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Configurational Effects on the Proton Magnetic Resonance Spectra of Six-membered Ring Compounds[1]

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The proton magnetic resonance spectra of six-membered ring compounds in their chair conformation indicate that the signals for protons in the axial orientation occur at higher field than those for equatorial hydrogens in some substituted cyclohexanes and symmetrical trioxanes, and this result was borne out with few exceptions for sixteen acetylated sugars. No exception was encountered, however, to the result that in fixed conformations the spin–spin coupling constant between neighboring hydrogens in the axial orientation is about 2 to 3 times larger than for neighboring hydrogens in other orientations. The chemical shifts for the methyl hydrogens of substituent acetoxy and methoxy groups are also characteristic of their orientation, the acetoxy groups usually giving rise to signals at lower field in the axial orientation than when in the equatorial orientation. By means of the chemical shift data and the magnitudes of the spin coupling constants, several determinations of configuration and conformation were achieved, especially for some acetylated aldopyranoses.

The correlation of several of the differences noted in the proton magnetic resonance spectra (hereafter called n.m.r. spectra) of acetylated aldopyranoses with the differences in configuration was reported in a preliminary communication.[2] These observations appeared to provide direct experimental evidence for the configurations and conformations of the compounds. It was therefore of interest to extend the work to simpler compounds in order to better establish the true significance of these results and their bearing on other types of six-membered ring compounds and, in particular, to gain direct experimental evidence for their conformations rather than to assume those predicted on the basis of the usual rules for conformational analysis.[3,4] A study of the effects of configurational changes on the n.m.r. spectra of compounds of known conformation therefore was undertaken. The *trans*- and *cis*-4-*t*-butylcyclohexyl alcohols and their acetates appeared to be appropriate compounds for this purpose. Winstein and Holness[5] have pointed out that application of the parameters established by Beckett, Pitzer and Spitzer[6] for the conformational stabilities of the methylcyclohexanes to the 4-*t*-butylcyclohexyl alcohols and their derivatives leads to the conclusion that these compounds must exist substantially entirely in conformations which have the *t*-butyl group in equatorial orientation. The validity of this conclusion depends, of course, upon the nature of the 1-substituent. The conclusion undoubtedly is valid for the 4-*t*-butylcyclohexyl alcohols and their acetates for temperatures well above 100°. The results of a number of experiments[5,7] are consistent with the assumed conformations of these compounds.

The conformations and n.m.r. spectra of the *trans*- and *cis*-4-*t*-butylcyclohexyl alcohols and their acetates are presented in Fig. 1. The signals are readily assigned to the various kinds of hydrogens on the basis of their relative intensities and structures. Thus, the strong *sharp* signals of appropriate intensities which occur in the region 262–274 c.p.s. in all the spectra and at 230 c.p.s. in the spectra of the acetates arise from the hydrogens of the *t*-butyl and acetyl groups, respectively. In the case of the alcohols, the signal for the hydrogen of the hydroxyl group (at lowest field) was readily recognized by the addition of hydrochloric acid since the resultant rapid proton exchange[8] brought about a shift of the hydroxyl group signal to lower field. The other signals of intensity one in the region 109–160 c.p.s. must therefore belong to the 1-hydrogen and those in the 233–262 c.p.s. region to the other nine hydrogens on the ring. The points of interest in these spectra are the half-widths of the bands for the 1-hydrogens. It is seen that the half-width of this signal for the *cis*-alcohol and *cis*-acetate is 7 c.p.s. as compared to about 22 c.p.s. for the *trans* isomers. The only plausible interpretation for the widths of these bands is that they represent unresolved multiplets arising from spin–spin coupling with the four hydrogens on the neighboring carbons. This coupling interaction is known[9] to be attenuated rapidly with increasing number of bonds between the coupled nuclei, although Baker[10] recently reported one noteworthy exception.

The main features of the fine structure can be assumed, therefore, to arise only from the coupling of a hydrogen with other hydrogens not separated by more than three bonds. On this basis, it is evident (from the relative widths of the signals) that the axial 1-hydrogens of the *trans* compounds are more strongly coupled with the neighboring axial hydrogens than are the equatorial 1-hydrogens of the *cis* isomers. Clearly, this suggests stronger coupling between axial hydrogens on neighboring carbons than between neighboring hydrogens in the other orientations, and this conclusion was verified by the spectra of other compounds (see below) in which the fine structure was sufficiently well resolved to allow the determination of the magnitude of the coupling constants.

The spectrum of 1α,3α-dimethoxy-2β-acetoxycyclohexane[11] (Fig. 2) provides a suitable example

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(2) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, THIS JOURNAL, **79**, 1005 (1957).

(3) O. Hassel and B. Ottar, *Acta Chim. Scand.*, **1**, 929 (1947).

(4) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(5) S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5562 (1955).

(6) C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, **69**, 2488 (1947).

(7) (a) E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957); (b) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5992, 5995 (1957).

(8) H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, **21**, 1688 (1953).

(9) H. S. Gutowsky, L. H. Meyer and D. W. McCall, *ibid.*, **23**, 982 (1955).

(10) E. B. Baker, *ibid.*, **26**, 960 (1957).

(11) R. U. Lemieux, R. K. Kullnig and R. Y. Moir, THIS JOURNAL, **80**, 2237 (1958).

