Cyclic Azo Dioxides. Preparation, Properties, and Consideration of Azo Dioxide–Nitrosoalkane Equilibria[1a,b]

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The cyclic azo dioxides, 3,3,6,6-tetramethyl-1,2-diazacyclohex-1-ene N,N'-dioxide (1), 1,4,4-trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene N,N'-dioxide (2), and 3,3,4,4-tetramethyldiazetine N,N'-dioxide (3), have been prepared and examined. Azo dioxides 1 and 3 are resistant to oxidation but may be reduced to azoxy and/or azo, leading in the case of azo dioxide 3 to the novel four-membered-ring azo compound 10, 3,3,4,4-tetramethyldiazetine. Photolysis of azo dioxides 1 and 2 affords the corresponding cyclic nitroxyl radicals (overall loss of NO). In solution, azo dioxide 2 is in equilibrium with the dinitroso compound; azo dioxides 1 and 3 give no evidence for the corresponding dinitroso forms. The equilibrium with azo dioxide 2 is solvent dependent, polar solvents favoring the azo dioxide form. In ethyl acetate, $\Delta H^\circ = 7 \pm 0.7$ kcal/mol; $\Delta S^\circ = 21 \pm 3$ gibbs/mol. Thermodynamic and kinetic considerations of azo dioxide dissociation are discussed. The results with 1, 2, and 3 are consistent with dissociation of azo dioxides via a "twisted" transition state, in general accord with orbital symmetry considerations. Attention is directed to the marked differences in properties, physical and chemical, of azo dioxides and nitroso species, and the potential control over the properties exhibited in a specific case by proper design to select the position of equilibrium desired.

Azo dioxides have been known for many years, including both cis and trans forms of which the latter are the more stable.[2] The functional group, possessing partial positive charges on adjacent nitrogens, has many aspects of interest, including (in a formal sense) the thermal cleavage of a double bond under mild conditions—dissociation of the azo dioxide to the corresponding nitroso compound (eq 1).

$$\text{R}\overset{+}{\text{N}} = \overset{+}{\text{N}} \text{R} \quad \rightleftharpoons \quad 2 \text{ RNO} \qquad (1)$$
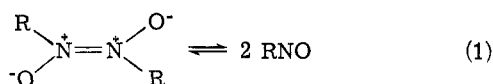
Both rates and equilibria have been studied for a number of acyclic systems.[2,3] The azo dioxide would appear to be a rather polar functional group; and the studies show considerable dependence on the nature of the solvent.[4] A theoretical study on the mechanism of dissociation and dimerization has appeared indicating a "non-least motion" path.[5] A few cyclic azo dioxides[1b,6] have been reported, including a compound to which a four-membered ring azo dioxide[7] structure was assigned.

The objective of the present study was to prepare some aliphatic cyclic azo dioxides and to examine the nature of this functional group, with special emphasis on the question of ring–chain isomerism.

Results

The three systems of interest in this study are **1, 2**, and **3**.

1   **2**   **3**
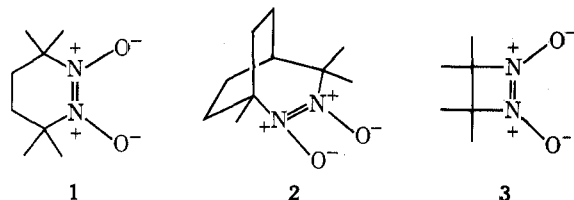
Compound **1**, 3,3,6,6-tetramethyl-1,2-diazacyclohex-1-ene N,N'-dioxide, was prepared by peracid oxidation of the corresponding azoxy compound, **4**, in turn prepared by oxidative cyclization of the diamine by tungstate, hydrogen peroxide. This latter step, patterned after a method for the oxidation of amines to nitroso compounds,[3a] represents a new route to a nitrogen–nitrogen bond in cyclic systems. Cyclization takes place at an early point in the reaction, since the cyclic azo compound may be isolated by use of a

Table I
Physical Data for Azo Dioxides 1–3

Compd	Ir, cm^{-1}	Uv,[a] nm (ε)	NMR	ESCA[b]
1	1460, 1410, 1335	273 (8100)	1.62 (12 H, s) 2.20 (4 H, s)	401.3
2	1480, 1390, 1325	277 (8100)	See text	
3	1540	255 (10,000)	1.59 (s)	401.4

[a] *trans*-$(CH_3NO)_2$, 276 nm (ε 10,700), *cis*-$(CH_3NO)_2$, 265 nm (ε 10,000); *trans*-$(i\text{-}PrNO)_2$, 280 nm (ε 10,000), *cis*-$(i\text{-}PrNO)_2$, 267 nm (ε 10,000), B. G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 1670 (1956); *trans*-$(c\text{-}C_6H_{11}NO)_2$, 292, *cis*-$(c\text{-}C_6H_{11}NO)_2$, 278 (ref 2a). [b] E_b (N 1s) in electron volts, relative to E_b (N 1s) for NaNO$_3$ at 407.4 eV and for NaNO$_2$ at 404.3 (ref 13).
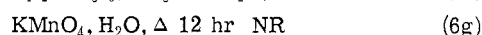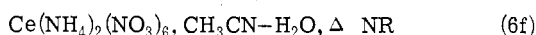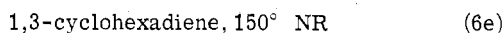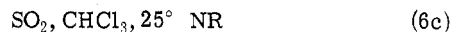
limited amount of oxidant. The results are summarized in eq 2 and physical data in Table I.

$$(2)$$
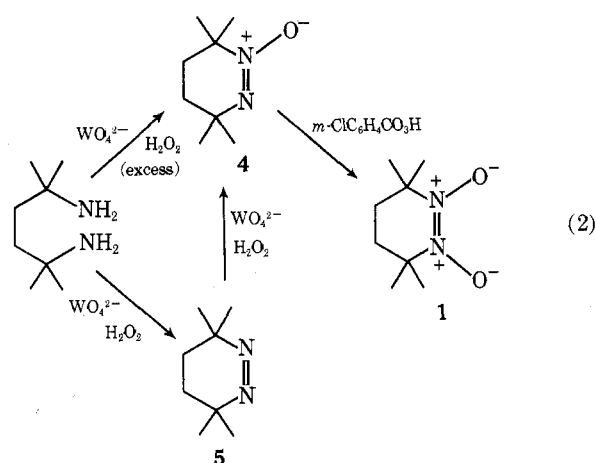
Compound **1** is assigned the intramolecular azo dioxide structure on the basis of its NMR, uv, mode of preparation, and reduction to the corresponding azoxy compound **4**.

