Bridged D-Ring Steroid Analogs XII: Effect of D-Ring Substituents on Chemical Shift of Angular Methyl Protons

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Abstract ☐ The chemical shifts of the C_{18}- and C_{19}-hydrogens of 30 $14\alpha,17\alpha$-bridged 20-ketopregnanes and of four $14\alpha,17\alpha$-bridged 17-cyanoandrostanes were correlated by means of additive substituent constants. Because the bridged D-ring of these steroids is a substituted bicyclo[2.2.1]heptane system, attempts were made to explain the magnitude of some of these substituent constants by analogy to empirical effects in other such systems as well as by reference to more general theory. The data indicate that the acetyl side chain of the bridged 20-ketopregnanes exists in one rotamer form if the D-ring bears no extra substituents or a 16α-substituent and that it exists in a second form if a 16β-substituent or a 16-substituent on a double bond is present. In the latter case, the carbonyl group deshields the C_{18}-hydrogens by an extra 0.11 p.p.m.

Keyphrases ☐ Steroids, bridged D-ring –effect of D-ring substituents on chemical shifts of angular methyl protons, NMR spectroscopy ☐ Pregnanes, $14\alpha,17\alpha$-bridged– effect of D-ring substituents on chemical shifts of angular methyl protons, NMR spectroscopy ☐ 5-Androstenes, 3β-acetoxy-$14\alpha,17\alpha$-ethano—effect of D-ring substituents on chemical shifts of angular methyl protons, NMR spectroscopy ☐ Bridged D-ring steroids—effect of D-ring substituents on chemical shifts of angular methyl protons ☐ NMR spectroscopy—substituent effect on chemical shifts of angular methyl protons in bridged D-ring steroids

During initial investigations of the $14\alpha,17\alpha$-etheno-20-ketopregnane system, the use of NMR for the determination of the stereochemistry of the bridged D-system was attempted. A comparison of the NMR spectra of some of the first compounds prepared in that series (e.g., X and XI in Table I), if considered according to the theory of that time (1), would have resulted in assignment of wrong stereochemistry for these compounds. Fortunately, internal inconsistencies in the NMR data, together with the fact that other evidence (2) tended to favor the correct structures, recommended the use of other methods. Since a large group of compounds of rigorously proved structure (3–5) is now available for this series, it seemed appropriate to reconsider the spectra of these compounds in the hope of correlating the chemical shifts of their C_{18}- and C_{19}-hydrogens and of explaining the origin of the shifts in terms of current theory.

DISCUSSION

Table I lists a variety of $14\alpha,17\alpha$-ethanopregnane derivatives and the positions of their angular methyl groups in the NMR. Six pairs of these compounds (I–II, V–VI, VII–VIII, IX X, XII–XIII, and XIV–XV) differ only in the presence or absence of a double bond in the $14\alpha,17\alpha$-bridge. These compounds show that such a double bond has essentially no effect on the C_{18}-hydrogens, even though it causes a shielding of the more distant C_{19}-hydrogens by 0.04 ± 0.005 p.p.m. In contrast, conversion of the saturated bridged D-ring to the doubly unsaturated system (compound pairs XI–XVI, XVIII–XIX, XXII XXIII, XXIV XXV, and XXVI–XXVII) results in a deshielding of the C_{18}-hydrogens by 0.30 ± 0.042 p.p.m. while shielding the C_{19}-hydrogens by 0.03 ± 0.008 p.p.m.

Recently, by synthesizing and determining the NMR of 3β-acetoxy-$14\alpha,17\alpha$-ethano-5,15-pregnadien-20-one (Compound XXX in Table I) the introduction of a 15,16-double bond was demonstrated to have almost no effect on the chemical shift of either the C_{18}- or C_{19}-hydrogens[1] (6).

Since introduction of a single double bond into either bridge of these D-rings has almost no effect on the chemical shift of the C_{18}-hydrogens, the shift of 0.30 p.p.m. which occurs on introducing double bonds into both bridges was considered to be anomalously large. This paper attempts to assess a variety of factors for their possible contributions to this effect.

