988. *Proton Resonance Spectra of Some* 11-*Keto-steroids.*

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The proton resonance spectra of a number of 11-keto-steroids and some derived enol acetates in chloroform solution have been studied. Referencing procedure for obtaining chemical shifts is examined. Characteristic chemical-shift values of substituent groups are obtained, together with constitutive values for their displacing effect upon the resonance positions of the angular 19- and 18-methyl groups.

Shoolery and Rogers [1] have described measurements of the proton resonance spectra of steroids in deuterochloroform solution and have drawn up many correlation rules of diagnostic value. The proton resonance absorption of the skeletal protons is complicated by strong spin coupling between them, and it usually appears as a broad unresolved "hump" the form of which is very sensitive to minor structural changes. Peaks due to individual skeletal protons may, however, be recognised if their environment causes a displacement of their chemical shifts well below the main region of skeletal absorption. On the other hand, proton resonances of substituents attached to the carbon framework by a single bond are often strong and sharp, because of the combined effects of an additional rotational degree of freedom and relatively simple spin–spin coupling. The most important structural correlations were derived from the shifts of the substituents. The resonance due to a substituent group often occurs at a characteristic position. Furthermore, the long-range shielding effects of several substituents upon the protons of the angular 19- and 18-methyl groups are to some extent additive, *i.e.*, a substituent in a particular skeletal position and configuration may be assigned an approximate displacing effect (generally to lower shielding) on each of the angular-methyl peaks. The effect of conformation upon both these correlations has been demonstrated by Slomp and McGarvey[2] for a series of 6-methyl steroids. The original communication was quickly followed by similar contributions from other workers.[2–5]

[1] Shoolery and Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.
[2] Slomp and McGarvey, *J. Amer. Chem. Soc.*, 1959, **81**, 2200.
[3] Buchschacher, Cereghetti, Wehrli, Schaffner, and Jeger, *Helv. Chim. Acta*, 1959, **42**, 2126.
[4] Slomp and MacKellar, *J. Amer. Chem. Soc.*, 1960, **82**, 999.
[5] Rosen, Ziegler, Shobica, and Shoolery, *J. Amer. Chem. Soc.*, 1959, **81**, 1687; Hirschman, Bailey, Walker, and Chemerda, *ibid.*, p. 2822; Slates and Wendler, *ibid.*, p. 5474; Nusskawn, Carlon Gould, Oliveto, Hershberg, Gilmore, and Charney, *ibid.*, p. 5230.

In connection with synthetic studies towards *C*-methylated 11-keto-steroids,[6] we have examined the spectra of a family of these compounds and are able both to confirm and in many ways to extend earlier results.

Results and Discussion

The results are summarised in the Table. The chemical shifts are given in c./sec. at 40 Mc./sec. relative to the benzene external reference, and the position of the tetramethylsilane resonance is also recorded. Positive values refer to higher applied fields. To convert the chemical shifts to the τ scale [7] in parts per million, the expression:

$$\tau = 10{\cdot}000 - (\nu_{SiMe_4} - \nu)/40$$

should be used, where ν_{SiMe_4} is the frequency of the internal reference with respect to the benzene reference, and ν is the frequency of the line concerned with respect to the external

Chemical shifts (c./sec.) at 40 Mc./sec. with reference to a benzene external standard.