Compound **1** is a stable, colorless solid. It melts with decomposition at 188–190°, giving no indication of a blue color (usually associated with the nitroso group). Various reagents effect reduction to azoxy, **4**, and to azo compound, **5** (e.g., Si_2Cl_6).[8] Compound **1** is resistant to further oxidation by aqueous permanganate or ceric ammonium nitrate.

Some reactions and nonreactions of **1** are summarized in eq 3–6.[9]

$$1 \xrightarrow[\text{CHCl}_3]{\text{Si}_2\text{Cl}_6} 5 \tag{3}$$

$$\xrightarrow{\text{LiAlH}_4} \textbf{4 and 5} \tag{4}$$

$$\underset{\text{CHCl}_3}{\overset{\text{TCNE}}{\rightleftharpoons}} \text{1:1 complex (red solution)} \tag{5}$$

$$p\text{-(CH}_3)_2\text{NC}_6\text{H}_4\text{N(CH}_3)_2, \text{CHCl}_3, 25° \quad \text{NR} \tag{6a}$$

$$\text{galvinoxyl,}^9 \text{C}_6\text{H}_6, 25° \quad \text{NR} \tag{6b}$$

$$\text{SO}_2, \text{CHCl}_3, 25° \quad \text{NR} \tag{6c}$$

$$i\text{-PrNC, octane, } \Delta \quad \text{NR} \tag{6d}$$

$$1,3\text{-cyclohexadiene, } 150° \quad \text{NR} \tag{6e}$$

$$\text{Ce(NH}_4)_2\text{(NO}_3)_6, \text{CH}_3\text{CN–H}_2\text{O}, \Delta \quad \text{NR} \tag{6f}$$

$$\text{KMnO}_4, \text{H}_2\text{O}, \Delta \text{ 12 hr} \quad \text{NR} \tag{6g}$$
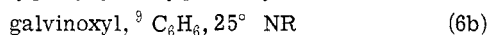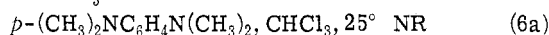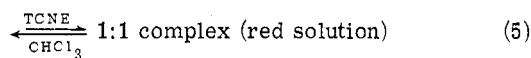
Compound **2**, 1,4,4-trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-dioxide, first reported by Rassat and Ray,[10] was prepared here in low yield by the oxidation of a cis-trans mixture of the diamine (eq 7). Compound **2** melts at

$$\tag{7}$$
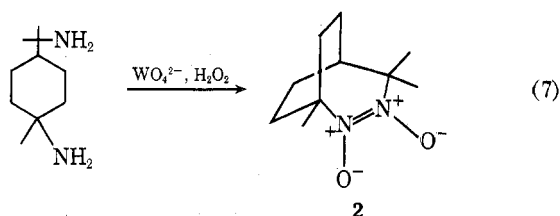
135–137° to a green liquid. Assignment of structure to **2** is based on the physical data (Table I), on equilibria data (eq 8 and Table II), and on oxidation in high yield to the corresponding dinitro compound (eq 9). Assignment of **2**, a well-

$$\tag{8}$$

$$\tag{9}$$
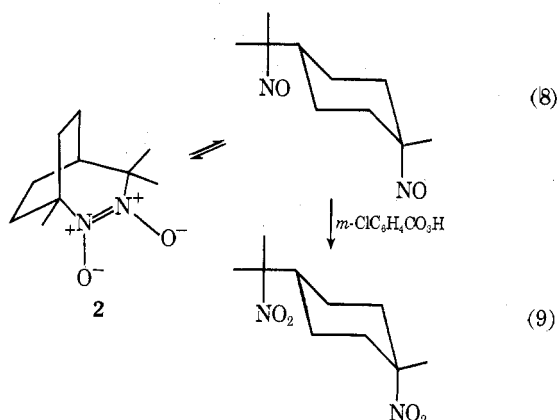
defined crystalline solid, as an intramolecular cis azo dioxide rather than a polymeric azo dioxide, **6**, is based on the

6
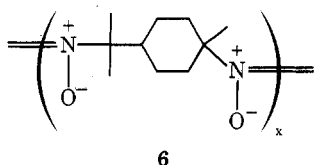
volatility of the compound (sublimes unchanged) and on the independence of *K* (azo dioxide ⇌ dinitroso) on concentration. Detailed consideration of this equilibrium is taken up later in this paper.

Compound **3**, 3,3,4,4-tetramethyl-1,2-diazetine *N,N'*-dioxide was recently reported by Ullman and Singh as the product of oxidation of bis hydroxylamine **7** with bromine (eq 10).[7] Physical data are summarized in Table I. Com-

Table II
Equilibrium between 1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-Dioxide (2) and 1,8-Dinitroso-*p*-menthane (eq 8)

A. Effect of Solvent

Solvent	K_{eq} (39°)
Ethanol	~0.04
Chloroform	~0.07
Ethyl acetate	~0.3
Benzene	~0.3

B. Effect of Temperature on *K* in EtOAc

Temp, °C	K_{eq}
12	0.10
15	0.12
20	0.15
25	0.18
29	0.22
33	0.26
38	0.31
42	0.36

$$\Delta H° \simeq +7 \pm 0.7 \text{ kcal/mol}$$
$$\Delta S° \simeq +21 \pm 3 \text{ gibbs/mol}$$

$$\tag{10}$$

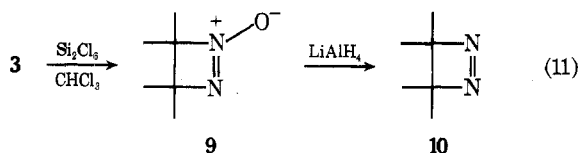**7**   **3**
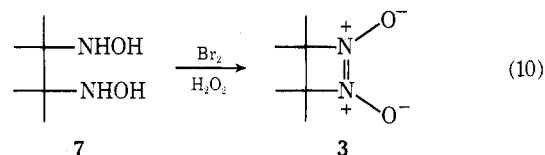
pound **3**, a colorless solid, melts with decomposition at 190–192°. Solutions of **3** remain colorless on warming. The stability of **3** toward ring opening to a dinitroso species (in contrast to **2**) and the differences in uv and ir led us to consider other possible structures such as **8**. Rapid equilibra-

8a   **8b**   **8c**
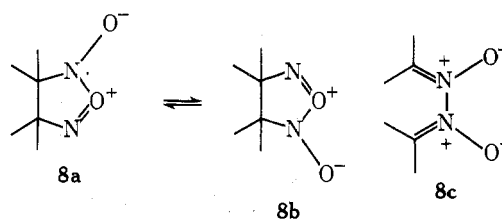
tion between **8a** and **8b**[11a] could account for the observed sharp singlet in the proton NMR, which remained sharp to −100° (lowest temperature measured). For **8a** ⇌ **8b**, the formal charge on each nitrogen may be near zero. Consequently, ^{13}C NMR data were examined. The results (C_α 80.6, C_β 19.0 ppm downfield from Me₄Si in CHCl₃ solution) indicate that **3** is much closer to nitro alkanes than to amines[11b] and are supportive of the azo dioxide structure **3**.

