

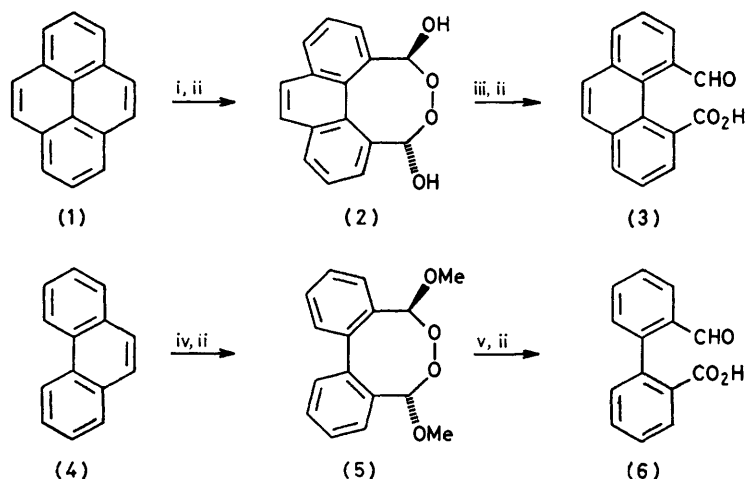
Ozonolysis of Tetrahydrophthalimides (Cyclohex-4-ene-1,2-dicarboximides): A Sterically Dependent Unsymmetrical Oxidative Cleavage Reaction¹

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Ozonolysis of *cis*-tetrahydrophthalimide or *cis-N*-phenyltetrahydrophthalimide in anhydrous methanol gives moderate yields of the unsymmetrical oxidative cleavage products, *cis*-3-(2,2-dimethoxyethyl)-4-methoxycarbonylmethylpyrrole-2,5(3*H*,4*H*)-dione and *cis*-3-(2,2-dimethoxyethyl)-4-methoxycarbonylmethyl-1-phenylpyrrole-2,5(3*H*,4*H*)-dione. In contrast to these results, the ozonization in methanol of the methylene-bridged analogues, *endo*-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione and *endo*-4-phenyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione, gives the symmetric oxidative cleavage products, *endo,endo,cis*-6,8-bis(dimethoxymethyl)-3-azabicyclo[3.3.0]octane-2,4-dione and *endo,endo,cis*-6,8-bis(dimethoxymethyl)-3-phenyl-3-azabicyclo[3.3.0]octane-2,4-dione. The latter bis-acetal could be converted under hydrolytic conditions into two other dialdehyde derivatives, *cis,exo*-8,10-dimethoxy-*cis,endo*-4-phenyl-9-oxa-4-azatricyclo[5.3.1.0^{2,6}]undecane-3,5-dione and *trans*-8,10-dihydroxy-*cis,endo*-4-phenyl-9-oxa-4-azatricyclo[5.3.1.0^{2,6}]undecane-3,5-dione. All structural assignments were confirmed with the aid of natural abundance 25.16 MHz carbon-13 magnetic resonance spectra including multiplicities and ¹³C-¹H coupling constants.

UNSYMMETRICAL oxidative cleavage of the symmetric carbon-carbon double bonds in pyrene² and phenanthrene^{3-5,†} are isolated examples of a synthetically intriguing transformation (see Scheme 1)

amino-ketones and α -ketols,⁸ and nucleophilic cleavage of α -diketone monothioacetals.⁹ Similar but less general oxidative cleavage reactions reported include the acid-catalysed fragmentation of cyclic tertiary-hydroper-



SCHEME 1 i, O₃-DMF; ii, H₃O⁺; iii, KOH and heat; iv, O₃-MeOH; v, NaOH and heat

Unsymmetrically oxidized products have, however, been produced in high yields through oxidative cleavage of cyclic ketones and their derivatives: *e.g.* nitrosolysis of ketones,⁶ Beckmann fragmentation of α -hydroxy-ketoximes,⁷ lead tetra-acetate-catalysed oxidation of α -

† The stereochemistry of the methoxy-groups in (5) originally^{3,4} was not assigned but is now known to be *trans*.⁵

¹ Preliminary report: A. H. Andrist and M. J. Kovelan, 173rd National Meeting of the American Chemical Society, New Orleans, March 1977, Abstract No. ORGN 150.

² R. E. Dessy and M. S. Newman, *Org. Synth., Coll. Vol. IV*, 1963, 484; also see M. G. Sturrock and R. A. Duncan, *J. Org. Chem.*, 1968, **33**, 2149.

³ P. S. Bailey, *J. Amer. Chem. Soc.*, 1956, **78**, 3811.

⁴ P. S. Bailey and R. E. Erickson, *Org. Synth., Coll. Vol. V*, 1973, 493.

⁵ A. H. Andrist and M. J. Kovelan, *Spectroscopy Letters*, 1975, **8**, 547; J. N. Brown, R. L. R. Towns, M. J. Kovelan, and A. H. Andrist, *J. Org. Chem.*, 1976, **41**, 3756.

⁶ M. M. Rogic, J. Vitrone, and M. D. Swerdloff, *J. Amer. Chem. Soc.*, 1975, **97**, 3848.

oxides,¹⁰ the cobalt(II)-catalysed oxygenation of 3-hydroxyflavones,¹¹ and the copper(I)-catalysed oxygenation of catechol.¹² Unsymmetrical alkenes are also

⁷ (a) D. Miljkovic, J. Petrovic, M. Stajic, and M. Miljkovic, *J. Org. Chem.*, 1973, **38**, 3585; (b) J. K. Paisley and L. Weiler, *Tetrahedron Letters*, 1972, 261.

⁸ (a) R. J. Anderson and C. A. Henrick, *J. Amer. Chem. Soc.*, 1975, **97**, 4327; (b) H. E. Baumgarten, D. F. McLean, and H. W. Taylor, *J. Org. Chem.*, 1971, **36**, 3668.

