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# THE EQUILIBRIA AND NMR SPECTRA OF HYDROXYMETHYLENE KETONES

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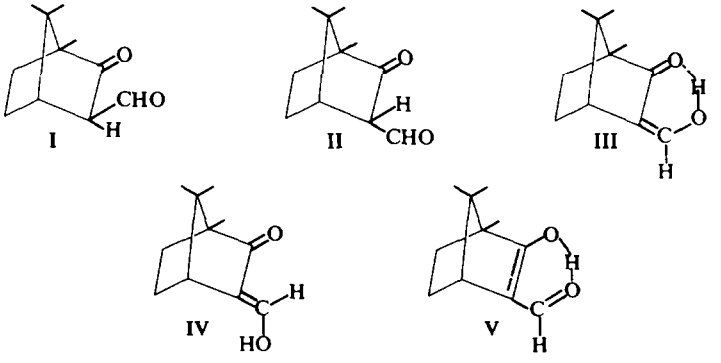
**Abstract**—The equilibrium mixture of 3-formylbornan-2-one and hydrogen bonding in this molecule are discussed in terms of its NMR spectrum. Variation in H—O—C—H coupling in hydroxymethylene ketones is explained and discussed.

HYDROXYMETHYLENE ketones, their aldo-enol equilibria, and their NMR spectra have been the subject of recent papers.[1-3] Particular attention has been centred on the NMR spectrum of 3-formylbornan-2-one where it has been shown that there are 4 species (I, II, III, IV) present in this equilibrium[1,3] and the possibility of a fifth (V)[2] which has not been substantiated. There are, however, some unexplained features of the NMR spectrum of this compound (Fig. 1a). Daniel and Pavia[3] remark that the aldehyde peaks at 9·80 and 9·75 $\delta$ (which we have shown do not decouple) are due to forms II and I, respectively, and have almost zero coupling with their respective $H_3$ protons (an effect also noticed in 2-formylcyclopentanone[4]), whereas normal coupling for this system is quite large. It is therefore suggested that the vicinal angle between the two protons concerned is approximately 90°, reducing coupling to a minimum as indicated by a Karplus type curve.[5] This means that the aldehyde groups in I and II are not free to rotate and must be held in one of two possible positions. The causes of this behaviour are somewhat obscure. It does seem, however, that the aldehyde carbonyl group is in such a position as to explain the deshielding of the $H_4$ proton in both *endo* and *exo* forms (II, I). It has been shown by formation[2] and isolation[7] of the methyl ethers of III, IV and V that the $H_4$ protons occur at 2·30, 2·82 and 2·93, respectively. These results[7] confirm and extend the observations of Daniel and Pavia[3] on the anisotropy of the hydroxymethylene group in this compound.



We have noticed that the addition of $D_2O$ to an NMR sample of 3-formylbornan-2-one produced marked reduction in size of the aldehyde peaks at 9·80 and 9·75 $\delta$ (Fig. 1b), increased the amount of III, and decreased the $H_3$ peaks of I and II by normal deuterium exchange. Both Garbisch[1] and Daniel[3] have shown that addition of DMSO to the NMR sample increased the amount of IV at the expense of I, II and III. These effects are probably a result of hydrogen bonding with the added molecule. It is known[8] that —O—H...O═S hydrogen bonding is stronger than —O—H...O═C bonding. Thus in the case where DMSO is added to the sample, the preferred species is that with DMSO hydrogen bound to the hydroxymethylene group, causing steric compression if the molecule were to revert to form III, and hence the preference is for the structure IV with DMSO attached. In forming IV it seems most likely that transformation occurs through either structures I or II where free rotation can occur, rather than through V where there would be at least some $\pi$-delocalization preventing rotation. Hydrogen bonding with water in the manner O—H...O—H is reported[8] to be stronger than either —O—H...O═C or —O—H...O═S bonding and hence the $D_2O$ molecule can be accommodated without steric compression, and therefore hydrogen bonding of both species ($D_2O$ and III) tends to favour structure III. The formation of IV in a similar manner on the addition of DMSO is obviously possible because of exchange of the $H_3$ protons, i.e. an equilibrium III $\rightleftharpoons$ II $\rightleftharpoons$ IV.