ESCA data for **1** and **3** are included in Table I.[12] The single maximum in each spectrum and the similarity of the results for **1** and **3** are consistent with the azo dioxide structure assigned. The potential charge system (two adjacent, partially positively charged nitrogen atoms) makes detailed interpretation difficult. Work with suitable model systems may lead to good estimates of the amount of charge on the nitrogen atoms.

Compound **3** is reduced by Si₂Cl₆[8] to the corresponding azoxy compound. Further reduction (with LiAlH₄) affords the diazetine **10** (eq 11). (Under comparable conditions, azo dioxide **1** is reduced by Si₂Cl₆ to the azo compound, eq 3.) One other monocyclic Δ¹-1,2-diazetine (the 3,3,4,4-tetraflu-

oro derivative)[13a] and three bicyclic derivatives[13b,c] have been reported. All of these diazetines, including **10**, are thermally rather stable. Pyrolysis of **10** at 130° in decane gives 2,3-dimethyl-2-butene and no acetone azine.

Photochemistry of Azo Dioxides 1, 2, and 3. Ullman and Singh observed a low-energy triplet state for azo dioxide **3** and described the products of photolysis in methanol.[7] We have briefly examined the photolysis of **1** and **2** (also examined by Rassat and Ray).[10] The results are summarized in Scheme I.

Scheme I
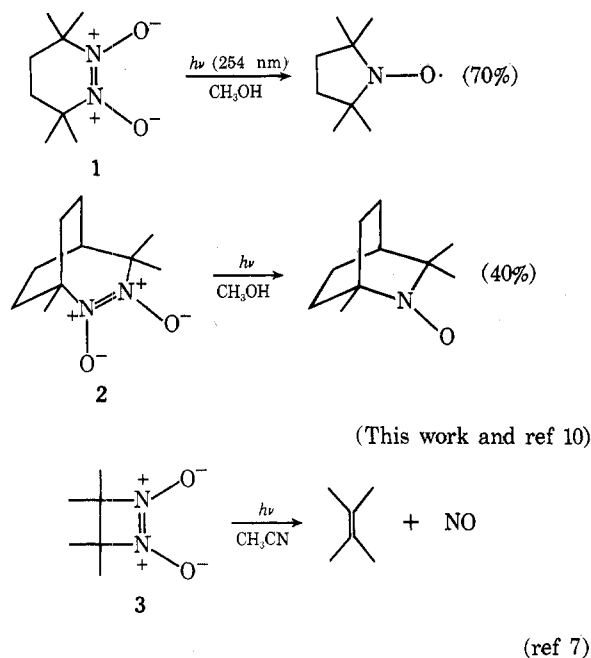
Complex Formation.[14] Azo dioxides **1** and **3** give red solutions with tetracyanoethylene in chloroform. The absorbing species for **1** has λ_{max} 490 nm and is a 1:1 complex of azo dioxide and TCNE. Ultraviolet and NMR evidence indicate that the equilibrium lies heavily on the side of the reactants, and azo dioxide can be recovered in high yield from the solution.

Azo Dioxide–Nitroso Equilibrium. As indicated above, the bicyclic azo dioxide **2** gives a blue solution on warming in benzene. Color formation is reversible and is dependent on temperature and solvent. The blue color (associated with the nitroso group) is observed on warming of solutions of **2** in solvents of E_T[15] less than 39. With more polar solvents (E_T > 40) the solutions remained colorless evennon heating to reflux, in general accordizith expectations that polar solvents should favor the azo dioxide form (eq 8).

The azo dioxide chromophore, λ_{max} 277 nm (ϵ 8100), has been used to measure the equilibrium. The small extinction coefficient for a nitroso group, coupled with the low solubility of **2** in nonpolar media and the one-sidedness of the equilibrium (favoring azo dioxide) in polar solvents, has prevented direct measurement of nitroso concentration. Qualitative values for K in several solvents are reported in Table IIA. In ethyl acetate the degree of ring opening to the dinitroso form was sufficient to determine K with

Table III
Thermodynamic Data for Azo Dioxide–Nitroso Equilibria

$$R\!-\!N_2O_2\!-\!R \;\rightleftharpoons\; 2RNO$$

R	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$ (20), kcal/mol	Solvent
tert-Butyl[a,b]	11.8	41.5	−0.4	CCl_4
Cyclohexyl[a,c]	20.6	41	8.6	C_6H_6
Cyclohexyl[a,d]	19.8	37	9.0	CH_3CN
Cyclohexyl[d,e]	17.4	37	6.6	CH_3CN
Benzyl[a,c]	20.4	36	9.9	C_6H_6

[a] Trans azo dioxide. [b] Reference 3a. [c] Reference 3b. [d] Reference 2a. [e] Cis azo dioxide.

greater confidence, and measurements were made over a 30° range in temperature. The results are summarized in Table IIB.

In perdeuteriobenzene, a qualitative[16] indication of the position of equilibrium was obtained by Fourier transform proton NMR (solvent absorbance precluded the uv method). At 25° the major peaks are those for **2** at 1.28 (s, 6 H) and 1.37 (s, 3 H), with small peaks at 0.53 (s, 3 H) and 0.62 (s, 6 H) associated with the methyl groups of the dinitroso form. Upon warming to 70° the peaks for **2** decrease and those for the dinitroso form increase to an approximate[16] ratio of azo dioxide/dinitroso of 1.3:1. No indication of coalescence is observed. At high temperatures some decomposition occurs.

In contrast to **2**, the six-membered and four-membered azo dioxides **1** and **3** give no indication of formation of blue color on heating.