Orientation of 17-Acetyl Side Chain—Examination of the pairs of compounds that were compared to determine the effect of introducing a single double bond into the bridged D-ring system reveals that, within each pair, the configuration of all substituents on the molecule (hydrogens excepted) remains constant. In contrast, in each pair in which two double bonds were introduced into the bridged D-ring system, a C_{16}-substituent or C_{15},C_{16}-disubstituents
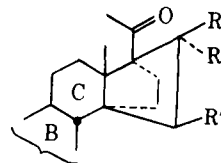
I, III, IV, V, VII, XXI: R = R' = R'' = H
IX, XII, XIV, XX: R = CO_2CH_3, R' = R'' = H
XVI: R = R'' = H, R' = CO_2CH_3
XVII: R = CO_2H, R' = R'' = H
XVIII: R = H, R' = R'' = CO_2CH_3
XXII, XXIV, XXVI: R = H, R' = R'' = CF_3
XXVIII, XXIX: R = I, R' = R'' = H
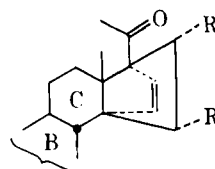
II, VI, VIII: R = H, R' = H
X, XIII, XV: R = CO_2CH_3, R' = H

XXXV: R, R' = $\overset{O}{\underset{}{\diagdown}}C-O-C\overset{O}{\underset{}{\diagup}}$
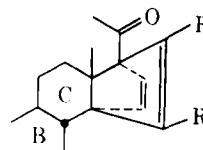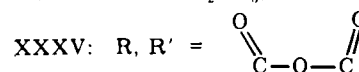
XI: R = CO_2CH_3, R' = H
XIX: R = R' = CO_2CH_3
XXIII, XXV, XXVII: R = R' = CF_3

Table I—Chemical Shifts[a] of Angular C18- and C19-Methyl Protons of 14α,17α-Bridged Pregnanes

Com- pound	Compound Name	Observed		Calc.	
		C_{18}	C_{19}	C_{18}	C_{19}
I	3β-Acetoxy-14α,17α-ethano-5-pregnen-20-one[b]	0.90	1.03	0.91	1.05
II	3β-Acetoxy-14α,17α-etheno-5-pregnen-20-one[c]	0.90	1.00	0.91	1.00
III	3β-Acetoxy-14α,17α-ethano-5α-pregnan-20-one	0.87	0.85	0.87	0.85
IV	3β-Hydroxy-14α,17α-ethano-5α-pregnan-20-one[d]	0.88	0.83	0.87	0.83
V	3β-Hydroxy-14α,17α-ethano-5-pregnen-20-one[e]	0.91	1.03	0.91	1.04
VI	3β-Hydroxy-14α,17α-etheno-5-pregnen-20-one[c]	0.92	1.00	0.91	0.99
VII	14α,17α-Ethano-4-pregnene-3,20-dione[e]	0.94	1.22	0.94	1.22
VIII	14α,17α-Etheno-4-pregnene-3,20-dione[c]	0.92	1.17	0.94	1.17
IX	3β-Acetoxy-14α,17α-ethano-16α-carbomethoxy-5-pregnen-20-one[d,f]	0.96	1.04	0.96	1.04
X	3β-Acetoxy-14α,17α-etheno-16α-carbomethoxy-5-pregnen-20-one[g]	0.96	1.00	0.96	0.99
XI	3β-Acetoxy-14α,17α-etheno-16-carbomethoxy-5,15-pregnadien-20-one[f]	1.29	1.01	1.29	1.01
XII	3β-Hydroxy-14α,17α-ethano-16α-carbomethoxy-5-pregnen-20-one[f]	0.97	1.03	0.96	1.03
XIII	3β-Hydroxy-14α,17α-etheno-16α-carbomethoxy-5-pregnen-20-one[g]	0.96	0.98	0.96	0.98
XIV	14α,17α-Ethano-16α-carbomethoxy-4-pregnene-3,20-dione[h]	1.00	1.22	1.00	1.21
XV	14α,17α-Etheno-16α-carbomethoxy-4-pregnene-3,20-dione[g]	0.98	1.18	1.00	1.16
XVI	3β-Acetoxy-14α,17α-ethano-16β-carbomethoxy-5-pregnen-20-one[f]	0.90	1.03	0.90	1.03
XVII	3β-Acetoxy-14α,17α-ethano-16α-carboxy-5-pregnen-20-one[d]	0.95	1.04	0.96	1.04
XVIII	3β-Acetoxy-14α,17α-ethano-15β,16β-dicarbomethoxy-5-pregnen-20-one	1.10	1.07	1.10	1.07
XIX	3β-Acetoxy-14α,17α-etheno-15,16-dicarbomethoxy-5,15-pregnadien-20-one[f]	1.33	1.03	1.33	1.03
XX	19-Nor-14α,17α-ethano-16α-carbomethoxy-4-pregnene-3,20-dione[h]	1.00	—	1.01	—
XXI	19-Nor-14α,17α-ethano-4-pregnene-3,20-dione[h]	0.97	—	0.96	—
XXII	3β-Acetoxy-14α,17α-ethano-15β,16β-di(trifluoromethyl)-5-pregnen-20-one[i]	0.99	1.05	1.00	1.07
XXIII	3β-Acetoxy-14α,17α-etheno-15,16-di(trifluoromethyl)-5,15-pregnadien-20-one[i]	1.30	1.02	1.29	1.03
XXIV	3β-Hydroxy-14α,17α-ethano-15β,16β-di(trifluoromethyl)-5-pregnen-20-one[i]	1.02	1.06	1.00	1.06
XXV	3β-Hydroxy-14α,17α-etheno-15,16-di(trifluoromethyl)-5,15-pregnadien-20-one[i]	1.30	1.01	1.29	1.02
XXVI	14α,17α-Ethano-15β,16β-di(trifluoromethyl)-4-pregnene-3,20-dione[i]	1.03	1.26	1.04	1.24
XXVII	14α,17α-Etheno-15,16-di(trifluoromethyl)-4,15-pregnadiene-3,20-dione[i]	1.31	1.23	1.32	1.20
XXVIII	3β-Acetoxy-14α,17α-ethano-16α-iodo-5-pregnen-20-one[d]	0.92	1.03	0.92	1.03
XXIX	3β-Hydroxy-14α,17α-ethano-16α-iodo-5-pregnen-20-one[d]	0.92	1.02	0.92	1.02
XXX	3β-Acetoxy-14α,17α-ethano-5,15-pregnadien-20-one[b]	0.89	1.04	0.89	1.04

