Spin–Spin Coupling Between Hydrogen and Steroid Angular Methyl Protons

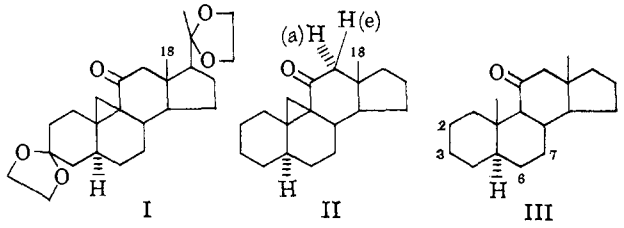
N. S. Bhacca, J. E. Gurst,[1a] and D. H. Williams[1]

Contribution from the Department of Chemistry, Stanford University, Varian Associates, Palo Alto, California, and the University Chemical Laboratories, Cambridge, England. *Received May 27, 1964*

It has been shown that the n.m.r. spectra of several 2- and 11-keto steroids exhibit doublet C-19 and C-18 methyl resonances, respectively. The stereochemical requirements for long-range coupling between the angular methyl and nuclear protons have been elucidated by deuterium labeling. Observations are also reported on the relative chemical shifts of protons adjacent to the carbonyl function and the stereochemical requirements of coupling "through carbonyl."

Introduction

Long-range spin–spin coupling between angular methyl protons and fluorine in certain fluorosteroids is a well-established phenomena.[2] The corresponding interaction between angular methyl protons and nuclear hydrogen atoms of the steroid skeleton has been reported in only two cases: the C-18 methyl resonance in the n.m.r. spectrum of the 9,19-cyclo-11-keto steroid I occurred as a three-proton doublet (J = 0.7 c.p.s.),[3] while the corresponding signal in the spectrum of the related ketone II was broadened due to the coupling of the C-18 protons with the axial proton attached to C-12.[4]



I II III

It therefore appeared that the stereochemical requirements of the long-range coupling were only satisfied upon suitable conformational distortion of ring C in the presence of the 9,19-cyclopropyl ring. In order to determine whether or not this was indeed the case, we decided to determine the spectra of a number of other related androstanes. Moreover, the statement[4] that the axial 12α-proton in II is coupled to the C-18 methyl group is based only on the assumption that the Δ^{11}-enol of II undergoes axial ketonization in the same manner as the corresponding Δ^{11}-enol of 5α-androstan-11-one (III).[5] In view of the finite possibility that such a course might be influenced by slight conformational changes on going from III to II, it was felt that an unambiguous experiment to determine the spatial requirements of the coupling should be devised. This feeling was considerably accentuated by the fact that in the n.m.r. spectrum of the cyclopropyl ketone II,[4] the ketonization experiments required the 12β-equatorial proton to resonate at lower field (2.58 p.p.m.) than the 12α-axial proton (2.04 p.p.m.). The relative positions of these two protons are reversed with respect to the order expected on the basis of the available literature. Thus, Williamson and Johnson[6] reported that the axial 3α-proton in 3β-acetoxy-5α-cholestan-2-one resonates at lower field than the comparable 3β-equatorial proton in the 3α-acetoxy epimer. Moreover, for a large number of epimeric steroidal α-haloketones it has been demonstrated that the signal for the epimer with an axial hydrogen adjacent to the ketone appears at lower field than that for the epimer with equatorial hydrogen.[7,8] Similar results are available for several epimer pairs of α-bromocyclohexanones[9] and for the relative positions of the 6-methylene protons in 5α-androstan-7-one[10] (for the numbering of the steroid skeleton, see III). Therefore, if our original assignment for the stereochemical requirements of long-range coupling involving the angular methyl group is correct, the data for the 11-ketone II provides the sole reported exception for the "rule" that an axial proton adjacent to a carbonyl group in a cyclohexanone ring will appear at a downfield position relative to its equatorial counterpart.[11]

Discussion

The obvious compound to study in an attempt to settle some of the points raised in the introduction is 5α-androstan-2-one (IV). The C-1 methylene protons bear the same relationship to C-19 as the C-12 methylene protons do to C-18 in 5α-androstan-11-one (III). Hence the possibility arises that they will be discernible as an AB system, in which only one proton is coupled to H-19.

