Photochemistry of Two β,β′-Epoxy Ketones, 3-Oxatricyclo[3.2.1.0^{2,4}]octan-8-one and 3-Oxatricyclo[3.3.1.0^{2,4}]nonan-9-one. Intramolecular Reactions of α,β-Unsaturated Aldehydo Ketenes

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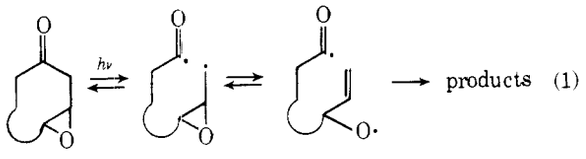
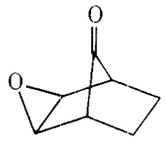
Received April 11, 1978

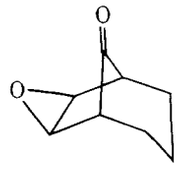
Photolysis of epoxy ketone **1** in benzene leads to aldehydo ketene **3** and β-lactone **4** as primary products. Subsequent addition of methanol furnishes the isolable products **6** and **7**. Secondary photolysis of **3** yields the cycloaddition product **5**. Photolysis of **1** in benzene containing 3% methanol gives **6** directly along with **10**. Similar irradiation of epoxy ketone **2** leads to aldehydo ketene **15**, which reacts with methanol to give the aldehydo esters **17** and **18**, and which is converted thermally to enol lactone **16**. These reactions provide novel information about the behavior both of 1,4 acyl alkoxy biradicals and of α,β-unsaturated aldehydo ketenes.

Relatively little information is available concerning the photochemical behavior of β,γ-epoxy cyclic ketones. Much of what is known is due to Murray and his co-workers, who suggested a sensible scheme, the key steps of which are shown in eq 1, to account for the observed photochemical rearrangement reactions of these compounds.[1] This scheme is closely analogous to one long used to explain photolysis products from β,γ-cyclopropyl ketones.[2] In the present report we describe the photolysis of ketones **1** and **2**, two simple tricyclic β,γ-epoxy ketones that, through their internal symmetry, can also be regarded as β,β′-epoxy ketones. As will be seen below, application of eq 1 to ketones with such symmetrically disposed epoxide rings leads to alkoxy acyl 1,4-biradicals, species whose behavior has not been explored in the past. In addition, since one type of product observed from these biradicals is an α,β-unsaturated aldehydo ketene, this work has also provided an opportunity to observe transformations involving intramolecular interaction of these reactive functional groups.





1



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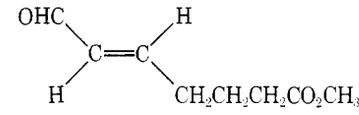
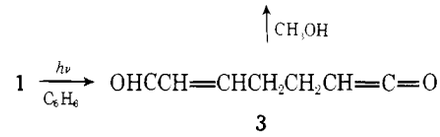
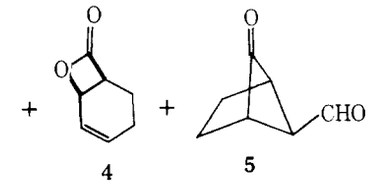
Photolysis Products. Irradiation of epoxy ketone **1**[3] in dry benzene (~0.025 M; λ > 2800 Å) led to products **3–5**. Neither the unstable aldehydo ketene **3** nor β-lactone **4** could be isolated, but the infrared spectra of solutions after photolysis gave typical absorption for each: 2117 cm^{-1} for **3** and 1832 cm^{-1} for **4**. Furthermore, addition of methanol to the solutions after photolysis led to replacement of these two bands with absorption typical for an ester (1740 cm^{-1}) and a carboxylic acid (3500–2500 and 1710 cm^{-1}), which are attributed to **6** and **7**, respectively. Subsequent isolation by preparative vapor phase chromatography (VPC) yielded **6**, the structure of which follows unambiguously from spectral properties showing it to be an α,β-unsaturated aldehyde with a trans disubstituted double bond, an unbranched carbon chain, and a carbomethoxyl group. Reaction of the photolysate solution with ethereal diazomethane after the methanol treatment permitted conversion of carboxylic acid **7** to the conveniently

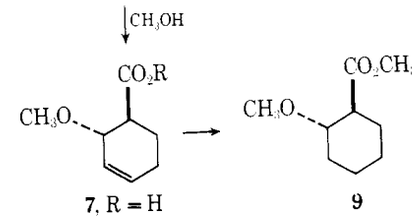


6





4 5



7, R = H
8, R = CH_3
9

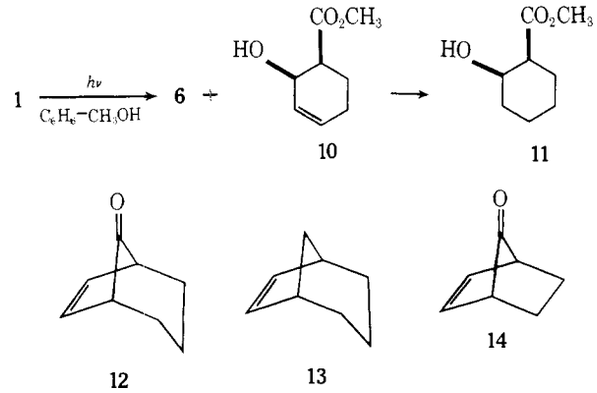
isolated (VPC) methyl ester **8**. Hydrogenation of **8** over palladium on barium sulfate in methanol containing a trace of aqueous sodium hydroxide led to methyl *trans*-2-methoxycyclohexanecarboxylate (**9**), which was identical with an authentic sample and readily distinguished from the related *cis*-methoxy ester.[4] The isolation of **8** provides excellent supporting evidence for the presence of **4** in the photolysate; under the neutral conditions employed methanol is expected[5] to open a β-lactone by preferential alkyl–oxygen cleavage with inversion, and the allylic nature of this center in **4** undoubtedly facilitates this process. It is difficult to conceive of alternative structures for the photoproduct that would lead to **7** on reaction with methanol in benzene under such mild conditions.

