Reaction of Dihydrohexamethyl(Dewar benzene) with Singlet Oxygen[1]

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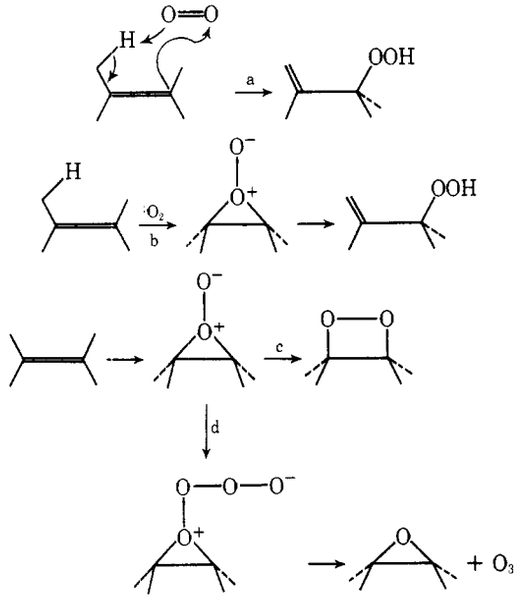
In connection with other studies we were interested in the reaction of hexamethyl(Dewar benzene) (HMDB) or its dihydro derivative **1** with singlet oxygen.

Two plausible mechanisms have been advanced for the "ene" reaction of olefins with $^1O_2$,[2] the concerted mechanism (path a)[3] and the perepoxide mechanism (path b).[4] The latter can be diverted to dioxetanes (path c) or epoxides (path d)

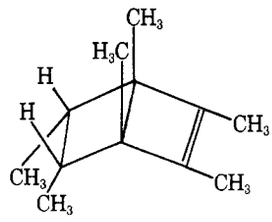


when no hydrogens are available for abstraction to give an "ene" reaction.[5] Intervention of dioxetanes is frequently invoked to explain the appearance of two carbonyl-containing fragments.

HMDB reacted rapidly with singlet oxygen to produce complex mixtures regardless of temperature, time, or method of generation of $^1O_2$. Use of TNB as a radical trap failed to simplify the reaction mixture. In the absence of sensitizer, i.e., with triplet oxygen, the only substances present after 1 h of photooxygenation were HMDB and hexamethylbenzene. The latter can be generated by thermolysis of HMDB,[6] but since the temperature was kept low, it is not clear what mechanism was operating in the present instance to produce hexamethylbenzene.[13]

To avoid these complications, dihydro-HMDB (**1**)[7] was prepared and photooxygenated in CH_2Cl_2 for 2 h. TLC and NMR analysis of the crude product revealed the presence of two major components, A and B. A was subsequently isolated and identified as the diketone **2** on the basis of spectral evidence [IR band at 1685 cm^{-1}, NMR signals at 1.98 (acetyl methyls), 1.34 (C-1 methyls), and an $X_3AA'X_3'$ system with X_3X_3' signals at 1.02 ppm (C-2 methyls) and AA' signals at 2.23 ppm (H-2's), similar to signals observed in the spectrum of **1**]. Since the NMR spectrum of the product mixture also exhibited two downfield one-proton singlets at 4.02 and 5.24 ppm appropriate for $=CH_2$, product B was presumed to be hydroperoxide **3**.

The crude product mixture was therefore stirred overnight with NaI in order to reduce the presumed hydroperoxide to **4**. However, the "reduction product" was essentially pure **2** and contained only traces of other substances. Similarly, an



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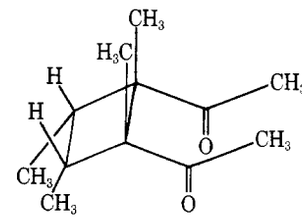

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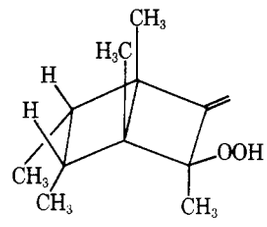

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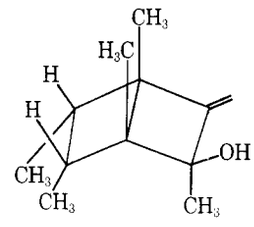

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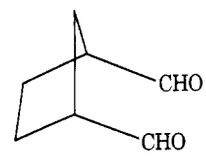

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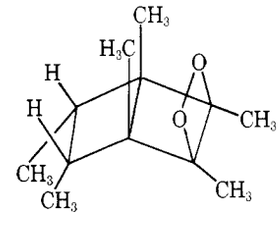

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attempt to separate **2** and B by preparative TLC gave three major bands, all of which contained **2** as the major component, but B was absent. Obviously, B was decomposing on the TLC plate.

