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THE STEREOCHEMISTRY OF RINGS A AND B IN 6-SUBSTITUTED - Δ^4-3-KETOSTEROIDS. A STUDY OF H^1 ALLYLIC SPIN-SPIN COUPLING IN RIGID SYSTEMS.

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THE endocrinological importance of a number of natural[1] and synthetic[2] 6-substituted steroid hormones makes their stereochemistry of special interest. We have prepared a number of 6-substituted-Δ^4-cholestene-3-ones and examined their NMR spectra to determine whether a general correlation could be made between the configuration (and conformation) at the 6-position and the character of the NMR signal attributed to the vinylic proton at C4.

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[1] Inter alia , A.G. Frantz , F.H. Katz , and J.W. Jailer , J.Clin. Endocrinol. Metab. 21 , 1290 (1961) ; J. C. Touchstone and W.S. Blakemore, Ibid. 21 , 263 (1961); A.G. Frantz, F.H. Katz, and J. W. Jailer, Proc. Soc. Exptl. Biol. Med. 105 , 41 (1960).

[2] A.Bowers , E. Denot, Maria Blanca Sanchez , L. M. Sanchez - Hidalgo , and H.J. Ringold , J.Amer. Chem. Soc. 81 ,5233 (1959) , and references quoted therein.

Table I ; NMR data[3,4] on 6-substituted-Δ^4-cholestene-3-ones.

6-substituent	τ H4 (multiplicity[5], W[6] or J in c.p.s.)	τ[7,8] H6	τ 19-CH_3
α-Me	4.35 (D,J=1.6)	Obscured	8.81
β-Me	4.36 (S,W=1.8)	Obscured	8.73
β-Et	4.41 (S,W=1.8)	Obscured	8.80
α-OH	3.81 (D,J=1.7)	5.7 V.B.	8.81
β-OH	4.38 (S,W=1.6)	5.8 B.	8.67
α-OAc	4.29 (D,J=1.7)	4.6 V.B.	8.75
β-OAc	4.19 (S,W=1.7)	4.7 B.	8.72
α-Br	3.78 (D,J=1.8)	5.2 V.B.	8.80
β-Br	4.25 (S,W=1.5)	5.1 B.	8.49
β-OMe	4.37 (S,W=1.5)	6.4 B.	8.75
β-OEt	4.38 (S,W=1.6)	6.3 B.	8.83
H	4.45 (S,W=3.2)	Obscured	8.83

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[3] Taken in dilute (less than 7%) solution in CCl_4 with tetramethylsilane as internal reference on a Varian A60 spectrometer. The τ values are believed to be accurate to within 0.03 p.p.m., and the J values to within 0.2 c.p.s. The latter are derived from first order considerations only.

[4] All new compounds quoted showed correct analyses and spectral characteristics.

[5] S= singlet, D= doublet.

[6] W= width (of singlets) at half height determined at maximum resolution. As oxygen was not excluded, the widths quoted are minimum values.

[7] Centre of gravity of multiplet. Values quoted to 0.1 p.p.m. as the origin cannot be determined (c f. G. Slomp, J.Amer. Chem. Soc. 84, 673 (1962).

[8] V.B. = very broad , B. = broad.

Table I shows that for the compounds examined , *the signal due to the proton at C4 is split when the substituent at C6 is α , and appears as a singlet when the substituent at C6 is β.*

While the conditions governing allylic spin-spin coupling are not fully understood[9-17] and no systematic studies on rigid systems have yet been reported , the correlation established above appears to be sufficiently general for stereochemical assignment. Assuming the chair conformation for ring B , examination of Dreiding models of either conformation of ring A shows that the angle between the plane H4-C4-C5-C6 and C6-H6 is approximately a right angle in the cases where H4-H6 coupling can be detected , and approximately zero when the H4 signal appears unsplit. This relation is in agreement with the recent results[16] of studies on allylic coupling in some linear systems. In the unlikely case of ring B being always in a boat conformation , the opposite relation would hold, i.e. the above-mentioned angle would be nearly zero for the cases where coupling occurred.

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[9] S. Alexander , *J. Chem. Phys*. **32** , 1700 (1960).

[10] J.H. Richards and W.F. Beach , *J.Org.Chem*. **26** , 623 (1961).

[11] R.R. Frazer and D.E. McGreer , *Can. J. Chem*. **39** ,505 (1961).

[12] L.M. Jackman and R.H. Wiley , *J. Chem.Soc*. 2880 (1961).

[13] R.B. Bates ,R.H.Caringhan,R.O. Rakutis, and J.H. Schauble, *Chem. and Ind*. 1020 (1962).

[14] A.Y. Jones and A.R. Katritzky, *Chem. and Ind*. 522 (1962).

[15] E.B. Whipple, J.H. Goldstein, and G.R.McClure, *J.Amer.Chem. Soc*. **82** , 3811 (1960).

[16] A.A. Bothner-By, C. Naar-Colin, and H. Gunther, *Ibid*. **84**, 2748 (1962).

[17] E.O. Bishop , *Ann. Reports* **58** , 60 (1961).

There appears to be some systematic variation in the chemical shift of C19 methyl (see Table I) , but this could only be used as confirmatory evidence in cases where both epimers are available.

Generally, equatorial protons are more deshielded than their axial counterparts [18] and in the present series one would predict that the axial protons at C6 in the 6α-series would appear upfield from those in the 6β-series. In fact, the differences are small and irregular, presumably because of different degrees of long range shielding by the enone system. That the H6 protons in the 6α-series are in fact axial is confirmed by the very broad appearance of the signals, due to the large[19] diaxial spin-spin coupling with one of the protons at C7.

