DERIVATIVES OF 5,10-DIHYDRO-5-PHENYLACRIDOPHOSPHIN-10-ONE—SYNTHESIS AND NMR ANALYSIS OF THESE "BUTTERFLY" COMPOUNDS

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CHAPTER I

HISTORICAL

Introduction of Dynamic NMR

High-resolution nuclear magnetic resonance spectroscopy has become an immensely efficient tool in structural studies in organic chemistry. Those applications which make use of the effect of chemical dynamics on NMR spectra have gradually increased in importance since the theory was developed some twenty years ago.[10,26] The technique of DNMR depends upon recording the temperature dependence of NMR spectra.

If the average lifetimes of a number of species in equilibrium exceed an upper limit, the NMR spectrum will show them as individual entities. Conversely, if the lifetimes are short with respect to the NMR time scale, one will obtain a single spectrum, in which the chemical shifts and, for intramolecular processes, also the coupling constants are statistically weighted averages of the corresponding values in the exchanging species, a feature which is especially valuable for conformational analysis.[8]

The barrier heights of dynamic process amenable to this technique conveniently extend just from the borderline (20-25 kcal/mole), where compounds become too unstable to be isolated chemically, down to activation energies of about 5-6 kcal/mole, below which another powerful tool, microwave spectroscopy, can be applied. Many rate processes

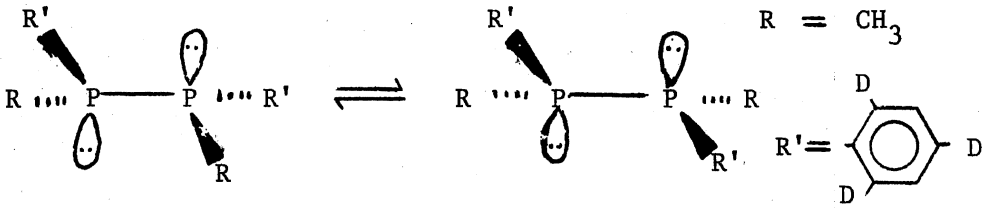
of fundamental importance in chemistry happen to fall into this formerly almost inaccessible gap between the realm of rotational spectra and conventional kinetic techniques.

Rate processes involving rotations around sterically crowded single bonds[45,51] and single bonds with partial double bond character,[42] inversion of lone electron pairs on nitrogen[57] and phosphorus,[3] inversion of carbocyclic and heterocyclic rings,[34,40] and degenerate valence isomerizations and intramolecular rearrangements are among the more common examples.

Inversion at Phosphorus

Although there have been sporadic reports concerning the pyramidal instability of the phosphine pyramid at elevated temperature,[29,30] DNMR information about inversion barriers in elements other than nitrogen is relatively scarce. Since it has been possible to prepare optically active phosphines,[4] the inversion barriers in phosphines must be substantially higher than the corresponding amines.

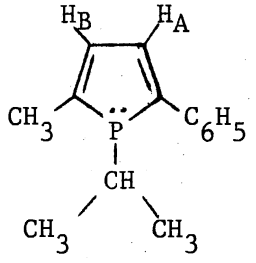
A "geminal phosphorus effect" in the diphosphines 1, presumably due to the availability of low-lying d levels in phosphorus, brings the barrier down to where it can be studied by DNMR. A single inversion at either phosphorus interconverts the meso and dl forms 1a and 1b.



(1a) (1b)

Lambert and Muller[41] were able to identify the changes in the spectra on alteration of the temperature with this process and to derive an activation energy of 26.0 ± 2.0 kcal/mole from a complete line shape fitting of the aromatic proton resonance in the deuterated compound 1. The preferred conformation and stereoisomerism of the diphosphine system has been established recently by measuring (P, C) spin-spin coupling constant.[27]

Phosphole systems, such as 1-isopropyl-2-methyl-5-phenylphosphole 2, have also been prepared[21] for investigating pyramidal inversion at phosphorus. By the total-line shape analysis of the temperature



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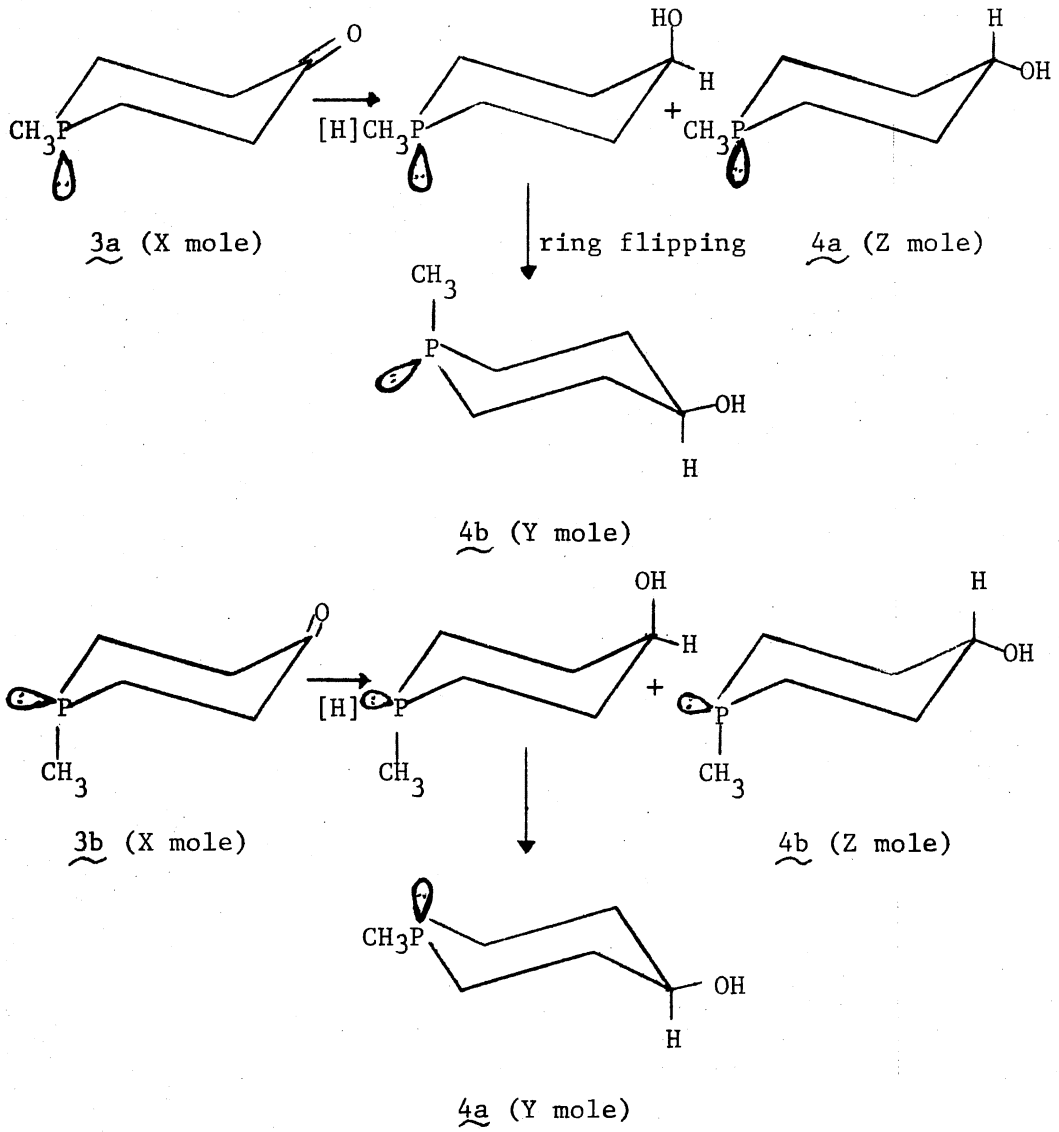
dependence of NMR spectra, Mislow found the activation energy of inversion barrier at phosphorus to be $\Delta G^{*}_{25°}$ = 16 kcal/mole. The extraordinarily low value for this compound suggested (3p-2p) π delocalization and aromatic qualities for the phosphole systems.

Recently, a study of the equilibration of inversion at phosphorus in cyclic phosphine 4 was attempted by Quin and Somers.[55] Reduction of 1-methyl-4-phosphorinanone (3) with several different reducing agents gave *cis* and *trans* 4 in nearly 1:1 mixture. This situation can be explained if the starting compound 3 lacks conformational bias and contains roughly equal amounts of conformers with PCH_3 at the axial (3b) and equatorial (3a) positions at equilibrium. One argument has been

advanced that the initially formed products with axial hydroxyl group will undergo "ring flipping" to the equilibrium composition, presumed to be dominated by the conformer with the equatorial hydroxyl group. The following scheme expresses these points:



3a (X mole) 4a (Z mole)

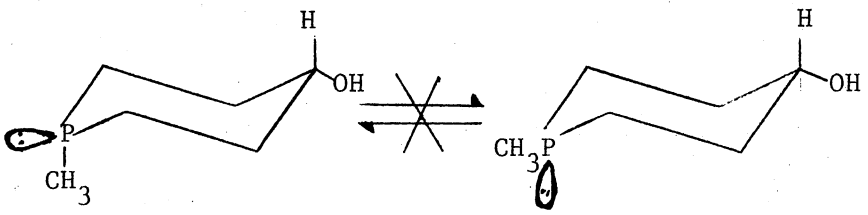
4b (Y mole)

3b (X mole) 4b (Z mole)

4a (Y mole)

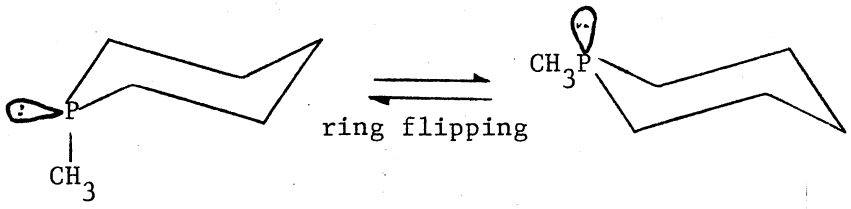
Equilibration via inversion at phosphorus was then attempted for further supporting evidence to the above arguments. Up to a temperature of 170°, no change in the isomer ratio was detected. Conclusions about this system should be drawn cautiously since hydrogen bonding could

influence conformer ratios.



4b 4a

In the absence of the hydroxyl group, 1-methylphosphorinane (5) should undergo rapid equilibration of conformers with axial and equatorial methyl and give PMR spectra at room temperature that are time-averaged.



5a 5b

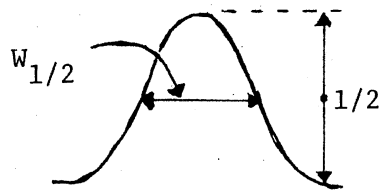
By DNMR study of this system Quin and Featherman[22] determined the ΔG^* value for the coalescence temperature at -75° as 9.2 kcal/mole on the basis of ^{31}PMR signal analysis.

DNMR Study in Phosphorus Chemistry

Determination of Rate Constants

In recent years, the use of fitting the theoretical spectra calculated according to the theory of Gutowsky and coworkers[26] to experimental spectra has become more and more widespread.[33] Computer programs of this type have been written for an AB exchange by Jones, Allerhand, and Gutowsky[31] and for a classical two-site exchange by Van der Werf, Olijnsma, and Engberts.[63] This program finds the "best" set of

parameters for each spectrum according to the method of least squares by assuming that the "error square sum" is a second-order function. An accurate knowledge of the coupling constants (J), chemical shifts (δ), and the transverse relaxation time (T_2) is related to the line width at half height, $W_{1/2}$, in the absence of exchange, by the equation (1):



$$T_2 = \frac{1}{\pi W_{1/2}} \qquad (1)$$

From the process of fitting the theoretical spectra to the observed spectra, the rate constant k (some authors prefer to use τ, which is defined as mean lifetime of the species and is equal to 1/k) may be determined.[31]

A recent paper[20] has made the comparison between the activation parameters calculated from theoretical total line-shape analysis and approximate equations[20] for the internal rotation in N,N-dimethyltrichloroacetamide. The deviation found for equations (2)-(5) is in the range of 12-15%, but for equation (6) the deviation is only 5%, which is in good agreement with those obtained by the complete line-shape fitting method.

The evaluation of exchange rates from exchange-broadened NMR spectra is often performed by measuring some characteristic parameter of the experimental spectrum, such as the peak separation (eqn. 2),

$$\tau = \frac{\sqrt{2}}{\pi\sqrt{(\Delta\nu)^2-(\Delta\nu_e)^2}} \qquad (2)$$

the ratio of the maximum height to the central minimum (eqn. 3),

$$\tau = \frac{\sqrt{2} \cdot \sqrt{r + \sqrt{r^2 - r}}}{\pi \cdot \Delta\nu} \tag{3}$$

or the half width of the signals (eqns. 4-6), and using approximate equations relating these parameters to the exchange rate.

$$\tau = \frac{1}{\pi(\Delta\nu_{1/2} - \Delta\nu^\circ)} \tag{4}$$

$$\tau = \frac{2(\Delta\nu_{1/2} - \Delta\nu^\circ)}{\pi \cdot (\Delta\nu)^2} \tag{5}$$

$$\tau = \frac{2(\Delta\nu_{1/2})}{\pi[(\Delta\nu)^4 + 2(\Delta\nu\Delta\nu_{1/2})^2 - (\Delta\nu_{1/2})^4]^{1/2}} \tag{6}$$

τ = the mean lifetime for exchanging protons at each site in the absence of equilibration.

$\Delta\nu$ = the peak separation in the absence of exchange.

$\Delta\nu_e$ = the peak separation at intermediate exchange rates.

r = the ratio of the peak maximum to the central minimum.

$\Delta\nu_{1/2}$ = the line-width at half of the maximum signal intensity.

$\Delta\nu^\circ = 1/\pi T_2$

T_2 = the spin-spin relaxation time.

Eqns. (2-4) can be used for calculation of exchange rates in the region between the slow exchange limit and the coalescence point, and eqns. (5) and (6) can be used for exchange rates between the coalescence point and the fast exchange limit.

Two approximate formulas have been used on a wide scale to provide a quick estimate of a rate constant at a single temperature, the so-called coalescence temperature, T_c: (a) $k_c = \pi\Delta\nu/\sqrt{2}$, for the coalescence of singlets associated with uncoupled diastereotopic atoms[54] and (b) $k_c = \pi\sqrt{(\nu_A - \nu_B)^2 + 6\ J_{AB}^2}\ /\sqrt{2}$, for the coalescence of the coupled AB spin system to a singlet.[39] The validity of these approximate equations has been discussed by Raban.[38] It was concluded that equation (a) yields reliable estimates of rates of coalescence in most cases when nuclei are not spin-coupled; equation (b) is valid only if the chemical shift difference greatly exceeds the coupling constants.

Calculation of Activation Parameters

In many applications of DNMR, only a single rate constant at the coalescence temperature has been calculated or, rather, estimated. As previously mentioned, approximate formulas are available for calculating the rate constant k_c at the coalescence temperature, T_c: (a) $k_c = \pi\Delta\nu/\sqrt{2}$, (b) $k_c = \pi\sqrt{(\nu_A - \nu_B)^2 + 6\ J_{AB}^2}\ /\sqrt{2}$. By means of the well-known Eyring equation (7),[7a,12] this rate constant k may be related to the free

$$k = n(k_B T/h)\ \exp\ (-\Delta G^*/RT) \qquad (7)$$

where

R = Gas constant (1.987 calories $^\circ K^{-1} mole^{-1}$)

T = Temperature

ΔG^* = Free energy of activation

k = Rate constant

k_B = Boltzmann constant (1.38×10^{-16} erg $^\circ K^{-1}$)

n = Transmission coefficient

h = Planck's constant (6.625×10^{-27} erg sec)

energy of activation, ΔG^*, at this temperature. For example, Dewar and Jennings[19] reported that dibenzylmethylamine exhibits slow nitrogen inversion at low temperature. At the coalescence temperature (-137°), with $\Delta\nu_{AB}$ = 29 Hz, J_{AB} = 11 Hz for the methylene protons, it was possible to calculate the free energy of activation, ΔG_c^* = 6.5 kcal/mole. With an assumed transmission coefficient n of 1, the Eyring equation gives:

$$\Delta G^* = 4.57\ T\ [10.32 + \log\ (T/k)]$$

At the coalescence temperature one has

$$k_c = \pi(\Delta\nu_{AB}^2 + 6\ J_{AB})^{1/2}/\sqrt{2}$$

and

$$\Delta G_c^* = 4.57\ T_c[9.97 + \log\ T_c/(\Delta\nu_{AB}^2 + 6\ J_{AB}^2)^{1/2}]$$

$$\Delta G_c^* = 4.57 \times 136\ [9.97 + \log\ 136/(841 + 726)^{1/2}]$$

$$= 6525.9\ \text{cal/mole} = 6.52\ \text{kcal/mole}$$

Since no meaningful standard deviation can be attached to the value, since the calculation makes use of an approximate formula, and since the measurement is performed at a rather ill-defined point, it is somewhat difficult to judge how far this quantity might deviate from the true value. Its significance for comparison purposes is further limited by the fact that its temperature dependence is not known.

If the rate constants have been obtained at a number of different temperatures, one may construct a linear Arrhenius plot[7b,12]

$$\ln k = -E_a/RT + \ln A \qquad (8)$$

and extract the activation energy $\underset{\sim}{E}_a$ from the slope and the frequency factor $\underset{\sim}{A}$ from the intercept. An Arrhenius plot, of course, involves the tacit assumption that both $\underset{\sim}{E}_a$ and $\underset{\sim}{A}$ are independent of temperature, which is only an approximation. Experience has shown this approximation to be a good one. In general, it would mean taxing the accuracy of the rate data beyond its limits to detect deviations from linearity with any degree of certainty. The modern literature seems to prefer enthalpies and entropies of activation in place of Arrhenius parameters. Substitution of

$$\Delta G^* = \Delta H^* - T\Delta S^* \tag{9}$$

into the Eyring equation (7) gives

$$k = n(k_B T/h) \exp(-\Delta H^*/RT) \exp(\Delta S^*/R) \tag{10}$$

ΔH and ΔS could, in principle, be obtained from the Arrhenius parameters by:

$$\Delta H^* = E_a - RT \tag{11}$$

$$\Delta S^* = R[\ln(hA/n\, k_B T) - 1] \tag{12}$$

However, with eqns. (11) and (12) one introduces a temperature dependence into ΔH^* and ΔS^*. This temperature dependence is really artificial, since it is based on the assumed temperature independence of E_a and A. A more reasonable approach is to assume temperature-independent ΔH^* and ΔS^* values and obtain them experimentally in a direct fashion. There are two ways to do this. One can make use of eqn. (10) and plot ln (k/T) versus 1/T to give a straight line with the slope $-\Delta H^*/R$ and the intercept $\ln(nk_B/h) + \Delta S^*/R$, or one may calculate ΔG^* from eqn. (7) for each temperature and plot ΔG^* versus T [eqn. (9)].[8]

The question of what to do about the somewhat mysterious transmission coefficient n still remains to be answered. The simplest way is to set it equal to 1 and thus dispose of this problem. In fact, there hardly seems to be a reasonable alternative. If exchange takes place between two unequally populated sites, the activation parameters of the forward reaction are of course different from those of the reverse path. Figure 1 illustrates their interrelation.