Direct VPC isolation after photolysis of **1** without the addition of methanol furnished **5**, which was identified from its spectroscopic properties as 6-oxobicyclo[2.1.1]hexane-*exo*-5-carboxaldehyde. Noteworthy spectroscopic features are strong infrared (IR) absorption at 1810[6] and 1730 cm^{-1}, a ^{13}C nuclear magnetic resonance (NMR) spectrum consisting of only five signals as required by the internal symmetry of structure **5**, and a ^{1}H NMR spectrum that permitted assignment of the indicated exo stereochemistry to the formyl group.

0022-3263/78/1943-3314$01.00/0

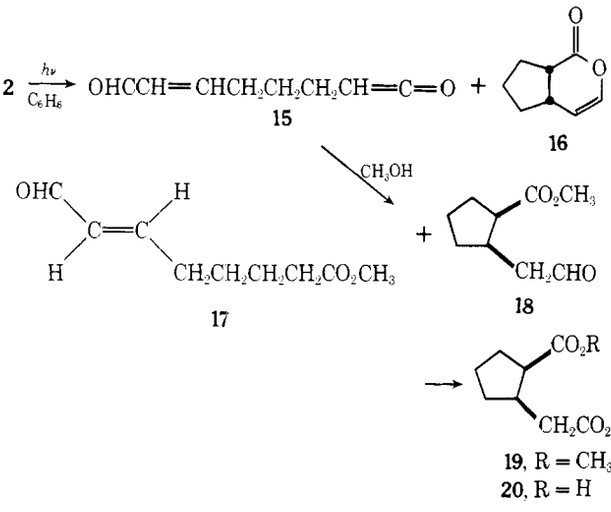
The signal for the aldehydic proton appears at δ 9.49 (d, J = 6.0 Hz), while the adjacent α proton [C(5)–H] also gives a doublet, δ 2.43 (J = 6.0 Hz), and thus is coupled only to the aldehydic proton. This lack of coupling with the adjacent bridgehead hydrogen atoms is typical for endo C(5) protons in bicyclo[2.1.1]hexanes; in contrast, epimeric exo protons at C(5) do show vicinal coupling to the bridgehead positions.[6,7]

Photolysis of 1 in benzene containing 3% (v/v, ~0.74 M) methanol furnished **6** directly, as well as the *cis*-hydroxy ester **10**. The structure of **10** follows from spectroscopic evidence



along with subsequent hydrogenation to form methyl *cis*-2-hydroxycyclohexanecarboxylate (**11**), which was identical with an authentic sample.[8]

Epoxy ketone **2**, the second substrate chosen for study, was available on oxidation of unsaturated ketone **12**[9,10] with *m*-chloroperbenzoic acid. The stereochemistry of **2** was assigned by analogy both with the rigorously proved[10] exo stereochemistry of epoxidation of the related olefin **13** as well as with the formation of **1** from norbornen-7-one (**14**).[3] Photolysis of **2** in dry benzene as described above for **1** gave the aldehydo ketene **15**. Under certain conditions discussed below, the enol lactone **16** was also obtained. The presence of **15** was signaled



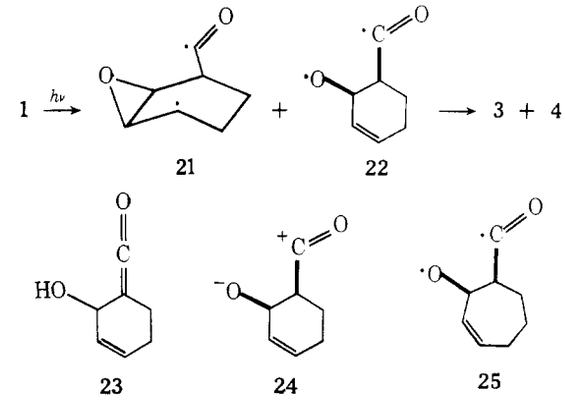
by infrared absorption at 2110 cm^{-1} as well as through isolation of ester **17** upon treatment of the benzene solution with methanol. The structure of **17** was secured through data analogous to those noted above for aldehyde ester **6**. The major product arising from **15** on reaction with methanol was the cyclic aldehydo ester **18**, the formation of which will be discussed later. This cyclopentane was fully characterized but was surprisingly readily oxidized; in air it was rapidly converted to the related ester carboxylic acid **19**. Acid-catalyzed hydrolysis of **19** gave *cis*-2-carboxycyclopentaneacetic acid (**20**), which was identical with an authentic sample.[11] The second product, **16**, could be obtained only by direct VPC analysis of photolysate solutions which had been irradiated a relatively short time. This limitation, along with the inherent instability of this enol lactone, made its isolation somewhat tedious. It was identified by conversion to **18** on brief exposure to dilute aqueous acid at room temperature followed by esterification with diazomethane. Spectroscopic properties of **16** agree well with those previously recorded for simple alkyl-substituted 3,4-dihydro-2-pyranones.[12] These include IR carbonyl absorption at 1765 cm^{-1} and NMR absorption for two vinyl protons at δ 4.98 (dd, J = 6.0, 3.7 Hz) and 6.36 (dd, J = 6.0, 0.9 Hz).

Photolysis of **2** in benzene containing ~6% methanol gave directly **17** and **18**, the two products previously formed from ketene **15** on reaction with methanol.