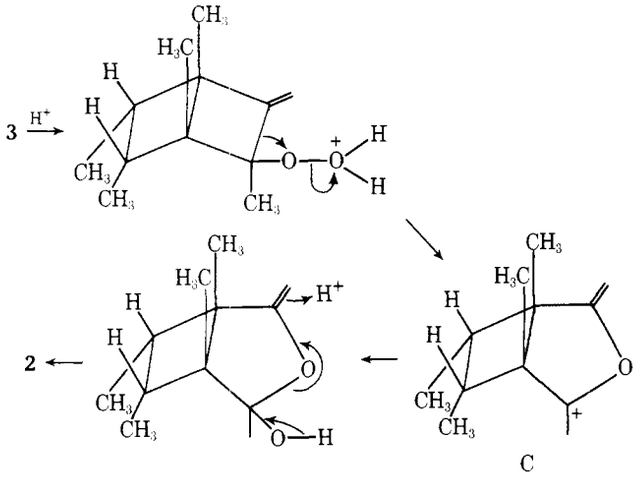
Photooxygenation of dihydro-HMDB at −78 °C followed by removal of solvent CH_2Cl_2 below 0 °C and analysis of the product mixture revealed B as the major product and only traces of **2**, but on standing overnight at room temperature in $CHCl_3$, B was converted completely to diketone **2**. Isolation of B at low temperature now permitted its identification as hydroperoxide **3** on the basis of its NMR spectrum, which exhibited signals at 5.23 (H-9b), 4.93 (H-9a), 2.38 m (H-5 and H-6), 1.46 (C-2 methyl), 1.13 and 1.09 (C-1 and C-4 methyls), and 1.04 d and 0.88 ppm d (J = 7 Hz, C-5 and C-6 methyls). Furthermore, photooxygenation of **1** at ambient temperature in CH_2Cl_2 in the presence of excess $P(OEt)_3$ resulted in formation of **4** as the only product by in situ reduction of **3**. Solvent removal followed by chromatography gave **4** in 55% yield as a low-melting, volatile solid with a camphoraceous odor. Its structure was evident from the spectra [IR bands at 3430, 3042, and 1642 cm^{-1}; NMR signals at 5.17 (H-9b), 4.76 (H-9a), and a singlet at 1.36 ppm characteristic of methyl on carbon carrying hydroxyl, as well as a two-proton multiplet centered at 2.42 (H-5 and H-6) and methyl singlets at 1.15 (C-1 methyl) and 1.09 (C-4 methyl) and doublets at 1.00 and 0.87 (J = 7 Hz, C-5 and C-6 methyls)]. The ^{13}C NMR spectrum (see Experimental Section) was also consistent with the assigned structure. The stereochemical assignment at C-2 is based on analogy to hydrogenation of HMDP and **1** which results invariably in exo addition and on the difference in chemical shift between the two singlet methyls.[7] Similar results have usually,[8] but not always,[9] been observed in other reactions of HMDB.

Dicarbonyls such as **2** may arise by thermal cleavage of dioxetanes. For example, the dialdehyde **5** obtained by photooxygenation of norbornene is almost certainly formed in this manner.[10] Such cleavage, if concerted, requires that one of the carbonyl fragments be produced in an excited state, leading to chemiluminescence or to "photochemistry without light", but unless care is taken to exclude quenching of the excited

molecules, the phenomenon may escape detection. However, there was no evidence of dioxetane (6) formation in the photooxygenation of 1, and indeed, the evidence presented in the previous paragraphs shows that 3, not the dioxetane 6, is the intermediate in the formation of 2. Moreover, when the decomposition of 3 was followed by NMR spectrometry in $CDCl_3$, no intermediate species could be detected and after 18 h, 3 had decomposed completely to 2. That the rearrangement of 3 to 2 is acid catalyzed could be demonstrated in the same manner; addition of a drop of HCl to an NMR tube containing 3 resulted in an exothermic reaction and immediate conversion to 2.

On the basis of these observations, a mechanism (Scheme I) similar to the rearrangement of cumene hydroperoxide to

Scheme I



phenol and acetone can be proposed for the conversion of 3 to 2. Protonation of 3, loss of water, and vinyl migration result in ion C. This reacts with water to form an enolic hemiacetal D which rearranges to 2. Rearrangement of allylic hydroperoxides in this fashion is well known and is referred to as the Hock cleavage.[11] The driving force for the facile rearrangement in the present case is undoubtedly the relief of strain in 3 on transformation to A.

