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# Photochemical, Thermal, and Acid-Catalyzed Rearrangements of α,β-Epoxy Ketones. Synthesis of Spiro β-Diketones[1]

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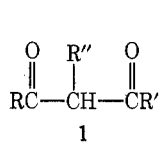
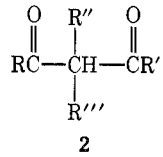
2-Cyclopentylidenecyclopentan-1-one oxide (**6**) and 2-cyclohexylidenecyclohexan-1-one oxide (**8**) have been isomerized thermally and photochemically *via* a 1,2-alkyl shift to spiro[4.5]decane-1,6-dione (**7**) and spiro-[5.6]dodecane-1,7-dione (**12**), respectively. Acid-catalyzed isomerization of **6** proceeds *via* a 1,2-acyl shift to yield spiro[4.5]decane-6,10-dione (**26**). Thermolysis of **8** also formed 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**17**) in low yield. The mechanisms of these reactions are discussed. Photolysis and thermolysis of the epoxy ketones **6** and **8** in the presence of tri-*n*-butylstannane yielded the enones, 2-cyclopentylidenecyclopentan-1-one (**21**) and 2-cyclohexylidenecyclohexan-1-one (**22**), respectively.

Recent work has indicated that isomerization of appropriately substituted α,β-epoxy ketones can serve as a useful preparative method for the synthesis of mono- (**1**) and disubstituted (**2**) β-dicarbonyl compounds.[2,3] This isomerization has been effected thermally,[4] photochemically,[5-14] and by using acidic catalysts.[2,3,15,16]

Owing to the number of isomerization products possible, it was of interest to learn the regiospecificity of the rearrangement for each of the various reaction conditions involved, and which was the preferred method to use synthetically.

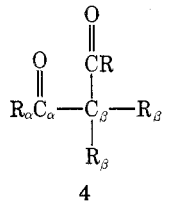


**1**

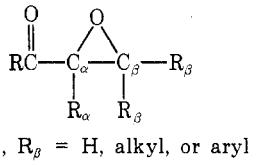


**2**

The isomerization of the α,β-epoxy ketones **3** can proceed *via* two major pathways. Isomerization *via* a 1,2-acyl migration yields the β-diketone **4**, whereas a 1,2-alkyl migration of $R_\beta$ affords the different β-diketone **5**. A 1,2-alkyl migration of $R_\alpha$ affords an α-diketone. In this paper we report the results of the photochemical, thermal, and acid-catalyzed isomerizations of a series of spiro α,β-epoxy ketones *via* 1,2-acyl and 1,2-alkyl shifts to yield spiro β-diketones.



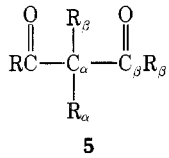
**4**



R, $R_\alpha$, $R_\beta$ = H, alkyl, or aryl

**3**

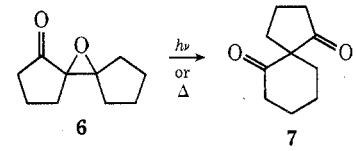
1,2-acyl migration
1,2-alkyl migration



**5**

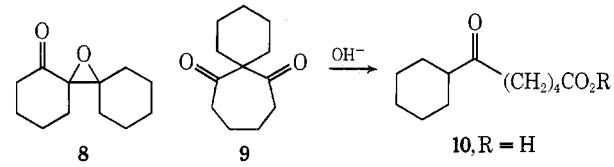
## Results and Discussion

Recent studies[17-19] on the photolysis of the α,β-epoxy ketone **6** led to the convenient preparation of the spiro β-diketone **7**. However, the yield of **7** *via* this path was low (30%).[17,19] To improve the yield of this reaction, **6** was heated for 15 min at 225° and **7** was obtained as the only product in 89% yield.



**6** **7**

This result is in sharp contrast to the results of House and Wasson,[2] who reported that thermolysis of the six membered ring homolog of **6**, *i.e.*, **8**, afforded the spiro β-diketone **9**.

