

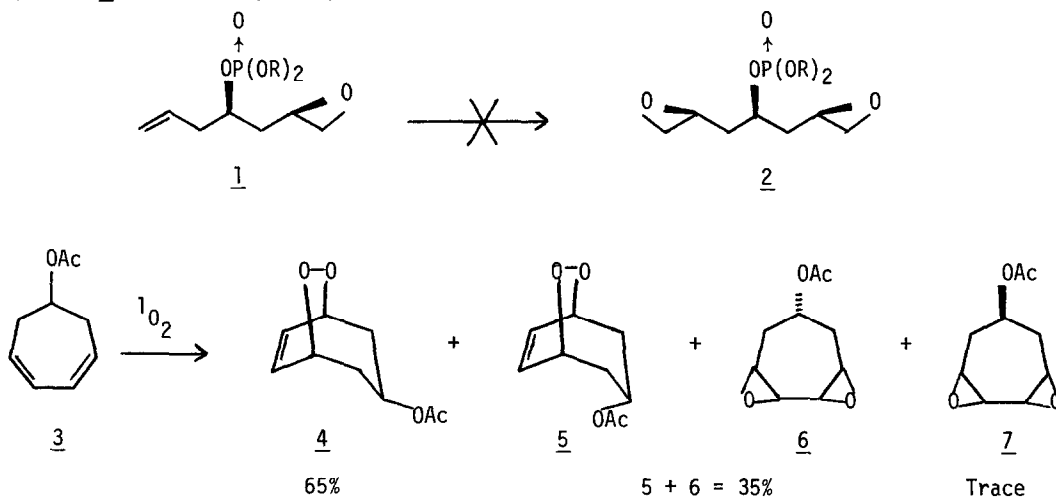
### PHOTOOXIDATION OF 1-ACETOXY-3,5-CYCLOHEPTADIENE

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**Summary:** A method for the preparation of *cis* oxygenated cycloheptyl systems has been developed. Photooxidation of 3 gives mainly 4, resulting from attack *syn* to the acetoxy substituent. The acetate function of both 4 and 5, the minor anti-product, appears to affect the rate of endoperoxide to diepoxide rearrangement.

We have been concerned with developing methods for the facile preparation of *cis* oxygenated polyacetate units suitable for further elaboration. Unlike the analogous polypropionate systems, very little control of stereochemistry could be expected from acyclic precursors.<sup>1</sup> To our knowledge the only highly stereoselective method for *cis* 1,3-induction in unbranched systems is Bartlett's "phosphate extension".<sup>2</sup> Our inability to readily convert the epoxyphosphate 1 to the diepoxide 2<sup>3</sup> led us to consider alternative approaches.

We have examined the addition of photo-generated singlet oxygen to 3,5-cycloheptadiene-1-ol (11) and its derivatives.<sup>4</sup> At this time, we wish to describe the photooxidation of the acetyl derivative 3<sup>5</sup> and the facile rearrangement of the minor endoperoxide product 5 to diepoxide 6 under both photolytic and thermal conditions.

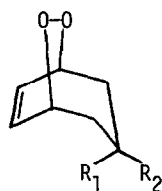


The reaction of 3, under standard conditions<sup>6</sup>, was complete in 4.5 to 5 hours and afforded three major products. Analysis by <sup>13</sup>C and <sup>1</sup>H nmr demonstrated that the mixture contained 65% of endoperoxide 4 (40% isolated by crystallization from ether)<sup>7</sup> and 35% of 5 and 6 combined. The ratio of 5 to 6 varied, perhaps due to variations in the amount of hematoporphyrin hydrochloride (Hem·HCl) used in individual experiments<sup>8</sup>.

Structural assignments were initially made by  $^{13}\text{C}$  and  $^1\text{H}$  nmr<sup>9</sup> and, in the case of the endoperoxide isomers 4 and 5, confirmed by single crystal X-ray analysis<sup>10</sup> of 1-O-acetyl-1,3,6-cycloheptatriol 8 obtained by hydrogenation of 4. Confirmation of structure 6 was obtained by comparison of its  $^{13}\text{C}$  spectrum to that of the diepoxide 7 formed by thermolysis of 4 (160°C, toluene, 3.25 hours; 50% as an oil from plc on silica). Structural and chemical studies on 5 were performed on a ca. 1:1 mixture of 4 and 5, obtained after crystallization of 4 and column chromatography on silica of the mother liquor to remove 6. All relevant  $^{13}\text{C}$  and  $^1\text{H}$  nmr data are listed in the Table. The chemical shifts of  $\text{H}_1$  and  $\text{C}_4$  are consistent with literature assignments in related systems.<sup>9</sup>

We were initially surprised to observe significant amounts of a diepoxide arising under the reaction conditions<sup>11</sup>, especially since both endoperoxides appeared to be stable for weeks at room temperature. The selectivity of the rearrangement was demonstrated by re-subjecting a 1:1 mixture of 4 and 5 to the reaction conditions<sup>6</sup>. After 10 hours a clean mixture of 4 and 6, with only traces of 5 remaining, was isolated. Further study showed that the mixture of 4 and 5 was unchanged by stirring in methanol (with and without added  $\text{Hem}\cdot\text{HCl}$ ) at ambient temperature and that 5 was only slowly rearranged to 6 when subjected to the light source in the absence of  $\text{Hem}\cdot\text{HCl}$ . However, photolysis in the presence of  $\text{Hem}\cdot\text{HCl}$  under an argon atmosphere effected the rapid isomerization of 5 to 6.<sup>8</sup> If relatively large amounts of  $\text{Hem}\cdot\text{HCl}$  are employed, 4 will also rearrange to the corresponding diepoxide 7. In fact,  $^{13}\text{C}$  nmr analysis of crude 5 obtained from preparative reactions showed it to contain 3-4% of 7.