(1) (a) Financial support of the work at Stanford University by the National Institutes of Health (Grants No. AM-04257 and CA-07195); (b) address inquires to D. H. W. at Cambridge, England.

(2) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962).

(3) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 44, 2162 (1963).

(4) D. H. Williams and N. S. Bhacca, *J. Am. Chem. Soc.*, **85**, 2861 (1963).

(5) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, **85**, 2091 (1963).

(6) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961).

(7) A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *ibid.*, **85**, 2185 (1963).

(8) N. L. Allinger, M. A. DeRooge, M. A. Miller, and B. Waegell, *J. Org. Chem.*, **28**, 780 (1963).

(9) K. M. Wellman and F. G. Bordwell, *Tetrahedron Letters*, 1703 (1963).

(10) R. Beugelmans, R. H. Shapiro, L. J. Durham, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 2832 (1964).

(11) The pair of epimeric 2-acetoxycholestan-3-ones are also exceptional, but as pointed out previously[6] the anomalous conformation of the 2β-acetate probably invalidates any conclusion regarding the chemical shifts of the epimeric C-2 protons in the two compounds. It should also be noted that ring C in compounds I and II is slightly distorted from the normal chair conformation. This conformational distortion may be invoked as the rationale for the anomalous relative positions of the C-12 methylene protons, but such reasoning does not serve to settle any small doubts which may exist as to the axial ketonization of II.

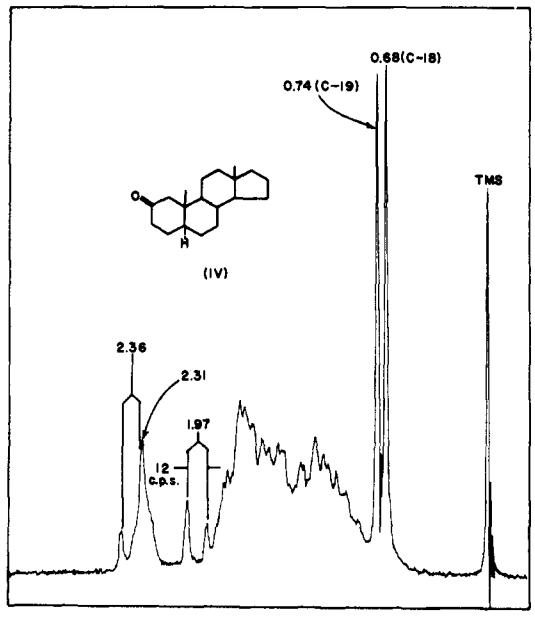


Figure 1. N.m.r. spectrum (100 Mc.) of 5α-androstan-2-one (IV).

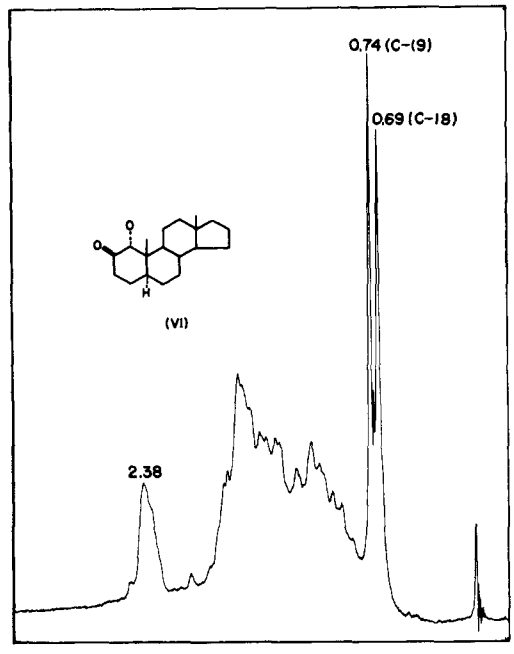
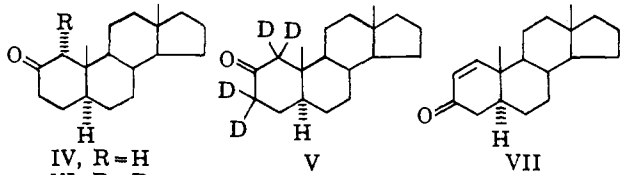