⁹ (a) B. M. Trost and M. Preckel, *J. Amer. Chem. Soc.*, 1973, **95**, 7862; (b) J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, 1974, **39**, 1814.

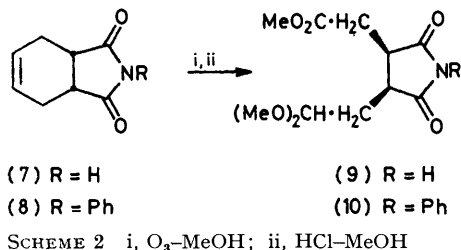
¹⁰ N. C. Deno, W. E. Billups, K. E. Kramer, and R. R. Lastomirsky, *J. Org. Chem.*, 1970, **35**, 3080; for a Lewis acid-catalysed tertiary-hydroperoxide cleavage, see: A. Afonso, *Canad. J. Chem.*, 1970, **48**, 691.

¹¹ A. Nishinaga, T. Tojo, and T. Matsuura, *J.C.S. Chem. Comm.*, 1974, 896.

¹² J. Tsuji and H. Takayanagi, *J. Amer. Chem. Soc.*, 1974, **96**, 7349; also see J. Tsuji and H. Takayanagi, *Tetrahedron Letters*, 1976, 1365.

known to give intermediates which have no plane of symmetry.^{13,14}

The synthetic advantage of a high-yield one-step conversion of a symmetric cycloalkene into a product with oxygenated carbons of differing oxidation states has led us to explore whether the reactions in Scheme 1 are of a more general nature. With this in mind, we have achieved unsymmetrical oxidations, in moderate yield, of *cis*-tetrahydrophthalimide (*cis*-cyclohex-4-ene-1,2-dicarboximide) (7) and its *N*-phenyl derivative (8).



RESULTS

Tetrahydrophthalimides.—The *cis*-tetrahydrophthalimide (7) was ozonolysed at -30°C in anhydrous methanol and gave after preparative liquid chromatography on Florisil, crude *cis*-3-(2,2-dimethoxyethyl)-4-methoxycarbonylmethylpyrrole-2,5(3*H*,4*H*)-dione (9). The structural assignment was confirmed by the results of elemental analysis, and natural abundance ¹³C n.m.r., ¹H n.m.r., i.r., electron impact, and chemical ionization mass spectroscopy.

The i.r. spectrum of (9) shows imide carbonyl (1715 cm⁻¹) and methyl ester carbonyl absorption (1745 cm⁻¹). The isobutane chemical ionization mass spectral fragmentations confirm the presence of methoxy-groups with $[M + H - \text{CH}_3\text{OH}]^+$ at m/e 228 and $(M + H - 2\text{CH}_3\text{OH})^+$ at m/e 196 whilst the 25.16 MHz ¹³C n.m.r. spectrum demonstrates the absence of a plane of symmetry in the molecule. The imide carbonyl carbons are magnetically nonequivalent and appear at 180.0 and 179.3 p.p.m. from internal SiMe₄. The ester carbonyl carbon occurs at 172.2 p.p.m. All three peaks remain as singlets in the single frequency off-resonance decoupled spectrum.

Similarly, ozonolysis of *cis*-*N*-phenyltetrahydrophthalimide (8) afforded the corresponding phenyl compound (10) the spectral data for which were consistent with the assigned structure (see Experimental section).

It is noteworthy that the two acetal methoxy-groups in (9) and (10) are diastereotopic since they have the same constitution, reside in diastereomeric environments, and cannot be interchanged by any symmetry operation; ¹⁵⁻¹⁸ this effect is manifested both in their ¹H and ¹³C n.m.r.

¹³ R. D. Clark and C. H. Heathcock, *Tetrahedron Letters*, 1974, 2027.

¹⁴ A. Greene and P. Crabbe, *Tetrahedron Letters*, 1975, 2215.

¹⁵ A. H. Andrist and M. J. Kovelan, *Spectroscopy Letters*, 1975, 8, 719.

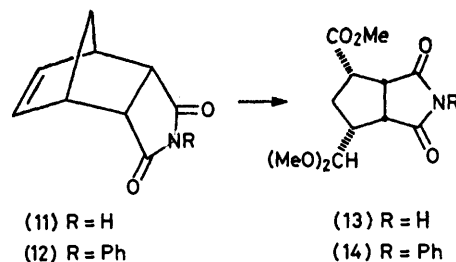
¹⁶ K. Mislow and M. Raban, *Topics in Stereochemistry*, 1967, 1, 1.

¹⁷ M. van Gorkom and G. E. Hall, *Quart. Rev.*, 1968, 22, 14.

spectra. Both show nonequivalent methoxy-protons (by 0.03 p.p.m.) and nonequivalent methoxy-carbons (by 0.2 and 0.3 p.p.m., respectively).¹⁵

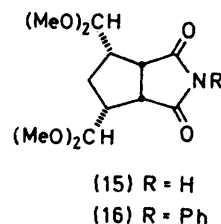
The chemical shift of the acetal methoxy-carbons in (9) and (10) are all within 2 p.p.m. of the reported chemical shifts for the methoxy-carbons of methyl α -D-glucopyranoside and methyl α -D-xylopyranoside.^{19,20} ¹³C-¹H Coupling constants, obtained from the gyro-gated spectrum, for the acetal methoxy-carbons of (9) are within 5 Hz of, while those for (10) are identical to, the $J(^{13}\text{C}-^1\text{H})$ value found in dimethyl ether.^{19,20}

Bridged Tetrahydrophthalimides.—In exploring the



generality of this unsymmetrical alkene oxidation, we prepared the methylene-bridged analogues (11) and (12) through Diels-Alder addition of the appropriate maleimide to cyclopentadiene and subjected each one to the specific oxidation conditions. The anticipated products were the unsymmetrically oxidized imides (13) and (14).