[a] Measured in parts per million downfield from internal tetramethylsilane in deuteriochloroform solution. [b] Reference 6. [c] Reference 9. [d] Reference 3. [e] Reference 10. [f] Reference 4. [g] Reference 11. [h] Reference 12. [i] Reference 13.

were oriented beta in the saturated member of the pair but shifted to the nodal plane of the 15,16-double bond in the unsaturated member of the pair.

Cross and coworkers (14, 15) demonstrated that interaction between substituents in 16,17-disubstituted steroids can lead to conformational changes in the D-ring and to changes in the preferred rotamer form of substituents, especially of a C17-acetyl group. These changes have been shown to result in appreciable changes in the chemical shift of the C18-hydrogens and numerous warnings have been given against too ready use of additive substituent constants for calculation of chemical shifts in cases where the substituents may interact sterically, by hydrogen bonding, or by dipole-dipole effects (15, 16).

In the present case, the rigidity of the bridged D-ring prevents any major conformational change in the C- or D-ring of the steroid. However, the possibility does remain that substituents, particularly those at C16, may cause a change in the preferred orientation of the 17-acetyl group and thereby cause an additional change in the chemical shift of the C18-hydrogens.

Previously, an X-ray structure determination on 3β-acetoxy-14α,-17α-ethano-16α-iodo-5-pregnen-20-one (XXVIII) was reported (3). It showed that, in the crystalline state, the acetyl group of XXVIII is oriented with the oxygen beta and at an angle of 38° with respect to the plane containing atoms C14, C15, C16, and C17.

In an attempt to find a structural abnormality that could explain the deshielding of the C18-hydrogens of the 15-dehydro-14α,17α-etheno compounds, an X-ray structure determination of XXVII was made. That study (5) disclosed no structural anomalies, but it did show that the vicinal angle defined by the acetyl group and the plane containing atoms C14, C15, C16, and C17 is 11° larger in XXVII than in XXVIII.

This change in orientation of the acetyl group is similar to the change postulated (15) to occur in 20-ketopregnanes when a 16β-substituent is introduced. Cross and Beard (15) assigned a ψ-equatorial conformation to the 16β-substituent; in that form, the relative orientation of the 13β-methyl, the acetyl group, and the 16-substituent is very similar to that of the corresponding groups in XXVII. If this analogy is valid, one could argue that the deshielding observed going from a 16α-substituted 14α,17α-ethenopregnan-20-one to the 15-dehydro analog (from X to XI) is, at least in part, the expected result of reorientation of the acetyl side chain. To the ex-

tent that this is true, it changes the task to that of explaining the relative lack of deshielding by the 16β-substituents.

