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M
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        O
          N - M - R

No. 31

Department of Chemistry,
Imperial College,
Imperial Institute Road,
London, S. W. 7
24. 5 1961.

Gentlemen:

In intervals between running high resolution spectra during the past year or so, we have been looking at some low resolution spectra, those of paramagnetic complexes of transition metal ions. Proton shifts in paramagnetic compounds have been measured earlier in solid free radicals (Gutowsky) and metal sandwiches (McConnell), and more recently in acetylacetonates (Forman, Murrell & Orgel) a nd nickel chelates (Ph illips & Benson). We are interested in aqueous solutions of complexes, in particular those of aminoacids. The rough diagram shows the sort of spectra we get. The samples are commonly 0.2M solutions, of volumes about 5cc.(H_2O) or 1cc. (D_2O) in 15mm. tubes; the signal/noise ratio is quite respectable, about 25:1 for the sharper lines.

Large shifts are produced by the isotropic contact interaction between a proton and the unpaired electron spin density on the ligand atom (C or N) to which the proton is bonded. The direction of the shift depends on the sign of the spin density on the atom, the magnitude depends on the magnitude of the spin density. With Co^{2+} a nd Ni^{2+}, protons in NH gr oups bonded directly to the metal shift upfield, a nd those in alkyl groups α to the amino group shift downfield, the sign of the spin dens ity cha nging from N to C. The shifts decrease along a saturated chain, where the contact effect is not necessarily the only c ause of the shifts, but it is usually possible to see separate lines from most of the proton-containing groups in a complex ion. In chelate rings, the differences between 5 and 6 ring CH positions can indicate which rings are formed by polydentate ligands.

There are also differences in the position of the same ligand group in 1:1, 1:2 and 1:3 complexes, as in the simple example of Co^{2+} with ethylene diamine. The changes in the line intensities as the stoichio-metric ratio of Co : en is changed can be used to estimate relative stability constants.

The lines sometimes get broader when the ligand is present in the higher ratios or in excess; this seems to be the result of an increased rate of exchange of ligand molecules on and off the complex. Since the shifts are big, the critical rates for exchange broadening are faster than for diamagnetic compounds, although the lines are already broadened by relaxation.

Similarly, the lines from NH protons can be seen, which in diamagnetic solutions often exchange too quickly. They still do exchange, of course, and the assignements can be aided by comparing spectra in H_2O and D_2O solutions. For example, the line at~3400cps. in the complex of Ni with glycylglycine in H_2O, is absent in D_2O, and probably represents an NH proton. Its position on the low field side suggests that it is not on a nitrogen bonded directly to the metal, but is next to a bonded group. A reasonable a ssignement is that it is the peptide NH, with the peptide C=O bonded to the metal, a s was suggested by Li et. al. (J.A.C.S. 79 5859 (1957). The spectrum becomes more complicated when more base is added to complex the COOH group.

Polydentate ligands give more than one chelate ring, and their assignements can be aided by comparison with simpler systems, a s was done with the nickel histidine complex. The main lines appear with less than ½ equivalent of base added to the starting solution (containing histidine hydrochloride), agreeing with the fact that the first chelate ring to be formed involves the two nitrogen atoms. The lines get stronger but do not shift as more basee is added. Just as the second equivalent of base per aminoacid is added, the line at~3800 cps. in H_2O solutions disappears, probably it is the imidazole NH proton. As an example of a more labile complex, EDTA gives a complex with Ni^{2+} in which two of the acetate groups form weaker chelate rings than the others, and these probably give the less shifted lines, which change more with pH.
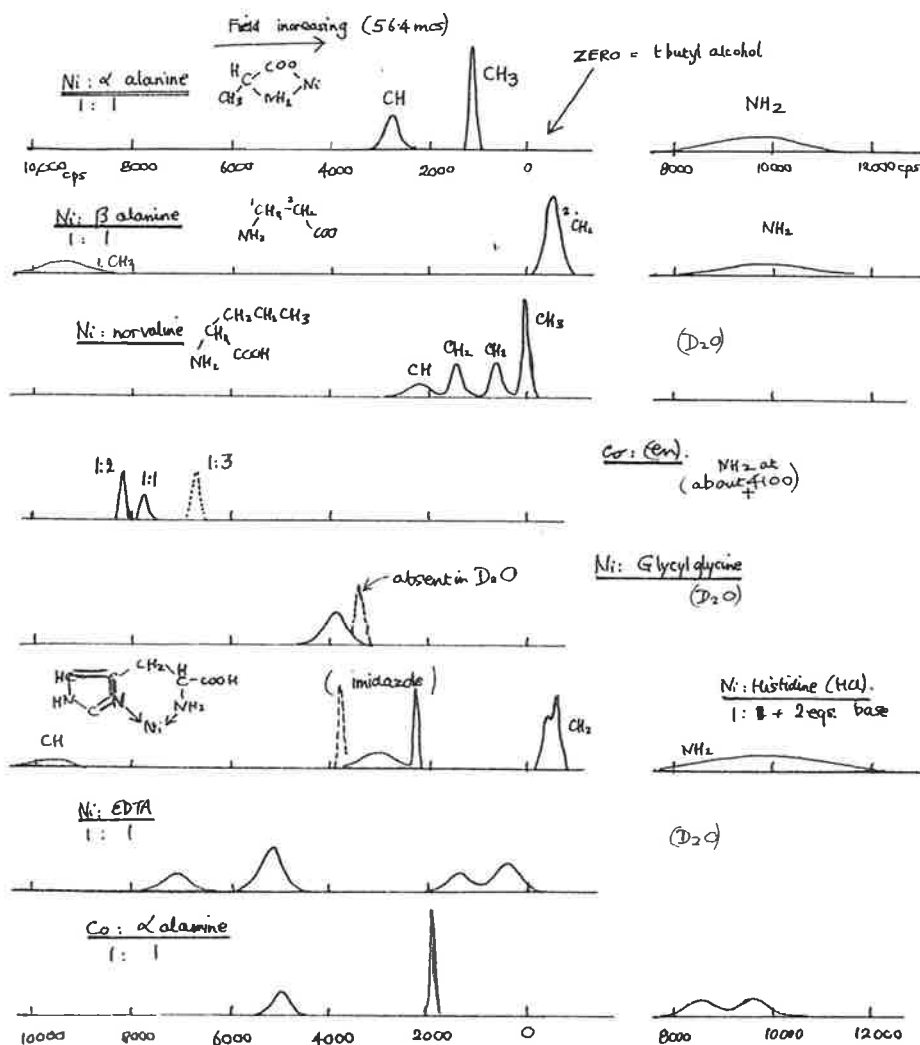
Cobaltous complexes are similar to those of nickel, although the lines are sharper and it is easier to see the difference between 1:2 and 1:1 positions. Another difference is that the cobalt solutions sometimes show more lines than expected, e.g., there are two NH lines in the spectrum of the 1:1 complex with L -α- alanine. The extra lines may be the result of residual " local field " effects,; cobalt complexes often show magnetic anisotropy.

I don't pretend to understand all that is happening in these spectra, but I think they are very interesting, a nd will be of some help in studying the structure and reactions of aqueous complexes.

Yours Sincerely,

L. Pratt

L. Pratt

Field increasing (564 mcs)

ZERO = t butyl alcohol

Ni : α alanine
1 : 1

H C COO Ni
CH₃ NH₂

CH

CH₃

NH₂

10000 cps   8000   6000   4000   2000   0   8000   10000   12000 cps

Ni: β alanine
1 : 1

¹CH₂ ²CH₂
NH₂   COO

²CH₂

NH₂

↳CH₂

Ni: norvaline
CH₂ CH₂ CH₃
CH₂
NH₂ COOH

CH   CH₂ CH₂   CH₃

(D₂O)

1:2   1:1   1:3

Co: (en)
NH₂ at
(about +100)

absent in D₂O

Ni: Glycylglycine
(D₂O)

HC   CH₂ H
HN   C-COOH
      N NH₂
         Ni
CH

(imidazole)

CH₂

Ni: Histidine (HCl).
1 : 1 + 2 eqs. base

NH₂

Ni: EDTA
1 : 1

(D₂O)

Co: α alanine
1 : 1

10000   8000   6000   4000   2000   0   8000   10000   12000

MODIFICATIONS OF THE ASSIGNMENTS OF THE ¹⁹F NMR SPECTRA OF NON-GEMINAL DIHYDRODECAFLUOROCYCLOHEXANES
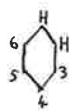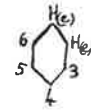
BY J. Feeney and L. H. Sutcliffe.

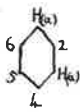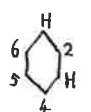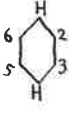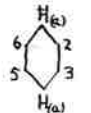Recently, we determined the ¹⁹F NMR spectra of some fluorinated cyclohexane derivatives[1] and made assignments based on a set of empirical rules. However, the data obtained by Tiers[2] for perfluorocyclohexane point the need for some modifications of the assignments of the dihydro derivatives. The presence of a chemical shift difference of 728 c/s at 40 Mc/s between the two geminal fluorine atoms[2] indicates that such atoms have not been affected appreciably by substituents and that the molecule is a fixed conformer. Because of the magnitude of this axial-equatorial chemical shift difference, the shielding rules given previously[1] need drastic revision. Since inductive effects operate equally on all the fluorine atoms in perfluorocyclohexane, the large shielding difference must be due to spatial interaction between fluorine atoms. Hydrogen substitution in the equatorial positions causes the geminal fluorine atoms in a neighbouring CF₂ group to be shielded equally in a fixed molecule as can be seen from an examination of the environment of the relevant fluorine atoms in the trans 1H/2H isomer (see table 3 of reference 1). It appears that the spatial effect is only operative when all the immediate neighbours of a given fluorine atom are themselves fluorine atoms. Spatial proximity to a hydrogen atom probably gives rise to an overall deshielding effect which is more important than inductive shielding effects. In the accompanying table is given our modified version

of the assignments of the spectra of the various dihydro isomers.
We have made use of the suggestion put forward by Thomas[3] that
axial fluorine atoms are less shielded than equatorial fluorine
atoms. Dr. J. I. Musher has kindly let us see a copy of his
paper prior to publication and from this we have taken some
ideas for the assignment of the cis 1H:2H and the cis 1H:3H isomers.

1. J. Feeney and L. H. Sutcliffe, Trans. Faraday Soc., 56, 1559, (1960)
2. G. V. D. Tiers, Proc. Chem. Soc., 391, (1960).
3. L. F. Thomas, private communication.

