Absolute Configuration of the C_{18} Juvenile Hormone: Application of a New Circular Dichroism Method Using Tris(dipivaloylmethanato)praseodymium

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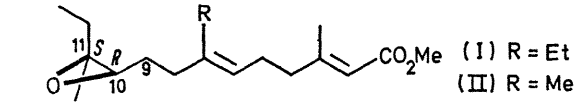
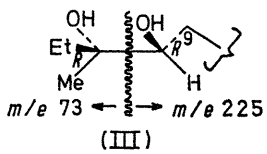
Summary The absolute configuration of the C_{18} juvenile hormone has been established as being (10*R*:11*S*)-(I); this is based on clarification of the mode of epoxide cleavage, and a determination of the chirality of the resultant α-glycol by a new c.d. method employing $Pr(dpm)_3$.

MEYER and HANZMANN[1] recently isolated a mixture of the C_{18} (I)[2] and C_{17} (II)[3] juvenile hormones (JH) and unsuccessfully attempted to calculate the absolute configurations from its positive rotation ($[\alpha]_D$ *ca.* +7°).[4]

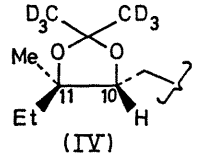
We report our findings based on new spectroscopic techniques, which lead to (10*R*:11*S*)-configurations. Model experiments were carried out on a 10-*cis*- and 10-*trans*-mixture (83:17, from n.m.r.) of synthetic (±)-C_{18} juvenile hormone. The glycol resulting from cleavage of the epoxide by treatment with a 1:1 mixture of 0·1N sulphuric acid and tetrahydrofuran for 4 h at room temperature,† showed a peak at *m/e* 73 [See (III), 17% (base peak: *m/e* 225)]. When the cleavage was carried out with 42 atom % $H_2{}^{18}O$, a peak at 75·0698 ($C_4H_9{}^{18}O$, calc. 75·0695) was observed in addition to the original peak at 73·0653 (C_4H_9O, calc. 73·0653). Calculations based on the relative intensities of peaks 73/75 and 225/227 showed that the epoxide was cleaved by almost exclusive attack by water at C-11 (97%, C-10 attack 3%) leading to the *threo*-isomer from the *cis*-epoxide (and *erythro*-isomer from *trans*-epoxide).

The *threo* nature of the major glycol was corroborated by a newly developed n.m.r. method[5] which can be used to distinguish between *threo*- and *erythro*-isomers of certain glycols. This is based on n.m.r. double-irradiation studies of the hexadeuterioacetonide derivatives of these glycols. Irradiation (n.m.r.) at 1·07 p.p.m. (11-Me, in C_6D_6) of the

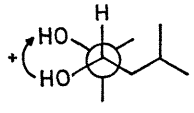




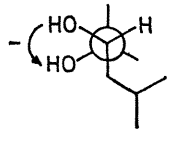
(III)



(IV)



(Va)



(Vb)

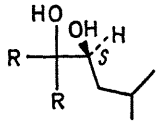
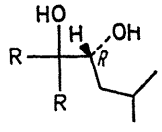
[$^2H_6$]acetonide (IV) resulted in a height increase of the 3·69 p.p.m. signal (10-H, dd) but no increase in the integrated area. Hence, a *W*-type coupling, but no NOE, is present between the 11-Me and 10-H, and so they are *trans* with

† The resultant *threo*- and *erythro*-glycols can be separated efficiently by high pressure liquid chromatography. The cleavage conditions were those recommended by Dr. Siddall.

respect to the acetonide ring [(IV) *i.e.*, *threo*-glycol]. Conversely, an NOE but no *W*-type coupling is observed between the Me and adjacent H in acetonides derived from *erythro*-glycols. Furthermore, the n.m.r. signals of Me group located *cis*- to the adjacent alkyl group [as in (IV), *threo*] appear 0·10—0·15 p.p.m. higher as compared to those located *trans* (*erythro*)[5], and this was so in the present case too, *i.e.*, 1·06 p.p.m. in the *threo*-glycol acetonide and 1·17 p.p.m. in the *erythro*-glycol acetonide (in $CDCl_3$). Thus it was established that acid cleavage of the trisubstituted epoxide results in attack at C-11, and that configurations at C-11 and C-10 are inverted and retained, respectively.