Cross and Beard's estimate (15) of the long-range shielding effect of different acetyl rotomers was qualitative and was based on Jackman's (1) early view regarding the shape of the carbonyl shielding cones. Since that time, more refined views of the long-range shielding effect of the carbonyl group have emerged (17-19) and the importance of also considering the shielding effects of carbon-carbon single bonds and of carbon-hydrogen bonds has been emphasized (8, 19). Accordingly, equations of ApSimon *et al.* (8, 18) were used to estimate the shielding effect exerted by the acetyl group, in its various rotomer forms, on the C18-hydrogens. These calculations showed a larger shielding for the 16α-substituted compound, XXVIII (−0.09 p.p.m.), than for the unsaturated compound, XXVII (−0.16 p.p.m.)². As shown in Fig. 1, the rotomer that points the acetyl oxygen toward the center of rotation of the C18-hydrogens would be maximally deshielded while the rotomer in which the carboxyl bond axis has been rotated by 180° would be maximally shielded. These results demonstrate that reorientation of the acetyl group may account for at least a small portion of the anomalous deshielding observed for the C18-hydrogens of the 14α,-17α-etheno-15-pregnen-20-ones.

17-Cyano Compounds—Because the calculation of the shielding of the C18-hydrogens by the acetyl group involves many assumptions, it was necessary to determine experimentally the magnitude of this effect. This was done by studying compounds in which the acetyl group was replaced by the axially symmetrical cyano group. Accordingly, 3β-acetoxy-17-cyano-5,14,16-androstatriene (2) was reacted with dimethyl acetylenedicarboxylate to afford 3β-acetoxy-17-cyano-15,16-dicarbomethoxy-14α,17α-etheno-5,15-androstadiene (XXXI)³. Hydrogenation of XXXI over palladium-on-charcoal afforded 3β-acetoxy-17-cyano-15β,16β-dicarbomethoxy-14α,-17α-ethano-5-androstene, XXXII.

² These calculations do not pertain to the compounds studied by Cross and Beard (15) since those compounds could undergo conformational changes in the D-ring as well as rotation of the acetyl group. Moreover, the torsional angle formed by the C13-C18 and C17-C20 bonds is greater in the present case than in the compounds of Cross and Beard (15).
³ Stereochemistry was assigned by analogy to that which was demonstrated in the corresponding 20-ketopregnane system (3, 4).

Table II—Chemical Shifts[a] of C_{18}- and C_{19}-Protons of 3β-Acetoxy-14α,17α-ethano-5-androstenes

| | | 17-Cyano | | | | 17-Acetyl | | | | |
| | | Observed | | Calculated | | Com- | Observed | | Calculated | |
Substituents	Compound Number	C_{18} H's	C_{19} H's	C_{18} H's	C_{19} H's	pound Number	C_{18} H's	C_{19} H's	C_{18} H's	C_{19} H's
15β,16β-Dicarbomethoxy	XXXII	1.12	1.06	1.13	1.07	XVIII	1.10	1.07	1.10	1.07
15,15'-Didehydro-15,16-dicarbomethoxy	XXXI	1.36	1.02	1.36	1.03	XIX[c]	1.33	1.03	1.33	1.03
15'-Dehydro-15α,16α-dicarboxyanhydride	XXXIII[b]	1.17	1.03	1.16	1.02	XXXV	1.02	1.02	1.02	1.02
15'-Dehydro-16α-carbomethoxy	XXXIV[b]	1.09	1.00	1.10	0.99	X[b]	0.96	1.00	0.96	0.99

[a] Parts per million downfield from tetramethylsilane in deuteriochloroform. [b] Reference 2. [c] Reference 4.