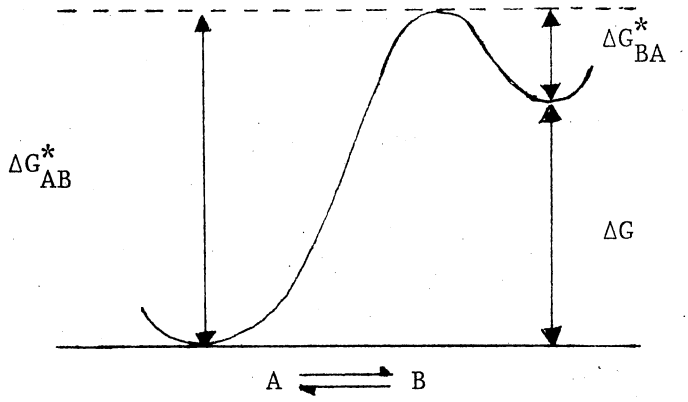


Figure 1. Relation Between Thermodynamic and Kinetic Parameters for an Exchange Between Two Unequally Populated Sites

ΔG stands for the free energy difference of the ground states at the same temperature to which ΔG^* refers and is given by:

$$\Delta G = -RT \ln (P_B/P_A) = -RT \ln K_{eq} \qquad (13)$$

Since the equilibrium constant K_{eq} is itself a function of temperature, the corresponding changes in the populations must be taken into account in line-shape calculations. It is sometimes possible to determine the thermodynamic functions from peak-area measurements at a series of temperatures below the slow exchange limit and extrapolate to the temperature region where broadened or collapsed spectra are obtained.[65] However, one may treat the populations as free parameters to be adjusted so as to give the correct line shape. Finally, it is clear that the NMR method for determining reaction rates will not be applicable at all when the ground-state energies differ vastly, because then one sees essentially only one species, and the line shapes do not respond to any exchange process that might still be going on.

Sources of Error

In this section errors which result from instrumental sources will be discussed. These errors have plagued DNMR studies from the beginning and are responsible, at least in part, for the wide variation in the thermodynamic values reported for systems[8] which have been studied by several different workers. Line broadening due to field inhomogeneity or saturation is a problem frequently encountered when the temperature within the probe is changed. Careful tuning of the instrument at each temperature using an internal standard such as H_2CCl_2 or $(CH_3)_4Si$ (TMS) is usually sufficient to minimize this problem. However, even tuning at each temperature does not give any indication of instrumental drift during the time necessary to record the spectra. The magnitude of this drift may be obtained by checking the internal standard after each trace and retuning if necessary.[8]

Temperature within the sample must be controlled and monitored accurately. Control of the temperature is generally obtained by a variable-temperature accessory available for most spectrometers. In the case of the Varian XL-100, the temperature can be regulated to 0.5 degree over a range of -120° to +200° C. Monitoring the temperature is usually accomplished by insertion of a capillary tube containing CH_3OH or $HOCH_2CH_2OH$ (depending on the temperature range) and measuring the shift between the OH proton and the CH protons. The temperature can then be interpolated from the plots of chemical shift vs temperature provided by Varian or calculated from equations provided by Van Geet.[64]

Errors introduced through failure[20] to control the temperature accurately are difficult to eliminate completely; however, methods to minimize this error have been discussed by several workers. Calibration of the standards (usually CH_3OH or $HOCH_2CH_2OH$) using a thermocouple over the range of temperatures to be studied permits a more accurate knowledge of the temperature. Since there is a temperature gradient around the glass insert of the probe, a minimum amount of sample should be used to reduce the effects of nonuniform sample temperature. A steady flow of carrier gas is also essential for maintaining a constant temperature (the use of two regulators in series will help to even the flow).

The following section will deal with errors introduced during the process of analyzing NMR data. Probably one of the most difficult parameters to determine accurately for the exchanging protons is the transverse relaxation time (T_2). There are two principal methods used to determine T_2, other than the use of pulsed NMR. One method[9,20]

is to measure the line width at half height, $W_{1/2}$, of an exchanging species in the limit of both fast and slow exchange and then plot these values versus the temperature. The line width at half height, $W_{1/2}$, at other different temperatures can now be read from the straight line between the points. The transverse relaxation time, T_2, can be calculated from equation (1): $T_2 = 1/\pi\ W_{1/2}$. However, this requires that T_2 be a linear function of temperature. Another method used to obtain an effective value for T_2 is by measuring the line width of some non-exchanging line in the spectrum, usually a line from an internal standard, such as TMS (however, the use of an external standard has been reported by Arlinger and coworkers[2]).

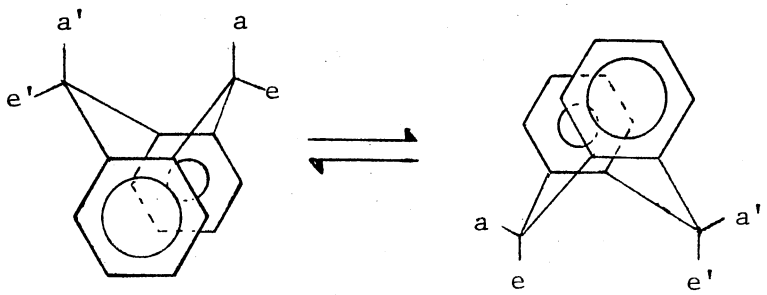
The magnitude of the errors in the thermodynamic values introduced by an inaccurate knowledge of T_2 has been discussed by Drakenberg and co-workers.[20] It was estimated to be on the order of $\pm$ 0.2 kcal/mole in both E_a and ΔH^*.

The chemical shifts and coupling constants (static parameters) of the exchanging species are also rather difficult to obtain. Unfortunately they can only be determined in the slow exchange limit where instrument stability is often a factor in determining the accuracy of these parameters. In addition, from this data (taken in the slow exchange limit) little is known about the temperature dependence of the chemical shifts. To some extent a correction for temperature variation in these parameters may be made by recording the spectrum at several temperatures in the slow exchange limit and plotting the chemical shift versus temperature. Extrapolation to higher temperature is now possible;[20] however, the assumption that the temperature dependence of the chemical shift is linear is inherent in this method.

Drakenberg and co-workers[20] have attempted to analyze the magnitude of this error in their study of N,N-dimethyltrichloroacetamide. They estimate that $\Delta\nu$ (chemical shift difference in the absence of exchange) at temperature below the coalescence point can be measured within about $\pm$ 0.2 Hz; this error would then cause an error in E_a and ΔH^* of about $\pm$ 0.3 kcal/mole.

"Butterfly" Compounds

There is general agreement that the central ring of 9,10-dihydroanthracene is nonplanar as shown by X-ray diffraction.[23] A recent NMR study[52] indicates that the molecule undergoes a rapid oscillating motion through the planar configuration at a temperature as low as -55°.

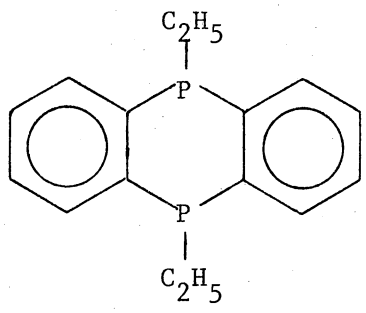


6a 6b

The derivatives[5] and heterocyclic analogs[46,59] of 9,10-dihydroanthracene 6 generally exist as folded structures capable of displaying a substituent bonded to a meso position in either the pseudo-axial (a') or the pseudo-equatorial (e') position. The barrier for conformational interconversion in 9,10-dihydroanthracene and structurally similar heterocycles is quite low, calculated to be on the order of 7 kcal/mole[13a] or less.[13b] Undoubtedly, a major factor responsible for establishing

this low barrier is the absence of the need for atoms bonded to the meso position to pass by the peri positions and the atoms bonded to them to achieve conformational exchange. One would imagine, then, that angle deformations of the bonds at the meso positions would account for a large portion of the barrier.[50]

Stereoisomers of P(III) compounds were first obtained by Davis and Mann[17] in a study of the chemistry of the 5,10-diethyl-5,10-dihydrophosphanthrene system. Two isomeric diphosphines 7 were obtained,



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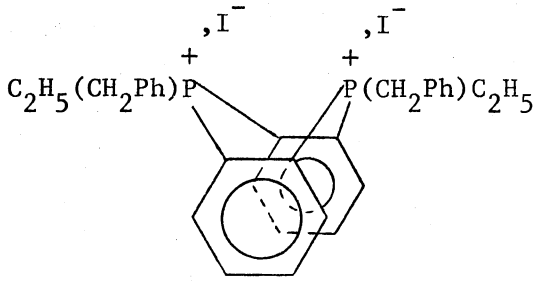
m.p. 52-53° and 96-97°, as also were two biquaternary salts 8 [m.p. 326° and 320-321°] by reaction of the crude phosphines with benzyl iodide. Two dioxides 9 [m.p. 234-235° and 257°] were formed via basic hydrolysis of the salts 8. The lower melting of the two dioxides had a dipole



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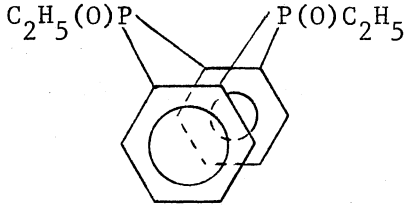

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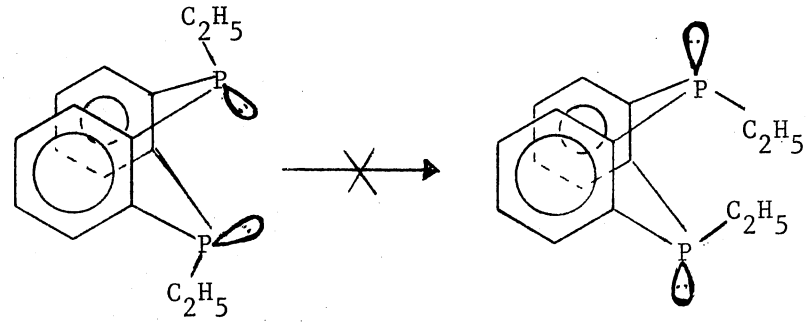
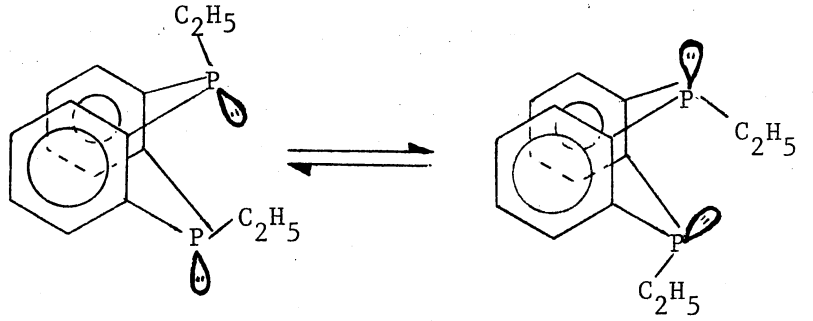
moment of 4.0 D and was hence assigned the cis configuration.[17] There was insufficient material with which to measure the dipole moment of the higher-melting dioxide which, if trans, should have nearly a zero moment. Unfortunately, the high-melting diphosphine was obtained in minute yield and no evidence of direct interconversion of isomers was obtained. The principal product of the reaction, the low-melting diphosphine 7, was considered to have the cis configuration 7a since it could be oxidized to the cis-dioxide 9 with hydrogen peroxide. The stereochemistry of these systems in terms of a molecule folded about the axis of the two heteroatoms (P,P) has also been discussed in the same paper.[17]

The cis form is shown as 7a, and the trans form as 7b.



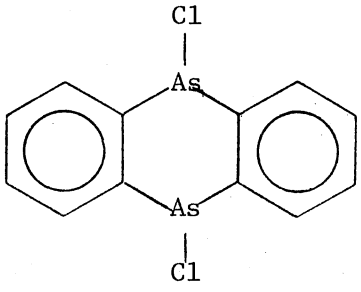
7a 7a'



7b 7b'

Theoretical evidence has been adduced by Mislow and co-workers[46] to show that both the cis-7a and the trans-7b can "flex" readily about the planar conformation of the tricyclic system. Moreover, this flexing may occur in solution where the degree of flexing would be determined mainly by the size of the substituent groups. Furthermore, Mann[17] has pointed out that when the trans-7b is flexed completely over to 7b', the latter still has the trans form, and therefore no configurational change (cis ⇌ trans) occurs in this process. Similar flexing of the cis-7a form over the planar position produces the form 7a'; in this case, however, the process is much less likely because of the mutual obstruction of the two alkyl groups.

The arsanthrene ring system was first synthesized by Kalb[35] with a low yield of 5,10-dichloro-5,10-dihydroarsanthrene (10), m.p. 182-183°,



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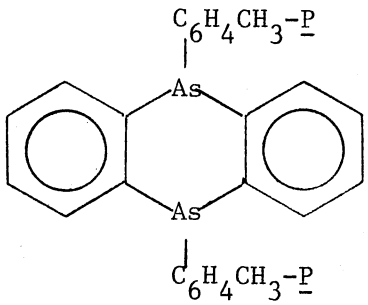
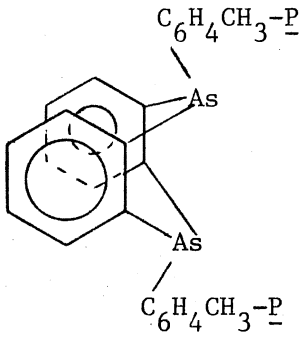


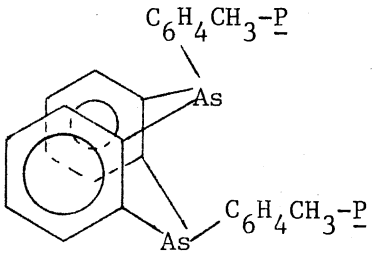
11

as product. In view of the stereochemistry of 5,10-disubstituted-5,10-dihydroarsanthrenes, Mann and Chatt[14] converted the 5,10-dichloro derivative 10 into the stable, highly crystalline 5,10-dihydro-5,10-di-p-tolylarsanthrene (11). Two isomeric forms of 11 were obtained, m.p. 178-179° and m.p. 179-181°. The two forms were, moreover, suprisingly stable, for each isomer could be kept in the molten condition at 190° for 10 minutes without any indication of conversion into

the other form or of chemical decomposition. It is not known which of these forms has the cis configuration 11a and which the trans configuration 11b, but evidence for folded configurations in this family is now decisive on the basis of X-ray work of the methyl-substituted compound[48] 12a rather than the p-tolyl derivative. Jones and Mann[32] had prepared

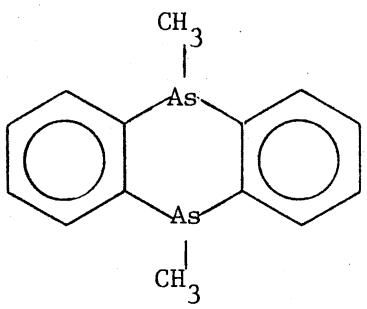


11a

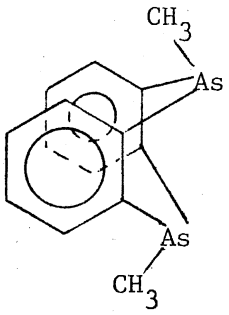


11b

the dimethyl derivative 12 by the action of methylmagnesium iodide on the dichloro derivative 10; excellent crystals (90%) of 12a could be obtained, m.p. 191-192.5°, after recrystallization from ethanol-chloroform. The X-ray crystallographic study[37] of this compound also shows conclusively that it has the "butterfly" conformation and consists solely of the form having cis methyl groups, 12a.

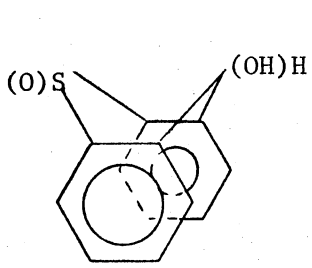


12



12a

The thioxanthene ring system also serves as an excellent model for stereochemical studies of butterfly compounds because of the conformational restrictions inherent in this heterocyclic ring system. Ternay, Chasar and Sax[61] prepared thioxanthen-9-ol 10-oxide (13). Two isomeric forms of 13 were obtained, m.p. 218-218.5° for 13a and a m.p. 205-206° for 13b. The configurations have been assigned to these isomeric compounds on the basis of single-crystal X-ray analysis of 13b.[61] The



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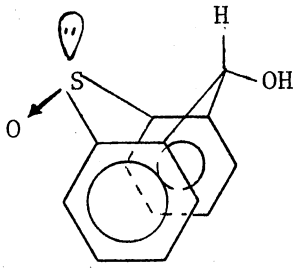
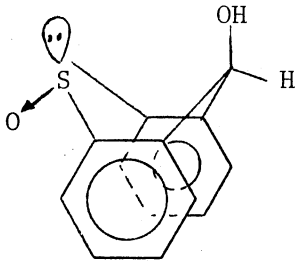
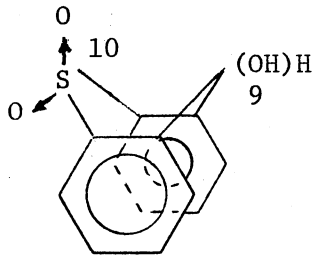


13a

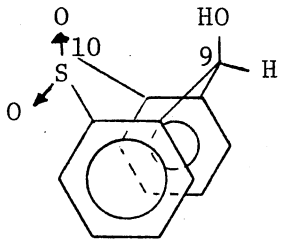


13b

X-ray analysis[61] of 13b (m.p. 206°) revealed the trans configuration. In the solid state, the sulfur-oxygen bond occupies a pseudo-equatorial position while the HOCH dihedral angle is 34°. Furthermore, Ternay and Chasar[62] have investigated the conformational preferences in solution of this system on the basis of NMR spectra. In order to assign conformational preference of isomeric compound 13 in solution, they also prepared thioxanthenol sulfone 14.[60] Compound 14 displays a moderately

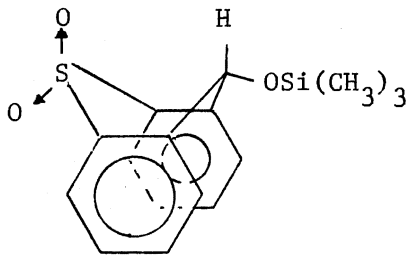


14



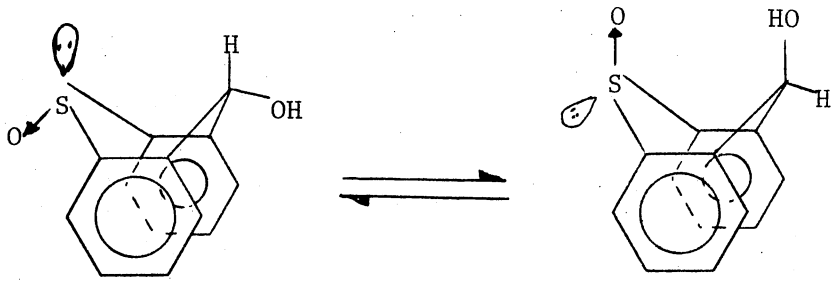
14a

intense absorption at 3508 cm^{-1} (1.3×10^{-5} CCl_4), considered to arise from an intramolecular hydrogen bond between the hydroxyl group and the sulfonyl group. The NMR spectrum of 14 offers support for the existence of this hydrogen bond. Thus, even in $DCCl_3$ it is possible to observe coupling between the methine proton (C-9) and the hydroxyl proton with J = 8.0 Hz. Since rapid exchange would be expected to average out this coupling, it was concluded that such rapid exchange did not occur; a hydrogen-bonded proton would be consistent with this interpretation. Thus, both the IR spectrum and the NMR spectrum indicate that thioxanthenol sulfone exists in the conformation of structure 14a. It was suggested that the line position of the methine proton of thioxanthenol sulfone 14 (δ 3.61) should be representative of a methine proton in this series, that is, in the pseudo-equatorial position and relatively removed from the magnetic anisotropy of the S-O bond. The trimethylsilyl derivative 15[62] of 14 was prepared for further evaluation of the above interpretation. On the basis of steric hindrance, compound 15 might be expected to prefer a conformation in which the 9-substituent exists in the pseudo-equatorial position. If this conformation was favored, one might anticipate a downfield shift of the methine proton resonance because of the deshielding of the sulfone. Indeed, the line position (δ 3.77) of this methine proton occurs 16 Hz downfield from



15

that of the corresponding alcohol. The resonance frequency (δ 3.59) of the methine proton of 13b in $DCCl_3$ was almost identical with that which was observed for the corresponding sulfone 14a. This suggested that the preferred conformation of 13b was that in which the methine proton showed pseudo-equatorial geometry. Thus, Ternay and Chasar[63a] concluded that the conformation observed for 13b in the solid state was also the preferred conformation in solution. cis-Thioxanthen-9-ol 10-oxide (13a) can be thought of as existing in two possible conformations in solution.



