Tetrahedron Letters No.34, pp. 2319-2322, 1964. Pergamon Press Ltd.
Printed in Great Britain.

LONG-RANGE SPIN-SPIN COUPLING
INVOLVING THE ANGULAR METHYL GROUPS IN STEROIDS.

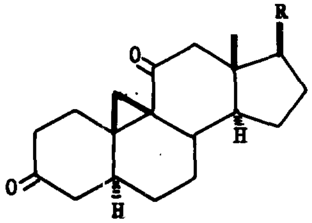
C.W. Shoppee, F.P. Johnson, Ruth Lack and S. Sternhell
Department of Organic Chemistry,
The University of Sydney
Sydney, Australia

(Received 6 July 1964)

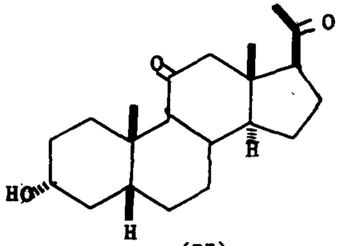
The angular methyl groups[involving $C_{(18)}$ and $C_{(19)}$] in the steroid nucleus give rise to easily identified signals in the p.m.r. spectra. These are usually described as "sharp" singlets, but in fact their width at half-height (W_H) is always significantly greater than that of a "genuine" singlet (such as that due to tetramethylsilane) at the same resolution. In the case of the modified steroid nucleus (I), the $C_{(18)}$-methyl was reported[1] to give rise to a doublet (splitting 0.8 c/s.) which was proved by spin decoupling experiments to be due to an interaction with the 12α-proton[2]. This type of long-range coupling across four bonds in a completely saturated system has many analogies[3], and the steric conditions for its occurrence have been defined[3,4] as the "tail-to-tail", "M" or "W" rule, to which only very few exceptions[3] have been reported.

We wish to report evidence that the broadening of the p.m.r. signals due to the $C_{(18)}$- and $C_{(19)}$-methyl groups in two typical steroids is due to this type of spin-spin interaction.

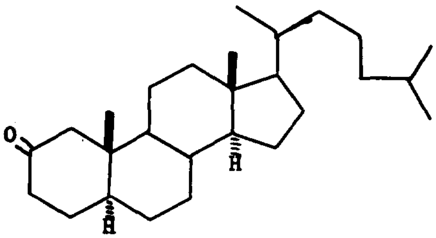
The signals due to the $C_{(18)}$- and $C_{(19)}$-methyl groups in most steroids can easily be assigned by the well-known additivity rules[5,6,7]. In the p.m.r. spectrum of 3α-hydroxy-5β-pregnane-11,20-dione[8] (II), the peak at 2.11 ppm was assigned to the $C_{(21)}$-methyl group, that at 1.15 ppm (W_H : 1.2 c/s.) to the $C_{(19)}$-methyl group, and that at 0.57 ppm (W_H : 1.6 c/s.) to the $C_{(18)}$-methyl group. The spectrum was taken as an approximately 15% solution in deuteriochloroform and the



(I)



(II)



(III)

resolution of the instrument (Varian, model A60) was such that the singlet due to tetramethylsilane used as internal reference had W_H : 0.5 c/s. A peak at 2.42 ppm was assigned to the 3α-hydroxyl proton by its easy exchange with deuterium oxide. A prominent peak at 2.56 ppm of two proton intensity was assigned[9] to the $C_{(12)}$-methylene group and a series of ill-defined signals of total intensity 3 protons between 2.25 and 3.0 ppm were assigned to $H_{(9)}$, $H_{(17)}$ and $H_{(1\beta)}$[10]. Treatment of (II) with deuterium oxide and base under conditions which would be expected[10] to lead to exchange of $H_{(9)}$, $H_{(12\alpha)}$, $H_{(17)}$ and $C_{(21)}$-methyl protons (but not of $H_{(12\beta)}$) gave a material whose p.m.r. spectrum no longer showed the signal assigned to the $C_{(21)}$-methyl group, and which had only signals due to 3 protons (disregarding the hydroxyl signal) between 2.25 and 3.0 ppm. Detailed examination of the p.m.r. spectrum in this region and analogy with published data[10] suggests that the two protons exchanged are $H_{(12\alpha)}$ and either $H_{(17)}$ or $H_{(9)}$ (or both $H_{(9)}$ and $H_{(17)}$ partially). The signal assigned to the $C_{(19)}$-methyl group had W_H : 1.1 c/s., and that assigned to the $C_{(18)}$-methyl group had W_H : 0.9 c/s. at a resolution at which the singlet due to tetramethylsilane had W_H : 0.5 c/s. We interpret this result as showing that the principal cause of broadening of the signal due to the $C_{(18)}$-methyl group in (II) is long-range spin-spin coupling with either $H_{(12\alpha)}$ or $H_{(17)}$, or both.

Analogous deuterium exchange on 5α-cholestan-2-one[11] (III), leading to the formation of a tri- or tetradeuterio-derivative (on p.m.r. evidence) altered the signal at 0.74 ppm assigned[5,6,7] to the $C_{(19)}$-methyl group from a partially resolved doublet (principal splitting 0.7 c/s., W_H : 1.8 c/s., W_H tetramethylsilane: 0.55 c/s.) to a singlet (W_H : 1.1 c/s., W_H tetramethylsilane : 0.5 c/s.). We interpret this change as due to the exchange of a proton(s) which had been involved in a long-range interaction with the $C_{(19)}$-methyl group, presumably principally $H_{(2\alpha)}$, by the "tail-to-tail" rule[3,4].

The apparent generality of long-range coupling involving the $C_{(18)}$- and $C_{(19)}$-methyl groups in the steroid skeleton has obvious stereochemical implications which are being investigated.

Acknowledgement: We wish to thank Mr. Karl Diehlsen for obtaining the p.m.r. spectra.

REFERENCES

(1) H. Wehrli, M.S. Heller, K. Schaffner and O. Jeger., Helv. Chim. Acta., 44, 2162 (1961).

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

(3) S. Sternhell, Revs. Pure. Appl. Chem., 14, 15 (1964).

(4) A. Rassat, C.W. Jefford, J.M. Lehn and B. Wagell, Tetrahedron Letters, 233 (1964).

(5) R.F. Zürcher, Helv. Chim Acta., 44, 1380 (1961).

(6) E.R. Malinowski, M.S. Manhas, G.H. Müller and A.K. Bose, Tetrahedron Letters,1161 (1963).

(7) A.D. Cross and I.T. Harrison, J. Am. Chem. Soc., 85, 3223 (1963) and references therein.

(8) J. von Euw, A. Lardon, and T. Reichstein, Helv. Chim. Acta, 27, 821 (1944).

(9) J.S. Cox, E.O. Bishop, and R.E. Richards, J. Chem. Soc., 5118 (1960).

(10) D.H. Williams, N.S. Bhacca and C. Djerassi, J. Am. Chem. Soc., 85, 2810 (1963).

(11) L. Ruzicka, P.A. Plattner and M. Turner, Helv. Chim Acta, 27, 524 (1944); C.W. Shoppee and T.E. Bellas, J. Chem. Soc., 3366 (1963).