Discussion

Thermodynamic Considerations. Thermodynamic data for the dissociation of several acyclic azo dioxides to nitroso compounds are summarized in Table III. The enthalpy term favors the azo dioxide form, and the entropy term favors the nitroso form; both terms make important contributions to the free energy. What estimates are appropriate for equilibrium between cyclic azo dioxides and the corresponding dinitroso species? The $\Delta S°$ for a ring–chain isomerism should be considerably smaller than for a monomer–dimer interconversion. The $\Delta H°$ might be approximated by selecting a base value for the conversion of azo dioxide to nitroso and applying correction terms, as needed, for factors such as strain release. Thus, by extrapolation of the results of Table III, nonstrained cyclic azo dioxides should heavily favor the cyclic azo dioxide form over the dinitroso form. A highly strained system might be expected to favor the dinitroso form (or an "intermolecular azo dioxide" form). How well do these notions fit to available data on **1**, **2**, and **3**? A base value for $\Delta H°$ may be taken as +20 kcal/mol for the conversion of trans azo dioxide to nitroso in nonstrained cases (Table III) (the lower value for the *tert*-butyl case is attributed to strain from methyl–O⁻ interactions). The $\Delta H°$ for eq 12 might be expected to be a
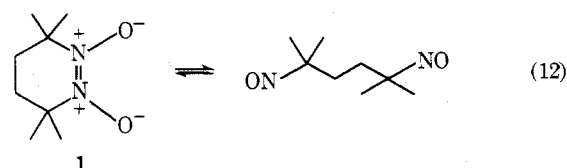
	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$, kcal/mol
estimated, gas phase, 20°	+18	+20	+12

little smaller than the ΔH^0 for the nonstrained azo dioxide cases (e.g., for the nitrosocyclohexane dimers of Table III the cis azo dioxide is 2.4 kcal/mol less stable than the trans isomer, acetonitrile solvent). A rough estimate of ΔS^0 for eq 12 is +20 gibbs/mol.[17] These considerations lead to the estimates for **1** shown in eq 12; compound **1** should be the more stable form and should remain so even at elevated temperatures (e.g., at 200°, $\Delta G^0 \sim >9$).

What would be appropriate estimates for equilibrium between azo dioxide **2** and the dinitroso species? A value for ΔH^0 may be obtained by combination of the above-derived value of ΔH^0 of +18 kcal/mol along with an assessment of the difference in strain energy between azo dioxide and dinitroso species. The strain energy in **2** is estimated to be ~15 kcal/mol, using the corresponding olefin as a model for the azo dioxide.[18,19] An estimate of ΔH^0 for the ring opening of **2** is then +3 kcal/mol. The ΔS^0 should be positive, and somewhat smaller than for ring opening of **1**, perhaps 10–15 gibbs/mol,[17] leading to the estimates for ring opening of **2** in eq 13.

$$ \text{(13)} $$
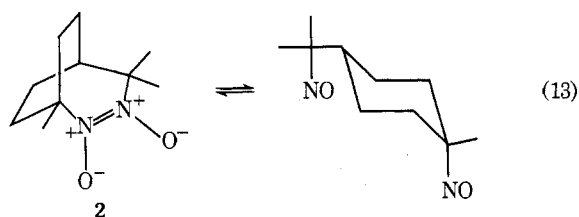
	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$, kcal/mol
estimated, gas phase, 20°	+3	10–15	~0
observed, EtOAc, soln, 20°	+7	+21	+1

The agreement, considering the rough nature of the estimates and the phase change, may be largely fortuitous. The principal point, however, is that the considerable strain in azo dioxide **2** which is relieved in the dinitroso species provides an adequate basis for the observation that the dinitroso species related to **2** *is* observed while that related to azo dioxide **1** *is not*.

Analysis of the four-membered ring azo dioxide **3** is made in the same way. For estimation of ΔH^0 for eq 14, the

$$ \text{(14)} $$
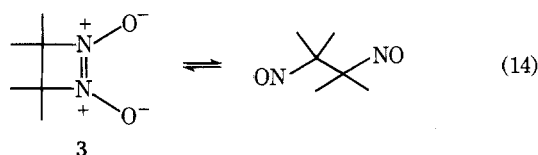
	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$, kcal/mol
estimated, gas phase, 20°	−12	positive	>−12

strain in **3** is approximated from the strain in cyclobutene (~30 kcal/mol).[19] The eclipsing interactions of the methyl groups in **3** (several kilocalories/mole) is considered to be largely balanced by strain remaining in the dinitroso species. The ΔS^0 should still be positive but smaller than ΔS^0 for **2**. The estimated values indicate that ΔG^0 at 20° is at least −12 kcal/mol. The experimental observation, however, is that **3** exists in the azo dioxide form, is quite stable to heat, and gives no indication of ring opening to the dinitroso form even at elevated temperatures.[20]

The apparent existence of **3** in the azo dioxide form might be explained in two different ways: (a) equilibrium control, with azo dioxide **3** more stable than the dinitroso form, associated with a much lower value for the strain energy in the four-membered ring azo dioxide than estimated

above, or (b) rate control, with azo dioxide **3** less stable than the dinitroso form but with a substantially greater activation barrier to ring opening than that associated with the opening of, e.g., **2**. Although we do not feel that the first explanation, a, can be summarily dismissed at this point, we think that the strain energy estimate for **3** is reasonable and also think that there is good reason mechanistically for explanation b, as indicated below.

Kinetic Considerations. Free energies of activation for dissociation of acyclic azo dioxides are in the range 21–28 kcal/mol.[3c] For bicyclic azo dioxide **2**, we can make some estimates in the following way. Peaks for both the azo dioxide **2** and the dinitroso species are seen in the NMR (separation, 50 Hz) in benzene and give no indication of coalescing up to 70°. Thus the rate constants for ring opening and closing must be no faster than 30 sec^{-1} at room temperature. Rapid mixing of a solution of **2** in ethyl acetate, cooled to 10°, with an equal volume of solvent at 40° afforded the final equilibrium value before measurement was started (~5 sec), setting a lower limit of 0.3 sec^{-1} on the rate of ring opening. These limits indicate a ΔG^0 for ring opening of **2** in the range 16–19 kcal/mol at 25°.

Azo dioxide **3** is stable up to 150°. A minimum estimate of ΔG^0 for ring opening at 150° is 35 kcal/mol (with the assumption that **3** is less stable than the dinitroso form).