Although the presence of a small amount of dioxetane 6 in the mixture from the photooxygenation of 1 cannot be excluded with certainty, the present work shows that the formation of dicarbonyl compounds or carbonyl fragments in photooxygenation reactions is not necessarily the result of dioxetane cleavage and that in such cases mechanistic speculations must be engaged in with caution unless the intervention of dioxetanes can actually be demonstrated.

Experimental Section[12]

Reaction of HMDB with Singlet Oxygen. A. This reaction was carried out by irradiation of 100 mg of the substrate and 5 mg of methylene blue in 50 mL of CH_2Cl_2 with a 150-W incandescent lamp placed near the reaction vessel. The solvent was removed at reduced pressure and the residue examined by TLC and NMR analysis. The following conditions were used, all giving complicated mixtures by NMR criteria: (1) 3 h, ambient temperature; (2) 1 h, ambient temperature; (3) 1 h, ambient temperature, 2 mg of TNB; (4) 15 min, −78 °C (in this run, the NMR spectrum indicated that little if any reaction had taken place).

B. A solution of 0.20 g of $P(OEt)_3$ in 50 mL of CH_2Cl_2 cooled to −78 °C was purged with oxygen, ozonized to exhaustion, and purged again with oxygen for 30 min. A solution of 0.1 g of HMDB in 20 mL of $CDCl_3$ was cooled to −78 °C, and added to the above. The mixture was allowed to warm to room temperature. Removal of solvent at reduced pressure and NMR analysis of the residue indicated a somewhat cleaner, but still rather complex, reaction.

Reaction of HMDB with Molecular Oxygen. A solution of 0.100 g of HMDB in 50 mL of CH_2Cl_2 was irradiated with a 150-W incandescent lamp for 1 h while a stream of oxygen was bubbled through the solution. After removal of oxygen, NMR and TLC analysis of the residue indicated the presence of starting material, hexamethylbenzene (characterized by a singlet at 2.20 ppm), and only traces of other substances.

Preparation of 1. Hydrogenation of HMDB with Pd/C by the literature method,[7] but purification by column chromatography or preparative TLC rather than distillation gave liquid 1 (which crystallizes in the freezer) whose NMR spectrum was identical with that reported. The ^{13}C NMR spectrum exhibited signals at 140.9 (C-2, C-3), 50.4 (C-1 and C-4), 37.6 d (C-5 and C-6) and 15.4 q, 11.7 q, and 11.1 ppm q (methyls).

Reaction of 1 with Singlet Oxygen. A. A solution of 0.500 g of 1 and 10 mg of methylene blue in 150 mL of CH_2Cl_2 was irradiated in a Hanovia-type reactor vessel using a Sylvania DVY tungsten–halogen lamp as an internal light source. The lamp was operated at 50–70 V and was cooled with a stream of air. A stream of oxygen was passed through the reaction mixture which was kept at ambient temperature by a water jacket placed between lamp and reaction mixture. After 2 h, TLC and NMR analysis indicated disappearance of 1 and formation of 2 and 3. The solution was stirred overnight with saturated aqueous KI, washed with saturated aqueous $Na_2S_2O_3$ and water, dried, and evaporated at reduced pressure. TLC of the residue indicated the presence of only one product. Preparative TLC yielded 371 mg (62%) of 2 as a low-melting solid whose NMR spectrum has been discussed previously. The analytical sample was repurified by preparative TLC.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 72.97; H, 10.14.

B. A solution of 0.500 g of 1 was photooxygenated as in A. The solvent was removed at low pressure below 25 °C and the mixture (two major and two minor products by TLC) purified by preparative TLC (eluent 3:7 ether–hexane). There were three major bands. The least polar band consisted of 2 and two minor products; the band of intermediate polarity contained mainly 2 and three minor products; and the most polar band was pure 2. 3 was completely absent.

C. Photooxygenation of 0.200 g of 1 was carried out as in A, but at −78 °C and with 3 mL of ethanol added to dissolve the sensitizer. After 1 h when TLC indicated disappearance of 1, the solvent was removed at reduced pressure below 0 °C. NMR analysis of the residue revealed the signals of 3 and traces of impurities including 2.