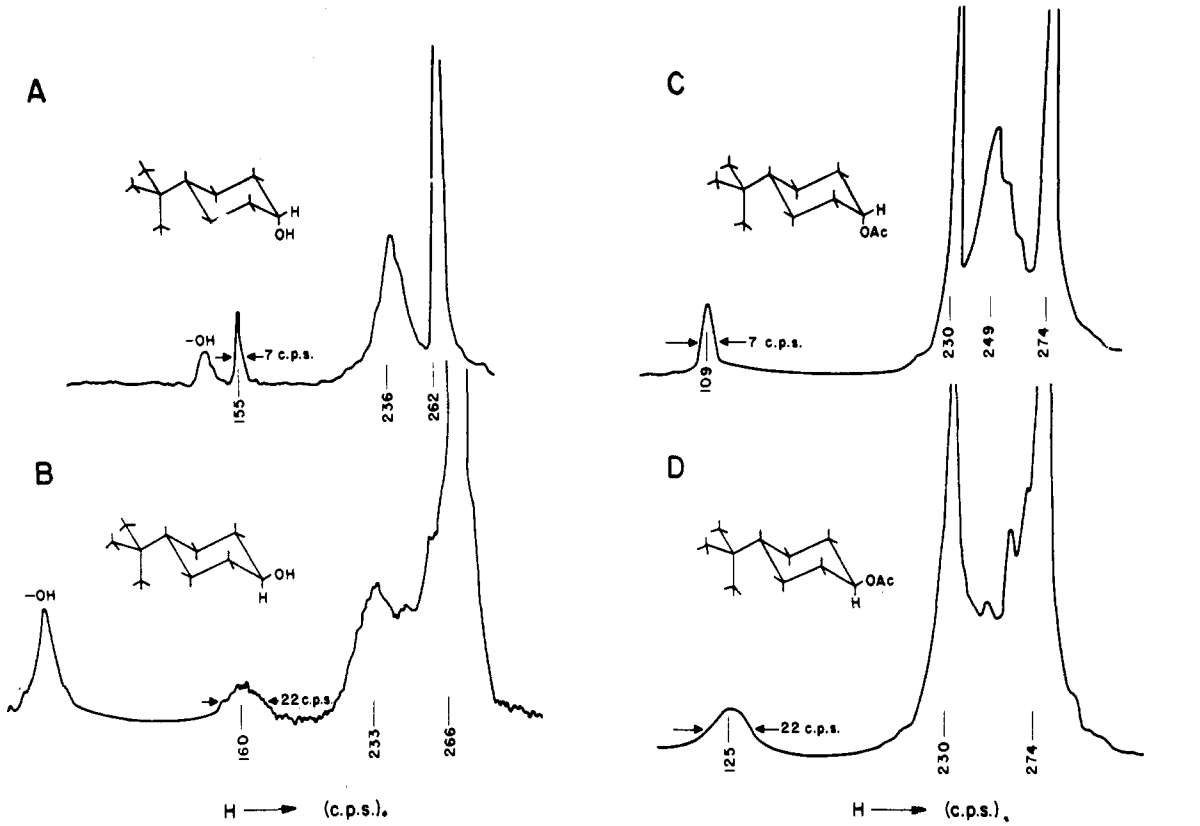

Fig. 1.—The proton magnetic resonance spectra in chloroform of the *cis*- and *trans*-4-*t*-butylcyclohexyl alcohols (A and B, respectively) and their *O*-acetates (C and D, respectively).

for obtaining the value of an axial–axial coupling constant. The signals for the 1- and 3-hydrogens are overlapped by the strong methoxy group signals. The signal of the 2-hydrogen of this compound appeared as three well resolved bands at 107, 116 and 125 c.p.s. This triplet structure arises from the spin–spin coupling of the 2-hydrogen with the *trans*-1- and *trans*-3-hydrogens. According to the notation of Bernstein, Pople and Schneider[12] the 2-hydrogen is the A-atom of an AX_2 system. This system is characterized by the ratio of the spin–spin coupling constant (J) of the nuclei A and X to the chemical shift $[\eta H_0(\sigma_B - \sigma_A)]$. Since the chemical shift is large (approximately 60 c.p.s.) compared to the spin–spin coupling constant, the coupling constant can be taken as the equal spacing between the bands in the triplet; *i.e.*, 9 c.p.s. The theoretical pattern for the triplet can be calculated using these values for the chemical shift and coupling constant and with the aid of Tables IV and V provided by Bernstein, Pople and Schneider.[12] The agreement between the calculated structure and that observed, shown in Table I, justifies the above interpretations.

The signals for the 2-hydrogen of 1α,3β-dimethoxy-2α-acetoxycyclohexane[11] (Fig. 2) occurred as a quartet of bands at 107.5, 110.0, 113.8 and 116.5 c.p.s. Bernstein, Pople and Schneider[12] classify this type of signal as part of the spectrum of an AXY system with A representing the 2-hydrogen. The spacing between the first and second components (or third and fourth) and that between the first and third (or second and fourth) of this quartet yield approximately the coupling constants, J_{AY} and J_{AX}, respectively. Thus, J_{AY} was found to be ~2.6 c.p.s. and J_{AX} ~6.4 c.p.s. The available information does not allow intensity calculations in this case. These results confirm the conclusion that the coupling between *trans*-hydrogens (A and X) on neighboring carbons is 2 to 3 times stronger than between *cis*-hydrogens on neighboring carbons (A and Y). Since the spectra of the 4-*t*-butylcyclohexyl derivatives require that the stronger coupling is associated with axial hydrogens, it is evident that the compound possesses the conformation shown in Fig. 2. Also, it can be concluded that 1α,3α-dimethoxy-2β-acetoxycyclohexane has the 1-, 2- and 3-hydrogens in axial orientation (as would have been anticipated from conformation analysis). Accordingly, the fine structure of the signal for a hydrogen on a six-membered ring can yield information about its configuration and con-

TABLE I

THE CALCULATED AND OBSERVED SIGNALS FOR THE 2-HYDROGENS OF 1α,3α-DIMETHOXY-2β-ACETOXYCYCLOHEXANE

Line	Energy difference Obsd.	Calcd.	Relative intensity Calcd.[a]
A1	107	107	0.85
A2	116[b]	115.2	1.0
A3	116[b]	116.7	1.0
A4	125	124.9	1.15

[a] Compare these values with those observed (see Fig. 2). [b] The theoretical doublet was not resolved.

