Acid-Catalyzed Rearrangements of Humulene

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Acid-Catalyzed Rearrangements of Humulene¹

William G. Dauben.* James P. Hubbell, and Noel D. Vietmeyer

Department of Chemistry, University of California, Berkeley, California 94720

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Upon extended treatment with acid, the sesquiterpene humulene yielded 20-25% α -caryophyllene alcohol and 70-75% mainly a new bicyclic sesquiterpene hydrocarbon. The structure of the material, as well as a series of its precursors, was established. The mechanism of the transformation was shown to proceed via a series of stepwise rearrangements.

In recent years considerable interest has been directed toward the biogenesis, rearrangement, and synthesis of polyisoprenoid natural products. The finding of the enzymatically induced cyclization of squalene epoxide to lanosterol called attention to the high degree of specificity of a polycyclization initiated by formation of a carbonium ion. The in vitro equivalent of the process, i.e., regiospecific carbonium ion generation, has been utilized by Johnson² to convert polyolefins to steroids, by Marshall³ to convert bicyclo[4.3.1]decanes to hydroazulenes, and by studies in this laboratory⁴ of the acid catalyzed rearrangement of the cyclopropyl-ene system in the sesquiterpene thujopsene to yield sesquiterpenes of the widdrene and chamigrene series.

In the Hendrickson biogenetic hypothesis for bicylic and tricyclic sesquiterpenes,⁵ key intermediates were the eleven-membered ring carbonium ions 2 and 3, respectively.



These ions were suggested to be the intermediates in the transformation of farnesol (1) to caryophyllene (4) and humulene (5). It was of particular interest that the ion 3 was related to humulene (5) by simple loss of a proton and such a relationship called attention to the possibility of the acid catalysis of the reverse process, 5 to 3.

The acid-catalyzed rearrangement of α -humulene, itself, was first reported by Nickon⁶ who reported that the hydrocarbon upon treatment with sulfuric acid in ether gave rise to alcohol 6 in 12-24% yield. The present studies were directed toward a more controlled reaction and investigation of all the products of the reaction. It was found that humulene (>97% pure) in refluxing dioxane-water containing 0.02 M perchoric acid yielded 20-25% of alcohol 6 (stable



under the reaction conditions) and that the 75-80% of the remaining material was more than 90% of one hydrocarbon. This major material was isolated and its structure established.

The product (7) was isomeric with humulene (mass spectrum) and possessed an s-trans conjugated diene chromophore (uv max 245 nm, ϵ 12,000). The nmr spectrum showed signals for one vinyl hydrogen atom, one vinyl methyl group, one quaternary methyl group, and an isopropyl group. The presence of the isopropyl group was further confirmed by double resonance studies and by an M - 43peak (93% of base peak) in the mass spectrum. These data indicated the absence of any additional double bond in the structure and with the conjugated diene accounting for only two degrees of ursaturation, the hydrocarbon 7 must be bicyclic. Furthermore, the quaternary methyl group most likely was at an angular position.

The material was dihydrogenated and vpc analysis of the crude reduction product showed the presence of 79% of hydrocarbon 8, 17% of hydrocarbon 9, and 4% of starting material. If the reaction mixture was allowed to remain under hydrogenation conditions for an extended period (6-8 hr) practically no further uptake of hydrogen occurred but the only product obtained was 9. The isomeric dihydro derivatives were isolated by preparative vpc. The nmr spectrum of 8 showed signals for one vinyl proton, an isopropyl group, an angular methyl group, and a new secondary methyl group but no vinyl methyl group. The final product 9 which was resistant to further hydrogenation showed no vinyl proton signals in the nmr spectrum but did show double bond absorption in the Raman spectrum. This unsaturated bond cannot be between two rings since there is an angular methyl group. Furthermore, since there is no vinyl methyl group, it follows that the isopropyl group must be on the tetrasubstituted double bond.

Treatment of hydrocarbon 8 with osmium tetroxide yielded diol 10 which was cleaved with lead tetraacetate to give a keto acid 11a. The ir spectrum of the keto acid and its methyl ester indicated the presence of a five-membered

	(Relative %		Hydrocarbon		
Time, hr	a-Humulene	Alcohol 6	Alcohol 21	ß-Humulene	7	19	20
0	100						
5	76			4.0			
8	57			4.6			
9	56						
13	46			5.7			
19	33	1.4	1.8	6.3			
35	20						
40	18	3.5	6.3	7.8	0.2	0.7	1.7
51	14.4	6,6	8.3	7.3	0.6	1.5	2.3
55	13.5	7.5	8.5		0.8	1.7	3.4
75	12	8.9	11.9	6.0	0.9	2.3	7.3
92				4.9			
134				4.4			
159	4.7	9.0	18.5	3.3	5.7	5.4	13.3
183	4	10.1	18.7		7.1	6.1	16.8
206	3.5	11.1	18.3	8.6	8.6	6.0	17.8
254	2.6	11.6	17.6		12.3	7.0	23.0
307	1.4	12.3	15.9		14.5	7.8	24.6
355		14.6	13.8		18.3	7.4	28.6
473		18.0	10.3		28.7	5.4	26.7