D. Photooxygenation of 0.500 g of 1 for 45 min as in A but with 0.700 g of $P(OEt)_3$ added, removal of solvent, and preparative TLC of the residue (eluent 1:3 ether–hexane) gave 344 mg (55%) of highly volatile 4 which melted below 20 °C. The NMR spectrum has been discussed previously; the ^{13}C NMR spectrum exhibited signals at 162.1 (C-3), 105.6 t (C-9), 80.6 (C-2), 51.1 (two narrowly separated singlets, C-1 and C-4), 39.4 d and 36.9 d (C-5 and C-6), 21.0 q, 19.2 q, and 14.6 q (C-1, C-2, and C-4 methyls), and 12.8 q and 11.1 ppm q (C-5 and C-6 methyls).

Anal. Calcd for $C_{12}H_{20}O$: mol wt, 180.1514. Found: mol wt, 180.1536 (mass spectrum).

Rearrangement of 3 to 2. A. Freshly prepared 3 was dissolved in $CDCl_3$ and placed in an NMR tube. The rearrangement was followed by NMR spectrometry and was complete after 18 h as shown by disappearance of the vinyl proton singlets at 5.23 and 4.93 ppm and the appearance of the methyl ketone singlets at 1.98 and 1.34 ppm.

B. Freshly prepared 3 was dissolved in $CDCl_3$ and placed in an NMR tube. The NMR spectrum showed the presence of a trace of 2. Addition of a drop of concentrated HCl caused a vigorous exothermic reaction. Redetermination of the NMR spectrum showed quantitative conversion of 3 to 2.

Registry No.—1, 2957-96-2; 2, 61477-44-9; 3, 61477-45-0; 4, 61477-46-1; HMDB, 7641-77-2; oxygen, 7782-44-7.

References and Notes

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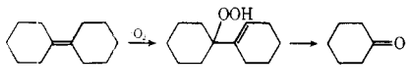
(11) See, for example, the decomposition of the hydroperoxide **8** (from **7**) to



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cyclohexanone; G. O. Schenck and K. H. Schulte-Elte, *Justus Liebigs Ann. Chem.*, **618**, 185 (1958).
(12) For experimental details, see J. A. Turner and W. Herz, *J. Org. Chem.*, in press.
(13) **Note Added in Proof.** Since hexamethylbenzene is a difficultly separable impurity in commercial HMDB, the hexamethylbenzene which we isolated may have been material originally present in the starting material.

Enzymatic and Chemical Resolution of 1-Octyn-4-ol

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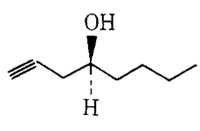
The alcohol 1-octyn-4-ol (I) is an intermediate in certain syntheses of prostaglandin analogues.[1] As such, it was important to have the racemate[2] resolved for stereospecific synthesis. Usually alcohols are converted to the half-phthalates and then resolved using such bases as brucine, dehydroabietylamine, or α-methylbenzylamine. In our hands these reagents were ineffective in this particular case. The enzymatic method of resolution is as old as the chemical method but organic chemists seldom avail themselves of this process.[3] In this note we would like to show that this method may be just as available to the chemist as the more popular chemical procedures.

We screened ten cultures in shaker flasks before finding one which selectively cleaved the benzoate of this alcohol. This culture, *Rhizopus nigricans* (Lederle culture R70), was then grown in a 30-L fermentor and the harvested cells were resuspended in distilled water and incubated with substrate. Using this technique, a free alcohol having a specific rotation of (−) 27 ± 2° (EtOAc) was obtained. This oil was reacted with (−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) chloride and the resultant ester examined by NMR in the methoxy region at δ 3.44 and 3.54 and found to be better than 95% optically pure.[4]

The (−)-I obtained by microbiological transformation was converted to the crystalline half-phthalate (−)-α-methylbenzylamine (MBA) salt. With the aid of these seed crystals a chemical resolution of (±)-I was achieved.



(−)-I

The unreacted benzoate of 1-octyn-4-ol recovered directly from our transformation work, while exhibiting good positive rotation, was not obtained optically pure. The optically pure positive rotamer was obtained, however, by processing the filtrates from the recrystallizations of (−)-MBA half-phthalate of (−)-I. These filtrates were stripped of (−)-MBA by HCl extraction and then treated with (+)-MBA. Repeated recrystallizations and careful manipulation of solvent composition finally yielded the pure salt (+)-MBA half-phthalate of (+)-I. When both enantiomorphs of 1-octyn-4-ol were obtained, a number of derivatives were made as shown in Table I. This table shows that the diastereoisomeric MBA salts, which are to be fractionally crystallized away from each other, melt only 9 °C apart, which may account in part for some of the difficulties of this resolution.

