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CYCLIZATION OF HUMULENE BY MEANS OF MERCURY(II) SALTS. TRANSANNULAR 1,6-HYDRIDE SHIFT IN THE COURSE OF THE REACTION

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In the biosynthesis of illudoids, cyclization of the precursor, humulene (1), is believed to be initiated by attack of proton at the 9,10-double bond of 1 to yield protoilludyl cation(3) [Fig 1]. On the other hand, in vitro cyclization reactions of humulene hitherto reported1) are, except examples by us,2,3) invariably started by attack of an electrophile at the 6,7-double bond. We described in previous papers humulene cyclization employing mercuric acetate3) (THF-H_2O(1/1)/rt, then $NaBH_4$) to 3,6-seco-protoilludane derivatives 4 and 5. Similarly, treatment with mercuric nitrate ($AcOH$-H_2O(2/1)/0 → 60 °C, then $NaBH_4$) afforded 6 ~ 8.2) Structures of these products suggested that they are formed through the initial attack of Hg^{++} at the 9,10 bond.3) The unusual in vitro reaction courses to these compounds have now been shown more complex than appearance.

Reduction of the above described intermediary mercurated products from humulene with $NaBD_4$ furnished five deuterated ethers ($4d_3$, $5d_1$, $6d_2$, $7d_2$ and $8d_1$). Mass spectra indicated the number of incorporated deuterium atoms (M^+=225, 221, 240, 240 and 221 respectively) and location of deuterium atoms was determined on the basis of cmr and pmr spectra as well as some reactions. Comparison of cmr spectra [Table] of deuterated and undeuterated pyranoid derivatives, 4, $4d_3$, 5 and $5d_1$ with that of $4d_2$, which was obtained by catalytic deuteration of 5, indicated clearly that two deuterium atoms of $4d_3$ were placed at C-5 and C-6 and another one was at one of the four methyl groups. It was also shown from the comparison that a deuterium atom of $5d_1$ was on the same methyl group as that of $4d_3$. In the lanthanide aided pmr spectrum of $9d_1$, which was derived from $5d_1$ by the previously described procedure,3) a deuterated methyl signal moved fastest with increasing addition of $Eu(fod)_3$, among four methyl groups. Therefore the location of three deuteriums of $4d_3$ and one deuterium of $5d_1$ was unambigously determined as shown in the formulas.

The location of the deuterium atoms of furanoids derivatives was deduced to be C-10 and C-13 from their cmr spectra [Table] and comparison of the pmr spectra of 7 and $7d_2$4) in the presence of $Eu(fod)_3$. The unexpected incorporation of a deuterium atom at C-13 (Me) in the pyranoid and furanoid products is rationalized by the attack of Hg^{++} on the 6,7 double bond at an early stage, prior to formation of the ether linkage, in such a manner as observed in the