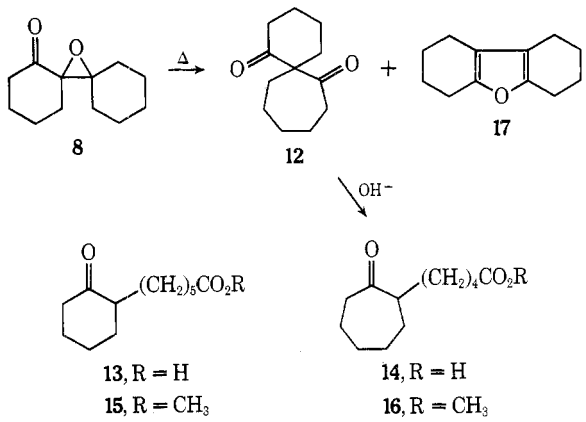


**8** **9** **10**, R = H; **11**, R = $CH_3$

Reexamination of their structure proof for **9** showed that their structure was wrong. Alkaline hydrolysis of the proposed spiro β-diketone **9** afforded a keto acid to which the structure **10** was assigned.[2] The keto acid was characterized as its semicarbazone, mp 270–271°.[2] However, the literature melting point of the semicarbazone of **10** was 175°,[20] thereby indicating that **10** was not the correct structure for the hydrolysis product. Furthermore, authentic keto acid **10** was prepared according to the method of Reese[20] and shown to be different from the keto acid obtained as a hydrolysis product.

Since the keto acids had melting points near room temperature and were difficult to recrystallize, their methyl esters were prepared. Again the authentic methyl ester **11** showed different spectral properties from those of the ester obtained from the hydrolysis product. Therefore, what is the structure of the hydrolysis product and that of the β-diketone from which it is derived?

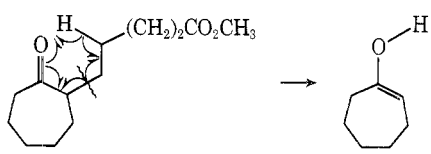
By analogy with the thermal isomerization of 6 to 7 and of pulegone oxide 23,[4] thermolysis of 8 should proceed *via* a 1,2-alkyl shift to yield the spiro β-diketone 12. Alkaline hydrolysis of 12 would then be expected to yield the keto acids 13 and 14, which should be converted to the methyl esters 15 and 16, respectively.




8 12 17

13, R = H 14, R = H
15, R = $CH_3$ 16, R = $CH_3$

Thermolysis of 8 yielded 12 (44%) together with 1,2,3,4,6,7,8,9-octahydrodibenzofuran (17) as a minor product (12%). The formation of 17 will be discussed later in this paper as part of the acid-catalyzed rearrangement products. Mass spectroscopy offered a very convenient method for distinguishing between the methyl esters 15 and 16. McLafferty rearrangement of each of the keto esters should result in the transfer of a hydrogen and cleavage of the side chain attached to the cycloalkanone.[21] The mass spectrum of the keto ester hydrolysis product showed a base peak at *m/e* 112, due to the ion 18. This indicates that the cycloheptanone 16 was the correct structure for the hydrolysis product. The structure of 16 was confirmed by synthesis from cycloheptanone and methyl 5-bromopentanoate.



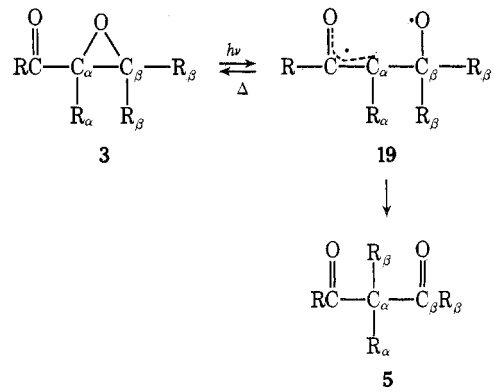

*m/e* 226 *m/e* 112

16 18

Therefore, it can be seen that thermolysis of the α,β-epoxy ketones 6 and 8 proceeds *via* 1,2-alkyl shifts to yield the spiro β-diketones 7 and 12, respectively. These observations confirm the results of other α,β-epoxy ketone thermolyses which may also be explained by 1,2-alkyl shifts.[4]

Since the photolysis of 6 proceeded *via* a 1,2-alkyl shift to yield 7, the photolysis of the epoxy cyclohexanone 8 was also investigated. Irradiation of 8 in acetone gave the expected 1,2-alkyl shift product 12 in 14% yield as the only product. A literature survey on the photolysis of epoxy ketones to yield β-diketones showed that all photoisomerizations may be explained by 1,2-alkyl shifts (R sometimes equals H) of the β substituent.[5-14,17-19]