To assign absolute configuration we carried out the Horeau test[5] on (−)-1-octyn-4-ol and recovered excess (+)-(*S*)-α-phenylbutyric acid. If we assume that the butyl group is larger than the propargyl group as suggested by Landor et al.,[6] then (−)-I should have the *S* configuration. Hence, this material falls in line with the negative rotamers of 1-octyn-3-ol[7] and 1-hexyn-3-ol,[5] both of which are of the *S* configuration. Mindful of the difficulties which Pappo et al.[8] had with the assignment of (−)-1-octyn-3-ol using the Horeau method, we reduced (−)-I to 4-octanol. This sweet-smelling oil failed to give a Horeau response. Indeed the material showed no specific rotation. There is no doubt about its optical activity since the benzoate had a specific rotation of −3° and the phthalate gave a value of −4°. Table II gives CD values on (+)-I, the phthalate of (+)-I, and the phthalate of (+)-4-octanol. There is no reversal of Cotton effect in replacing the ethynyl group by an ethyl group; consequently (+)-4-octanol is likely to have the *S* configuration.

Experimental Section

TLC was carried out on silica gel thin layers with fluorescent indicator supplied by Brinkmann. IR spectra were taken either in KBr pellets or as smears between salt plates using an Infracord spectrophotometer. Mass spectra were run on a high-resolution direct inlet AEI MS9 instrument. NMR spectra were made using a Varian HA-100 instrument. Melting points were taken in capillaries and are uncorrected. CD spectra were supplied by Professor K. Nakanishi of Columbia University and were recorded on a Jasco spectropolarimeter.

Flask Screening Procedure. About 5 mL of sterile medium was used to wash out an agar slant of each culture using a sterile pipet. The inoculum wash was then divided between two Erlenmeyer flasks each containing 50 mL of medium which consisted of 2% edamine, 0.72% corn steep liquor, and 2% dextrose in water with pH adjusted to 6.8. The flasks were set on a rotary shaker at 28 °C for 72 h at which time 50 mg of the benzoate of (±)-I in 0.1 mL of acetone was aded to one of the flasks and the fermentations were continued. Samples of 5-mL volume were taken at 16 and 40 h after substrate addition. The samples were extracted with $CHCl_3$. The extracts were dried, concentrated to dryness, and reconstituted to 0.1 mL with MeOH. Approximately 25 μL of the reconstituted samples was applied to thin layers and developed using 90:10 hexane–EtOAc. The spots were visualized by UV scanning and by H_2SO_4 charring and compared with control spots. By this procedure it was found that *Rhizopus nigricans* (Lederle culture R70) transformed the negative benzoate rotamer to the free alcohol.

Thirty-Liter Tank Conversion of Substrate by R70. Two Erlenmeyer flasks of the previously described medium were inoculated from a slant of culture R70 and grown for 3 days and then used to inoculate a 1-L bottle of the same medium. This second stage inoculum was grown for 1 day and then added to a 30-L fermentor. After 24 h of growth in the tank at 25 °C with aeration and agitation, 8.5 g of the benzoate of (±)-I in 25 mL of acetone was added. The tank was harvested 9.5 h later. The cells were filtered off using cheese cloth and set aside for further work. The filtrate was extracted with ⅕ volume of EtOAc which yielded 6.4 g of an oil. Chromatography of this oil over adsorbent silica yielded 1 g of the benzoate of I, $[\alpha]^{25}_D$ +21 ± 1° (*c* 1.65, EtOAc), and 250 mg of 1-octyn-4-ol, $[\alpha]^{25}_D$ −10 ± 1° (*c* 1.65, EtOAc). The cells from the above procedure were washed with H_2O and then resuspended in 15 L of H_2O with 15.0 g of substrate in 5 mL of acetone added. After agitating overnight without air supply, the cells were again removed using cheese cloth. Extraction of the filtrate with EtOAc yielded 7.0 g of an oil which when subjected to adsorbent silica chromatography yielded 1.8 g of I, $[\alpha]^{25}_D$ −18 ± 2° (*c* 1.60, EtOAc).

About 120 mg of this preparation was distilled in a Kugelrohr apparatus at 75 °C under 250-μm pressure to get 66 mg of a mobile, colorless oil: $[\alpha]^{25}_D$ −27 ± 2° (*c* 0.41, EtOAc); ^1H NMR ($CDCl_3$) δ 0.92 (3 H, t, terminal CH_3), 1.41 [6 H, m, $-(CH_2)_3CH_3$], 1.91 (1 H, t, $-C{\equiv}CH$), 2.28 (2 H, m, $HC{\equiv}CCH_2$), 3.66 (1 H, m, >CHOH); IR