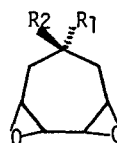
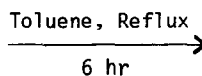
Similar results were obtained under thermal conditions. Heating endoperoxide 4 in toluene at reflux took approximately 96 hours to effect complete conversion of 7 and some minor products. Under identical conditions, 5 completely rearranged to diepoxide 6 in less than 5 hours. As a point of reference, the thermal rearrangement of 2-cycloheptene-1,4-endoperoxide<sup>12</sup> (9) to diepoxide 10 was examined. Comparing the extent of reaction of 4, 5 and 9 in refluxing toluene for 6 hours showed conversions to the corresponding diepoxides 7, 6 and 10 to be 11%, ~100% and 71% respectively. Thus, it appears that while the anti-acetate group of 5 is definitely facilitating the rearrangement of 5 to 6, the syn-acetate of 4 is retarding the rearrangement of 4 to 7. At this time, it is not possible to differentiate between the interaction of the pendant acetoxy function with some diradical intermediate<sup>8,13</sup> and the effects on the conformation of the cycloheptene ring that the acetoxy substituent imparts.



4  $\text{R}_1 = \text{H}; \text{R}_2 = \text{OAc}$

5  $\text{R}_1 = \text{OAc}; \text{R}_2 = \text{H}$

9  $\text{R}_1 = \text{R}_2 = \text{H}$

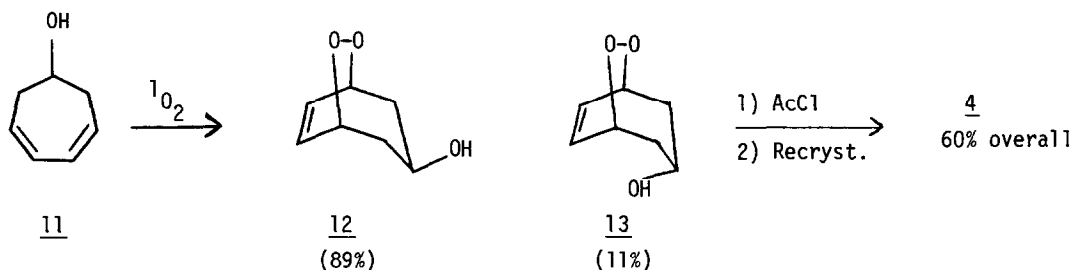


7 11% (By  $^1\text{H}$  nmr analysis)

6 ~100%

10 71%

In terms of our synthetic goal, we have observed a highly stereoselective singlet oxygen addition to the parent alcohol 11. Thus standard conditions gave an 80% yield of an 89:11 mixture of the desired *exo*-isomer 12 to the *endo*-isomer 13 after column chromatography on silica. Only trace amounts of bis-epoxide products were observed by  $^{13}\text{C}$  and  $^1\text{H}$  nmr analysis of the crude reaction mixture. Formation of the acetoxy derivatives (AcCl, pyr.,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ) and recrystallization from ether afforded pure 4 in 60% overall yield from 11.

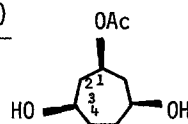


The results of chemical transformation of 4 and its analogs as well as further work on the substituent effects on the endoperoxide to diepoxide rearrangement will be reported in due course.

NMR Data in  $\text{CDCl}_3$  (ppm)

Assignment

	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>
C-1	67.9	68.8	67.8	67.7	69.5
C-2	36.9	38.4	32.4	31.3	44.8
C-3	72.9	74.4	51.3	51.5	68.8
C-4	128.5	130.4	52.9	52.7	31.8
H-1	ca. 4.95 $\delta$ (quintet)	5.43 $\delta$ (quintet)			



References

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- 1 was homogeneous by  $^{13}\text{C}$  nmr; upon reaction with  $\text{I}_2$  in  $\text{CH}_3\text{CN}$  a complex mixture was obtained in very low yield.
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- 6) Preparative reactions were conducted by irradiation in methanol (1g/50 ml) with a 650W tungsten-halogen lamp (water cooled immersion well) under a stream of oxygen using Hem-HCl as the sensitizer.
- 7) All crystalline compounds gave satisfactory C and H analyses. The uncorrected melting points of these compounds are as follows; **4**, 93.5-95°C (ether); **6**, 81-82°C (ether-hexane); **8**, 126-127°C (ethyl acetate); **9**, 110-115°C (ether); and **10**, 44-45.5°C (ether).
- 8) Photochemical rearrangements of endoperoxides to diepoxides are accelerated by triplet sensitizers, K.K. Macheshwari, P. DeMayo, and D. Wiegand, *Can. J. Chem.*, **48**, 3265 (1970).
- 9) See Ref. 1 d,e. For related systems see Y. Hawakawa, Y. Baba, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1786 (1978); A.P. Cowling and J. Mann, *J. Chem. Soc., Perkin I*, 1564 (1978).
- 10) We thank Dr. J. Z. Gougoutas and Ms. B. Toeplitz for performing this analysis.
- 11) Usually much more vigorous conditions are associated with this rearrangement. See Refs. 4a and 8.
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