Peracid Oxidation of Methylenecyclopropanes[1a]

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Several substituted methylenecyclopropanes were reacted with peracid. In general, this resulted in a direct conversion to cyclobutanones, although in the case of **18** an intermediate oxaspiropentane was characterized. Methylenecyclopropane **26** gave lactone **27** rather than a cyclobutanone product. The mechanisms of these conversions are discussed, with an emphasis on their stereochemical features.

Subsequent to our initial disclosure of the synthesis of an oxaspiropentane derivative,[2] several laboratories have described the generation of this highly strained heterocyclic system, either by the epoxidation of methylenecyclopropanes[3] or by the condensation of carbonyl compounds with cyclopropyl sulfur ylides.[4] The synthetic potential of oxaspiropentanes as intermediates has also been explored in some detail, most notably by Trost and co-workers.[5] The most commonly observed reaction of this system is a facile, acid-catalyzed transformation into an isomeric cyclobutanone.[3,4] In the present report we describe further examples of the peracid oxidation of methylenecyclopropane derivatives which reveal some unexpected complications in the oxaspiropentane–cyclobutanone rearrangement.

The oxidation of benzylidenecyclopropane (**1**) with an excess of *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 solution at 0 °C gave a 95% yield of 2-phenylcyclobutanone (**2**) (Scheme I). The presumed oxaspiropentane intermediate **3** was not observed in this reaction, although it has been prepared by the sulfur ylide method and shown to isomerize to **2**.[4] In a similar fashion diphenylmethylenecyclopropane (**4**) was converted into 2,2-diphenylcyclobutanone (**5**) (Scheme I).

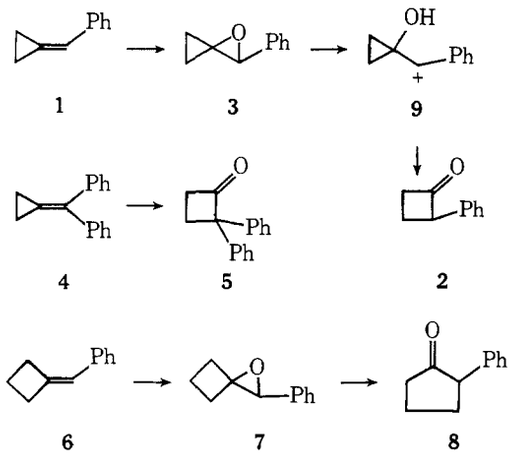
For comparison purposes, benzylidenecyclobutane (**6**) was subjected to the reaction conditions used for the oxidation of **1** (Scheme I). In this case, the spiroepoxide **7** was easily obtained. The analogous rearrangement of **7** to 2-phenylcyclopentanone (**8**) could be accomplished in high yield, but more rigorous conditions were required. For example, **8** was formed by heating a benzene solution of **7** containing *p*-toluenesulfonic acid to reflux for several hours, or by simply heating a benzene solution of **7** in a sealed tube to 150 °C.

Thus, it appears that the cyclopropyl moiety of **3** seems to greatly facilitate its rearrangement relative to that of **7**. The phenyl substituent of **3** must also contribute to its lability, since the parent oxaspiropentane has been isolated from an epoxidation reaction conducted under similar conditions to those used for **1**.[3a,b] These features are explained by protonation of the intermediate oxaspiropentane followed by ring opening to give a cyclopropylcarbinyl cation (e.g., **9**), which subsequently undergoes pinacolic rearrangement[6] to generate a cyclobutanone.[3a] Stabilization of the intermediate cation by cyclopropyl and phenyl substituents should enhance its formation.