 Table I

 Acid-Catalyzed Rearrangement of Humulene^a

^a A 0.105 M solution of humulene in a 20% aqueous dioxane, 0.02 M in HClO₄, was heated at 67°.

ring ketone (1739 cm⁻¹). Thus, the other ring of this bicyclic system must be seven membered. Further structural information was gained by high resolution mass spectrometry. The base peak for the keto ester 11b had an m/e of 140 and by exact mass measure was $C_{\theta}H_{16}O$. The loss of mass 128 ($C_7H_{12}O_2$) most likely resulted from the McLafferty rearrangement as shown in Scheme I and showed that this piece derived from the seven-membered ring portion of the





molecule could not contain the isopropyl group. Further evidence for the assignment of the isopropyl group on the cyclopentanone ring was the loss of 43 (C_3H_2) from the m/e140 peak to form C_6H_9O (m/e 97). Some evidence suggesting the position of the tertiary methyl group in hydrocarbon 8 was derived from the appearance of m/e 88. This peak could result from a McLafferty rearrangement involving the ester function and would require a methyl group α to the ester function.

The isomeric monoolefin 9 with the tetrasubstituted double bond was also converted to a glycol and cleaved to yield the dione 12. Since the earlier discussed nmr data showed the isopropyl group was on the double bond, the unsaturated linkage containing it must be exocyclic to a



rived from the sesquiterpene carotol.⁷ Using high resolution mass spectral data, the peak of m/e 140 (C₉H₁₆O) was shown by a metastable ion study to have a parent of m/e238 (C₁₅H₂₆O₂). The loss of C₆H₁₀O would easily be ex-



plained by a McLafferty rearrangement. This fragmentation pattern when coupled with the earlier discussed placement of the isopropyl group established that diketone 12 must contain a seven membered ring with two methyl groups $(m/e \ 140, C_9H_{16}O)$.

These degradational and spectral studies established the structure of the basic ring system of the rearrangement hydrocarbons. Further supporting evidence was obtained by allylic oxidation of olefin 9 to give the conjugated cyclopentenone 14. The most characteristic change in the nmr spectrum of this product was the appearance of a sharp twoproton singlet corresponding to a methylene group between the carbonyl group and a quaternary center. This finding is direct evidence for the placement of an angular methyl group. The degradational studies are summarized in Scheme II.

To obtain additional information with regard to the reaction pathway, the rearrangement of humulene was run at a lower temperature and the course of the reaction was



followed by vpc. The results (Table I, and Figure 1-3) showed that the initial products formed were humulol (15) and β -humulene (16).⁸ The nmr spectrum of humulol was



identical with a major alcohol isolated from hop oil by Buttery,⁹ and later by Naya and Kotake.¹⁰ To establish the correctness of structure 15 for the natural humulol, the material was synthesized in an unequivocal manner. Humulene was converted to the monoepoxide 17 (humulene ep-



oxide II) by treatment with *m*-chloroperbenzoic acid and the resulting epoxide was allowed to react with lithium in ethylamine¹¹ to give humulol (15) in 9% yield and isohumulol (18) in 56% yield. The synthetic 15 possessed the same ir, nmr., and mass spectra as well as vpc retention time (500 ft \times 0.02, PPE) as the natural humulol.

Next, the major hydrocarbon intermediates formed during these controlled reactions were examined. The nmr spectrum of 19 showed signals for three vinyl protons, two



vinyl methyl groups, and one quaternary (angular) methyl group. The infrared spectrum showed bands at 890 and 1640 cm⁻¹, indicating the hydrocarbon possessed an unsymmetrical disubstituted methylene group. Specific hydrogenation of this double bond gave rise to a dihydro isomer which was shown to possess an isopropyl group by nmr analysis. The mass spectrum of this material showed a



Figure 1. Relative composition *vs.* time: humulene (5), \bullet ; humulol (15), Δ ; β -humulene (16), O.



Figure 2. Relative composition vs. time: α -caryophyllene alcohol (6), Δ ; alcohol 21, \bullet .



Figure 3. Relative composition vs. time: hydrocarbon 7, \bullet ; hydrocarbon 19, O; hydrocarbon 20, \triangle .

fragmentation pattern almost identical with that of hydrocarbon 7, suggesting that both materials possessed the same carbon skeleton. This conclusion was verified by the finding that 19 upon treatment with acid was converted to 7. Thus, the isopropenyl structure shown in 19 was established.

