a light yellow solid. This was recrystallized to afford a white solid: mp 35.5–36 °C; IR (CCl_4) 2980, 1600, 1495, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.8–7.45 (m, 10), 4.15–4.5 (m, 2), 1.4–2.2 (m, 4), 1.3 (d, 6, J = 7 Hz), 0.9 (t, 6, J = 7 Hz); UV (cyclohexane) λ 337 nm (ϵ 19 000), 305 sh (ϵ 12 000), 257 (ϵ 9400). Anal. Calcd for $C_{20}H_{28}N_4$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.15; H, 8.70; N, 17.23.

Generation and Decomposition of 1,1-Diazenes 6–8 by the Benzenesulfonamide/Base Route. In a typical run 150–300 mg of the deuterium-labeled benzenesulfonamide **15** or **21** was dissolved in 1.5–4 mL of dry diglyme and placed in one side of a two-fingered sealable reaction cell. The other finger was charged with 0.8 equiv of sodium 2-(2-ethoxyethoxy)ethoxide in 2-(2-ethoxyethoxy)ethanol and 2–4 mL of diglyme. The reaction cell was degassed and sealed under vacuum. After the cell was heated to 100 °C in an oil bath, the base and benzenesulfonamide solutions were mixed, and heating at 100 °C was continued for 3–4.5 h. The reaction mixture was frozen with liquid nitrogen, and the reaction cell was broken open and immediately connected to a vacuum manifold by means of a standard taper joint. The reaction mixture was vacuum transferred to another tube, and after warming −78 °C the solution was analyzed for C_1–C_4 hydrocarbons by VPC ($\beta\beta$, 0 °C). For yield determination 1,3-butadiene was used as internal standard. No C_1–C_3 hydrocarbons were observed in these reactions. The absolute yield of C_4 hydrocarbons was typically 60%. The mixture was connected to the vacuum line, and the volatile hydrocarbons were isolated by repeatedly exposing the reaction mixture to a large volume, isolating the reaction mixture, and condensing the contents into a new tube. Finally, the volatile hydrocarbons were frozen with 0.25–0.3 mL of 2,2,4-trimethylpentane on the vacuum line. This mixture was removed from the line, warmed to −78 °C, and injected into a preparative VPC by means of a chilled syringe. 1-Butene, *trans*-2-butene, and *cis*-2-butene were separated and isolated by preparative VPC (DMS, 25 °C). The isolated hydrocarbons were analyzed for purity by condensing small portions of the samples with 2,2,4-trimethylpentane on a vacuum line for VPC analysis (β,β, 0 °C). The isolated butene samples were dried by transferring them on a vacuum line from a tube at −78 °C to one cooled with liquid nitrogen. The dry purified butene samples were then analyzed for deuterium content by ion cyclotron resonance (ICR). The unlabeled 1,1-diazene **6** was generated in a similar manner on a smaller scale. Benzene, 3,4-dimethylhexane, and (1-methylpropyl)benzene products were analyzed by analytical VPC (Carbowax 20 M Capillary, 100 °C).

Generation and Decomposition of 1,1-Diazenes 6–8 by the Alkylphenylhydrazine/Oxidation Route. In a typical run 300–400 mg of deuterium-labeled 1-(1-methylpropyl)-1-phenylhydrazine **14** or **20** was dissolved in 25 mL of diglyme and placed in one chamber of a sealable reaction cell with two chambers separated by a Teflon vacuum valve. The other chamber was charged with a 10-fold excess of nickel peroxide in 25 mL of diglyme. The reaction cell was degassed and sealed under vacuum. After heating to 100 °C in an oil bath, the valve separating the chambers was opened, and the solution of labeled 1-(1-methylpropyl)-1-phenylhydrazine was gradually mixed with the nickel peroxide over a 15-min period while heating was continued. After cooling, the mixture was analyzed and separated as described above for the benzenesulfonamide route. The absolute yield of C_4 hydrocarbons ranged 5–13%. No butadiene or methane was generated in these reactions. The unlabeled 1,1-diazene **6** was generated in a similar manner from **9** on a smaller scale. Benzene, 3,4-dimethylhexane, and (1-methylpropyl)benzene products were analyzed by analytical VPC (Carbowax 20M Capillary, 100 °C). Generation of labeled and unlabeled [*N*-phenyl(1-methylpropyl)amino]nitrene by this route also gave trace variable amounts of C_2 and C_3 hydrocarbons. The ranges observed for C_2 and C_3 hydrocarbons are given as follows as molar percent of the C_2–C_4 mixture: propene, ≤0.4%; propane, ≤0.2%; ethene, 0.4–5.7%; ethane, ≤1.0%. Heating diglyme and nickel peroxide together at 100 °C in the absence of **9** afforded no C_1–C_4 hydrocarbons.

