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ACID CATALYZED ISOMERIZATION OF HUMULENE (PART 2)

STEREOCHEMISTRY AND THE REACTION PATHWAYS

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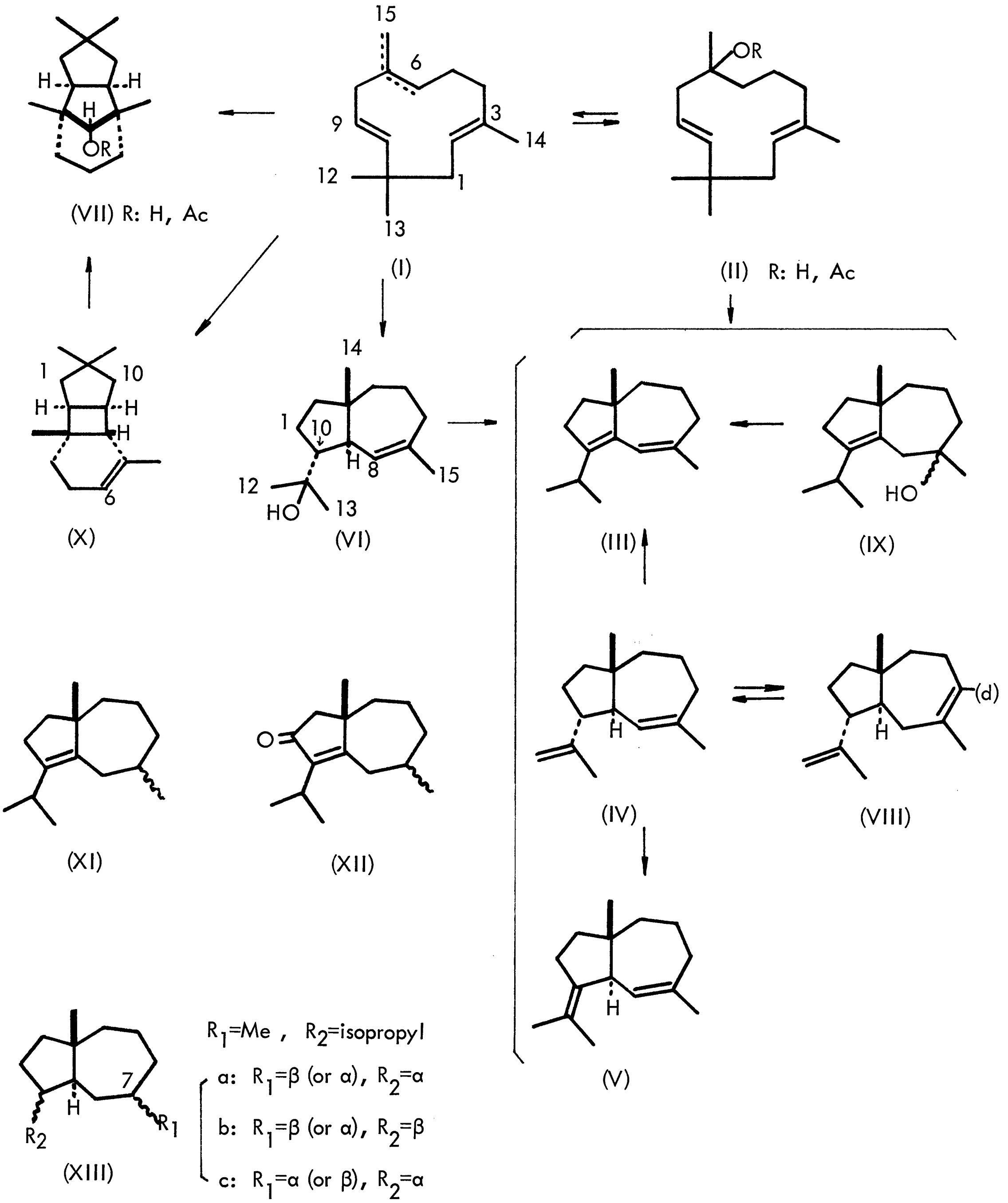
Cyclization products of humulene were studied with special emphasis on their stereochemistry and the reaction mechanisms were established with the aid of deuterium labeling.