Figure 2. N.m.r. spectrum (100 Mc.) of 1α-d_1-5α-androstan-2-one (VI).

The 100 Mc. n.m.r. spectrum of 5α-androstan-2-one (IV)[12] is reproduced in Figure 1.[13] Appearing at slightly higher frequency than the low-field fringe of the methylene envelope, three lines of an AB pattern are clearly resolved (Figure 1). The chemical shift of proton A is 1.97 p.p.m., while proton B resonates at δ = 2.36 p.p.m. One line of the doublet due to proton B is hidden beneath a two-proton signal centered at 2.31 p.p.m. The coupling constant (J_{AB}) is 12 c.p.s., consistent with geminal coupling of the two isolated C-1 methylene protons. The broad, two-proton resonance at 2.31 p.p.m. is attributed to the C-3 methylene protons which are apparently chemically equivalent.



IV, R = H
VI, R = D

V

VII

These assignments may be readily confirmed by the n.m.r. spectra of deuterated derivatives. Thus, the spectrum of 1,1,3,3-d_4-5α-androstan-2-one (V)[12] shows no signals below δ = 1.9 p.p.m. Moreover, in the spectrum (Figure 2) of 1α-d_1-5α-androstan-2-one (VI),[12] the high-field portion of the AB pattern has disappeared while the low-field portion has the appearance of a singlet. This results in a very broad three-proton resonance centered at 2.38 p.p.m. (Figure 2). The α-configuration of the deuterium atom in VI is known with certainty since it was introduced through catalytic deuteration of Δ^1-5α-androsten-3-one (VII) and subsequent conversion of the derived 3-ketone to a 2-ketone by standard procedures.[12] The catalytic reduction of a Δ^1-3-ketone moiety by either deuterium or hydrogen has been established to proceed from the α-face in several closely related compounds.[14-16]

One conclusion of importance which may immediately be derived from Figure 2 is that as far as the C-1 methylene group adjacent to the keto function is concerned, the equatorial proton appears at lower field than its axial counterpart by 0.39 p.p.m. This observation would seem to preclude the statement of any rule as to the relative positions of axial and equatorial protons in a methylene group adjacent to a ketone within the steroid framework (or related compounds such as polycyclic terpenes or sapogenins). This situation is not too surprising, for even if the carbonyl group acts in such a manner on α-protons as to tend to reverse the usual "equatorial downfield of axial" relationship for cyclohexane systems,[17] the end result will also be dependent on the difference in chemical shift, δ_{ae}, of the two protons within the methylene envelope of the deoxo compound, *i.e.*, 5α-androstane in the case under discussion.

By reasoning similar to that outlined in the previous paragraph, it is possible that subsequent investigation of steroidal α-haloketones will uncover instances in which, contrary to all cases so far known,[7] the anisotropy of the ring system causes an equatorial proton (H*, see VIII) to resonate at lower field than the corresponding axial proton in the epimeric compound.

However, there appears to be a fundamental difference, pertinently noted by Nickon and co-workers.[7] between ketones (IX) and axial bromoketones (VIII) in that the transformation X → VIII results in shielding

(12) J. E. Gurst and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 5542 (1964).

