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BASE CATALYSED REARRANGEMENTS OF α-KETOLS

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RECENTLY we have described a conversion of decalins into perhydroazulenes using an irreversible pinacolic type rearrangement.[1] We wish to report now a conversion of perhydroazulenes to decalins using a reversible, base catalysed stereospecific α-ketol rearrangement.

A-homo-B-nor-6βH-cholestan-5-one (I)[1] was reduced with lithium aluminium hydride to the corresponding alcohol (II, R=H, m.p. 57-59°; $[\alpha]_D$ +46°) which was tosylated in pyridine to give (II, R=Ts, m.p. 97-98°; $[\alpha]_D$ + 21°). The tosylate with lithium aluminium hydride in tetrahydrofuran or with sodium iodide in 2-butanone underwent elimination to the olefin (III, m.p. 84-86°; $[\alpha]_D$ -2°). Treatment of III with osmium tetroxide in pyridine yielded the diol (IV, m.p. 142-144°; $[\alpha]_D$ +44°), which was then oxidized with pyridine-chromate to the ketol (V, m.p. 188-189°; $[\alpha]_D$ +31°).

The stereochemistry of V was established from its infra-red and ultra-violet absorption spectra. The hydroxyl stretching frequency indicated intramolecular hydrogen bonding[2] (Table 1). The maximum in the ultra-violet associated with the carbonyl group was shifted hypsochromically by

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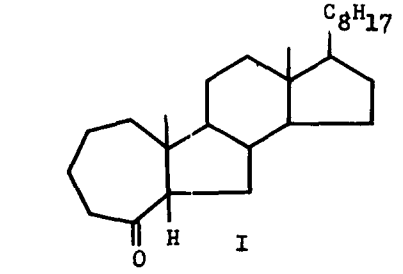
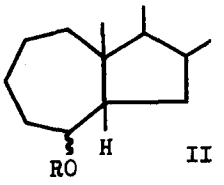
[1] Y. Mazur and M. Nussim, J.Amer.Chem.Soc. 83, 3911 (1961).

[2] For analogous systems see: A.C. Huitric and W.D. Kumler, J.Amer. Chem.Soc. 78, 1147 (1956).



I



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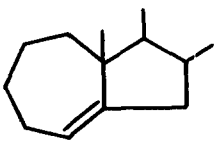

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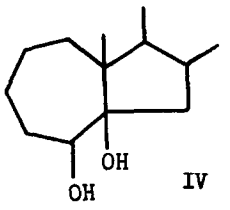

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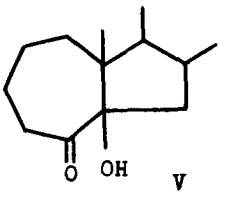

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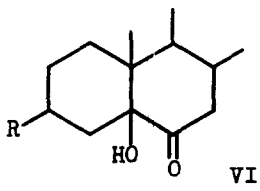

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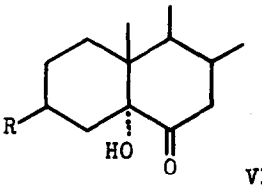

VII

5 mμ because of the adjacent hydroxyl group;[3] this is supported by the position of the first maximum in the rotatory dispersion curve[4] (Table 2). Both values indicated the proximity of the $\rangle$C-OH and —C=O groups. This is possible only when the seven- and the five-membered rings of V are cis fused; hence the angular hydroxyl is in the β-position.

Ketol V on boiling for 1 hr in methanolic potassium hydroxide (2%) rearranged to the isomeric ketol (VI, R=H).[5]

A perhydroazulene ketol was postulated by Shoppee et al. to explain the formation of cholestane-5β,6α-diol on reducing cholestane-5α-ol-6-one (VII,

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[3] R.C. Cookson and S.H. Dandegaonker, J.Chem.Soc. 352 (1955).

[4] Cf. C. Djerassi, Optical Rotatory Dispersion pp.111-114. McGraw-Hill, New York (1960).

[5] D.N. Jones, J.R. Lewis, C.W. Shoppee and G.H.R. Summers, J.Chem.Soc. 2876 (1955).

Table 1
OH Stretching Frequencies in cm^{-1}*

	Free OH	Hydrogen bonded OH
V		3495
VI R=H		3505
VI R=OH	3612	3515
VII R=H	3615	
VII R=OH	3612	

* All measurements were made with a Perkin-Elmer infra-red spectrometer, Model 12 C, in carbon tetrachloride (c 0.0012 moles/l.).

R=H) with sodium in n-propanol.[5] This prompted us to investigate the possible base isomerization of this ketol. Treatment of the trans-ketol (VII, R=H) with boiling methanolic potassium hydroxide (10%) for 8 hr resulted in 92% conversion to the cis-ketol (VI, R=H). The same equilibrium mixture was obtained on treating (VI, R=H) similarly. This thermodynamic equilibrium corresponds to a free energy difference of 1.7 kcal $mole^{-1}$. The main contribution to the stability of (VI, R=H) comes probably from the hydrogen bonding between the hydroxyl and carbonyl as indicated by the hydroxyl stretching frequency at 3500 cm^{-1} in the infra-red as compared with the non-bonded hydroxyl frequency at 3612 cm^{-1} of (VII, R=H) (Table 1).[6]

Similar rearrangements of α-ketol systems were studied extensively in the D-homo-steroids, where stereospecificity and reversibility were established. The assumption was made that the concerted electron shift leads to a product in which the C-OH bond assumes the same direction in space as the respective C=O bond in the parent compound.[7]

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[6] For relations between OH frequency differences and energy differences due to hydrogen bonding; R.M. Badger and S.H. Bauer, J.Chem.Phys. 5, 839 (1937).