Previous study[1] showed that under the mild acidic conditions α- and β-humulenes (I) yielded mainly humulol (II) and under more drastic conditions cyclization products (III ~VII) were predominantly obtained. The structures of cyclization products III ~VI were assigned mainly based on physical data and the framework of the hydrocarbon III, whose structure had been established by Dauben et. al.[2] We describe here additional evidences of the structures of those compounds and other minor reaction products (VIII ~X), and also discuss the stereochemistry of the cyclization products and the reaction pathways.

Dihydro compound (XI)[1] prepared from III was oxidized with tert-butyl chromate in AcOH-Ac_2O to afford the conjugated five membered cyclic ketone (XII) [λ_{max} 234 mμ (ϵ, 21,000), ν, 1690 cm^{-1}] which had a tertiary methyl group δ[3] 1.09 (3H, s), three secondary methyl groups δ 1.15 (6H, d, J=6.5), 1.12 (3H, d, J=6.5), and an active methylene detected by dideuteration [D_2O/K_2CO_3-CH_3OD, m/e 222 (M^+)]. Thus, bicyclo[5.3.0]-decane skeleton of III was confirmed.

Upon hydrogenation with PtO_2 in AcOH, IV afforded a single tetrahydro derivative (XIII-a)[m/e 208 (M^+)] , which had a tertiary methyl group δ 0.82 (3H, s), and three secondary methyl groups δ 0.79 (3H, d, J=6), 0.87 (6H, d, J=6), while V gave three products XI (11%), XIII-a (72%), and (XIII-b) (17%). The last compound possesses a tertiary methyl group δ 0.83 (3H, s), and three secondary methyl groups δ 0.79 (3H, d, J=6), 0.87 (6H, d, J=6), and shows a closely resembled MS pattern with that of XIII-a. It is now clear that IV and V have the same skeleton with III, and XIII-b is an isomer of XIII-a retaining the native configuration at C-10 in IV. Further, hydrocarbons III, IV, and V were also produced when the alcohol VI was passed through preparative GLC (OV-17,



(VII) R: H, Ac

(I)

(II) R: H, Ac

(X)

(VI)

(III)

(IX)

(IV)

(VIII)

(V)

(XI)

(XII)

(XIII)

R_1=Me , R_2=isopropyl

- a: R_1=β (or α), R_2=α
- b: R_1=β (or α), R_2=β
- c: R_1=α (or β), R_2=α

at 170°C) as same as upon acid treatments[1]. Now, configuration of VI was studied by use of a shift reagent[4] [Eu(DPM)$_3$] . Protons located nearby a hydroxyl group were assigned, in combination with proton-decoupling, based on the plots of their chemical shifts with significant slopes which depended on the concentration of a shift reagent. The results evidenced the *trans* ring junction, and the *cis* relationship between a dimethylcarbinol group and a C-9 H is shown in the following order from down- to upfield chemical shifts: C-12 and C-13 (6H), C-10 (1H), C-9 (1H), C-1 (1H), C-8 (1H), C-14 (3H), C-15 (3H). Observation of the coupling constant (J=5) between C-9 H and C-8 H also supports the *trans* ring junction.

Hydrocarbon (VIII), [m/e 204 (M^+), 93 (100%)] , contains a tertiary methyl group δ 0.87 (3H, s), two vinylic methyl groups δ 1.63 (3H, broad s), 1.65 (3H, b.s), a terminal methylene δ 4.63 (2H, d, J=5) (ν, 3070, 1780, 1640 890 cm^{-1}), and a vinyl proton δ 5.3 (1H, $W_{h/2}$=15). The structure was supported by the formation of a single tetrahydro compound upon hydrogenation (XIII-c), [m/e 208 (M^+)] , being different from XIII-a and XIII-b in their IR spectra but identical with XIII-a in their MS spectra. Since further treatment of VIII with aq. acetic acid gave III and IV, XIII-c would be an isomer of XIII-a at C-7(R_1=α(or β), R_2=α). IV was also converted to VIII accompanied with III and V on the further aq. acetic acid treatment. The above interconvertible reaction between IV and VIII would involve a double bond transfer *via* a C-7 carbonium ion; this will be referred subsequently in the discussion of the reaction mechanisms.