Hydrocarbon 20 also showed a mass spectral fragmentation pattern similar to that of 7. The nmr spectrum showed



signals for one vinyl proton, three vinyl methyl group, and one quaternary (angular) methyl group. Also, the spectrum possessed a one-proton multiplet absorption at δ 3.20, characteristic of a doubly allylic hydrogen atom. Based upon these spectral features and its conversion to 7 upon acid treatment, the isopropylidene structure shown in 20 was established. The alcohol 21 formed in the controlled studies was next studied. This material could only be obtained in 90% purity



with α -caryophyllene alcohol being the only impurity. The nmr spectra of the material showed signals for one vinyl proton, two equivalent methyl groups α to a carbon atom holding a hydroxyl grouping, one vinyl methyl group, and one quaternary (angular) methyl group. The mass spectral fragmentation pattern, after loss of water, was similar to those of hydrocarbons 7, 19, and 20. The alcohol was dehydrated via treatment of its mesylate with triethylamine and the hydrocarbon mixture obtained as shown, by vpc analysis, contained 16% of 7, 30% of 19, and 54% of 20. All these results establish the structure 21 for the alcohol.

The structural assignments for the hydrocarbons 19 and 20 and for the alcohol 21 recently have been corroborated by Naya and Hirose¹² in an independent study, the gross carbon skeleton being based upon the present structural proof for the hydrocarbon 7.

From the structures of the various intermediates formed in the controlled acid-catalyzed rearrangement of humulene and from the simple kinetic studies, it appears that humulol was first formed from humulene in a reversible reaction. Then, humulol via an intermediate(s) formed α caryophylene alcohol (6) and alcohol 21, the latter, in turn, being converted to hydrocarbons 19, 20, and 7.

Attention was next directed to the details of the rearrangement pathway followed by humulene. Recent chemical studies by Nickon⁶ and ¹³C nmr studies by Nickon and Stothers¹³ have elaborated the pathway leading to the formation of α -caryophyllene alcohol (6) and showed the requirement of the intermediate triene 22 in the rearrange-



ment process. To determine whether this same triene was a required intermediate in the formation of alcohol 21, a time study was done for the conversion of humulene to 6 and 21 under reaction conditions of perchloric acid in refluxing dioxane-water. It was found that the ratio of their formation changed with time, the values for the ratio of 21 to 6 at 1, 2, and 4 hr being 0.6, 0.9, and 1.2, respectively. These data clearly indicate that triene 22 although a required intermediate for 6 is not so required for the formation of 21. Also, if 21 came via triene 22, a protonation of the isolated double bond would be required for the cyclization. Such a protonation should be reversible but Nickon and Stothers did not find a deuterium at this position in their study of the formation of 6 in D_2SO_4 .

A sample of deuterated 7 was prepared from humulene under the same conditions used above for the preparation of deuterated $6.^{13}$ Under these conditions, the deuterium incorporation was extensive and the material contained 11% d_0 , 15% d_1 , 17% d_2 , 17% d_3 , 14% d_4 , and 13% d_5 , by mass spectral analysis. The nmr spectrum showed a significant loss (~30-40%) of absorption at the vinyl methyl group (C-15 humulene numbering) and a slight loss (~10-15%) of intensity at the isopropyl group (C-12 and C-13). There was no loss of absorption at the angular methyl group (C-14).



O = minor deuterium location

To obtain the placement of the other deuteria, hydrocarbon 7, and its dihydro derivative 9 and deuterated 7 were submitted to ¹³C nmr analysis. With the knowledge that α -humulene, β -humulene, and humulol are rapidly interconverted (see Figure 1) and by comparison of the absorptions of 7 with dihydro 9, the assignment of the allylic methylene at C-6 was made. Also, in making some of the other assignments it was assumed that the absorpion bands of all carbons except 5, 6, 7, 8, 9, and 15 would not shift greatly upon dihydrogenation of 7 to 9. The assumption was based upon the fact that the rigidity of the five-membered ring in 9 was retained. This analysis permitted assignment of C-2 in the spectrum. With deuterated 7, major deuterium concentration was at carbons 2, 6, and 15; a





minor amount was located in the isopropyl carbons 11, 12, and 13.

With these data, the mechanism for the humulene interconversions can be accounted for as shown in Scheme III. First, the 6, 7 double bond of humulene is blocked by selective protonation either as humulol or β -humulene. This transformation directs the second protonation to occur at the 2,3 double bond, forming a tertiary carbonium ion which, in turn, cyclizes on the disubstituted double bond to yield the [5.4.0] bicycloundecane ring system. Finally, ring contraction with either concomitant dehydration (if humulol is the precursor) or double bond migration (if β -humulene is the precursor) leads to the products 7, 19, 20, and 21. Naya and Hirose^{12,14a} have also studied the humulene isomerization and a similar mechanism to that first postulated by us was set forth on their minimal data.^{14b}

Finally, it should be reemphasized that only a small amount of deuterium (<10%) was incorporated at C-11 of the isopropyl group. If, indeed, 21, 19, and 20 were required intermediates in the generation of 7, then, as show, normal amounts of deuterium would have been found at C-11. Such not being the case indicates that under the conditions employed in this labeled experiment the majority of the final product 7 arose via a 1,2-hydride shift from C-10 to C-11, shown below.



