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THE MECHANISM OF THE REGIO- AND STEREOSPECIFIC PHOTOREARRANGEMENT OF HUMULONE TO THE BEER BITTER COMPONENT TRANS ISOHUMULONE

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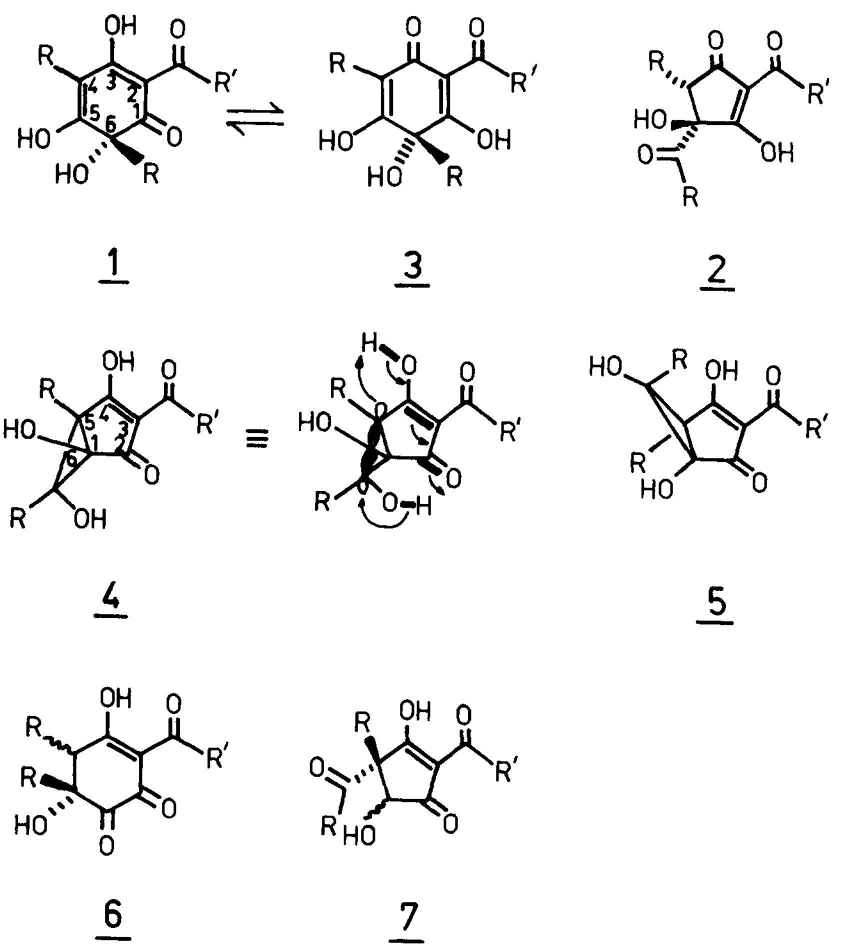
Upon irradiation, at either 254 or 350 nm, of the main hop α-acid, (-) (R) humulone (1, fig. 1), a very specific rearrangement occurs[3]. A single isomerization product, trans isohumulone (2, fig. 1), the main beer bitter principle[4], is formed in a quantum yield of 0.48 (350 nm, ferrioxalate actinometry). Considering the chemical yield of 90 % and the optical purity of over 95 % obtained[5], it is obvious that a fully regio- and stereospecific photorearrangement prevails.

It is experimentally very difficult to ascertain unambiguously the multiplicity of the reactive excited state since : a) the extremely weak luminescence of hop bitter acids[6] prohibits any luminescence studies; b) high quencher concentrations are required to observe a small amount of quenching, hence the reactive state must be very short-lived; c) sensitization experiments are difficult to interprete due to the tail absorption of humulone itself into the visible region of the spectrum.

One might view the reaction as proceeding via the well-known "lumiketone" rearrangement of the tautomeric 2,5-cyclohexadienone 3[7] (fig. 1). This is not the case. Indeed, since the equilibrium between 1 and 3 is shifted far to the left[8], almost all the incident 350 nm-light is absorbed by 1. This implies a very small quantum yield for product formation from 3, which clearly contrasts with the experimental finding. Also, eventual photoenolization of 1 would only lead to the ground state of 3[9]. The rearrangement must thus proceed via the dienol form 1. The usual photoreaction of 2,4-cyclohexadienones is α-cleavage to a diene ketene with loss of the stereochemical integrity at the α-carbon atom[10]. The lack of racemization in the present case excludes this mechanism.

Fig. 1



$R = -CH_2CH=C(CH_3)_2$

$R' = -CH_2CH(CH_3)_2.$

However, the reaction can take a different course when the irradiation is carried out in a polar media[11] and/or when the substrate is heavily substituted[10,11]. In these cases, a lumiketone type product is formed by a (1,2) acyl shift or oxa di-π-methane rearrangement (ODPM). Hart[11] suggested that these requirements, which are both fulfilled in the humulone rearrangement, lower the energy of the π,π^* excited singlet state, relative to the n,π^* state The difference in reactivity would then be explained by invoking a n,π^* state for the ketene formation and a π,π^* state for the ODPM rearrangement.

The ODPM reaction may be viewed as a concerted $[_\pi 2 + _\pi 2]$ cycloaddition between the C_1-C_6 σ-bond and the C_4-C_5 π-bond. The reaction is photochemically allowed only if both bonds react in a suprafacial or in an antarafacial manner[12]. The suprafacial reaction is impossible, since it would yield a trans-fused bicyclo[3.1.0] system.

The antarafacial participation of the σ-bond then implies inversion at C_6[13]. Since addition across the double bond can be either on top or bottom, two diastereoisomers, 4 and 5 (Fig. 1) respectively, can be formed. These intermediates cannot be isolated due to the ready cyclopropanol type rearrangement[14]. Although cleavage of each of the cyclopropane bonds is possible, only the C_5-C_6 bond is opened, thus assuring the regiospecificity of the reaction. Indeed, compounds 6 or 7 (fig. 1), which would result from the two alternative splittings, were not found. We believe this to be caused by a SE_1 mechanism with the enolic hydrogen atom acting as internal electrophile. The geometry is such that the proton attack is "end-on" with respect to the σ-bond being broken. Only in such cases inversion at the reacting centre is observed[14], while configurational retention is usually found when the electrophile reacts in an "edge-on" fashion[15]. This accounts for the stereospecificity of the reaction. The ready regio- and stereospecific ring opening undoubtedly owes its very specific character to the pericyclic nature of the rearrangement within a Hückel system (4, fig. 1). This rationale is further justified by the fact that lupulone, which has a 3-methylbut-2-enyl group at C_6 substituted for the hydroxylgroup of humulone, reacts in totally different way under identical reaction conditions[16]. Only intermediate 4 is compatible with the experimental stereochemical results. Indeed, the cyclopropanol rearrangement of 5 would lead to the enantiomer of 2 and should thus cause racemization of the isohumulone. Similar specificity in the formation of bicyclo[3.1.0] hexenones from photoisomerization of alkyl substituted cyclohexa-2,5-dienones has been reported[17]. It was shown that the stereochemistry is controlled mainly by steric factors. In the present case, stereochemical control is exercized by the pseudo-equatorial alkyl group at C_6, which comes exo in 4 and endo in 5.

The ODPM rearrangement, described here, is not only stereospecific with complete inversion at C_6, but also regiospecific since exclusively the intermediate 4 (fi(1) is formed. Further, the cyclopropanol type rearrangement of 4 occurs both in a stereospecific way with full inversion at the reacting centre and in a regiospecific way by cleavage of only one particular cyclopropane bond.

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