Alcohol (IX),[m/e 222 (M^+), 137 (100%)] , exhibits the presence of a tertiary hydroxyl group (δ 1.90) with no signal around δ 4 (ν, 3550, 1105 cm^{-1}non-H-bonded OH), a tertiary methyl group at δ 0.86 (3H, s), a tertiary methyl group on a carbon bearing a hydroxyl δ 1.17 (3H, s), two secondary methyl groups at δ 0.90, and 1.05 (each 3H, d, J=7), and an allylic methine proton at δ 2.67 (1H, q. J=7) being quite similar with that of XI. Since no signal of vinyl proton was observed, the existence of a tetrasubstituted double bond at C-9,10 is suggested. Upon GLC (FS-1265, at 190°C) or aq. acetic acid treatment, IX was mainly converted into III (72%). Thus, the alcohol is illustrated by the structure IX.

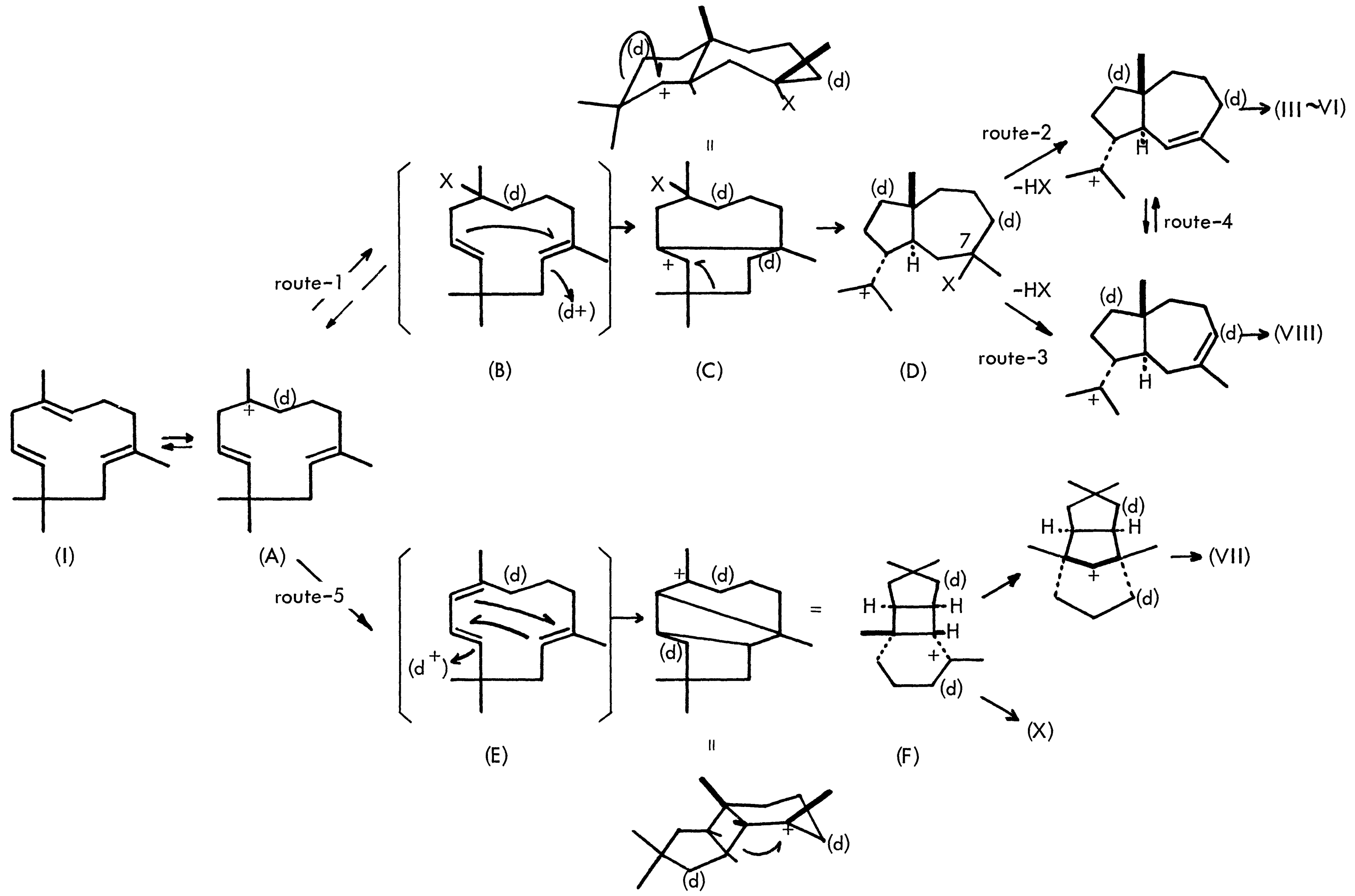
Hydrocarbon (X) was successfully converted into VII with aq. acetic acid. Hence, X is a key substance to elucidate the reaction mechanism for a long-known α-caryophyllene alcohol VII. All physical data well account for the structure X: three tertiary methyl groups at δ 0.80, 0.90, and 1.11 (each 3H, s), a methyl attached to a double bond δ 1.52 (3H, d, J=1.5), and a vinyl proton of the type -CH=$\overset{|}{C}$- [ν, 1660, 800, 840 cm^{-1} δ, 5.35 (1H, $W_{h/2}$=15)]; MS spectrum [m/e 204 (M^+), 108 (100%), 93 (70%)] . Stereochemistry of X would easily be defined in connection with VII[5].