The ozonolysis of (11) in methanol at -30°C required 4 h. A white solid was isolated from the concentrated reaction mixture after it had been heated under reflux for 24 h in acidified methanol. Repeated recrystallization from acetone afforded analytically pure material, whose structure was readily assigned as that of (15) on the basis of its elemental analysis, and its ¹³C and ¹H n.m.r., i.r., and isobutane chemical ionization mass spectra. No



evidence was obtained for the presence of (13) in the reaction mixture.

Similarly the ozonolysis of (12) in methanol at -30°C for 3 h gave a reaction mixture which after being heated briefly under reflux in acidified methanol or treated with dimethyl sulphide gave (16). Again no evidence for the expected unsymmetrical product (14) was obtained.

¹⁸ W. B. Jennings, *Chem. Rev.*, 1975, 75, 307.

¹⁹ G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley-Interscience, New York, 1972.

²⁰ J. B. Stothers, 'Carbon-13 N.m.r. Spectroscopy,' Academic Press, New York, 1972.

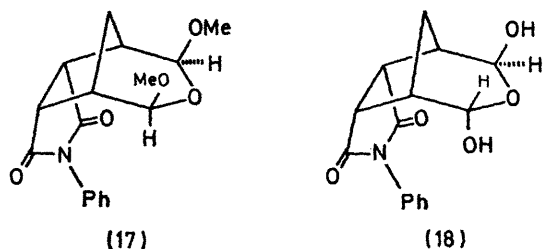
²¹ A. H. Andrist and M. J. Kovelan, *Spectroscopy Letters*, 1977, 10, 127.

The i.r. spectra of (15) and (16) revealed only one absorption band in the carbonyl region for the imide group. The isobutane chemical ionization mass spectra of each revealed the presence of methoxy-groups with significant $[M + H - CH_3OH]^+$ fragmentation ions.

The fact that (15) and (16) contain molecular planes of symmetry is confirmed by their ^{13}C n.m.r. spectra since each contains only one carbonyl carbon. Moreover, the methoxy-carbons appear within 2 p.p.m. of the chemical shifts for the methoxy-carbons of the methyl glycosides, and the ^{13}C - 1H coupling constants from the gyro-gated spectra are identical to the $J(^{13}C-^1H)$ for dimethyl ether.^{19,20}

Since C-6 and C-8 are chiral centres in (15) and (16) while C-9 and C-10 are prochiral, each set of geminal methoxy groups are diastereotopic.¹⁵⁻¹⁸ For (9) and (10), the chiral centres are four covalent bonds removed from the diastereotopic carbons while they are only three bonds removed in (15) and (16). The logical expectation is for enhanced magnetic nonequivalence in the latter two cases. The geminal methoxy-protons in (15) and (16) are magnetically nonequivalent by 0.10 and 0.09 p.p.m. in the 1H n.m.r. spectrum while the geminal methoxy-carbons are nonequivalent by 1.1 and 1.2 p.p.m., respectively, in the ^{13}C n.m.r. spectrum.¹⁵

When heated in aqueous acidic methanol the imide (16) produced two new compounds: a soluble compound (17)



which crystallized as the solution cooled, and an insoluble compound (18). These were identified on the basis of their respective elemental analyses and isobutane chemical ionization mass spectra.*

The i.r. spectrum of (18) confirms the presence of the hydroxy-group while the isobutane chemical ionization mass spectra reveal prominent fragmentation ions consistent with $[M + H - CH_3OH]^+$ for (17) and $[M + H - H_2O]^+$ for (18). The presence of a plane of symmetry in (17) and the absence thereof in (18) are conclusively demonstrated in their ^{13}C n.m.r. spectra. The imide (17) exhibits one carbonyl carbon while the imide (18) shows two. The methoxy-carbons of (17) are magnetically equivalent and possess the same $J(^{13}C-^1H)$ as dimethyl

* The dialdehyde obtained from the ozonolysis of acenaphthylene leads to an analogous cyclic hemiacetal.²²

† The expanded Criegee mechanism, or the Bauld-Bailey *syn-anti* zwitterion mechanism covers the stereoselectivity of ozonolysis reactions.²⁵

²² J. K. Stille and R. T. Foster, *J. Org. Chem.*, 1963, **28**, 2703.

²³ P. S. Bailey, *Chem. Rev.*, 1958, **58**, 986.

²⁴ R. Criegee, *Angew. Chem. Internat. Edn.*, 1975, **14**, 745.

²⁵ N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *J. Amer. Chem. Soc.*, 1968, **90**, 1822.

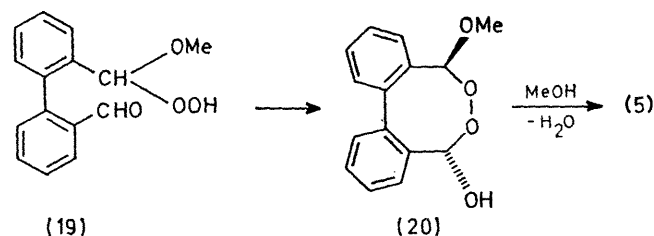
ether.^{19,20} The *cis-exo*-configuration for the methoxy-substituents in (17) is distinguished from the *cis-endo*-configuration on the basis of the ^{13}C n.m.r. chemical shifts. It is well known that sterically compressed groups experience downfield 1H n.m.r. chemical shifts and *upfield* ^{13}C n.m.r. shifts relative to unstrained models.^{19,20} Using the imides (9), (10), (15), and (16) as models, the methoxy-carbons all appear within the chemical-shift range of 54.9 ± 1.0 p.p.m. The methoxy-carbons for the imide (17) are 0.3 p.p.m. outside this range, but on the *downfield* side suggesting even less steric compression within (17) than within the models.