Compound	19-Me	18-Me	$SiMe_4$	Other substituents
(I) 3α-Acetoxy-5β-androstan-11-one	209	229½	254·7	OAc 176; CH_2·CO 164½
(II) 3-Ethylenedioxy-5β-androstan-11-one	209	229½	253·4	Ketal 99; CH_2·CO 165½
(III) 3α,20β-Diacetoxy-12α-bromo-5β-pregnan-11-one	209½	225½	255·0	2(OAc) 174½; 21-Me 208 (*J* 5·8)
(IV) 3α-Acetoxy-12α-bromo-5β-androstan-11-one	209½	221½	254·8	OAc 174½
(V) 3α,20β-Diacetoxy-5β-pregnan-11-one	210	233	255·8	2(OAc) 175½; CH_2·CO 161½; 21-Me 210 (*J* 5·9)
(VI) 3-Ethylenedioxy-12α-methyl-5β-androstan-11-one	208	227	253·8	Ketal 99; 12-Me 212 (*J′* 6·1)
(VII) 3α-Hydroxy-5β-androstane-11,17-dione	212	226	—	3-OH 122; CH_2·CO 163½
(VIII) 3β,20-Diacetoxy-5α-pregn-17(20)-en-11-one	215	225	256·6	3-OAc 176; 20-OAc 171½; CH_2·CO 155; 21-Me 185
(IX) 3α,20β-Diacetoxy-12α-methoxy-5β-pregnan-11-one	208	233½	254·8	2-(OAc) 173½; OMe 121½; 21-Me 208½ (*J* 5·8)
(X) 12α-Bromo-5β-androstane-3,11-dione	206	219½	255·5	—
(XI) 3-Ethylenedioxy-9α-bromo-5β-androstan-11-one	195 *	226	—	Ketal not located. ? Hydrolysis
(XII) 3α,11-Diacetoxy-5β-androst-9(11)-ene	211	225	254·7	2(OAc) 173½ partially resolved
(XIII) 3α-Acetoxy-9α-bromo-5β-androstan-11-one	??	228½	—	OAc 174½
(XIV) 3α,20β-Dibenzoyloxy-9α-bromo-5β-pregnan-11-one	206½	231½	—	21-Me 207 (*J* 5·8)
(XV) 12α-Bromo-3-ethylenedioxy-5β-androstan-11-one	208½	221	255·5	Ketal 98
(XVI) 3β-Acetoxy-5α-androstan-11-one	215½	230½	(257·4)	OAc 174; CH_2·CO 162½
(XVII) 3α,11,20β-Triacetoxy-5β-pregn-7,9(11)-diene	214½	235	255·8	11-OAc 172; 3,20-$(OAc)_2$ 176½; 21-Me 210 ($J \leqslant 6{\cdot}6$)
(XVIII) 3β-Acetoxy-5α-pregnane-11,20-dione	215	233	256·0	OAc 175½; COMe 172½; CH_2·CO 155
(XIX) 3α-Benzoyloxy-5β-pregnane-11,20-dione	211 (−3)	235½ (−3)	258 (−3)	CH_2·CO 155 (−3); COMe 175 (−3)
(XX) 3β-Acetoxy-9α-bromo-5α-androstan-11-one	207½	227½	255·2	OAc 174½
(XXI) 3α,20β-Diacetoxy-5β-pregn-8-en-11-one	207	228½	255·6	
(XXII) 11-Acetoxy-3α,20β-dibenzoyloxy-5β,14β-pregna-7,9(11)-diene	207½ (−2)	217 (−2)	257 (−2)	11-OAc 176 (−2); 21-Me 204½ (−2)
(XXIII) 3α,20β-Dibenzoyloxy-5β,14β-pregn-8-en-11-one	209 (−3½)	218½ (−3½)	258·7 (−3½)	21-Me 205½ (−3½)

* Impure compound; assignment uncertain.

benzene reference. The Figure shows the appearance of the spectra obtained in some typical cases.

The chemical shifts are discussed below in three sections. In the first section the chemical shifts of the substituent groups are considered in relation to their position, and

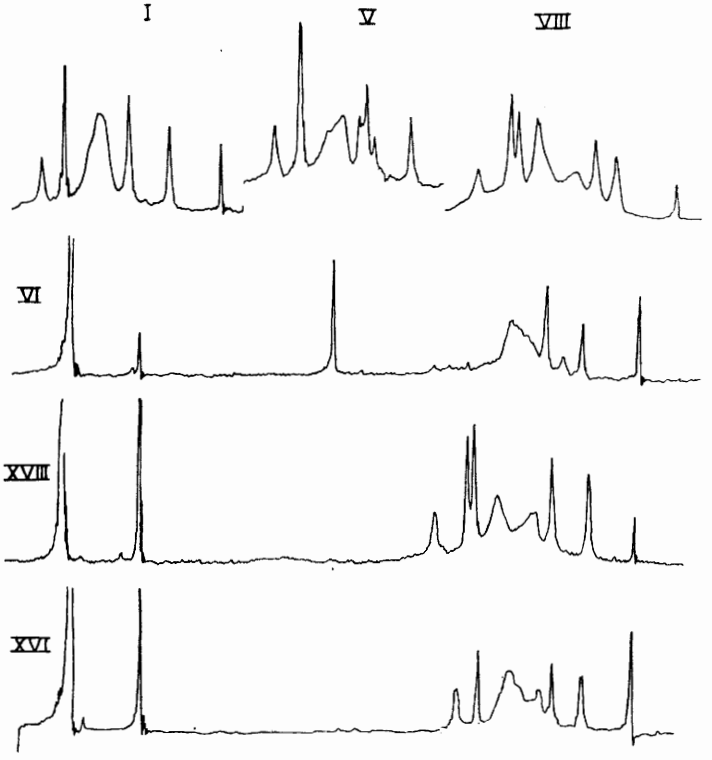
[6] (*a*) Jones, Meakins, and Stephenson, *J.*, 1959, 907; (*b*) Cox and Wluka, and (*c*) Binns, Cox, Jones, and Ketcheson, unpublished work.

