Notes

Interconversion of Eremophilone and Isoeremophilone and Related Reactions

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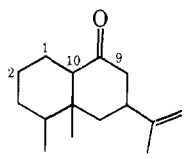
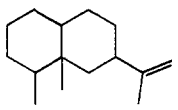
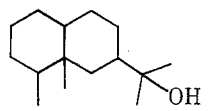
Eremophilone (1), probably the best known sesquiterpene because of its unique nonisoprenoid structure,[2,3] has only recently been synthesized,[4] culminating over 40 years of fascinating chemistry. A few years ago we demonstrated the cooccurrence of the β,γ-unsaturated isomer of eremophilone, $7\alpha(H)$-eremophila-1,11-dien-9-one (**2**), in the ether extract of the wood of *Eremophila mitchelli*.[5] We now report the efficient conversion of natural eremophilone into $7\alpha(H)$-eremophila-1,11-dien-9-one by alkaline deconjugation using potassium *tert*-butoxide. Thus, an eremophilone-rich (92% eremophilone, 5% $7\alpha(H)$-eremophila-1,11-dien-9-one) mixture, on stirring for 1 hr at room temperature with 5.6 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol, gave, after quenching with water, a mixture containing 88% $7\alpha(H)$-eremophila-1,11-dien-9-one and 6% eremophilone. It is interesting that the equilibrium composition of a mixture of ketones **1** and **2** comprises approximately a 1:1 ratio of the two rather than a great preponderance of the α,β-unsaturated ketone as might have been expected. The apparent decreased stability of **1** must arise from the increased steric interaction of the C-4 and C-5 methyl groups in **1** as compared to **2**. As previously mentioned, this presumably is responsible for the deshielding (~0.1 ppm) of the C-4 methyl group in **1** relative to the corresponding methyl group in **2**.[5]



1, $\Delta^{1(10)}$
2, $\Delta^{1(2)}$
5, $10\beta(H)$



3, $\Delta^{1(10)}$
4, $\Delta^{9(10)}$



6, $\Delta^{1(10)}$
7, $\Delta^{9(10)}$

When eremophilone was reduced with lithium aluminum hydride in the presence of aluminum chloride (1:2 molar ratio of $LiAlH_4$ to $AlCl_3$) in ether, a complex mixture of products was obtained, which was separated by chromatography on alumina into a hydrocarbon fraction (42% by weight) and a ketone fraction (58%). The hydrocarbon fraction was composed of two major components (50 and 30%, respectively, by GLC), which were collected by preparative GLC. The major hydrocarbon (>98% pure by GLC) appeared similar to eremophilene on cursory inspection (ir, NMR), but direct comparison with an authentic sample of eremophilene (**3**) showed that, in fact, the two hydrocarbons differed by GLC and in their ir, NMR, and mass spectra.[6] However, under identical conditions both this hydrocarbon and eremophilene were reduced to the same saturated hydrocarbon, eremophilane. On the basis of its NMR spectrum, in particular the appearance of olefinic protons at δ 5.40 (1, m) and δ 4.78 (2 H, br s), its nonidentity with eremophilene (**3**), and its method of preparation, this product has been assigned the structure $7\alpha(H)$-eremophila-9,11-diene (**4**). Owing to insufficient material, the second hydrocarbon has not been fully characterized, but it is not identical with eremophilene and appears to be a rearranged product. It has been reported that a 1:2 ratio of $LiAlH_4$ to $AlCl_3$ leads to preferential shifting of the double bond to the original carbonyl carbon.[8]

The above-mentioned ketone fraction consisted predominantly of one substance (70% by GLC) which was collected by preparative GLC and shown to be identical with *cis*-dihydroeremophilone (**5**) by GLC and ir, NMR, and ORD spectral comparisons. The conjugate reduction of α,β-unsaturated carbonyls with mixed hydrides has previously been reported and appears to be sensitive to the $LiAlH_4$ to $AlCl_3$ ratio.[9] Attempts to convert eremophilone into eremophilene via reduction of the thioketal or by Wolff–Kishner reduction met with no success. Likewise, plans to convert eremophilone into valencene were frustrated when preferential oxidation of the isopropenyl group by the Lemieux von Rudloff reagent or by osmium tetroxide failed.

On treatment with *m*-chloroperbenzoic acid, eremophilone gave eremophilone 11-oxide, obtained in pure form (>95% by GLC) by chromatography on neutral alumina. Reduction of this oxide with lithium aluminum hydride in ether gave a complex mixture, the GLC of which showed two major components (50 and 30%, respectively). On further reduction with lithium aluminum hydride–aluminum chloride, as described above, this mixture gave a complex mixture containing only one major component (52% by GLC). Chromatography on alumina gave a pure product (>97% by GLC), similar to but distinctly different by ir and NMR from eremoligenol (**6**).[10] In view of its spectral properties, in particular the appearance in the NMR of a single olefinic proton at δ 5.40, similarity to eremoligenol, and the above-mentioned results, this product has been assigned the structure $7\alpha(H)$-eremophila-9-en-11-ol (**7**).