(12) H. J. Bernstein, J. A. Pople and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).

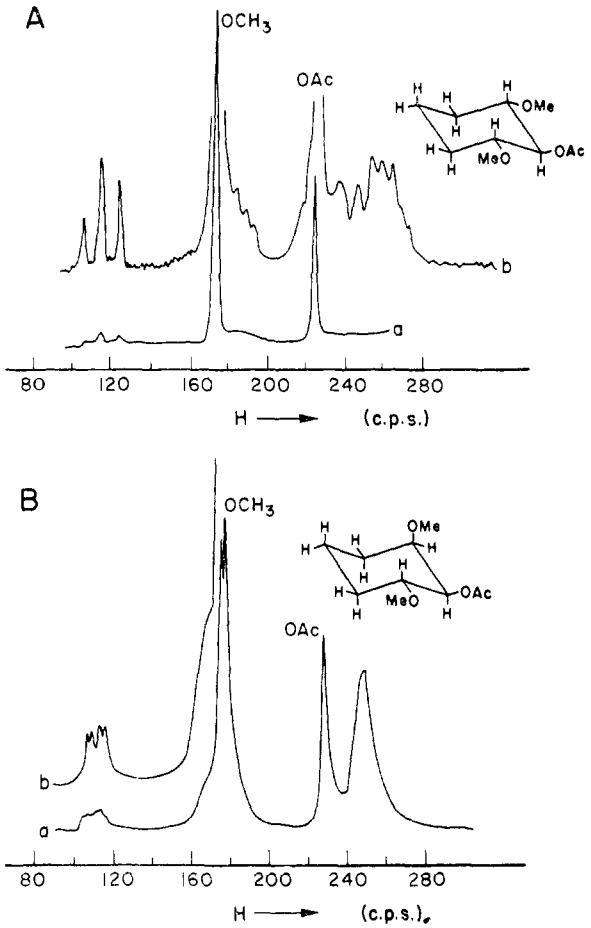

Fig. 2.—The proton magnetic resonance spectra in chloroform of the 1α,3α-dimethoxy-2β-acetoxycyclohexane (A) and 1α,3β-dimethoxy-2α-acetoxycyclohexane (B).

formation. It is of interest to note that the two different spin–spin coupling constants which have been observed for hydrogens on neighboring carbons in the n.m.r. spectra of 1-chloro-2-bromoethane[13a] and dioxane[13b] can be related to the dependence of the coupling on orientation in the manner noted above.

The four groups of signals which normally are present in the n.m.r. spectrum of an acetylated aldopentapyranose (Fig. 3) can be assigned convincingly to the different kinds of hydrogens in the molecule simply through inspection of the intensities, positions and fine structure of the bands. The anomeric hydrogen is a unique type of hydrogen in the molecule and is clearly responsible for the signal of intensity one which occurs at lowest field in the region 45–75 c.p.s. The position of the signal is not surprising since it is the only hydrogen attached to a carbon which is bonded to two oxygen atoms and, consequently, its nucleus should be somewhat less shielded. The fact that this signal often occurred as a doublet is in agreement with this conclusion since the anomeric hydrogen is only strongly coupled with the 2-hydrogen. Direct experimental justification for its assignment was obtained by its absence from the spectra of either the α- or β-anomers of 1-deuterated-D-glucopyranose pentaacetate. The intensities of the bands in the region 70–105 c.p.s. (Fig. 3) clearly indicate that they arise from the three hydrogens on the secondary carbons of the acetylated aldopentopyranoses. The similar kind of hydrogens in the polyol acetates also gave rise to signals in this region and it is noteworthy that it is possible to determine the number of such hydrogens in a polyol acetate in this way. For example, ethylene glycol diacetate and pentaerythritol tetraacetate did not have a signal in this region. Consequently, n.m.r. spectroscopy provides a new tool for detecting branches in carbohydrate structures. The signals of intensity two in the 120–150 c.p.s. region (Fig. 3) necessarily arise from the methylene hydrogens of the acetylated aldopentopyranose ring. The sharpness and strong intensities of the signals in the 210–230 c.p.s. region definitely relates these signals to the twelve hydrogens of the four acetoxy groups in the pentose tetraacetates. The gross features of the spectra of the aldohexopyranose pentaacetates are not appreciably different from those of the aldopentopyranose tetraacetates. Of course, in the case of the hexose pentaacetates the signal of intensity three in the 120–150 c.p.s. region arises from the 5-hydrogen and the two 6-hydrogens. This assignment is consistent with the

(13) (a) J. A. Pople, W. G. Schneider and H. J. Bernstein, *Can. J. Chem.*, **35**, 1060 (1957); (b) A. D. Cohen, N. Sheppard and J. J. Turner, *Proc. Chem. Soc.* (*London*), 118 (1958).