In Table II, the chemical shifts of the angular methyl hydrogens of four 17-cyano-14α,17α-bridged steroids are compared to those of the corresponding 17-acetyl compounds. The C_{18}-hydrogens of the 16α-substituted 17-acetyl compounds, XXXV and X, are shielded by 0.14 ± 0.01 p.p.m. relative to those of the cyano steroids, XXXIII and XXXIV. By contrast, both in the case of 16β-substituted steroids and in the case of 16-substituted 15,15'-didehydrosteroids, the acetyl compounds are shielded by only 0.03 ± 0.01 p.p.m. relative to the cyano compounds. These data can be rationalized by postulating a change in orientation of the acetyl group on going from the 16α-substituted compounds, XXXV and X, to the 15,15'-didehydro-16-substituted or 16β-substituted compounds, XIX and XVIII. This change in rotomer form would be accompanied by a decrease in shielding of 0.11 ± 0.01 p.p.m. Such a change in shielding is in reasonable agreement with that calculated (0.07 p.p.m.) to occur going from the 16α-substituted compound, XXVIII, to the unsaturated compound, XXVII. The unique geometry of the 16β-substituted series would be expected to lead to a new shielding curve similar to those in Fig. 1. However, the similarity of the curves in Fig. 1, for the range of interest, leads to the expectation that the similar shielding effect of the acetyl group in the 16β-substituted series and in the doubly unsaturated bridged series reflects a similar orientation of the group in the two series.
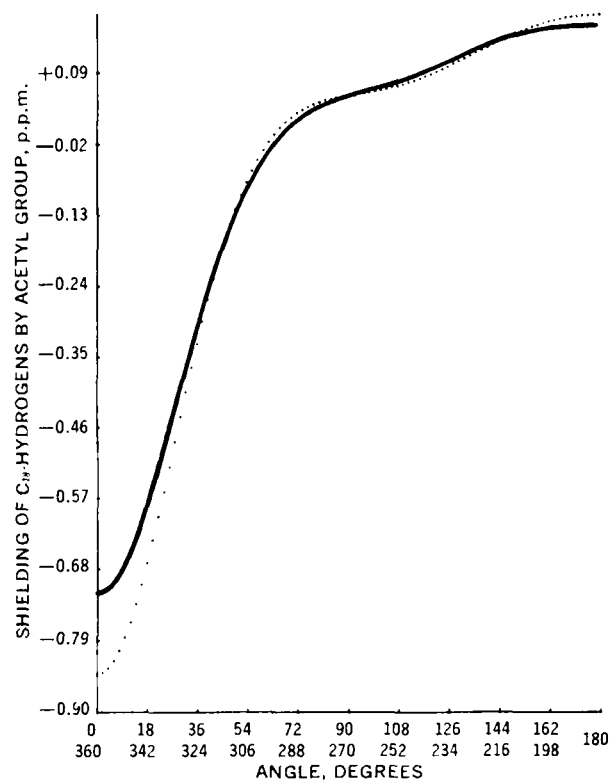
While, as discussed previously, the data in Table II do confirm[4] that a change in acetyl rotomer form is responsible for a small part of the increased deshielding of the C_{18}-hydrogens of 16-substituted 15,15'-didehydropregnan-20-ones as compared to those of the corresponding 16α-steroids, they also clearly show that some additional factor must contribute to the deshielding of the C_{18}-hydrogens of the didehydrosteroids as compared to those of either the 16α- or the 16β-substituted steroids. Alternatively, the data could be explained by assuming that some factor causes the C_{18}-hydrogens of the 16α- and/or the 16β-steroids to be excessively shielded.

Substituent Constants—As a further test for unusual factors affecting the shielding of the angular methyl groups of these bridged steroids, an attempt was made to correlate their chemical shifts by the use of additive substituent constants after the manner of Zurcher (20). By using the values shown in Table III together with Zurcher's values (20) for substituents in the A- or B-ring, one can obtain the values shown as "calculated" in Tables I and II.

Shielding by Substituents at C_{15} and C_{16}—The constants in Table III clearly illustrate that 16β-trifluoromethyl and 16β-carbomethoxy groups cause little deshielding of the C_{18}-hydrogens, and correlations with the cyano steroids show that this effect is not caused by changes in orientation of the 17-acetyl group. Initially, these results were surprising because it was known that, in accord with theory (21), substituents such as halogen and hydroxyl, located 1-3 to a methyl on a cyclopentane ring, generally cause a greater deshielding of the methyl group when they are cis to it than when

[4] In response to a referee's suggestion that the restricted conformational freedom, postulated for the 17-acetyl compounds, should be partly cancelled by an increase in temperature, the effect of temperature on the chemical shift of the C_{18}-hydrogens of progesterone and of Compounds III, XIV, and XXII was studied. The C_{18}-hydrogens of all of these compounds appear to be less shielded at higher temperatures. While this could be interpreted as supporting the present position, it was decided not to attribute any significance to these data because: (a) in carbon tetrachloride or deuteriochloroform, the shifts are so small as to be only slightly greater than the probable error of the measurements; (b) the shifts are solvent dependent (larger in dioxane and much larger in dimethyl sulfoxide than in carbon tetrachloride or deuteriochloroform; and (c) other peaks such as that of the C_{19}-hydrogens also shift with temperature. Effects (b) and (c) could result from temperature-dependent solvent-solute interactions of sufficient magnitude as to obscure the observation of the rotational isomerism.