With the exception of **10**, the compounds isolated from these photolyses are secondary transformation products of the initially formed aldehydo ketenes **3** and **15** or the β-lactone **4**. This fact, along with the observed photochemical and thermal instability of the primary products, has made the determination of yields rather inaccurate. Our best estimates for the primary products at ~80% conversion of starting epoxy ketone are **3** (~10%), **4** (15–20%), and **15** (60–70%). For the secondary products **5** and **16**, yields were quite variable since these compounds are also rather unstable under the conditions of their formation. Based on unrecovered epoxy ketone, the best observed yields were **5** (~7%) and **16** (25%). On the basis of available aldehydo ketene then, the yield of **5** was ~70% and that of **16** was ~38%. In addition to these various compounds, the photolysis of **1** also furnished at least four minor products (each <3%) that were detected by NMR and/or VPC analysis.

Discussion

The formation of **3** and **4** may be explained readily by way of α cleavage of **1** to **21** followed by rupture of the oxirane to



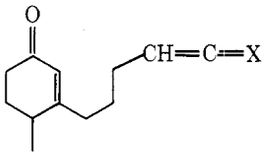
furnish **22**, steps that follow the general scheme of eq 1. Additionally, formation of **22** from **21** involves cleavage of that bond of the epoxide which is consistent with stereoelectronic control of this process and is therefore similar to the photochemical behavior of stereochemically related β,γ-cyclopropyl ketones.[13] Biradical **22** may then couple to give **4** in analogy with the formation of larger ring lactones from longer chain alkoxy acyl biradicals.[1] In agreement with the behavior of other types of 1,4-biradicals, **22** may also fragment to **3**. As initially formed, **3** presumably should have a cis disubstituted double bond, but there is ample opportunity for this to undergo subsequent photochemical isomerization before isolation as **6**. A more novel question, however, is posed by the formation of **10** on photolysis in the presence of methanol. Hydrogen migration in **22** to yield ketene **23** and subsequent stereospecific addition of methanol seemed a mechanistically unlikely path to **10**, and indeed this was ruled out by the observation that irradiation of **1** in benzene containing metha-

nol-*O*-*d* furnished **10** without incorporation of carbon-bound deuterium.[14] Suitable controls demonstrated that **10** does not arise from a dark reaction of **1** with methanol nor from either a photochemical or a dark reaction of **4** with methanol. These findings require that **10** result from interception by methanol of some transient species lying between **1** and **4**. Although a nonpolar radical would not be expected to react with methanol in this fashion, there are good theoretical grounds for assigning considerable polar character to biradical **22**.[15] Thus, **24** should contribute importantly to the structure of **22** or indeed may be a better representation than **22** for the species involved, and reaction of zwitterion **24** with methanol should quite specifically furnish **10**. On this interpretation then the polarization inherent in this alkoxy acyl intermediate permits a type of reaction with methanol that is not seen in alkyl acyl or dialkyl 1,4-biradicals but that here competes effectively with the coupling and fragmentation processes common to these three types of biradicals.

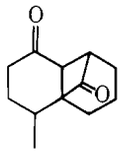
The same general explanation as that for the formation of **3** can account for isomerization of **2** to **15**. It is noteworthy that no substantial amount of β-lactone or hydroxy methyl ester is produced in this case. There was some spectroscopic evidence for a β-lactone from **2** [IR absorption at 1830 cm^{-1} in the crude photolysate and a small NMR signal at δ 3.4 (s) after treatment of the mixture with methanol], but no products corresponding to **4**, **7**, or **10** were isolated. The greater flexibility of the seven-membered ring of **25** may permit orientations of the 1,4-biradical that can fragment more rapidly than can **22**; in addition, this flexibility should allow the alkoxy and acyl radical centers to move much farther apart in **25** than in **22**, thus disfavoring collapse of **25** to the β-lactone.

We turn attention now to compounds **5**, **16**, and **18**, which are regarded as secondary products derived from the α,β-unsaturated aldehydo ketenes **3** and **15**. One current limitation in understanding the formation of these products is that it is impossible with the information now at hand to determine with certainty whether these cyclization products arise from the cis isomers of **3** and **15**, which presumably are the primary photoproducts, or from the trans isomers, the presence of which is indicated by isolation of **6** and **17**, or from both of these geometric isomers. Some suggestive evidence on this point is detailed below.

We consider keto aldehyde **5** to be a [2 + 2] product formed on crossed cycloaddition of the olefinic double bonds of **3**. Suitable control experiments indicated that this is a photochemical and not a thermal reaction. To our knowledge the only previously reported examples of intramolecular [2 + 2] cycloaddition of ketenes to α,β-unsaturated carbonyl compounds are the four cases reported by Becker,[16] who also showed in two instances that the sense of the cycloaddition was reversed for the ketenes relative to that observed for the analogous allenes. Thus, irradiation of ketene **26** furnished **27**, while allene **28** gave **29**. Since **26** and **28** are formally 1,6-heptadiene derivatives, the expected[17] sense of addition is straight (as **29**) rather than crossed (as **27**). In all four of Becker's ketenes the regiospecificity of cycloaddition was the opposite of that expected from earlier work on variously substituted dienes. It is noteworthy then that from **3** the crossed bicyclo[2.1.1]hexane **5** is the observed product; **3** is formally a 1,5-hexadiene, and such systems normally lead to crossed products.[17] That is to say, unlike the cases described by Becker, no reversal of the normal regiospecificity of addition is observed with ketene **3**.[18] If conversion of **3** to **5** is a concerted, photochemically allowed [$_\pi 2_s + _\pi 2_s$] reaction, it is the trans isomer of **3** that would lead to the observed exo aldehyde **5**.