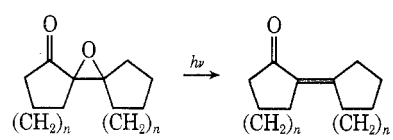
The most rational mechanism for the thermolysis and photolysis reaction is that they proceed *via* a reversible homolysis of the $C_\alpha$-O bond. The carbonyl can then stabilize the radical charge at $C_\alpha$ as shown in the structure 19. Concurrently or at a later stage $R_\beta$ migrates to $C_\alpha$, forming a carbonyl at $C_\alpha$. However, recent quantum-yield data on the photolysis of optically active 6[19] exclude one common diradical intermediate of type 19 for the three reaction paths involved (photoisomerization and photorearrangement to each isomer of the new product) in both the singlet and the triplet reactions. The quantum-yield data require that the rate of rearrangement is greater than the rate of rotation around the $C_\alpha$-$C_\beta$ bond in 19, and that the rate difference is greater in singlet generated 19 than in the triplet analog.[19] Another possible explanation is that the $C_\alpha$-$C_\beta$ bond is cleaved followed by rotation which leads to racemization of 6. In the formation of optically active 7 it is the $R_\beta$ which is cis to the acyl group which migrates fastest in both the singlet and triplet reactions.



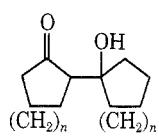

3 19

5

In an effort to trap the intermediate oxy radical 19, 6 and 8 were photolyzed in the presence of tri-*n*-butylstannane. However, none of the hydroxy ketone 20 was isolated; instead of starting enones 21 and 22 were obtained in very good yield. The above solutions were also heated at 50° for 2 hr and 30% of 21 and 20% of 22 were obtained.

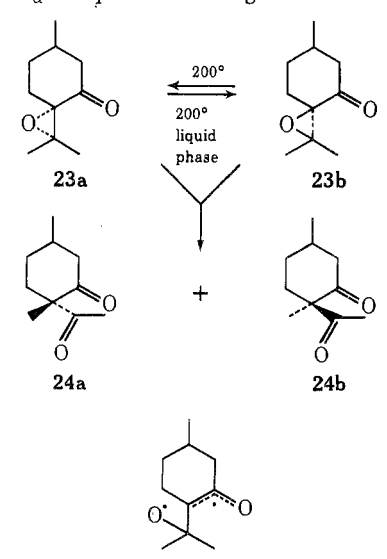



6, *n* = 1 21, *n* = 1
8, *n* = 2 22, *n* = 2



20

A similar stereospecificity has also been observed in the thermolyses of pulegone oxide.[4] The thermolysis of optically active pulegone oxide 23a and 23b in oxygen-containing solvents leads to the formation of 24a and 24b in relatively constant ratio. Here again the postulate of the thermolytic $C_\alpha$-O epoxide cleavage to the intermediate 25



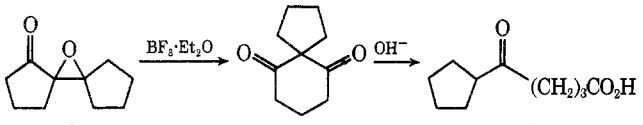

23a 23b

24a 24b

25

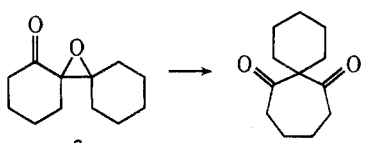
for the rearrangement requires that the rate of rearrangement is greater than the rate of rotation around the $C_\alpha$–$C_\beta$ bond in **25**. This result has been explained on the basis of a solvation complex.[4]

Since House and Wasson[2] had originally been interested in the acid-catalyzed rearrangement of **8**, we investigated the acid-catalyzed rearrangement of the previously uninvestigated epoxy ketone **6**. Treatment of **6** with boron trifluoride etherate afforded the spiro β-diketone **26**, which was different from that prepared by photolysis and thermolysis. Basic hydrolysis of the β-diketone **26** afforded the keto acid **27**. The spiro β-diketone **26** had previously been prepared by peroxytrifluoroacetic acid–boron trifluoride etherate oxidation of the enone **21**.[22]