TABLE II

PROTON MAGNETIC RESONANCE SPECTRA FOR THE ANOMERIC HYDROGEN OF ACETYLATED ALDOPYRANOSES

Fully acetylated aldopyranose	Position in the magnetic field, c.p.s.[a]	Spin–spin coupling constant
1. Axial anomeric hydrogen		
(a) Axial 2-hydrogen		
β-D-Xylose[b]	75	6
β-D-Ribose[b]	62	5
α-L-Arabinose[b]	73	~8
β-D-Glucose[b]	69	8
β-D-Allose[c]	60	8
β-D-Galactose[b]	72	6
(b) Equatorial 2-hydrogen		
β-D-Mannose[b]	63.5	3
2. Equatorial anomeric hydrogen		
(a) Axial 2-hydrogen		
α-D-Xylose[b]	49.5	3
α-D-Ribose[d]	58	2
β-D-Arabinose[b]	46	3[e]
α-D-Glucose[b]	51	3.2
α-D-Galactose[b]	47	3
α-D-Gulose[b]	55	6.2[e]
(b) Equatorial 2-hydrogen		
α-D-Lyxose[b]	63	3
α-D-Mannose[b]	52	3
α-D-Altrose[f]	63	3[e]

[a] Relative to the signal for the chloroform used as solvent and taking the mid-point between the two signals of the doublet. [b] *F. J. Bates and Associates*, "Polarimetry, Saccharimetry and the Sugars," U.S. Govt. Printing Office, Washington, 1942. [c] R. U. Lemieux and C. Brice, *Can. J. Chem.*, **34**, 1006 (1956). [d] Prepared by P. Chu and to be reported in a separate communication, m.p. 75–78°, $[\alpha]^{20}D$ +54° (chloroform). [e] The width of the signal at half its height. [f] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941).

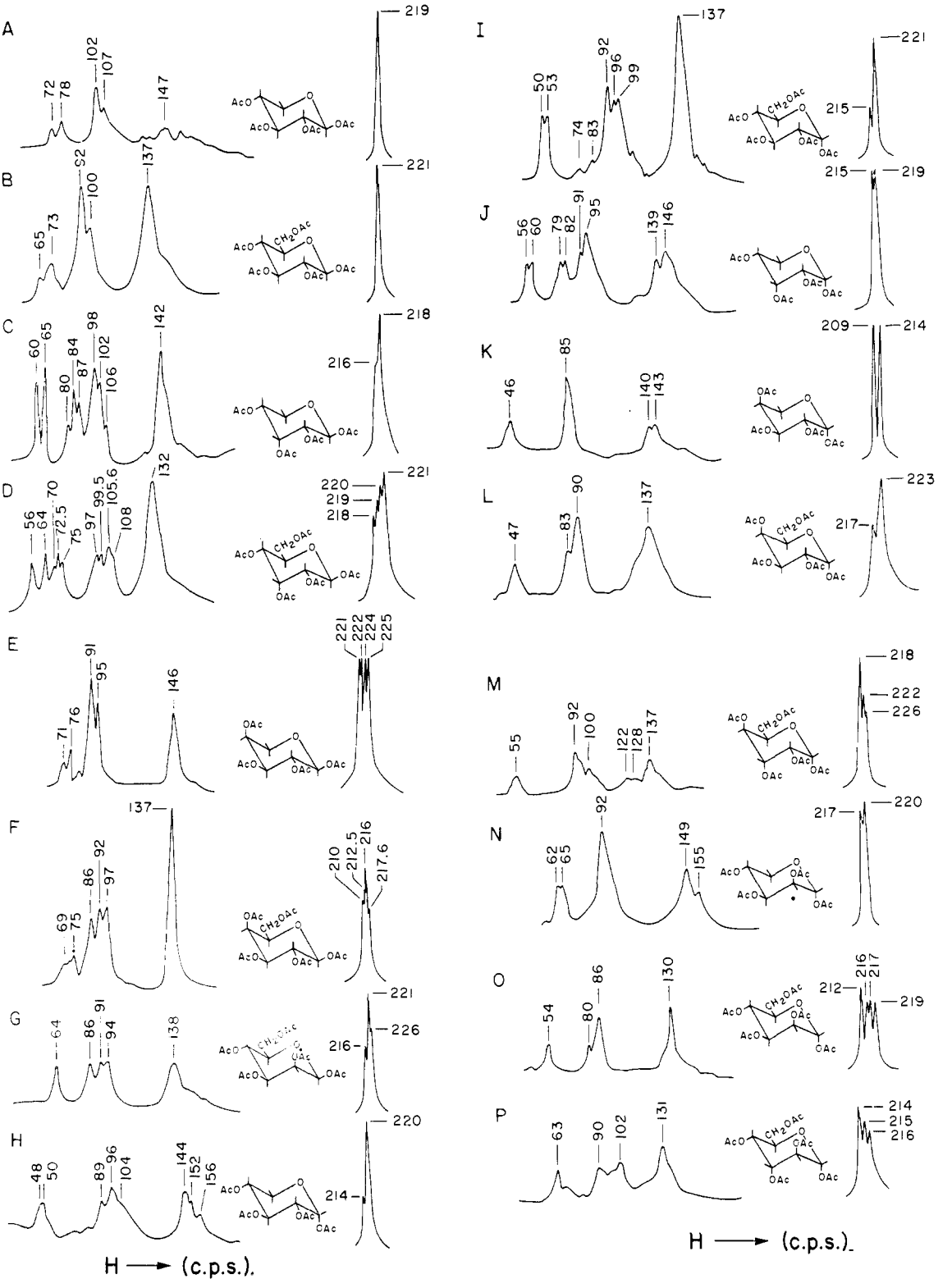

Fig. 3.—The proton magnetic resonance spectra in chloroform of acetylated glycopyranoses: β-D-xylose tetraacetate (A), β-D-glucose pentaacetate (B), β-D-ribose tetraacetate (C), β-D-allose pentaacetate (D), α-L-arabinose tetraacetate (E), β-D-galactose pentaacetate (F), β-D-mannose pentaacetate (G), α-D-xylose tetraacetate (H), α-D-glucose pentaacetate (I), α-D-ribose tetraacetate (J), β-L-arabinose tetraacetate (K), α-D-galactose pentaacetate (L), β-L-gulose pentaacetate (M), α-D-lyxose tetraacetate (N), α-D-mannose pentaacetate (O), α-D-altrose pentaacetate (P).

fact that the methylene hydrogens of acetylated sugar alcohols also have signals in this region. It is of interest that, in view of the characteristic positions for the signals of the different kinds of hydro-

gens in a sugar acetate, n.m.r. spectroscopy can be used to distinguish ketoses from aldoses [compare, for example, the spectrum of β-D-fructopyranose pentaacetate[14] (Fig. 4) with those of the aldohexose pentaacetates (Fig. 3)].