26, X = O
28, X = CH_2



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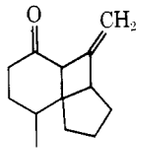

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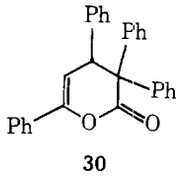

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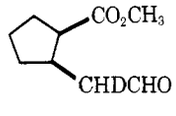
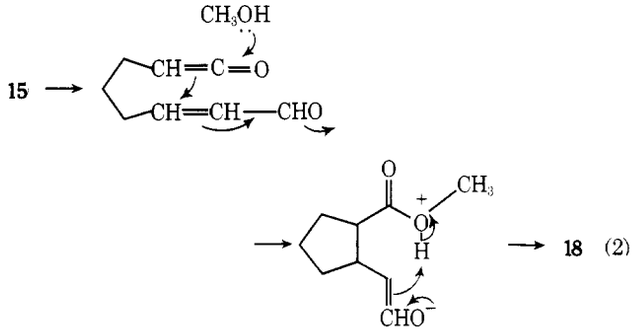


18d

Several observations indicate that enol lactone **16** is a thermal product formed only at elevated temperatures on VPC analysis of photolysis solutions containing **15**. This enol lactone appears in VPC traces after as little as 5% conversion of epoxy ketone **2**, making it unlikely that **16** is formed by secondary photolysis of the small amount of ketene **15** then present. Reaction mixtures which give VPC evidence for 20–25% of enol lactone **16** show no appropriate IR absorption at 1765 cm^{-1} for this product when examined directly before VPC. In keeping with these observations, the amount of **16** detected in VPC traces following on-column injection is considerably enhanced by raising the column temperature from 160 to 170 °C. Finally, continued irradiation of solutions containing **15** does not lead to increased formation of **16**, but rather to reduced yields of this product. This is not only consistent with the thermal formation of **16** but also suggests that **16** arises solely from *cis*-**15**, which is photochemically isomerized to the trans isomer on prolonged irradiation. There are few prior examples of [2 + 4] addition of the olefinic double bond of a ketene to an α,β-unsaturated carbonyl compound functioning as a diene,[19] although the reaction has been known since 1913 when Staudinger described the addition of diphenylketene to chalcone to furnish lactone **30**.[20]

The cyclic aldehydo ester **18** is clearly a nonphotochemical product from **15** since it is formed on methanol addition after irradiation, and the amount of **17** plus **18** isolated parallels the amount of ketene present as indicated by IR absorption. The amount of **18** relative to **17** decreases, however, with continued irradiation. This observation, along with the absence of the cis isomer of **17** among the isolated products, strongly suggests that *cis*-**15** is specifically converted to **18** on reaction with methanol and that only *trans*-**15** yields an open-chain aldehyde ester. A straightforward mechanism (eq 2) is available



(2)

to account for this cyclization, and this pathway is consistent with our observation that use of methanol-*O*-*d* led to the monodeuterated aldehyde ester **18d**. It is less obvious, however, why such cyclization should lead only to the cis disubstituted cyclopentane. Reaction of simple ketenes with alcohols in inert solvent is known to be third order in alcohol, and a highly ordered cyclic intermediate has been suggested to account for this result.[21] It seems possible that formation of **18** involves a related intermediate with the ketene and enal

functionalities and methanol in an array that leads stereospecifically to the cis isomer observed.

These secondary reactions of the α,β-unsaturated aldehydo ketenes **3** and **15** thus provide a glimpse of the varied behavior possible when these two π systems are incorporated in a single simple molecule. It is clear that these processes require further study in less complex reaction mixtures under conditions that permit control of the geometric configuration of the conjugated double bond, and such a study is now in hand.

We note in closing that α cleavage of **1** and **2** leads to a simple secondary alkyl radical center (as in **21**) and that **1** and **2** are the first β,γ-epoxy ketones of this sort to yield recognizable products on photolysis. In previously examined β,γ-epoxy ketones it was found necessary that this be a stabilized alkyl radical (tertiary alkyl, benzyl, or cyclopropylcarbinyl) for significant formation of monomeric products.[1]

Experimental Section

General. All VPC was carried out on a Varian Aerograph Model 700 Autoprep or a Model A-90-P gas chromatograph using columns prepared from aluminum tubing and operating at a helium flow rate of 100–120 mL/min. A 5 ft × 0.25 in column packed with 25% QF-1 on 40/60 Chromosorb W was used for analytical work and isolation of compounds. A 10 ft column of the same type was used for repurification of most liquid samples for elemental analysis.

Unless otherwise specified, IR and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237 B spectrophotometer and the latter on a Varian T-60A (60 MHz) spectrometer. Varian HR-220 (220 MHz; FT mode) and Bruker HX-90 (22.63 MHz; for ^{13}C) spectrometers were also used as indicated. Melting points were determined on a Thomas-Hoover apparatus and are corrected (all temperatures are given in °C). Solutions were dried over $MgSO_4$, Na_2SO_4, or K_2CO_3. Unless otherwise noted, solvents were removed in vacuo with a rotary evaporator. All new pure compounds for which melting points are not given were obtained as colorless oils.

Procedure for Photolysis of Ketones 1 and 2. A solution of the ketone (2–5 mg/mL) in anhydrous benzene (containing 0–6% methanol, as specified) contained in a toroidal Pyrex glass vessel (capacity ~70 mL) was flushed with dry nitrogen for 30 min and irradiated with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. The mixture was kept in a 30 °C water bath and under nitrogen atmosphere throughout the photolysis.

***exo*-3-Oxatricyclo[3.2.1.0^{2,4}]octan-8-one (1).** Oxidation of *anti*-7-norbornenol following the procedure of Ratcliffe and Rodehorst[22] gave bicyclo[2.2.1]hept-2-en-7-one (**14**).[3] Epoxidation with *m*-chloroperbenzoic acid for 8 h at room temperature (see procedure for **2**) gave **1**:[3] IR 3039 (w), 3006 (w), 2972 (w), 2944 (w), 2911 (w), 2877 (w), 2840 (w), 1858 (m), 1788 (s), 1758 (w), 1459 (w), 1443 (w), 1366 (w), 1288 (w), 1247 (w), 1211 (w), 1138 (w), 1118 (m), 1020 (w), 980 (w), 956 (w), 872 (s), 827 (m) cm^{-1}; NMR δ 1.53–2.10 (m, 4 H), 2.20–2.50 (br s, 2 H), 3.46 (m, 2 H). A trace amount (<5%) of the Baeyer–Villiger oxidation product was observed. **1** was purified by recrystallization from hexane or by VPC (150 °C) prior to photolysis.