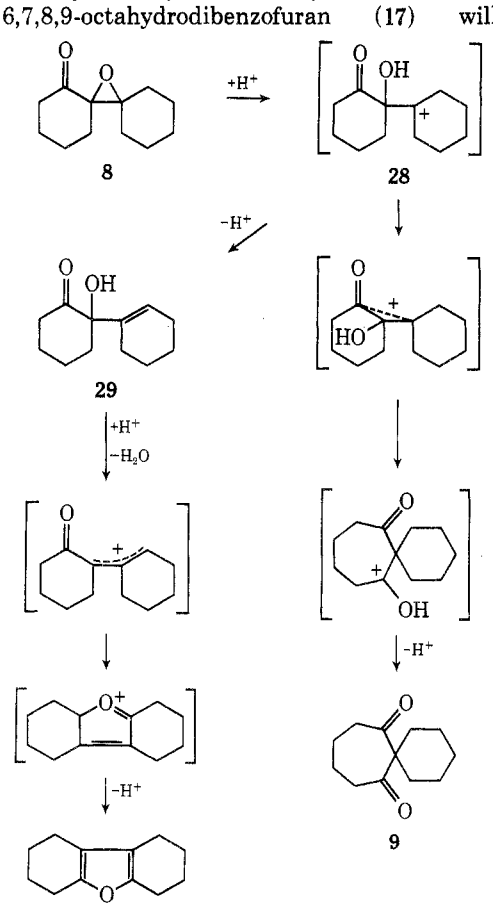

**6** **26** **27**

More recently **8** has been isomerized to **9** in 93% yield using antimony pentachloride in liquid sulfur dioxide as the acidic catalyst.[16]



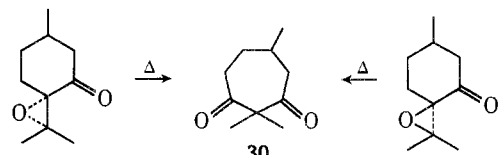
**8** **9**

In both of the above cases the reaction can best be explained by a 1,2-acyl shift. Protonation of the epoxide **8** should cause the $C_\beta$–O bond to cleave, forming the hydroxy ketone **28**. If acyl migration now occurs, then the spiro β-diketone is formed. However, if a proton is lost from **28** to yield **29**, followed by loss of water, then 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**17**) will be formed.[16] Thus it appears that the Lewis acid sites of the Pyrex glass surface in the thermolysis of **8** have resulted in the formation of a small amount of the dibenzofuran **17**. To confirm this hypothesis the glass surface was thoroughly washed with ammonia to remove these Lewis acid sites, and this resulted in a large decrease in the amount of **17** formed upon thermolysis.




**8** **28** **29** **9** **17**

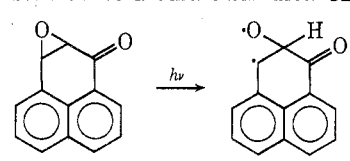
Similar 1,2-acyl shifts caused by Lewis acid sites in the Pyrex glass surface were also observed for the thermolysis of pulegone oxide **23** in the gas phase, resulting in the formation of the β-diketone **30**.[4]



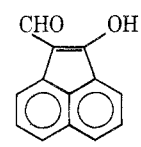

**23a** **30** **23b**

Thus it appears that 1,2-alkyl migrations of $R_\alpha$ in α,β-epoxy ketones to yield β-diketones are best carried out thermally making sure all acidic catalysts have been removed. Acid-catalyzed rearrangements of α,β-epoxy ketones lead to a different β-diketone *via* a 1,2-acyl shift.

As with all generalizations, there is an exception. Recently, the photolysis of phenalenone oxide **31** to yield acenaphthen-1-one-2-carboxaldehyde (**33**) provided the first unambiguous example of a photochemical 1,2-acyl migration.[23] However this may be explained in that the $C_\beta$–O oxide bond in **31** would be expected to cleave first, leading to the stable intermediate biradical **32**.




**31** **32**




**33**

## Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined in methanol with a Cary 14 recording spectrometer. Nmr spectra were obtained with Varian A-60A and XL100 spectrometers. The mass spectra were measured on an AE1 MS-9 mass spectrometer at an ionizing energy of 70 eV. Microanalyses were performed by Micro-Analysis Inc., Wilmington, Del. Vapor phase chromatography was done using an Aerograph, 90 P-3, on a 4 ft × 0.25 in. column which was packed with 20% Carbowax 20M on 60–80 mesh Chromosorb W AW-DMCS (column A) and on a 6 ft × 0.25 in. column which was packed with 15% SE-30 on 60–80 mesh Chromosorb W AW-DMCS (column B).