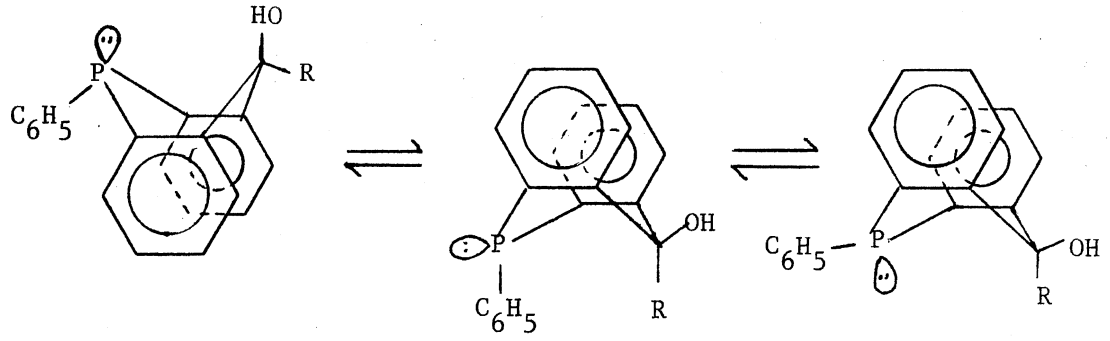
13a 13a'

The NMR spectrum of 13a showed the methine proton resonance frequency was upfield (δ 3.30) instead at δ 3.60 as in the trans form 13b. This increased shielding is interpreted by Ternay and Chasar as signifying a preponderance of conformer 13a rather than 13a'.

CHAPTER II

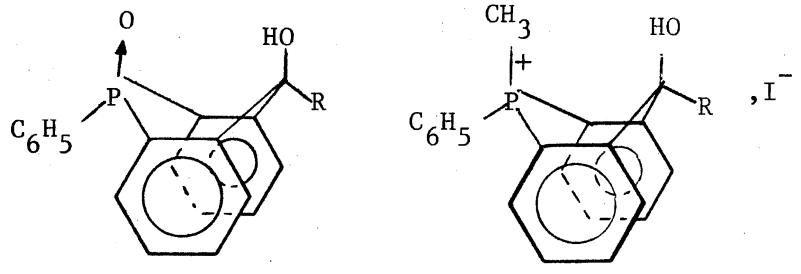
RESULTS AND DISCUSSION

The primary objective of this research was to develop a synthetic approach to certain tricyclic phosphorous compounds 16 ("butterfly" compounds) and to evaluate, via NMR analysis, "ring flipping" and if



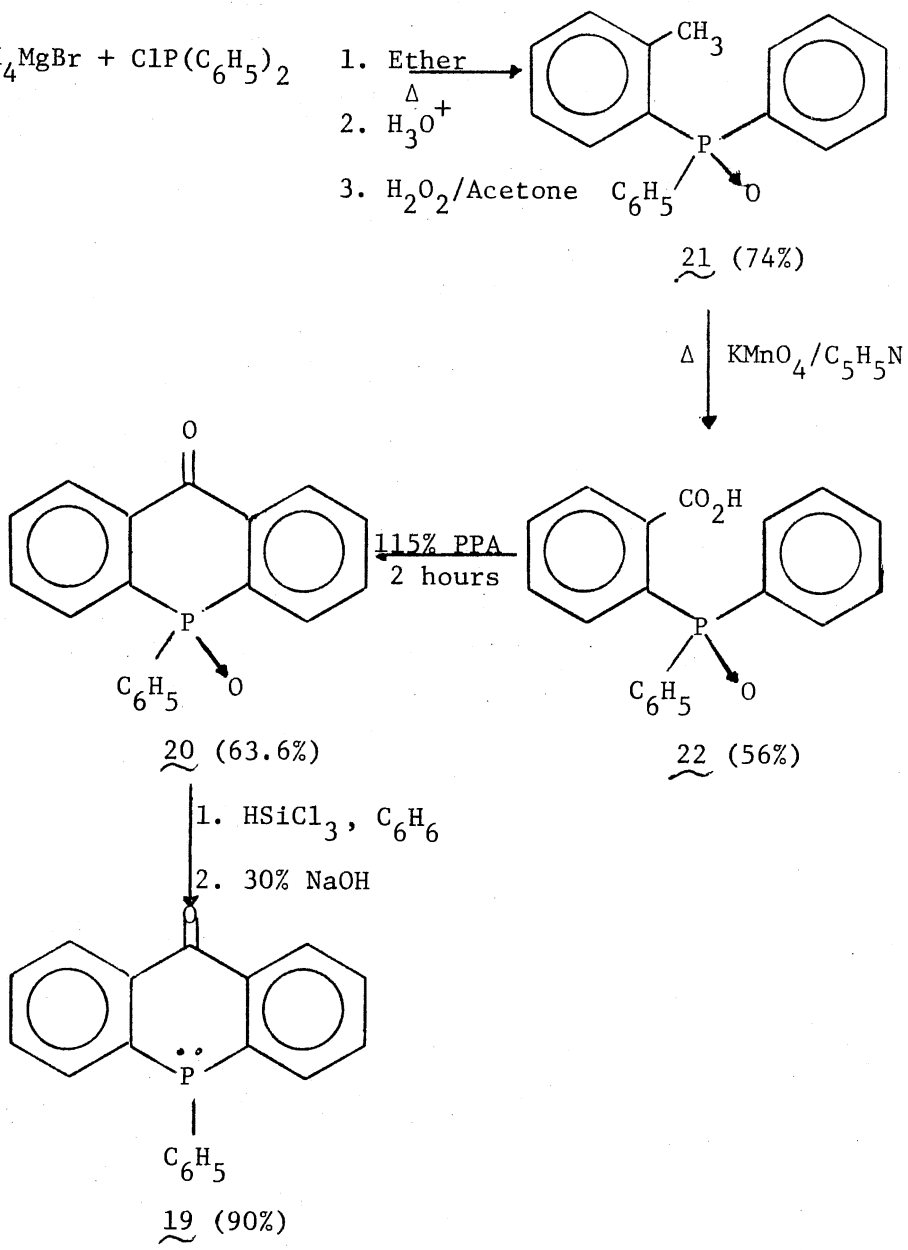
16 16a 16b

possible, inversion at P. Success has been partially realized in that several members, 16, 17, and 18, have been obtained. The key starting



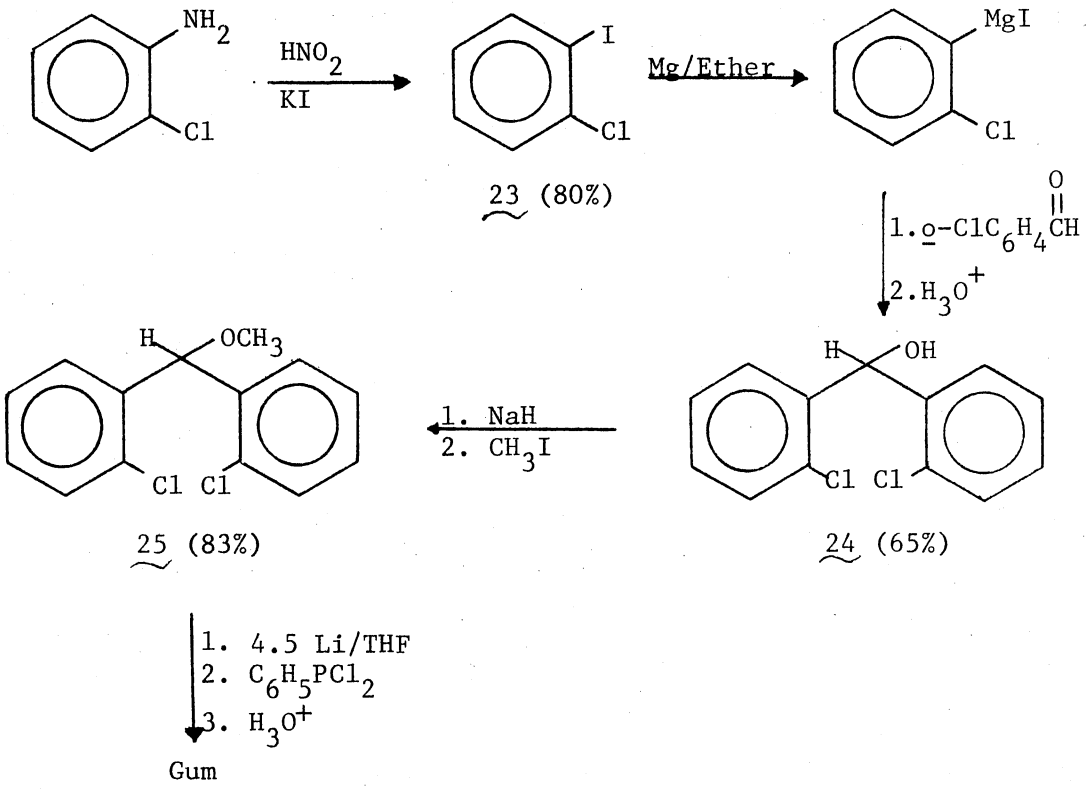
17 18

material was 19 which was prepared from 20 via the reaction sequence shown below.[58]

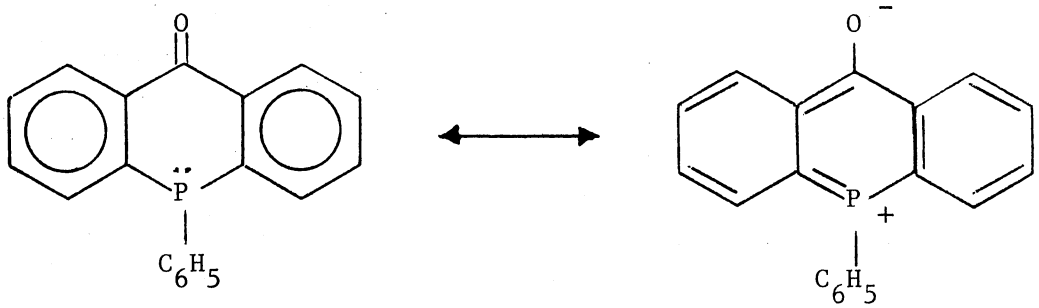


An alternative scheme illustrated (initiated early in the project) gave a heavy gum which did not crystallize within a month upon standing in the cold (-10°). No additional effort has been made to date to

purify this mixture.

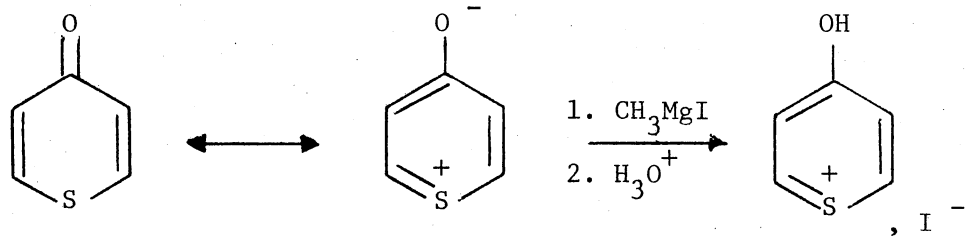


Intuitively, one might suspect delocalization of the pair of electrons on P into the ring system as depicted by the valence bond forms 19 ⟷ 19a. Consequently, nucleophilic addition by Grignard or lithium reagents might be difficult.



19 19a

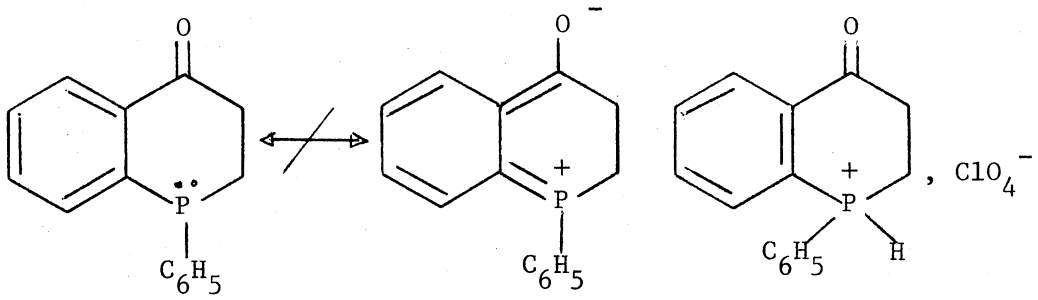
It has been reported that the action of Grignard reagents[53] on 1-thio-4-pyrone (26) yield 4-hydroxythiopyrylium salts 27 which were



26 26a 27

identical with those obtained directly from 26 and mineral acids.[53] The implication is that the polar form 26a is an important contributor to the hybrid in this situation.

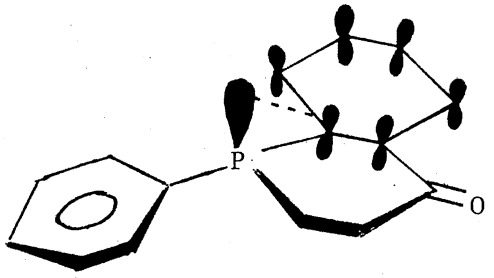
In contrast, the oxo-phosphine 28 did not display the same behavior as compound 26 with protonic acids.[24] A perchlorate 29 was formed with aqueous perchloric acid and no absorption for a hydroxyl group was



28 28a 29

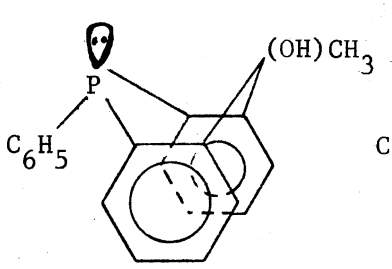
observed in the IR spectrum. The IR spectra of 26 gave an absorption band $\nu_{C=O}$ at 1609 cm^{-1}, while 28 had $\nu_{C=O}$ at 1680 cm^{-1} and 19 had $\nu_{C=O}$ at 1650 cm^{-1}. Thus, it seems that the electron pair on phosphorus (as in 28) may not be as delocalized as in the sulfur analog 26. Since d orbital participation may occur in both cases, the explanation is not obvious but may involve a steric factor in the case of 28. Perhaps the

possible low contribution of 28a to the hybrid structure rests in an unfavorable orbital alignment. However, to form a π orbital from d-p



overlap does not necessarily require coplanar groups attached to the atom with the d orbital, other parameters need to be evaluated. No UV spectrum of 28 has yet been published, unfortunately. No additions via Grignard reagents are yet recorded.

In our study, 19 reacted in boiling THF with CH_3MgI and $(CH_3)_3CLi$ to give phosphines 30 and 31 respectively, although phosphine 31 was



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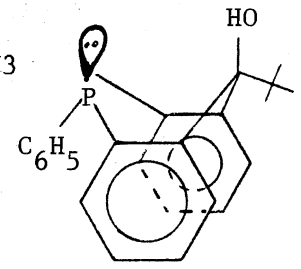
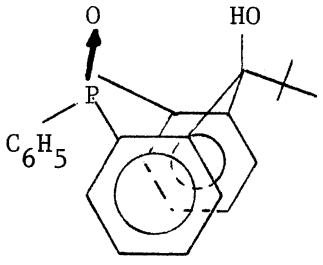


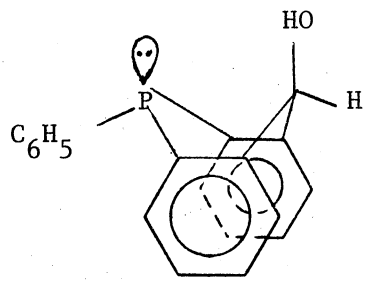
31



31a

extremely sensitive to oxidation in air and was best converted to the oxide 31a with hydrogen peroxide. The yield was low.

Reduction of 19 with $NaBH_4$ in ethanol gave crude 32 which could only be isolated as the oxide 33. Also, 33 could be obtained by reduction of 20 with $NaBH_4$ in ethanol.