While the imide (18) contains no methoxy-carbons, the chemical shifts of the methine carbons which are bonded to two oxygens can be examined. The ^{13}C n.m.r. chemical shift data clearly require that (18) contain one sterically compressed and one unperturbed methine carbon bonded to two oxygens, while (17) must contain one methine carbon bonded to two oxygens which experiences steric compression intermediate between the two in (18).

DISCUSSION

The successful unsymmetrical oxidation of the tetrahydrophthalimides (7) and (8) as well as the symmetric cleavage of the methylene-bridged analogues (11) and (12), by the following reasoning, appear consistent with the Criegee ozonolysis mechanism.^{23-26,†}

First, it is known^{3,4} that ozonolysis of phenanthrene in methanol produces the peracetal (5) from the addition of methanol to the corresponding, and isolable, hemiperacetal (20).³ The latter arises from the intramolecular addition of hydroperoxy and carbonyl groups in the initial adduct (19). Support for this last step is derived from two observations: (1) methoxyhydroperoxides can be isolated after ozonization of acyclic alkenes in methanol,^{23,26-28} and (2) hydroperoxides readily add to



aldehydes.^{27,29} Thermal or catalytically-induced methanol fragmentation from (5) yields the product of unsymmetrical oxidative cleavage, the acid (6), by way of the corresponding methyl ester. Secondly, it is known²⁶ that ozonolysis of cyclohexene in methanol leads to mixtures of polymeric peroxides. Presumably the initially formed adduct is conformationally mobile enough to effect either

²⁶ P. S. Bailey, *J. Org. Chem.*, 1957, **22**, 1548 and references cited therein.

²⁷ J. G. Wallace, 'Hydrogen Peroxide in Organic Chemistry,' E. I. duPont De Nemours & Co., Wilmington, Delaware, 1960.

²⁸ A. H. Andrist and M. J. Kovelan, *Spectroscopy Letters*, 1975, **8**, 547 and references cited therein.

²⁹ M. G. Sturrock, E. L. Cline, and K. R. Robinson, *J. Org. Chem.*, 1963, **28**, 2340.

intra- or inter-molecular addition of hydroperoxy and carbonyl groups. Here, as in other ring-closure procedures, formation of the eight-membered ring in the hemiperacetal does not provide enough of a driving force for the intramolecular reaction to prevail over the intermolecular pathway.

The two extremes of alkene ozonolysis in methanol are, therefore, represented by phenanthrene and cyclohexene. The adduct derived from the first hydrocarbon gives exclusive *intramolecular* addition while the latter one exhibits exclusive *intermolecular* addition. Obviously the presence of conformationally restricting groups, such as two fused benzene rings, favours intramolecular addition leading eventually to an unsymmetrically oxidized product. Our results with the imide (7) and its *N*-phenyl derivative (8) suggest that the pyrroledione ring group when *cis*-fused to cyclohexene at C-4 and C-5 similarly constrains the adduct to add preferentially in the intramolecular fashion.

Unlike cyclohexene, norbornylene undergoes ozonolysis in methanol to produce an adduct which apparently gives exclusive intramolecular carbonyl addition.³⁰ To test for the effect of reduced conformational mobility on the ozonolysis of tetrahydrophthalimides in methanol, two methylene-bridged analogues of (7) and (8) were prepared and subjected to ozonolysis. Similar to the norbornylene result,³⁰ only symmetric cleavage products (15) and (16) were isolated.

It is noteworthy that alkene ozonolysis reactions in participating solvents offer a diversity of experimental results. For example, Nebel³¹ has found that increased yields of aliphatic ketones may be obtained if the ozonolysis mixture is set aside overnight in the presence of water, while Subluskey³² found that an identical procedure leads to a decreased yield of aromatic aldehydes. The experimental findings reported here also offer some puzzling reactivity differences, in this case, between the bridged and unbridged systems. There are a number of mechanistic possibilities which may explain these results. (1) The bridged and unbridged systems may give totally different peroxidic ozonolysis products. It is possible, for example, that the methylene-bridged systems exclude the proton-active solvent well enough to favour intramolecular [3 + 2] addition of the carbonyl oxide to the carbonyl group rigidly secured in the favourable *cis*-orientation. This would lead to the usual ozonide, a 1,2,4-trioxolan.* (2) The acid-catalysed solvolysis of the initial peroxidic ozonolysis products may be quite sensitive to steric effects. Conceivably methanol may be expelled in one case while methyl hydroperoxide is eliminated in the other.

The final resolution of the mechanistic aspects of this reaction must await a complete characterization of the

initially formed peroxidic ozonolysis products within the two series.

Conclusions.—Ozonization of symmetric cycloalkenes in methanol generally produces a carbonyl oxide-methanol adduct, a methoxyhydroperoxide carbaldehyde. (1) In the absence of steric constraints, intermolecular addition of hydroperoxy and carbonyl groups occurs to yield polymeric peroxides. (2) In the presence of moderate steric constraints (*e.g.* two fused benzene rings or the pyrroledione group), intramolecular addition of hydroperoxy and carbonyl groups gives a monomeric hemiperacetal which undergoes fragmentation to an aldehyde methyl ester. The overall process is an *unsymmetrical* cycloalkene oxidative cleavage. (3) When steric constraints are more demanding (*e.g.* with a methylene-bridge or a methylene-bridge plus the pyrroledione group), intramolecular addition of hydroperoxy and carbonyl groups may occur, but the hemiperacetal must lose methylhydroperoxide (or its functional equivalent) to afford the dialdehyde tetramethylacetal, the product of a *symmetric* cycloalkene oxidative cleavage reaction.

EXPERIMENTAL

General.—The ozone source was a Welsbach T-408 Laboratory Ozonator using dry (in-stream CaSO₄ drying tube) oxygen to produce a 6% ozone concentration as measured by titration with a standardized potassium iodide solution.