To summarize: Compound **1** exists in the azo dioxide form and gives no indication of ring opening to the dinitroso form; these findings are consistent with estimates for ΔG^0, ΔH^0, and ΔS^0. Compound **2** is isolated in the azo dioxide form; in solution it is in equilibrium with the ring-opened dinitroso form; these findings also are consistent with estimates for ΔG^0, ΔH^0, and ΔS^0. Compound **2** differs from **1** in ring strain (~15 kcal/mol) which is relieved on going from azo dioxide to dinitroso; compound **2** uses this driving force to surmount the activation barrier at a total cost of 16–19 kcal/mol instead of the usual 21–28 kcal/mol. Compound **3** is isolated in the azo dioxide form, would appear to have considerably greater strain than **2**, but gives no indication of ring opening, appears unable to use the strain to aid in ring opening.

These findings, at first sight anomalous, appear well fitted to the considerations of Hoffmann, Gleiter, and Mallory[5] on "non-least motion" modes of dissociation of an azo dioxide group. Dissociation by stretching of the nitrogen–nitrogen bond while retaining coplanarity of the N_2O_2 moiety is "symmetry forbidden".[21] Allowed paths involve twisting about the nitrogen–nitrogen bond. Many variants are possible, involving the different locations for the two oxygen atoms relative to the R's and the N's, e.g., B and C.
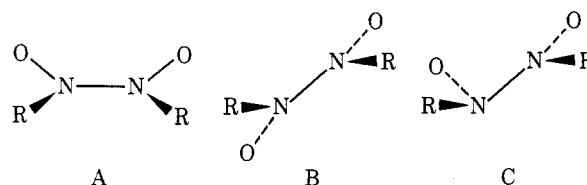
Although both **2** and **3** are strained systems, they are of different types. Examination of models suggests that the strain in **2** is in part a torsional strain, relieved by twisting about the nitrogen–nitrogen bond; i.e., the type of strain in **2** *decreases* the barrier between reactant and an "orbital symmetry allowed" transition state. In compound **3**, however, the small angles force the system to be planar; twisting about the nitrogen–nitrogen bond would produce an increase in angle strain elsewhere in the system; i.e., the type of strain in **3** may *increase* the barrier between reactants and the proposed transition state.

In compound **1**, a "twisted" transition state should be ac-

cessible, and perhaps at not much greater cost than the activation barriers for other strain-free cases. The lack of observation of any dinitroso form for this case may be due simply to a high rate of ring closure. Establishment of the barrier to ring opening might be possible by a sequence as shown in eq 15. Efforts to date to find reagents sufficiently
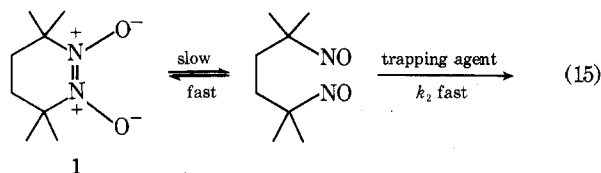
reactive to trap an intermediate dinitroso species have been unsuccessful (e.g., see eq 6): refluxing **1** in aqueous permanganate for 12 hr led only to recovery of **1**, indicating both the need for a more effective trapping agent and the high stability of the azo dioxide to further oxidation.

The likelihood that **3** is less stable than the corresponding dinitroso species has prompted attempts to synthesize the latter and to examine the reaction by which **3** is formed from the bis hydroxylamine **7** (eq 10): (a) oxidation of **7** with tungstate–hydrogen peroxide gave acetone oxime in low yield and no **3**; (b) the azoxy compound, prepared separately, is not the precursor of **3**; (c) use of a large excess of bromine in the oxidation of **7** still afforded **3** in high yield, suggesting that the iminoxyl radical $(CH_3)_2C=NO\cdot$ is not the precursor of **3**. Thus, the actual precursors of **3** are not known (probably are N-bromo species) but the dinitroso compound is not a required intermediate.

The few examples described here point to many additional aspects for investigation in the azo dioxide–nitroso species equilibria, and more generally in the little-investigated area of ring–chain isomerism in aprotic systems. Of particular interest are the marked differences in properties (solubility, reactivity) of azo dioxides and nitroso species, and potential control over the properties exhibited by a specific system by proper design to select the position of equilibrium desired.

Experimental

3,3,6,6-Tetramethyl-1,2-diazacyclohexene N-Oxide (4). 2,5-Diamino-2,5-dimethylhexane (30 g, 0.208 mol) (Aldrich) and sodium tungstate dihydrate (3 g, 9.1 mmol) were dissolved in 200 ml of distilled water and cooled while hydrogen peroxide (95 g of a 30% solution, 0.832 mol) was added slowly. The rate of peroxide addition was such that the temperature of the reaction never rose above 30°. The solution was stirred for 1 hr and then extracted with 3 × 100 ml of 2 N HCl and 2 × 100 ml of distilled water and dried (MgSO₄), and the chloroform was removed under reduced pressure. The residue was recrystallized from pentane: yield 23.5 g (72.5%); mp 119–121°; uv (pentane) λ_{max} 234 nm (ϵ 9350); ir (CHCl₃) 2960 (s), 1470 (s), 1395 (w), 1370 (m), 1345 (w), 1310 (m), 1215 (s), 1180 (w), 1130 cm⁻¹ (w); NMR (CDCl₃) 1.35 (s, 6 H), 1.61 (s, 6 H), 1.90 ppm (m, 4 H); mass spectrum m/e (rel intensity) 156 (69), 141 (20), 111 (48), 96 (24), 87 (48), 69 (56), 57 (84), 56 (100), 55 (50).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32. Found: C, 61.42; H, 10.49.

3,3,6,6-Tetramethyl-1,2-diazacyclohexene (5). 2,5-Diamino-2,5-dimethylhexane (10 g, 0.069 mol), sodium tungstate dihydrate (0.5 g, 1.5 mmol), and hydrogen peroxide (15.7 g of a 30% solution, 0.139 mol) were allowed to react as above. After the chloroform was removed under reduced pressure, the solution was filtered to remove the 3,3,6,6-tetramethyl-1,2-diazacyclohexene N-oxide (4), 1.65 g (15.5%). The residue was distilled, giving 4.0 g, bp 48–50° (4.2 mm), of a mixture of the starting material and 3,3,6,6-tetramethyl-1,2-diazacyclohexene (5). Analysis of this mixture by NMR indicated that 72% was compound **5**, which corresponds to a 33% yield. Compound **5** may be obtained in pure form by washing the mixture with 2 N HCl, drying (MgSO₄), and removing all solvents under reduced pressure: ir (CCl₄) 2960 (s), 1565 (m), 1475 (s), 1460

(s), 1380 (s), 1360 (s), and 1340 cm⁻¹ (s) [lit.²² ir (CCl₄) 1565 cm⁻¹]; NMR (CCl₄) 1.28 (s, 12 H) and 1.48 ppm (s, 4 H) [lit.²² NMR (CCl₄) 1.25 (s, 12 H) and 1.45 ppm (s, 4 H)].