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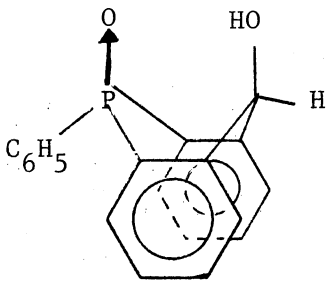
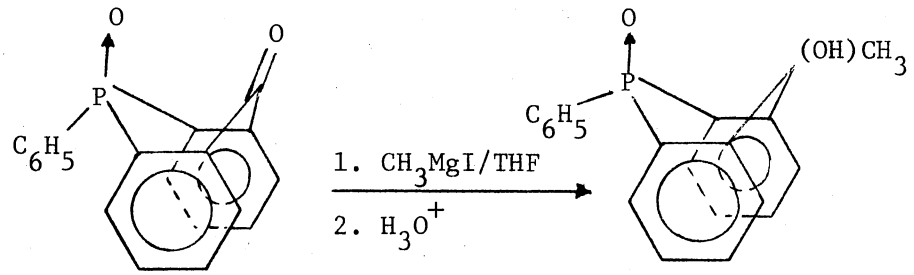


33

Keto oxide 20 also reacted with CH_3MgI to give two isomeric forms of 34 (m.p. 329-330° and m.p. 261-262°) which were completely separated by very meticulous fractional recrystallization. The PMR spectrum in (DMSO-d_6) showed a sharp singlet for the methyl protons, at δ 1.14 for the higher-melting oxide 34a and at δ 1.76 for the lower-melting isomer 34b. Attempted reduction of 34 to the phosphine 30 with $HSiCl_3$ and Si_2Cl_6 was determined to give a heavy mixture. PMR analysis of the crude product showed that the reducing agent had also caused the loss of

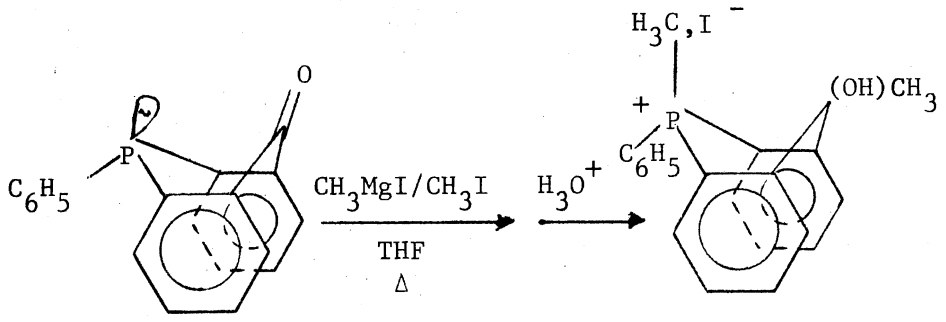


20 34

the OH group as well as the P→O group.

In an analogous situation, keto phosphine 19 reacted with CH_3MgI-CH_3I to give two isomeric phosphonium salts 35 (m.p. 282-283° and m.p. 276-277.5°) which could be separated by fractional recrystallization. The PMR spectrum (in DMSO-d_6) showed a sharp singlet at δ 1.30 (methyl protons at C-10 position), and a doublet centered at δ 3.11

(J_{PCH} = 14 Hz) (methyl protons attached to P) for the higher melting salt 35a. The lower melting isomer 35b had value at δ 1.74 for the methyl protons at C-10, and at δ 2.96 (J_{PCH} = 14 Hz) for the CH_3-P protons.

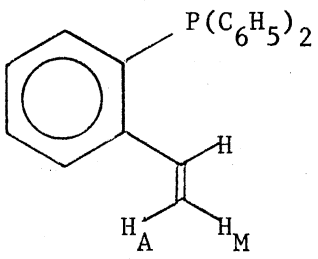


19 35

Our efforts to examine the "flipping of ring" and stereochemistry centered upon ^{31}PMR analysis, H-$\{^{31}P\}$ spin-decoupling, and PMR analysis of 30 over a wide temperature range. The PMR spectrum (in $DCCl_3$) of 30 gave a doublet for the methyl protons at δ 1.6 with a Δν of 1.6 Hz (Plate XXXI). Interestingly, if the solvent was changed to benzene[56] the doublet split into four lines observable at a sweep width of 25 Hz. This situation was reproducible on several samples. By irradiation of ^{31}P, the quartet was observed to collapse to two lines with Δν = 0.45 ± 0.05 Hz (Plate XXXIV).

These data strongly indicate that 30 exists as two conformers in solution and probably in an equilibria. The chemical shift difference in $DCCl_3$ was apparently too small to be observed. "Benzene shifts" are well known[56] in many different systems. The long-range spin-spin coupling of the methyl protons in 30 with ^{31}P (PCCCCH ≈ 1.6 ± 0.2 Hz) was confirmed by the decoupling experiments. Such $^5J_{PH}$ are not common but are known in conjugated systems.[49] For example, a long range

spin-spin coupling of H_A with ^{31}P in compound 36 (PCCCCH $\approx$ 1.10 $\pm$ 0.05 Hz) has been reported.[49] The coupling between H_M and ^{31}P was



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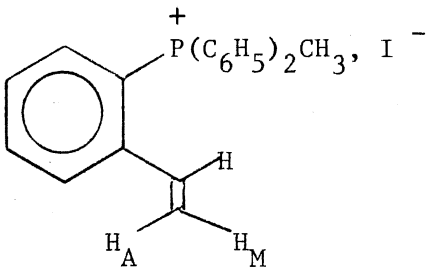
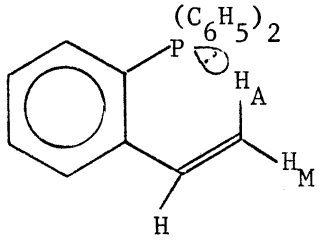


37

small (0.05 $\approx$ 0.10 Hz) and was likely outside instrument capability. No evidence of significant long-range ^{31}P-H coupling was found for 37. An explanation given was that there was direct overlap of the lone pair electrons on phosphorus with the σ-electrons of H_A. Also it was observed that the H_A proton exhibited a downfield shift compared to H_M and supposedly supported the above assumption that 36a was the major

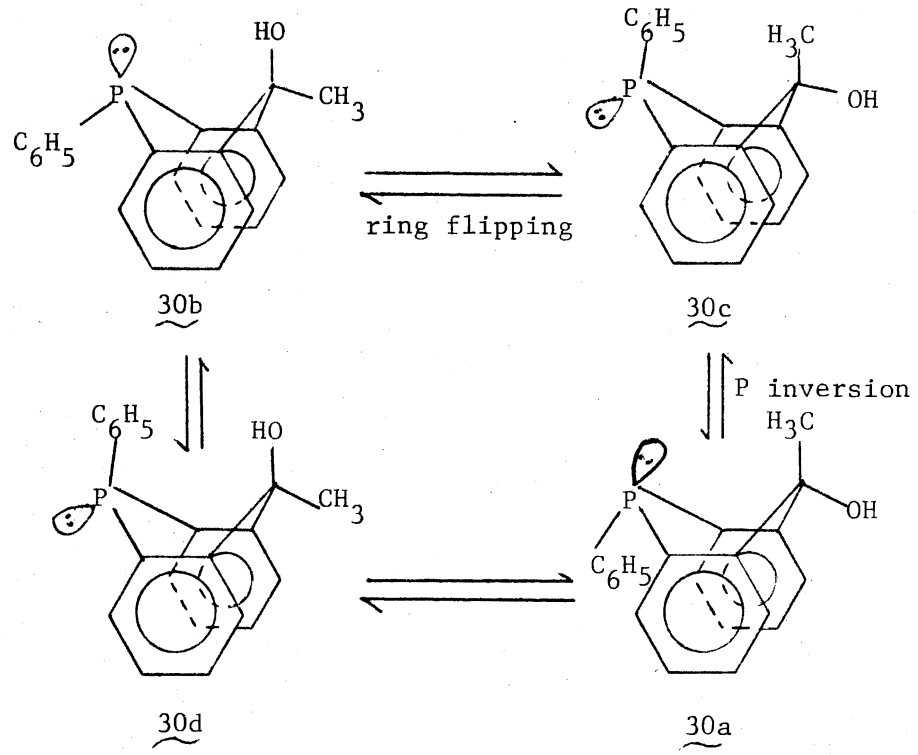


36a

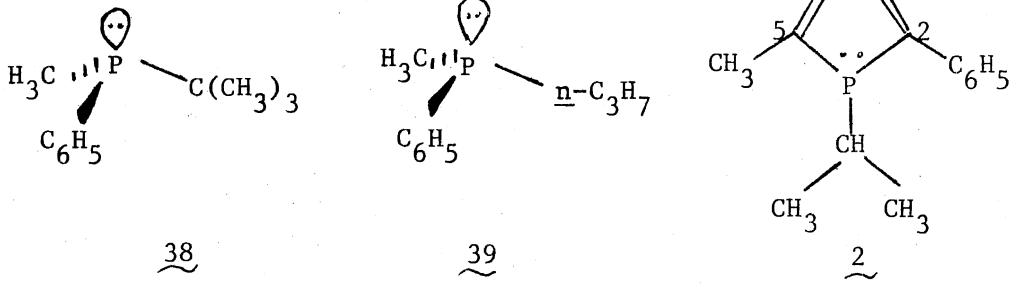
conformer rather than 36. In our opinion, this is not a defensible position since the steric effects in 36a must be very large and the P-H_A interaction would be difficult to predict.

An examination of the molecular models (COURTAULD models) was instructive. In the equilibria shown, conformers 30a and 30b appear to be the most favored structures, from steric considerations alone.

In our opinion the energy barrier to "butterfly flipping" in 30b ⇌ 30c



may be severe but P inversion in 30c could give, supposedly, more stable 30a. High energy barriers to pyramidal inversion on P in phosphines is reportedly common, such as in 38 and 39.[4] However, in optically



38 39 2

active 2 the inversion barrier was lowered (16 kcal/mole) as racemization occurred at 25° C.[21] Apparently, the strain imposed by the three substituents in close proximity at positions 1, 2, and 5 facilitated the epimerization process. Then, 30c and 30d likely have inherent strain

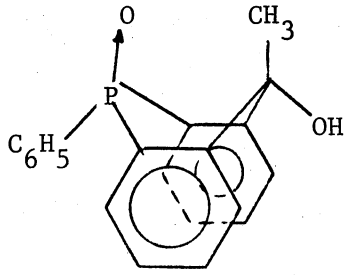
from nonbonded repulsive forces arising from methyl-phenyl and hydroxy-phenyl interactions. Consequently, there may be considerable driving force for the P inversion to produce what is in effect an observable equilibrium of 30a $\rightleftharpoons$ 30b.

PMR study of 30 from -30° to +110° was performed with the XL-100 (15) NMR spectrometer. The temperature calibration showed a deviation of $\pm$ 0.5° over this range. During the low temperature study (30° to -30°) in $DCCl_3$, the doublet was observed to coalesce to a singlet just at -20°. Unfortunately, only when the resolution on the spectrometer was maintained at maximum (R > 0.25 Hz) was the field separation sufficiently great to show the two doublets for each isomer and only in benzene. Since benzene freezes at 4°C, the variable temperature could only be conducted in $DCCl_3$ (Plate XXXIII). No other solvent system examined to date has provided adequate solubility, separated the signals for each conformer, or provided a wide temperature range for V. T. studies. Assuming that the broad singlet observed at -20° in $DCCl_3$ with 30 is due to the presence of one conformer, the $^5J_{PCCCCH}$ coupling is not adequately resolved. This could be due to the lack of resolving power of the NMR unit at -20°C, a change in the average angle between the orbitals on P (bonding and nonbonding) and the C-H in the methyl group, or reaction of $DCCl_3$ with the phosphine. Preliminary PMR evidence suggests the latter occurs but to less than 3% at room temperature and very slowly. The overall reaction depicted

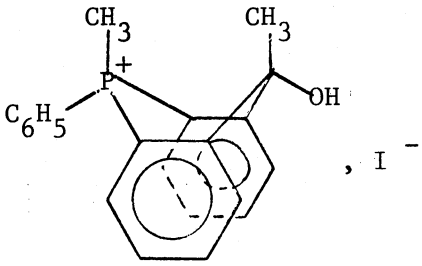
$$R_3P: + HCCl_3 \longrightarrow R_3\overset{+}{P}CHCl_2,\ \overset{-}{Cl}$$

is known but usually requires severe heating.[11]

With the above assumptions that the broad singlet is for one conformer, the flexible system can be treated roughly as undergoing an exchange process in which one group ($C-CH_3$) moves between two sites. From $k_c = \pi\Delta\nu/\sqrt{2}$, a k_c can be estimated using $\Delta\nu$ = 0.2 and 0.45 Hz to be 0.444 sec^{-1} and 0.999 sec^{-1}, respectively. Using equation 7 (HISTORICAL), ΔG^* is found to range from 15.11 to 14.71 kcal/mole. This range of values is still low and in agreement with a rapid equilibrium as predicted. In our opinion, the selection of 30a as the major conformer present at -20° in $DCCl_3$ is based on the following data. Molecular models (COURTAULD) suggest less hindrance in 30a compared to 30b. Oxidation of 30 by H_2O_2 (10%) in benzene at room temperature over 12 hours (slow stir) gave a nearly quantitative yield of the lower melting oxide (m.p. 261-262°).[34b] Similarly, quaternization of 30 with CH_3I at room temperature for 24 hours (slow stir) gave a quantitative yield of the lower-melting salt 35b (276-277.5°). Both processes are known to proceed with retention of configuration.[18] In both cases, also, the signal for $C-CH_3$ occurred at lower field δ 1.76 (oxide) and δ 1.75 (salt) in DMSO-d_6 compared to the higher melting oxide and salt, respectively. In fact, the positions of the signals are nearly identical and therefore the relative configurations are likely the same as illustrated in 41 and 42. Of course, one assumes that deshielding of the $C-CH_3$ group by $P\rightarrow O$ and P^+-CH_3 are nearly the same. This is debatable but not unreasonable. It is noteworthy that the phosphine 30 has a signal at δ = 1.40 (in DMSO-d_6) for $C-C\underline{H}_3$ which occurs at δ 1.14 in 34a (higher melting oxide) and δ 1.30 in 35a (higher melting salt); the changes are relatively small. One would not expect an identical value for the $C-C\underline{H}_3$ in these three molecules since

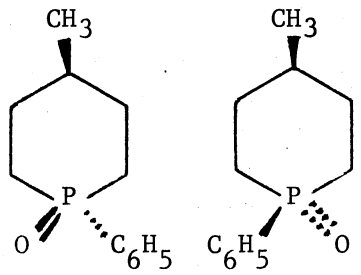


41



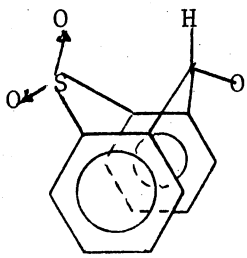
42

solvation of 30 would be different from that of 34a and 35a. It has been reported that a cis 1,4-methyl-P→O arrangement in a phosphorinane results in a greater deshielding of the CH_3 protons than in the trans arrangement [as in 43 and 44].[44] Of course, these systems are not



43-cis

44-trans



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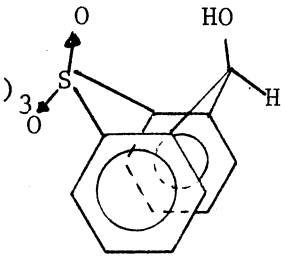
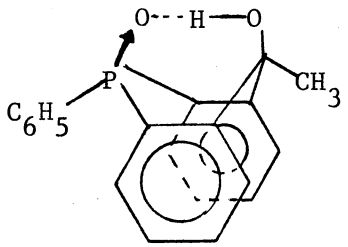


14a

likely in a boat form which is suggested for 41 (and 42). It has also been noted that the deshielding of the pseudo axial methine proton at C-9 of 15 (377 Hz) was greater than in 14a (361 Hz).[62]

Symmetry considerations of 45 (epimer of 41) would also predict



45

it to have the higher m.p. of the two oxides. Unfortunately, low solubility in all useful solvents examined to date has prevented an evaluation (via IR analysis) of the possible intramolecular H-bonding in 45 (or 30 for that matter).

Careful sublimation of crude 30 onto glass wool has provided triclinic crystals. It appears possible to perform an X-ray analysis of the phosphine. Such data is now being taken at the University of Oklahoma in a collaborative effort with Professor Dick van der Helm. These data will be instructive as to the shielding difference of P-C_6H_5 versus P → O on C-H in a P-C=C-C-CH arrangement, will determine if bond angles in a pseudo 7-membered, P-containing ring are strained, and will indirectly establish the probable structure of the major conformer of 30 present in benzene. From the oxidation and alkylation studies, it is apparent that the relative accessibility of the electron pair on P varies between the two conformers as only one product is found and that in high yield.

CHAPTER III

EXPERIMENTAL[a-f]

Preparation of o-Chloroiodobenzene (23).[28] In a 2000-ml. beaker fitted with a thermometer and mechanical stirrer were placed 12 N HCl (500 ml.) and o-chloroaniline (229.1 g., 1.8 mole) [commercial product from Aldrich Chemical Company]. After brief stirring (0.3 hour), ice (300 g.) was added and the beaker was kept in an ice-salt bath (temperature 0° to -10°). The solution was then diazotized by dropwise addition of a solution of sodium nitrite (139 g., 2.0 mole) [commercial product from J. T. Baker Chemical Company] in 500 ml. of water, the

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[a]Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected.

[b]Proton magnetic resonance spectra were taken on a Varian XL-100 (15) high resolution NMR spectrometer using tetramethylsilane (TMS) as the internal standard.

[c]Infrared spectra were taken on a Beckman IR-5A spectrophotometer with samples as films on sodium chloride discs or in potassium bromide pellets.

[d]Low and high resolution mass spectra were obtained on a CEC 21-110 B double-focusing mass spectrometer.

[e]Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

[f]Commercially available reagents were used without further purification unless otherwise stated. One hundred and fifteen percent polyphosphoric acid (82.3% P_2O_5, guaranteed minimum) was obtained from FMC Corporation.

temperature being kept at 0°-5°. After stirring the diazotized solution for 15 minutes, it was slowly poured through a glass-wool fiber into a solution of KI (498 g., 3 mole) in 500 ml. of water. After standing for two days with occasional stirring, the heavy oil was separated and washed successively with 10% of NaOH, water, 5% $NaHCO_3$, and water again. The oil was dissolved in 200 ml. of ether and the solution was dried ($MgSO_4$). Distillation twice under reduced pressure gave compound 23 as a colorless liquid (343 g., 80%; b.p. 58-59°/0.7 mm, lit.[66] b.p. 234-235°/760 mm; n_D^{22} 1.6325, lit.[52] n_D^{25} 1.6331). IR and NMR spectral data (Plates I and II) support the structure of 23. Upon standing in light the colorless liquid turns a light pink color.

Preparation of Bis(2-chlorophenyl)methanol (24). A solution (10 ml.) of o-chloriodobenzene (23) (238.5 g., 1 mole) in 150 ml. of anhydrous ether was added dropwise at room temperature to magnesium (25 g., 1.03 g. at.) covered with 10 ml. of dry ether. As soon as the reaction started, the remainder of the o-chloroiodobenzene in ether was added over a 2-hour period. After the addition, the mixture was well stirred for 2 hours and boiled for 0.5 hour, and then cooled to room temperature. o-Chlorobenzaldehyde (140.6 g., 1 mole) [commercial product from Eastman Chemical Company] in 100 ml. of anhydrous ether was added dropwise to the freshly prepared Grignard reagent. After the addition was completed, the mixture was boiled for 2 hours and stirred for 10 hours at room temperature under N_2. Hydrolysis was performed by slowly pouring the mixture into dilute HCl (1 N, 500 ml.). The organic layer was separated and the aqueous layer was extracted with two 100-ml. portions of ether. The ethereal extracts were combined with the organic layer, and the resulting solution was washed with dilute $NaHCO_3$ solution (5%)

and then with water. After drying ($MgSO_4$) overnight, the solution was distilled under reduced pressure to give crude alcohol 24 (164.90 g., 65%, m.p. 80-84°, b.p. 145-148°/0.6 mm). Recrystallization from hexane gave white crystals of alcohol 24 (m.p. 87-88°, lit.[16] m.p. 90°). IR and NMR spectral data (Plates III and IV) confirmed the structure of 24.