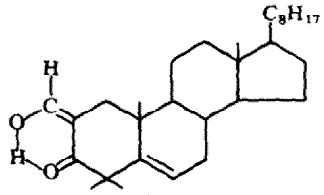
Forsen and Nilsson[9] observe coupling between enol and vinyl protons for a number of acyclic formyl ketones and consider that the coupling should disappear on rapid intramolecular exchange between the two possible forms, and since in several instances there was no evidence for the existence of any aldo–enol form, they concluded that the formylketones existed in the hydroxymethylene form.

Garbisch[1] considers, however, that coupling between H—O—C—H protons should vanish only for intermolecular exchange processes and points out that Forsen and Nilsson[9] consider 2-formylcyclohexanone to exist in the aldo–enol form solely because of the fact that it shows no coupling. Forsen and Nilsson's argument is also contrary to the results obtained for 3-formylbornan-2-one where there is no contributor V and no coupling. Garbisch[1] implies that the value of the coupling constant ($J$) depends on the proportion of the 2 enol forms and shows a linear relationship for a series of cyclic formyl derivatives.

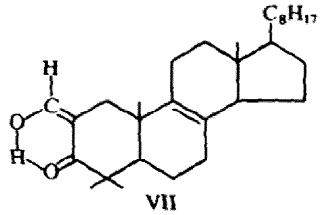
We have prepared 2-hydroxymethylene-4,4-dimethylcholest-5-en-3-one (VI) and 2-hydroxymethylenelanost-8-en-3-one (VII) which are completely enolized (from the NMR spectra) and although coupling between enolic and vinyl protons is observed in both cases the value of $J$ differs markedly. $J = 6$ c/s for VI and $J = 3$ c/s for VII. We also find that on addition of a trace of acid, the observed doublets for enolic and vinyl protons collapse to broad singlets and a separate water peak (5·20 $\delta$) occurs. This shows that the intermolecular exchange (catalysed by acid as in the case of ethanol[10]) is fast enough to prevent coupling but not fast enough to prevent the observance of hydroxyl protons due to both species. Since our results and those of Garbisch[1] indicate that $J$ does not vary with temperature, it is clear that intermolecular hydrogen bonding and temperature variations do not affect the *value* of $J$ but simply whether or not coupling occurs. It is also conceivable that rapid intramolecular exchange between the two enol forms would remove coupling, merely

because the lifetime of the proton in the bonded hydroxymethylene form may become too small for coupling to occur.

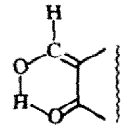
We suggest that the value of the coupling constant is indirectly related to structural effects and not to the proportion of enol forms. In the series considered by Garbisch[1] it is apparent that with increasing $J$ value, the ability of each molecule to form a planar hydroxymethylene system (VIII) increases. In the ring systems studied by