Deuterium Analyses.[15] The butenes that were isolated by VPC from decomposition of 1,1-diazenes **7** and **8** had the following isomeric purities: 1-butene, >99.9%; *trans*-2-butene, >99.0%; *cis*-2-butene, >98.5%. The isotopic compositions of the 1-butene samples were determined by dividing the ICR peak heights by respective peak masses. For *trans*-2-butene and *cis*-2-butene corrections were applied where needed for the presence of the ^{13}C peak in the ICR. For *trans*-2-butene and *cis*-2-butene analyses, corrections were made for trace contamination by other butene isomers. These corrections were based on the concentrations, labeling, and relative ionization cross sections of the contaminants. The contributions of nondeuterated 1,1-diazene precursor to the *trans*-2-butene and *cis*-2-butene data were then determined. The percentage of deuterated material in the 1-butene sample for a given run was recorded and taken as a measure of the isotopic purity of the 1,1-diazene (typically 98% d_1). From this value, the butene product ratios for decomposition of **7** and **8**, and the butene product ratios for the decomposition of unlabeled **6**, it was possible to determine the unlabeled 1,1-diazene contribution to the m/e 56 peak of the *trans*- and *cis*-2-butene ICR spectra. These contributions were subtracted from the ICR data before these data were used to calculate the isotopic compositions of the 2-butenes. The data in Table VI are corrected for the presence of wrong

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Table VI. Isotopic Compositions (% D) of Butenes from Thermolysis of 7 and 8 at 100 °C

precursor	1-butene	*trans*-2-butene	*cis*-2-butene
15	98.2	97.9	3.6
14	98.8	98.6	2.6
21	98.5	1.8	97.1
20	98.7	1.8	96.4

butene isomers but are not adjusted to correspond to 100% D starting material. The data in Table IV are corrected to correspond to 100% D starting material and 100% isomerically pure butene products.

Thermolysis of Tetrazene 22. 1,4-Bis(1-methylpropyl)-1,4-diphenyl-2-tetrazene (**22**) was heated for 5.5 h at 100 °C as a degassed solution in diglyme. This resulted in the formation of <0.1% C_1–C_4 hydrocarbons.

Registry No. **6**, 84695-40-9; **7**, 84695-41-0; **8**, 84695-42-1; **9**, 84695-43-2; **10**, 84695-44-3; **11**, 10277-60-8; **12**, 7429-10-9; **13**, 84695-45-4; **14**, 84695-46-5; **15**, 84695-47-6; **17**, 10277-59-5; **18**, 7429-09-6; **19**, 84695-48-7; **20**, 84695-49-8; **21**, 84695-50-1; **22**, 84695-51-2; *N*-(1-methylpropyl)aniline, 6068-69-5; nickel peroxide, 1314-06-3; *O*-mesitylenesulfonylhydroxylamine, 36016-40-7; *trans*-2-butene, 624-64-6; aniline, 62-53-3; imidogen, 13774-92-0.

Formation of Isoxazolyl Hydroperoxides via a Novel Oxidative Fragmentation of Bicyclic Isoxazolidines

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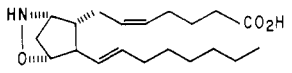
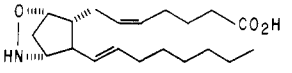
(5*Z*,9α,11α,13*E*)-9,11-(Epoxyimino)prosta-5,13-dienoic acid (**2**) and the corresponding methyl ester **3** undergo a novel oxidative fragmentation reaction in the presence of air. The resulting four isomeric isoxazolyl hydroperoxides **4a,b** and **5a,b**, formed cleanly in similar amounts and in good combined yield, have been characterized spectrally and by further chemical transformations. The novel oxidative fragmentation reaction is very facile with the strained bicyclic [2.2.1]isoxazolidine ring system (e.g., **3**) but occurs (more slowly) in less constrained substrates as well. The new isoxazolyl hydroperoxides, as well as the corresponding alcohols and ketones, are potent inhibitors of PGH_2-induced human platelet aggregation.