Preparation of Bis(o-chlorophenyl)methoxymethane (25). A solution of alcohol 24 (84.3 g., 0.33 mole) in 100 ml. of THF was added dropwise to a mixture of NaH (14.3 g., 55.6% in mineral oil, 0.33 mole) and methyl iodide (50 g., 0.352 mole) covered by 100 ml. of THF. The system was maintained under N_2. During the addition period, the only evidence of reaction was the evolution of hydrogen gas. After completing the addition, the mixture was boiled for 4 hours and then stirred at room temperature for 2 hours. Decomposition of excess sodium hydride was effected by adding a small amount of methanol with caution and very slowly. The solvent THF was removed by rotary evaporation. A brown-colored residue was dissolved with 100 ml. of ether; the solution was washed with 10% sodium bisulfite solution and water and was then dried ($MgSO_4$, 2-3 hours). The solvent was evaporated and crude ether 25 was recrystallized (80% ethanol) to give pure ether 25 (73.6 g., 83%; m.p. 53.5-54°). IR and NMR spectral data (Plates V and VI) support the structure of 25.

Anal. Calcd. for $C_{14}H_{12}OCl_2$: C, 62.92; H, 4.49.

Found: C, 62.68; H, 4.47.

Preparation of o-Tolyldiphenylphosphine Oxide (21).[6,25,47] In a dry, 1-liter, three-necked, round-bottom flask fitted with a nitrogen inlet, a mechanical stirrer, a condenser and a 250-ml. pressure-

equalized addition funnel was placed magnesium turnings (12.2 g., 0.5 g. at.). Anhydrous ether (100 ml.) was added. Then 10 ml. of a solution of freshly distilled o-bromotoluene (85 g., 0.5 mole) [commercial product from Matheson Coleman and Bell Chemical Company] in 100 ml. of anhydrous ether was added slowly. As soon as the reaction started, the remainder of the o-bromotoluene in ether was added over 1 hour. After the addition was completed, the mixture was boiled gently for about 4 hours with constant stirring. The Grignard solution was cooled to 0° in an ice bath, and a solution of diphenylphosphinous chloride (110.3 g., 0.5 mole) in 50 ml. of ether was added dropwise with stirring. The reaction mixture was allowed to come to room temperature (≈0.5 hour) and was then boiled for 16 hours with constant stirring under N_2. After cooling to room temperature, the reaction mixture was poured into a mixture of 43 ml. of conc. HCl and 250 g. of ice with care. The organic layer was separated and the aqueous layer was washed with two 100-ml. portions of ether. A combined solution of the organic layer and the ethereal extracts were washed with 10% $NaHCO_3$ and reduced in volume to about 150 ml. on the rotatory evaporator under reduced pressure. Addition of 300 ml. of 95% ethanol gave a white precipitate which was filtered off and proved to be the crude phosphine 21a. This material was immediately suspended in 500 ml. of acetone, and 10% H_2O_2 (1 equiv.) was added slowly. Crude o-tolyldiphenylphosphine oxide (21) precipitated from solution during the oxidation reaction and, after standing overnight, was collected by filtration and washed with water. After vacuum drying in the drying oven (10 hours, 70°) crude oxide 21 was obtained (107.5 g., 74%; m.p. 124-125°, lit.[25] m.p.

122-123°). IR and NMR spectral data (Plates VII and VIII) support the structure of the phosphine oxide 21.

Preparation of o-Carboxyphenyldiphenylphosphine Oxide (22).[48,58] The o-tolyldiphenylphosphine oxide (64 g., 0.22 mole) (21) was dissolved in 265 ml. of pyridine and 140 ml. of water was added. The solution was heated to a boil and powdered potassium permanganate (158 g., 1.0 mole) was added portionwise over a 5-hour period. After the mixture was boiled for 3 hours, the addition was complete and stirring was continued overnight. The reaction mixture was then filtered and the crude cake of manganese dioxide was added to a pyridine-water mixture, which was heated and refiltered. The filtrates were combined and cooled by the addition of ice (≈200 g.). The product was precipitated by addition of conc. HCl (to pH≈1). After filtration, the product was washed with distilled water and redissolved in a solution of 10% $NaHCO_3$. The solution was heated in a steam bath for 20 minutes and filtered to remove unreacted starting material 21 (22.6 g., 35%). The acid was precipitated with conc. HCl, filtered, washed with water, and dried in vacuo to give crude 22 (45.1 g., 64%). Recrystalization from 70% ethanol gave 39.3 g. (56%) of pure acid 22, (m.p. 269-271°, lit.[58] m.p. 274-275°). IR and NMR spectral data (Plates IX and X) confirm the structure of 22.

Preparation of 5,10-Dihydro-5-phenylacridophosphin-10-one-5-Oxide (20).[58] In a 1000-ml. beaker was placed 400 ml. of 115% PPA which was then heated on a hot plate to 175°. To this was slowly added acid 22 (19.5 g., 0.06 mole) over a 1-hour period followed by an additional 1 hour of stirring. The reaction mixture became pink at the beginning and gradually darkened. After the solution was cooled to 80°, it was

slowly poured into 2000 ml. of ice water and stirring was continued to produce a homogeneous mixture (≈2 hours). After standing overnight, the solution deposited a white solid which was filtered off and washed with a small amount of water. The crude oxide 20 was then suspended in a solution of 10% $NaHCO_3$, stirred for 0.5 hour, and then allowed to stand for 2 days. Unreacted acid 22 and acidic impurities were dissolved in $HaHCO_3$ solution, and crude oxide 20 slowly precipitated. By using a disposable pipette, it was possible to remove (with much care) the top aqueous layer without disturbing the fine, powdery precipitate. After most of the bicarbonate solution was removed, the remaining solid was slowly filtered out and air-dried to give crude oxide 20. Recrystalization of crude 20 (absolute ethanol) gave 11.7 g. (63.6%) of pure oxide 20, m.p. 219-220° (lit.[58] m.p. 222-223°). IR and NMR spectral data (Plates XI and XII) support the structure of 20.

Preparation of 5,10-Dihydro-5-phenylacridophosphin-10-one (19).[43] Trichlorosilane (13.55 g., 0.10 mole) [commercial product from Aldrich Chemical Company] in 20 ml. of dry benzene was added dropwise to a solution of compound 20 (6.08 g., 0.02 mole) in 80 ml. of dry benzene. The mixture was then boiled gently under N_2 for 10 hours. Hydrolysis with a large excess of 20% NaOH (about 100 ml.) was performed cautiously, with ice-bath cooling, to give a clear solution. The benzene layer was removed, and the aqueous layer was extracted with 50 ml. of benzene. The extracts were combined with the organic layer, and the resulting solution was washed with 10 ml. of saturated NH_4Cl (aq.) and 10 ml. of water, dried (Na_2SO_4), and concentrated to give 5.85 g. of crude phosphine 19. Recrystallization (absolute ethanol) gave pure

19 (5.16 g., 90%; m.p. 138-140°, lit.[58] m.p. 135°). IR and NMR spectral data (Plates XIII and XIV) support the structure of keto-phosphine 19.

Preparation of 5,10-Dihydro-5-methyl-5-phenylacridophosphinium Iodide (46). Keto-phosphine (19) (1.44 g., 5 mmole) was dissolved in 20 ml. of dry benzene, and methyl iodide (1.42 g., 10 mmole) in 20 ml. of dry benzene was added. The mixture was then boiled under N_2 (10 hours). A brown precipitate was obtained. The solution was allowed to cool and was then filtered to give crude salt 46. Recrystallization (absolute ethanol) gave pure salt 46 (1.74 g., 81%; m.p. 254.5-255.5°). An alcoholic solution of the phosphonium salt 46 gave a yellowish precipitate with silver nitrate solution. IR and NMR spectral data (Plates XV and XVI) confirm the structure of 46.

Anal. Calcd. for $C_{20}H_{16}OPI$: C, 55.81; H, 3.72; P, 7.21.

Found: C, 56.00; H, 3.78; P, 7.34.

Preparation of cis- and trans-5,10-Dihydro-10-methyl-5-phenyl-acridophosphin-10-ol 5-Oxide (34). Methylmagnesium iodide was prepared by adding methyl iodide (14.2 g., 0.1 mole) in 100 ml. of anhydrous ether to magnesium turnings (2.43 g., 0.1 g. at.) covered with 50 ml. of anhydrous ether. The reaction was completed in 5 hours with constant stirring (magnetic) at room temperature and under N_2. Freshly distilled anhydrous THF (250 ml.) was slowly poured into the Grignard solution, which was then concentrated to remove about 200 ml. of solvent. By this procedure, ether in the Grignard solution was replaced by THF. Keto-phosphine oxide 20 (6.08 g., 0.02 mole), previously dissolved in 200 ml. of hot anhydrous THF, was added through an addition funnel dropwise but rapidly into the Grignard solution,

kept at room temperature. When the addition was complete, 100 ml. more of hot THF was added to the addition funnel to dissolve a small amount of compound 20 which had crystallized out from THF and had remained in the addition funnel. The reaction mixture was then boiled for 10 hours under N_2. After cooling in the ice-water bath, the mixture was concentrated to approximately 20 ml.; this was followed by hydrolysis with saturated NH_4Cl solution ($\approx$ 20 ml.) and the resulting mixture was stirred for 1 hour and allowed to stand for 1 hour more. The crude product precipitated out as a white solid which was filtered off and recrystallized (absolute ethanol) to give pure oxide 34a (cis or trans isomer) (1.53 g., 24%; m.p. 329-330°). IR and NMR spectral data (Plates XVIII and XIX) confirm the structure of 34a.

Anal. Calcd. for $C_{20}H_{17}O_2P$: C, 75.00; H, 5.31; P, 9.70.
Found: C, 75.10; H, 5.48; P, 9.74.

The solvent from the mother liquor was evaporated to give a gummy solid which was dissolved in 20 ml. of benzene; this solution, after standing for 5 hours, slowly deposited a small amount of white solid. This was identified by IR analysis to be starting material keto-phosphine oxide 20. The benzene layer was then decanted and evaporated to give a gummy solid which was recrystallized by dissolving the solid in minimum benzene and slowly adding hexane to cloudiness. A white solid precipitated slowly (overnight). According to the NMR spectrum (Plate XX), the product appeared to be a mixture of both isomers 34a and 34b. By the ratio of NMR signals for methyl protons at δ 1.14 and δ 1.76, isomer 34b (δ 1.75) constituted approximately 80% of this mixture.

In each of three recrystallizations, the compound was dissolved in minimum ethanol and benzene added (300%); the solution was concentrated to one-half volume, and diluted with more benzene, and allowed to stand overnight. Nearly all of the ethanol had to be displaced before crystals deposited. By such purification, isomer 34b was obtained (1.2 g., 20%; m.p. 261-262°). IR and NMR spectral data (Plates XXI and XXII) confirm the structure of 34b.

Anal. Calcd. for $C_{20}H_{17}O_2P$: C, 75.00; H, 5.31; P, 9.70.

Found: C, 75.30; H, 5.27; P, 9.73.

All the mother liquors were combined and then concentrated to give a mixture of isomers 34a and 34b (1.0 g., 15%). However, further separation was not attempted.

Preparation of 5,10-Dihydro-10-ethyl-5-phenylacridophosphin-10-ol 5-Oxide (47). The procedure was similar to that used for the preparation of compounds 34a and 34b. Ethylmagnesium bromide was prepared by addition of ethyl bromide (2.18 g., 20 mmole) in anhydrous ether (15 ml.) to magnesium (0.486 g., 0.02 g. at.) covered with 5 ml. of anhydrous ether. The solvent (ether) was distilled off while being replaced by THF (50 ml.). Keto oxide 20 (1.52 g., 5 mmole) in 50 ml. of hot anhydrous THF was added to the freshly prepared Grignard reagent. The reaction mixture was boiled for 10 hours under N_2. The product was worked up as before and the crude product was recrystallized (absolute ethanol) to give pure alcohol 47 (0.51 g., 30%; m.p. 269-271°). Isolation of the other isomer was not attempted. IR and NMR spectral data (Plates XXIII and XXIV) confirm the structure of 47.

Anal. Calcd. for $C_{21}H_{19}O_2P$: C, 75.45; H, 5.65; P, 9.30.

Found: C, 75.49; H, 5.71; P, 9.34.

Preparation of cis- and trans-5,10-Dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium Iodide (35). To the Grignard reagent prepared by adding methyl iodide (9.94 g., 70 mmole) in 30 ml. of THF to magnesium (1.215 g., 0.05 g. at.) covered with 25 ml. of THF was added slowly, with cooling, keto phosphine 19 (1.44 g., 5 mmole) in 50 ml. of freshly distilled THF. After the addition was completed, the reaction mixture was boiled overnight (about 12 hours). After cooling in the ice-water bath, hydrolysis was performed by slowly adding saturated NH_4Cl solution ($\approx$20 ml.). The product was a gummy solid which would not dissolve in the THF but was, however, soluble in methylene chloride (50 ml.). Consequently, the organic layer was separated and the aqueous layer was extracted with 50 ml. of methylene chloride. The combined organic layers were dried ($MgSO_4$, 2-3 hours). Removal of the solvent using a rotary evaporator gave 1.5 g. of crude product. Recrystallization (twice) from benzene [as described for purification of isomer 34b except more ethanol ($\approx$20 ml.) was used] and then once from absolute ethanol gave shiny crystals of pure salt 35a (0.16 g., 8%; m.p. 282-283°). IR and NMR spectral data (Plates XXV and XXVI) confirm the structure of 35a.

Anal. Calcd. for $C_{21}H_{20}OPI$: C, 56.50; H, 4.48; P, 6.95.

Found: C, 56.63; H, 4.57; P, 6.96.

All the mother liquors were combined and the solution was concentrated to give a mixture of isomers 35a and 35b [as shown in NMR spectrum (Plate XXVII)]. After two recrystallizations (benzene-ethanol; same technique as cited previously), isomer 35b was obtained in the pure form (0.7 g., 29%; m.p. 276-277.5°). IR and NMR spectral data (Plates XXVIII and XXIX) confirm the structure of 35b.

Anal. Calcd. for $C_{21}H_{20}OPI$: C, 56.50; H, 4.48; P, 6.95.

Found: C, 56.52; H, 4.11; P, 7.12.

Preparation of 5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol (30). Methylmagnesium iodide was prepared by adding methyl iodide (1.78 g., 12.5 mmole) in 20 ml. of anhydrous ether to magnesium turnings (0.304 g., 0.0125 g. at.) covered with 10 ml. of anhydrous ether. The reaction was completed in 4 hours when all the magnesium was consumed. Cold THF (100 ml.) was poured into the Grignard solution and again ether was distilled out. Keto-phosphine 19 (1.44 g., 5 mmole) in 50 ml. of freshly distilled THF was added to the Grignard solution at room temperature under N_2. After the addition ($\approx$1 hour), the reaction mixture was stirred at room temperature for 1 hour and heated for 2 hours at gentle reflux. After the mixture was cooled, saturated NH_4Cl solution (10 ml.) was added. The THF layer was separated, and the aqueous layer was extracted with two 50-ml. portions of benzene. The combined organic layers were dried ($MgSO_4$, 2-3 hours). Removal of the solvent using a rotary evaporator gave 1.45 g. of crude alcohol 30. Recrystallization (benzene-hexane; same technique as for crude 34b) gave 30 in crystal form (1.25 g., 81%; m.p. 141-142°). The NMR spectrum showed the presence of recrystallization solvent trapped in the crystals which could not be removed by vacuum drying (110°/0.01 mm). However, a small amount of the crystals was ground to a fine powder and then sublimed at 135°/0.025 mm to give pure phosphine 30 (m.p. 156-157°). IR and NMR spectral data (Plates XXX and XXXI) support the structure of 30.

Anal. Calcd. for $C_{20}H_{17}OP$: C, 78.95; H, 5.59; P, 10.20.

Found: C, 79.28; H, 5.51; P, 10.25.

Phosphine 30 (100 mg.) in 20 ml. of benzene was converted to the oxide 34b by using an excess (≈ 5 ml.) of 10% H_2O_2. After stirring at room temperature for 12 hours, a quantitative yield of the product 34b (m.p. 261°) was obtained. On the basis of m.p., mixed m.p., NMR and IR spectral data, the product was found to be identical to compound 34b previously prepared. Phosphine 30 (100 mg.) was converted to the phosphonium salt 35b by addition of an excess of methyl iodide (93.4 mg., 0.7 mmole). After stirring at room temperature for 24 hours, the mixture gave a quantitative yield (150 mg.) of the methyl iodide salt 35b. On the basis of the m.p. (276-277°), mixed m.p., NMR and IR spectral data, the salt was identical to compound 35b cited previously.

Preparation of 5,10-Dihydro-5-phenylacridophosphin-10-ol 5-Oxide (33).[60] Keto-phosphine oxide 20 (0.76 g., 2.5 mmole) was dissolved in 70 ml. of hot 95% ethanol. After the solution had slowly cooled to room temperature, it was treated with sodium borohydride powder (0.28 g., 7.5 mmole) slowly. After being stirred at room temperature for 2 hours, the reaction mixture was treated with water (5 ml.) and warmed on a steam bath for 5 min. The mixture was cooled in an ice-bath and the resulting solid was filtered off to afford 0.76 g. of crude 33 (m.p. 225-230°, 100%). The solid was recrystallized from absolute ethanol to give 0.6 g. of pure product 33 in nice crystalline form (m.p. 249.5-250.5°, 80%). IR and NMR spectral data (Plates XXXV and XXXVI) confirm the structure of 33.

Anal. Calcd. for $C_{19}H_{15}O_2P$: C, 74.51; H, 4.90; P, 10.13.

Found: C, 74.33; H, 5.04; P, 10.05.

Attempted Preparation of 5,10-Dihydro-5-phenylacridophosphin-10-ol (32). Keto-phosphine 19 (0.72 g., 2.5 mmole) was dissolved in 50 ml.