[7] Van D. Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.

in the second section the effects of these substituents on the shifts of the angular methyl group resonances are discussed. In the third section, comments are made on the absorption of the protons attached to the main skeleton of the molecule.

Chemical Shifts of Substituent Groups.—Acetoxy-groups. These give sharp unsplit peaks in all the compounds studied. When the acetoxy-group is in the 3-position, the shifts for the α-oriented substituent with an A/B-*cis* ring junction (8 compounds) are: 176 (I; for compounds represented by this and similar Roman numerals, see the Table), 174½ (III, IV, and XIII), 175½ (V), 173½ (IX and XII), and 176½ (XVII) c./sec., whilst

Proton resonance spectra of compounds (I), (V), (VII), (VI), (XVIII), *and* (XVI) (*for names see Table*).



the β-oriented group exhibits a shift of 176, 175½, 174½ c./sec. in three compounds with an A/B-*trans* junction (VIII, XVIII, and XX). These are in accord with the range [1] of 175 ± 2 c./sec. for the 3β-acetoxy-group, and the results indicate that there is no significant difference between the 3α- and the 3β-equatorial acetoxy-shifts. In our compounds there is no double bond at the A/B ring junction, and all the acetoxy-groups are in the equatorial conformation.

The side-chain 17β-CHMe·OAc is present in four of the above compounds (III, V, IX, and XVII) and in each case only a single unsplit peak ascribable to the 3- and the 20-acetate group was observed; it had approximately double the intensity of either of the angular-methyl peaks. The 20β-acetoxy-group has therefore essentially the same chemical shift (175 ± 2 c./sec.) as the 3α-group, in contrast to the lower shielding recorded by Shoolery for the 21-acetoxy-20-keto-group.

An enol acetate :CMe·OAc occurs in compound (VIII), together with a 3β-acetoxy-group, and here there are two separated acetoxy-peaks at 171½ and 176 c./sec. Since the latter is normal for 3β-acetoxyl, the resonance at 171½ c./sec. is ascribed to the enol acetate

group, so that the paramagnetic contribution of the olefinic bond has reduced the acetoxy-proton shielding. A precisely similar effect is observed for the $\Delta^{9(11)}$-11-acetoxy-grouping in conjugation with a 7,8-double bond in compound (XVII) where two peaks ascribable to acetate groups fall at 172 and 176½ c./sec. Since the intensity ratios are approximately 1 : 2 it is reasonable (from the above data) to ascribe the peak at lower field to the enol acetate group, and that at higher field to a superposition of 3- and 20-acetate resonances. However, in compound (XII) the 11- and the 3α-acetoxy-group seem to give practically coincident resonances (however, the purity of this sample is in doubt).

17β-CHMe·OAc *and related side chains.* In the four compounds containing the CHMe·OAc side-chain, the 20β-acetoxy-group exhibits the same shift as in the 3-position. The secondary 21-methyl resonance is observed in three cases to be split into a sharp doublet by the lone 20-hydrogen atom, the components lying roughly symmetrically on either side of the 19-methyl peak. In the fourth compound (XVII), with a higher 19 methyl shift, the high-field component of the 21-methyl doublet almost certainly lies beneath the 19-methyl peak. Both the 21-methyl chemical shift (mid-point of the doublet) and coupling constant to 20-hydrogen (component separation) seem to be characteristic of this side-chain. The following values are obtained:

Compound	III	V	IX	XVII	XIV
21-Me shift	208	210	208½	210	207
J (20-H–21-Me)	5·8	5·9	5·8	6	5·8

In compound (XIV) the acetoxy-group has been replaced by benzoyloxy in both the side-chain and the 3-position; the complex resonance of the aromatic ring lies immediately below the solvent chloroform peak and is probably partially obscured by it. The 21-methyl shift and spin–spin splitting retain their characteristic values.

For the enol acetate grouping $=C_{(20)}OAc{-}C_{(21)}H_3$ encountered in compound (VIII), the tertiary 21-methyl peak is expected to be unsplit by spin coupling. The only experimental peak ascribable to this is somewhat broadened, and occurs at considerably lower field (185 c./sec.) than for the saturated side-chain. This is qualitatively expected for a methyl group attached to an olefinic group; a smaller effect was observed also for the 20-acetoxyl resonance.