(13) All the n.m.r. spectra were obtained either on a Varian A-60 or HR-100 spectrometer. The samples were run as deuteriochloroform solutions, with a trace of tetramethylsilane added to act as internal reference.

(14) Δ^1-5α-Cholesten-3-one: F. J. Schmitz and W. S. Johnson, *Tetrahedron Letters*, 647 (1962).

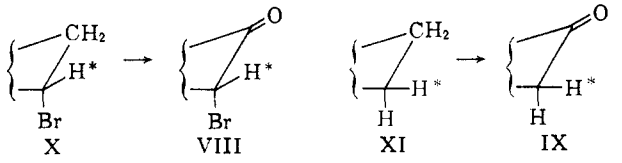
(15) Δ^1-5α-Androsten-3,17-dione: H. J. Ringold, M. Gut, M. Hayano, and A. Turner, *ibid.*, 835 (1962); H. J. Ringold, M. Hayano, and V. Stefanovic, *J. Biol. Chem.*, **238**, 1960 (1963).

(16) Δ^1-5α-Androsten-3,11-dione: D. H. Williams, N. S. Bhacca, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2810 (1963).

(17) L. M, Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy to Organic Chemistry," Pergamon Press, London, 1959, p. 116.

Figure 3. Expanded n.m.r. spectrum (60 Mc.) of δ = 0.6–0.8 p.p.m. region of 4,4-d_2-5α-androstan-2-one (XII).

of H*, while the conversion XI → IX causes deshielding of H*, despite the fact that both changes merely involve the introduction of a keto group. The origin of this difference is obscure at the moment, but it appears likely that the effects of the bromine and/or carbonyl group are modified by mutual interaction. Experiments to establish the absolute shifts of both methylene protons on passing from a system such as XI to IX are at present underway in our laboratories.



It is also evident by comparison of Figure 1 and Figure 2 that the C-19 protons are indeed coupled to the 1α-proton in 5α-androstan-2-one (IV). The half-width of the C-19 methyl resonance in Figure 1 is 2.6 c.p.s., whereas it is reduced to 1.8 c.p.s. in Figure 2; the sharpening of the C-19 resonance in Figure 2 is evident on a comparison of the relative heights of the C-18 and C-19 peaks in the two figures. Much more compelling evidence of long-range coupling is given by the presence of the C-19 methyl resonance as a doublet (J = 1.0 c.p.s.) in the 60 Mc. spectrum of 4,4-d_2-5α-androstan-2-one (XII)[12]; the effect has been greatly accentuated in Figure 3 by employing a sweep width of 50 c.p.s. on the A-60 chart. Determination of the 5α-androstan-2-one (IV) spectrum using the same sweep width results in similar resolution of the 19-methyl resonance, and the introduction of deuterium at C-4 in XII is not thought to have any intrinsic effect on the long-range coupling.

The evidence available therefore points to the fact that the C-18 and C-19 doublet methyl resonances may occur in the spectra of 11-ketones and 2-ketones, respectively. The stereochemical requirements of the long-range coupling have been partly defined and it is

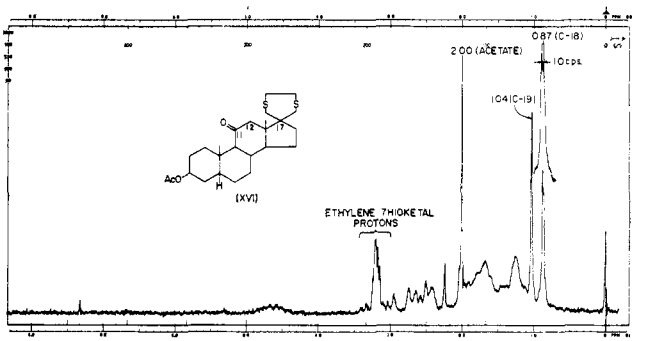
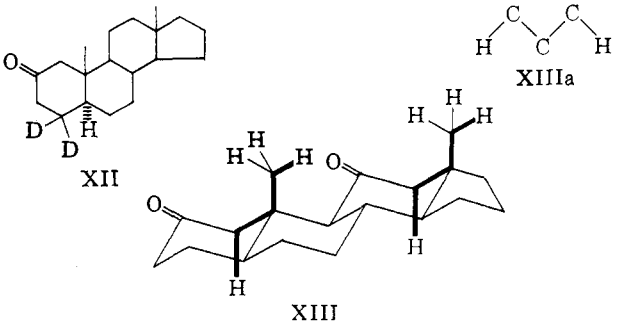