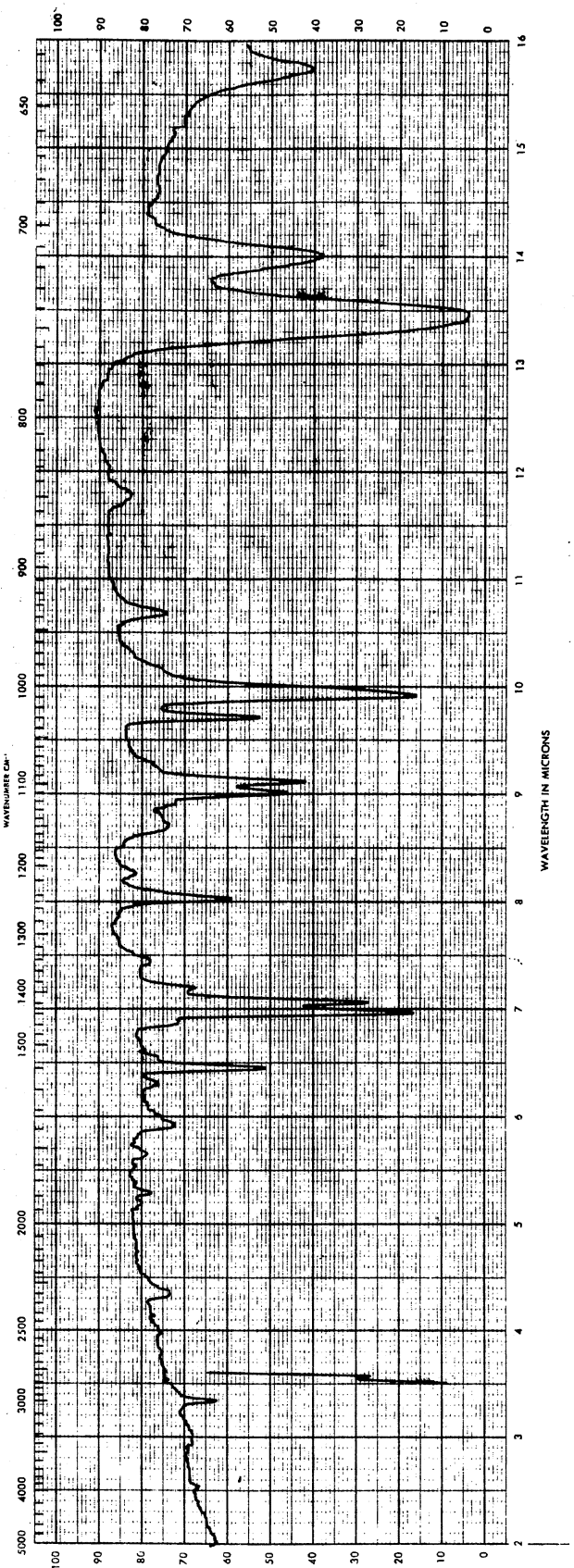
of hot absolute ethanol under N_2. After the solution had slowly cooled to room temperature, it was treated with solid sodium borohydride (0.28 g., 7.5 mmole). After being stirred at room temperature for 2 hours, the reaction mixture was treated with water (5 ml.) and stirred for 20 minutes. The mixture was concentrated to approximately 5 ml.; this was followed by extraction with two 20-ml. portions of benzene. The combined organic layers were dried ($MgSO_4$, 2-3 hours). Removal of the solvent using a rotatory evaporator gave a gummy solid. Recrystallization of this gummy product did not succeed. However, it was converted to the oxide 33 by using an excess of 10% H_2O_2.

Attempted Preparation of 5,10-Dihydro-10-tert-butyl-5-phenyl-acridophosphin-10-ol (31). Keto-phosphine 19 (0.72 g., 2.5 mmole) in 20 ml. of freshly distilled THF was added dropwise over 1 hour to 5 ml. of 1.6 M tert-butyllithium (8 mmole) in 20 ml. of THF. The reaction was performed under N_2 and the temperature was kept below -30°. After the addition was completed the mixture was stirred for 3 hours and then cautiously hydrolyzed by adding 10 ml. of water dropwise. After separation of the organic layer, the aqueous layer was extracted with 50 ml. of benzene. The combined organic layers were dried ($MgSO_4$) and then stripped of solvent on a rotatory evaporator leaving a gummy residue. Recrystallization of this gummy product did not succeed. However, it was converted to the oxide 31a by using excess 10% H_2O_2 (m.p. 283-284°). IR and NMR spectral data (Plates XXXVII and XXXVIII) confirm the structure of 31a. Yield of 31a based on 31 was 72% (0.65 g.).

Anal. Calcd. for $C_{23}H_{23}O_2P$: C, 76.24; H, 6.35; P, 8.56.

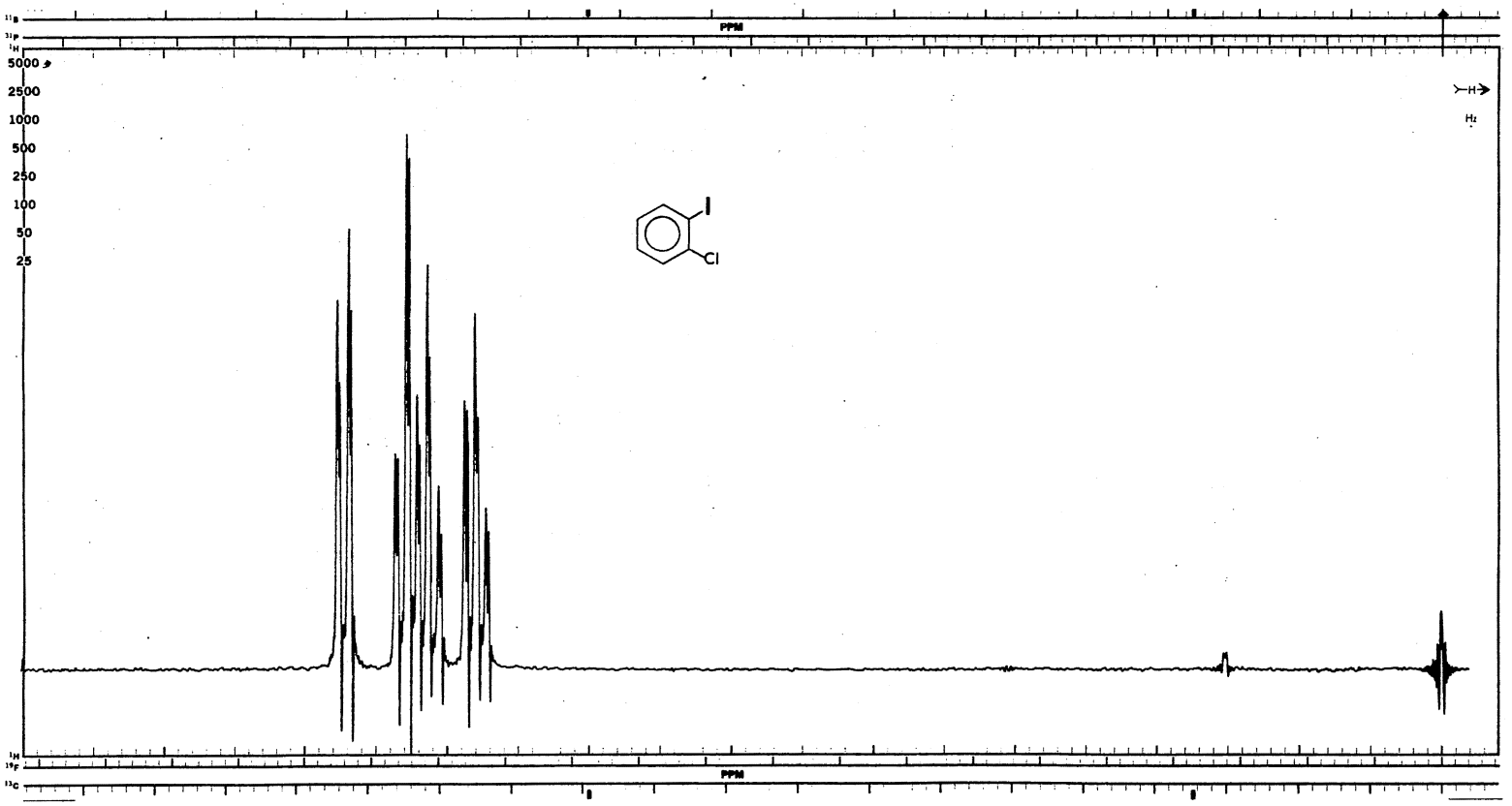
Found: C, 76.10; H, 6.41; P, 8.65.

PLATE I



o-Chloroiodobenzene (23), Film

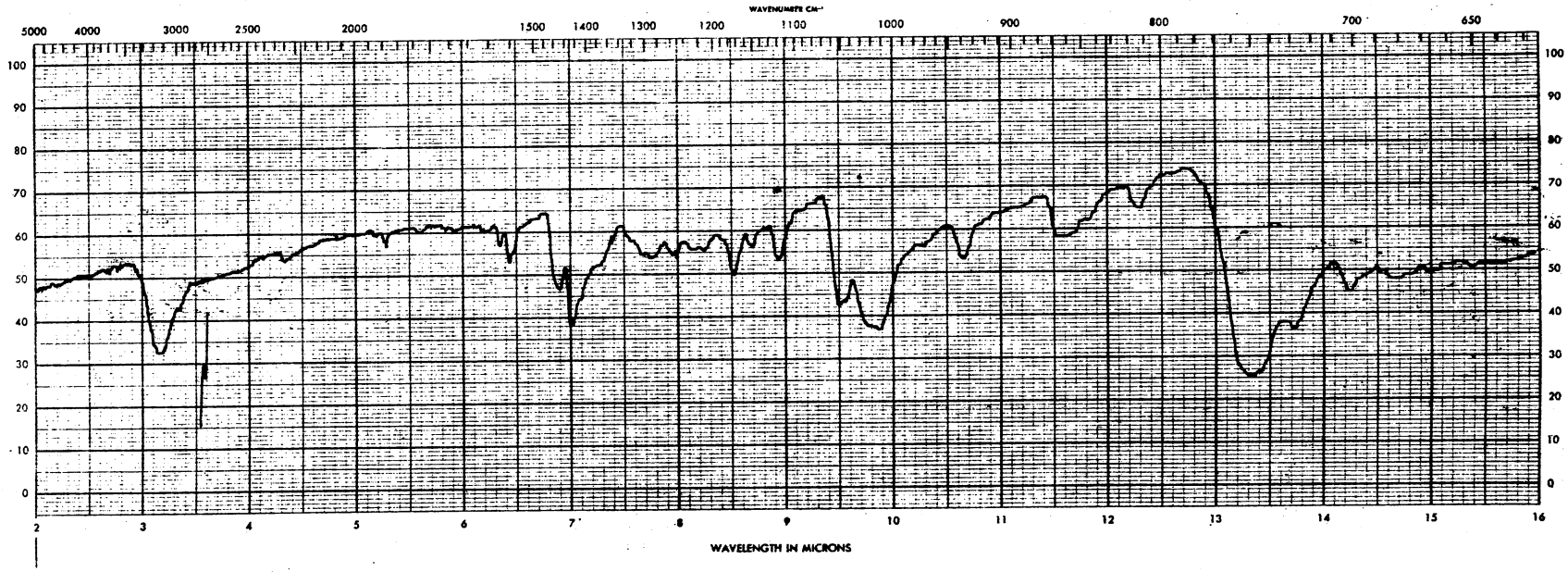
PLATE II



o-Chloroiodobenzene (23)

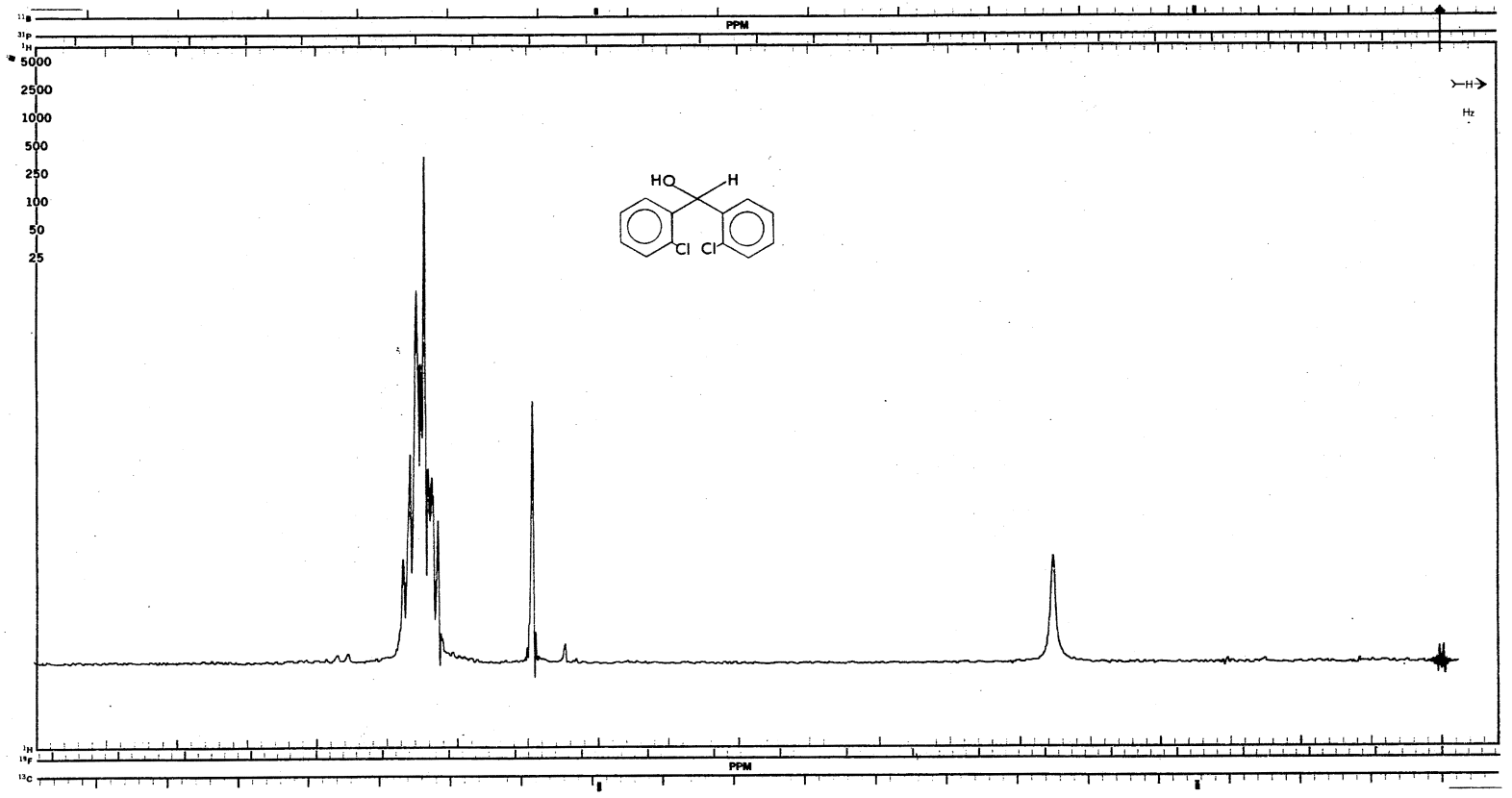
Solvent. . . $DCCl_3$ O.F. . . 100.1 MHz F.B. . . 2 Hz R.F. . . 60 dB
S.W. . . . 1000 Hz S.T. . . . 250 sec S.O. . . 83701 Hz S.A. . . . 2.0 Lock. .HOMO

PLATE III



Bis(2-chlorophenyl)methanol (24), KBr Pellet

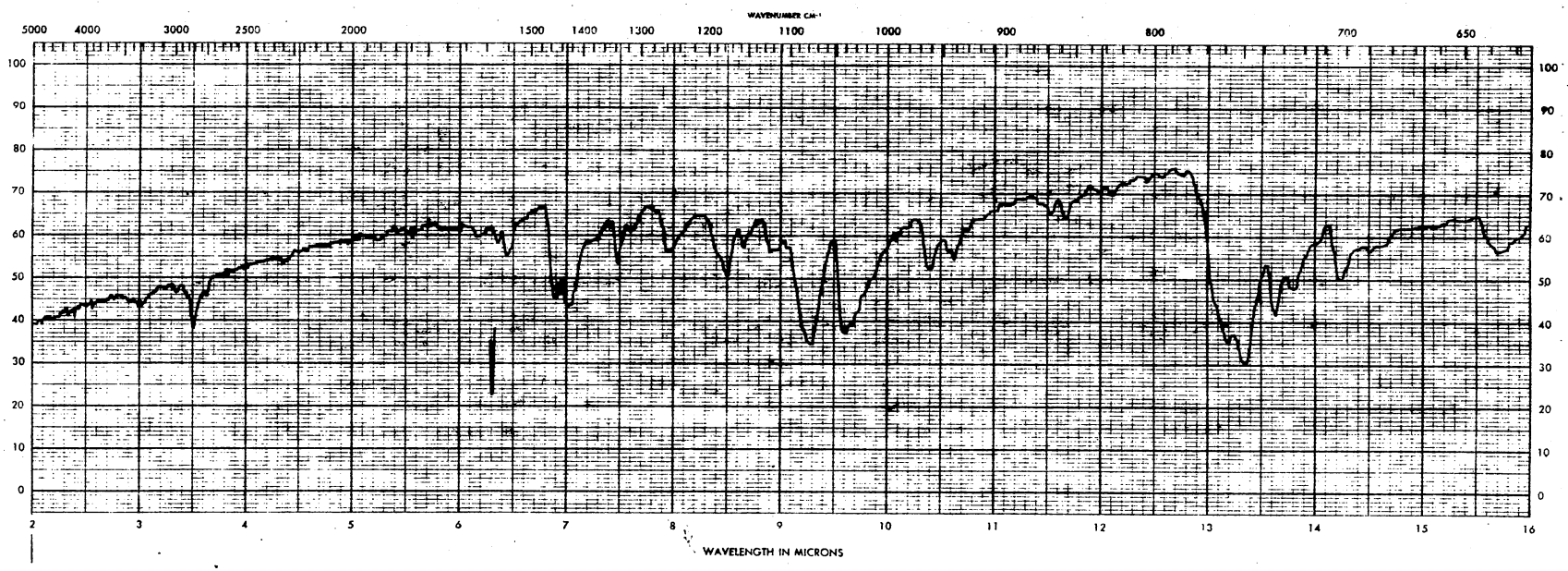
PLATE IV



Bis(2-chlorophenyl)methanol (24)