Ethylene ketal group. Three compounds have been examined in which both skeletal protons in the 3-position are replaced by an ethylene ketal ring $(\cdot CH_2 \cdot O \cdot)_2$. This substituent gives a single sharp peak, indicating that its protons are equivalent (or very nearly so), at shifts of 99, 99, and 98 c./sec. in compounds (II), (VI), and (XV) respectively. This characteristic shift is at lower field than that for any other substituent peak of comparable intensity, and therefore identifies the 3-ketal group unambiguously.

$C_{(12)}$ α-*Secondary methyl group.** In compound (VI) the introduction of an additional methyl group was confirmed by the present results (see below and ref. 6*c*). The spectrum shows a peak, ascribable to a 12-methyl group, midway between those for the 19- and the 18-methyl peaks and of approximately half the intensity of either. The 19-methyl peak shows some sign of incomplete resolution from an underlying component, and it is inferred that the low-field member of the expected 12-methyl doublet is present. The shift of the latter would then be 212 c./sec., and the coupling constant to the skeletal 12-proton would be $6 \pm \frac{1}{2}$ c./sec. The shielding is considerably higher than that found for a secondary 6-methyl group by Slomp and McGarvey [2] but is, somewhat fortuitously, similar to those (208½, 210 c./sec.) which we find for two secondary equatorial 10-methyl groups in two steroid fragments in which ring A has been removed.

Further substituents. Introduction of a 12-methoxy-group in compound (IX) was confirmed by the presence of a strong, unsplit peak at 121½ c./sec., and by features discussed

* The configuration of the 12-methyl group was established as axial (α) by optical rotatory dispersion measurements.

below. The shift agrees very closely with the value of 122 c./sec. for a single 3-methoxy-steroid.[1] The 17-acetyl resonance in compound (XVIII) occurs at 172½ c./sec. (cf. range of 171 ± 1 c./sec.[1]). In compound (VII), the 3α-hydroxy-resonance falls at 163½ c./sec.

Substituent and Conformation Effects on the Chemical Shifts of the Angular Methyl Groups.—With the exception of the two enol acetates (XII, XVII), all the present compounds possess an 11-keto-group, which is reported by Shoolery and Rogers (with the assumption of additivity of group shielding effects) to cause a lowering of the 19-methyl resonance by ~7 c./sec., whilst having little effect on the 18-methyl resonance. We were, however, able to examine a number of compounds completely free from side-chain in the 17-position.

The majority of the present compounds have an A/B-*cis* ring junction. The stereochemistry of the A/B junction would be expected to have very little effect on the shift of the remote 18-methyl resonance, but might be a potential complication in interpreting 19-methyl shifts, particularly if ring A carries any substituents which have a powerful displacing effect on the 19-methyl resonance. Reversal of the ring junction with a 3-hydroxy- or 3-keto-group present is reported [1] to have no significant effect.

The present results are considered under the substituent concerned.

3-*Acetoxy-group*. For a substituent attached to ring A by a single bond, the steric relation to the angular methyl groups is affected not only by the local configuration (*i.e.*, α or β) but also by the nature of the A/B ring junction (*cis* or *trans*), thus representing four distinct possibilities. Of these, only those two with the 3-substituent equatorial are of much importance in natural product chemistry, *viz.*, 3α,A/B-*cis* (5β-androstane series), and 3β,A/B-*trans* (androstane series). Both classes of 3-acetoxy-compound were included in the present study.

(*a*) 3α-Acetoxy-group (A/B-*cis*). We must first assume the previous report [1] that the 11-keto-group causes the 19-methyl resonance to be displaced some 7 c./sec. below an unperturbed resonance position of 220 c./sec. The observed position of 209 c./sec. in (I), with only 3-acetoxy- and 11-keto-substituents, therefore indicates that the 3-acetoxy-group has a lowering effect of ~4 c./sec. on the 19-methyl resonance; and this is supported by the consistent resonance position of 209 ± 1 c./sec. observed in five compounds (I, III, IV, V, IX) in which these two substituents are likely to be the only ones involved. There is no evidence that the 3-acetoxy-group has any effect on the 18-methyl resonance.