Photolysis of *exo*-3-Oxatricyclo[3.2.1.0^{2,4}]octan-8-one (1). A. In 3% (v/v) Methanol/Benzene. A solution of **1** (158 mg, 1.3 mmol) in benzene (50 mL) containing 3% methanol was irradiated for 6.5 h according to the general procedure (ca. 93% conversion). VPC of the crude mixture (150 °C) showed two major products which were isolated (8 and 16% recovered yields) and identified as esters **6** and **10**, respectively. For **6** (retention time, 14–17 min): IR 3025 (w), 2988 (w), 2940 (m), 2840 (w), 2800 (w), 2713 (w), 1740 (s), 1695 (s), 1639 (w), 1433 (m), 1200 (m), 1153 (m), 1115 (m), 965 (m) cm^{-1}; NMR δ 1.50–2.10 (m, 2 H), 2.10–2.63 (m, 4 H), 3.63 (s, 3 H), 6.06 (dd, J = 16, 7.5 Hz, 1 H), 6.69 (dt, J = 16, 6.4 Hz, 1 H), 9.48 (d, J = 7.5 Hz, 1 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.61; H, 7.66.

For **10** (retention time, 5–6 min): IR 3600 (w), 3575–3350 (m), 3029 (w), 2950 (w), 2840 (w), 1740 and 1722 (s, merged), 1648 (w), 1433 (m), 1297 (w), 1225 and 1198 (m, merged), 1164 (m), 1092 (w), 1060 (w), 1020 (m), 983 (w), 886 (w), 857 (w), 674 (w) cm^{-1}; NMR δ 1.50–2.27 (m, 4 H), 2.27–2.70 (m, 2 H; chemical shift of one proton is variable), 3.70 (s, 3 H), 4.17–4.50 (m, 1 H), 5.53–5.83 (m, 2 H; apparent s at δ 5.60 and d at δ 5.77, J = 2.5 Hz, both broadened by further coupling). Double resonance experiments revealed coupling between the signals centered at δ 4.30 and 5.77.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.42; H, 7.69.

A sample of **10** (25 mg) in methanol (0.5 mL; containing 25 μL of aqueous 5% NaOH) was hydrogenated (1 atm) over 5% Pd/$BaSO_4$. The product (**11**) isolated by VPC (128 °C) had identical IR and NMR spectra with an authentic sample of methyl *cis*-cyclohexan-2-ol-1-carboxylate prepared according to the procedure of Pascual et al.:[8] IR 3660 (w), 3650–3200 (m), 2985 (w), 2930 (m), 2857 and 2840 (w, merged), 1739 (w, sh), 1718 (s), 1440 (w, sh), 1433 (m), 1400 (w), 1350 (w), 1318 (w), 1243 (m), 1192 (m), 1171 (m), 1113 (w), 1068 (w), 1030 (w), 977 (w) cm^{-1}; NMR δ 1.00–2.13 (m, 8 H), 2.13–2.58 (m, 1 H), 2.90 (br s, 1 H; variable), 3.67 (s, 3 H), 4.02 (br s, 1 H).

At least four minor products (each <3%, based on **1**) were detected in the NMR spectrum and/or VPC analysis of the crude photolysate. One of these appeared to be **7** (methoxy signal at δ 3.3; see C below) and a second one (isolated at retention time 12–13 min) the cis isomer of **6**: IR 2944 (w), 2911 (m), 2840 (m), 2810 (w), 2710 (w), 1742 (s), 1684 (s), 1608 (w), 1432 (m), 1358 (w), 1200 (m), 1158 (m) cm^{-1}; NMR δ 1.5–2.6 (m), 3.63 (s), 6.5 (m), 10.00 (d, J = 7.5 Hz).

B. In 3% (v/v) Methanol-*O*-*d*/Benzene. Photolysis of **1** as in A gave **6-*d*** [deuterated α to the ester; multiplet at δ 2.10–2.63 (3 H instead of 4 H) and a splitting pattern different in the δ 1.50–2.10 region] and **10** (no deuterium incorporated; NMR signals and integrals were identical with those given above).

C. In Benzene. A solution of **1** (320 mg, 2.6 mmol) in benzene (70 mL) was irradiated for 3.5 h (80% of **1** photolyzed). Aliquots taken during the photolysis revealed the formation of a ketene aldehyde (**3**; IR bands at 2117 and 1690 cm^{-1} in the original benzene solution) and at least three minor products (VPC). After removal of solvent, IR (CCl_4) and NMR ($CDCl_3$) spectra of the crude mixture revealed the major product (15–20%) to be β-lactone **4** (IR 1832 cm^{-1}; apparent dd at δ 4.85 in NMR; see D for reaction with methanol), which was not observed by IR spectroscopy in benzene or by VPC. A second product seen in the crude spectra was isolated by VPC (150 °C retention time, 8.5 min) in 6% yield and identified as 6-oxobicyclo[2.1.1]hexane-*exo*-5-carboxaldehyde (**5**): IR 3010 (w), 2955 (w), 2910 (w), 2879 (w), 2840 (w), 2821 (w), 2726 (w), 1810 (s), 1789 and 1767 (w, shoulders), 1729 (s), 1417 (w), 1275 (w), 1161 (w), 1118 (w), 1066 (w), 1000 (w, br), 953 (w), 897 (w) cm^{-1}; NMR (220 MHz) δ 1.89–2.09 (m, apparent 12 lines, 4 H), 2.43 (d, J = 6 Hz, 1 H), 3.15 (br s, 2 H), 9.49 (d, J = 6 Hz, 1 H); ^{13}C NMR (C_6F_6) δ (Me_4Si) 23.10, 55.65, 60.36, 199.11, 201.10 (relative integral values of tertiary carbon signals at δ 55.65 and 60.36, 1:2; C–H coupled spectrum gave the following multiplicities: t, d with further fine coupling, d, s, and d, respectively). No increase in the yield of **5** was observed after 60–80% conversion of **1**.