A variety of prostaglandin endoperoxide (PGH_2) analogues have been synthesized in which one or both of the peroxide oxygens have been replaced by methylene groups or other heteroatoms. Many of these chemically stabilized PGH_2 analogues share with PGH_2 the ability to raise blood pressure, constrict smooth muscle, and aggregate platelets. The corresponding endoperoxide mimics without the C-15 hydroxyl group usually lack the typical PGH_2 agonist activities and tend to be inhibitors or antagonists of the further metabolism of the natural endoperoxide PGH_2 (and therefore useful biochemical tools for investigations into the complex metabolism of arachidonic acid). For example, (5*Z*,9α,11α,13*E*)-11,9-(epoxyimino)prosta-5,13-dienoic acid (**1**)[1] is a potent inhibitor of the conversion of



1

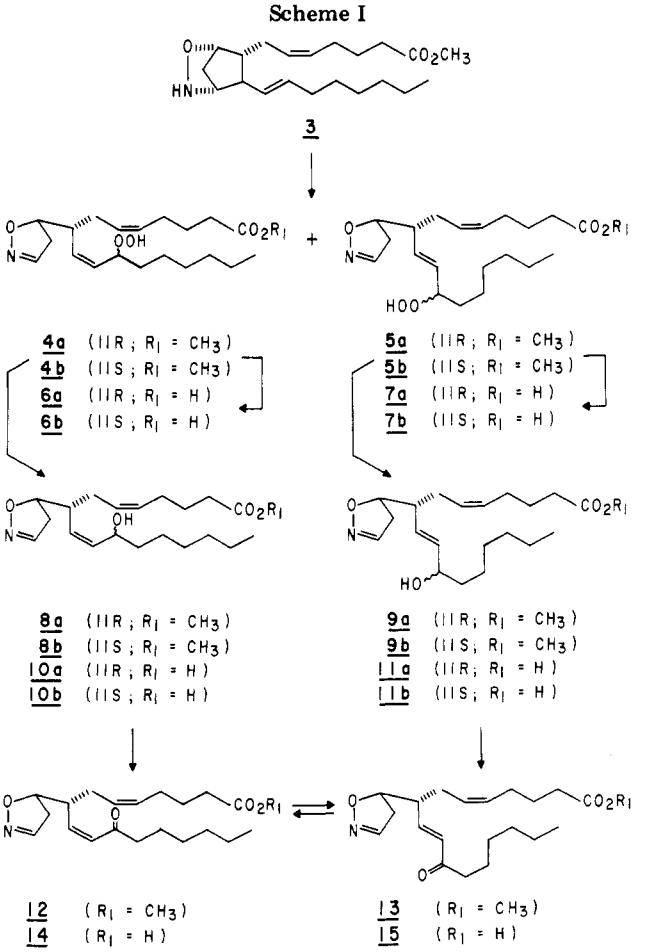


2

PGH_2 to thromboxane A_2 (TXA_2) at concentrations (10^{-4}–10^{-6} M) which have minimal effect on the formation of the endoperoxide or its conversion to prostacyclin.[2] Regioisomeric 9,11-epoxyimino analogue **2** does not inhibit the formation of TXA_2 in platelets but will prevent preformed TXA_2 from exerting its usual biological effect (i.e., **2** is a TXA_2 receptor-level antagonist).[3]

11,9-Epoxyimino isomer **1** is a crystalline solid (mp 53–54 °C) and has shown no sign of instability either neat or in solution. On the other hand, the 9,11-epoxyimino isomer **2** (and its methyl ester **3**) have never been obtained completely free from several less polar impurities.[4] Even when completely clean (by TLC) chromatographic frac-

Scheme I



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(3) Fitzpatrick, F. A.; Bundy, G. L.; Gorman, R. R.; Honohan, T. *Nature (London)* **1978**, *275*, 764.

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