(*b*) 3β-Acetoxy-group (A/B-*trans*). The compounds (I) and (XVI) differ structurally in a change of the A/B junction from *cis* to *trans*. The inversion at position 5 causes a concomitant change of the 3-substituent from α to β. The chemical shift of the 19-methyl group is displaced from 209 to 215½ c./sec., whilst that of the 18-methyl group is virtually unchanged. A precisely similar effect is observed on comparing the data for compound (XVIII) with those obtained [1] for the A/B-*cis*-analogue. Thus in compound (XVIII), the 19-methyl shift has been displaced from 210 to 215 c./sec., whilst the 18-methyl shift is unchanged at 233 c./sec. The same 19-methyl shift of 215 c./sec. is recorded for a further A/B-*trans*-compound (VIII); this differs from (XVI) only in the presence of a substituent in position 17, which is probably too remote to have any effect on the 19-methyl resonance. The observed shift is approximately that expected [1] for the presence of the 11-keto-group alone and we infer that the shielding effect of the 3β-acetoxy-group (A/B-*trans*) on the 19-methyl group must be small, in contrast to that of the A/B-*cis* series. This is surprising in view of the fact that the acetate group in this configuration (A/B-*trans*, ring A chair) is somewhat nearer to the 19-methyl group than is the 3α-acetoxy-group with A/B-*cis* (ring A chair). Contribution from the boat form of ring A may however be significant in the latter case.[8]

3-*Ketal group*. Compounds (II) and (XV) differ from (I) and (XIV) respectively only in replacement of an acetoxy- by a ketal group in the 3-position, and both the 19- and the 18-methyl resonance agree within 1 c./sec. in each of the pairs. It is clear that the 3-ketal

[8] Nace and Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 4063.

group causes the same displacement of the 19-methyl resonance (to lower field by ~4 c./sec.) as does the 3α-acetoxy-group for A/B-*cis*, and again has no effect on the 18-methyl resonance.

12α-*Bromine atom.* Four compounds containing this group were investigated. Comparison of compounds (I), (II), and (V) with the 12-brominated analogues (IV), (XV), and (III) respectively reveals that the bromine substituent has lowered the 18-methyl resonance by 8, 8½, 7½ c./sec. whilst leaving the 19-methyl resonance constant to ½ c./sec. (Relative to the tetramethylsilane internal standard, these values become 8½, 10½, 6½ c./sec. respectively.) This is consistent with the fact that the 12α-bromine atom is considerably closer to the 18- than to the 19-methyl group. A slightly larger effect was observed for compound (X), where if the 3-keto-group is assumed to have no lowering effect on the 18-methyl resonance,[1] the effect of the 12α-bromine atom will be 10—12 c./sec.

17β-CHMe·OAc *Group.* In contrast to all other substituents, this appears to cause a slight *increase* in shielding of the 18-methyl group. Comparison of compounds (I) and (IV) with the analogues containing side-chains, (V) and (III) respectively, shows that the 19-methyl resonance is little affected, whilst the 18-methyl peak is moved to higher field by 3½ and 4 c./sec. respectively (or 2 and 4 c./sec. relative to tetramethylsilane), thus indicating a mean increase of ~3 c./sec.

17-(:CMe·OAc) *Group.* Compound (VIII) differs from the closest comparable compound (I) which has no side-chain in having an A/B-*trans* ring junction. The change in 19-methyl resonance from (I) to (VIII) can be accounted for entirely by the change in the A/B junction and the 3-acetoxy-configuration, and there is no reason to suppose that the 17-side-chain plays any part in this. Conversely, a change in A/B junction has very little effect on the 18-methyl resonance, so that the displacement to lower field by 4½ or 6½ c./sec. (relative to benzene or tetramethylsilane standards) indicates a lowering effect of the side-chain by ~5 c./sec. in contrast to the behaviour of its saturated analogue. It is not known which of the two possible geometrical isomers is present.

9α-*Bromine atom.* The most reliable evidence for the shielding effect of this group is provided by a comparison of the A/B-*trans*-compound (XVI) and its 9α-brominated analogue (XX). The large displacement of the 19-methyl resonance indicates that the 9α-bromine atom interacts strongly with this group and diminishes its shielding by some 8 c./sec. Unfortunately, poor spectra were obtained for the related 9-bromo-compounds (XI) and (XIII). The former gave rise to additional peaks, probably owing to considerable hydrolysis of the ketal group, following elimination of a trace of hydrogen bromide; the latter gave several low intensity lines in the expected 19-methyl region. The 18-methyl shifts (226, 228½), however, appear to be fairly reliable in view of their similarity to that for compound (XX), namely, 227½ c./sec., and suggest that the 9α-bromine atom may have a slight decreasing effect on the 18-methyl shift also (by 1—2 c./sec. only). These results are in accord with the much closer approach of a 9α-bromine atom to the 19- than to the 18-methyl group. These compounds are known to isomerise readily to the 12-bromo-analogues, where the closer approach of the bromine atom to the 18-methyl group has been shown above to cause a markedly different spectrum. The isomerisation may be followed readily by observing the proton resonance spectrum, and the present samples were observed to undergo this change slowly, even in absence of added acid catalyst. It is hoped to investigate the kinetics of the reaction by this means.