3,3,6,6-Tetramethyl-1,2-diazacyclohexene N,N'-Dioxide (1). 3,3,6,6-Tetramethyl-1,2-diazacyclohexene N-oxide (4, 5 g, 0.032 mol) and m-chloroperbenzoic acid (6.5 g, 85% peracid, 0.032 mol) were dissolved in 100 ml of methylene chloride and stirred for 2 days. The solution was filtered, saturated with dry NH₃, and filtered again.²³ The solvent was removed under reduced pressure to give a white, crystalline solid, **1**, recrystallized from a mixture of CHCl₃ and CCl₄: yield 4.0 g (72%); mp 188–190° dec; uv (CH₃OH) λ_{max} 273 nm (ϵ 8160); ir (CHCl₃) 2980 (s), 1470 (sh), 1460 (m), 1410 (m), 1370 (m), 1335 (s), 1250 (m), 1125 cm⁻¹ (m); NMR (CDCl₃) 1.62 (s, 12 H), 2.20 ppm (s, 4 H); mass spectrum m/e (rel intensity) 172 (16), 142 (24), 112 (5), 86 (8), 74 (46), 69 (43), 57 (19), 56 (100), 55 (26), 41 (54).

Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.78; H, 9.37. Found: C, 55.61; H, 9.48.

1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene N,N'-Dioxide (2). *cis*- and *trans*-1-Methyl-4-(1-amino-1-methylethyl)-cyclohexylamine (10 g, 0.058 mol, technical grade) and sodium tungstate dihydrate (0.5 g, 1.5 mmol) were dissolved in 50 ml of H₂O and cooled while hydrogen peroxide (26.7 g of a 30% solution, 0.236 mol) was added slowly. The reaction mixture was stirred for 2 hr while slowly warming to room temperature and then extracted into CHCl₃. The CHCl₃ was washed with H₂O and dried (MgSO₄) and the solvent was removed under reduced pressure. Diethyl ether was added to the residue, at which point the cis azo dioxide **2** crystallized from solution. The cis azo dioxide can be recrystallized from tetrahydrofuran, and it sublimes unchanged at 115° (0.17 mm): yield 0.90 g (8%); mp 135–137° (to a green liquid that resolidifies to a greenish material) (lit.¹⁰ mp 161°; in spite of this difference in melting point, the compounds are thought to be the same, based on the available physical and chemical data); ir (CHCl₃) 2980 (m), 1470 (m), 1450 (sh), 1380 (m), 1350 (m), 1340 (m), and 1325 cm⁻¹ (m); NMR (CDCl₃) 1.60 (s, 3 H), 1.66 (s, 6 H), 2.04 ppm (m, 9 H); uv (EtOH) λ_{max} 277 nm (ϵ 8100).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.57; H, 9.15. Found: C, 60.57; H, 9.14.

3,3,4,4-Tetramethyldiazetine N,N'-Dioxide (3). 2,3-Dihydroxylamino-2,3-dimethylbutane²⁴ (2.40 g, 0.016 mol) and sodium carbonate (3.36 g, 0.032 mol) were dissolved in 20 ml of H₂O and stirred while bromine (5.1 g, 0.032 mol) was added dropwise. After 10 min the solution was extracted into CHCl₃, washed with H₂O, and dried (MgSO₄). The solvent was removed under reduced pressure to give 1.78 g (77%) of the diazetine dioxide: mp 190–192° dec (lit.⁷ mp 190–192° dec); ir (CHCl₃) 2980 (m), 1560 (m), 1465 (s), 1380 cm⁻¹ (m); NMR (CDCl₃) 1.59 ppm (s); mass spectrum m/e (rel intensity) 144 (6.5), 114 (16), 84 (69), 69 (100), 41 (58).

Reduction of 3,3,6,6-Tetramethyl-1,2-diazacyclohexene N,N'-Dioxide (1). A. With Hexachlorodisilane.⁸ Compound **1** (0.10 g, 0.58 mmol) was stirred in 5 ml of dry CHCl₃ under a nitrogen atmosphere while hexachlorodisilane (0.20 ml, 1.2 mmol) was added. The solution was stirred for 1 hr and then quenched with 1 N NaOH, washed with H₂O, and dried (MgSO₄). The solvent was removed under reduced pressure to give 0.083 g (99%) of a yellow oil whose ir spectra were identical with the ir spectra of 3,3,6,6-tetramethyl-1,2-diazacyclohexene (**5**).

B. With Lithium Aluminum Hydride. Compound **1** (0.2 g, 1.16 mmol) and lithium aluminum hydride (excess) were stirred in 20 ml of anhydrous diethyl ether for 1 hr. Work-up afforded 0.1 g of an oil; NMR analysis indicated azo, azoxy, and azodioxy compounds **5**, **4**, and **1** in the ratio 4:2:1.

Attempted Reactions of Azo Dioxide 1. Several unsuccessful attempts were made to react 3,3,6,6-tetramethyl-1,2-diazacyclohexene N,N'-dioxide (**1**) with different reagents. The results are summarized in eq 6.

Reaction of 1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene N,N'-Dioxide (2) with m-Chloroperbenzoic Acid. Compound **2** (0.124 g, 0.626 mmol) and m-chloroperbenzoic acid (0.27 g, 87% peracid, 1.33 mmol) were dissolved in 10 ml of benzene, refluxed for 2 hr, and then stirred at room temperature overnight. Dry NH₃ was bubbled through the solution and the precipitate was filtered.²³ The solvent was removed under reduced pressure to give 0.129 g (89%) of 1,8-dinitro-p-menthane [1-(1-methyl-1-nitroethyl)-4-t-methyl-4-c-nitrocyclohexane]: mp 103–104° (lit.²⁵ mp 104–106° from oxidation of a cis–trans mixture of diamines); ir (CHCl₃) 2940 (m), 1535 (s), 1450 (m), 1400 (m), 1375 (m), 1350 (m), and 1210 cm⁻¹ (br); NMR (CDCl₃) 1.48 (s, 6 H) and 1.53 ppm (s, 3 H).