Experimental Section[11]

$7\alpha(H)$-Eremophila-1,11-dien-9-one (2). Forty milligrams of an eremophilone-rich mixture (92% eremophilone, 5% $7\alpha(H)$-eremophila-1,11-dien-9-one by GLC) in 2 ml of dry *tert*-butyl alcohol was added to a solution prepared by adding 40 mg of potassium to 25 ml of dry *tert*-butyl alcohol.[12] After stirring at room temperature in a nitrogen atmosphere for 1 hr, 100 ml of water was added and the solution was extracted with ether. Washing with water, drying (sodium sulfate), and removal of the ether gave 37 mg of a pale yellow oil, which on GLC analysis (3% SE-30) showed 88% $7\alpha(H)$-eremophila-1,11-dien-9-one identified by ir, NMR, and ORD comparisons with an authentic sample.

Equilibration of 1 and 2. In an attempt to establish the equilibrium between **1** and **2**, 10 mg of a mixture of eremophilone and isoeremophilone (57:43) was added to 2 ml of ethanol, and to this 2 ml of 0.5 *N* hydrochloric acid was added and the solution was allowed to stand in a nitrogen atmosphere at room temperature. Periodic analysis by GLC (3% SE-30) showed essentially no change in composition of the mixture, even after 24 hr. In another experiment, to 10 mg of the above-mentioned eremophilone–isoeremophilone mixture in 2 ml of methanol was added a solution containing 1 mg of sodium methoxide in 2 ml of methanol in a nitrogen atmosphere. After 1 hr at room temperature there was no change in the mixture composition. Likewise, there was no change after 2 hr of reflux. Use of more concentrated base and more drastic conditions resulted in the destruction of **1**.

Reduction of Eremophilone with $LiAlH_4$–$AlCl_3$. To 0.152 g of lithium aluminum hydride in 20 ml of dry ethyl ether was added 1.06 g of anhydrous aluminum chloride followed by 0.218 g of ere-

mophilone in 5 ml of dry ether. The reaction mixture was stirred for 1 hr at room temperature, refluxed for 2 hr, then cooled in an ice bath and cold water was added until no further reaction occurred. After filtration, the solution was extracted with ether and the latter extract was washed with aqueous bicarbonate, then brine and finally dried and concentrated to give 0.179 g of a pale yellow, mobile liquid. Chromatography of the latter on 10 g of activity I neutral alumina gave 0.074 g of a hydrocarbon fraction in the petroleum ether eluent and 0.102 g of a ketone fraction in the ethyl ether eluent. GLC analysis (5% Carbowax column) of the hydrocarbon fraction showed two major components (50 and 30%, respectively), while GLC analysis of the ketone fraction (3% SE-30) showed one major component (70%). Preparative GLC (5% Ucon polar) gave 7$\alpha(H)$-eremophila-9,11-diene (**4**) as the major component (>98% purity by GLC): ν_{max} (CCl_4) 1640, 882 cm^{-1}; δ (CCl_4) 0.94 (3 H, d, J = 6 Hz), 1.03 (3 H, s), 1.82 (3 H, s), 4.78 (2 H, br s), 5.40 (1 H, m); ORD (c 0.06, CH_3OH), plain negative curve $[\phi]_{589}$ −80.2°; mol wt by mass spectrometry (peak-to-peak distance measurement using 1,2-dichlorooctafluorocyclohexene-1 as reference) 204.186 (calcd for $C_{15}H_{24}$, 204.188).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.00; H, 11.90.

A comparison of the ir and NMR spectra of 7$\alpha(H)$-eremophila-9-11-diene (**4**) with those of eremophilene (**3**) showed that they were not identical and a direct comparison with an authentic sample of eremophilene by GLC showed their nonidentity (5% Carbowax column).[6] However, hydrogenation (Pt, EtOH) of both dienes gave the same saturated hydrocarbon as determined by GLC (5% Carbowax column) and mass spectral analysis. The major component of the ketone fraction was collected by preparative GLC (3% SE-30 column) and was identified as *cis*-dihydroeremophilone[7] by GLC, ir, ORD, and NMR: δ (CCl_4) 0.93 (d, J = 5 Hz), 1.15 (3 H, s), 1.87 (3 H, s), 4.85 (2 H, br s).

7$\alpha(H)$-Eremophil-9-en-11-ol (7). To 0.436 g of eremophilone (containing ~15% isoeremophilone) in 15 ml of anhydrous ether, 0.406 g of *m*-chloroperbenzoic acid (85% active) was added and the solution was stirred at room temperature for 24 hr. After addition of water, the solution was extracted with ether and the combined ether extracts were washed with aqueous sodium bicarbonate, then brine and finally concentrated to give 0.45 g of a colorless liquid. GLC analysis (3% SE-30 column) showed one major peak (80%). No starting material remained. Chromatography on neutral alumina (activity II–III) gave eremophilone 11-oxide (95% purity by GLC) in the benzene eluent: δ (CCl_4) 0.97 (3 H, s), 0.99 (3 H, d, J = 5.5 Hz), 1.27 (3 H, s), 6.46 (1 H, t, J = 3.8 Hz); complete disappearance of band at 896 cm^{-1} in ir.