**Photolysis of 2-Cyclopentylidenecyclopentan-1-one Oxide (6).** A solution of **6** (132 mg) in acetone was photolyzed to yield **7** (40 mg) as previously reported.[17] Extensive attempts to isolate and characterize a by-product were unsuccessful.

**Thermolysis of 2-Cyclopentylidenecyclopentan-1-one Oxide (6).** **6** (42 mg) was sealed in a 7-mm test tube and heated for 15 min at 225°. After cooling, the product was isolated from the amber oil by preparative vpc on column A. A total of 37 mg (89%) of spiro[4.5]decane-1,6-dione (**7**) was obtained as a clear oil: bp 238–241° (lit.[17] bp 238–241°); ir ($CHCl_3$) 1732 (cyclopentanone C=O) and 1698 $cm^{-1}$ (cyclohexanone C=O); mass spectrum (70 eV) *m/e* (rel intensity) 166 (38, $M^+$), 148 (14), 138 (35), 137 (20), 111 (100), 110 (90), 95 (34), 91 (27), 67 (52), 55 (74), 44 (95), 41 (67), identical with that of authentic **7**.

**Thermolysis of 2-Cyclohexylidenecyclohexan-1-one Oxide (8).** 8 (500 mg), synthesized according to the method of Reese,[20] was sealed in a 7-mm test tube and heated for 30 min at 250°. The residue was separated by preparative vpc on column A to yield 80 mg of reactant 8, 51 mg (12%) of 1,2,3,4,6,7,8,9-octahydrodibenzofuran (17)[16] as a clear oil, ir ($CCl_4$) 1600 and 1140 $cm^{-1}$ (furan ring), nmr ($CCl_4$) δ 2.70–2.06 (m, 8 H) and 2.06–1.48 (m, 8 H), mass spectrum (70 eV) *m/e* (rel intensity) 176 (26, $M^+$), 148 (100), 120 (60), 105 (19), 92 (28), 91 (74), 79 (35), 77 (46), 65 (36), 51 (48), 41 (80), 39 (84), and 220 mg (44%) of spiro[5.6]dodecane-1,7-dione (12) as a colorless oil, bp 223–224° dec, ir ($CCl_4$) 1711 (cyclohexanone C=O) and 1696 $cm^{-1}$ (cycloheptanone C=O), nmr ($CDCl_3$) δ 2.71–2.04 (m, 6 H) and 2.04–1.25 (m, 12 H), mass spectrum (70 eV) *m/e* (rel intensity) 194 (12, $M^+$), 176 (5), 166 (33), 148 (57), 125 (24), 124 (43), 123 (83), 119 (24), 111 (50), 109 (70), 98 (82), 97 (86), 95 (82), 91 (45), 81 (91), 79 (90), 67 (93), 55 (100), and 41 (98).

The diketone formed a monosemicarbazone which crystallized from ethanol as white plates, mp 223–224° (lit.[2] mp 224°).

To remove the Lewis acid sites, the 7-mm test tubes were immersed in concentrated ammonia for 3 days and oven dried before use. Using these base-washed tubes and following the method cited above, analysis of the reaction products by vpc on column B afforded 12 and 17 in the ratio 7.4:1, whereas without base washing the ratio was 3.8:1.

**Hydrolysis of Spiro[5.6]dodecane-1,7-dione (12).** A solution of 396 mg (2.04 mmol) of 12 and 2.0 ml (12 mmol) of 6 *N* aqueous sodium hydroxide in 14 ml of ethanol was refluxed for 30 min. After cooling, the reaction mixture was acidified with 10% aqueous hydrochloric acid and extracted three times with 30 ml of ether. The ether extracts were combined, washed with water until neutral, dried ($Na_2SO_4$), and evaporated *in vacuo*.

A total of 280 mg (65%) of 5-(2-cycloheptanone)pentanoic acid (14) was obtained as a clear oil. The product would not crystallize: ir (neat) 3100 (broad, OH of a carboxyl group) and 1700 $cm^{-1}$ (broad, C=O of a carboxyl group and a ketone); nmr ($CDCl_3$) δ 10.72 (s, 1 H, acid OH), 2.80–2.10 (m, 5 H), and 2.10–0.94 (m, 14 H).