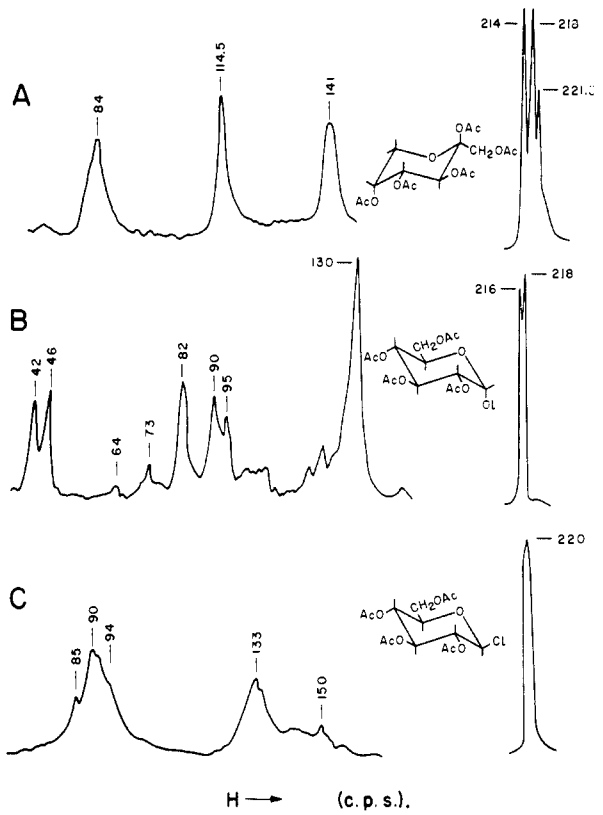

Fig. 4.—The proton magnetic resonance spectra of β-D-fructopyranose pentaacetate (A), and the α- and β-D-glucopyranosyl chloride tetraacetates (B and C, respectively).

The signals for the anomeric hydrogens of the acetylated aldoses are essentially part of an AB-system[12] and, as expected, appeared as doublets in most cases. In some cases the doublet was not resolved. The coupling constants, derived by measuring the spacing of the doublets, are given in Table II. The results are seen to be in agreement with the above conclusions on the magnitudes of the coupling constants for neighboring hydrogens in axial–axial, axial–equatorial and equatorial–equatorial orientation and, except for α-D-gulopyranose pentaacetate, clearly support the conformations for the various sugar acetates shown in Fig. 3. That an anomaly should arise for the gulose derivative need not be surprising since the two chair conformations probably differ little in stability and both may contribute to an important extent to the spectrum. This situation probably exists also for the altrose derivative. In principle, this interpretation might be confirmed by studying the temperature dependence of the n.m.r. spectrum.

The data in Table II clearly suggest that a change in the configuration at the anomeric center produces a chemical shift toward lower field when the hydrogen passes from an axial to an equatorial orientation. The magnitude of the shift varies considerably from one pair of anomers to another. Thus the shift is 27 c.p.s. for the arabinose derivatives and only 4 c.p.s. for the ribose derivatives. The position (63 c.p.s.) of the signals for the anomeric hydrogens of α-D-lyxopyranose tetraacetate and α-D-altropyranose pentaacetate appears at anomalously high field for equatorial hydrogens. Unfortunately, it was not possible to obtain the anomeric forms in a pure crystalline state.

The spectra of the α- and β-D-glucopyranosyl chloride tetraacetates[14] (Fig. 4) indicate a change of chemical shift of at least 40 c.p.s. for the anomeric hydrogens. Intensity measurements show the signal for the β-anomeric hydrogen to be in the same region as those for the hydrogens on the secondary carbons.

The spectra (Fig. 1) of the 4-*t*-butylcyclohexyl alcohols and acetates also show that the signal for the 1-hydrogen occurs at lower field when in the equatorial orientation than when in axial orientation. The signals for the hydrogens on the secondary carbons of the ribose and allose derivatives (Fig. 3) provide another example. It is seen that for these compounds the signals for the equatorial 3-hydrogens are at lower field than the signals for the axial 2- and 4-hydrogens.

The spectrum of the methylene hydrogens at the 5-position of β-D-xylopyranose tetraacetate (Fig. 5)

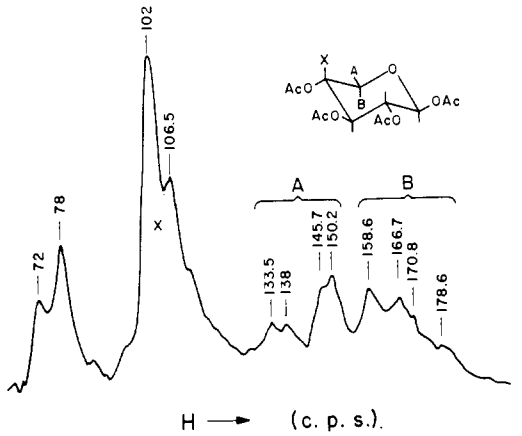

Fig. 5.—High resolution spectrum for β-D-xylopyranose tetraacetate in chloroform solution to show the fine structure for the signal of the two 5-hydrogens (133.5–178.6 c.p.s.).

is of special interest since a detailed theoretical analysis as an ABX system[12] yields the chemical shift and spin coupling constants for the axial and equatorial hydrogens (B and A) on the *same carbon*. The following parameters were obtained from the analysis

chemical shifts, $\eta H_0 (\sigma_B - \sigma_A) = 24.2$ c.p.s.
$\eta H_0 (\sigma_B - \sigma_X) = \sim 64$ c.p.s.
coupling constants, $J_{AB} = 12$ c.p.s.
$J_{BX} = 8$ c.p.s.
$J_{AX} = 3.2$ c.p.s.