Experimental Section

Microanalysis and mass spectra were obtained from the Microchemical and Mass Spectrometry Laboratories, College of Chemistry, University of California. Raman and some nmr (100 MHz) spectra were kindly provided by the U.S. Department of Agriculture Regional Laboratories, Albany, Calif. Unless noted, the infrared spectra were taken in carbon tetrachloride and the nmr spectra were taken in carbon tetrachloride with TMS as the internal standard. All carbon-13 nmr spectra were obtained at 25.2 MHz with a Varian XL100 spectrometer, with chloroform as a solvent and TMS as an internal reference, and were kindly provided by the Space Science Laboratory, University of Calif. Melting points were determined in open capillary tubes in a Buchi meltingpoint apparatus and are uncorrected.

In working up a reaction all solutions were dried by filtration through a small amount of anhydrous magnesium sulfate and were concentrated by rotary evaporation at reduced pressure with a water aspirator. Purification of compounds by column chromatography was carried out using Woelm neutral alumina or silica gel from E. M. Reagents.

All samples for analysis by vpc in kinetic studies of acid-catalyzed rearrangement reactions were neutralized by saturated sodium bicarbonate solution. The organic material was extracted with ether and the ether extract was dried and concentrated. If the samples were to be analyzed on capillary columns of OV101, OV225, or Apiezon, the alcohols were removed by chromatography on a short column of dry-packed activity III Woelm alumina.

Acid Treatment of Humulene. Into a 500-ml, three-necked flask fitted with a reflux condenser, stopper, serum cap, and a magnetic stirrer, under a nitrogen atmosphere, was added 180 ml of dioxane, 20 ml of water, 0.8 ml of 70% perchloric acid, and 4.2 g (20.6 mmol) of humulene. The solution was refluxed for 1 week at which time by vpc analysis (10 ft \times $\frac{1}{8}$ in. 5% KDH, 5% Carbowax 20M) it showed the presence of one major hydrocarbon. The reaction mixture was quenched with saturated sodium bicarbonate solution, the rearrangement products were extracted with hexane, and the extract was dried and concentrated. The residual oil was chromatographed on 80 g of dry-packed activity II alumina to give 2.1 g of hydrocarbons (hexane eluate) and 1.8 g of alcohols (ether eluate). Analysis of the hydrocarbon fraction by vpc (500 \times 0.02" OV101) showed one hydrocarbon was present to at least 90%. Collection of this hydrocarbon by vpc (10 ft \times % in. 10% KOH, 10% Carbowax 20M) gave pure hydrocarbon 7: ir (CCl₄, CS₂) 1380, 1372, 1369, 1360, 861 cm⁻¹; Raman 1650 cm⁻¹; uv (95% EtOH) 245

nm (ϵ 12,000); nmr δ 5.86 (s, 1), 2.70 (septet, 1, J = 7 Hz), 1.72 (s, 3), 0.94 (d, 3, J = 7 Hz), 0.92 (s, 3), 0.90, (d, 3, J = 7 Hz); cmr 143.2 (s), 139.1 (s), 137.2 (s), 119.3 (d, C-8), 50.1 (s, C-3), 42.4 (t, C-1), 40.4 (t, C-6), 37.0 (t, C-2), 27.6 (t and q, q = C-15), 27.1 (d, C-11), 24.8 (q, C-12 or C-13), 24.9 (t, C-4), 21.6 (q, C-12 or C-13), 20.7 ppm (q, C-14); mass spectrum (70 eV) m/e (rel intensity) 204 (100), 189 (100), 163 (93), 133 (25), 119 (21), 105 (26). The mass spectrum gave a parent peak at mass 204.1881 (called for C₁₅H₂₄, 204.1878).

Fractional crystallization of the alcoholic fraction gave 1.3 g of a pure alcohol whose ir, nmr, and mass spectrum were identical with those of α -caryophyllene alcohol (6).

Formation of Humulol (15). To a stirred solution of 3.3 g (16.2 mmol) of humulene, 120 ml of dioxane, and 30 ml of water heated in an oil bath at 47° (to 67°) was added 0.6 ml of 70% HClO₄. The reaction was followed by vpc (6 ft $\times \frac{1}{6}$ in., 10% SE-30) and stopped when 50 to 60% alcohol 15 was formed (less than 5% other products except starting humulene, at 47° approximately 2 weeks, at 67° approximately 6 hr). The crude product was chromatographed on neutral Woelm alumina (activity I) to give 1.3 g of humulene (hexane eluate) and 1.9 g of alcohol 15 (97% pure, ether eulate): ir 3570, 1385, 1377, 1364, 1111, 999 cm⁻¹; nmr δ 5.20 to 4.73 (m, 3), 1.58 (s, 3), 1.12 (s, 6), 1.06 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 222 (8), 204 (14), 125 (24), 122 (20), 103 (66), 82 (100).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 80.83; H, 11.51.