¹H N.m.r. spectra were obtained on a Varian T-60 instrument. Chemical shifts reported are relative to internal SiMe₄. I.r. spectra were recorded on a Beckman IR-20 spectrophotometer. U.v. spectra were obtained on a Cary 15 u.v.-visible spectrophotometer. Mass spectra were secured on a Finnigan 1015D quadrupole spectrometer. High resolution liquid chromatographic analyses were performed on a 25-X 0.32-cm 5 μ LiChrosorb column using an Altex model 153 Analytical UV Detector operated at 254 nm. Preparative separations were achieved on the indicated columns with 254 nm peak detection from an Instrument Specialties Company Type I Optical Unit.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy.—Natural abundance ¹³C n.m.r. spectra were secured on a Varian Associates Model XL-100 Magnetic Resonance Spectrometer in 12-mm tubes at 25.16 MHz employing a Varian 620L computer to accumulate free induction decay data and to perform the necessary Fourier transformation. A pulse width of 5–30 μ s (usually 15 μ s) was employed where 43 μ s is typically a 90° pulse. With a true spectral width of 5 120 Hz, an acquisition time of 0.8 s was used for the required data length of 8 192. Pulse delays were set at 0.5–2.0 s (typically 1.2 s). Approximately 1 000–3 000 transients were collected for each spectrum. An internal ²H lock was employed as CDCl₃, (CD₃)₂CO, or (CD₃)₂SO. Fourier transformation of the accumulated free induction decay transients gave a frequency spectrum, which directly provided the chemical shift of each carbon relative to internal SiMe₄. A time constant of 0.2–0.8 s, corresponding

³¹ C. Nebel, *Chem. Comm.*, 1968, 101.

³² L. A. Subluskey, G. C. Harris, A. Maggiolo, and A. L. Tumolo, *Adv. in Chem. Ser.*, 1959, 21, 149; also see M. G. Sturrock, B. J. Crary, and V. A. Wing, *Canad. J. Chem.*, 1971, 49, 3047.

* Ozonolysis of one tetrasubstituted and two pentasubstituted cyclobutenes in a methanol-methylene chloride solvent has been observed to yield the usual ozonides: H. G. Reinhardt, G. A. Doorakian, and H. H. Freedman, *J. Amer. Chem. Soc.*, 1968, 90, 5934.

³⁰ R. H. Perry, jun., *J. Org. Chem.*, 1959, 24, 829.

with the decay time constant of the observed free induction decay, was used in the exponential weighting function to achieve sensitivity enhancement. To determine the number of directly bonded protons for each observed carbon resonance, single frequency off-resonance decoupled spectra were obtained with narrow-band irradiation at 46 401 Hz (*ca.* 1 000 Hz above the normal proton region). While the off-resonance decoupling technique accurately reveals multiplicities, the true coupling constants must be obtained from an undecoupled spectrum. For this purpose, the gyro-gate method of spin decoupling was employed. This approach provides an undecoupled spectrum with most of the nuclear Overhauser enhancement in signal sensitivity retained, since the 3 KHz bandwidth of heteronuclear noise decoupling is turned off during the acquisition time.

cis-3-(2,2-Dimethoxyethyl)-4-methoxycarbonylmethyl-pyrrole-2,5-(3H,4H)-dione (9).—To a 500-ml 3-necked flask fitted with a sintered glass gas dispersion inlet tube and an outlet leading first to a dry trap and then to a trap containing aqueous potassium iodide was added *cis*- Δ^4 -tetrahydrophthalimide (7) (5.0 g, 33 mmol) (Aldrich) in freshly distilled anhydrous methanol (200 ml). The mixture was cooled to -30°C in a solid CO_2 -acetone bath and ozone was passed through it at a flow rate of 0.8 s.l.p.m. (standard 1 min^{-1}) for 2 h. The solution was then acidified with concentrated HCl (2 drops) and then heated at reflux for 2 h. After concentration to a syrup on a Büchi rotary evaporator, the reaction mixture was adsorbed onto 60–100 mesh Florisil and placed on a 78×4 cm column of 60–100 mesh Florisil. Elution with diethyl ether followed by an increasing gradient of 2–16% (v/v) of methanol in diethyl ether gave one major fraction (8.50 g, 95%). Repeated recrystallization of this material from anhydrous tetrahydrofuran gave a white crystalline solid (1.78 g): m.p. $117\text{--}118^\circ\text{C}$; i.r. (CHCl_3) $\bar{\nu}_{\text{NH}}$ at 3 240, $\bar{\nu}_{\text{CH}}$ at 3 010—2 850, $\bar{\nu}_{\text{CO}}$ at 1 745 and 1 715, and $\bar{\nu}_{\text{COC}}$ at 1 125 cm^{-1} ; m.s. (electron impact) $[M - \text{CH}_3]^+$ at *m/e* 244 and $[M - \text{OCH}_3]^+$ at 228; m.s. (isobutane chemical ionization) $[M + \text{H} - \text{CH}_3\text{OH}]^+$ at *m/e* 228 and $[M + \text{H} - 2\text{CH}_3\text{OH}]^+$ at 196; ^1H n.m.r. (CDCl_3 , 60 MHz) δ (SiMe_4) 8.60br (1 H, s, imide), 4.50 (1 H, dd, $J_1 = 6\text{ Hz}$, $J_2 = 4\text{ Hz}$, methine), 3.62 (3 H, s, ester methoxy), 3.30 (3 H, s, methoxy), 3.27 (3 H, s, methoxy), 3.25 (2 H, methine), 2.80 (2 H d, $J = 5\text{ Hz}$, methylene), and 1.90 (2 H, m, methylene); ^{13}C n.m.r. (CDCl_3 , 25.16 MHz) δ (SiMe_4) 180.0 (s, imide carbonyl), 179.3 (s, imide carbonyl), 172.2 (s, ester carbonyl), 103.4 (d, dimethoxymethine, $J = 165\text{ Hz}$), 54.1 (q, methoxy, $J = 145\text{ Hz}$), 53.9 (q, methoxy, $J = 145\text{ Hz}$), 52.1 (q, ester methoxy, $J = 150\text{ Hz}$), 41.2 (d, ring methine, $J = 135\text{ Hz}$), 39.9 (d, ring methine, $J = 135\text{ Hz}$), 31.2 (t, ester methylene, $J = 130\text{ Hz}$), and 29.8 (t, methylene, $J = 130\text{ Hz}$) (Found: C, 51.0; H, 6.65; N, 5.3. Calc. for $\text{C}_{11}\text{H}_{17}\text{NO}_6$: C, 50.97; H, 6.56; N, 5.41%).