Assignments for the 40 Mc/s ¹⁹F NMR Spectra of Some Dihydrodecafluorocyclohexanes at Room Temperature.

Compound	Assignment	Band	Chemical Shift (c/s)
cis 1H:2H † b.p. 90.8°		1	1680
	3,3',6,6'*	2	1950
		3	2035
	4,4',5,5'	4	2250
	impurity?	5	5610
	1,2	6	5780
		7	5820
cis 1H:3H b.p. 90.9°	impurity?	1	1265
	2e,2a	2	1570
		4	1790
	4a,6a	3	1650
		5	1930
	4e,6e	6	2050
		8	2330
	5e,5a	7	2250
	impurity?	9	5550
	1e,3e	10	5730
		11	5770
cis 1H:4H † b.p. 85.4°	2,2';3,3'	1	1670
		2	1950
	5,5',6,6'	3	2080
		4	2370
	1,4	5	5940
		6	5980

Compound	Assignment	Band	Chemical Shift (c/s)
trans 1H/2H b.p. 70°	4a,5a	1	1790
		3	2070
	3e,3a,6e,6a	2	1860
		4	2155
		5	2420
		6	2550
	4e,5e	7	2840
	1a,2a	8	5850
		9	5900
mixture of trans 1H/3H trans⁺ 1H/4H b.p. 79°	2,2'	1	1815
		2	2010
	4,4',6,6'	3	2085
		5	2255
	5,5'		
	1,3	6	5860
		7	5905
	2e,2a,3e3a 5e,5a,6e,6a	4	2100
	1e,4e	8	6120
		9	6165

* Atoms marked with a prime are trans to the nearest hydrogen atom via the bonds in an interconverting molecule.

† The boiling points quoted in the paper by F. Johncock, W. K. R. Musgrave, J. Feeney and L. H. Sutcliffe, Chem. and Ind., 1514, (1959), require interchanging.

NATIONAL RESEARCH COUNCIL

CANADA

DIVISION OF APPLIED CHEMISTRY

OTTAWA 2, 10 April 1961.

Dr. A. Bothner-By,
Director of Research,
Mellon Institute,
4400 Fifth Avenue,
Pittsburgh 13, Pa.
U.S.A.

Dear Aksel:

Your subscription renewal letter arrived today and prodded my guilty conscience. I am sorry to have caused you that trouble. Before getting to technical details I would like to applaud you for the excellent biliography in MELLONMR. It is an extremely valuable feature.

Following are some details on chemical shifts as a function of conformation, and relative conformational energies for 2,5-dimethyl-2,5-dimethoxy-3,4-diphenylhexane.
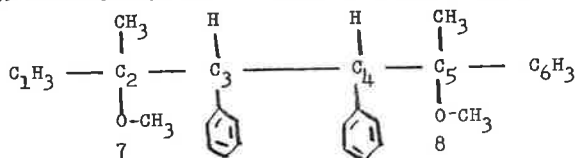
There is a high barrier to rotation about the 3-4, 2-7, and 5-8 bonds. No hindrance to rotation was observed for the other bonds. For the 3-4 bond the rate of rotation is less than 2.5 sec^{-1} at 390°K for both the meso and d, l isomers. The various possible conformations about the 3-4 bond are shown below.
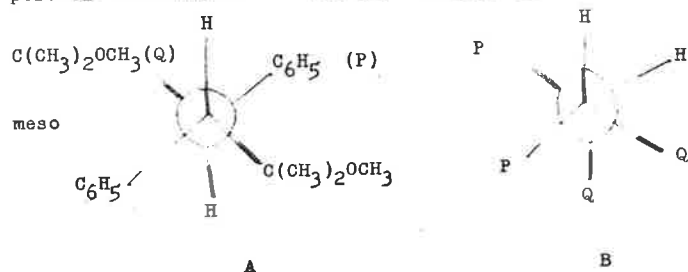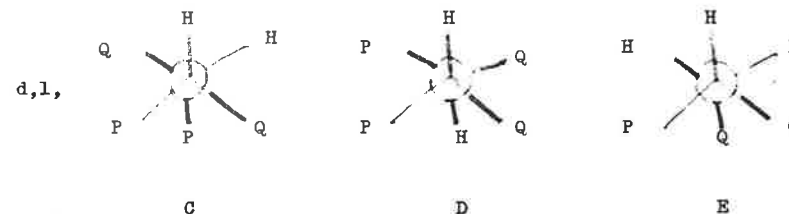

.... 2

Dr. A. Bothner-By, (continued)   10 April 1961.

d,l,

C   D   E

Conformation A is more stable than B by 1.7 ± 0.1 kcal/mole and conformation D is more stable than C by 1.9 ± 0.1 kcal/mole. No signals were observed which could be attributed to conformation E. The assignments to the various conformations were made by the following table. The shifts are in cycles / second to low field of tetramethylsilane with a transmitter operating at 56.4 Mc/sec. The doubling of the methyl resonance is caused by the same symmetry situation as in $CH_2X-CXYZ$.

	meso			d,l,		
Intense CH_3	23.8	42.7	A	52.0	63.1	D
Weak CH_3	52.1	62.2	B	25.8	42.9	C
Intense OCH_3		158.8	A		178.1	D
Weak OCH_3		177.0	B		160.6	C
Intense CH		186.5 †	A		191.6 †	D
Weak CH	179.9	188.9 *	B		188.5 *	C

B is the only conformation in which the hydrogens on carbon atoms 3 and 4 are non-equivalent. The positions given are the calculated chemical shifts. The spin coupling constant is 1.55 cycles which compares nicely with a predicted value of 1.7 cycles by the Karplus theory of spin coupling. Since the assignments can definitely be made for conformations A and B a comparison of the environment of the groups in the various conformations suggests the assignments to the d, l isomer. Although this is not positive proof it seems quite likely.

The preferred conformation about the 2-7 and 5-8 bonds is with the methoxyl group between the two methyls. Above 345°K another peak at 56.0 cycles appears for the meso isomer. Also the
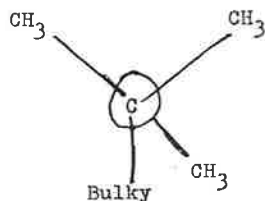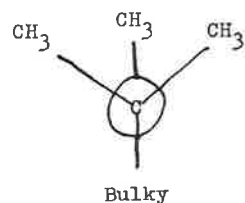
... 3

31-4

Dr. A. Bothner-By   (Continued)   10 April 1961.

peaks at 52.1 and 62.2 cycles are not of equal intensities. This is attributed to a slight contribution in conformation B when the methoxyl group is as in diagram G instead of the more stable F.

F   G

The intensities involved were too weak to get energies for this situation.

These compounds were supplied by Professor G.F. Wright. Other compounds in which the dimethyl methoxy is replaced by other groups are also being investigated.

Yours truly,

S. Brownstein

SB:gr

HUMBLE OIL & REFINING COMPANY
BAYTOWN, TEXAS

RESEARCH AND DEVELOPMENT

April 17, 1961

Dr. Aksel A. Bothner-By
Mellon Institute
4400 Fifth Avenue
Pittsburgh 13, Pennsylvania

Dear Dr. Bothner-By:

I regret that we have tarried so long in sending a contribution to MELLONMR. A description of Rollie Williams' method for measuring the magnitude of H_1, the rf magnetic field strength, is attached.

Our interest in knowing H_1 stems largely from the fact that quantitative NMR intensity measurements are a function of this parameter. The maximum per cent saturation, which is equal to the maximum per cent error, can be read directly from Figure 2 when the scan rate and H_1 are known. We have found that the rf field attenuators on the Varian instrument are accurate within a few per cent. Hence, it is necessary to determine H_1 at only a single db setting. The H_1 corresponding to other attenuator settings can then be readily calculated. In practice H_1 remains quite constant over a period of several months unless components of the circuit are replaced. Therefore, this measurement need not be repeated often.

Cotton and Klapper have pointed out that the separation between a central band and the first modulation side band is a function not only of the modulation frequency but also of the magnitude of H_1 (MELLONMR No. 28). The assumption that the separation is exactly equal to the modulation frequency can lead to significantly large errors when H_1 is large. They cite an error of about 1% for an H_1 of 1 milligauss and a modulation frequency of 25 cps. However, it is rarely necessary to operate at such a high H_1 level. At 0.1 milligauss the error is about 0.01%. If a higher H_1 is required for very weak signals the correction can be calculated if the magnitude of H_1 is known.

Sincerely yours,

Ferdinand C. Stehling

FCS:vct

Determination of RF Magnetic Field Strength, H_1

Principle:

This method for determining the rf magnetic field strength H_1 is based on the saturation of the area of the absorption mode as a function of the scan rate. For $S \to \infty$ ($S = \gamma^2 H_1^2 T_1 T_2$), the area under the absorption band as a function of H_1 and scan rate is given by *

1) $$\frac{A}{A_0} = \frac{1-e^{-2\alpha}}{2\alpha}$$

Here

2) $$\alpha = \frac{\gamma^2 H_1^2}{4r}$$ where γ = gyromagnetic ratio (for H^1 nuclei, $\gamma = 2\pi \cdot 4.26$ if H_1 in mGauss)

r = scan rate in cps/s

A = area under the band at a given α

A_0 = area under the band at $\alpha = 0$ (zero saturation), i.e. at infinite scan rate

For an inhomogeneously broadened band, the ratio $\frac{A}{A_0}$ is equal to the ratio of the corresponding peak heights. In this procedure, the signal height of an inhomogeneously broadened, readily saturatable band is determined at varying scan rates and constant H_1. A plot of the signal height versus $\frac{1}{r}$ extrapolated to $\frac{1}{r} = 0$ gives the signal height at infinite scan rate. Thus at any r, the ratio of the peak height to the extrapolated peak height gives $\frac{A}{A_0}$ for that scan rate. The corresponding value of α can then be calculated from 1). Knowing α, H_1 can be calculated from 2). Although 1) applies rigorously only when $S \to \infty$, the error introduced when $S > 100$ is negligibly small for practical purposes.

Procedure

1. A sample of benzene, tetramethylsilane, or some other compound which is easily saturated and gives a single band is selected, and the field homogeneity is deliberately decreased so that a broad band is obtained. The purpose of this is not only to secure an inhomogeneously broadened band but also to suppress "wiggles" which would otherwise occur at fast scan rates. However, the band should not be excessively broadened because at very high field gradients molecular self-diffusion will lead to erroneously small measured values of H_1. Care should also be taken to

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* R. B. Williams, Ann. N. Y. Acad. Sci. 70, 763 (1958). This result comes from the exact solution of eq.(7), p.892, for $S = \infty$; it corresponds to the bottom curve of Figure 1, p.893.

