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THE ABSOLUTE CONFIGURATION OF VALERANONE

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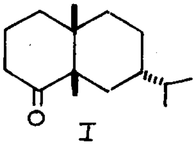
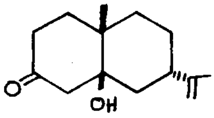
A recent report of the synthesis of L-valeranone (I) (1) prompts us to report our results in this field which confirm and supplement the results already published (1).

The ketol (II; m.p. 110-1°; $[\alpha]_D$ -58°; ORD(MeOH) a^{301}_{265} +25; NMR($CCl_4/SiMe_4$) 8.3, 8.8 τ(singlets)) was prepared by the reaction of (-)-dihydrocarvone, 1-chlorobutan-3-one and NaH in tetrahydrofuran. The absolute configuration was confirmed as that shown by a comparison of the ORD curve with that of the ketol (III)(a^{304}_{264} +27) of known absolute configuration (2). The NMR spectrum of the ketol (II) showing only two singlet methyl peaks rules out the possibility of a bridged structure (IV) for this ketol (3).


I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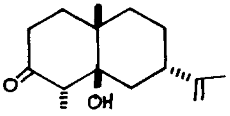
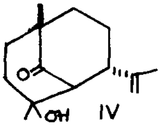

III

The ketol (II) on treatment with ethanolic hydrochloric acid at 20° gave the ketone (V; $[\alpha]_D$ +185°; n_D^{20} 1.5353; ν_{max} 1665, 1640, 893 cm^{-1}; λ_{max} 241mμ(ε=16200); ORD(MeOH) a_{310}^{353}+24.5; 2:4-DNP, m.p. 139-40°) which with concentrated sulphuric acid gave the ketone (VI; $[\alpha]_D$ +608°; n_D^{20} 1.5622; ν_{max} 1670, 1645, 1605 cm^{-1}; λ_{max} 295mμ(ε=24600); 2:4-DNP, m.p. 183-4°) thus confirming the α-orientation of the isopropyl group (2). Hydrogenation of the ketol (II) gave the corresponding saturated ketol (m.p. 61-2°; $[\alpha]_D$ -64°) which on treatment with ethanolic hydrochloric acid at 20° gave the ketone (VII; $[\alpha]_D$ +170°; n_D^{20} 1.5205; ν_{max} 1660, 1640, 865 cm^{-1}; λ_{max} 240mμ(ε=15500); 2:4-DNP, m.p. 160-1°; semicarbazone, m.p. 264-5°) previously prepared by Djerassi and his co-workers (4).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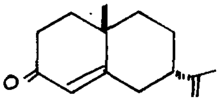
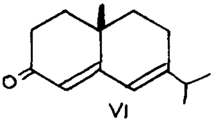
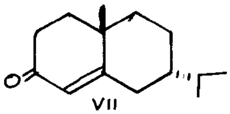
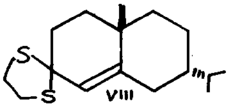

V


VI

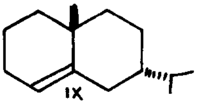
This ketone was converted in high yield into the thioketal (VIII; m.p. 130-1°; ν_{max} 1640, 855 cm^{-1}; $[\alpha]_D$ +121°; NMR(CCl_4/$SiMe_4$) 4.6 τ(singlet)) which was desulphurised by W2 Raney Ni in ethanol to give the olefin (IX; b.p. 55-60°/0.4mm; $[\alpha]_D$ +52°; n_D^{20} 1.4910; ν_{max} 1380, 1360, 1015, 995, 810, 800 cm^{-1}). This olefin on borohydration in ether at 20° under the usual conditions gave in high yield a single crystalline alcohol (X; m.p. 87-8°; $[\alpha]_D$ -31°) formulated as shown with a <u>cis</u> A/B ring-fusion. The reason



VII

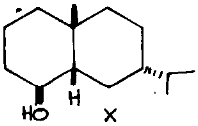


VIII

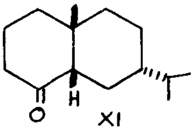


IX

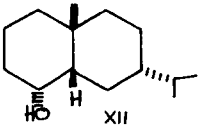
for this is as follows. On oxidation with 8N CrO_3 in acetone the alcohol (X) gives an oily ketone (XI; B.p. 95-8°/0.1mm; $[\alpha]_D$ +76°; n_D^{20} 1.4887; ν_{max} 1710 cm^{-1}; ORD(hexane) a_{271}^{315}+110; 2:4-DNP, m.p. 172-3°; semicarbazone, m.p. 168-70°) which was recovered unchanged from a refluxing solution of NaOEt in ethanol, from a solution of KOH in aqueous ethanol, and from acidifying its enol formed with NaH in boiling tetrahydrofuran. Reduction of the ketone (XI) with sodium in ethanol yielded a new alcohol (XII; m.p. 91-2°; $[\alpha]_D$ -8°) which can only be different from the alcohol (X) in the configuration of the hydroxyl group since the ring fusion has been shown to be stable under these conditions.



X



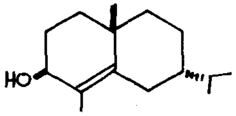
XI



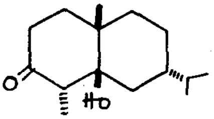
XII

These results suggest that in the alcohol obtained by the borohydration of the olefin (IX) the hydroxyl group has the less stable axial orientation. Given the accepted mechanism of <u>cis</u>-addition during borohydration, the stereochemistry of the alcohol (X) follows. The anomaly in this situation is evidently then the stability of the ketone (XI) to epimerising conditions. And this clearly has to do with the isopropyl group, and whether it is to take up an equatorial or axial orientation the energy difference between which is 2-2.5 kcals/mole(1,5).

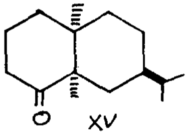
A point of interest in this connection arises from the borohydration of the alcohol (XIII; m.p. 88-9°; $[\alpha]_D$ +19°). The product from this reaction was not crystalline, but on oxidation with 8N CrO_3 in acetone at 0° avery high yield of the ketol (XIV) was obtained (70% based upon the alcohol (XIII)). In this instance the double bond in XIII being tetrasubstituted, there are no important electronic factors to influence the course of the addition of the diborane. However the eventual orientation of the isopropyl group is clearly important in directing the borohydrationto take place on the β-face to give the cis-fusion in XIV, where the isopropyl group can be equatorial in the non-steroidal conformation. This result adds further support for the formulation of the alcohol (X) and so the ketone (XI).



XIII



XIV



XV

The ORD curve of the ketone (XI), a_{271}^{315}+110 can be compared with that of natural D-valeranone, a_{273}^{323} −116. Since the only difference between these structures lies in the absence of a methyl group at position 5 in (XI), the rotatory dispersion curves indicate that the ketone (XI) and D-valeranone are stereochemically enantiomeric. And since the ketone (XI) is of known absolute configuration, that of D-valeranone follows as (XV)(6).

Satisfactory elemental analyses were obtained for all compounds quoted.

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