Reaction of 3,3,4,4-Tetramethyl-1,2-diazetine *N,N'*-Dioxide (3) with Hexachlorodisilane. Compound 3 (0.6852 g, 4.75 mmol) and hexachlorodisilane[8] (0.9 ml, 4.8 mmol) were dissolved in 25 ml of dry $CHCl_3$ under a nitrogen atmosphere. The solution was stirred at room temperature for several hours and then quenched with 5 ml of 1 *M* NaOH. The $CHCl_3$ layer was separated, washed with H_2O, dried (K_2CO_3), and the solvent removed under reduced pressure to give 0.6068 g (99%) of 3,3,4,4-tetramethyldiazetine *N*-oxide (9): mp 168–169° (lit.[7] mp 170°); ir ($CHCl_3$) 2990 (s), 1555 (s), 1470 (m), 1465 (m), 1400 (m), 1390 (s), 1380 (s), 1265 (m), and 1215 cm^{-1} (br); NMR ($CDCl_3$) 1.47 (s, 6 H) and 1.52 ppm (s, 6 H).

3,3,4,4-Tetramethyl-Δ^1-1,2-diazetine (10). 3,3,4,4-Tetramethyldiazetine *N*-oxide (0.1006 g, 0.853 mmol) and an excess of $LiAlH_4$ were dissolved in 15 ml of anhydrous ether and stirred at reflux under a nitrogen atmosphere for 1 hr. The remaining hydride was quenched with wet ether, the solution was extracted with H_2O, and the ether phase was dried (K_2CO_3). The ether was removed by distillation through a Vigreux column with a total reflux stillhead and the residue was recrystallized from diethyl ether at −78° to give 0.0208 g (22%) of 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine, a volatile solid: mp 83–85°; ir ($CHCl_3$) 2970 (s), 1480 (m), 1450 (w), 1390 (w), 1375 (s), 1220 (br), and 1140 cm^{-1} (m); NMR ($CDCl_3$) 1.15 ppm (s); uv (pentane) highly structured 325 nm (ϵ 57), 333 (86), 340 (121), 347.5 (136), 356 (103); mass spectrum *m/e* (rel intensity) 112 (2), 97 (2), 84 (39), 69 (100), 55 (18), 41 (100). Pyrolysis of 10 at 130° in decane afforded 2,3-dimethyl-2-butene (>80% yield), identified by comparison with authentic material. No other products were seen in the VPC trace of the reaction mixture. An authentic sample of acetone azine was prepared, and shown not to be a product of thermolysis of diazetine 10.

ESCA Spectra of 3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N,N'*-Dioxide (1) and 3,3,4,4-Tetramethyldiazetine Dioxide (3). The photoelectron spectra of the nitrogen 1s electrons of the azo dioxides were obtained on a Hewlett-Packard 5958 ESCA spectrometer using Al Kα irradiation. The samples were prepared by grinding up weighed amounts of azo dioxide and a standard, either $NaNO_3$ or $NaNO_2$, adding graphite, and pressing into a pellet.[26] Each azo dioxide was run with both standards to determine the peak positions. The graphite pellets were placed in a sample holder in the instrument, and the entire system was pumped down to 10^{-8} Torr. The spectra were obtained at 10^{-8} Torr and ambient temperature. Results are summarized in Table I.

Photolysis of Azo Dioxides in Methanol at 254 nm. A. Compound 1 (0.2047 g, 1.19 mmol) was dissolved in 50 ml of MeOH and purged with dry nitrogen for 30 min. The solution was irradiated for 2.5 hr in a Rayonet reactor at 254 nm in a quartz vessel. The MeOH was removed by distillation through a Vigreux column with a total reflux stillhead and the residue was analyzed by VPC on 15% SE-30 (temperature programmed at 80° and 2°/min), showing one major peak corresponding to an 80% yield of the nitroxyl radical, 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl: ir ($CHCl_3$) 2960 (s), 1460 (m), 1370 (m), 1330 (w), and 1210 cm^{-1} (m); uv (EtOH) λ_{max} 232 nm (ϵ 2850), 400 (14) [lit.[27] uv (MeOH) λ_{max} 233 nm (ϵ 2500), 410 (6)]; ESR (cyclohexane) triplet a_N 13.5 G.

B. Compound 2 (0.100 g, 0.503 mmol) was dissolved in 50 ml of MeOH, irradiated, and worked up as described above. VPC on 15% SE-30 showed only one major product, in 41% yield, identified as the nitroxyl radical, 1,3,3-trimethyl-2-azabicyclo[2.2.2]octane-*N*-oxyl: ir ($CHCl_3$) 2920 (s), 1465 (m), 1455 (s), 1375 (m), and 1355 cm^{-1} (m); uv (MeOH) λ_{max} 246 nm (ϵ 2020) and 418 (12) [lit.[10] uv λ_{max} 238 nm (ϵ 2480) and 450 (10.4)]; ESR (cyclohexane) triplet, a_N 15.0 G.

3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N,N'*-Dioxide (1) and Tetracyanoethylene. Compound 1 (8.6 mg, 0.05 mmol) and tetracyanoethyene (6.4 mg, 0.05 mmol) were mixed as solids and a red color soon developed. When the mixture was dissolved in 2 ml of $CDCl_3$ the solution was bright red, and the NMR of the solution was identical with the NMR of pure 1: NMR ($CDCl_3$) 1.62 (s, 12 H) and 2.20 ppm (s, 4 H). The uv and visible spectrum showed absorptions due to 1, TCNE, and a new band at 490 nm. The dependence of the intensity of the band at 490 nm on the concentration of the TCNE and azo dioxide 1 indicated a 1:1 complex.[28] The NMR results (above) indicate that $K \ll 1$. 3,3,4,4-Tetramethyldiazetine dioxide (3) and TCNE react to give an orange-colored solution in chloroform with λ_{max} 452 nm.

Study of the Equilibrium between 1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-Dioxide (2) and 1,8-Dinitrosomenthane. The equilibrium constant for this system was determined in a variety of solvents by measuring the concentration of

azo dioxide as a function of temperature by ultraviolet or NMR spectroscopy.