---

obtain only the absorption mode signal because the admixture of a dispersion mode component will decrease the accuracy of the determination, especially at large values of α.

2. Scan the band at different rates at a constant H_1 setting. About five or more relaxation times should be permitted between scans to allow nuclear polarization to be restored.

3. Plot the peak height against the reciprocal of the scan rate $(\frac{1}{r})$ and extrapolate to $\frac{1}{r} = 0$. Tabulate $\frac{A}{A_0}$, which is equal to the ratio of the peak height at each scan rate to the extrapolated peak height.

4. H_1 may now be calculated as follows. For each $\frac{A}{A_0}$ value determine the corresponding value of α. Since 1) cannot be solved explicitly for α, it is necessary to construct a plot of $\frac{A}{A_0}$ versus α (Figure 1) and to read the value of α corresponding to a particular value of $\frac{A}{A_0}$ from the graph. Now H_1 may be calculated from 2) for each scan rate. Of course, the scan rate must be accurately known in order to obtain an accurate H_1.

Alternatively, H_1 may be read directly from the curves presented in Figure 2. Here the per cent saturation, which is equal to $100\left(1 - \frac{A}{A_0}\right)$, is plotted against H_1 for various scan rates. These particular curves apply only to hydrogen nuclei.

Typical Determination

Sample: Cyclohexane
RF Setting: 40 db. attenuation of maximum H_1
Data:

r	$\frac{1}{r}$	Relative Signal, $\frac{A}{A_0}$	$100\left(1-\frac{A}{A_0}\right)$	H_1 (From Figure 2)
1 cps/s	0.1	0.545	45.5	0.073 milligauss
2	0.5	0.721	27.9	0.065
5	0.2	0.873	12.7	0.063
10	0.1	0.919	8.1	0.069
∞ (Extrapolated)	0	1.000	0	--
			Average	0.068 milligauss

Advantages

The advantages of this method for determining H_1 are:

1) It is simple, rapid, and requires no accessory equipment.

2) The method is directly applicable to the determination of H_1 values of the order of magnitude used in typical quantitative analytical determinations, i.e., 0.01 to 0.1 milligauss.

(F. C. Stehling, R. B. Williams)

FCS:vt

$$\frac{A}{A_0} = \frac{1 - e^{-2\alpha}}{2\alpha}$$

where

$$\alpha = \frac{\gamma^2 H_1^2}{4r}$$

$$\alpha = \frac{179 H_1^2}{r} \text{ for } H_1 \text{ in milligauss and } r \text{ in cps/s}$$
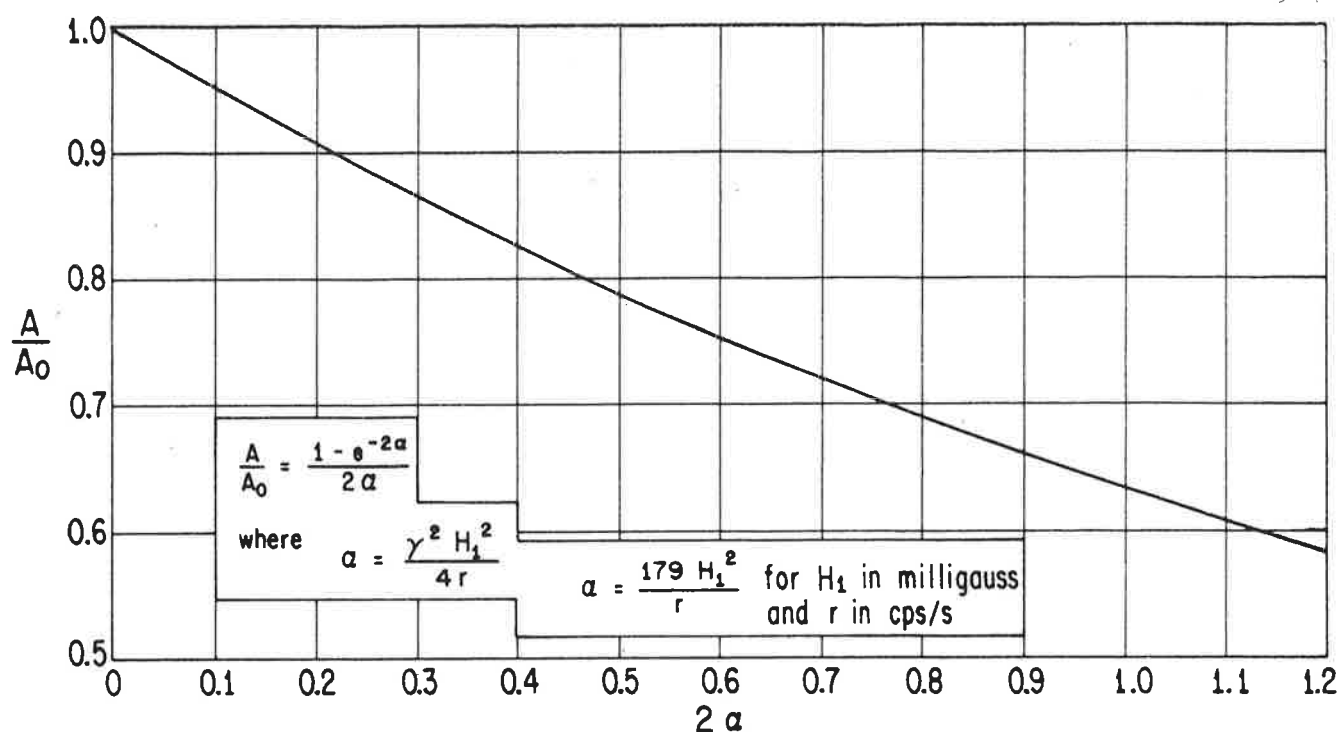
Fig. 1. SATURATION AS A FUNCTION OF 2α

FIGURE 2

Per Cent Saturation of Area as a Function of H_1 and Scan Rate
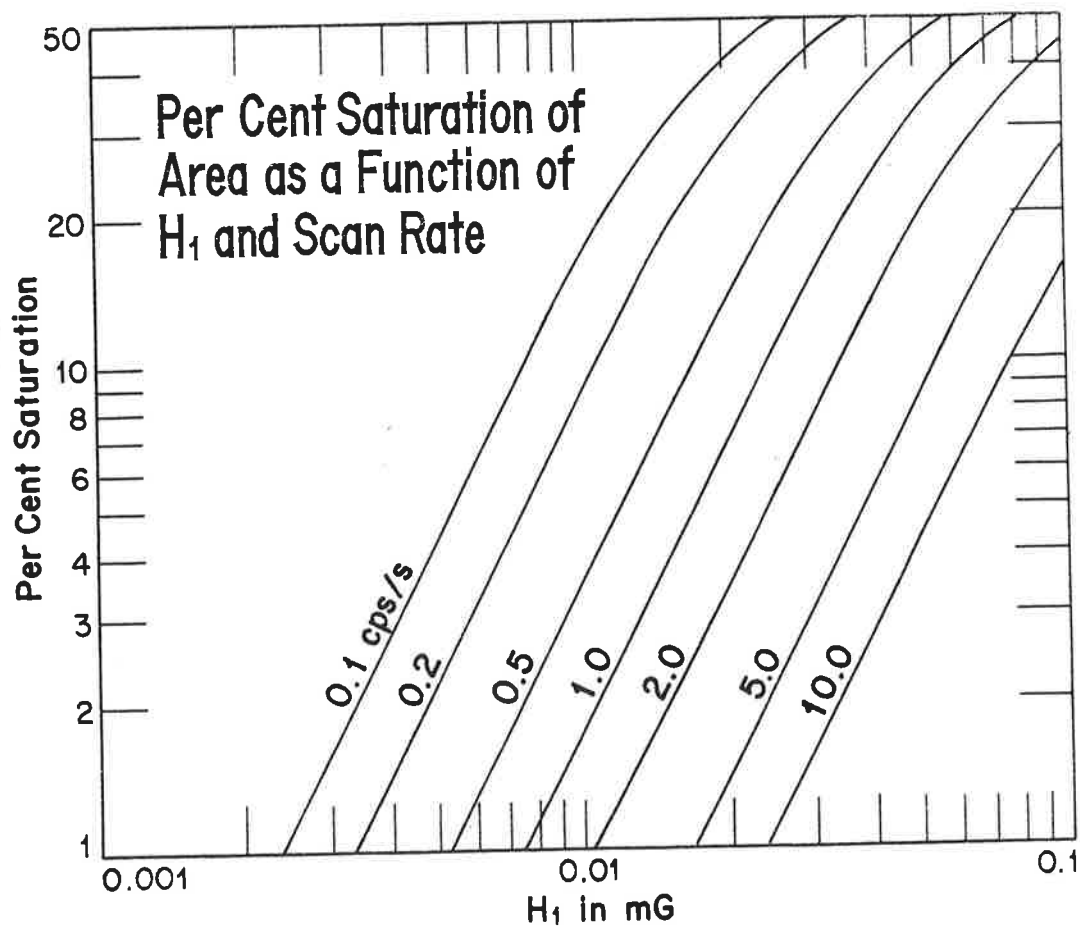
THE UPJOHN COMPANY

FINE PHARMACEUTICALS SINCE 1886

KALAMAZOO, MICHIGAN

April 14, 1961

SCIENTIFIC ADMINISTRATION
301 HENRIETTA STREET

Dr. Aksel A. Bothner-By
Director of Research
Mellon Institute
4400 Fifth Avenue
Pittsburgh 13, Pennsylvania

Dear Dr. Bothner-By:

The attached spectra were abstracted from a seminar on NMR Spectroscopy of Steroids and may be of interest to readers of the Mellon NMR Letter. They illustrate the effectiveness of NMR studies on steroids and describe a convenient method for predicting the absorption frequencies for the angular methyls from the magnetic anisotropy contributions of the various substituent groups.

Figure 1 summarizes the special features of steroids which are important in NMR spectroscopy. The nucleus is rigid; it does not ring convert and it tumbles poorly. Many of the protons have short transverse relaxation times causing broad absorption lines. The nuclear protons tend to be in similar environments and to couple with several neighbors. The resulting broad multiplets overlap and result in a broad methylene envelope in the range 170 to 220 cps.[1]. The absorptions of greatest value in steroid work, therefore, are those which protrude from the envelope or fall outside of it. These include methyl groups, methylenes adjacent to multiply bonded systems, hydrogens on carbons bearing O, F, Cl, or N, hydrogen on oxygen, olefinic hydrogens, etc. (see Figures 2-4).