The ABX spectrum calculated with these parameters gave excellent agreement with the observed spectrum. The calculated spectrum for the 4-hydrogen (X) is overlapped by the band in the region

(14) See footnote *c*, Table II.

102–107 c.p.s. The value of the constant J_{AB} is in good agreement with the value (12.4 c.p.s.) obtained from the spectra of CH_3D and CH_2D–CCl_3.[15] Also, the chemical shift of the A and B protons is in accordance with the above conclusion on the effect of the orientation of a hydrogen on the position of the signal in the field.

The isomeric 2,4,6-trichloromethyltrioxanes[16] provide another example of the chemical shift difference between axial and equatorial hydrogens uncomplicated by strong spin–spin coupling of the hydrogens. As seen in Fig. 6, the spectra clearly

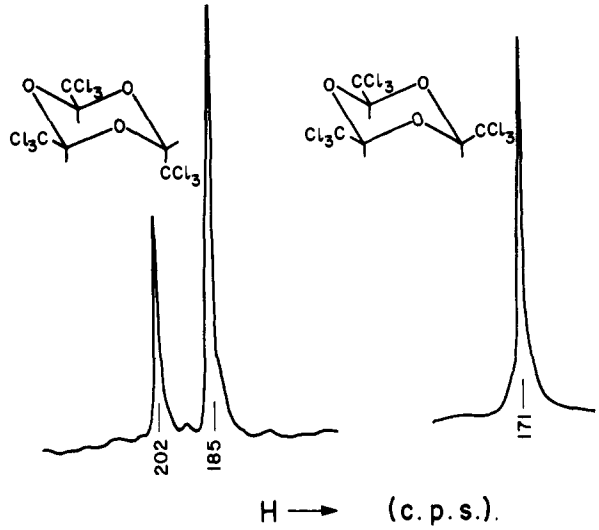

Fig. 6.—The proton magnetic resonance spectra in dioxane solution for the 2,4,6-trichloromethyltrioxanes.

identify the configurations of the compounds. Obviously, the compound with the single signal has three conformationally equivalent hydrogens and must be in the conformation shown. It is not possible to decide with certainty whether or not the other isomer is in fact in the chair conformation indicated in Fig. 6 rather than in a boat form. However, the magnitude and direction of the chemical shifts clearly suggest the chair conformation. This has been confirmed by infrared and dipole measurements.[16]

The spectra of the α-, β-, γ-, δ- and ϵ-isomers for 1,2,3,4,5,6-hexachlorocyclohexane[17] are shown in Fig. 7. The spectra of β-, δ- and ϵ-isomers are as expected. The single signal observed for the γ-isomer is also in agreement with expectation, since the two chair forms for this compound are identical and the interconversion of the two forms undoubtedly is very rapid. The extensive band splitting observed in the case of the α-isomer was unexpected and is, as yet, unaccountable. Although it is not possible to make an unequivocal assignment of the signals in the α-isomer, it is likely that the fine structure arises mainly from the four axial hydrogens. It is of interest that *l*-inositol hexaacetate, which possesses a similar configuration, also shows no resolution of the signals for the two equatorial

(15) M. Karplus, D. H. Anderson, T. C. Farrar and H. S. Gutowsky, *J. Chem. Phys.*, **27**, 597 (1957).

(16) A. Novak and E. Whalley, *Can. J. Chem.*, in press.

(17) E. L. Lind, M. E. Hobbs and P. M. Gross, THIS JOURNAL, **72**, 4474 (1950).

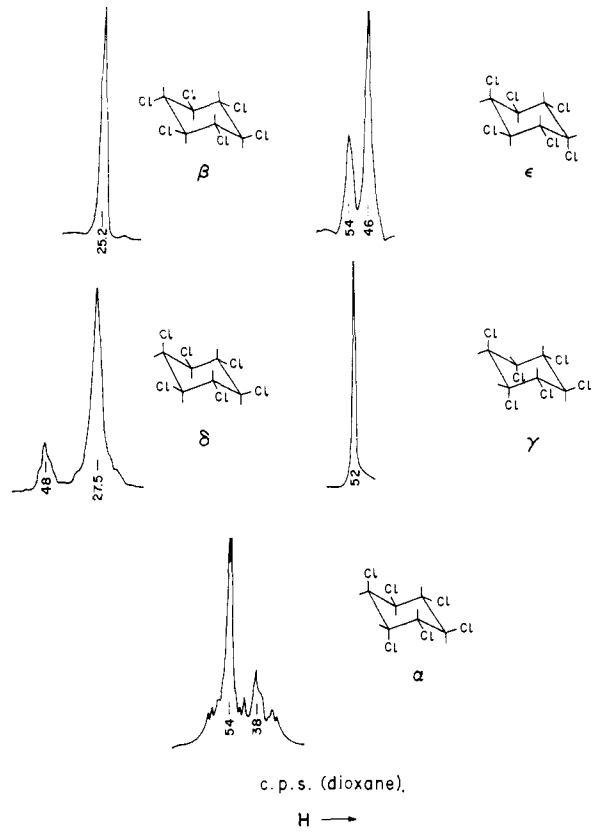

Fig. 7.—The proton magnetic resonance spectra of the α-, β-, γ-, δ- and ϵ-1,2,3,4,5,6-hexachlorocyclohexanes.