Rearrangement pathways of humulene upon acid treatment have been investigated with the aid of deuterium labeling (80%-$AcOD/D_2O$). The extent of deuterium incorporation depends on the reaction conditions, and the stepwise labeled compounds permitted identification of labeled sites.

Under the mild condition, the dideuterated compounds (III-d_2 $\sim$ IX-d_2) were mainly obtained besides monodeuterated β-humulene and humulol (β-I-d_1 , II-d_1). Upon further treatment ($AcOH/H_2O$) of monodeutero humulol II-d_1 , whose isotope location should be at C-6, undeuterated and monodeutero products (III-$d_{0,1}$ $\sim$ IX-$d_{0,1}$) were mainly obtained. Formation of undeuterated compounds (III-d_0 $\sim$ IX-d_0) suggested that the first incorporated isotope at C-6 has been eliminated to yield α-humulene which underwent subsequent proton attack. On the other hand, obtaining of monodeutero compounds (III-d_1 $\sim$ IX-d_1) in the same reaction suggests the involvement of only C-7 carbonium ion (A) without α-humulene state in the cyclization pathways (Scheme-1). In addition, formation of the both unlabeled and monodeuterated IX as minor products in a comparable amount means that IX is probably a secondary product from the hydrocarbon III *via* *route-1* involving a reversible pathway between I and A.