Shoolery and Rogers[2] have already shown that the resonance frequencies of the angular methyl groups, which give intense sharp lines owing to freedom of rotation, are in part determined by the magnetic effects of substituents in the rings and side chain. These effects include (a) changes in electron shielding due to inductive effects transmitted through bonds or across space, (b) second order paramagnetic effects due to changes in bond angles and hybridizations, and (c) magnetic anisotropy arising from position of certain substituents. The first two are usually relatively small effects because substituents must be at least four atoms away. The last one appears to be of greatest magnitude and is approximately additive except in cases where a change in geometry at or near a bridgehead causes a large displacement of the anisotropic substituent such as 3-keto-allo, vs. 3-keto-normal vs. 3-keto-Δ^4 systems (see Figure 1).

In a study of about 800 steroids it was convenient to make an empirical correlation of angular methyl absorption frequency with structure by choosing a basic steroid structure and tabulating shift contributions of various substituents (see Figures 5,6,7,10, and 14). The basic steroid selected (I)
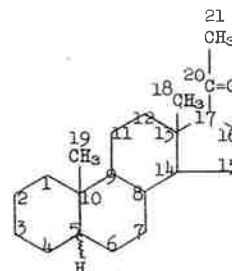
I

was an imaginary one having an unspecified configuration at C-5 and a ketone at C-20. In this system the 19-hydrogens absorb[1] at 228 cps. and the 18-hydrogens at 241 cps. Thus the contribution for allo (5αH) was +5 ± 0.3 cps., etc. (see Table I). In this way the 19-methyl contributions from 142 structural modifications have been tabulated and 151 have been tabulated for the 18-methyl[3].

The calculations can be extended to other methyls, too, such as, for example, the 6-methyls[4] where the basic steroid structures are 6α- and 6β-methyl-3β-hydroxyallopregnanes (see Figure 6).

An interesting spin-spin splitting by fluorine is seen in Figure 7 where it is apparent that the 19-hydrogens are split by the axial (closer) fluorine. The splitting of the 4-hydrogen in the 6β-fluoro isomer may arise from the nearly coplanar 6α-hydrogen. The pseudo axial 17α-fluorine (in Figure 8) also splits the 18-hydrogens. Additional fluorosteroids are presently under investigation.

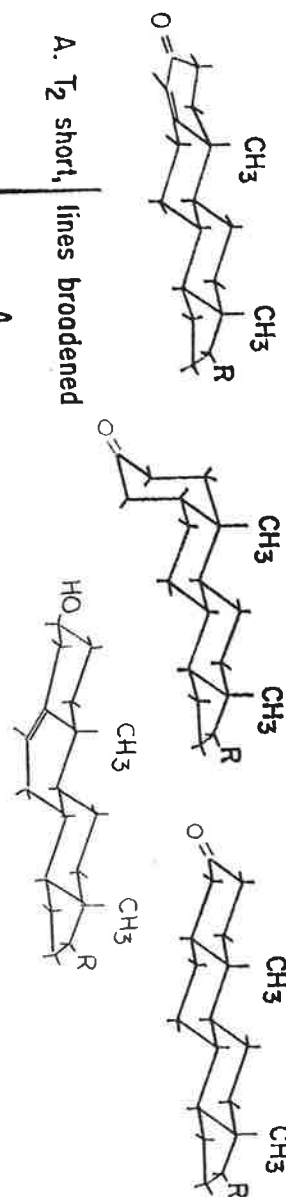Some additional examples of the application of NMR studies to steroid structure problems are summarized in Figures 8-17.

The spectra were observed at room temperature on a Varian 4300-2 spectrometer operating at 60 mc. (unless otherwise noted) on solutions (ca. 0.3 ml., ca. 0.15 molar) of the steroids in deuterochloroform. The spectra were calibrated against internal tetramethylsilane using the audiofrequency side-band technique.

TABLE I.   Some Examples of Substituent Effects on the Absorption Frequency

of the 19-Methyl Group in Steroids

Substituent	Range	No. of Examples	Average	Standard Deviation
5αH	+4.5 to +6	10	+5	± 0.5
5βH		2	-5	
3-keto-5αH	-8 to -9.5	10	-9	± 0.4
3-keto-5βH	-7 to -10.5	19	-9	± 0.5
Δ^4	-10 to -11	3	-10	
Δ^5		1	-7.5	
3-keto-Δ^4	-17.5 to -21	48	-19[*]	± 0.8

[*] a preliminary value of 18 was used in several of the figures.

References.-

1. All frequencies are reported in cps. at 60 mc. relative to tetramethyl-silane as 280 (water = 0, benzene = -102 cps.) unless otherwise noted.

2. J. N. Shoolery and M. T. Rogers, J.A.C.S., 80, 5121 (1958). See also J. S. G. Cox, E. O. Bishop, and R. E. Richards, J. Chem. Soc., 1960, 5118.

3. A publication on these data is in preparation.

4. G. Slomp and B. R. McGarvey, J.A.C.S., 81, 2200 (1959).

5. Prepared by Dr. E. V. Jensen, University of Chicago.

Very truly yours,

George Slomp

George Slomp
Physical and Analytical Chemistry

prv

SPECIAL FEATURES OF STEROIDS

FIGURE 1.--

I. Rigid Rings

A. T$_2$ short, lines broadened

B. Conformational effects axial different from equatorial splitting related to dihedral angle

C. Magnetic anisotropy

Angle, °	Coupling Constant, cps.	
	Calc'd	Found
0	8.2	
20	6.0	
60	1.2	2-4
90	-0.28	
120	2.2	
150	6.9	
180	9.2	5-8

II. Many interactions

III. Many similar H

IV. Useful data obtained outside CH$_2$ envelope

13-Me

4α-Me

10-Me

4β-Me

17α-Me

4α-Me
13 -Me

228

207

4β-Me
10 -Me
17α-Me

ACETONE
(SOLVATE)

ACETONE
(SOLVATE)

IMP. IN
PYRIDINE

151

280

266

255 248

245 248

211

OH CH₃

CH₃ CH₃

FIGURE 4. - Some Absorptions Occurring Outside CH₂ Envelope in Deutero-
chloroform and in Pyridine

-7-
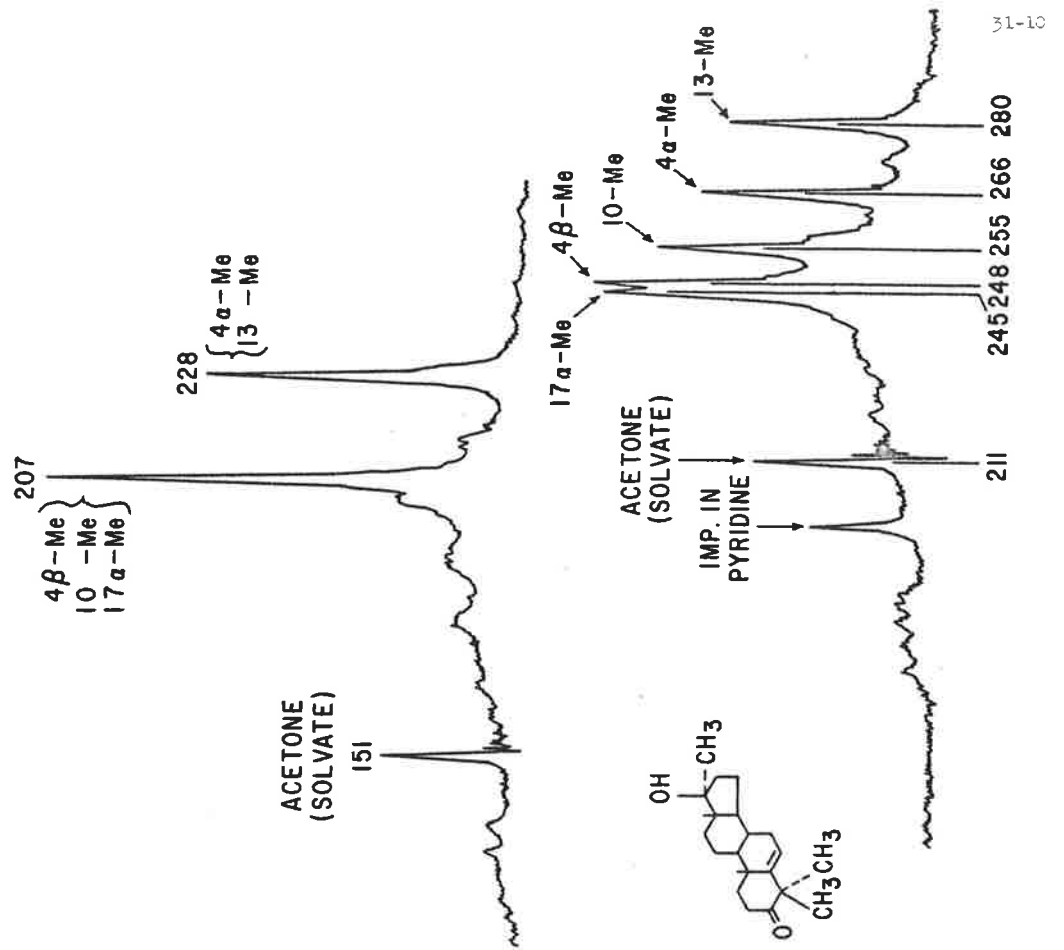
FIGURE 2. - Some Absorptions Occurring Outside CH₂ Envelope

11.5 mg. /.2 ml. (0.2 molar)

65 down
4.00
10 x 40

19-H

21-H

18-H

6β-CH₃

2,12-H

1,7,14,15,
16-H

4-H

9,17-H

6αH

-62   0   106 125 141 155   191 202 209   240
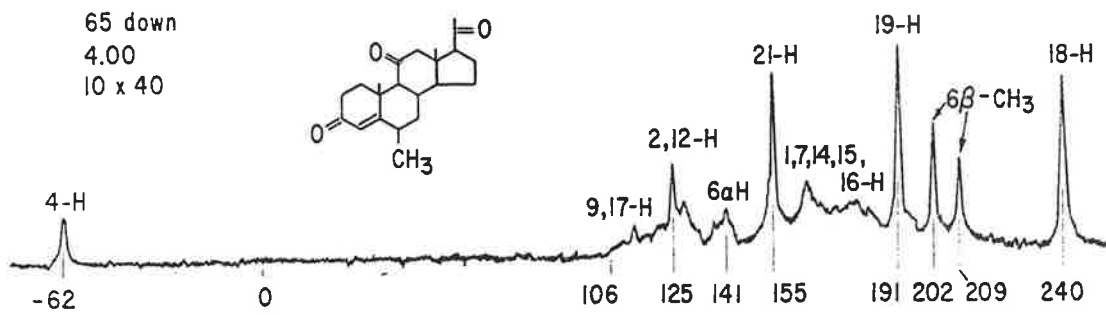
FIGURE 3. More Absorptions Occurring Outside CH₂ Envelope