they are trans to it (20, 22-24). Of particular pertinence, because the bridged D-ring of these steroids constitutes a 7-methylbicyclo-[2.2.1]heptane system (where the 7-methyl is C_{18} of the steroid), is the fact that this effect has been confirmed in a variety of 7-methyl-bicyclo[2.2.1]heptanes (25). In the latter series, exo-substituents deshield the 7-syn-methyl group by 0.16-0.31 p.p.m., which is 2-6 times more than that caused by the corresponding endo-substituents. Calculations show that such substituents, when located at the 2-position of a 7-syn-methylbicyclo[2.2.1]heptane, should deshield the methyl hydrogens least when the substituent is endo, slightly more in the 2-dehydro compound, and most when the substituent is exo (21).

In view of this dicussion, the 16β-substituted compounds listed in Table I appear to show surprisingly little deshielding of the C_{18}-hydrogens by the 16β-substituents. For example, in Compounds IX, X, XII, XIII, XIV, and XV the endo-carbomethoxy group causes a deshielding of the C_{18}-hydrogens, which averages 0.06 p.p.m., but the exo-carbomethoxy group of Compound XVI has no apparent effect on them. Also, an alternative estimate of the effect of such a carbomethoxy group can be made by assuming that the effect of a 2-substituent on the 7-syn-methyl in the bornane system is a linear function of Taft's σ_I value (26) for such a substituent; such a relationship has been shown to hold for hydrogens on the carbon beta (27) or alpha (28) to the substituted one. Extrapolation

Figure 1—Shielding of C_{18}-hydrogens by acetyl group versus the angle defined by the C_{20}-oxygen bond axis and the vector that is perpendicular to the C_{17}-C_{20}-bond axis and that passes through the center of rotation of the C_{18}-hydrogens. The solid line was calculated for XXVII, and the dotted line was calculated for XXVIII.

from the known effect of 2-substituents in the bornane system (25) leads to the prediction that a 16α-carbomethoxy group, in the bridged steroids, should cause a deshielding of the C_{18}-hydrogens of 0.06 p.p.m., as observed, and that a 16β-carbomethoxy group should cause a deshielding of 0.20 ± 0.05 p.p.m. By a similar process, one can estimate that the effect of a 16β-trifluoromethyl group on the C_{18}-hydrogens should be to deshield them by 0.24 ± 0.05 p.p.m.

In the discussion of the effects on the shielding of the C_{18}-protons resulting from changes in configuration of 16-substituents, calculations were based on the geometry that would be obtained if the substituent were a halide or hydroxyl group. However, the results of those calculations might not be valid for the trifluoromethyl or carboxy ester groups. To avoid the problems introduced by possible hindered rotation of the carbomethoxy group, calculations were based on the trifluoromethyl group and were further simplified by considering only the effects caused by the net dipole of the trifluoromethyl group. These calculations (21) indicate that, to the extent that deshielding of the C_{18}-protons by the trifluoromethyl group is caused by a direct electrostatic effect rather than by a classical inductive effect, the deshielding should be greatest when the trifluoromethyl group is *endo* (alpha). The change in geometry caused by introduction of a 15,16-double bond should cause the deshielding to decrease by 50%, and a change to an *exo*- (beta) orientation of the trifluoromethyl group should result in a *shielding* twice as great as the *deshielding* caused by the field effect of the *endo*-isomer. While these results are based on crude approximations[5], they do correlate exactly with the chemical shifts found for the 16α- and 16β-carboxy ester substituted compounds. The possibility of undefined vicinal interactions in the 15,16-disubstituted compounds makes them a less reliable test of the validity of this approach. While the deshielding caused by the 15-dehydro-16-carbomethoxy moiety is clearly excessive in terms of the predictions, a number of factors, including resonance interactions which put a partial positive charge at C_{18}, could easily account for the discrepancy. This is unfortunate in the sense that the plurality of possible explanations could mask a small but anomalous deshielding peculiar to the 7-methylbicyclo-[2.2.1]heptadiene system[6].

EXPERIMENTAL[7]

3β-Acetoxy-14α,17α-ethano-5α-pregnan-20-one (III)— A solution of 291 mg. of II in 100 ml. of ethanol and 4 ml. of water was reduced over 52 mg. of 10% palladium-on-charcoal, at an initial pressure of 3.71 kg./cm.[2], for 18 hr. at room temperature. Standard workup of the reaction mixture afforded 235 mg. of III as white flakes from methanol, m.p. 177–179°.

