Tetrahedron Letters No. 15, pp. 647-652, 1962. Pergamon Press Ltd. Printed in Great Britain.

THE PROTON MAGNETIC RESONANCE SPECTRA OF THE 1α-DEUTERIO-2-ACETOXYCHOLESTANE-3-ONES. A CONTRIBUTION TO THE MECHANISM OF DEHYDROHALOGENATION OF α-HALO KETONES

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(Received 24 May 1962)

SEVERAL examples have appeared recently in which a complete analysis of nuclear magnetic resonance spectra of the ABC and ABX classification has revealed opposite signs for vicinal and geminal coupling constants.[1] In several instances it has been shown that more than one set of spin-coupling and chemical shift parameters can yield essentially identical theoretical spectra which are consistent with the experimental spectrum.[1b] These reports have pointed out the need for exercising caution in assuming like signs for all coupling constants, especially in the absence of an analysis of the total spin-spin coupling pattern. The accumulation of examples of negative coupling constants in saturated organic molecules, complemented

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[1] a R. R. Fraser, R. U. Lemieux and J. D. Stevens, J. Amer. Chem. Soc. 83, 3901 (1961).

b F. Kaplan and J. D. Roberts, J. Amer. Chem. Soc. 83, 4666 (1961).

c F. A. L. Anet, J. Amer. Chem. Soc. 84, 1053 (1962).

by theoretical considerations[2] of the dependence of the X portion of an ABX system on the relative signs of J_{AX} and J_{BX}, underlines the uncertainty which accompanies any assignment of specific coupling constants by simple inspection of such spectra. Furthermore, it has been pointed out[2] that no line spacings in the X portion of an ABX spectrum correspond simply to either J_{AX} or J_{BX}, although they may provide useful approximations.[3] In view of these developments, we felt that it was necessary to obtain unequivocal evidence for some coupling constants that had been obtained in our laboratory by the approximation method.[4]

The resonance lines associated with the proton on the acetate-bearing carbon atom of both 2α- and 2β-acetoxycholestane-3-one appear as a quartet due to the X proton in an ABX system.[4] The chemical shift of the protons on carbon-1 is not sufficient to separate their absorption lines from the rest of the protons in the molecule and allow complete analysis of the ABX pattern. The coupling constants, J_{ae} and J_{aa}, were therefore assigned[4] by an assumptive pairing of the lines in the quartet observed at low field. We have now selectively eliminated one of the vicinal coupling constants by deuterium substitution and have thus obtained a simplified spectrum from which unambiguous individual coupling constants have been measured directly.

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[2] J. D. Roberts, "An Introduction to the Analysis of Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra," W. A. Benjamin, Inc., New York, N.Y., 1961, Chap. 3.

[3] R. W. Fessenden and J. S. Waugh, J. Chem. Phys. 31, 996 (1959).

[4] K. L. Williamson and W. S. Johnson, J. Amer. Chem. Soc. 83, 4623 (1961).

1α-Deuteriocholestane-3-one, m.p. 127-128°, was prepared by catalytic deuteration of Δ^1-cholestene-3-one[5] in dioxane solution over 10% palladium-on-carbon followed by treatment of the crude product with potassium hydroxide in methanol at 25° overnight to remove the labile deuterium at C-2. Although catalytic deuteration is often attended by excess deuterium incorporation because of the exchange of allylic hydrogen atoms,[6] the unique environment of the double bond in Δ^1-cholestene-3-one precludes such scattering of deuterium, and the final product was shown by mass spectrometric analysis to be 80% mono-deuterated (balance non-deuterated). The assignment of the α-orientation to the incorporated deuterium is based on the general rule of catalyst adsorption from the less hindered side and is also consistent with Hadler's product-resembling complex theory.[7] This assignment is substantiated by the fact that the observed coupling constants, 6.4-7.0 c.p.s. (see below), for the 1α-deuterio-2-acetoxycholestane-3-ones and 1α-deuterio-2α-bromocholestane-3-one are of the magnitude expected for a pair of vicinal, axial-equatorial protons and are in distinct contrast with that expected for a vicinal diaxial pair of protons, 10-14 c.p.s., which should be observed if the deuterium were β-oriented.

1α-Deuteriocholestane-3-one was converted into 1α-deuterio-2β-acetoxycholestane-3-one, m.p. 145-147°, and the 2α-epimer, m.p. 124-

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[5] G. F. H. Green and A. G. Long, J. Chem. Soc., 2532 (1961).

[6] Cf. inter alia J. F. Sauvage, R. H. Baker and A. S. Hussey, J. Amer. Chem. Soc. **83**, 3874 (1961).