Ozonolysis of *cis*-tetrahydrophthalimide (7) in methanol, as described above, and subsequent treatment with 10% BF_3 in methanol gave a clear viscous residue upon solvent evaporation which was shown to be a mixture of three additional products besides (9) by t.l.c. on Bakerflex Silica Gel 1B-F 20×5 cm plates with 4% methanol in diethyl ether as eluant. Treatment of the initial ozonolysis mixture with concentrated HCl or glacial acetic acid produced similar results.

Ozonolysis of (7) (7.62 g, 50 mmol) in methanol as described above followed by concentration to 100 ml, addition of 97% formic acid (17.5 ml) and 30% hydrogen peroxide (8.0 ml), heating at reflux for 2 h, cooling, filtering, and washing with

diethyl ether gave a white crystalline solid (1.30 g, 12%) identified as *meso*-butane-1,2,3,4-tetracarboxylic acid, m.p. $192\text{--}193^\circ\text{C}$; ^1H n.m.r. [$(\text{CD}_3)_2\text{CO}$, 60 MHz] δ (SiMe_4) 6.18br (4 H, s, acid), 3.33 (2 H, m, methine), and 2.68 (4 H, m, methylene).

cis-3-(2,2-Dimethoxyethyl)-4-methoxycarbonylmethyl-1-phenylpyrrole-2,5-(3H,4H)-dione (10).—To a 500-ml 3-necked flask was added 2.50 g (11 mmol) of *cis*-*N*-phenyl-tetrahydrophthalimide (8), m.p. $116\text{--}118^\circ\text{C}$ [from a Diels–Alder reaction of *N*-phenylmaleimide (Aldrich) and butadiene (Matheson) carried out in 89% yield in a pressure bomb at 80°C for 5 days] in freshly distilled anhydrous methanol (200 ml). The flask was fitted with a sintered glass gas dispersion inlet tube and an outlet leading to a dry trap and to a potassium iodide trap. The mixture was cooled to -30°C in a solid CO_2 -acetone bath and ozone was passed through the solution at 0.8 s.l.p.m. for 2 h. After addition of conc. HCl (2 drops), the ozonolysis mixture was heated at reflux for 24 h, concentrated on a Büchi rotary evaporator, adsorbed onto 60–100 mesh Florisil, and placed on a 78×4 cm column filled with 60–100 mesh Florisil. Elution with diethyl ether followed by an increasing gradient of 2–25% methanol in diethyl ether gave five fractions, the initial and major one being identified as (10) (1.47 g, 40%): i.r. (CHCl_3) $\bar{\nu}_{\text{CH}}$ at 3 015—2 880, $\bar{\nu}_{\text{CO}}$ at 1 745 and 1 715, $\bar{\nu}_{\text{C=C}}$ at 1 603, and $\bar{\nu}_{\text{COC}}$ at 1 130; m.s. (electron impact) $[M]^+$ at *m/e* 335 and $[M - \text{OCH}_3]^+$ at 304; m.s. (methane as well as isobutane chemical ionization) $[M + \text{H}]^+$ at *m/e* 336, $[M + \text{H} - \text{CH}_3\text{OH}]^+$ at 304, and $[M + \text{H} - 2\text{CH}_3\text{OH}]^+$ at 272; ^1H n.m.r. (CDCl_3 , 60 MHz) δ (SiMe_4) 7.30 (5 H, m, aromatic), 4.57 (1 H, dd, $J_1 = 6\text{ Hz}$, $J_2 = 4\text{ Hz}$), 3.62 (3 H, s, ester methoxy), 3.35 (3 H, s, methoxy), 3.32 (3 H, s, methoxy), 3.27 (2 H, m, methine), 2.90 (2 H, d, $J = 4\text{ Hz}$, methylene), and 2.00 (2 H, m, methylene); ^{13}C n.m.r. (CDCl_3 , 25.16 MHz) δ (SiMe_4) 178.4 (s, imide carbonyl), 177.8 (s, imide carbonyl), 172.2 (s, ester carbonyl), 132.4 (s, quaternary aromatic), 129.0 (d, $J = 160\text{ Hz}$, aromatic), 128.4 (d, $J = 165\text{ Hz}$, aromatic), 126.6 (d, $J = 165\text{ Hz}$, aromatic), 103.6 (d, $J = 165\text{ Hz}$, dimethoxymethine), 54.4 (q, $J = 140\text{ Hz}$, methoxy), 54.1 (q, $J = 140\text{ Hz}$, methoxy), 52.1 (q, $J = 145\text{ Hz}$, ester methoxy), 39.9 (d, $J = 135\text{ Hz}$, ring methine), 38.6 (d, $J = 135\text{ Hz}$, ring methine), 31.4 (t, $J = 130\text{ Hz}$, ester methylene), and 29.5 (t, $J = 130\text{ Hz}$, methylene) (Found: C, 60.7; H, 6.15; N, 4.3. Calc. for $\text{C}_{17}\text{H}_{21}\text{NO}_6$: C, 60.90; H, 6.27; N, 4.18%).