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.61; H, 6.64.

D. In Benzene, Followed by Addition of Methanol. Photolysis of **1** (285 mg) in benzene (70 mL) for 5.5 h (>90% conversion) gave a crude mixture containing **4** and **5** (ca. 8:3 in crude NMR; **4** was the major product in IR, strong band at 1832 cm^{-1}; very little **3**). The benzene solution was treated with 6% methanol (v/v) and stored overnight at 4 °C. An aliquot of this mixture was irradiated for an additional hour. VPC analysis showed no new photoproducts (only a trace of **6** and **10** due to the presence of **1** and **3**.) This aliquot was also stored at 4 °C. After removal of solvent, the spectra of the aliquot and the main reaction mixture (230 mg crude; 20–25% material loss during photolysis) both revealed the same new product, *trans*-2-methoxycyclohex-3-ene-1-carboxylic acid (**7**), formed from opening of the β-lactone: IR 3500–2500 (s), 1710 (s, br), 1644 (w), 1095 (m, br) cm^{-1}; NMR δ 1.43–2.83 (m), 3.30 (s, 3 H), 4.0 (m), 5.70 (s with fine structure, 2 H), 9.70 (br s, 1 H; variable).

The crude mixture was taken up in methanol and treated with diazomethane in ether. The major product was isolated by VPC (150 °C; retention time, 4 min; ca. 6% recovered yield based on **1**) and characterized as methyl *trans*-2-methoxycyclohex-3-ene-1-carboxylate (**8**): IR 3025 (w), 2950 (m), 2842 (w), 2810 (w), 1738 (s, br), 1428 (m), 1375 (w), 1294 (w), 1203 (w), 1189 (w), 1163 (m), 1098 (m), 1036 (w), 1017 (w), 925 (w), 906 (w), 680 (w) cm^{-1}; NMR δ 1.40–2.20 (m, 4 H), 2.20–2.67 (m, 1 H), 3.30 (s, 3 H), 3.65 (s, 3 H), 3.97 (m, 1 H), 5.68 (s with fine structure, 2 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.47; H, 8.37.

A sample of **8** (15 mg) was hydrogenated (100%) using the same conditions as for **10**. The product was identified as methyl *trans*-2-methoxycyclohexane-1-carboxylate (**9**), having IR and NMR spectra identical with an authentic sample[4] prepared from methyl *trans*-cyclohexan-2-ol-1-carboxylate[8] by treatment with diazomethane in the presence of boron trifluoride etherate: IR 2933 (s), 2856 (w), 2824 (w), 1738 (s), 1447 (w), 1428 (w), 1374 (w), 1358 (w), 1322 (w), 1258 (w), 1242 (m), 1188 (m), 1167 (m), 1121 (w), 1096 (m), 1033 (w), 989 (w), 925 (w) cm^{-1}; NMR δ 0.95–2.45 (m, 9 H), 3.23 and 3.27 (overlapping s, 3 H, and m, 1 H, respectively), 3.60 (s, 3 H).

A sample of methyl *cis*-2-methoxycyclohexane-1-carboxylate was prepared in the same manner and was shown to be different (IR, NMR) from **9**.

***exo*-3-Oxatricyclo[3.3.1.0^{2,4}]nonan-9-one (2).** Bicyclo[3.2.1]-oct-6-en-8-one[9,10] (**12**; 1.0 g, 8.2 mmol crude) in methylene chloride (28 mL) was added to a cold (4 °C) solution of *m*-chloroperbenzoic acid (1.85 g, 9.0 mmol; 85% pure) in methylene chloride (42 mL) and stirred for 3 h at room temperature under nitrogen. The resulting mixture was washed with 5% NaOH, 10% Na_2SO_3, 5% NaOH, water, and brine and dried. Removal of solvent gave a white solid (1 g). VPC analysis (165 °C) revealed a trace of starting material and ca. 6% of the Baeyer–Villiger oxidation product in addition to the desired product. Recrystallization from hexane followed by VPC of the remaining supernatant liquid gave **2** (total 836 mg; 74% yield): mp (sealed capillary) 216.5–217.5 °C; IR 3020 (w), 2940 (m), 2855 (w), 2840 (w), 1795 (m, sh), 1770 and 1760 (s), 1445 (m), 1382 (m), 1290 (w), 1250 and 1240 (w), 1195 (m), 1165 (m), 1072 (m), 976 (m), 952 (w), 914 (m), 883 (w), 835 (s) cm^{-1}; NMR δ 1.15–2.33 (m, 6 H), 2.33–2.60 (m, 2 H), 3.47 (s, 2 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.37; H, 7.16.

Photolysis of 2. A. In 6% (v/v) Methanol/Benzene. A benzene solution of **2** (100 mg, 0.73 mmol) containing 6% methanol was irradiated for 2.5 h according to the general procedure. VPC analysis of the crude mixture (160 °C) revealed starting material (17%), two major (ca. 6 and 80% of the observed volatile products) products, and several minor products. The two major compounds were isolated by VPC (4 and 44% recovered yields) and characterized as **17** and **18**, respectively. For **17** (retention time, 12–15 min): IR 3020 (w), 2940 (m), 2857 (w), 2810 (w), 2715 (w), 1735 (s, br), 1694 (s), 1636 (w), 1443 (w), 1433 (w), 1370 (w, br), 1290 (w), 1194 (w), 1164 (m, br), 1120 (w), 967 (w) cm^{-1}; NMR δ 1.40–2.00 (m, 4 H), 2.00–2.63 (m, 4 H), 3.62 (s, 3 H), 6.03 (dd, J = 7.2, 15.5 Hz, 1 H), 6.68 (dt, J = 6.3, 15.5 Hz, 1 H), 9.47 (d, J = 7.2 Hz, 1 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.22; H, 8.52.