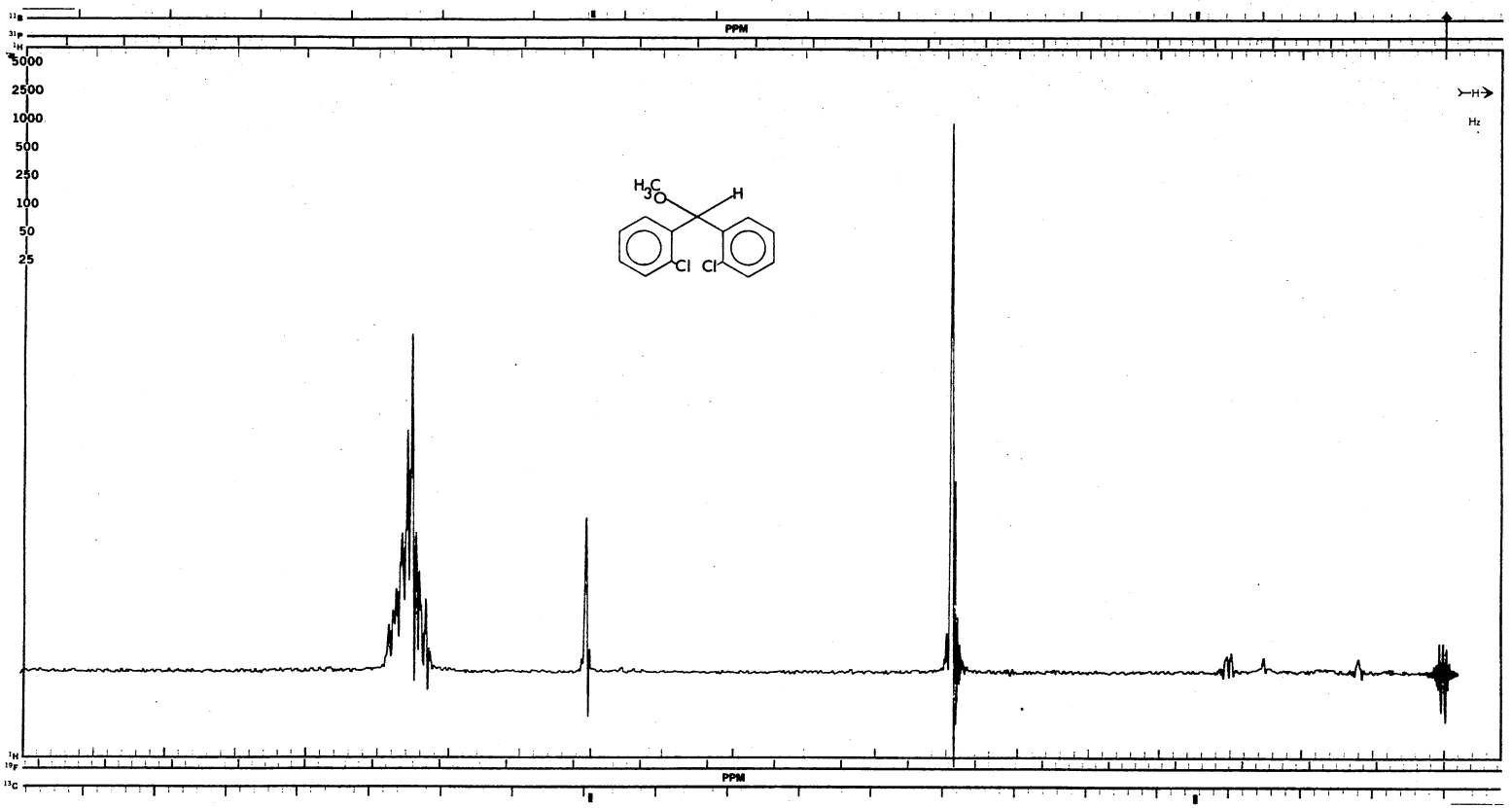
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 67 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 1.6 Lock. .HOMO

PLATE V



Bis(o-chlorophenyl)methoxymethane (25), KBr Pellet

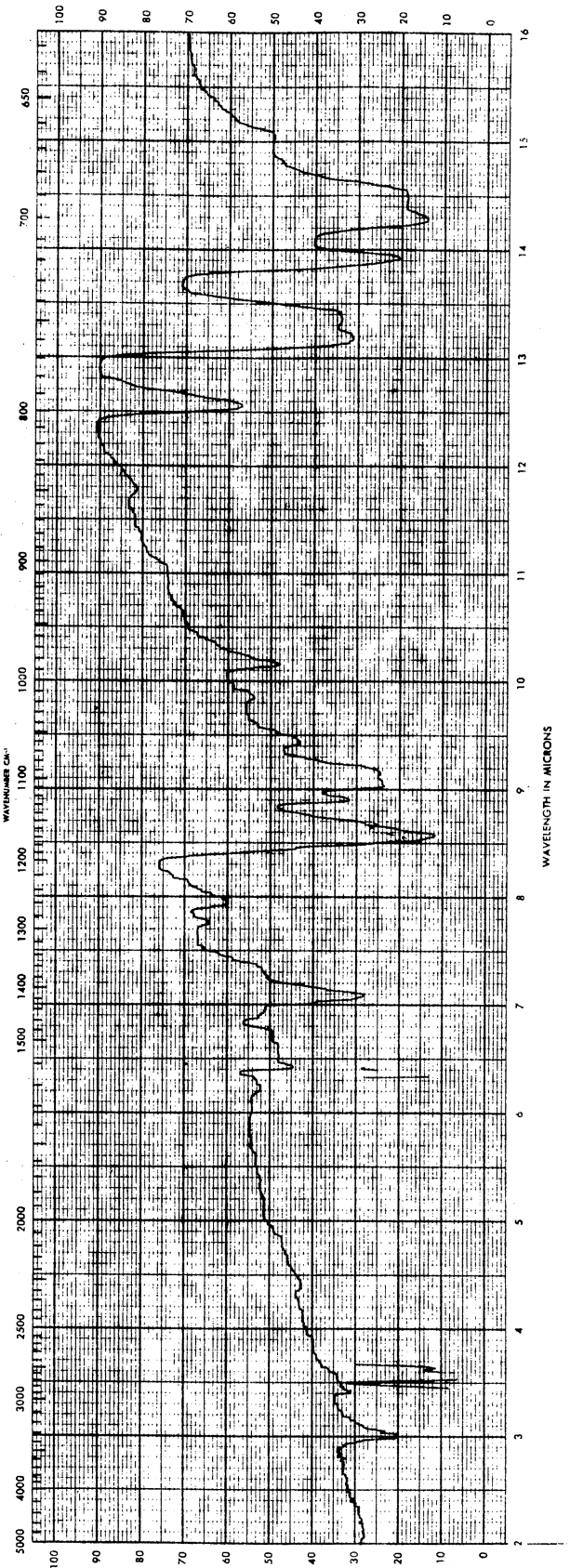
PLATE VI



Bis(o-chlorophenyl)methoxymethane (25)

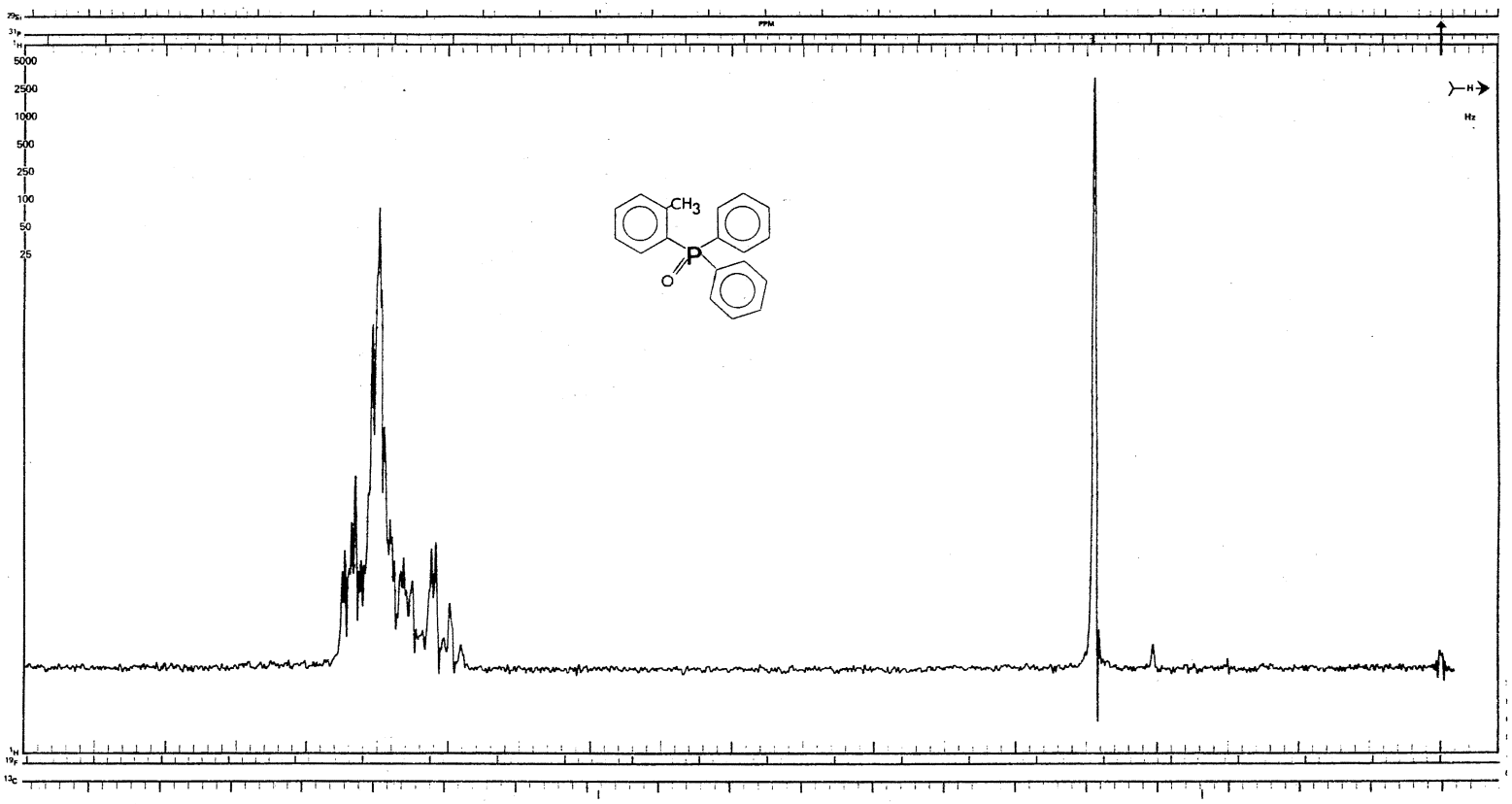
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 67 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 2.0 Lock. .HOMO

PLATE VII



o-Tolyldiphenylphosphine Oxide (21), KBr Pellet

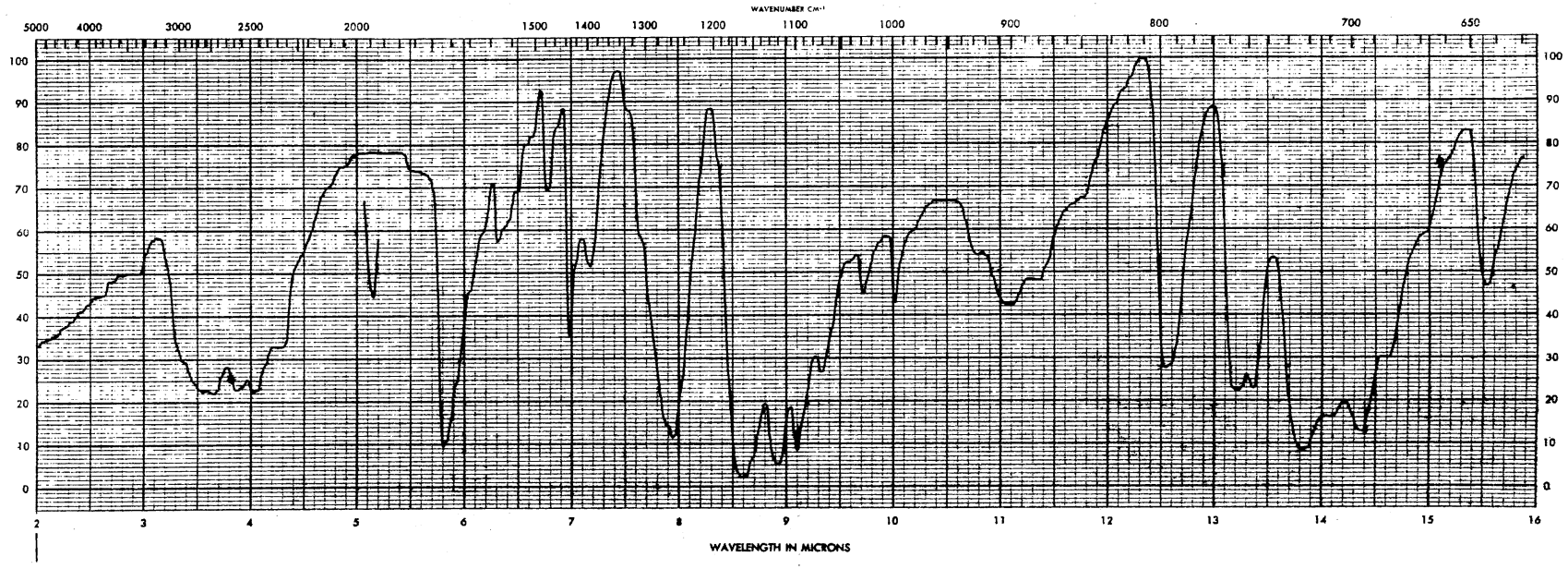
PLATE VIII



o-Tolyldiphenylphosphine (21)

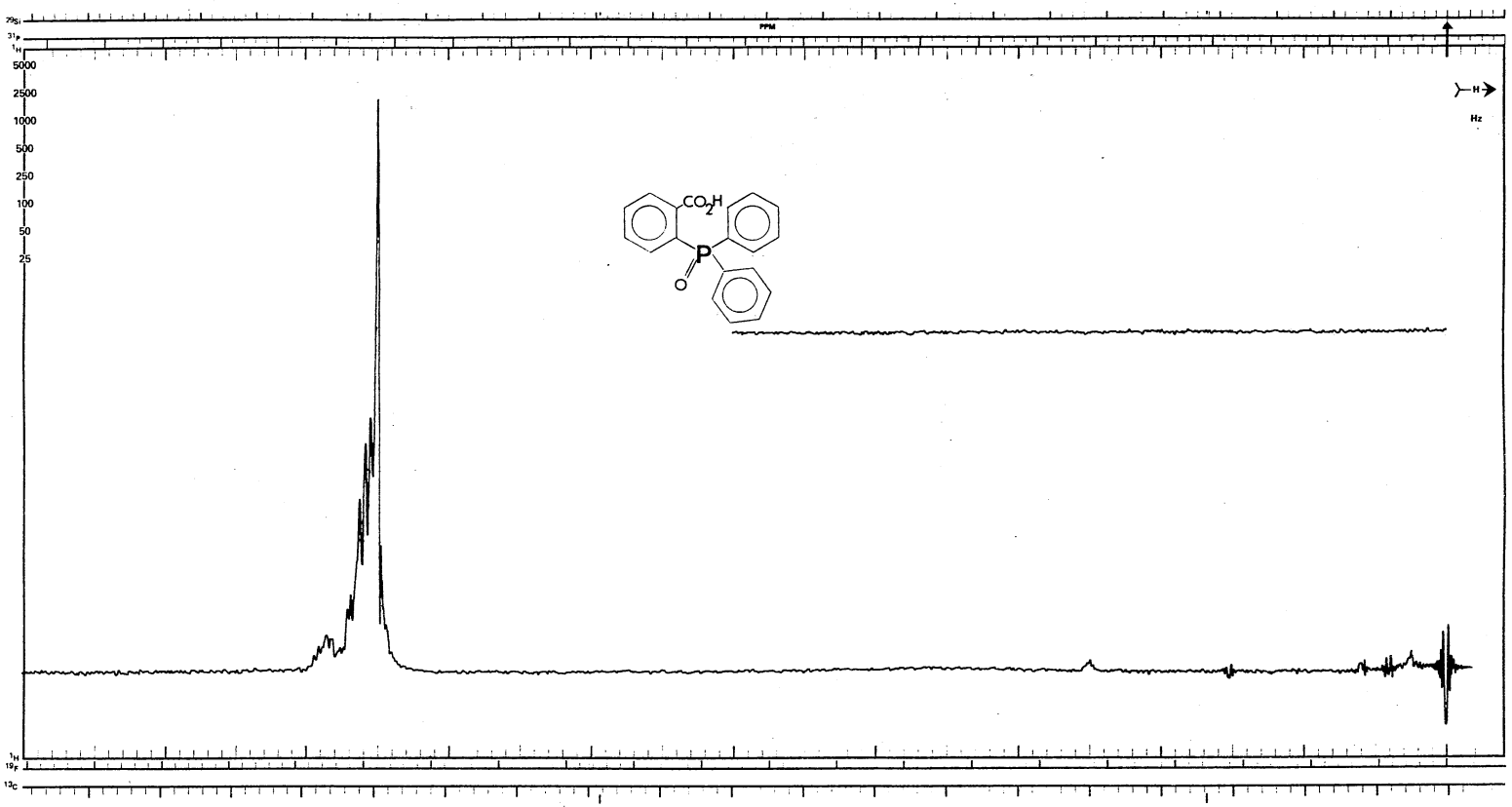
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 69 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 6.3 Lock. .HOMO

PLATE IX



o-Carboxyphenyldiphenylphosphine Oxide (22), KBr Pellet

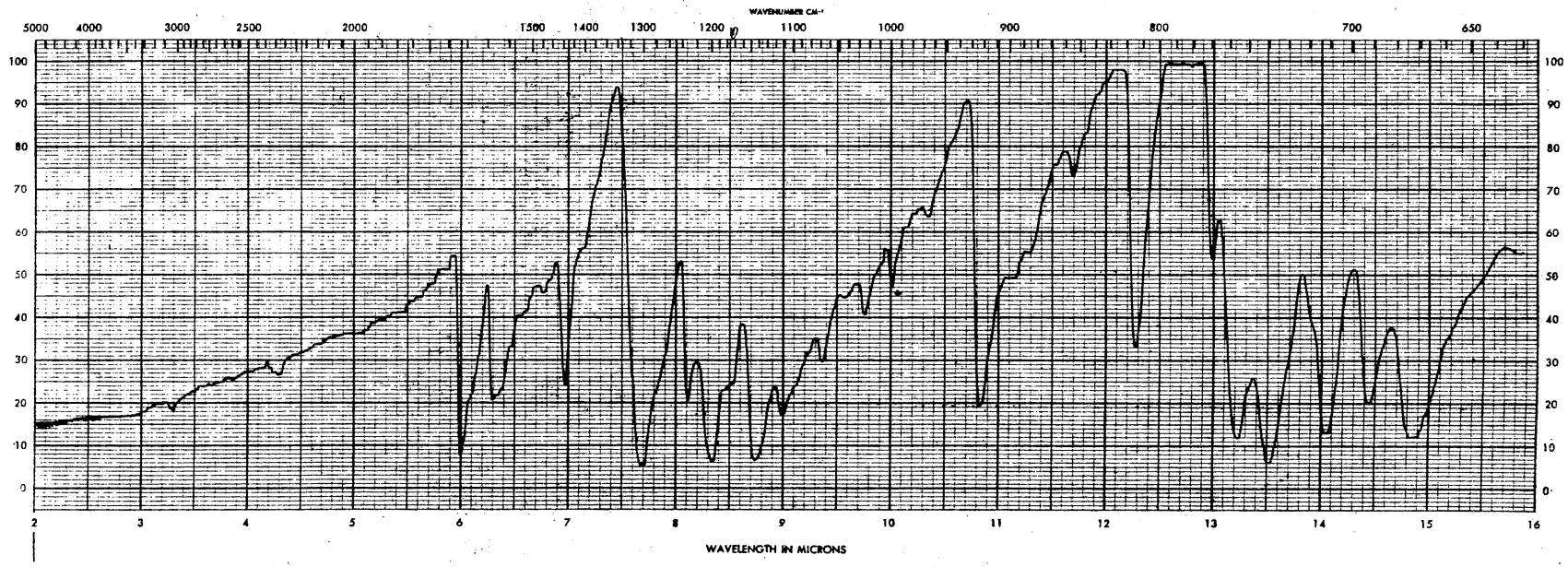
PLATE X



o-Carboxyphenyldiphenylphosphine Oxide (22)