Fig 1

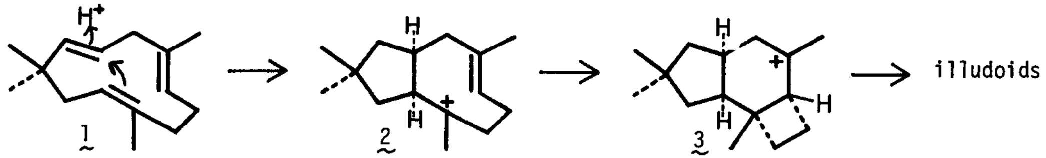


Fig 2

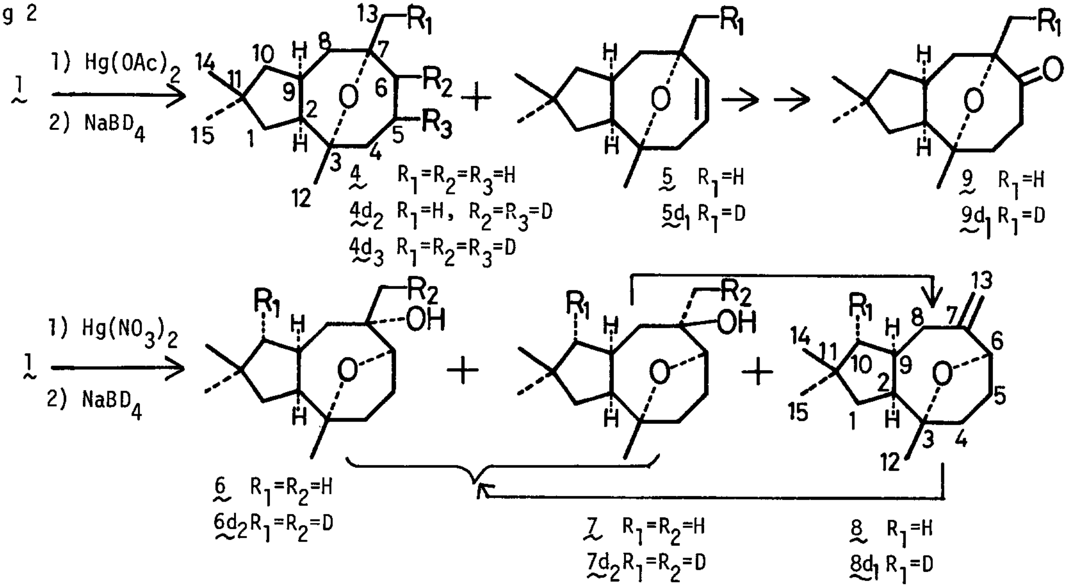
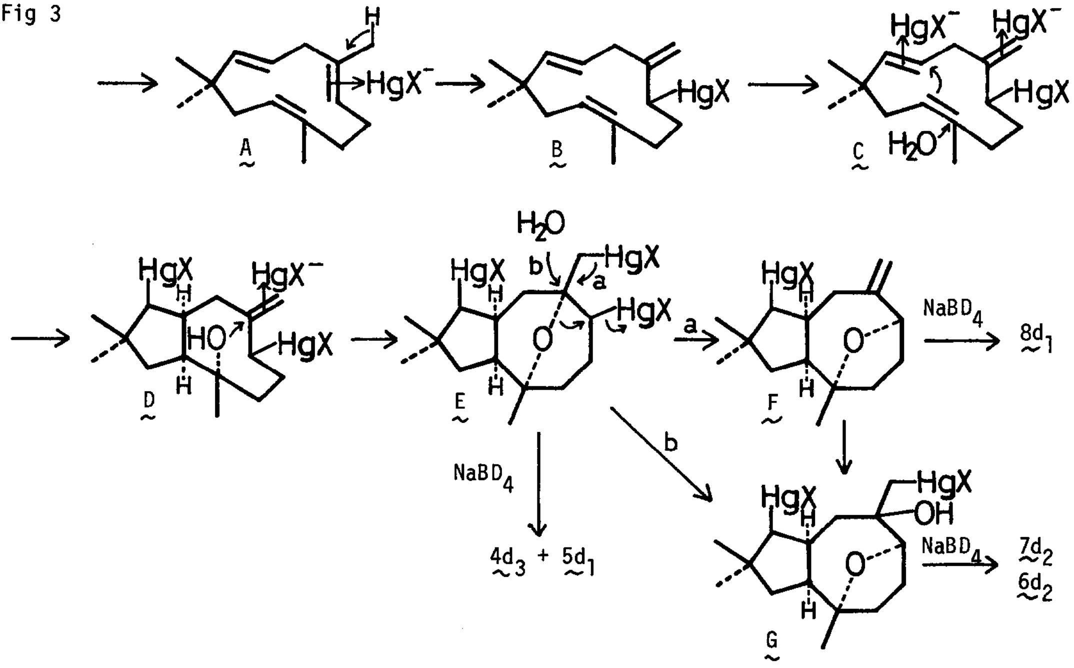
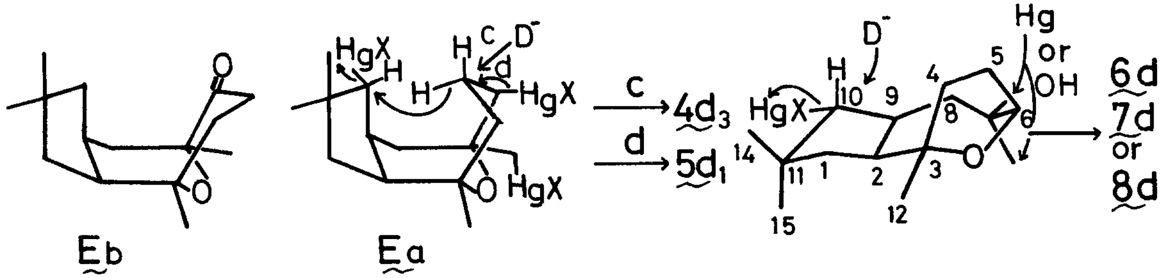


Fig 3



oxidation of α-pinene.[5] Absence of deuterium at C-13 of 8d$_1$ can be explained by assuming a double demercuration process E→F (Fig 3). Intervention of E in the $HgNO_3$ reaction is supported by the fact that 4 and 5 can be isolated by quenching the reaction by neutralization (3N NaOH) of the reaction mixture before raising the temperature to 60 °C.

A remarkable difference between the pyranoid and furanoid deuterated products is distribution pattern of the deuterium atoms in these compounds, particularly at C-10. While the furanoid group (6d$_2$, 7d$_2$ and 8d$_1$) carries deuterium at C-10, no deuterium was found at that position in pyranoid products. This can be explained by difference between conformations of the two groups of ethers as follows. In both cases oxymercuration of humulene affords at first ethereal compound E bearing mercury at C-10 as an intermediate. Considering the conformation of 9 (Eb) obtained by X-ray crystallographic analysis,[3] E can take a conformation Ea, in which C-5 and C-10 are close enough to allow the 1,6-hydride shift (Fig 4, course c). Attack of the deuteride at C-5 with concurrent 1,6-hydride shift would give 4d$_3$, while elimination of HgX at C-6 accompanied by the 1,6-hydride shift would yield the olefinic ether 5d$_1$ (course d). On the other hand in the corresponding conformer Fa (or Ga) of F (or G), formed by route a or b (Fig 3), steric situation is different and the 1,6-hydride shift would be difficult. The C-10 deuterated products would thus be formed.