hydrogens from those of the four axial hydrogens (Fig. 8). On the other hand, as observed for the δ-hexachloride, *myo*-inositol hexaacetate[18] gave a spectrum (Fig. 8) with the position of the signal for the equatorial hydrogen 8 c.p.s. toward lower field than that for the five axial hydrogens. The signals for the axial and equatorial hydrogens and those for the axial and equatorial acetoxy groups of *cis*-inositol hexaacetate[19] (Fig. 8) were not resolved. This result, like that for the γ-benzene hexachloride, probably is due to the equivalence of the two chair forms and their rapid rate of interconversion.

Chemical shifts also have been observed to occur for the signal of the hydrogens of acetoxy and methoxy groups when the orientation of one of these groups on a six-membered ring is changed. This is seen, for example, in the spectra (Fig. 8) of the *myo*- and *l*-inositol hexaacetates. In both cases, the relative intensities of the two signals which are produced by the acetyl hydrogens show that axial acetoxy groups produced signals at lower field than did the equatorial acetoxy groups. This characteristic of the n.m.r. spectra also is observed in the majority of the spectra for the sugar acetates (see Fig. 3). For these compounds, none of the acetoxy groups are strictly equivalent and, consequently, none of their signals need be at the same position in the field. Nevertheless, in most cases, the spectra indicate clearly the ratio of equatorial to axial acetoxy groups in the molecule. The sig-

(18) M. Maquenne, *Ann. chim. phys.*, [6] **12**, 80 (1887).

(19) S. J. Angyal and D. J. McHugh, *J. Chem. Soc.*, 3682 (1957).

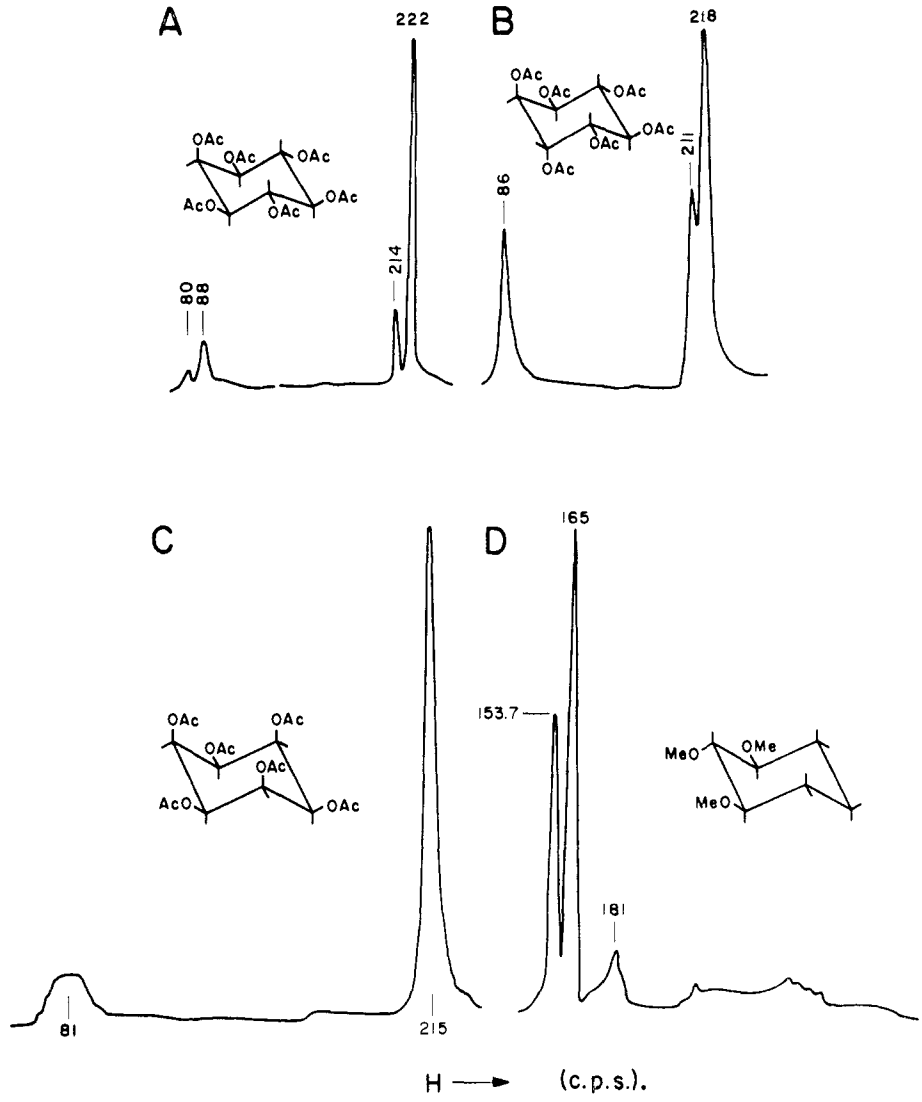

Fig. 8.—The proton magnetic resonance spectra in chloroform solution of the hexaacetates of *myo*-, *l*- and *cis*-inositols (A, B and C, respectively) and of 1α,2β,3α-trimethoxycyclohexane (D).

nals for the methoxy groups of 1α,3β-dimethoxy-2α-acetoxycyclohexane were separated by 1.7 c.p.s.[11] It is to be stressed, however, that substituents (groups or hydrogens) which are not strictly equivalent are expected to produce signals at different positions in the field regardless of whether or not their orientations on the six-membered ring are the same. For example, 1α,2β,3α-trimethoxycyclohexane, which undoubtedly has the three methoxy groups in equatorial orientation, possesses a spectrum in which the signal for the 2-methoxy is 11 c.p.s. at lower field than that for the two equivalent methoxy groups. Although the triacetates of the 1,6-anhydro-derivatives of D-glucopyranose, D-galactopyranose, D-mannopyranose, D-idopyranose, D-gulopyranose and D-altropyranose gave spectra which have the signals for the three acetoxy groups in fair agreement with expectation, the agreement was not sufficiently good to permit unambiguous conclusions about their configurations or conformations. Of course, several of these compounds must have highly strained structures.