The keto acid 14 was converted to its semicarbazone, which crystallized from ethanol as colorless needles: mp 158–160°; ir (KBr) 3460 (unassociated NH), 3250 and 3180 (associated NH superimposed upon a broad OH peak), 1708 (C=O of a carboxyl group), and 1660 $cm^{-1}$ (C=O of an amide).

*Anal.* Calcd for $C_{13}H_{23}N_3O_3$: C, 58.09; H, 8.61; N, 15.60. Found: C, 58.18; H, 8.83; N, 15.37.

**Preparation of Methyl 5-(2-cycloheptanone)pentanoate (16).** To a solution of 250 mg (1.18 mmol) of 14 in 15 ml of dry ether was added slowly an ether solution of diazomethane until the solution remained yellow. Excess diazomethane was destroyed with 1 drop of 5% aqueous acetic acid. The reaction mixture was washed with water until neutral, dried ($Na_2SO_4$), and evaporated *in vacuo*. The product was isolated by preparative vpc on column A, which gave 150 mg (56%) of methyl 5-(2-cycloheptanone)pentanoate (15) as a clear oil: bp 275–276° dec; ir ($CCl_4$) 1740 (ester C=O) and 1702 $cm^{-1}$ (cycloheptanone C=O); nmr ($CCl_4$) δ 3.56 (s, 3, $CH_3O$–); mass spectrum (70 eV) *m/e* (rel intensity) 226 (8, $M^+$), 195 (6), 177 (11), 166 (10), 159 (4), 149 (44), 137 (12), 123 (22), 112 (100), 98 (48), 97 (50), 87 (38), 84 (45), 74 (42), 67 (46), 55 (62), and 41 (58).

*Anal.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.04; H, 9.85.

**Preparation of Methyl 6-Cyclohexyl-6-ketohexanoate (11).** To a solution of 27 mg (0.13 mmol) of 6-cyclohexyl-6-ketohexanoic acid (10)[20] in 5 ml of dry ether was added slowly an ether solution of diazomethane until the solution remained yellow. The reaction was worked up as in the previous case. The product was isolated by preparative vpc on column A, which gave 20 mg (69%) of methyl 6-cyclohexyl-6-ketohexanoate (11) as a clear oil: bp 280–281°; ir ($CCl_4$) 1740 (ester C=O) and 1710 $cm^{-1}$ (cyclohexanone C=O); nmr ($CDCl_3$) δ 3.64 (s, 3, $CH_3O$–); mass spectrum (70 eV) *m/e* (rel intensity) 226 (18, $M^+$), 195 (6), 185 (4), 177 (17), 170 (13), 166 (7), 158 (9), 153 (6), 149 (36), 143 (50), 139 (13), 115 (55), 111 (90), 101 (12), 97 (31), 87 (51), 83 (100), 81 (48), 73 (50), 67 (45), 59 (39), 55 (100), and 41 (53).

*Anal.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.09; H, 9.61.

**Preparation of Methyl 5-(2-Cycloheptanone)pentanoate (16).** To a suspension of 0.066 g (3.64 mmol) of sodium hydride in 10 ml of freshly distilled DMF was added slowly 0.25 g (2.23 mmol) of cycloheptanone and 0.44 g (2.25 mmol) of methyl 5-bromopentanoate. The yellow solution was stirred under nitrogen for 3 hr at 80°. After cooling, 25 ml of water was added, and the reaction mixture was concentrated. The residue was extracted with ether (3 × 50 ml). The ether extract was washed with brine until neutral, dried ($Na_2SO_4$), and evaporated *in vacuo*. The product was isolated by preparative vpc on column A, which gave 50 mg (10%) of methyl 5-(2-cycloheptanone)pentanoate (16) as a clear oil: bp 275–276° dec; ir ($CCl_4$), 1740 (ester C=O) and 1702 $cm^{-1}$ (cycloheptanone C=O); nmr ($CCl_4$) δ 3.56 (s, 3, $CH_3O$–); mass spectrum (70 eV) *m/e* (rel intensity) 226 (8, $M^+$), 195 (6), 177 (11), 166 (10), 159 (4), 149 (45), 137 (12), 123 (22), 112 (100), 98 (48), 97 (50), 87 (38), 84 (45), 74 (42), 67 (47), 55 (62), 41 (58).