Reaction of α -Caryophyllene Alcohol with Acid. Using the procedure and conditions for the rearrangement of humulene with perchloride acid, 136 mg (0.61 mmol) of α -caryophyllene alcohol was refluxed for 4 days. The product of the reaction was found from analysis by nmr and tlc to be the starting alcohol. No other products were found.

Hydrogenation of Hydrocarbon 7. To a shaking suspension of 200 mg of prehydrogenated PtO2 in 80 ml of acetic acid (or ethyl acetate) at room temperature and atmospheric pressure was added 2.0 g (9.8 mmol) of hydrocarbon 7. The volume of hydrogen uptake was followed until 9.8 mmol of hydrogen was absorbed (~1 hr). The reaction mixture was filtered, diluted with hexane, and washed several times with water and then saturated sodium bicarbonate solution to remove the acetic acid. The neutralized hexane solution was dried and concentrated to yield 1.95 g (9.5 mmol) of hydrocarbons. Analysis by vpc (500 ft \times 0.02 in. OV225) showed 4% starting material, 17% of hydrocarbon 8, and 79% of hydrocarbon 9. Pure hydrocarbon 8 was obtained by preparative vpc (10 ft × % in. 10% KOH, 10% Carbowax 20M): nmr δ 5.18 (d of d, 1, J_1 = 2 Hz, J_2 = 2.5 Hz), 1.02 (d, 3, J = 7 Hz), 1.00 (d, 3, J = 7 Hz), 0.92 (s, 3); mass spectrum (70 eV) m/e (rel intensity) 206 (19), 191 (25), 163 (100), 107 (19), 81 (22). The mass spectrum gave a parent peak at mass 206.2036 (calcd for $C_{15}H_{26}$: 206.2034).

To obtain pure hydrocarbon 9, the mixture of hydrogenated hydrocarbons was placed under the hydrogenation conditions above for 6 to 8 hr. Analysis by vpc (500 ft \times 0.02 in. OV225) showed hydrocarbon 9 was present in greater than 90% purity. Pure hydrocarbon 9 was obtained by preparative vpc (10 ft \times % in. 90% KOH, 10% Carbowax 20M): ir (CCl₄, CS₂) 1381, 1375, 1370, 1360, 1182, 784, 762 cm⁻¹; Raman 1665 cm⁻¹; nmr δ 2.6 (septet, 1, J = 7 Hz), 0.96 (s, 3); cmr 140.89 ppm (s), 140.5 (s), 49.9 (s, C-3), 41.1 (q), 37.5 (t), 36.9 (d, C-8), 33.1 (t), 27.1 (t), 26.9 (d, C-11), 25.7 (q), 23.9 (q, C-12 or C-13), 21.8 (q, C-14); mass spectrum (70 eV) m/e (rel intensity) 206 (32), 191 (65), 163 (100), 121 (36), 95 (37).

Anal. Calcd for $C_{15}H_{26}$: C, 87.38; H, 12.62. Found: C, 87.17; H, 12.63.

Osmylation of Hydrocarbon 8. A solution of 600 mg (2.9 mmol) of 79% pure hydrocarbon 8, 50 ml of dry ether, 2 ml of dry pyridine, and 800 mg (3.15 mmol) of OsO_4 was stirred at 25° in the dark for 1 week. To the reaction mixture was added 3 g of sodium bisulfite and 100 ml of 95% ethanol and the mixture refluxed for 6 hr. The solution was allowed to cool to room temperature and the inorganic material was removed by filtration. The organic filtrate was dried and rotary evaporated and the crude brownish diol was chromatographed on silica gel. The major product was fractionally crystallized from hexane to give 100 mn (0.42 mmol) of pure diol 10: mp 82-83°; mmr δ 3.66 (d, 1, J = 7 Hz), 2.78 (d of septet, 1, $J_{Ax} = 7$ Hz, $J_{Bx} = 2$ Hz), 1.03 (d, 3, J = 7 Hz; 0.98 (s, 3), 0.94 (d, 3, J = 5 Hz), 0.92 (d, 3, J = 7 Hz); mas spectrum (70 eV) m/e (rel intensity) 222 (12), 204 (54), 199 (100), 161 (58), 105 (50).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 75.00; H, 11.67. Found: C, 75.00; H, 11.74.