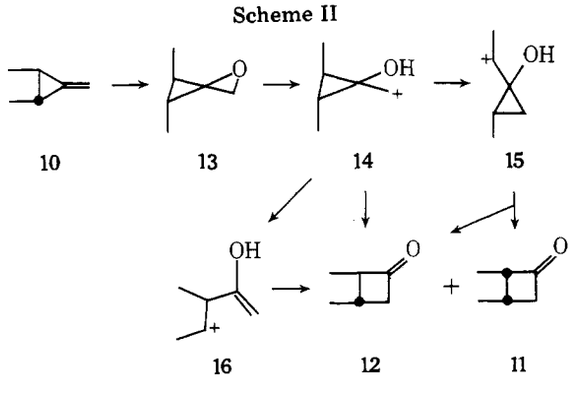
Further insight into the oxaspiropentane–cyclobutanone rearrangement is provided by the MCPBA oxidation of *trans*-2,3-dimethylmethylenecyclopropane (**10**). In this instance, a 40:60 ratio of *cis*- and *trans*-2,3-dimethylcyclobutanone (**11** and **12**, respectively) was obtained. This product ratio appears to be kinetically derived, since the two cyclobutanones did not interconvert under simulated reaction conditions. Thus, the migrating center has suffered stereochemical randomization in the transformation of oxaspiropentane **13** into product. This is not consistent with a simple alkyl migration mechanism, where retention of configuration is the rule for migrating groups.[6] However, a more elaborate form of the mechanism described above can satisfactorily account for the facts (see Scheme II). The key intermediate is again a cyclopropylcarbinyl cation. In this instance, the initially formed cation **14** (which would be expected to rearrange exclusively to the *trans*-cyclobutanone **12**) isomerizes to a secondary cyclopropylcarbinyl cation **15**. Rotation about the bond joining the cationic carbon to the cyclopropyl ring effectively randomizes the initial stereochemistry. Preferential migration of the methyl-substituted carbon of **14** now generates both cyclobutanone products.[3b] (The 2,4-dimethylcyclobutanones expected from migration of the primary cyclopropyl carbon of **15** were not observed). It is surprising that the interconversion of the cyclopropylcarbinyl cations is competitive with pinacolic ring expansion, which should be an energetically favorable process. An alternative mechanism to account for the stereochemical results involves fragmentation of **14** to the open-chain cation **16**, which then recloses efficiently to cyclobutanones **11** and **12**.

Additional complications arise with methylenecyclopropanes substituted on the ring with an ester group. Inter-

Scheme I



Scheme II



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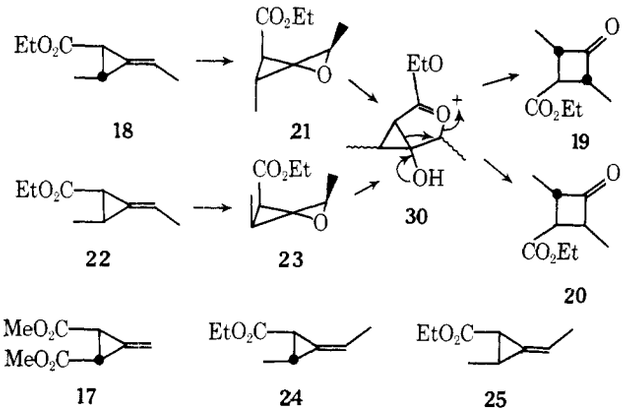
Scheme III

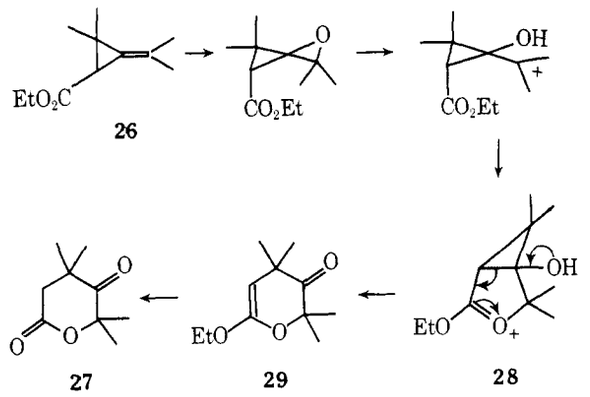


estingly, the dimethyl ester of Feist's acid (**17**; *trans*-2,3-dicarbomethoxymethylenecyclopropane) did not react with *p*-nitroperbenzoic acid (PNPBA).[3e] Apparently the neighboring ester groups greatly deactivate the double bond toward epoxidation.[7] Reaction of monoester **18** yielded a mixture of cyclobutanones **19** and **20** in a 28:72 ratio (Scheme III). These products are stable to the reaction conditions. In this case, careful workup of the reaction mixture prior to completion of the peracid oxidation revealed the formation of an intermediate. Thus, the NMR spectrum showed (among other signals) a sharp doublet at δ 1.43 (J = 5 Hz) and a quartet at δ 3.42 (J = 5 Hz). No cyclobutanone carbonyl was visible in the IR spectrum. Refluxing this material in benzene solution or simply passing it through a GLC column transformed it into a mixture of cyclobutanones **19** and **20.** This information is most readily interpreted in terms of the oxaspiropentane structure **21** for the labile intermediate. The clean NMR is consistent only with a stereoselective epoxidation. The indicated stereochemistry is assigned on the basis of peracid attack on **18** from the face of the molecule away from the carbethoxy group. This preference is expected by analogy with other rigid olefins possessing neighboring ester functions[7] and is consistent with the lack of reactivity of **17.**