**Photolysis of 2-Cyclohexylidenecyclohexan-1-one Oxide (8).** A solution of 2.500 g (2.5 mmol) of 8 in 110 ml of acetone was stirred with a stream of nitrogen and irradiated with a 450-W Hanovia lamp through a Vycor filter. The reaction was stopped after 2 hr. The acetone solution was concentrated and preparative vpc on column B was used to collect 270 mg (54%) of reactant, 8, and 68 mg (14%) of spiro[5.6]dodecane-1,7-dione (12) (spectra identical with the spectra of the product obtained by thermolysis of the epoxide, 8).

**Photolyses of 6 and 8 in Benzene with Tri-*n*-butylstannane.** A solution of 10 mg of 6, 0.25 ml of benzene, and 85 mg of tri-*n*-butylstannane in a degassed 7-mm Pyrex test tube was irradiated with a 450-W Hanovia lamp for 2 hr. The vpc on column A indicated that over 95% of the reactant had been converted to 2-cyclopentylidenecyclopentan-1-one (21). The same procedure was used with compound 8, and, after 4-hr irradiation, over 90% of the reactant had been converted to 2-cyclohexylidenecyclohexan-1-one (22).

Duplicates of the above solutions were heated in a water bath at 50°. After 2 hr, 6 gave only 30% of 21, and, after 4 hr, 8 gave only 20% of 22.

**Acidic Rearrangement of 2-Cyclopentylidenecyclopentan-1-one Oxide (6).** A solution of 200 mg of 6 in 15 ml of benzene was treated with 0.2 ml of boron trifluoride etherate, and the resulting mixture was stirred at room temperature for 5 min. The reaction mixture was diluted with ether, washed with water, dried ($Na_2SO_4$), and concentrated under vacuum. The product was isolated by preparative vpc on column A. A total of 138 mg (69%) of spiro[4.5]decane-6,10-dione (26) was obtained as a clear oil: mp 10–11° (lit.[22] mp 11.5–12.5°); ir ($CCl_4$) 1725 and 1696 $cm^{-1}$ (β-diketone); nmr ($CCl_4$) δ 2.57 (t, 4, methylene protons α to carbonyls) and 2.45–1.54 (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 166 (40, $M^+$), 138 (18), 137 (22), 125 (17), 111 (10), 110 (63), 109 (29), 97 (21), 96 (70), 95 (44), 79 (15), 77 (18), 70 (20), 68 (55), 67 (70), 66 (25), 55 (100), 43 (36), 42 (96), 41 (92), 40 (70), and 39 (94).

A solution of 97 mg (0.58 mmol) of 26 and 0.6 ml (3.6 mmol) of 6 *N* sodium hydroxide in 5 ml of ethanol was refluxed for 30 min. The product, after acidification with dilute aqueous hydrochloric acid, was extracted with ether. After removing the solvent the residue was converted directly to its semicarbazone, mp 180–181° (lit.[22] mp 180–182°).

**Preparation of 6-Cyclohexyl-6-ketohexanoic Acid (10).**[20] To a solution of 0.50 g (2.73 mmol) of 2-cyclohexylcyclohexan-1-one[20] in 0.6 ml of acetic acid was added slowly a solution of 0.9 g (11.1 mmol) of chromium trioxide, 1.25 ml of acetic acid, and 0.44 ml of water. This mixture turned dark green after a 5-min stirring over a steam bath. Then 1.75 ml of sulfuric acid in 25 ml of water was added, and the mixture was concentrated. The residue was extracted with ether (3 × 30 ml). The ether extract was washed with 50% sodium bicarbonate solution. The base wash was acidified with 10% hydrochloric acid and extracted with ether. The ether layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was crystallized with ether–petroleum ether (bp 30–60°) to give 0.26 g (45%) of 6-cyclohexyl-6-ketohexanoic acid as colorless needles: mp 54–55° (lit.[20] mp 58°); ir (KBr) 3200 (broad, OH of a carboxyl group) and 1700 $cm^{-1}$ (broad, C=O of a carboxyl group and a ketone).

The keto acid was converted to its semicarbazone, which crystallized from methanol as colorless needles: mp 174–176° (lit.[20] mp 175°); ir (KBr) 3460 (unassociated NH), 3240 (broad, OH of a carboxyl group), 1708 (C=O of a carboxyl group), and 1660 $cm^{-1}$ (C=O of an amide).