Unsaturated steroids. The following correlations are based mainly on comparison of data for isolated pairs of compounds with few cross-checks, so the results must be taken as provisional. The displacing effect of skeletal double bonds upon the angular methyl shifts may depend on their state of conjugation, thereby causing some departure from additivity, although conjugation effects in a rigid ring system may be limited.

(*a*) 8,9-Unsaturation. Compound (XXI) differs from (V) only in the presence of an olefinic bond. The spectrum was obtained from a weak solution and impurity peaks, probably due to ethanol, are superimposed; but the two angular methyl peaks can be identified with reasonable certainty. Comparison with the peak locations for (V) shows

that the 8,9-double bond has caused a low-field displacement of the shifts of both angular methyl groups, the 19-group and the 18-group by 4½ c./sec.

(*b*) $\Delta^{(9)11}$-11-Acetate enol acetate group. Replacement of the 11-keto-group in compound (I) to give the corresponding enol acetate (XII) causes an increase in shielding of the 19-methyl group by 2 c./sec. and diminution in 19-group shielding by 4½ c./sec. If it is assumed [1] that the 11-keto-group displaces the 19-methyl resonance by ~7 c./sec. to low field whilst having little effect on that of 18-methyl group, it appears that the $\Delta^{9(11)}$-11-acetate grouping affects both the 19- and the 18-methyl shielding to a similar extent, lowering the resonance position of each by 4—5 c./sec. It is noted that the 9(11)-olefinic bond was reported previously [1] to displace the 19-methyl resonance by ~6 c./sec. to lower field but no conclusions can be drawn regarding the 18-methyl group.

(*c*) Conjugated 7,9(11)-unsaturation. Comparison of the results for compounds (XII) and (XVII) shows that the introduction of a 7-double bond and 17-CHMe·OAc groups in the latter causes an increase in shielding of the 19-methyl group by 3½ and of the 18-methyl group by 10 c./sec. (or 1 c./sec. less in each case relative to tetramethylsilane as standard). The effect on the 18-methyl group is partially due to the 17-side-chain, which has been shown above to displace its shift to higher fields by about 3 ± 1 c./sec., whilst having no effect on the shift of the 19-methyl group. With allowance for this, it appears that 7,8-unsaturation causes an *increase* in shielding of both angular methyl groups (19-methyl by ~3 c./sec. and 18-methyl by somewhat more). This is in agreement with the previous report [1] that 7,8-unsaturation causes a unique enhancement of 19-methyl shielding (by 4 c./sec.), and, whilst the effect on the 18-methyl group was not mentioned explicitly, the published results for one pair of compounds indicate an upfield displacement of 3 c./sec. on introducing a 7,8-conjugated to a 5,6-double bond.

Benzoyloxy-groups. In estimating the displacing effect of benzoyloxy-groups on the shifts of the angular methyl groups, allowance must be made for the abnormal positions of the standard peaks in all but very dilute solutions of such steroids. Data for the 3α-benzoyloxy-group may be obtained by comparison of the " corrected " shifts (see p. 5126) of ~208 and 232½ c./sec. for the 19- and 18-methyl group respectively in compound (XIX) with those (210, 233 c./sec.) recorded [1] for the analogous compound with a 3-acetoxy- in place of a 3-benzoyloxy-group. The displacing effect of a benzoyloxy-group on the 19-methyl peak (to low field) is thus quite similar to that of a 3α-acetoxy-group (it may be ~2 c./sec. greater), whilst neither is observed to have any measurable effect on the 18-methyl peak.

Comparison of data for compounds (XIII) and (XIV) shows that introduction of the 17-CHMe·OBz group increases the shielding of the 18-methyl group, but this effect may be small when allowance is made for the probable abnormality of the benzene shift in the latter (tetramethylsilane was not measured). It is probably not very different from that of the 17-CHMe·OAc group.