Methylenecyclopropane **22** (a stereoisomer of **18**) was oxidized to essentially the same mixture of cyclobutanones **19** and **20** as obtained from **18.** The spiropentane intermediate was not pursued in this instance, but it surely possesses structure **23.** Finally, a mixture of **18, 22,** and small quantities of the other two stereoisomers **24** and **25** also gave the same mixture of cyclobutanones. The small amounts of these other compounds would not be expected to perturb product ratios appreciably, but the formation of positional isomers of **19** and **20** would have been observed. Thus, stereochemistry is lost in the rearrangement process just as it was with **10,** and common intermediates in the reactions of **21** and **23** appear likely. The most curious feature of these reactions is that the observed products can only be rationalized by preferential migration of the ester-bearing carbon to the electron-deficient center of a cyclopropylcarbinyl cation. This is not at all the expected substituent effect for such an electron-withdrawing group. (The fragmentation–cyclization mechanism mentioned above is even less appealing for similar reasons.)

A possible clue to this puzzle was provided by the peracid oxidation of methylenecyclopropane **26,** a reaction in which no cyclobutanone product was observed. Instead, a clean conversion to keto lactone **27** took place. This transformation can be understood in terms of the mechanism indicated in Scheme IV. The key feature of this explanation is intramolecular trapping of the cationic center by the neighboring ester function to give **28.** The indicated ring opening of **28** gives enol ether **29,** which must have been hydrolyzed to **27** under the reaction or workup conditions. Thus, the ester group plays an active role in this situation.

Scheme IV



A similar intermediate **30** can be proposed in Scheme III. In order to account for the loss of stereochemistry the interconversion of cyclopropylcarbinyl cations must be a competitive process as elaborated above. If, for stereoelectronic reasons, the cyclobutanes are formed directly from **30** with exclusive migration of the cyclopropyl bond that is coplanar with the bridging ester group, then migration of the carbon bearing this group follows as a natural consequence of the intervention of cation **30.** It is not at all clear why cyclobutanones are formed from **18** and **22,** whereas **26** leads to lactone **27,** although the degree of substitution at the original exocyclic olefinic carbon is probably the key difference.

Experimental Section

General. NMR spectra were recorded on a Varian HR-220 spectrometer. Infrared spectra were recorded on a Perkin-Elmer IR-7 prism spectrophotometer. Commercial *m*-chloroperbenzoic acid was recrystallized from CH_2Cl_2 and determined to be >99% peracid; *p*-nitroperbenzoic acid was used in commercial form (>97%). Anhydrous Na_2SO_4 was used as a drying agent.

Peracid Oxidation of Benzylidenecyclopropane (1).[8] A mixture 175 mg of **1** and 400 mg (1.75 equiv) of MCPBA in 5 mL of CH_2Cl_2 was stirred at 0 °C for 1 h. The solution was washed successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$ and dried. Removal of the solvent and GLC isolation gave 2-phenylcyclobutanone (**2**) (95%): IR 5.62, 6.72, 6.93, 8.56, 13.3, 14.3 μm; NMR δ 2.18 (m, 1), 2.48 (m, 1), 2.98 (m, 1), 3.11 (m, 1), 4.44 (t, 1, J = 5 Hz), 7.19 (m, 5). NMR and IR analysis of the crude product indicated only **2.**

Peracid Oxidation of Diphenylmethylenecyclopropane (4).[9] A mixture of 1.0 g of **4** and 1 g of PNPBA was stirred at 25 °C for 24 h. After addition of 20 mL of pentane and cooling to 0 °C the slurry was filtered. Removal of the solvent gave 0.96 g (88%) of 2,2-diphenylcyclobutanone (**5**) as a clear liquid: IR 5.61 μm; NMR δ 2.76 (t, 2, J = 8.5 Hz), 3.08 (t, 2, J = 8.5 Hz), 7–7.8 (m, 10). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 5.92. Found: C, 86.4; H, 5.9.

Peracid Oxidation of Benzylidenecyclobutane (6).[10] A mixture of 80 mg of **6** and 250 mg (2.5 equiv) of MCPBA in 5 mL of CH_2Cl_2 was stirred at 0 °C for 30 min, washed successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$, and dried. Removal of solvent gave 75 mg (85%) of 1-oxa-2-phenylspiro[2.3]hexane (**7**): IR 6.72, 6.85, 6.94, 7.08, 9.04, 10.3, 11.5, 13.2, 14.3 μm; NMR δ 1.61 (m, 1), 1.83 (m, 2), 2.34 (m, 2), 2.50 (m, 1), 3.65 (s, 1), 7.12 (m, 5). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.3; H, 7.6.