-5-

70 d
3.00
10 x 40

60 mc

65 d
4.00
10 x 40

-22   121 137 155 172   202   224 242

cps AT 60 mc. (RELATIVE TO WATER)

-6-

FIGURE 5.- Magnetic Anisotropy Contributions of Substituents to Absorption
Frequencies of Angular Methyl Groups

FIGURE 6.- Magnetic Anisotropy Contributions of Substituents to Absorption
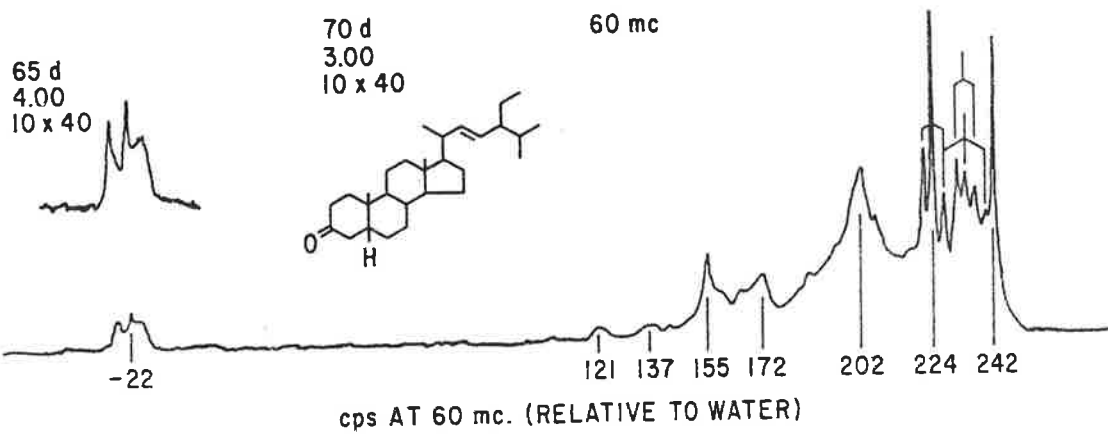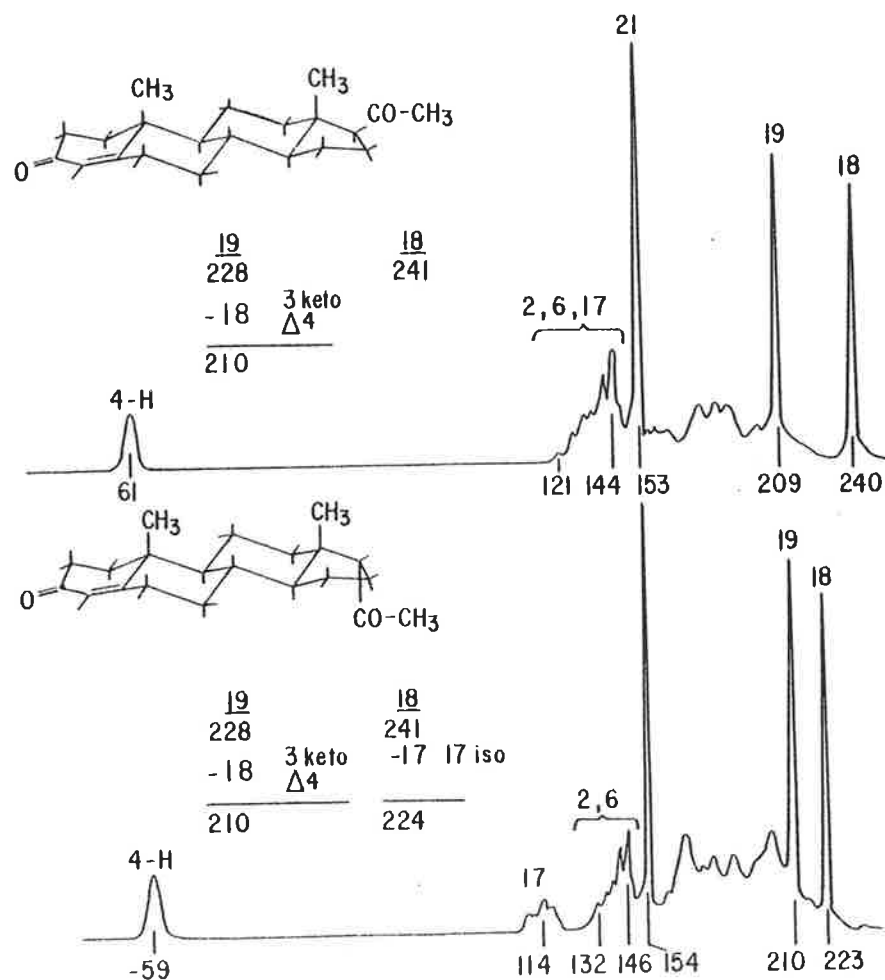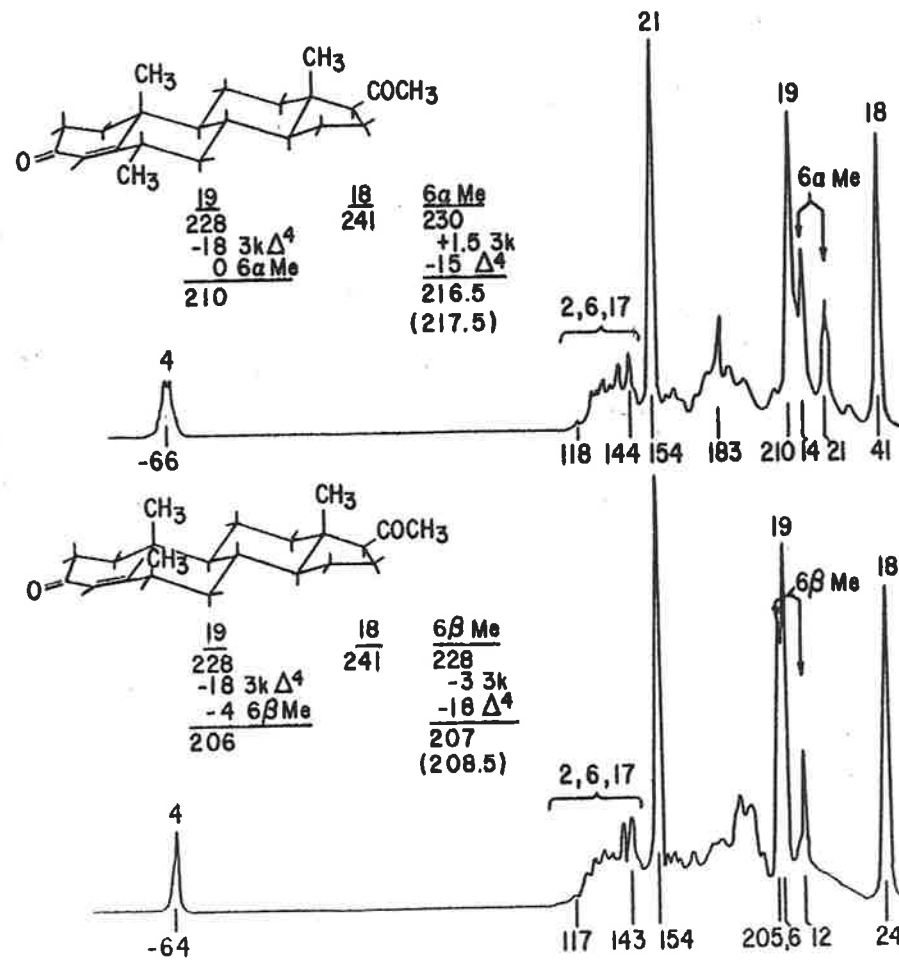Frequencies of Methyl Groups

Figure 5 (top spectrum):

CH$_3$ CH$_3$ CO-CH$_3$ O=

$\frac{19}{228}$ $\frac{18}{241}$

-18 3 keto Δ^4

$\overline{210}$

4-H 61

2,6,17

21 19 18

121 144 153   209 240

Figure 5 (bottom spectrum):

CH$_3$ CH$_3$ CO-CH$_3$ O=

$\frac{19}{228}$ $\frac{18}{241}$

-18 3 keto Δ^4 -17 17 iso

$\overline{210}$ $\overline{224}$

4-H -59

2,6   17

21 19 18

114 132 146 154   210 223

Figure 6 (top spectrum):

CH$_3$ CH$_3$ COCH$_3$ O= CH$_3$

$\frac{19}{228}$ $\frac{18}{241}$ $\frac{6\alpha Me}{230}$

-18 3k Δ^4 +1.5 3k

0 6α Me   -15 Δ^4

$\overline{210}$ $\overline{216.5}$

(217.5)

4 -66

2,6,17

21 19 6α Me 18

118 144 154 183 210 14 21 41

Figure 6 (bottom spectrum):

CH$_3$ CH$_3$ COCH$_3$ O= CH$_3$

$\frac{19}{228}$ $\frac{18}{241}$ $\frac{6\beta Me}{228}$

-18 3k Δ^4 -3 3k

-4 6β Me   -18 Δ^4

$\overline{206}$ $\overline{207}$

(208.5)

4 -64

2,6,17

19 6β Me 18

117 143 154   205,6 12   241

FIGURE 7.- Magnetic Anisotropy Contributions of Substituents to Absorption Frequencies of Angular Methyl Groups

CH₃   CH₃   COCH₃

$\frac{19}{228}$ $\frac{18}{241}$

-18 3kΔ4 (240)

6β − 16αF

$\frac{}{209}$

(208)

4

-83 -60 -42 -11 +6

2,17

118 142 153   208 240

21 19 18

CH₃ CH₃ COCH₃

$\frac{19}{228}$ $\frac{18}{241}$

-18 3kΔ4 (239)