In summary, the proton magnetic resonance spectra of a variety of six-membered ring compounds have revealed that the n.m.r. technique can provide information on the configurations and conformations of these compounds. In the case of the acetylated aldopyranoses, the spectra clearly substantiated the ring structures and anomeric configurations previously established or assumed for these compounds. Furthermore, in most cases the spectra provided direct evidence that these compounds exist in the chair conformations which have the least number of substituents in axial orientation. A more detailed consideration of this matter is reserved for a forthcoming publication in which further pertinent data derived from studies of anomeric equilibria will be presented.

Experimental

The spectra were measured at room temperature with a Varian V-4300 n.m.r. spectrometer, equipped with a field stabilizer, at a fixed frequency of 40 Mc.p.s. The positions of the prominent signals in a spectrum were measured by

the side band technique of Arnold and Packard.[20] The positions of the remaining signals were measured by interpolation on the record chart. The sample contained in a 5 mm. (diam.) spinning tube, was usually a nearly saturated solution of the compound in chloroform or dioxane (see figures of spectra for the solvent used). The signal for the hydrogens of the solvent was in each case used as an internal standard for establishing the positions of the signals in the magnetic field. In several instances the spectra were determined in carbon tetrachloride and in the liquid state and the separation of the signals was found to be nearly the same as those obtained in chloroform or dioxane.

The acetates of the *cis*- and *trans*-4-*t*-butylcyclohexyl alcohols ($n^{24.5}$D 1.4491 and $n^{23.5}$D 1.4512, respectively) were prepared by heating the alcohols with acetic anhydride and sodium acetate. The products, isolated in the usual fashion, were purified by distillation *in vacuo* and possessed the expected saponification equivalents.

All the other compounds are reported in the literature references cited in the text. In all cases, the compounds were of high purity as gauged from the reported physical constants.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. XCIX. Synthesis of Ring B Oxygenated Estrogens[1]

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Osmium tetroxide oxidation of 6-dehydroestrone or estradiol derivatives gave the corresponding 6α,7α-glycols which on treatment with acid were inverted to the 6β,7α-glycols. Peracid oxidation of the Δ⁶-compounds yielded the 6α,7α-oxides which underwent acid opening to the 6β,7α-glycols or hydride reduction to the 7α-alcohols. Oxidation of 7α-hydroxyestrone furnished 7-ketoestrone which was converted to the 7β-alcohol by catalytic reduction of the 7-enol acetate. Elimination reactions of the 7α and 7β alcohols led only to the Δ⁶-compound rather than to equilin.

Of all the naturally occurring biologically active steroid hormones only equilin (7-dehydroestrone), which was first isolated by Girard, *et al.*,[2] from mare's urine, had resisted both partial and total synthesis at the time this work was initiated.[3] The work described herein, aimed at the synthesis of this hormone, basically involved the introduction of a hydroxyl function at the 7-position of an estrone or estradiol derivative followed by the elimination of this group with the hope that a new double bond could be introduced between carbon atoms 7 and 8. In particular, the possibility existed that pyrolysis of a 7-ester group would lead, as in the cholestane[4] and sapogenin[5] series, to the Δ⁷-compound although it was recognized that conjugation of the newly introduced double bond with the benzene ring was more likely. This latter path, leading to 6-dehydroestrone, indeed was the only recognizable reaction in various eliminations of both 7α- and 7β-hydroxy estrogens.

However, it should be noted that almost all of the oxygenated estrogens herein described are new compounds. Their essential inactivity as estrogens offer valuable structure–activity relationships and even a possible utility as so-called "non-estrogenic" estrogens which are of potential interest in the treatment of certain hormone dependent tumors and in atherosclerosis.

7-Monohydroxy Estrogens.—Introduction of a C-7 oxygen function was accomplished starting with the readily available 6-dehydroestrone (Ia).[6] The 17-cycloethylene ketal (Id) of this compound on treatment with monoperphthalic acid at low temperature led to the 6α,7α-oxido compound IIb which after lithium aluminum hydride reduction and acid hydrolysis gave 7α-hydroxyestrone (IIIa). That the alcohol thus obtained was the C-7 alcohol was proved by the direct oxidation of IIIa with the Jones reagent[7] to the known 7-ketoestrone IIIf, a compound first prepared by Pearlman and Wintersteiner[8] from equilin. These workers also prepared a 7-hydroxyestrone by the catalytic hydrogenation in acetic acid, of the enol acetate of 7-ketoestrone (IV).[8] Repetition of Pearlman and Wintersteiner's[8] sequence gave a compound (IIIh) whose constants agreed with the reported ones, but which was different from IIIa. On steric considerations we assign the 7β-configuration to the alcohol derived from the hydrogenation of the enol acetate and conversely the compound from hydride reduction of the epoxide is 7α-hydroxyestrone and the starting epoxide II must be the α-epoxide. Thus, cleavage of the epoxide follows the normal stereochemical course[9] with axial hydride attack and axial alcohol formation, a reaction even more favored in this case since the cleaved bond is benzylic.

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