The NMR spectrum of VIII-d_2 clearly established that one of the isotopes was located in the place of the vinyl proton (C-6) on the basis of disappearance of the corresponding absorption. Upon the isomerization through GLC (FS-1265, at 170°C), the above specimen (d_1 23%, d_2 69%, d_3 8%)[6] afforded the products (III-d_{1-3} $\sim$ V-d_{1-3}) with recovered VIII, whose isotope distribution has changed into the following percentage: (d_1 47%, d_2 40.7%, d_3 12.3%). Similar distribution was observed with VIII derived from dideutero compound IV-d_2 (d_2 70%) by the chemical reaction ($AcOH/H_2O$), that is, VIII-d_{1-3} (d_1 44%, d_2 55.5%, d_3 0.5%). Indeed, it is observed that the double bond transfer between C-6,7 and C-7,8 *via* carbonium ion at C-7 is always accompanied with decrease of the isotope at C-6. In a word, the isotope elimination in *route-4* is not stereospecific. Therefore, if VIII-d_2 has predominantly arose through IV-d_2 (route-2-4), the isotope distribution around 40 $\sim$ 50% (d_1) would be observed. However, the experimental results contradict to this assumption and the pathway (route-3) well accounts to the disappearance of the signal corresponding to a vinyl proton in the NMR spectrum of VIII-d_2 obtained from α-humulene by cyclization ($AcOD/D_2O$). Abundance of dideuterium incorporation in (III-d_2 $\sim$ VI-d_2) (d_2 ca. 70%) suggested that those compounds arose rather from the *route-2* than from the *route-3-4*.

It may be concluded that the first attack by a proton (deuterium) on the humulene (I) must occur at C-6 on the *trans* double bond to give C-7 carbonium ion state which may leads to a *cis* double bond C-6,7 or C-7,8 being capable of the succeeding cyclization. So, the intermediate (E) containing a *cis* double bond (C-7,8) may lead to the bicyclic compounds having C-7, 8 double bond (III $\sim$ VI). However, the conjugated diene system will be attacked next by proton (deuterium) at C-10 but not at C-2 according to the electromeric effect and the inductive effect of the neighboring gem-dimethyl group. Involvement of E in the formation of the bicyclic system requires


(I)
(A)
(d)
+
route-1
route-5
(B)
X
(d)
(d+)
(C)
(D)
7
H
-HX
route-2
route-3
route-4
(III~VI)
(VIII)
(E)
(d$^+$)
(F)
H
(VII)
(X)

Scheme 1

unfavorable two steps, protonation at C-2 and succeeding electrophillic attack at C-9 of the C-9,10 double bond by C-3 carbonium ion. Therefore, we favor route-1 for the formation of the all bicyclic products. The stereochemistry of the concerning compounds accords with the above described pathways. VII had been successfully synthesized⁷⁾ in accordance with the hypothetical reaction pathway, which is now confirmed by obtaining X. In agreement with our observation, the isotopic location of VII revealed in the recent report⁸⁾, wherein the reaction pathway was not mentioned, is also well accounted by the above described reaction pathway.

References and Footnotes

1) Y. Naya and Y. Hirose, Chem. Lett., 1973, 133.
2) Private communication from Professor William G. Dauben, Univ. of Calif., Berkeley, U.S.A. In the previous paper,¹⁾ we had used an unsuitable word "confirmed" instead of "established".
3) NMR spectra were measured at 60 MHz in CCl_4 on a Hitachi R-20 B spectrometer and the chemical shifts (δ) are expressed in ppm from internal TMS and coupling constants (J) in Hz. All MS spectra were taken by a Hitachi RMU-6 mass spectrometer (ionization energy, 80 eV; ion-accelerating voltage, 2KV).
4) P.V. Demarco, T.K. Elzey, R. Burton and E. Wenkert, J. Am. Chem. Soc., 23, 5734 (1970).
5) K.W. Gemmell, W. Parker, J.S. Roberts, and G.A. Sim, J. Am. Chem. Soc., 86, 1438 (1964); A. Nickon, J.F. McGuire, J.R. Mahajan, B. Umezawa, and S.A. Narang, ibid., 86, 1437 (1964).
6) Proportions were calculated from MS spectra. Cf. K. Bieman, "Mass Spectrometry Organic Chemical Applications" McGraw-Hill (1962), p. 212.
7) E.J. Corey and S. Nozoe, J. Am. Chem. Soc., 86, 1652 (1964).
8) J.B. Stothers, C.T. Tan, A. Nickon, F. Huang, R. Sridhar and R. Weglein, ibid., 94, 8581 (1972).

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