C/D-cis *Ring junction.* Two compounds containing the unnatural C/D-*cis* junction were examined, namely, (XXII) and (XXIII). Unfortunately both differ from the closest C/D-*trans*-analogues (XVII) and (XXI) in that they contain 3- and 20-benzoyloxy- instead of acetoxy-groups. It is seen however that the shielding effects of these groups in both the 3- and the 20-position upon each angular methyl group are similar, so that a rough comparison may be made relative to tetramethylsilane = 255 c./sec. Thus from the pair (XXI, XXIII) it is seen that changing the C/D junction from *trans* to *cis* causes a *large decrease* in shielding of the 18-methyl group (by 10—12 c./sec.), whilst the 19-methyl group is little affected. The difference between the values for compounds (XVII) and (XXII) is, however, unexpectedly great, and a determination of similar compounds is to be desired.

The Resonance of Skeletal Protons.—(a) *General absorption of skeletal protons.* This consists generally of a single broad hump, very variable in form, but in seven cases is split into twin broad peaks, partially overlapping and of comparable intensity. This seems

likely to occur in compounds with an A/B-*trans* ring junction (VIII, XVI, and XVIII; three cases out of four) or a 12α-bromine atom (IV, XV, and the isomerisation product of XIV; three cases out of five). Compound (VII) also shows this feature. The twin peaks are shown in the Fig. for (VIII) (in which a part of the lower field component is ascribed to the 20-methyl group) and (XVIII).

(b) *Skeletal protons at position* 12. The presence of a sharp peak, of amplitude corresponding to two protons, within the range 150—160 c./sec., has been reported [1] as diagnostic of 11-keto-steroids. This was ascribed to the resonance of the two skeletal protons at position 12, unsplit because of the absence of protons on adjacent carbon atoms and of equivalent chemical shift, and displaced below the region of main skeletal absorption by proximity to the 11-keto-group. No steroids monosubstituted at position 12 were reported.

The present results confirm that account, with the reservation that the range of shifts may extend slightly to higher field, particularly in compounds containing no 17-side-chain. Thus, resonances of the expected amplitude are observed at 161½, 163½, 155, 155, 155(-3) c./sec. in the spectra of compounds (V, VII, VIII, XVIII, and XIX respectively). The shifts in three compounds unsubstituted at position 17 are 164½, 165½, 162½ c./sec. (for I, II, and XVI). We observe also that the resonances of the 12-methylene group are generally slightly broader than the substituted peaks, as would occur if there were very slight non-equivalence of the protons. Three 9α-bromo-steroids (XIII, XIV, and XX) give a peak in the expected region, but of much lower intensity than predicted. It is possible that this substituent, which isomerises readily to give the 12-α-bromo-analogue, may interact with the hydrogen atom at this position and cause considerable non-equivalence of the proton shielding.

This characteristic feature is lost upon introduction of a 12-substituent (α-Br, -Me, or -OMe), and the resonance of the remaining proton at position 12 could not be identified with certainty. Four low-intensity peaks observed in the spectrum of compound (VI) may be the lone $C_{(12)}$-proton resonance split into a quartet by the 12-α-methyl group. The low-field methylene resonance is also absent in three compounds in which the 11-keto-group has been converted into an enol acetate (XII, XVII, and XXII).

Experimental

Proton resonance spectra were obtained with the permanent magnet spectrometer described by Leane, Richards, and Schaefer,[9] at a frequency of 29·9200 Mc./sec. Chemical shifts were measured to an accuracy of ±½ c./sec.

Previous authors have employed deuterochloroform as a solvent (the use of pyridine also has been described recently [4]). We find however that, at the steroid concentrations available in most cases, the impurity peaks in " AnalaR " chloroform are of insufficient intensity to cause any difficulty in interpretation of the main steroid features, and we have employed this throughout. The solvent peak does not normally obscure any part of the steroid spectrum. Chemical shifts are referred to a benzene external standard except where stated otherwise. Further, for comparison with other work,[1] all are multiplied by a factor of 1·337 to convert them into values at 40 Mc./sec. When the measurements for one compound (pregnane-3,11,20-trione) given in ref. 1 were repeated, our chemical shifts (converted to 40 Mc./sec.) agreed with the published values within ½ c./sec. As a further check on the validity of the chemical-shift measurements, the position of the tetramethylsilane resonance as an internal standard (concentration about 2%) was also measured for most samples.

Referencing of Steroid Peaks.—It has been stated [1] that steroid chemical shifts measured in strong (~M)solution in deuterochloroform, relative to a benzene external standard, are moved by ~2 c./sec. to higher field than in dilute solution, this being interpreted as due to a change in bulk susceptibility. Reference to tetramethylsilane as an internal standard would

[9] Leane, Richards, and Schaefer, *J. Sci. Instrum.*, 1959, **36**, 230.

eliminate any bulk susceptibility effect, and would therefore be preferable if anisotropic shielding by the steroid molecules is not significant.