Figure 4. N.m.r. spectrum (60 Mc.) of 5α-androstan-3β-ol-11,17-dione acetate 17-ethylene thioketal (XVI).

interesting to note that if the 4σ-bond coupling occurs through the bonds indicated by heavy outline in XIII, the "M" spatial arrangement (XIIIa) which is thought to be optimal for long-range proton–proton coupling[18a]



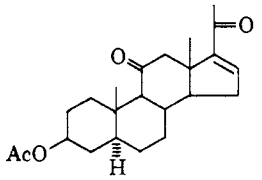
is satisfied.[18b] Whether similar couplings will be observable between 19- and 5α-protons in 4- and 6-ketones remains to be seen. In this respect, it is pertinent to note that although 5α- and 9α-fluorosteroids which have been so far examined exhibit no 19H–F coupling, 18H–F coupling has been observed in 12α- and 17α-fluorosteroids.[19,20] Hence, the demonstration of 19–1α and 18–12α proton–proton coupling does not necessarily imply that superficially similar 19–5α, 19–9α, and 18–14α couplings will be observable.

In order to test our hypothesis that doublet methyl resonances may be a general phenomena in 2- and 11-ketones, we have determined the spectra of a number of other related ketones. In the spectra of XIV and XV, the C-18 methyl resonances were not observable as doublets at normal sweep rates, but were appreciably broader than the H-19 resonances; the occurrence of 18–12α proton–proton coupling was demonstrated in both compounds by direct observation of the broad signals due to the 12α-protons or by double resonance, exactly as described previously.[4] However, in the spectrum (Figure 4) of the 11-ketone XVI, the H-18 signal is readily resolved into a doublet. In the spectrum of 5α-androstane-2,11-dione (XVII), the H-19 resonance is evident as a doublet (J = 1 c.p.s.), whereas the H-18 signal is unsplit.

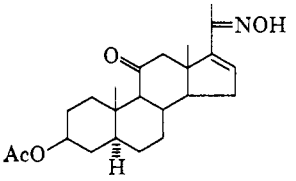
(18) (a) A. Rassat, C. W. Jefford, J.-M. Lehn, and B. Waegell, *Tetrahedron Letters*, 233 (1964). (b) Similar generalizations have been reported since this manuscript was submitted; see C. W. Shoppee, F. P. Johnson, R. Lack, and S. Sternhell, *ibid.*, 2319 (1964).

(19) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **86**, 4005 (1964).

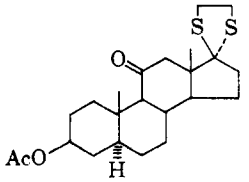
(20) Report at the International Congress on Hormonal Steroids, Milan, May 1962, by P. A. Diassi, J. Fried, R. M. Palmere, and P. A. Principe.