Cleavage of Diol 10. To a stirred solution of 4.5 ml of benzene

and 39 mg (0.17 mmol) of pure diol 10 under nitrogen atmosphere was added 85 mg (0.18 mmol) of Pb(OAc)₄. The reaction mixture was neutralized after 1 hr with 4.5 ml of 25% saturated sodium bicarbonate solution. The organic material was extracted with ether, and the extract was dried and concentrated to yield 32 mg (0.13 mmol) of keto acid 11a: ir (crude) 1709, 1739 cm⁻¹. The acid was esterified with diazomethane to yield keto ester 11b: ir 1736 cm^{-1} ; mass spectrum (70 eV) m/e (rel intensity) 268 (2), 237 (9), 140 (100), 97 (35), 88 (20). The mass spectrum gave a parent peak at mass 268.2047 (calcd for C16H28O3: 268.2038).

Oxidation of Hydrocarbon 9. Following the procedure used for the osmylation and cleavage of hydrocarbon 8, 400 mg (1.65 mmol) of hydrocarbon 9 (90% pure) and 0.5 g (1.93 mmol) of osmium tetroxide gave, after work-up, 200 mg of a crude diol. The crude diol was cleaved with a 10% molar excess of $Pb(OAc)_4$ and the product was isolated by chromatography on silica gel. The pure diketone 12 (120 mg, 0.48 mmol) had the following properties: ir 1712, 1700 cm^{-1} ; nmr δ 1.03 (d, 6, J = 7 Hz), 1.00 (s, 3), 0.97 (d, 3, J = 7 Hz).

Anal. Calcd for C15H26O2: C, 75.63; M, 10.92. Found: C, 75.44; H, 10.89.

Allylic Oxidation of Hydrocarbon 9. Using the procedure of Mazur,¹⁵ 100 mg (0.05 mmol) of hydrocarbon 9, 0.175 g (0.05 mmol) of HgBr₂, and 120 ml of freshly distilled tert-butyl alcohol were placed in a quartz flask. The solution was irradiated in a Rayonet reactor at 254 nm with air bubbled through the solution for 1.75 hr. The mixture was diluted with hexane and the mixture was washed thoroughly with water. The organic material was dried and concentrated, and the residue was chromatographed on silica gel to give 60 mg (0.27 mmol) of pure enone 14: ir 1698, 1634 cm⁻¹; uv max (95% EtOH) 241 nm (ϵ 9000); nmr δ 2.06 (s, 2), 1.16 (d, 3, J = 7 Hz), 1.14 (d, 3, J = 7 Hz), 1.08 (s, 3); mass spectrum (70 eV) m/e(rel intensity) 220 (100), 205 (94), 191 (27), 178 (35), 177 (36).

Anal. Calcd for C15H24O: C, 81.82; H, 10.91. Found: C, 81.61; H, 10.74.

Formation of Intermediate Hydrocarbons 19 and 20. Humulene was treated with acid in the usual manner and product formation followed closely by vpc (15 ft $\times \frac{1}{8}$ in. 1% OV1) until hydrocarbon 19 represented 6% of the reaction mixture and hydrocarbon 20 18% of the mixture. The reaction mixture was worked up in the usual manner and collection by vpc (10 ft \times 0.25 in. 2% SF96) gave pure hydrocarbons 19 and 20. Hydrocarbon 19 had the following properties: ir (CCl₄, CS₂) 2178, 1642, 1374, 886, 860, 539 cm⁻¹; Raman 1642, 1669 cm⁻¹; nmr (100 MHz) δ 5.02 (s, 1), 4.62 (s, 3), 1.69 (s, 3), 1.63 (s, 3), 0.78 (s, 3); mass spectrum (70 eV) m/e (rel intensity) 204 (92), 189 (100), 161 (60), 148 (30), 133 (35), 121 (67) 107 (39), 93 (36); mass spectrum (70 eV, high resolution) 204.1889 (calcd for C15H24: 204.1878). Hydrocarbon 20 had the following properties: ir 1374, 1182, 1147, 983, 864 cm⁻¹; Raman 1678, 1662 cm^{-1} ; nmr (100 MHz) δ 5.51 (m, 1), 3.20 (broad s, 1), 1.73 (t, 3, J =1.5 Hz), 1.57 (s, 6), 0.70 (s, 3); mass spectrum (70 eV) m/e (rel intensity) 204 (72), 189 (100), 161 (80), 133 (24), 122 (22), 119 (30), 105 (30), 91 (27), 41 (30); mass spectrum (70 eV, high resolution) 204.1877 (calcd for $C_{15}H_{24}$: 204.1878).

Hydrogenation of Hydrocarbon 19. To a stirred suspension of 30 mg of prehydrogenated PtO2 in 10 ml of ethyl acetate was added a solution of 19 mg (0.093 mmol) of hydrocarbon 19 in 1 ml of ethyl acetate. Stirring was continued until approximately 2.7 ml (0.12 mmol) of hydrogen was absorbed by the hydrocarbon. The solution was filtered and was concentrated to yield the crude hydrogenated hydrocarbon: nmr δ 5.16 (m, 1), 1.70 (s, 3), 0.88 (d, 3, J = 7 Hz), 0.83 (d, 3, J = 7 Hz), 0.75 (s, 3); mass spectrum (70 eV) m/e (rel intensity) 206 (26), 191 (14), 162 (72), 135 (13), 123 (100), 109 (48), 93 (22), 81 (39)

Rearrangement of Hydrocarbon 19 with Acid. Using the procedure and conditions for the rearrangement of humulene with perchloric acid, 5 mg (0.024 mmol) of hydrocarbon 19 was refluxed for 1 day. The reaction mixture was worked up and analysis by vpc $(500 \text{ ft} \times 0.02 \text{ in. OV101})$ showed greater than 90% hydrocarbon 7.