Anal.—Calc. for $C_{23}H_{36}O_3$: C, 77.68; H, 9.91. Found: C, 77.76; H, 9.85.

3β-Acetoxy-14α,17α-ethano-15β,16β-dicarbomethoxy-5-pregnen-20-one (XVIII)—A solution of 1.0 g. of XIX in 200 ml. of methanol was hydrogenated over 150 mg. of 10% palladium-on-charcoal at an initial pressure of 3.71 kg./cm.[2] for 13 hr. at room tempera-

ture. Standard workup afforded XVIII, in a yield of 698 mg., as white rods from ethanol, m.p. 176–177°; ν (mineral oil): 1735 (sh), 1730, 1690, and 1625 cm.[-1]. The NMR spectrum has singlets at δ 2.06 [OC(═O)CH₃], 2.22 (C_{21} H's), 3.75, and 2.85 [C(═O)OCH₃].

Anal.—Calc. for $C_{29}H_{40}O_7$: C, 69.58; H, 8.05. Found: C, 69.53; H, 7.85.

3β-Acetoxy-17-cyano-15,16-dicarbomethoxy-14α,17α-etheno-5,15-androstadiene (XXXI)—A mixture of 314 mg. of 3β-acetoxy-17-cyano-5,14,16-androstatriene (2), 5 mg. of hydroquinone, and 1.0 ml. of dimethyl acetylenedicarboxylate was heated at 128–130°, in a sealed tube, for 148 hr. The crude product was chromatographed over 12 g. of acid-washed alumina[8]. Elution with benzene afforded XXXI as a foam (from ether) in a yield of 285 mg. (68%); ν (mineral oil): 2242 and 1730 cm.[-1]. The NMR spectrum had singlets at δ 2.02 [OC(═O)CH₃] and 3.82 (OCH₃), a multiplet at δ 5.35 (C_6 H), and doublets at δ 6.83 and 6.88 (bridge vinyl hydrogens).

Anal.– Calc. for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92. Found: C, 70.36; H, 7.26; N, 2.76.

3β-Acetoxy - 17 - cyano - 15β,16β - dicarbomethoxy - 14α,17α - ethano-5-androstene (XXXII)—A solution of 151 mg. of XXXI in 200 ml. of methanol and 5 ml. of water was reduced over 22 mg. of 10% palladium-on-charcoal for 18 hr. at room temperature under an initial pressure of 3.65 kg./cm.[2]. The product was chromatographed over 15 g. of neutral activity III alumina[9]. Elution with mixtures of ethyl acetate and benzene afforded XXXII as a glass, in a yield of 96 mg.; ν (CHCl₃): 2335 and 1722 cm.[-1]. The NMR spectrum had singlets at δ 2.04 [OC(—O)CH₃] and 3.84 [C(═O)-OCH₃] and a multiplet at δ 5.35 (C_6 H).

Anal.—Calc. for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90. Found: C, 69.49; H, 7.64; N, 2.80.

3β-Acetoxy-14α,17α-etheno-15α,16α-dicarboxyanhydride-5-pregnen-20-one (XXXV)—A mixture of 0.35 mg. of 3β-acetoxy-5,14,16-pregnatrien-20-one, 0.45 g. of maleic anhydride, and 15 mg. of hydroquinone was heated at 95–100° for 25 hr. in a sealed glass tube under nitrogen. The unreacted maleic anhydride was removed by distillation under reduced pressure at 100°. The residue was chromatographed over 15 g. of silica gel. Benzene containing up to 10% ethyl acetate eluted XXXV as a foam in a yield of 0.32 mg.; ν (mineral oil): 1830, 1765, 1720, and 1685 cm.[-1]. The NMR spectrum has singlets at δ 2.04 [OC(═O)CH₃] and 2.31 (C_{21} H's), doublets at δ 3.50, 4.45 [J = 8 Hz., CC(═O)H], 6.39 and 6.49 (J = 6.5, CH═CH), and a multiplet at 5.46 (C_6 H).

Anal.—Calc. for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.57; H, 7.20.