[7] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N.Y., 1959, pp. 271-274; see also L. H. Zalkow, F. X. Markley and C. Djerassi, J. Amer. Chem. Soc. **82**, 6354 (1960).

124.3°, by procedures already described,[8] and into 1α-deuterio-2α-bromocholestane-3-one, m.p. 168.5-171°, by direct bromination.

The NMR spectra[9] of 1α-deuterio-2α-acetoxycholestane-3-one and 1α-deuterio-2α-bromocholestane-3-one each exhibited a distinct doublet, J_{ae} = 6.4 c.p.s., centered at 4.93 and 5.43 τ respectively due to the resonance of the proton on carbon-2.[10] The spectrum of 1α-deuterio-2β-acetoxycholestane-3-one showed a clear doublet, J_{ae} = 7.0 c.p.s., centered at 4.86 τ. These values are in complete agreement with those estimated earlier[4] as are the respective coupling constants, J_{aa} = 13.1, 9.8 c.p.s., calculated by subtracting J_{ae} of the deuterated α-acetoxy ketones from the total line spacing $J_{ae} + J_{aa}$ in the spectra of the non-deuterated analogs. If it is assumed that J_{ae} and J_{aa} are opposite in sign, a similar calculation yields ridiculously large coupling constants for protons attached to adjacent saturated carbon atoms. Thus the initial first-order approximation of the coupling constants for these α-acetoxy ketones has given reasonably accurate values, and hence the revision[4] of the Karplus equation based on these data seems justified.

In connection with efforts to obtain 1β-deuteriocholestane-3-one, we envisaged the possibility of preparing 1-deuterio-Δ^1-cholestene-3-one

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[8] K. L. Williamson and W. S. Johnson, J. Org. Chem. **26**, 4563 (1961).

[9] Determined with a Varian A-60 spectrometer. Carbon disulfide was employed as the solvent with tetramethylsilane as internal standard.

[10] Shortly before this work was completed we received copies of the NMR spectra of 2α-bromo- and 1α-deuterio-2α-bromoandrostane-3,17-dione in a private communication from Dr. H. J. Ringold, whom we wish to thank for advising us of his unpublished results. These spectra exhibit the same coupling constants as the respective bromocholestanones.

by dehydrohalogenation of 1α-deuterio-2α-bromocholestane-3-one. This study also promised to shed some further light on the mechanism of the dehydrohalogenation of α-halo ketones.[11] That the preferred pathway is by an E_2 trans elimination mechanism is supported by the observation that methyl 3α-acetoxy-11β-bromo-12-ketocholanate (11β-Br/9α-H trans diaxial) undergoes dehydrohalogenation more readily than the 11α-epimer (11α-Br/9α-H cis equatorial-axial). Furthermore 3α-acetoxy-16α-deuterio-17α-bromopregnane-11,20-dione (16β-H/17α-Br trans) undergoes dehydrohalogenation to the α,β-unsaturated ketone with almost complete retention of deuterium. On the other hand, a cyclic cis mechanism has also been suggested.[11]

The various possibilities for the dehydrohalogenation of 1α-deuterio-2α-bromocholestane-3-one are as follows: (1) the elimination is a trans process involving the 2α-bromo ketone which would lead to retention of deuterium; (2) the elimination is a cis process involving the 2α-bromo ketone which would lead to loss of deuterium; (3) the 2α-bromo ketone isomerizes to the 2β-bromo epimer prior to elimination which then can proceed by a trans diaxial process leading to loss of deuterium; (4) the 2β-bromo isomer (from prior isomerization) undergoes a cis elimination which would lead to retention of deuterium

The decomposition of 1α-deuterio-2α-bromocholestane-3-one either (a) by heating with calcium carbonate in refluxing dimethylacetamide[5] or (b) via formation of the semicarbazone in acetic acid followed

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[11] Cf. inter alia N. L. Wendler, D. Taub and H. Kuo, J. Amer. Chem. Soc. **82**, 5701 (1960).

by cleavage to the ketone with pyruvic acid[5,6] gave Δ^1-cholestene-3-one which had lost 72.5% and 86.3% respectively of the original deuterium content as shown by mass spectrometric analysis. The fact that loss of the axial proton predominates in this reaction is thus established, and either mechanism (2) or (3) but not (1) or (4) is the preferred pathway for dehydrohalogenation under the conditions examined.

Acknowledgements. We wish to express our appreciation to Dr. L. J. Durham for obtaining the NMR spectra and to Dr. H. Budzikiewicz for the mass spectrometric analyses. We also thank the National Science Foundation and the U. S. Public Health Service for providing support for this study.

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[6] C. Djerassi, J. Amer. Chem. Soc. 71, 1003 (1949).