Pyrolysis of 7. A 15-mg sample of **7** in 10 mL of benzene was heated in a sealed tube at 150 °C for 24 h. Removal of solvent gave 14 mg (93%) of 2-phenylcyclopentanone (**8**): IR 5.75, 6.74, 6.27, 14.4 μm.[11]

Acid-Catalyzed Rearrangement of 7. A 10-mg sample of **7** in 10 mL of benzene was refluxed with 1 mg of *p*-toluenesulfonic acid for 24 h. The solution was washed with a solution of $NaHCO_3$ and dried. Removal of the solvent gave 9.5 mg (95%) of 2-phenylcyclopentanone (**8**).

Peracid Oxidation of *trans*-2,3-Dimethylmethylenecyclopropane (10).[12] A mixture of 100 mg of **10** and 0.5 g (2.4 equiv) of MCPBA in 5 mL of CH_2Cl_2 was stirred at 25 °C for 24 h. GLC analysis indicated 50% conversion of **10** to two compounds in a 40:60 ratio. GLC isolation gave *cis*-2,3-dimethylcyclobutanone (**11**) and *trans*-2,3-dimethylcyclobutanone (**12**) (85% total yield) identified by spectral comparison.[13] Analysis of the crude reaction mixture by NMR and IR indicated the presence of starting material and the two cyclobutanones. The cyclobutanones were independently shown to be stable

to a 1:1 solution of MCPBA and *m*-chlorobenzoic acid in CH_2Cl_2 at 25 °C for 72 h and to the GLC analysis conditions.

Peracid Treatment of 17. A mixture of 1.0 g of **17** and 5.0 g of PNPBA in 20 mL of CH_2Cl_2 was refluxed for 48 h. After the addition of 20 mL of pentane and cooling to 0 °C the slurry was filtered. The solvent was removed from the filtrate to give 0.91 g (91%) of recovered **17**.

2-Methyl-3-ethylidene-1-carbethoxycyclopropane. To a stirred mixture of 65 g of 3-iodo-2-pentene[14] and 0.5 g of electrolytic copper at 100 °C was added 50 mL of ethyl diazoacetate over a 12-h period. Distillation of the resulting mixture [118–121 °C (20 mm)] gave 29 g of 3-iodo-3-ethyl-2-methyl-1-carbethoxycyclopropane. To this material in 600 mL of ether was added 24 g of a 50% oil dispersion of sodium hydride, followed by 6 mL of ethanol which caused the solution to reflux. After stirring for 2 h, a solution of 40 mL of acetic acid in 40 mL of ether was added cautiously. After 100 mL of H_2O was added slowly, the solution was washed with H_2O and $NaHCO_3$ solution and dried. Distillation gave 10 g (63%) of 2-methyl-3-ethylidene-1-carbethoxycyclopropane [90–95 °C (30 mm)]. GLC analysis indicated the presence of the four possible isomers, **24, 25, 18,** and **22,** in a 5:8:75:12 ratio. Products **18** and **22** were collected by preparative GLC.[15]

Peracid Oxidation of *trans*-2-Methyl-*anti*-3-ethylidene-1-carbethoxycyclopropane (18). A mixture of 147 mg of **18** and 183 mg (1.1 equiv) of PNPBA in 5 mL of CH_2Cl_2 was stirred at −15 °C for 24 h. The solution was washed successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$ and dried. Removal of solvent under vacuum at 0 °C gave a liquid whose NMR indicated the presence of 20% starting material and 80% of a new product assigned as *anti-trans*-3,4-dimethyl-5-carbethoxy-2-oxaspiro[2.2]pentane (**21**): NMR δ 1.25 (t, 3, J = 7 Hz), 1.26 (d, 3, J = 5 Hz), 1.43 (d, 3, J = 5 Hz), 1.70 (d, 1, J = 5 Hz), 3.42 (quart, 1, J = 5 Hz), 4.03 (m, 2). The remaining proton is not visible, but integration shows it to be in the δ 1.15–1.30 region.