endo,endo,cis-6,8-Bis(dimethoxymethyl)-3-azabicyclo-[3.3.0]octane-2,4-dione (15).—To a 500-ml 3-necked round-bottomed flask with a sintered glass gas dispersion tube and outlet tube leading to a dry trap and a potassium iodide trap was added 8.92 g (55 mmol) of *endo*-4-azatricyclo-[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (11), m.p. $186\text{--}188^\circ\text{C}$ [from a Diels–Alder reaction of maleimide (Eastman) and cyclopentadiene carried out in 95% yield at 25°C], in 400 ml of freshly distilled anhydrous methanol. After the mixture had been cooled to -30°C in a solid CO_2 -acetone bath, ozone was passed through the solution at 0.8 s.l.p.m. for 4 h. Conc. HCl (4 drops) was added to the reaction mixture which was then heated at reflux for 24 h. The solution was then concentrated by distillation and the residual syrup dissolved in dry acetone (10 ml), cooled, and filtered to give a white crystalline solid (1.49 g, 18%) which was homogenous by t.l.c. (Bakerflex silica gel 1B-F 20×2.5 cm plates with 4% methanol in diethyl ether as eluant). The product was clearly identified as having structure (15), m.p. $138\text{--}140^\circ\text{C}$; i.r. (CHCl_3) $\bar{\nu}_{\text{NH}}$ at 3 420, $\bar{\nu}_{\text{CH}}$ at 3 020—2 850, $\bar{\nu}_{\text{CO}}$ at 1 720, and

$\bar{\nu}_{\text{COC}}$ at 1 065; m.s. (isobutane chemical ionization) $[M + H - \text{CH}_3\text{OH}]^+$ at m/e 256; ^1H n.m.r. (CDCl_3 , 60 MHz) δ (SiMe_4) 8.92br (1 H, s, imide), 4.50 (d, $J = 6$ Hz, 2 H methine), 3.40 (6 H, s, methoxy), 3.30 (6 H, s, methoxy), 3.37 (2 H, m, methine), 2.35 (2 H, m, methine), and 1.72 (2 H, m, methylene); ^{13}C n.m.r. (CDCl_3 , 25.16 MHz) δ (SiMe_4) 178.3 (s, imide carbonyl), 104.6 (d, $J = 160$ Hz, dimethoxymethine), 55.2 (q, $J = 140$ Hz, methoxy), 54.1 (q, $J = 140$ Hz methoxy), 47.7 (d, $J = 135$ Hz, bridgehead methine), 45.7 (d, $J = 135$ Hz, ring methine), and 27.1 (t, $J = 130$ Hz, methylene) (Found: C, 54.1; H, 7.4; N, 4.9. Calc. for $\text{C}_{13}\text{H}_{21}\text{NO}_6$: C, 54.35; H, 7.37; N, 4.88%).

endo,endo,cis-6,8-Bis(dimethoxymethyl)-3-phenyl-3-azabicyclo[3.3.0]octane-2,4-dione (16).—In a 250-ml 3-necked flask was placed at 10.30 g (28.4 mmol) of *endo-4-phenyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione* (12), m.p. 142—145 °C [from a Diels–Alder reaction of *N*-phenylmaleimide (Aldrich) and cyclopentadiene carried out in 97% yield at 25 °C], in freshly distilled anhydrous methanol (100 ml). The flask was fitted with a sintered glass gas dispersion tube as well as an outlet tube leading to a dry trap and to a potassium iodide trap. The mixture was cooled to –30 °C in a solid CO_2 –acetone bath, ozone was passed through the solution at 1.0 s.l.p.m. for 3 h. To the cold mixture was added dimethyl sulphide (10 ml). After being stirred 1 h at –10 °C, 1 h at 0 °C, and overnight at room temperature, the reaction mixture was extracted with H_2O (250 ml). A sticky white precipitate which separated from the extract was dissolved in diethyl ether (250 ml), washed with H_2O (3 \times 50 ml), dried (MgSO_4), and concentrated to give a yellow residue (8.40 g). Upon cooling, both the residue and the combined water washes produced a crystalline product which was recrystallized from methanol (5.04 g, 49%) and then readily assigned structure (16), m.p. 105.5–107 °C; i.r. (CHCl_3) $\bar{\nu}_{\text{OH}}$ at 3 010–2 845, $\bar{\nu}_{\text{C=O}}$ at 1 710, $\bar{\nu}_{\text{C=CH}}$ at 1 600, $\bar{\nu}_{\text{COC}}$ at 1 187, and $\bar{\nu}_{\text{CO}}$ at 1 070 cm^{-1} ; u.v. (CH_3OH) shoulder absorption at 260 nm (ϵ 418); m.s. (isobutane chemical ionization) $[M + H - \text{CH}_3\text{OH}]^+$ at m/e 332; ^1H n.m.r. [$(\text{CD}_3)_2\text{CO}$, 60 MHz] δ (SiMe_4) 7.25 (5 H, m, aromatic), 4.59 (2 H, d, $J = 6$ Hz, dimethoxymethine), 3.32 (6 H, s, methoxy), 3.3 (2 H, m, bridgehead methine), 3.23 (6 H, s, methoxy), 2.6 (2 H, m, ring methine), and 1.7 (2 H, m, methylene); ^{13}C n.m.r. (CDCl_3 , 25.16 MHz) δ (SiMe_4) 176.4 (s, imide carbonyl), 132.3 (s, quaternary aromatic), 129.1 (d, $J = 165$ Hz, aromatic), 128.6 (d, $J = 150$ Hz, aromatic), 126.8 (d, $J = 165$ Hz, aromatic), 104.6 (d, $J = 160$ Hz, dimethoxymethines), 55.9 (q, $J = 140$ Hz, methoxy), 54.7 (q, $J = 140$ Hz, methoxy), 46.4 (d, $J = 130$ Hz, bridgehead methine), 46.1 (d, $J = 130$ Hz, ring methine), and 26.4 (t, $J = 135$ Hz, methylene) (Found: C, 62.9; H, 7.0; N, 4.0. Calc. for $\text{C}_{19}\text{H}_{15}\text{NO}_6$: C, 62.80; H, 6.93; N, 3.85%).