Formation of Alcohol 21. Humulene was treated with perchloric acid in the usual manner and product formation followed closely by vpc (15 ft \times $\frac{1}{6}$ in. 1% OV1) until alcohol 21 represented about 15% of the reaction mixture (approximately 7.0 hr). The reaction was worked up in the usual manner and collection by vpc (10 ft \times 0.25 in. 2% SF96) gave alcohol 21 with approximately 10% α -caryophyllene alcohol as an impurity. Alcohol 21 had the following properties: ir 3640, 3470, 1375, 1369, 938, 875 cm⁻¹; nmr δ 5.32 (m, 1), 1.73 (t, 3, J = 1 Hz), 1.12 (s, 6), 0.77 (s, 3); mass spectrum (70 eV) m/e (rel intensity) 222 (8), 204 (80), 189 (100), 161 (63), 121 (16), 108 (21), 107 (19).

Dehydration of Alcohol 21. A stirred solution of 15 ml of dry

ethyl ether, 6 ml of triethylamine, and 10 mg (0.045 mmol) of alcohol 21 in a 50-ml, round-bottomed flask with nitrogen atmosphere was cooled to -20° in a Dry Ice-carbon tetrachloride bath. To this solution was added 50 μ l (0.64 mmol) of mesyl chloride and stirring was continued for 20 min. The solution was warmed to room temperature and poured into a solution of 20 ml of saturated sodium bicarbonate solution. The organic material was extracted with ether and the ether extract was washed with 5% hydrochloric acid. saturated with sodium bicarbonate, dried, and concentrated to yield the crude hydrocarbons. The crude hydrocarbon mixture on analysis by vpc (500 ft \times 0.02 in. OV101) showed 16% of hydrocarbon 7, 30% of hydrocarbon 19, and 54% of hydrocarbon 20.

Dehydration of Humulol. Humulol (100 μ l) was injected on a 10 ft \times 0.25 in. SF96 gas chromatographic column at 230° with a flow rate of 10 cm³/min. The hydrocarbons were collected and analysis by vpc (500 ft \times 0.03 in. Apiezon) showed 75% α -humulene and 25% β -humulene.

Epoxidation of Humulene. To a stirred solution of 3 g (14.7 mmol) of humulene and 20 ml of CHCl₃ at -20° was added 2.5 g (82.5% 14.5 mmol) of m-chloroperbenzoic acid dissolved in 100 ml of CHCl₃. The solution was stirred for 2 hr at the same temperature, washed twice with 20% potassium hydroxide and saturated sodium chloride, dried with $MgSO_4$, and concentrated. Analysis of the residue by vpc (6 ft \times ½ in. 10% SE30) showed 63% epoxide and 37% humulene. The product mixture was chromatographed on neutral Woelm alumina (activity III) to give 1.8 g (8.18 mmol) of pure epoxide. The ir and nmr of the epoxide were identical with humulene epoxide 17.16

Lithium, Ethylamine Opening of Epoxide 17. A dark blue solution of 1.9 g (8.6 mmol) of epoxide 17 and 3 g (0.43 mmol) of lithium in 100 ml of ethylamine, cooled in a Dry Ice-CCl₄ bath, was stirred for 3 hr at which time tlc showed complete disappearance of starting material. Saturated ammonium chloride solution was added and the ethylamine evaporated. The organic material was extracted with ether and the extract was dried and concentrated. Analysis of the reaction product by vpc (6 ft $\times \frac{1}{8}$ in. 10% SE-30) showed four major alcohols. The crude product was chromatographed on silica gel and the major fractions were purified by preparative vpc (10 ft \times $\frac{1}{4}$ in. 2% SF96) to give compounds 18, 15, and two other products. Compound 18 (56%) had the following properties: nmr & 5.30-4.75 (m, 3), 3.63 (m, 1), 1.57 (s, 3), 1.07 (s, 3), 1.02 (s, 3), 0.83 (d, 3, J = 6 Hz); mass spectrum (70 eV) m/e (rel intensity) 222 (64), 151 (29), 123 (26), 110 (100), 95 (50), 82 (98); mass spectrum (70 eV, high resolution) 222.1986 (calcd for C15H26O: 222.1983). Compound 15 (9%) spectral properties (ir, nmr, and mass spectrum) were identical with humulol.⁹ Two compounds were isolated in 10 and 24% yields whose mass spectrum (70 eV) show parent peaks at mass 226 and 224, respectively.