For **18** (retention time, 5.5 min): IR 2940 (m), 2905 (w), 2865 (w), 2840 (w), 2810 (w), 2710 (w), 1736 and 1730 (s, merged), 1430 (w), 1375 (w, br), 1189 (m), 1167 (m, br) cm^{-1}; NMR δ 1.10–2.17 (m, 6 H), 2.17–3.07 (m, 4 H), 3.59 (s, 3 H), 9.68 (t, J = 1.1 Hz, 1 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.19; H, 8.24.

The ratios of **17** to **18** as well as the total yields were affected by the scale of the reaction and the length of irradiation; **18** was always the major product.

Upon exposure to air, **18** was readily oxidized to acid **19** (retention time, 10–14 min; 160 °C): IR 3500–2400 (s), 1736 and 1712 (s, merged), 1430 (w), 1295 (w), 1275 (w), 1188 (w), 1162 (m) cm^{-1}; NMR δ 1.17–2.13 (m, 6 H), 2.13–3.10 (m, 4 H), 3.60 (s, 3 H), 10.73 (br s, 1 H; variable).

Hydrolysis of **19** in concentrated HCl (110 °C, 2 h) gave *cis*-2-carboxycyclopentaneacetic acid (**20**), having identical IR and NMR spectra and melting point with an authentic sample:[11] mp (recrystallized from hexane/ether) 87–88 °C; mp (authentic sample, from saturated aqueous HCl) 89–91 °C (lit.[11] mp 87–89 °C); mmp 88–90 °C; IR ($CHCl_3$) 3500 (w), 3500–2300 (s), 1711 (s, br), 1419 (m, br), 1394 and 1375 (w, merged), 1225 (m, br), 1125 (w), 1031 (w), 915 (m, br) cm^{-1}; NMR ($CDCl_3$) δ 1.35–2.20 (m, 6 H), 2.20–2.73 (m, 3 H), 2.73–3.17 (m, 1 H), 10.88 (br s, 2 H).

B. In 25% (v/v) Methanol-*O*-*d*/Benzene. Photolysis of **2** in benzene containing 25% CH_3OD gave the two products described in A (ca. 1:10). The NMR spectrum revealed the major product to be **18d**. The aldehyde signal of δ 9.68 appeared as a doublet (J = 1 Hz); the integral of the δ 2.17–3.07 region was equivalent to 3.2 H (80% d_1), and the multiplets revealed more fine structure.

C. In Benzene. A solution of **2** in benzene was photolyzed as above. The reaction was followed by IR (C_6H_6, original concentration) and VPC. The only new product observed by IR was ketene aldehyde **15** (2110 and 1690 cm^{-1}), which increased steadily until 80–90% of **2** was converted (ca. 1.5 h) and then decreased slowly upon continued irradiation through a uranium filter (6 h) or standing in the dark at 30 °C (12 h). When benzene was removed from an aliquot containing the maximum amount of ketene and the IR spectrum (CCl_4) of the crude product was taken, ketene was absent and the only significant band observed was at 1830 cm^{-1} (trace of β-lactone analogous to **4**). VPC analysis (column 165 °C, injector 215 °C) of aliquots during the progress of the reaction revealed a new product (retention time, 5 min) whose increase (maximum yield 20–25%, based on reacted **2**) and decrease paralled that of the ketene. When the ketene was destroyed due to long irradiation time, removal of solvent, standing in solution overnight, or reaction with water or alcohols, none of this new product could be observed. Concentration of the original photolysate resulted in ca. 90% loss of the product, and changes in VPC conditions greatly influenced the amount observed. The product was collected and repurified by VPC (<1% yield) and identified as enol lactone **16**: IR 3090 (w), 3060 (w), 2950 (m), 2868 (w), 1765 (s, br), 1662 (w), 1450 (w), 1349 (w), 1330 (w), 1227 (m), 1202 (w), 1100 (m), 1061 (m), 1036 (m), 1011 (w), 883 (w), 717 (w) cm^{-1}; NMR (220 MHz) δ 1.32–2.50 (m, 6 H), 2.73–2.88 (m, 2 H), 4.98 (dd, J = 3.7, 6.0 Hz, 1 H), 6.36 (dd, J = 0.9, 6.0 Hz, 1 H); (60 MHz) irradiation at δ 4.98 caused the δ 6.36 signal to collapse to a singlet, and irradiation at δ 6.36 gave a doublet ($J \simeq$ 3.6 Hz) at δ 4.98; mass spectrum, m/e 138.0668 (M^+; calcd for $C_8H_{10}O_2$, 138.0682).

A sample of **16** (ca. 3 mg) was treated with 5% aqueous HCl at room temperature for 2 h. The mixture was extracted with one portion of ether. The solution was dried and the solvent removed. IR spectroscopy of the crude product revealed no **16** but did indicate the presence of an acid aldehyde [3600–2500 (br), 2810 and 2715 (w), 1725 and 1705 (s) cm^{-1}]. Treatment of this material with diazomethane gave ester aldehyde **18**, identified by its VPC retention time and characteristic IR spectrum.

D. In Benzene, Followed by Addition of Methanol. The photolysis was conducted and followed as in C. Each aliquot was immediately treated with methanol (6% by volume) in the dark. VPC revealed products **17** and **18** formed immediately. The total yield of the two paralleled the intensity of the ketene IR band prior to methanol addition and appeared to be ca. 50% at 80% conversion. The ratio of **17** to **18** varied from 1:>6 at low conversion to 1:1 at >90% conversion. Products **17** and **18** were collected by VPC (22% total recovered yield; ratio of 3:4 at 90% conversion) and shown to be identical with the products described in A (IR and NMR).

