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(20) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee 1972-1977 and Fellow of the Alfred P. Sloan Foundation 1973-1975.

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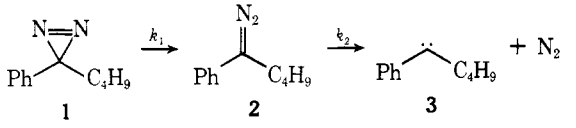
Mechanism of Thermal Decomposition of Diazirine. Evidence for Diazomethane Intermediate

Sir:

The intermediacy of diazomethane in the decomposition of diazirine has been the subject of discussion for many years.[1-3] While there is sufficient evidence for the diazomethane intermediate in the photolysis of diazirine,[4] its presence in the thermal decomposition has only been implicated, and no diazomethane intermediate has ever been isolated from a diazirine pyrolysis experiment.[5-7] In one report,[8] the attempted synthesis of 3,3-diphenyldiazirine resulted in the formation of diphenyldiazomethane; however, the precursory existence of diazirine was never verified. Only in the case of 3-methyl-3-vinyldiazirine has the linear diazo isomer been observed[7] as its subsequent reaction product, 3-methylpyrazole. We wish to report here evidence for the formation of 1-phenyl-1-diazopentane (**2**) in the thermolysis of 3-*n*-butyl-3-phenyldiazirine (**1**). This represents, to the best of our knowledge, the first account of the isolation of a diazomethane from the thermolysis of a simple diazirine and serves to support the mechanism for diazirine decomposition shown in Scheme I.

Scheme I



1 2 3

Diazirine **1** was synthesized in 40% overall yield from valerophenone by the method of Schmitz and Ohme.[9,10] Thermolysis of dilute Me_2SO solutions (0.1 M) of **1** at 100 °C for 3 h resulted in a quantitative evolution of nitrogen (measured by gas burette) and the formation of *cis*- and *trans*-1-phenyl-1-pentenes (ratio cis:trans = 1:5, determined by GLC) plus a small amount (<5%) of valerophenone, all (presumably) via carbene **3**. Surprisingly, no azine was detected.[11] When the reaction was followed by uv or ir spectroscopy, an intermediate species was observed to form rapidly and subsequently diminish; uv_{max} at 500 nm (low ϵ) and ir_{max} at 4.90 μ are consistent with this intermediate being assigned and the diazo structure **2**. Interruption of the reaction after 1 h followed by extraction with petroleum ether (30-60 °C) permitted the isolation of **2** along with unreacted **1** and small quantities of the 1-phenyl-1-pentenes. Compound **2** appears to be very stable, as the red petroleum ether solution remained unchanged at room temperature for several days. Addition of acetic acid to the red solution resulted in immediate discoloration and subsequent isolation of 1-phenyl 1-pentylacetate.[12]

Table I. First-Order Rate Constants at 100.2 °C

Solvent	Uv method 10^4k_1 (s^{-1})	N_2 evolution 10^4k_2 (s^{-1})
Me_2SO	6.75 ± 0.02	2.23 ± 0.16
HOAc	5.24 ± 0.07	5.78 ± 0.19

The rate of decomposition of **1** at 100.2 °C was determined by measuring the disappearance of it's uv_{max} at 371 nm (k_1) and by measuring the evolved nitrogen during the reaction (k_2).[13] The first-order rate constants are presented in Table I. That the two measurements in Me_2SO solvent differ by a factor of three suggests that in fact two different rates are being measured; k_1 can therefore be taken as the rate of isomerization of **1** to **2**, while k_2 may be regarded as the rate of decomposition of **2**, giving nitrogen and **3**. As such, k_1 is in good agreement with reported rate constants for decomposition of other diazirines,[6] while k_2 agrees with the reported rate constant for thermal decomposition of diphenyldiazomethane.[14]

The assignment of k_1 and k_2 above finds further support in their measurement in acetic acid (Table I). It is well established that diazirine decomposition is unaffected by acid[1] while the decomposition of diazomethanes is acid catalyzed.[15] Thus in this case, the isomerization of **1** to **2** would be the rate determining step in the overall reaction and k_2 would be expected to equal k_1, which is the experimental observation. Workup of the acetic acid reaction mixture resulted in the isolation of 1-phenyl 1-pentylacetate in 75% yield, and a mixture of *cis*- and *trans*-1-phenyl-1-pentenes in 20% yield.