SUMMARY

Correlation of the chemical shifts of 30 14α,17α-bridged 20-ketopregnanes and of four similarly bridged 17-cyanoandrostanes, by means of additive substituent constants, requires the assumption that, depending upon the substitution pattern at C_{16}, the acetyl group of the pregnanes exists in one of two possible rotomer forms. Thus, introduction into these bridged pregnanes of a 16β-substituent or of a 16-substituent on a 15,16-double bond presumably causes the β-oriented carbonyl group to rotate toward C_{18}, which results in a 0.11 p.p.m. deshielding of the C_{18}-hydrogens. Support for this assumption is provided by X-ray crystal structures which were determined for 3β-acetoxy-14α,17α-ethano-16α-iodo-5-pregnen-20-one and for 14α,17α-etheno-15,16-di(trifluoromethyl)-4,15-pregnadiene-3,20-dione. Calculation, by the method of ApSimon *et al.* (8, 18), of the shielding effect of the acetyl group for each of the above structures indicates that the C_{18}-hydrogens of the latter compound should be deshielded by 0.07 p.p.m. relative to those of the former.

The finding that carboxy ester and trifluoromethyl groups substituted at the 15β- and/or 16β-positions of these bridged steroids cause little deshielding of the C_{18}-hydrogens contrasts sharply with the known tendency of 2-*exo*-halide functions to deshield 7-*syn*-methyl groups strongly in bicyclo[2.2.1]heptane systems. However, the dipoles of the former substituents bear a different geometrical relationship to the methyl than do those of the latter. Calculation of the expected field effects for these compounds shows that the observed chemical shifts are normal. Calculations also reveal that

[5] Approximations because: (*a*) the calculated values show large changes for relatively small variations in molecular geometry, (*b*) the geometry shown in the Dreiding models for the β-isomer is not correct in that it does not compensate for the crowding between the trifluoromethyl and methyl groups, (*c*) the authors did not correct for any partial charge transfer from the trifluoromethyl group to C_{18} or for the interaction of the 16-substituent with the double bond in the 15-dehydro compound, and (*d*) the method of calculation may be invalid for the β-isomer because of th proximity of the trifluoromethyl and methyl groups.
[6] Introduction of double bonds into norbornanes has been found to cause the chemical shifts of the C_7-hydrogens to change anomalously (7, 29, 31). While a partial explanation for this phenomenon has been advanced (28, 30, 31), recent data raise doubts as to its adequacy (32), and no satisfactory explanation has yet been put forward for the unusual deshielding of the corresponding hydrogens of norbornadiene (29). A similar effect of reduced magnitude seems to be shown by the methyl hydrogens of 7-methylbicyclo[2.2.1]heptadiene (33) which are more deshielded than the corresponding hydrogens of either of the 7-methylbicyclo[2.2.1]heptenes (7). In contrast, the *tert*-butyl hydrogens of the corresponding 7-*tert*-butyl compounds appear to have normal chemical shifts (34).
[7] Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. NMR spectra were determined in CDCl₃ on a Varian A-60 spectrometer and are reported in parts per million downfield from a tetramethylsilane internal standard.

[8] Merck.
[9] Woelm.

Table III—NMR Substituent Constants[a] for 14α,17α-Ethano Bridged Steroids

Substituent	C_{18}-Hydrogens, p.p.m.	C_{19}-Hydrogens, p.p.m.
14α,17α-Ethano-5α-pregnan-20-one	0.865	0.80
17α-Cyano-14α,17α-ethano-5α-androstane	1.005	0.80
15-Dehydro	−0.02	−0.01
15′-Dehydro	0.0	−0.05
16β-Substituent or Δ¹⁵-16-substituent in pregnane series	0.11	0
16α-Carboxy	0.055	−0.01
16α-Carbomethoxy	0.055	−0.01
16β-Carbomethoxy	−0.12	−0.02
15α,16α-Dicarboxyanhydride	0.11	0.02
15β,16β-Dicarbomethoxy	0.08	0.02
15β,16β-Di(trifluoromethyl)	−0.015	0.02
16α-Iodo	0.015	−0.02
19-Nor	0.015	---
15-Dehydro-16-carbomethoxy	0.27	0.01
15-Dehydro-15,16-dicarbomethoxy	0.31	0.03
15-Dehydro-15,16-di(trifluoromethyl)	0.27	0.03

[a] For solution in deuteriochloroform. A positive shift indicates a shift downfield from tetramethylsilane.

the strong deshielding associated with a substituted 15,16-double bond could be a normal consequence of a field effect arising from the dipole created by electron donation from the double bond to the substituent.

While it appears possible to explain the NMR observations on these compounds, many discussed effects could not have been anticipated. Because of this situation and because of continuing reports of anomalies in related small bridged ring compounds (35, 36), caution should be used in interpreting the NMR spectra of such substances.

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