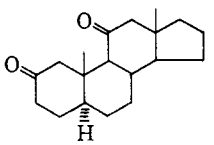
XIV



XV

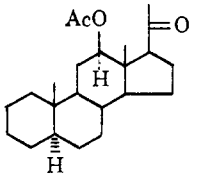


XVI



XVII

In summary we can only state that C-18 and C-19 doublets *may* be observed in 11-ketones and 2-ketones. The factors which determine whether the long-range coupling will be observable or not must be very subtle. Probably very small conformational changes will affect the magnitude of the coupling constant through four σ-bonds. It is evident that finite long-range coupling of angular methyl protons occurs in most steroids, since the signals due to them are usually broader than the methyl resonance of an acetate function within the same molecule, for example.[21] This broadening is almost certainly due in part to 18–12α and 19–1α proton–proton couplings.[22] The possibility that splittings may be observable in 2-ketones and 11-ketones merely because the 1α- and 12α-protons have suffered a downfield shift in such oxo compounds appears unlikely, since no $J_{18,12\alpha}$ is observable in the 12β-acetate XVIII. For structural work, the most important point is that the appearance of angular methyl resonances as doublets in 2- and 11-ketones should not be associated with an impure product.



XVIII

It may of course be the case that subsequent further sophistication in instrumentation will permit more routine resolution of angular methyl group resonances. Under such circumstances the observation of doublet methyl resonances may even prove of structural utility.

(21) See, for example, spectra 350, 353, and 361, N.M.R. Spectra Catalog, Varian Associates, Palo Alto, Calif.; see also Figure 4.

(22) The possibility that this broadening of angular methyl resonances (relative to methyl resonances of acetate functions) is due to differing relaxation times cannot be rigorously excluded, but it is felt that long-range coupling is the most important factor.

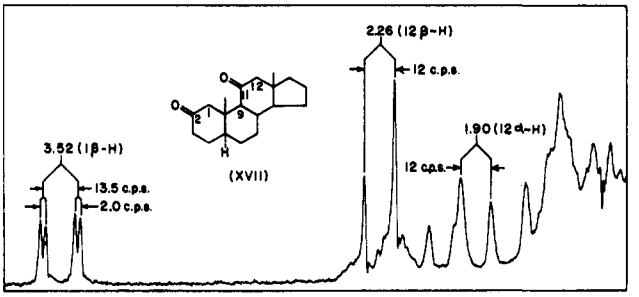
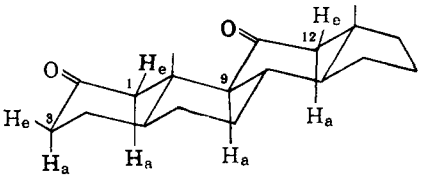


Figure 5. N.m.r. spectrum (100 Mc.) of 5α-androstan-2,11-dione (XVII) in benzene solution.

Finally, we wish to present results which give insight as to the stereochemical requirements of coupling "through carbonyl."[23]

In the 100 Mc. spectrum (Figure 5, δ = 1.3–3.8 p.p.m., benzene solution) of 5α-androstan-2,11-dione (XVII), the two pairs of lines centered at 1.90 and 2.26 are characteristic of the C-12 methylene protons (J_{gem} = 12 c.p.s.) and the high-field pair of lines, corresponding to the axial 12α-hydrogen, are broadened through interaction with the C-18 protons. The sharpness of the low-field pair centered at 2.26 illustrates that coupling of equatorial 12β-H to axial 9α-H through carbonyl is negligible. In contrast, the equatorial 1β-proton resonance at 3.52 is split not only by a geminal interaction (13.5 c.p.s.) but also by a coupling (2.0 c.p.s.) through carbonyl which is almost certainly to the equatorial 3β-proton (see XVIIa). Thus, when coupling through carbonyl does occur, it appears to be greatest when the interacting protons take on a pseudo-1,3-diequatorial relationship. It is interesting that the spectrum of XVII in deuteriochloroform shows only a broad pair of lines for the 1β-proton resonance at 60 or 100 Mc. Whether this is due to small, solvent-induced conformational changes in ring A of XVII, a solvent effect on nuclear relaxation times, or solvent-induced changes in chemical shifts is difficult to say at the moment.



XVIIa

Acknowledgment. We thank Dr. Lois J. Durham of Stanford University for assistance in obtaining several of the spectra for this study.

(23) J. R. Holmes and D. Kivelson, *J. Am. Chem. Soc.*, **83**, 2959 (1961).