The evidence reported here clearly establishes that the primary mode of diazirine decomposition is via its linear diazo isomer, as shown in Scheme I, although we cannot at present completely rule out the possibility that decomposition also occurs via a minor pathway directly to carbene. Kinetic experiments on this system are in progress to further clarify these points.

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(10) Uv_{max} (hexane) 371 (ϵ 234), 382 nm (ϵ 214); ir (CCl_4) 6.35 (N=N) μ; NMR (CCl_4) τ 2.8 (m, 3), 3.13 (m, 2), 8.07 (br t, 2), 8.7 (m, 4), 9.1 (br t, 3); *m/e* 146 ($M^+ - 28$).
(11) C. G. Overberger and J-P. Anselme, *J. Org. Chem.*, **29**, 1188 (1964).
(12) Spectral data: ir (CCl_4) 5.74)c=O) μ; NMR (CCl_4), τ 2.77 (s, 5 aromatic), 4.35 (t, 1, J = 6.5 Hz, methine), 8.04 (s, 3, methyl), 8.2 (m, 2), 8.7 (m, 4), 9.13 (t, 3, J = 6 Hz, methyl); *m/e* parent 206.
(13) The determination of k_2 in Me_2SO by N_2 evolution method requires elaboration. The first-order plot from N_2 measurements does not give a straight line; in fact, there is a slight curvature (convex) during the first 20-30 min of the reaction. This curvature is due to the buildup of the diazo compound. After such time, N_2 evolution begins to approximate first-order behavior and it is in this portion of the graph that k_2 was taken. In order to confirm the value of k_2, we have synthesized 1-phenyl-1-diazopentane from a separate experiment, and its N_2 evolution in Me_2SO was measured. The first-order rate constant determined in this manner was within 3% of the value reported in Table I.

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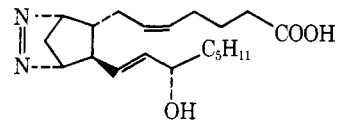
A Direct, Stereocontrolled Total Synthesis of the 9,11-Azo Analogue of the Prostaglandin Endoperoxide, PGH_2

Sir:

The 9,11-azo prostanoid **1** has recently been synthesized[1] and found to exhibit biological activity comparable to the naturally occurring prostaglandin (PG) endoperoxides PGH_2 (**2**) and PGG_2 (**3**)[2] in known test systems (e.g., with respect to human platelet aggregation and release reactions).[3] Interest in the synthetic azo analogue **1** has developed rapidly since its use provides a number of important advantages in the investigation of the biological effects of PG endoperoxides, and a wide variety of biological studies involving **1** are currently underway.[4] In contrast to the highly labile (and not easily available) PGG_2 and PGH_2 which rapidly decompose at 25 °C in neutral aqueous solution, **1** is very stable and convenient to use. Further, **1** is not subject to the rapid enzymic conversion to the highly active substance thromboxane A_2,[5] which is characteristic of PGG_2 and PGH_2 and which markedly complicates their study.



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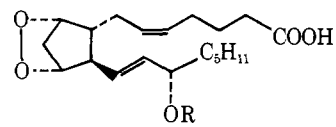
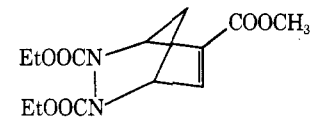


2, R = H
3, R = OH

The azo analogue **1** was originally synthesized[1] by a six-step sequence (overall yield ca. 11%) starting with PGA_2 methyl ester acetate.[6] Since it became clear that there would be a widespread and continuing demand for **1**, we have sought a more direct route, not dependent on the availability of PGA_2. An effective total synthesis by a novel route is reported here.[7] This process has obvious utility also for the synthesis of a large number of analogues of **1**.