Acknowledgment. We thank Mr. William Rosenstein and Mr. William Wittbold for technical assistance, Mr. S. T. Bella for microanalyses, and Dr. W. Benz of Hoffmann-La Roche, Inc., Nutley, N.J., for the mass spectrum. The 220-MHz NMR spectra were obtained on an instrument at The Rockefeller University operated by a consortium supported in part by NSF Grant PCM74-12247. This research was supported by the National Science Foundation (Grant CHE74-21436) and by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1**, 66688-16-2; **2**, 66688-17-3; **3**, 66688-18-4; **4**, 66688-19-5; **5**, 66688-20-8; **6**, 66688-21-9; *cis*-**6**, 66688-31-1; **7**, 66688-22-0; **8**, 66688-23-1; **9**, 13640-66-9; **10**, 66688-24-2; **11**, 936-03-8; **12**, 22241-76-5; **14**, 694-71-3; *cis*-**15**, 66688-25-3; *trans*-**15**, 66688-26-4; **16**, 66688-27-5; **17**, 66688-28-6; **18**, 66688-29-7; **19**, 66688-30-0; **20**, 18314-54-0.

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Microbial Reduction of a Series of Substituted Benzils. Optical Properties and Nuclear Magnetic Resonance Spectra of Products

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Received February 23, 1978

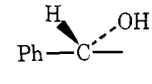
A series of para-substituted symmetric and unsymmetric benzils were reduced using *C. macerans* to yield the threo (*R,R*) diols of high optical purity and the (*S*)-benzoins with enantiomeric excesses of 20–30%. The absolute stereochemistry of the diols was established from CD measurements of the sign and magnitude of the 225-nm band and, in select cases, by chemical transformation to compounds of known configuration. The stereospecificity and/or high selectivity of these reductions are discussed. The proton NMR spectra of the isomeric erythro and threo diols were measured and assigned. Potential uses of coupling constants and chemical shifts to assign stereochemistry are discussed.

As part of a study on the stereochemical preferences of a mammalian enzyme, "hydrase", the absolute stereochemistries of several threo diols, obtained from enzymatic hydration of optically active substituted *cis*-stilbene oxides, were determined.[1] In order to examine aspects of the chemistry and spectroscopy of transformation products of these diols, we required a synthetic route capable of yielding reasonable quantities of these optically active compounds. The cis-substituted stilbene oxides had been prepared from the appropriate optically active mandelonitrile or mandelamide. This route could not be used to prepare optically active threo diols as the latter isomers were only minor products (formed in only 10–20%) in the hydride reduction of the intermediate, optically active benzoin.

One solution to this problem followed logically from our recent studies[2] on the stereospecific reductions of acetophenone and a series of substituted α-tetralone derivatives: the use of microbial reductions of substituted benzil derivatives to prepare the optically active threo diols. Prelog reported[3] that the reduction of benzil by *Curvularia falcate* yielded a mixture of erythro and threo (*S,S*) diols, in approximately equal amounts, as well as (*S*)-benzoin. In earlier studies Prelog et al. had formulated a rule,[4] shown in Figure 1, to account for the observed stereochemistry: if the ketone is placed with the larger group on the observer's left, the hydroxyl group formed is closer to the observer.

We first examined the reduction of benzil by *Cryptococcus macerans*, a microorganism that efficiently reduces acetophenone to (1*S*)-phenylethanol.[2] Microbiological reduction of benzil (**1a**) yielded (−)-(*S*)-benzoin (**2a**) and (+)-(1*R*,2*R*)-diphenylethanediol (**3a**) and only traces of the erythro isomer **4a**. The NMR spectrum of the crude extract was examined, in which the erythro and threo isomers showed easily distinguishable proton resonances for the protons on the benzylic carbons.[1] Although (*S*)-**2a** was formed in both our study and that reported by Prelog et al.,[3] there were two differences in our results. First, Prelog et al. obtained (−)-**3a** whereas (+)-**3a** formed with *C. macerans*, and second, appreciable quantities of the erythro isomer (**4a**) were obtained in their study while only traces were observed in our reduction. In addition, formation of (*S*)-**2a** and (*R,R*)-**3a** in our reductions was particularly perplexing because it was not apparent why the configuration about the hydroxyl-bearing carbons in the two compounds differed. In order to understand how or why this occurred, we investigated the mechanism of the reduction.

In order to establish that **2a** can be reduced to **3a**, racemic **2a** was examined under standard conditions as a substrate, and it was found to be efficiently converted to (*R,R*)-**3a** in greater than 50% yield by *C. macerans*. When unreduced **2a** was reisolated, it was found to be levorotatory, i.e., to contain an excess of the *S* enantiomer. These results require (*R*)-**2a** to be reduced much more easily than the *S* enantiomer, and since the (*R,R*) diol is obtained in greater than 50% yield, a mechanism for equilibrating *R* and *S* enantiomers exists. Since under our experimental conditions **2a** formed or recovered in these reductions is optically active, the rate of equilibration (racemization) is slower than the rate of reduction. These conclusions are incorporated in Scheme I which describes the course of these reductions. No conclusion as to the stereospecificity of the conversion of **1a** to **2a** can be made on the basis of our results. However, reduction of **2a** to **3a** is remarkable in the ability of the enzyme to reduce (*R*)-**2a** while effecting very little reduction of (*S*)-**2a**. Similar differences in the reduction rates of various substituted cyclohexanone derivatives were explained by Prelog as resulting from steric interferences between substituents on the substrate with the coenzyme on the enzyme surface.[5] Our results can be rationalized if the enzyme treats the phenyl group as the large substituent and the α-hydroxybenzyl



as the small one.