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**Registry No.**—**6**, 36803-49-3; **7**, 36803-48-2; **8**, 26870,38-2; **10**, 20606-25-1; **10**, semicarbazone, 50803-78-6; **11**, 50803-79-7; **12**, 50803-80-0; **14**, 33371,95-8; **14** semicarbazone, 50803-81-1; **16**, 50803-82-2; **17**, 1010-77-1; **26**, 6684-66-8; cycloheptanone, 502-42-1; methyl 5-bromopentanoate, 5454-83-1; 2-cyclohexylcyclohexan-1-one, 90-42-6.

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# Synthesis and Photorearrangement of 4,5-Epoxy-4,5-dihydropyrene


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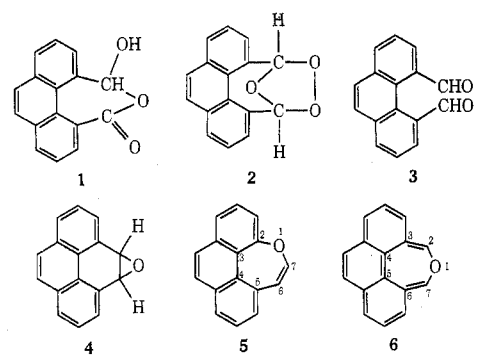
The title compound, 4,5-epoxy-4,5-dihydropyrene, which is important in cancer research was synthesized from pyrene *via* its ozonide and 4,5-phenanthrenedicarboxaldehyde. On ultraviolet irradiation, this epoxide rearranges to 2,3:3,4:4,5-tribenzoxepin, a new oxepin, 4-hydroxypyrene, pyrene, and other not yet identified products.


The importance of epoxides as intermediates in the metabolic detoxification of aromatic hydrocarbons has been established.[1] Aromatic epoxides can react to form a variety of products, including phenols and oxepins.[1,2] In recent years there has been considerable interest in synthesizing the K-region epoxides of carcinogenic hydrocarbons such as dibenz[*a*,*h*]anthracene,[3] benzo[*a*]pyrene, and 7,12-dimethylbenz[*a*]anthracene,[4] since these have been suggested as the possible carcinogenic metabolic intermediates in carcinogenesis by aromatic hydrocarbons.[5] Pyrene, a related noncarcinogenic hydrocarbon, is useful for comparative metabolic studies in laboratory animals and in *in vitro* cell culture studies.[6] Although important, the oxides of pyrene have not been successfully synthesized up to now. Boyland and Sims[6a] reported that in the oxidation of pyrene with perbenzoic acid an intermediate is formed which they believed to be 4,5-epoxy-4,5-dihydropyrene. This epoxide has also been detected as a microsomal metabolite of pyrene.[6c] The present paper describes the first reported synthesis of pure 4,5-epoxy-4,5-dihydropyrene (**4**). This epoxide is photochemically unstable and rearranges to form several products. It was of added importance, therefore, to study its photochemical rearrangement, as the intermediates formed therein may be of significance in the carcinogenic or detoxification processes of aromatic hydrocarbons.

Two general approaches have been used for the synthesis of K-region epoxides: (1) the conversion of dialdehydes[7] obtained by chemical oxidation of polycyclic aromatic hydrocarbons to the epoxide by the use of Mark's reagent, tris(dimethylamino)phosphine; (2) the cyclization of trans dihydrodiols with the dimethyl acetal of dimethylformamide.[4]




Previous attempts[8] to synthesize 4,5-phenanthrenedicarboxaldehyde by the catalytic hydrogenation of pyrene ozonide under various experimental conditions have resulted in the formation of 5-formyl-4-phenanthroic acid in the lactol form, I.[8] However, Sturrock and Duncan[9a] reported the formation of unstable, uncrystallizable, and impure dialdehyde in poor yield from the iodide reduction of pyrene monozonide. Criegee,[10] who prepared the dialdehyde by oxidation of *trans*-4,5-dihydroxy-4,5-dihydropyrene with lead tetraacetate, also reported similar findings. Both methods thus seemed unsuitable as preparative procedures.

In the present work, ozonization of a dilute solution of pyrene in anhydrous methylene chloride at −70° using 1 mol of ozone afforded mainly a colorless compound, mp 159–161°, in good yield. Based on its uv, ir, nmr, mass spectral, and C, H analysis, it was characterized as the monomeric monozonide of pyrene, **2**.[9a,b] Catalytic hydrogenation of the ozonide **2** over Pd/C in ethyl acetate