6α − 7 6βF

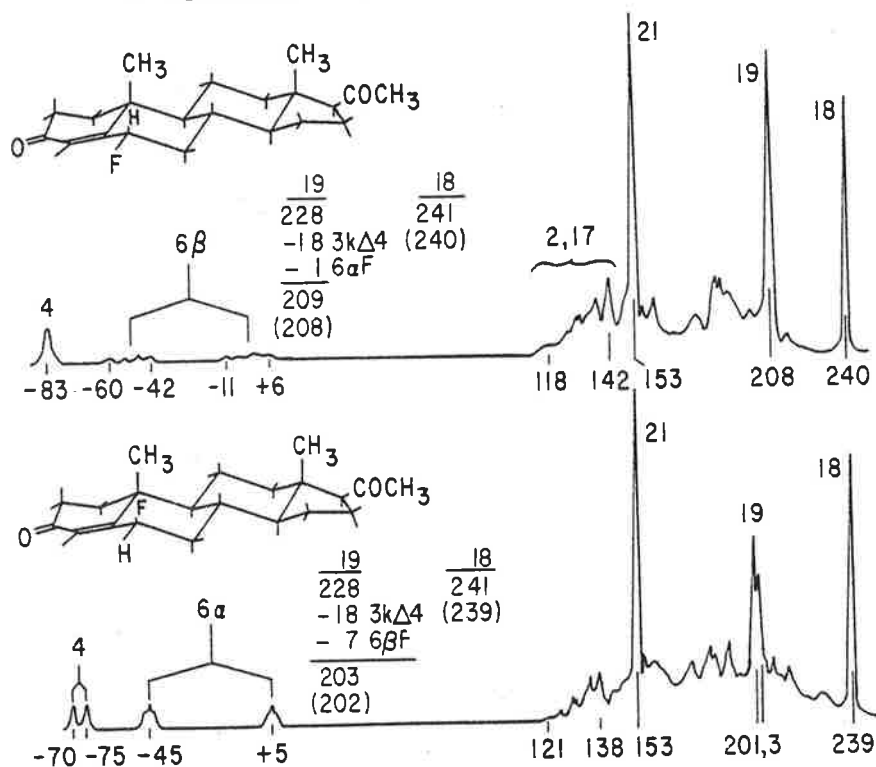$\frac{}{203}$

(202)

4

-70 -75 -45   +5

121 138 153 201,3 239

21 19 18

FIGURE 8.- Examples. This trifluorinated steroid[5] was identified as structure 3 from the absorption of the 13- and 21-hydrogens.

A   F C F   =O H

AcO   H

B   H C F   =O F

AcO   H

J=53

J=3

OAc   19   18

21   6   3   4,7

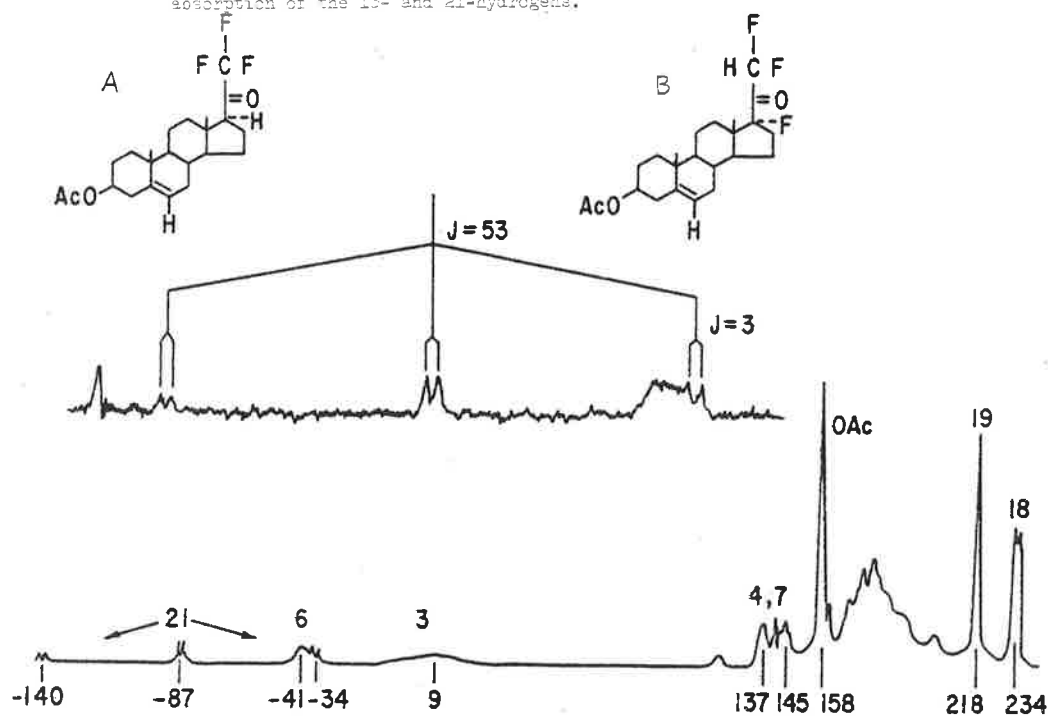-140   -87   -41 -34   9   137 145 158   218 234

FIGURE 9.- Examples. This dehydration product was shown to be an approximately 65 to 35 mixture of isomeric olefins A and B. Spectrum obtained at 40 mc.

A

B

21A

21B

19A

12A

19B

18B 18A

4 11A

11,12B

-67 -57 -39 -33 -27
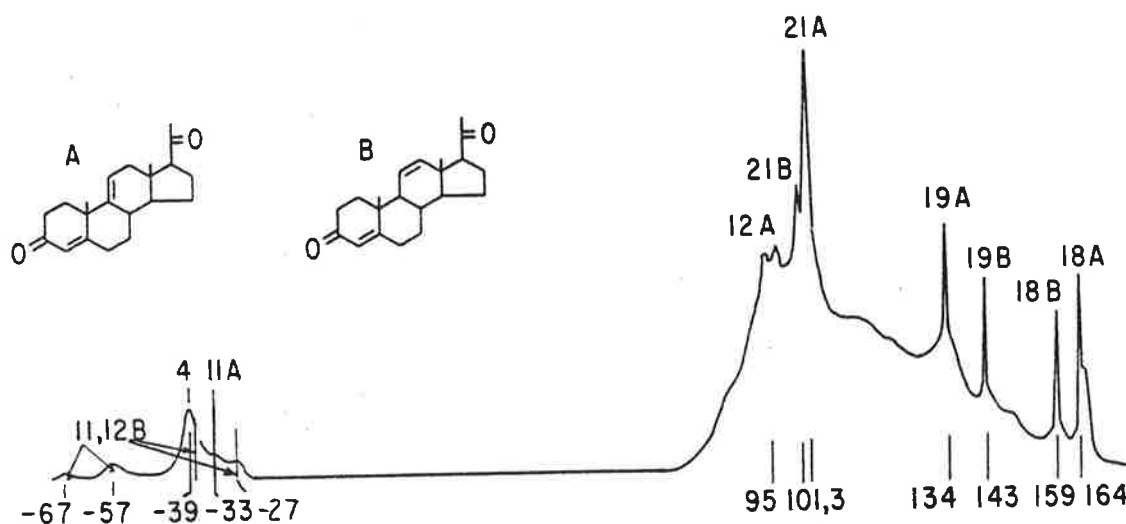
95 101,3   134 143 159 164

FIGURE 10.- Examples. These isomeric Favorski esters were assigned structures from the shifts of the 18-hydrogens and the perturbation of the 12-methylene. Spectra obtained at 40 mc.
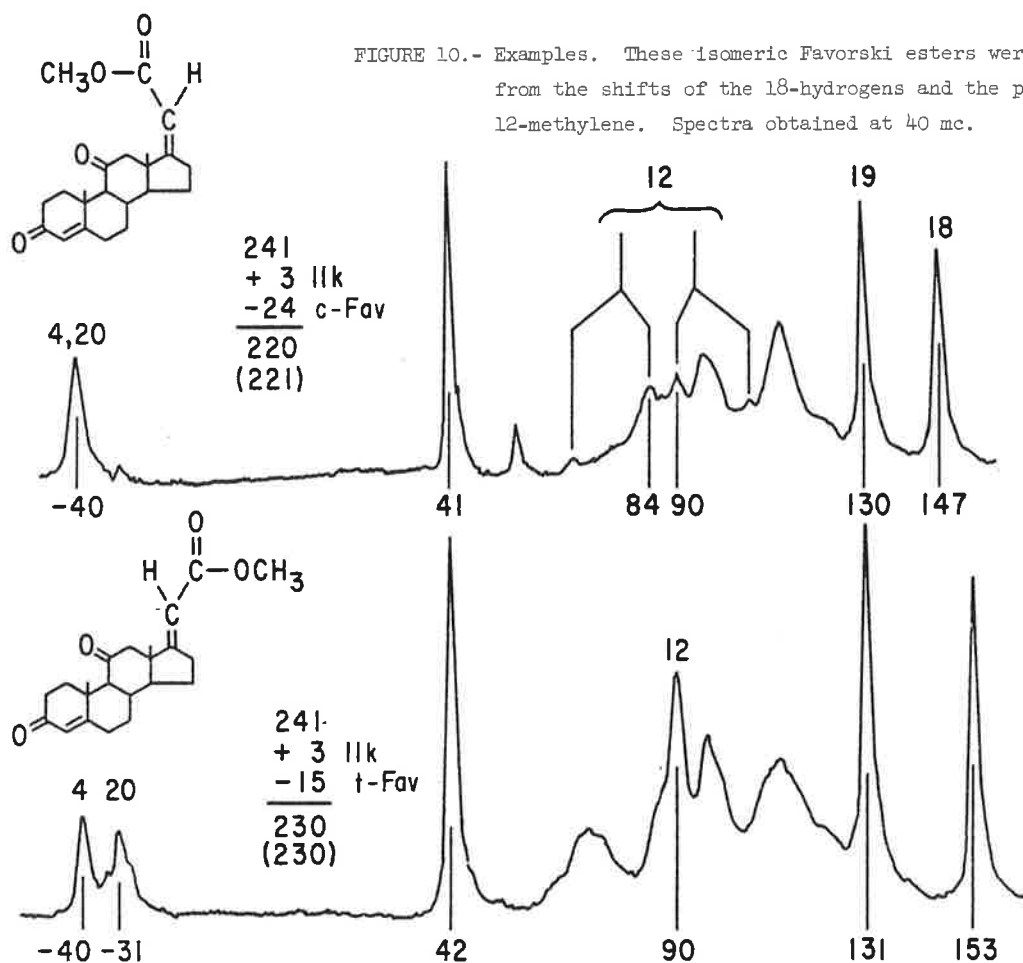
CH_3O-C O H

12

19

18

241
+ 3 llk
−24 c-Fav
―――
220
(221)

4,20

-40   41   84 90   130 147

H C−OCH$_3$ O

241
+ 3 llk
−15 t-Fav
―――
230
(230)