GLC of this material gave a 25% yield of *trans-trans*-2,4-dimethyl-3-carbethoxycyclobutanone (**19**) and a 65% yield of *trans-cis*-2,4-dimethyl-3-carbethoxycyclobutanone (**20**). Compound **19**: IR 5.62, 5.78, 7.30, 8.28, 8.55, 9.70 μm; NMR δ 1.20 (d, 6, J = 7 Hz), 1.30 (t, 3, J = 7 Hz), 2.20 (t, 1, J = 7 Hz), 3.46 (quin, 2, J = 7 Hz), 4.18 (quart, 2, J = 7 Hz). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.2; H, 8.5. Compound **20**: IR 5.62, 5.80, 7.30, 8.50, 9.70 μm; NMR δ 1.14 (d, 3, J = 7 Hz), 1.22 (d, 3, J = 7 Hz), 2.75 (d of d, 1, J = 8 Hz, J = 7 Hz), 3.48 (m, 1), 3.69 (m, 1), 4.17 (m, 2). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.3; H, 8.4.

Independent submission of **19** and **20** to a 1:1 mixture of *p*-nitrobenzoic acid and PNPBA in CH_2Cl_2 under the above conditions gave no interconversion of isomers by GLC analysis.

Oxidation of **18** at 25 °C gave cyclobutanones **19** and **20** in a 28:72 ratio in 95% yield by GLC analysis against an internal standard.

Peracid Oxidation of 22. A 15-mg sample of **22** was oxidized with PNPBA as described above at 25 °C to **19** and **20** in a 25:75 ratio in 96% yield.

Peracid Oxidation of 2-Methyl-3-ethylidene-1-carbethoxycyclopropane. The mixture of the four stereoisomers obtained by synthesis was oxidized as above at 25 °C to give **19** and **20** in a 27:73 ratio in 92% yield by GLC.

Rearrangement of 21. The mixture of **18** and **21** obtained above was refluxed for 2 h in 2 mL of benzene. Analysis by NMR indicated conversion of **21** to **19** and **20.** GLC integration indicated 18% **18,** 21% **19,** and 53% **20.**

2,2-Dimethyl-3-isopropylidene-1-carbethoxycyclopropane (26). To a mixture of 50 g of tetramethylallene and 0.25 g of electrolytic copper at reflux was added 100 g of the ethyl diazoacetate over a 12-h period. Distillation of the crude reaction mixture gave 20 g of starting allene and 51 g (52%) of **26:** bp 93–96 °C (30 mm). GLC gave a pure sample: IR 5.83, 7.33, 7.49, 8.69 μm; NMR δ 1.25 (t, 3, J = 7 Hz), 1.25 (s, 3), 1.28 (s, 3), 1.72 (s, 3), 1.80 (s, 3), 1.86 (m, 1), 4.01 (m, 2). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.2; H, 10.0.

Peracid Oxidation of 26. A mixture of 1.0 g of **26** and 1.0 g (1 equiv) of MCPBA in 50 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. Washing the mixture successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$ and then drying and removal of the solvent gave a mixture of starting material (3%) and 3,3,5,5-tetramethyl-4-keto-5-hydroxpentanoic acid δ-lactone (**27;** 91%): IR 5.70, 5.80, 7.30, 8.80, 9.04, 10.0 μm; NMR δ 1.18 (s, 6), 1.47 (s, 6), 2.67 (s, 2); mass spectrum *m/e* (rel intensity) 170 (6), 142 (6), 114 (10), 88 (40), 70 (13), 59 (87), 56 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.5; H, 8.1.

An experiment using PNPBA at −10 °C under the above conditions also gave **27** (95%). An experiment using 10% methanol in CH_2Cl_2 as the solvent under these conditions gave **27** as the only product (90%).

Registry No.—**1,** 7555-67-1; **2,** 42436-86-2; **4,** 7632-57-7; **5,** 24104-20-9; **6,** 5244-75-7; **7,** 66826-70-8; **10,** 5070-00-8; **17,** 14750-79-9; **18,** 40897-15-2; **19,** 66826-71-9; **20,** 66826-67-3; **21,** 66826-68-4; **22,** 40897-16-3; **24,** 40897-13-0; **25,** 40897-14-1; **26,** 1131-99-3; **27,** 14744-26-4; 3-iodo-2-pentene, 40897-12-9; ethyl diazoacetate, 623-73-4; 3-iodo-3-ethyl-2-methyl-1-carbethoxycyclopropane, 66826-69-5; tetramethylallene, 1000-87-9.

References and Notes

(1) (a) Support by a grant from the National Science Foundation is acknowledged. (b) National Institutes of Health Predoctoral Fellow, 1970–1973.
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