The course of the cyclization reactions can thus be summarized as shown in Fig 3. So far as we are aware, 1,6-hydride shift has been only rarely observed.[6] All these cyclization reactions required empirically 3 equivalents of the mercuric salt. This observation coincides with the above proposed reaction paths.

References and Notes

1) Y. Naya, Y. Hirose, Chem. Lett., 133 and 727 (1973); W. G. Dauben, J. P. Hobbell, N. D. Vietmeyer, J. Org, Chem., 40, 479 (1975); D. Baines, J. Forrester, W. Parker, J. Chem. Soc. Parkin I, 1598 (1978) and references cited therein.

2) S. Misumi, T. Ohtsuka, Y. Ohfune, K. Sugita, H. Shirahama, T. Matsumoto, preceding paper.

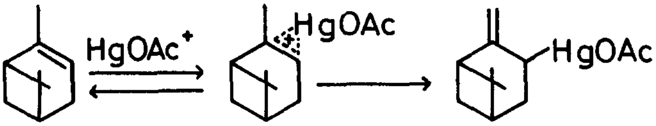
3) S. Misumi, Y. Ohfune, A. Furusaki, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 2865 (1976).

4) Comparison of these spectra indicated marked decrease of intensities of signals due to C-13 Me and C-10α H. At $Eu(fod)_3/7$ = 0.274 (CCl_4); δ 1.33, s (15Me); 1.47, s (14Me); 2.20, s (12Me); 1.98, t, J=12 (10β); 2.08, t, J=12 (1β); 2.22, dd, J=12, 8 (1α); 2.32, dd, J=12, 2 (10α)*; 2.81, td, J=11, 2 (4β); 3.96, dd, J=12, 8 (2α); 4.06, m (4α); 3.94, m (5β); 4.4, m

(9β); 5.6, s (13Me); 6.68, dd, J=13, 6 (8β); 6.86, dd, J=13, 7 (8α); 6.98, m (5β); 9.10, bd, J=6 (6α).

* This signal was not observed in the spectrum of **7d**$_2$.

5) The following reaction was observed; K. B. Wiberg and S. D. Nielson, J. Org. Chem., **29**, 3353 (1964).



6) The following example has been known. V. Prelog, J. G. Traynham, "Molecular Rearrangements" edited by P. de Mayo, Vol. 1, p.593, John Wiley & Sons, 1963, New York.

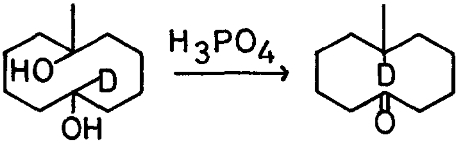


Table ^{13}C-Chemical Shifts (ppm) of the ethers (CDCl$_3$)

	1	2	3	4	5	6	7	8or10	9	8or10	11	Me	13	Me	Me
4	32.3^t	46.4^d	72.1^s	37.8^t	18.2^t	37.3^t	69.6^s	41.6^t	34.1^d	48.2^t	38.1^s	29.1^q	31.3^q	30.8^q	32.0^q
4d$_2$	*	*	*	*	D	D	*	*	*	*	*	*	*	*	*
4d$_3$	*	*	*	*	D	D	*	*	*	*	*	*	D	*	*
5	32.1^t	46.6^d	72.4^s	36.2^t	134.9^d	123.7^d	69.5^s	43.0^t	35.4^d	46.6^t	37.7^s	30.4^q	29.4^q	30.7^q	32.8^q
5d$_1$	*	*	*	*	*	*	*	*	*	*	*	*	D	*	*
								8		10					
6	32.3^t	52.4^d	85.9^s	45.9^t	42.2^t	87.3^d	73.4^s	27.4^t	34.1^d	50.6^t	38.6^s	30.2^q	26.5^q	26.8^q	29.4^q
6d$_2$	*	*	*	*	*	*	*	*	*	D	*	*	D	*	*
8	33.1^t	52.4^d	85.2^s	45.3^t	38.3^t	84.0^d	151.1^s	31.0^t	40.4^d	50.6^t	38.6^s	30.5^q	111.2^t	27.1^q	29.5^q
8d$_1$	*	*	*	*	*	*	*	*	*	D	*	*	*	*	*

* Practically same chemical shifts as those of the corresponding non-deuterated compounds are observed.

Symbols, s, d, t and q denote multiplicity of signals under the off-resonance decoupled conditions.

D indicates the location of deuterium.

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