VI




VII




VIII

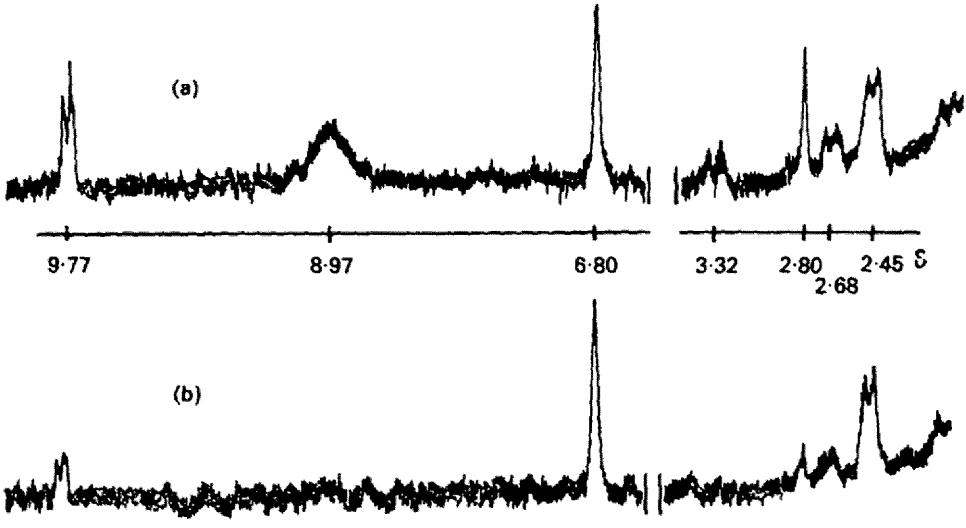



FIG. 1. NMR spectrum of 3-formylbornan-2-one. (a) Normal spectrum in $CCl_4$. (b) $D_2O$ added to $CCl_4$ solution.

Garbisch, there are 2 competing effects—non-bonded interactions across the ring, and hydrogen bonding in the system VIII and it is therefore difficult to predict the exact conformation of VIII. In the limit 4,4-dimethyl-6-hydroxymethylenecyclohex-2-enone and 3-hydroxymethylenebornan-2-one are almost completely planar and have large $J$ values.[1] With an exactly planar system VIII, the vicinal angle H—O—C—H is such that coupling becomes a maximum according to a Karplus type calculation.[5] Garbisch[1] implies that $J$ is directly related to the proportions of each enol form, but we suggest that the ability to form the hydroxymethylene compound which is the only form in which coupling can occur depends on effects within the rest of the molecule. In the examples VI and VII prepared by us the hydroxymethylene form is probably preferred over the aldo–enol form because of a reduction of ring strain. Preparation of 2-hydroxymethylenecholest-4-en-3-one and NMR examination shows that this molecule does not exist in the hydroxymethylene form.

The slight variations in the basic steroid structure alter the configuration of ring A, thus altering the vicinal angle H—C—O—H and hence altering the value of the coupling constant. It is impossible to predict how much coupling would be altered in such a system unless such factors as the amount of $\pi$-delocalization in the system VIII are known. Forsen and Nilsson[9] obtain a $J$ value of $\sim$6 c/s in all cases they consider, mainly because of structural and steric similarities.

In $H^1$ coupling through the system H—O—C—H of hydroxymethylene ketone compounds, the value of the coupling constant is determined by the vicinal angle H—O—C—H which is in turn strongly affected by structure.

## EXPERIMENTAL

NMR spectra were measured with a Varian A-60 spectrometer with a probe temp of 34° and samples were not degassed.

*2-Formyl-4,4-dimethylcholest-5-en-3-one* (VI). Finely divided Na (0·98 g) was added to a vigorously stirred mixture of 4,4-dimethylcholest-5-en-3-one[11] (0·94 g) and benzene (30 ml). After ½ hr, n-amyl formate (2·1 g) was added slowly (10 min) and after further stirring (2 hr), the excess Na was destroyed by addition of water. After acidification with 2N $H_2SO_4$, ether extraction gave an orange solid which was recrystallized from aq acetone as needles of *2-formyl-4,4-dimethylcholest-5-en-3-one* (0·67 g, 62%), m.p. 88–90°, M.W. (mass spec.) 440·3657 ± 0·0004; $C_{30}H_{48}O_2$ requires 440·3654, $\nu_{max}$ 1665, 1640, 1590 $cm^{-1}$.

*2-Formyllanost-8-en-3-one* (VII). A mixture of lanost-8-en-3-one (1·0 g), in benzene (30 ml) and Na-wire (0·7 g) was stirred for 15 min under $N_2$. Ethyl formate (1·2 ml) was then added and the mixture stirred for a further 5 hr. Working up as for VI gave *2-formyllanost-8-en-3-one* (0·97 g, 91%) as needles from $CHCl_3$–MeOH, m.p. 123·5–125°, $\nu_{max}$ 3525, 1665, 1630, 1650 $cm^{-1}$, $\lambda_{max}$ 294 mμ ($\varepsilon$ = 6800).

*3-Formylbornan-2-one* was prepared by standard methods[12] and *2-formylcholest-4-en-3-one* by the method of Burr *et al.*[13]

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