8,10-cis-exo-Dimethoxy-cis-endo-4-phenyl-9-oxa-4-azatricyclo[5.3.1.0^{2,6}]undecane-3,5-dione (17).—To a 25-ml Erlmeyer flask containing methanol (3.0 ml) and 3*N*-HCl (10 drops) was added (16) (1.00 g, 2.75 mmol). The mixture was heated under reflux for several minutes and then H_2O (8 ml) was added to it; upon cooling, colourless plates were formed. These were filtered off and dried (0.40 g, 46%); the

product was assigned structure (17), m.p. 180–184 °C; i.r. (CHCl_3) $\bar{\nu}_{\text{OH}}$ at 3 020–2 840 cm^{-1} , $\bar{\nu}_{\text{C=O}}$ at 1 710, $\bar{\nu}_{\text{C=C}}$ at 1 600, and $\bar{\nu}_{\text{COC}}$ at 1 110; m.s. (isobutane chemical ionization) $[M + H]^+$ at m/e 318 and $[M + H - \text{CH}_3\text{OH}]^+$ at 286; ^1H n.m.r. (CDCl_3 , 60 MHz) δ (SiMe_4) 7.30 (5 H, m, aromatic) 4.60 (2 H, m, methine), 3.43 (6 H, s, methoxy), 2.77 (4 H, m, methine), and 1.60 (2 H, m, methylene); ^{13}C n.m.r. (CDCl_3 , 25.16 MHz) δ (SiMe_4) 176.3 (s, imide carbonyl), 129.2 (d, $J = 165$ Hz, aromatic), 128.8 (d, $J = 160$ Hz, aromatic), 127.0 (d, $J = 160$ Hz, aromatic), 123.5 (s, quaternary aromatic), 99.8 (d, $J = 170$ Hz, dimethoxymethine), 56.2 (q, $J = 140$ Hz, methoxy), 46.8 (d, $J = 140$ Hz, methine), 40.8 (d, $J = 140$ Hz, methine), and 27.9 (t, $J = 135$ Hz, methylene) (Found: C, 64.15; H, 5.8; N, 4.35. Calc. for $\text{C}_{17}\text{H}_{19}\text{NO}_5$: C, 64.34; H, 6.03; N, 4.41%).

trans-8,10-Dihydroxy-cis-endo-4-phenyl-9-oxa-4-azatricyclo[5.3.1.0^{2,6}]undecane-3,5-dione (18). The ozonolysis of (12) (10.78 g, 45 mmol) in methanol (150 ml) was conducted in a 500-ml 3-necked flask fitted with a sintered glass gas dispersion tube and exit tube leading to a dry trap and a potassium iodide trap. With cooling to –30 °C in a solid CO_2 –acetone bath, ozone was passed through the methanol solution at 0.8 s.l.p.m. for 3 h. To the cold solution was added dimethyl sulphide (10 ml). After the reaction mixture had been warmed to room temperature, it was reduced in volume to 50 ml on a Büchi rotary evaporator, acidified with 3*M*-HCl (1.0 ml), heated briefly in a hot water-bath, diluted with hot H_2O (150 ml), and allowed to cool slowly. After 3 days, the crystalline product precipitated from the reaction mixture was filtered off and dried (1.54 g, 12%). Its structure was assigned as (18), m.p. 204–206 °C; i.r. (CH_3CN) $\bar{\nu}_{\text{OH}}$ at 3 635–3 540 and $\bar{\nu}_{\text{C=O}}$ at 1 810 and 1 735 cm^{-1} ; m.s. (isobutane chemical ionization) $[M + H - \text{H}_2\text{O}]^+$ at m/e 272; ^1H n.m.r. (CDCl_3 , 60 MHz) δ (SiMe_4) 7.30 (5 H, m, aromatic), 5.77 (1 H, d, $J = 5$ Hz, hemiacetal methine), 5.52 (1 H, d, $J = 5$ Hz, hemiacetal methine), 3.2 (6 H, m, methine plus hydroxyl), and 1.90 (2 H, m, methylene); ^{13}C n.m.r. [$(\text{CD}_3)_2\text{SO}$, 25.16 MHz] δ (SiMe_4) 174.4 (s, imide carbonyl), 171.6 (s, imide carbonyl), 137.3 (s, quaternary aromatic), 128.7 (d, $J = 165$ Hz, aromatic), 125.7 (d, $J = 160$ Hz, aromatic), 122.7 (d, $J = 160$ Hz, aromatic), 102.2 (d, $J = 185$ Hz, hemiacetal methine), 89.3 (d, $J = 180$ Hz, hemiacetal methine), 48.0 (d, $J = 140$ Hz, methine), 45.3 (d, $J = 140$ Hz, methine), 42.8 (d, $J = 135$ Hz, methine), 39.9 (d, $J = 135$ Hz, methine), and 25.2 (t, $J = 135$ Hz, methylene) (Found: C, 66.7; H, 4.9; N, 5.2. Calc. for $\text{C}_{15}\text{H}_{15}\text{NO}_5$: C, 62.28; H, 5.23; N, 4.84. Calc. for $\text{C}_{15}\text{H}_{15}\text{NO}_5 - \text{H}_2\text{O}$: C, 66.41, H, 4.83; N, 5.16%).

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