The synthesis of the first key intermediate (**4**) for the construction of the desired azo analogue is not possible by the obvious route, a direct Diels–Alder reaction, since the required diene component is unavailable by direct preparation and in any event would be subject to rapid isomerization and dimerization. Nonetheless **4** could be prepared in good yield from the known mixture of dimers of methyl cyclopentadienecarboxylate[8] under carefully chosen conditions which allow both retro-Diels–Alder reaction to a mixture of monomers and formation of cross adducts with diethyl azodicarboxylate reversibly and under thermodynamic control. Specifically, upon heating 1 equiv of diethyl azodicarboxylate with 2.2 equiv of methyl cyclopentadienecarboxylate dimers in chlorobenzene (7 ml/g of azo ester) for 50 h at 125 °C under argon, **4** was formed without significant accompaniment by position isomers,[9] and could be isolated in 65% yield after column chromatography on silica gel using petroleum ether–ether (2:3) as eluent.[10] Reaction of **4** with various Gilman (cuprate) reagents derived from 3-[dimethyl-*tert*-butylsilyloxy]-*trans*-1-octenyllithium[11] at low temperatures (mildest possible conditions) produced only the product of conjugate addition plus subsequent elimination (**5**) and none of the desired bridged adduct (silyl ether corresponding to **9**). Conjugate addition of nitro-



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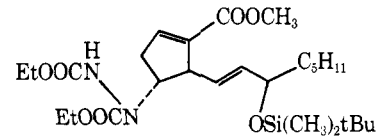

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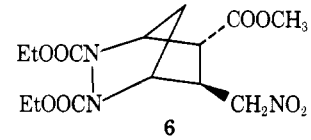
methane to **4** was successful under closely defined conditions, nitromethane–water–methanol (1:1. 8:1 by volume; total 6.3 ml/mmol of **4**), 4.25 h at 23 °C in the presence of a catalytic amount (0.1 equiv based on **4**) of 1,1,3,3-tetramethylguanidine,[12] to form **6** as a crystalline solid, mp 119–121 °C, in 71% yield.[13] Treatment of the nitro compound **6** in THF (10 ml/g) with 1.01 equiv of 0.1 N aqueous potassium hydroxide for 5 min at 0 to 5 °C, subsequent removal of THF under reduced pressure, and addition of 2 M aqueous magnesium sulfate (excess) followed by 0.05 M aqueous potassium permanganate (dropwise, 0.67 mol equiv based on **6**, reaction temperature 0–5 °C, vigorous stirring)[14] afforded after workup the aldehyde **7** in high yield. The stereochemistry of **7**, a crucial element in the synthesis and expected from previous experience,[15] was confirmed by proton magnetic double resonance spectra with spin decoupling ($J_{AB} \cong J_{BC} \cong 3.5$ Hz; $J_{CD} \cong 0$ Hz).



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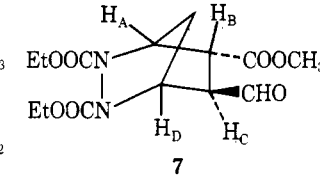

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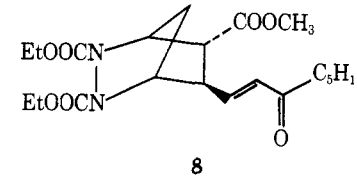
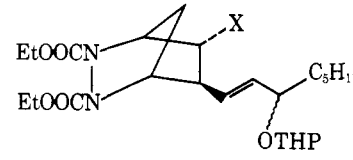
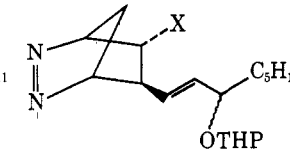


8

The aldehyde **7** was converted by the Emmons–Horner method[16] to the enone **8** (68% overall from **6**), and thence to a diastereomeric mixture of allylic alcohols (1.1 equiv of lithium selectride in THF at −78 °C for 30 min) and the corresponding tetrahydropyranyl ethers **9**[16] (95% from **8**). At this point in the synthesis, the successful accomplishment of the remaining structural modifications, generation of the azo



9, X = $COOCH_3$
10, X = COOH
11, X = CH_2OH



12, X = CH_2OH
13, X = CHO
14, X = CH=$CHOCH_3$
15, X = CH_2CHO