To 50 mg of lithium aluminum hydride in 20 ml of anhydrous ether was added a solution of 400 mg of eremophilone 11-oxide in 5 ml of dry ether and the solution was stirred at room temperature for 1 hr and then refluxed for 2 hr. The solution was then cooled, moist ether was added, and, after filtration, the ether layer was dried and concentrated to give 0.375 g of a colorless, viscous liquid, the GLC (3% SE-30) of which showed a complex mixture containing two major components (50:30). This crude product (0.242 g) was dissolved in 10 ml of anhydrous ether containing 0.133 g of anhydrous aluminum chloride and this was added to a solution of 0.076 g of lithium aluminum hydride and 0.399 g of anhydrous aluminum chloride in 15 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 1 hr and then refluxed for 2 hr. After the usual work-up, 0.201 g of a viscous liquid was obtained, the GLC (3% SE-30) of which showed a complex mixture with one component (51%). Chromatography on 10 g of neutral alumina (activity II–III) gave in the benzene–ether (96:4) eluent 16 mg of 7$\alpha(H)$-eremophil-9-en-11-ol (**7**, 97% by GLC on 3% SE-30 and 15% Carbowax 2014 columns). This product was not identical, by ir and NMR comparisons, with eremoligenol (**6**):[10] ν_{max} (CCl_4) 3600, 3460, 1665 cm^{-1}; δ (CCl_4) 0.93 (unresolved doublet, $J \simeq 6$ Hz), 1.04 (3 H, s), 1.22 (3 H, s), 1.27 (3 H, s), 5.40 (1 H, m); mol wt by mass spectrometry (peak-to-peak distance measurement using 1,2-dichlorooctafluorocyclohexene-1) 222.187 (calcd for $C_{15}H_{26}O$, 222.198).

Registry No.—**1**, 562-23-2; **2**, 22489-11-8; **4**, 54868-40-5; **5**, 54814-46-9; **7**, 54832-19-8; eremophilone 11-oxide, 54814-47-0; $LiAlH_4$, 16853-85-3.

References and Notes

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(6) We thank Professor V. Herout (Czechoslovak Academy of Science) for a sample of eremophilene and for its ir and NMR spectra (Oct 9, 1968).
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(9) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, p 91.
(10) We thank Dr. H. Ishii (Shionogi Research Laboratory, Osaka, Japan) for copies of the ir and NMR spectra of eremoligenol. Unfortunately, an authentic sample was no longer available (Oct 18, 1968).
(11) Ir spectra were recorded with a Perkin-Elmer 237B spectrophotometer, NMR spectra were obtained with a Varian A-60 spectrometer, and mass spectra were obtained using a Varian M-66 mass spectrometer. GLC analyses were performed using a F & M biomedical gas chromatograph, Model 400.
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A New Mild Conversion of Ketones to the Corresponding Methylene Derivatives

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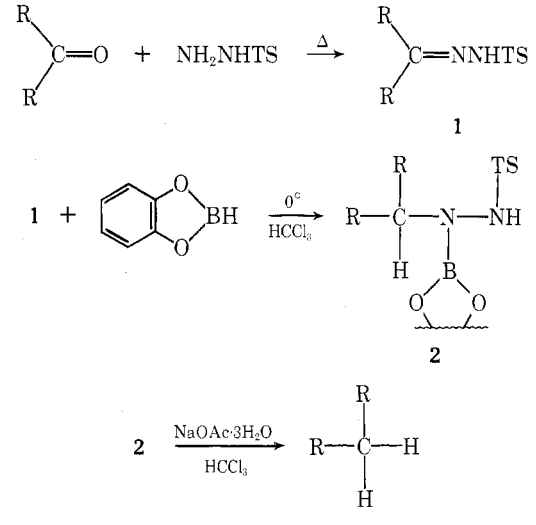
We wish to report a new, mild conversion of ketones to the corresponding methylene derivatives. The conversion involves the reduction of tosylhydrazones with catecholborane followed by decomposition of the reduction product (Scheme I).

Scheme I



The conversion of carbonyl compounds to their corresponding methylene derivatives is one of the key transformations in organic synthesis. Not surprisingly, a great deal of literature exists concerning this transformation.[1] The reduction procedures that are generally employed utilize strong acids or bases which preclude the presence of sensitive functional substituents.[2] The more recently reported reduction procedures involve the less reactive hydride reagents and carbonyl derivatives.[3,4] However, these new procedures involve the utilization of large excesses of hydride.[3] We felt that the reduction of tosylhydrazones with catecholborane would be an ideal way to achieve the reduction of carbonyl compounds. The tosylhydrazones are readily prepared, requiring no acid or base catalysis.[3a] Furthermore, the use of the mild, commercially available (Aldrich) catecholborane negates the need for excess hydride, which