4 20

12

19

18

-40 -31   42   90   131   153

FIGURE 11.- Examples. The product from the reaction of A with SOCl₂ and R₃N was identified as
the allylic isomer B from the absorption of the 16-, 20-, and 21-hydrogens. Note the
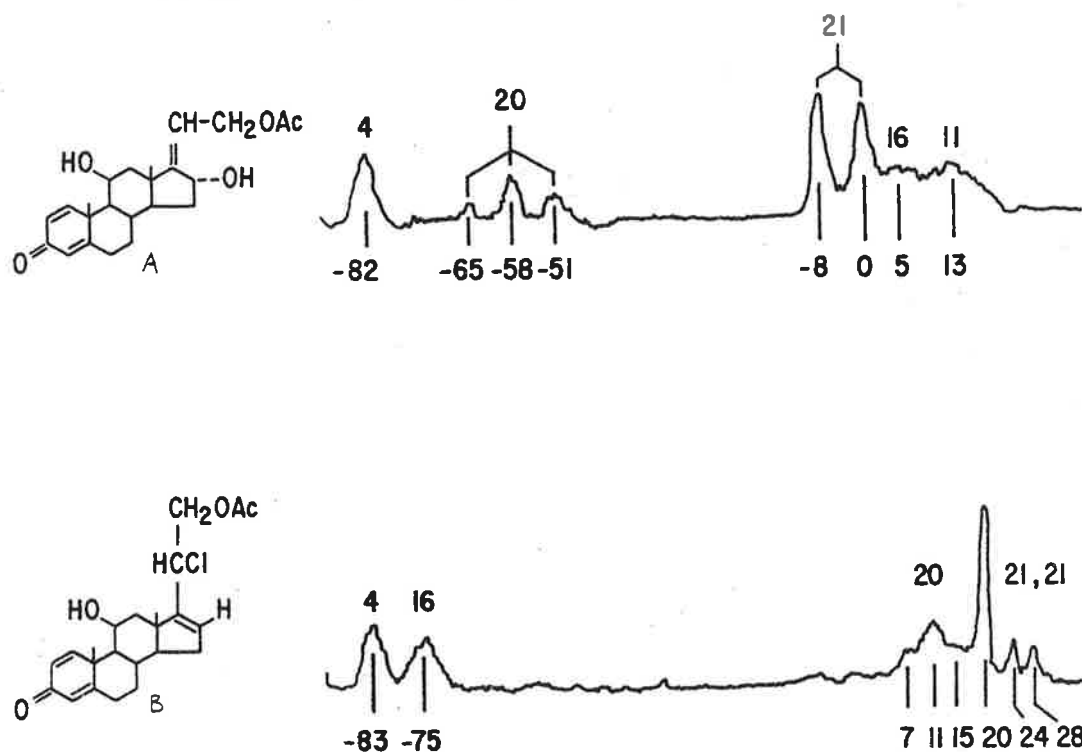AB₂ system with J/δ of about 0.25.

FIGURE 12.- D-Homosteroids. This rearrangement product of A was identified as B from the
16-methylene absorption and the coplanar intramolecularly bonded OH absorption
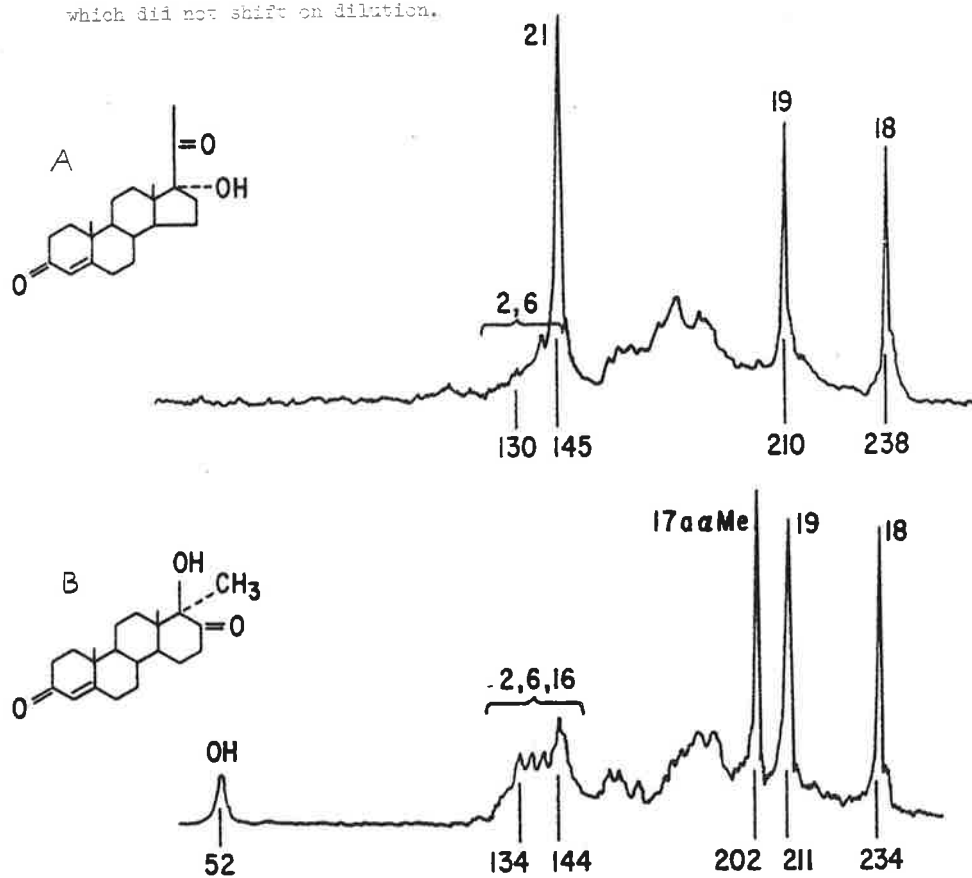which did not shift on dilution.

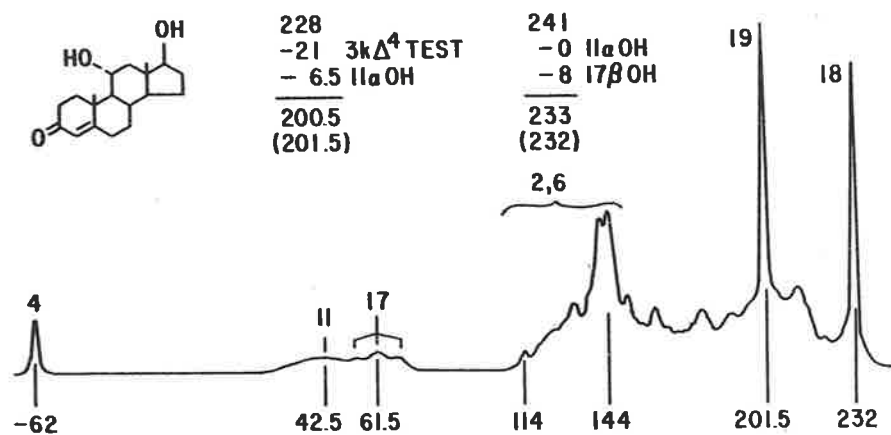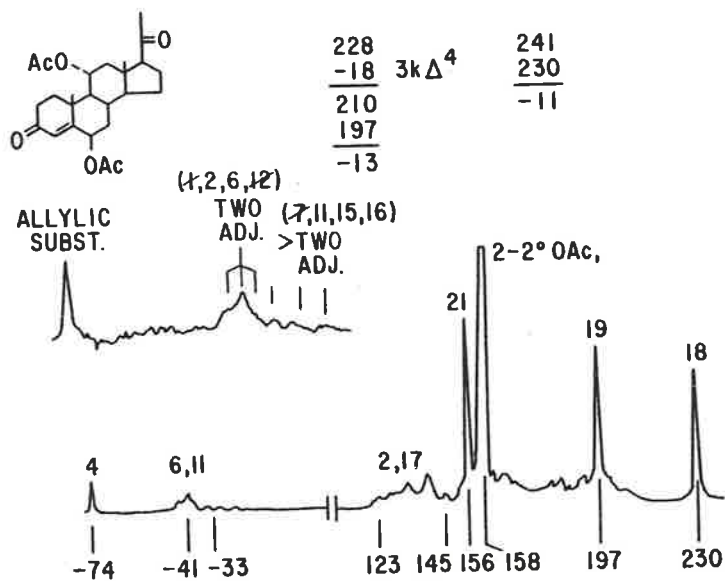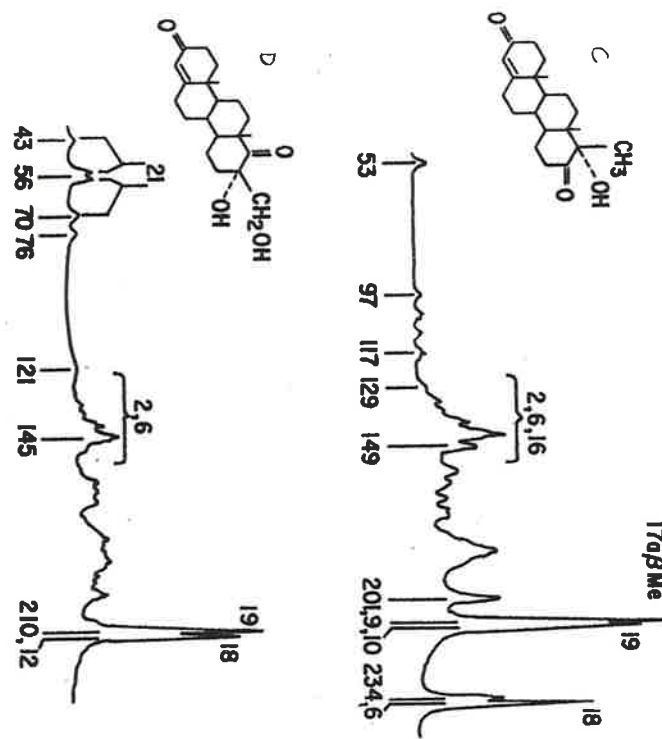FIGURE 14.- Examples. Identification of product from biooxidation of testosterone. Proof of 11α-hydroxylation.

228
-21 3k∆⁴ TEST
- 6.5 11αOH
───
200.5
(201.5)

241
- 0 11αOH
- 8 17βOH
───
233
(232)

2,6

19

18

4

11

17

-62

42.5 61.5

114   144

201.5   232

FIGURE 15.- Examples. Identification of diacetate from biooxidation of progesterone.