In Δ^4-cholestene-3-one itself (see Table I) H4 appears as a broad singlet rather than the expected doublet . This is most likely due to the lack of angular distortion in the absence of 6- substituents. However, even in this case , the width of the signal due to H4 is at least twice as great as that of the corresponding singlets in the 6β - substituted series.

As expected, changes in substitution in the 17- position do not affect the coupling between H4 and H6. Thus , the vinylic H4 in 6α-methyl-17α-ethynyltestosterone , 6α-methyl-Δ^4-androstene-3,17-dione, and 6α-methyl-17α-acetoxyprogesterone gives rise to a doublet (J = approximately 1.7 c.p.s.).

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[18] L.M. Jackman , "Applications of NMR Spectroscopy in Organic Chemistry" p.117. Pergamon Press (1959).

[19] Ref.18, pp.83-89 .

It has been suggested, on the basis of ORD measurements[20], that bulky substituents in the 6β- position in some Δ^4-3-keto-steroids affect the conformation of rings B and/or A. Our results indicate that the conformation of ring B in all of the 6- substituted -Δ^4-3-ketosteroids investigated is essentially the same. This confirms the conclusion of Whalley[21] that changes in the sign of the Cotton effect in Δ^4-3-keto-steroids with 6β- substituents of different sizes are due to changes in the chirality[21,22] of the Δ^4-3-ketone chromophore.

The correlation established on the basis of the results quoted in <u>Table I</u> cannot be assumed to hold for 6- substituted -Δ^4-steroids lacking the carbonyl function at C3 because of altered geometry of ring A, and complications arising from possible coupling of H4 with H3. We have examined the NMR spectra of Δ^4-cholestene-3β-ol and its acetate, and found that in both cases the vinylic proton appears as a broad singlet (W = 4 to 5 c.p.s.) showing no splitting of the magnitude expected[19] (approx. 6 to 10 c.p.s.) for the coupling between H4 and a pseudo equatorial H3. This indicates that H3 is pseudo axial, but the width of the line is too great to determine with certainty whether coupling with H6 is taking place.

The angular dependence of allylic coupling in rigid systems indicated above appears to be general. Thus we have found that the vinylic protons H12 of glycyrrhetinic acid (I, R=H) and

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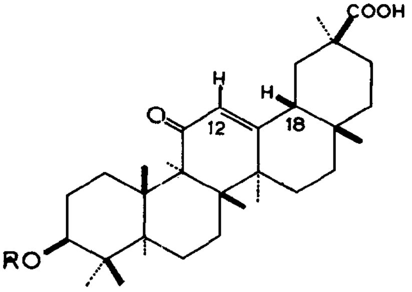
[20] C.Djerassi, O.Halpern, V.Halpern, and B.Riniker, J.Amer.Chem.Soc. **80**, 4001 (1958).

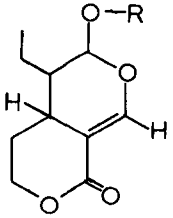
[21] W.B. Whalley, Chem. and Ind. 1024 (1962).

[22] C. Djerassi, R.Records, E.Bunnenberg, and K. Mislow, J.Amer. Chem. Soc. **84**, 870 (1962).

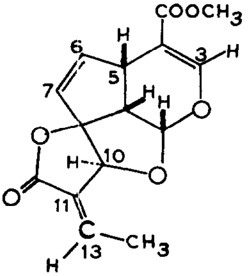
its acetate (I, R= OAc) give rise to narrow (W = 1.5 c.p.s.) singlets while the corresponding proton in the 18α- epimer[23] gave rise to a poorly resolved doublet (estimated J = 1 to 1.5 c.p.s. , W= 3.5 c.p.s.). In the completly rigid C/D ring system of glycyrrhetinic acid there are no ambiguities due to conformational changes.



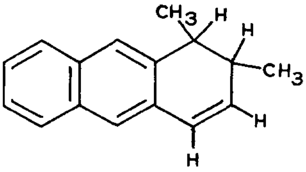
(I)



(II)



(III)



(IV)

Other examples can be found in the literature. The vinylic proton of a derivative of gentiopicroside[24](II) was found to be split (J = approx. 2 c.p.s.). This is an example of

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[23] J.M.Beaton and F.S. Spring, J.Chem.Soc. 3126 (1955).

[24] L. Canonica, F.Pelizzoni, P.Manito, and G.Jommi, Tetrahedron **16** , 192 (1961).

transoid rather than cisoid allylic coupling[11], again with a non-eclipsed relationship between the allylic and vinylic protons. The rigid structure of plumericin[25](III) affords several examples of allylic coupling. The vinylic proton H3, which is nearly eclipsed by the transoid allylic proton H5 (estimated angle approx. 10°) is reported to give rise to a singlet. The NMR features assigned to H5 and H7 (transoid system, nearly perpendicular) indicate coupling between them. The angle between the plane H13-C13-C11-C10 and H10 (which gives rise to a poorly resolved doublet) is approximately 130°, suggesting that this configuration represents an intermediate case.

If the angular dependence of allylic coupling could be firmly established by a sufficient number of examples it would have obvious uses in conformational as well as configurational analysis. Thus in the case of 1,2-dimethyl-1,2-dihydroanthracene (IV) there appears to be no coupling[26] between the vinylic H4 and the allylic H2, suggesting that the latter is more likely to be pseudo equatorial (nearly eclipsed) than pseudo axial. The conformation of the dihydroaromatic ring is therefore defined.

Thus, in spite of complications arising from the difficulty of accurate measurements of the small allylic coupling constants , and the risks of estimating angles from the study of models , the authors accept as a preliminary

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[25] G.Albers-Schonberg, and H.Schmid, Helv. Chim. Acta. 44,1447 (1961).

[26] R.Gerdil and E.A.C.Luchen , Ibid. 44 , 1978 (1961).