[7] Cf. inter al., R.B. Turner, J.Amer.Chem.Soc. 75, 3484 (1953); N.L. Wendler, D. Taub and R.W. Walker, Tetrahedron 11, 163 (1960).

Table 2
Ultra-violet and Rotatory Dispersion Data

Substance	U.V. max mμ	RD first extremum mμ	[A]
I	289	312.5	+ 85
V	284	302.5	- 26
Coprostan-6-one	292	312.5**	- 113**
VI R=H	284	302.5	- 144
VI R=OAc	281	302.5	- 186
3β-Acetoxy-cholestan-6-one	291	306**	- 76**
VII R=H	302	320	- 83
VII R=OAc	303	322.5	- 110

* All measurements were taken in dioxane; [A], the amplitudes as defined by C. Djerassi and W. Klyne, Proc.Chem.Soc. 55 (1957).

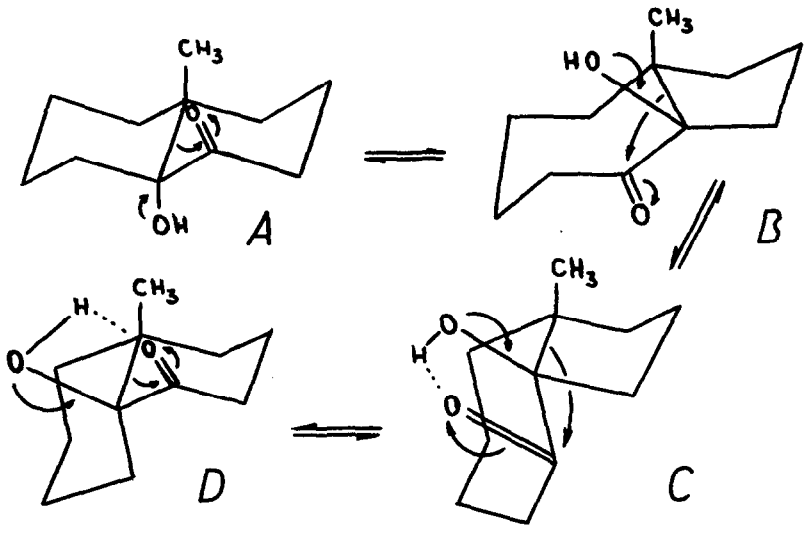
** These values were taken from: C. Djerassi, W. Closson and A.F. Lipman, J.Amer.Chem.Soc. 78, 3163 (1956); C. Djerassi and W. Closson, Ibid. 78, 3761 (1956).

Accepting that the perhydroazulene ketol is an intermediate in the reversible conversion of (VII, R=H) to (VI, R=H) and taking into account the steric requirements of a concerted electron shift we propose a reaction course described in the reaction scheme on page 821.

Of the two conformations B and C of the cycloheptanone ring, C is stabilized by hydrogen bonding. The fact that V rearranges to (VI, R=H) with 2% methanolic potassium hydroxide, whereas (VII, R=H) is unchanged under the same conditions can explain why V is not found in the equilibrium mixture of (VI,R=H) and (VII, R=H).

Treatment of (VII, R=OH) with base resulted in its conversion to the 5β-isomer (VI, R=OH)[8] [(acetate (VI, R=OAc; m.p. 141-142° $[\alpha]_D$ - 16°)].

[8] This compound is identical with the diol-one described by I.M. Heilbron, E.R.H. Jones and F.S. Spring, J.Chem.Soc.801 (1937) and assumed to be (VI, R=OH); L.F. Fieser and M. Fieser, Steroids pp.297-298. Reinhold, New York (1959).



It is evident from Table 2 that in the ketols VI where the hydroxyl is equatorial to ring B, the carbonyl n→π* band and the maximum of the first extremem in the rotatory dispersion curve are shifted to shorter wavelength. Bathochromic shifts are observed for the ketols VII, where the hydroxyl is axial.[3,4] It is to be noted that the assumed conformation of V differs from that of the ketone I (and also from that of its 6αH isomer[1]) and hence the different sign and magnitude of its Cotton effect.

This type of decalin-perhydroazulene-ketol rearrangement is not confined to the steroid system and has been postulated to explain a number of conversions in other natural products, e.g. marrubin[9] and grayanotoxin I[10].

The analogous ketol rearrangements in the decalin series are being investigated.

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[9] D.G. Hardy, W. Rigby and D.P. Moody, J.Chem.Soc. 2955 (1957); W. Cocker, J.T. Edward, T.F. Holley and D.M.S. Wheeler, Chem. & Ind. 1485 (1955).

[10] H. Kakisawa, M. Kurono, S. Takahashi and Y. Hirata, Tetrahedron Letters No. 2, 59 (1961).