A weighed amount of azo dioxideiwas dissolved in a pure solvent and diluted to the proper concentration at ambient temperature. The ultraviolet spectrum was determinednon a Guilford Model 222 spectrometer equipped with a thermostatted cell, a nitrogen inlet *to purge the cell compartment, and a copper–constantan* thermocouple to measure the temperature of the cell. The temperature of the cell was regulated by a Haake constant-temperature circulating bath in the temperature range of 5–45°. Below 0° a Cary instrument with low-temperature cell compartment was used; dry nitrogen was passed through a heat exchanger cooled by liquid nitrogen and then into the thermostatting section of the cell compartment. The sample was placed in a glass-stoppered quartz uv cell and several determinations of the absorbance over the temperature range were recorded. All work was done at the wavelength of maximum absorption. The results are summarized in Table III and in the microfilm edition.[28]

A 7.3×10^{-2} *M* solution of 2 in $CHCl_3$ was studied by variable temperature visible spectrometry. The change in the absorbance at 700 nm (nitroso) was from 0.012 to 0.016 when the temperature was changed from 20 to 40°, not large enough to give reliable results.

Estimation of Rates of Ring Opening and Closing. A. From NMR Evidence. The NMR spectrum of 1,4,4-trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-dioxide (2) in benzene shows methyl peaks assignable to azo dioxide and to nitroso approximately 50 Hz apart. No broadening is seen with increasing temperature up to 70°, at which point decomposition of sample begins indicating an upper limit of 30 sec^{-1} for the rate of ring opening at room temperature.

B. Modified "Temperature Jump." A solution of 2 in ethyl acetate at 10° was rapidly mixed with an equal volume of pure ethyl acetate at 40° in a uv cell thermostatted at 25°. No change in the absorbance of the solution as a function of time was observed, i.e., equilibrium was established upon mixing, indicating a τ of less than 2 sec. The expected change in the absorbance was from 0.494 to 0.445. From these results a lower limit to the rate of ring opening and ring closing is 0.3 sec^{-1}.

Control Experiments on the Oxidation of 2,3-Dihydroxylamino-2,3-dimethylbutane with Bromine. A. Use of 1 Equiv of Bromine. To a solution of 2,3-dihydroxylamino-2,3-dimethylbutane (0.20 g, 1.35 mmol) and sodium carbonate (0.5 g, 4.8 mmol) in 10 ml of H_2O was slowly added a solution of bromine (0.216 g, 1.35 mmol) in 10 ml of H_2O. The solution was stirred for 30 min, extracted into $CHCl_3$, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 0.10 g (51%) of 3,3,4,4-tetramethyldiazetine dioxide (3), mp 190–192° (lit.[7] mp 190–192°).

B. Use of 10 Equiv of Bromine. To a solution of 2,3-dihydroxylamino-2,3-dimethylbutane (0.20 g, 1.35 mmol) and sodium carbonate (0.50 g, 4.8 mmol) in 10 ml of H_2O was added bromine (2.1 g, 13.5 mmol). The solution was stirred for 30 min, extracted into $CHCl_3$, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 0.193 g (99%) of 3,3,4,4-tetramethyldiazetine dioxide (3), mp 190–192° (lit.[7] mp 190–192°).

C. Reaction of 3,3,4,4-Tetramethyldiazetine *N*-Oxide (9) with Bromine. Compound 9 (0.10 g, 0.78 mmol) and sodium carbonate (0.50 g, 4.8 mmol) were dissolved in approximately 50 ml of warm water. The water solution was warmed slightly to ensure the dissolution of all the azoxy. Bromine (0.50 g, 3.12 mmol) was added and the solution was stirred for 3 hr, extracted into $CHCl_3$, and dried ($MgSO_4$). The solvent was removed under reduced pressure, giving 90% recovery of the starting material: mp 166–168°; ir identical with ir of starting material.

(105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1409.

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Synthesis of Metabolites of Prostaglandin $F_{2\alpha}$ Resulting from β-Oxidation of the Carboxylic Acid Side Chain

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A synthetic sequence has been developed that leads to metabolites of $PGF_{2\alpha}$ having the carboxylic acid side chain shortened by four carbons. The readily available lactol **2** is treated with (methoxymethyl)triphenylphosphorane, giving enol ethers **3** and **4**. Acid-catalyzed hydrolysis and cyclization in aqueous methanol gives the acetal **5**. Hydrogenation of **5** gives **6** while oxidation of **5** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gives **10**. Hydrogenation of **10** gives **11**. The methyl acetals of **6** and **11** may be hydrolyzed, giving **7** and **12**, respectively. Oxidation of **7** and **12** with silver oxide results in formation of 9α,11α,15α-trihydroxy-2,3,4,5-tetranorprostanoic acid (**8**), a metabolite of $PGF_{2\alpha}$ found in urine of the rabbit, and 9α,11α-dihydroxy-15-oxo-2,3,4,5-tetranorprostanoic acid (**14**), a metabolite of $PGF_{2\alpha}$ found in urine of the rat, the rabbit, the guinea pig, and the monkey, respectively. Compounds 8 and 14 were isolated and characterized as the corresponding lactones **9** and **13**. Compound 9 was converted via the sodium salt of its ditetrahydropyranyl ether derivative (**15**) to 11α,15α-dihydroxy-9-oxo-2,3,4,5-tetranorprostanoic acid (**16**), a metabolite of PGE_1 found during in vitro metabolism studies that used rat liver mitochondria.

The prostaglandins are a class of C-20 fatty acids found distributed throughout most mammalian systems and having potent physiological effects in many of these systems. Although widespread throughout the body, the quantity of prostaglandins found in any single tissue is exceedingly small and may fluctuate considerably. As a consequence of this situation, it has been difficult to develop methods for the assay of prostaglandins at physiological concentrations. One approach to this problem has been to develop assays based on the urinary excretion of prostaglandin metabolites.[1]

The metabolism of the prostaglandins has been studied in a number of mammalian systems and the details have been described in several review articles.[2,3] To summarize, for the purposes of this discussion, it may be noted that three portions of the prostaglandin nucleus appear to be the most susceptible to the generally oxidative processes of metabolism. The first of these is the allylic alcohol system at C_{13}–C_{15}, which undergoes oxidation of the alcohol and reduction of the double bond, resulting in a series of "primary" metabolites.[3] The second is the carboxylic acid side chain, which is susceptible to β-oxidation. The third is the