We have recently developed a spectroscopic method[6] for the determination of the chirality of cyclic α-glycols, which involves mixing of dilute solutions of $Pr(dpm)_3$ or $Eu(dpm)_3$ and the substrate glycols (2×10^{-4}M-solutions in dry CCl_4, $CHCl_3$, n-hexane, *etc.*) and measuring the c.d. Cotton effect around 310 nm. *The sign of this Cotton effect is identical with the chirality of the two hydroxy-groups*,‡ which is defined as positive if they are twisted clockwise in the Newman projection. Beacuse of the large $\Delta\epsilon$ values ($\Delta\epsilon$ 5—13) only minute amounts of the glycol are necessary, and it is also applicable to glycols containing tertiary-hydroxy-groups. Subsequent experiments[7] have shown that acyclic α-glycols are amenable to similar treatment. [The $\Delta\epsilon$ values in the case of acyclic glycols are more sensitive to experimental conditions. Moisture must be rigorously excluded, otherwise no Cotton effect is observed. In the present measurement of sec./tert.-glycols, a freshly prepared solution of $Pr(dpm)_3$ (*ca.* 2×10^{-4} mol l^{-1}) in *dry* n-hexane was added to a solution of the glycol in *dry* n-hexane (*ca.* 10^{-3} mol l^{-1}), and the c.d. was recorded after 5—10 minutes. As in the case of cyclic glycols[6]‡ a second c.d. extremum of opposite sign is observed at *ca.* 285 nm.]

TABLE. *C.d. Cotton effects of acyclic glycols in presence of* $Pr(dpm)_3$

	$\Delta\epsilon$ (nm)
 (V) R = Me	+4·5 (314)
(VI) R = Et	+1·0 (308)
 (VII) R = Me	−3·2 (314)
(VIII) R = Et	−1·6 (308)
glycol from (+)-JH (III)	−1·1 (312)
glycol from (−)-JH	+0·8 (313)

Accordingly, two enantiomeric sets of appropriate models (V)/(VII) and (VI)/(VIII) (Table), having known configurations, were prepared. Reaction of *S*-leucine with nitrous acid followed by esterification gave ethyl (2*S*)-2-hydroxy-4-methylpentanoate (retention of *S*-configuration[8]) which was treated with MeMgBr and with EtMgBr to give, respectively (V), oil $[\alpha]_D^{25}$ −42·7° (*c* 1·01, $CHCl_3$), and (VI) m.p. 59·5—60·5° $[\alpha]_D$ −35·7° (*c* 0·93); similarly, *R*-leucine yielded the *R*-enantiomers (VII), oil $[\alpha]_D^{25}$ + 37·6° (*c* 1·44), and (VIII) m.p. 58—60° $[\alpha]_D$ +39·8° (*c* 1·13). As shown in the Table, the *S*-glycols exhibit negative c.d. with $Pr(dpm)_3$. These results, together with other data[7] may be tentatively rationalized in the following simplified fashion. (3*S*)-2,5-dimethylhexane-2,3-diol (V) has to adopt either conformation (Va) (positive chirality) or (Vb) (negative chirality) in order that the two hydroxy-groups be in positions required for complex formation and observation of Cotton effects.[6] Of the two conformers (Va) would be more favoured for the approach of $Pr(dpm)_3$ because of less steric hindrance between the substrate alkyl group (Me) and the reagent Bu^t groups; the positive chirality of the two hydroxy-groups in this conformer is in accord with the observed positive Cotton effect.

Synthetic (+)-JH (natural)[9] was cleaved under conditions described above to give the glycol, and its c.d. was recorded in the presence of $Pr(dpm)_3$, $\Delta\epsilon$ −1·1 (312 nm) (Table). This leads to a (10*R*:11*S*)-configuration [see (III)] for the glycol, and hence a (10*R*:11*S*)-configuration (I) for the natural (+)-JH, which is considerably more active than its enantiomer.[9] The glycol derived from 2·1 mg of (−)-JH had a positive c.d. (Table), and therefore (−)-JH has a (10*S*:11*R*)-configuration.

Recently we learned that Faulkner and Petersen had arrived at the same conclusion *via* a synthetic route.[10]

We are grateful to Prof. Johnson and Dr. Siddall for gifts of optically active and racemic JH respectively. The work was supported by a P.H.S. grant.

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‡ A second Cotton effect of opposite sign is observed around 290 nm. It is as yet not clear whether or not the two c.d. extrema are related to exciton splitting encountered in the aromatic chirality method: *cf.* N. Harada and K. Nakanishi, *J. Amer. Chem. Soc.*, 1969, **91**, 3989; *Accounts Chem. Res.*, in the press.

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[5] (a) For another application see M. Koreeda, D. A. Schooley, K. Nakanishi, and H. Hagiwara, *J. Amer. Chem. Soc.*, 1971, **93**, 4084. (b) The results of a variety of glycol isomers and a general discussion will be reported elsewhere; D. A. Schooley, M. Koreeda, I. Miura, and K. Nakanishi.
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