228
-18 3k∆⁴
───
210
197
───
-13

241
230
───
-11

ALLYLIC
SUBST.

(1,2,6,12)
TWO
ADJ.

(7,11,15,16)
>TWO
ADJ.

2-2° OAc,

21

19

18

4

6,11

2,17

-74

-41 -33

123 145 156 158

197   230

FIGURE 13.- Additional D-Homosteroids. Note that C is contaminated with some isomer B.

C

CH₃
OH
O

17αβMe

53

97 117 129 149

2,6,16

201,9,10 234,6

19

18

D

CH₂OH
OH

43 56 70 76

121 145

2,6

210,12

19

18

April 24, 1961.

IN YOUR REPLY
REFER TO FILE NO.
15.7

* Dr. Aksel Bothner-By
Mellon Institute
4400 Fifth Avenue
Pittsburgh 13, Pa.

Dear Dr. Bothner-By,

I should very much appreciate your including this letter in MELLONMR. It is a follow-up on earlier work (MELLONMR 25, p.14 and J.Phys.Chem. 65, 491 (1961)) and also reports on some work in progress on syn-anti isomerism in ketoximes. One result, namely that on cyclohexanone oxime (see below) is in agreement with that by T.F. Page, Jr., and R.J.Jakobsen (MELLONMR 29, p.10).

Most of the data presented below were obtained after a cooling-water control and shim coils had been installed in our spectrometer; both devices resulted in vastly improved performance of the instrument. Most of the conclusions of the earlier work cited are unchanged, but a major new result is that aromatic groups need not always be present to reveal the non-equivalence of α and α' protons relative to the oximino group. The case of diisopropyl ketoxime, where the spectrum of a 50% CCl_4 solution showed two methine septets separated by about 54 c/s, has already been reported. Data for similar cases are given in the following table. (All data refer to $H_0 = 60$ mc/s.)

Line Separations δ (c/s) for Protons in Symmetrical Ketoximes

Oxime of	Benzene Solution %	δ	CCl_4 Solution %	δ
Acetone	10	5.0	10	1.0
Diethyl Ketone	50	13.5	20	7.5[a]
	10	19.8		
Cyclobutanone	25	6.3	25	0
Cyclopentanone	10	8.7	10	?[b]
Cyclohexanone	30	13.8	30	9.8

a about the same in pure liquid   b ill-resolved multiplet

- 2 -

Again benzene enhances the separation of peaks, and it still may be true that in some cases an aromatic solvent is required to effect a significant separation. If the methyl hydrogens in acetone oxime are substituted symmetrically by methyl groups, the separation of lines for any remaining hydrogens increases. In the cyclo-alkanone oximes listed, the separation of α and α' proton lines becomes "easier" with increasing ring size.

In an attempt to gain further insight into the steric effects undoubtedly responsible for this situation, as well as into the role of the ring-current effect, the spectra of two structurally similar molecules were studied: that of phenyl-acetone oxime (cf. also earlier work) and that of cyclohexylacetone oxime.

Line Separations (c/s) for α Protons in Cyclohexylacetone Oxime
and Phenylacetone Oxime

Solvent	Cyclohexylacetone Oxime δ_{CH_2}	δ_{CH_3}	Phenylacetone Oxime δ_{CH_2}	δ_{CH_3}
Carbon Tetrachloride	5.5	0	14.8	0
Benzene	11.6	2.6	18.2	7.0

These figures were obtained from 20 % solutions of the isomeric mixtures of the oximes as obtained in their preparation. In both cases the non-equivalence of the methylene protons in the syn and anti isomers was revealed regardless of the aromatic character of the solvent, whereas the methyl protons gave two resonances only in benzene solution. Here again the CH_2 shifts are larger than the CH_3 shift. In both compounds, a methyl hydrogen has been substituted by a relatively bulky group, which is aromatic in one and non-aromatic in the other. Regardless of the aromatic character of the substituent group, the non-equivalence of the methylene hydrogens in the syn and anti forms appears both in CCl_4 and C_6H_6 solutions, whereas that of the methyl hydrogens appears only in C_6H_6. Thus it looks as though the aromaticity of a substituent group is less important than its shape, as far as making the syn and anti hydrogens look non-equivalent is concerned.

In non-aromatic solvents the separation of, say, the methylene quartets in di-ethyl ketoxime can be regarded as a true chemical shift attributable largely to the oxygen atom (cf. W.D. Phillips, Ann.N.Y.Acad.Sci., 70,817(1958); also E.Lustig, J.Phys.Chem. loc.cit.). The purely chemical shift and that caused by the ring-current effect of the solvent appear to be in the same direction.- Thus the quartet at lower field belongs to the syn-methylene protons. Such an assignment is of importance in the determination of isomeric species in unsymmetrical ketoximes, examples of which are given above and in reports on earlier work. The considerations about the sequence of resonance lines given in the latter apply in the present cases as well. It appears that in all cases of methyl ketoximes $CH_3-C(NOH)-R$ studies so far, the syn-methyl form is the more abundant one. This is plausible for steric reasons.

Best regards and good wishes for continues success of MELLONMR.

Sincerely yours,

Ernest Lustig

31-16

April 24, 1961

Dr. Aksel A. Bothner-By
Assistant Director of Research
Mellon Institute
4400 Fifth Avenue
Pittsburgh 13, Pennsylvania

Dear Dr. Bothner-By:

In the last issue of MELLONMR, Dr. J. Lee asked whether the α proton in 2-fluoropyridine is broadened by ^{14}N quadrupole relaxation. This is in fact the case for pyridine itself as shown by ^{14}N-proton double resonance experiments. The effect of decoupling the ^{14}N spin from the α protons is shown in Figure 1. The spectra of the α protons of pyridine in the pure liquid taken at 40 Mc/s. are shown with and without the second radio frequency field at the ^{14}N resonance frequency.

A similar broadening of a proton resonance two bonds removed from an ^{14}N nucleus has been observed in N-methylformamide. In this molecule, the CH resonance shows no structure in the absence of decoupling, and indeed the CH resonance can hardly be resolved from the broader NH peak. The effect of ^{14}N-proton double resonance on the CH and NH groups of N-methylformamide in water solution is shown in Figure 2. The proton spectrum was taken at 60 Mc/s. with a strong r.f. field at the ^{14}N resonance frequency. In addition to ^{14}N-proton coupling through two bonds, the spectra of this molecule show rather complicated solvent effects. The coupling constant between the CH and NH protons, as well as the chemical shifts of these protons depend on the solvent. Similar solvent effects upon coupling constants have been noticed in ^{15}N substituted formamide.[1]

Broadening of the β and γ protons as well as the α protons of the pyridinium ion has been noticed by Smith and Schneider.[2] However, double-resonance at the ^{14}N resonance frequency apparently has no visible effect on the ring protons at least at 40 Mc/s. It is probable that a second broadening mechanism is present. Exchange of the NH proton could effectively broaden the ring protons, depending on the magnitude of the NH-ring proton coupling constant. In a 5% solution of pyridine in trifluoro-acetic acid, the exchange rate of the NH proton is low enough so that the triplet arising from ^{14}N coupling to the NH proton can be observed.[2] This triplet shows the relative line widths, 3:2:3, characteristic of ^{14}N quadrupole relaxation. In fact, by observing the change in structure of this

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Dr. Aksel A. Bothner-By   -2-   April 24, 1961

triplet as a function of the frequency of the second r.f. field, the ^{14}N resonance frequency can be determined. The appearance of the NH proton as a triplet does not preclude the possibility of broadening of the ring protons by an exchange process, since the ^{14}N-proton coupling constant is large - about 70 cps - while the coupling of the NH proton to the ring protons should be at most several cycles per sec. Thus exchange rates of several seconds^{-1} would collapse structure arising from spin-spin coupling of the NH proton with the ring protons, and would only broaden the individual components of the triplet arising from ^{14}N-proton coupling. We are studying the effect of acid concentration on these resonances to settle this point.

The double resonance technique provides a rather neat method of obtaining ^{14}N chemical shifts, and we are using it to study the effects of ring substitution on the ^{14}N resonance frequency of substituted pyridines. The effect of N-protonation of pyridine is to shift the ^{14}N resonance to high field by about 70 ppm. In ammonia, however, protonation produces a smaller shift which is in the opposite sense to low field.[3] We suggest that the ^{14}N resonance in pyridine is to low field of that in pyridinium ion because of a paramagnetic effect resulting from the greater ease of promotion of a nitrogen lone-pair electron, as opposed to an electron in an NH bond, to the antibonding ring orbitals.

Yours sincerely,

John D. Baldeschwieler

John D. Baldeschwieler

Edward W. Randall

Edward W. Randall

JDB:EWR:br

1. B. Summers, L. H. Piette, W. G. Schneider, *Canad. J. Chem.*, **38**, 681 (1960).

2. I. C. Smith and W. G. Schneider, private communication.

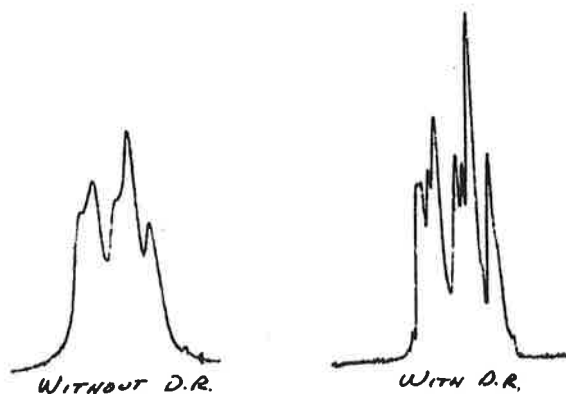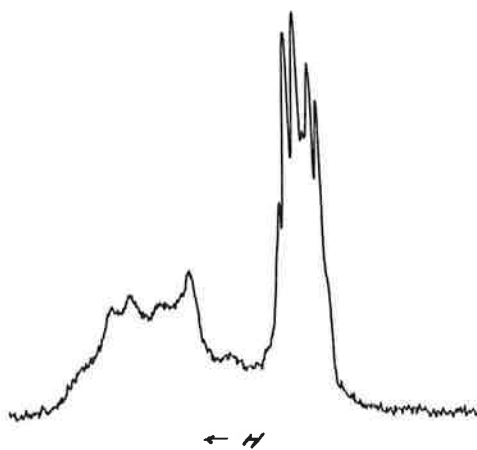3. J. D. Baldeschwieler, unpublished results.

WITHOUT D.R.   WITH D.R.

← H

FIGURE 1

← H

FIGURE 2