Rearrangement of Humulene with D_2SO_4 .¹⁷ To a stirred solution of 10 ml of dry ether and 1 g (4.9 mmol) of humulene at 0° and under a nitrogen atmosphere was added $3 \text{ g of } D_2SO_4$. Stirring was continued for 18 hr. The reaction mixture was slowly poured into a solution of saturated sodium bicarbonate solution. The organic material was extracted with ether and the ether extract was washed with water, dried, and concentrated to yield the crude products. Column chromatography on a short column of alumina activity III gave the hydrocarbon products (hexane eluent). Collection by vpc (10 ft \times ¼ in. 2% SF96) gave pure deuterated hydrocarbon 7.

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Registry No.-5, 6753-98-6; 7, 41370-41-6; 8, 53643-37-1; 9, 43161-84-8; 10, 53643-38-2; 11a, 53643-39-3; 11b, 53643-40-6; 12, 53643-41-7; 14, 43161-77-9; 15, 24405-58-1; 17, 19888-34-7; 18, 53643-42-8; 19, 41370-42-7; 20, 41370-43-8; 21, 41370-40-5.

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Photolysis of 2-Alkoxy-1,4-naphthoquinones

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Photolysis of 2-Alkoxy-1,4-naphthoquinones

J. V. Ellis and J. E. Jones*

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

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The photolysis of 2-methoxy- and 2-ethoxy-1,4-naphthoquinones in acetic anhydride solution caused dimerization and subsequent cyclization of the alkoxy group to spiro-3-oxetanols in high yield. Similar photolysis of the 2-isopropoxy derivative produced no dimer but a product in which ring closure via the keto group adjacent to the alkoxy group formed the acetate of 3,4-isopropylidenedioxy-1-naphthol. Photolyses of film coatings of various 2alkoxy- and 2-aralkoxy-1,4-naphthoquinones produced reducing species that are believed to be the 3,4-alkylidenedioxy-1-naphthols.

It is well known that certain alkoxy- and alkylaminosubstituted quinones are photolyzed by intramolecular hydrogen abstraction and ring closure to produce substituted hydroquinones.¹⁻⁶ An interest in the photochemistry of quinones led us to investigate the photolysis of naphthoquinones containing alkoxy groups with more easily extractable H atoms, with the expectation that the cyclization reaction might occur more readily.

Results

Photolysis of 2-methoxy-1,4-naphthoquinone in acetic anhydride solution produced mainly two dimers (1 and 2),



neither of which was reported by Baldwin and Brown.¹ One (1) crystallized from the solvent in yellow prisms during photolysis, and the other (2) was recovered from the filtrate. Small quantities of the acetylated hydroquinone (3) and its rearrangement product (4) obtained by Baldwin and Brown may have been formed, but no attempt was made to isolate them.



Prolonged photolysis resulted in lower yields of 1 and larger quantities of 2, suggesting that the ring closure to the oxetanol structure occurred from irradiation of 1. The structure of 1 was assigned by analogy to the photooxidation of 2-methyl- 7 and 2-hydroxynaphthoquinone, 8 whose dimeric products are the result of head-to-head coupling. No attempt was made to determine the steric arrangement about the cyclobutane ring.

Upon being melted at a normal rate, the dimer (1) cleaved to the monomer, but when immersed in a preheated apparatus, the dimer melted rapidly only at temperatures above 210°. It was insoluble in all common solvents, and an nmr spectrum was unobtainable. It was cleaved when heated with solvents such as acetic anhydride or acetic acid during attempts at recrystallization. Although the dimer was detectable as a trace by mass spectrography, it was cleaved during analysis, giving relatively large quantities of the monomer; a fragmentation pattern characteristic of the monomer was observed. Its ir spectrum (KBr pressing) was different from that of the starting material.

The structure of 2 was assigned on the basis of its ir spectrum, which showed a very sharp OH band at 3500 cm^{-1} and a carbonyl band at 1680 cm^{-1} , its proton nmr spectrum, which showed two doublets characteristic of an AB system involving the -CH₂-group of a 3-arvl-substituted 3-oxetanol,^{9,10} and its C¹³ nmr spectrum.

The compound lost two molecules of formaldehyde in the determination of the mass spectrum. The major component was mass 316 and the fragmentation pattern was nearly identical with that of the dimer of 1,4-naphthoquinone. The silated compound also lost formaldehyde thermally; the heaviest fragment observed was the tetrasilated dimer of 1,4-naphthoquinone.

Photolysis of an acetic anhydride solution of 2-ethoxy-1,4-naphthoquinone with narrow-band irradiation centered at 436 nm produced the simple dimer 5 in 90% yield. This dimer, whose absorption tailed out weakly to 400 nm. was converted to the spirooxetanol 6 upon being irradiated