Two " blank " samples containing a benzene-filled capillary and tetramethylsilane added to chloroform only were measured, and the concordant shifts (for 40 Mc./sec.) relative to the benzene external standard were −34·3 c./sec. (to low field) for the solvent peak, and +256·3 c./sec. for tetramethylsilane. The mean values which we observe for solutions of steroids not possessing benzoyloxy-groups are −37·9 c./sec (range 5·8 c./sec.) for the chloroform peak, and +255·1 c./sec. [range 3·2 c./sec., the anomalous result for compound (XVI) being neglected]. The larger and more variable displacement of the chloroform peak to low field indicates some association with the solute. The average displacement of the tetramethylsilane peak by 1·2 c./sec. to *low field* from its position in the " blank " experiments is contrary to the direction expected from ref. 1 if it were due entirely to a change in the bulk susceptibility, when displacements of steroid peaks should correspond to that of tetramethylsilane. For three of the steroids containing benzoyloxy-groups, the tetramethylsilane resonance occurs at higher fields (shift 257—259 c./sec.), which is in the direction expected for anisotropic shielding by the aromatic ring. The chloroform resonance in these solutions also appears to be at higher shielding than for other steroid solutions of comparable concentration (mean −34·7 c./sec.; four cases), as also do the steroid peaks for compound (XIX), for which prediction can be made.

In order to study the concentration-dependence of these shifts more reliably, measurements were repeated on selected steroids in both very weak (0·1M) and very strong (1·0M or 1·5M)-solutions. The 20β-hydroxy-analogue (XXIV) of (V) dissolves only to the extent of a 1M-solution. Relative to the benzene external standard, the peak due to the steroid 3-acetoxy-group was displaced slightly to *lower* field (by 0·6 c./sec.) than the position (175·1 c./sec.) observed for the 0·1M-solution, whilst the peak due to the tetramethylsilane internal standard showed a displacement in the same direction and of similar magnitude (0·8 c./sec.). The solvent peak moved to higher field by 4½ c./sec. Measurements on the more soluble diacetate (V) did not show any displacement of the single steroid acetate peak or of the tetramethylsilane peak on changing from 0·1M- to 1·5M-solution. The solvent peak again underwent a large displacement (by 7 c./sec.) to higher field. Neither of these cases, therefore, shows the displacement of steroid peaks to higher field found by Shoolery and Rogers,[1] and the small displacements of the tetramethylsilane peak to lower field measured for compound (XXIV), and inferred for most other 11-keto-steroids, indicate that either standard is sufficiently constant to be employed in deducing steroid correlations, although double checking is of course advisable. It seems reasonable, however, at least for the present compounds, to take a value of 255 c./sec. for the separation between the benzene external and the tetramethylsilane internal peak in comparing steroid shifts relative to either, rather than that (256·3 c./sec.) for the " blank " determination. The parallel displacements of steroid and tetramethylsilane peaks for compound (XXIV) suggest that the effect may be largely one of changing the bulk susceptibility, but the values are too small to be conclusive on this point. The large displacements of the solvent peak demonstrate the inadequacy of this as a reference.

Measurements were conducted also with compound (XIX) at 0·1M- and 1·5M-concentration as an example of a steroid containing the benzoyloxy-group. The anomalous displacement of both steroid and tetramethylsilane peaks to high field is confirmed. Thus the peak due to the 17β-acetyl group exhibits a shift of 171·4 c./sec. in 0·1M-solution, very close to the characteristic value of 171(±1) c./sec.,[1] but this is increased by 3·5 c./sec. in 1·5M-solution. The tetramethylsilane resonance is elevated by a smaller amount (1·6 c./sec.), but since its average position in our steroid solutions is 1·2 c./sec. below that in the " blank " determination (or very dilute solution) the anomaly introduced by the benzoyloxy-group may be 3 c./sec. This would suggest that the tetramethylsilane internal standard may be a better reference for strong solutions of such steroids, and corrections to tetramethylsilane = 255 c./sec. are indicated in parentheses in the Table. Magnetic susceptibility data for steroids are scarce, but it seems rather unlikely that the anomalous effect of the benzoyloxy-group would be due to a change merely of the bulk susceptibility.

From these experiments it may be concluded that at normal concentrations (about 0·5M) in chloroform solution, the chemical shifts of steroids not containing benzene rings may be recorded with reference to an external benzene sample, or to an internal tetramethylsilane reference, with some confidence. Data for steroids containing the benzoyloxy-substituent should be regarded with circumspection unless they are obtained from very dilute solutions.

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