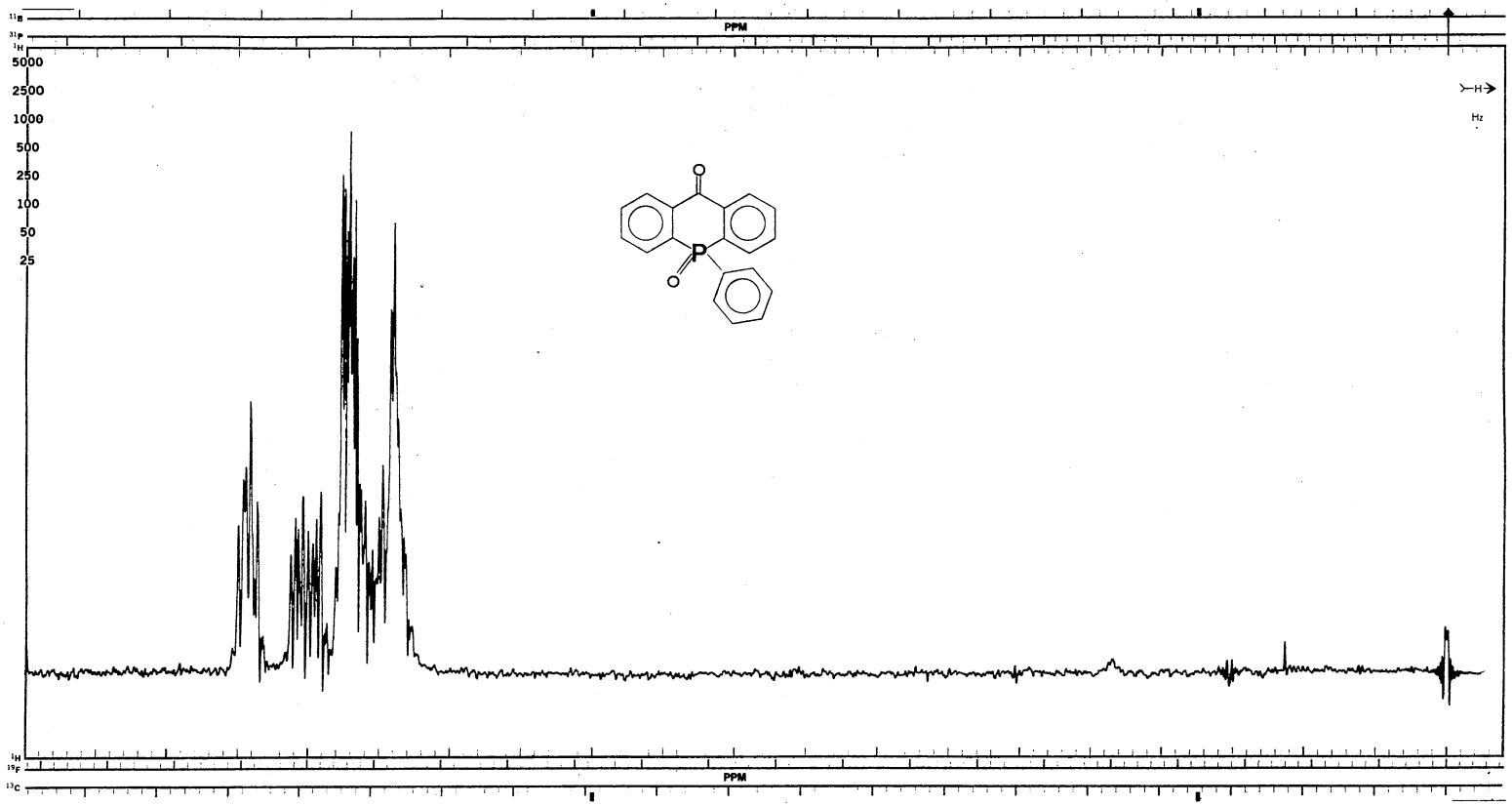
Solvent. . . DMSO-d_6 O.F. . . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 68 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 3.2 Lock. .HOMO

PLATE XI



5,10-Dihydro-5-phenylacridophosphin-10-one 5-Oxide (20), KBr Pellet

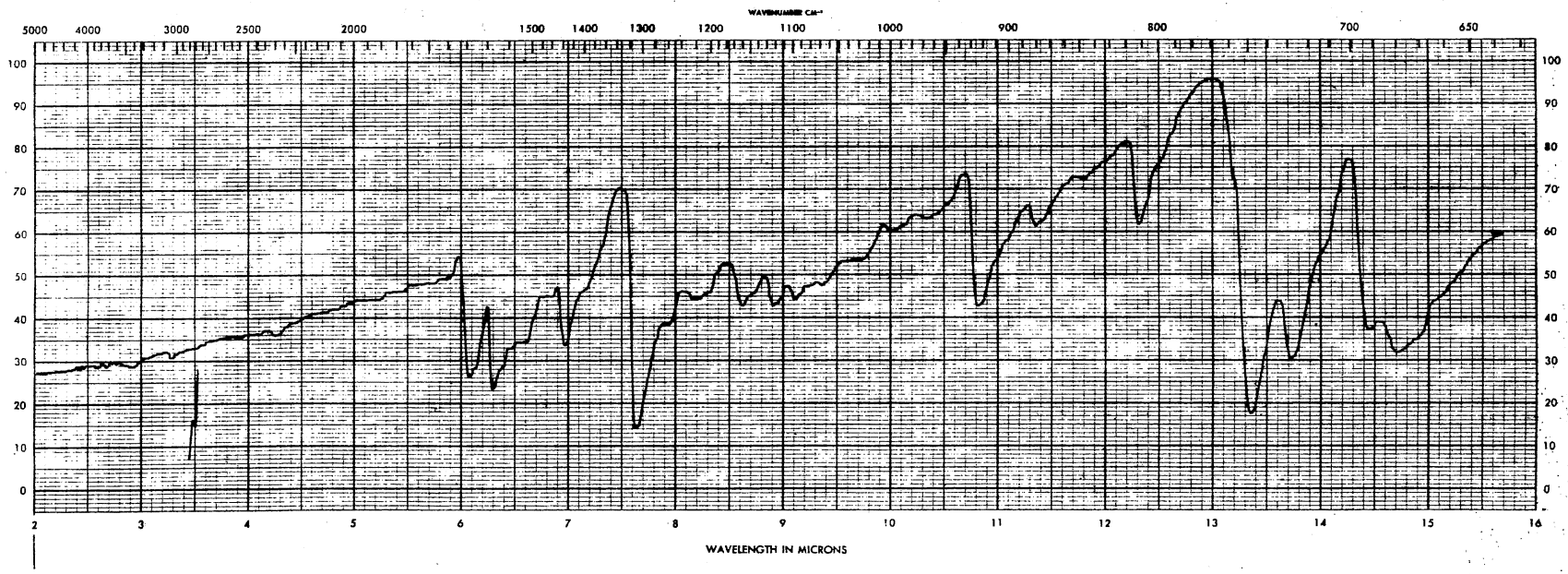
PLATE XII



5,10-Dihydro-5-phenylacridophosphin-10-one 5-Oxide (20)

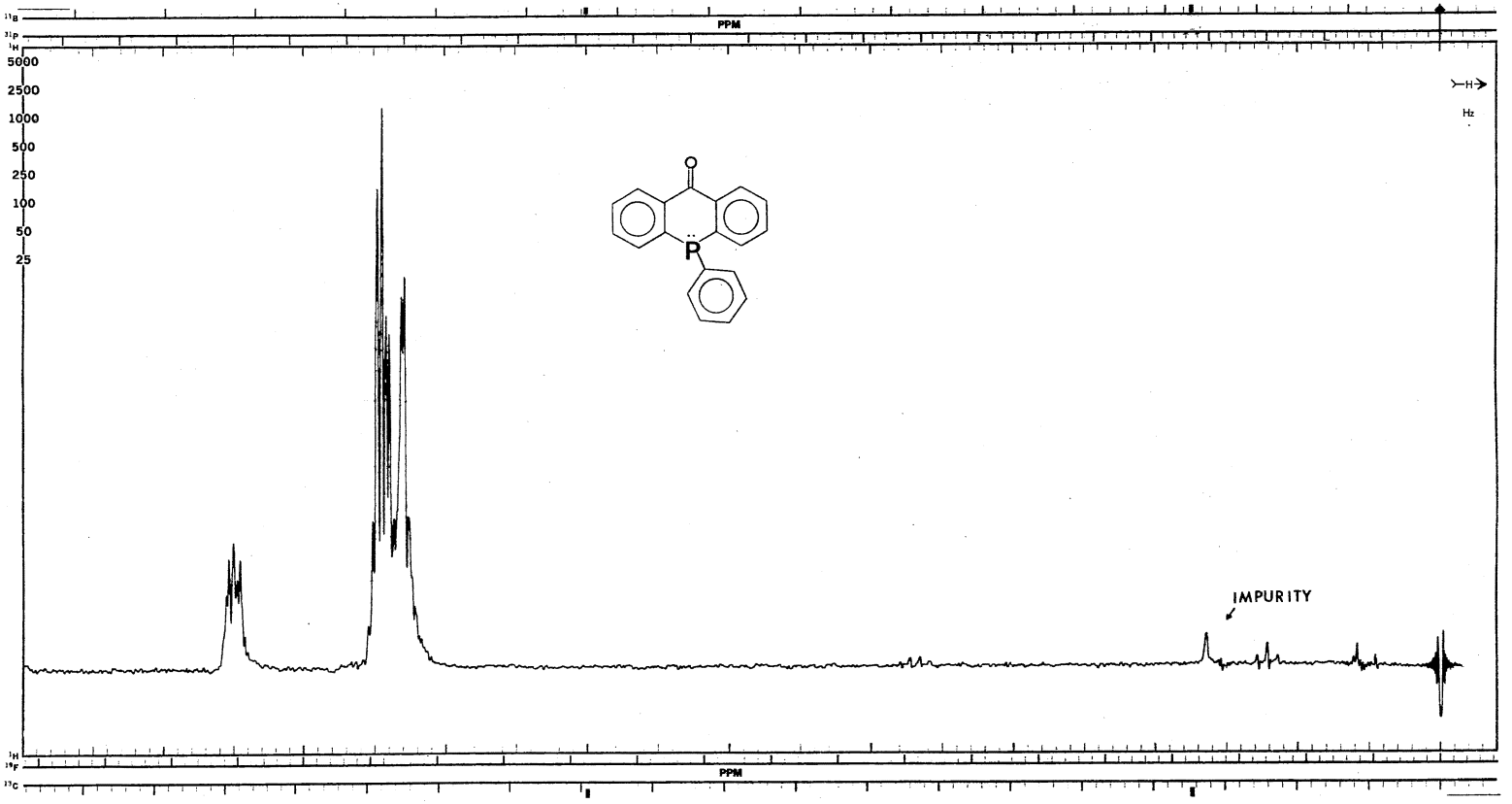
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 72 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . . . 2 Hz S.A. . . . . 8.0 Lock. .HOMO

PLATE XIII



5,10-Dihydro-5-phenylacridophosphin-10-one (19), KBr Pellet

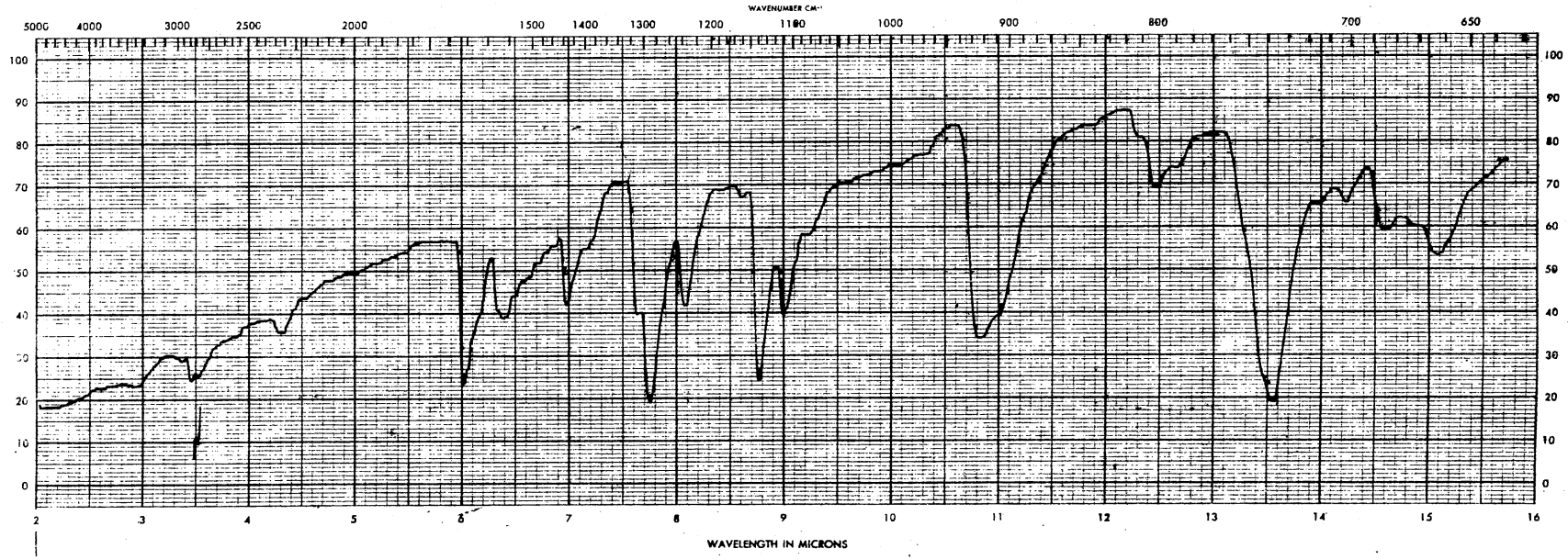
PLATE XIV



5,10-Dihydro-5-phenylacridophosphin-10-one (19)

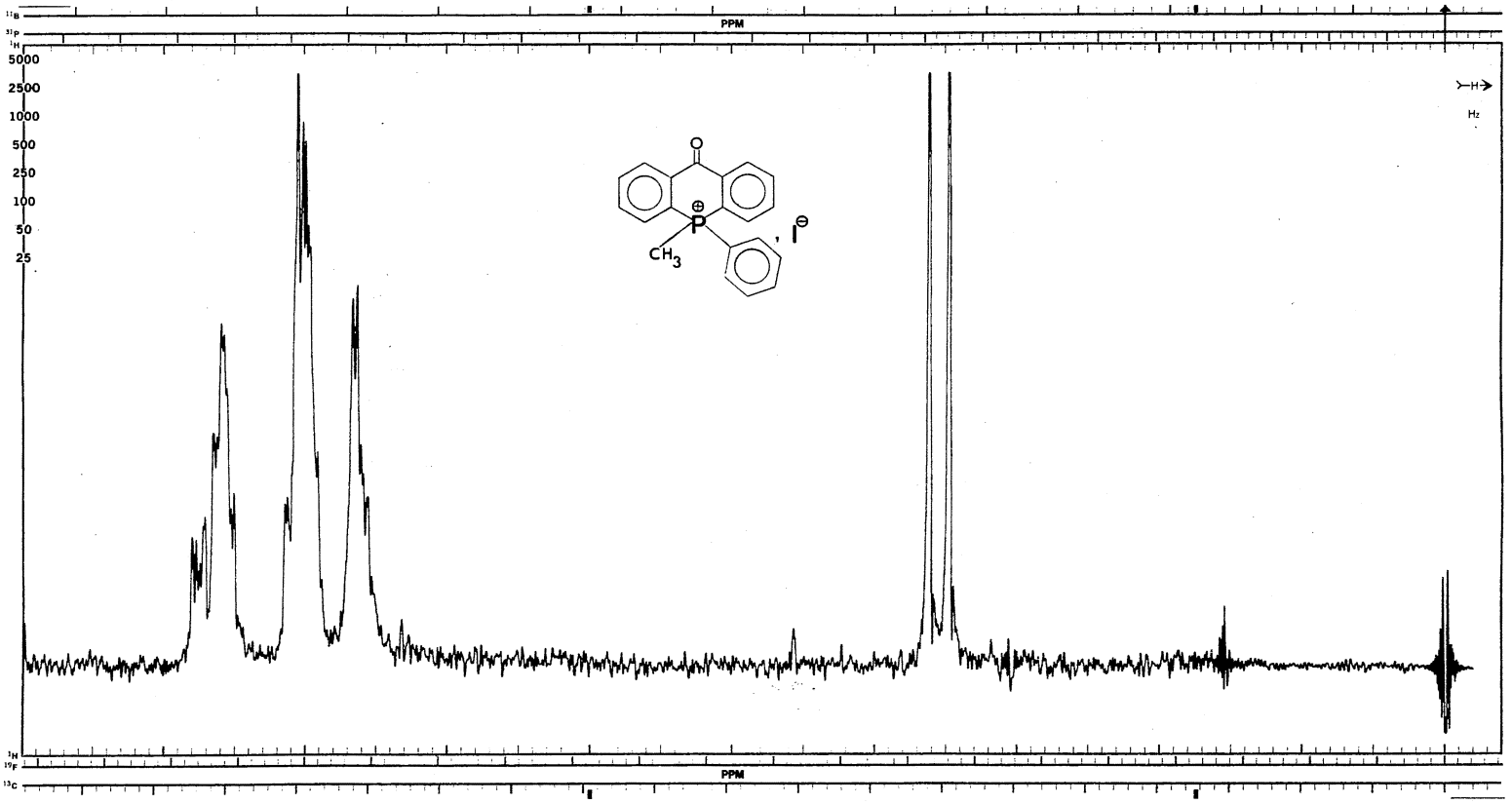
Solvent. . . $DCCl_3$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 72 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 4.0 Lock. .HOMO

PLATE XV



5,10-Dihydro-5-methyl-5-phenylacridophosphinium Iodide (46), KBr Pellet

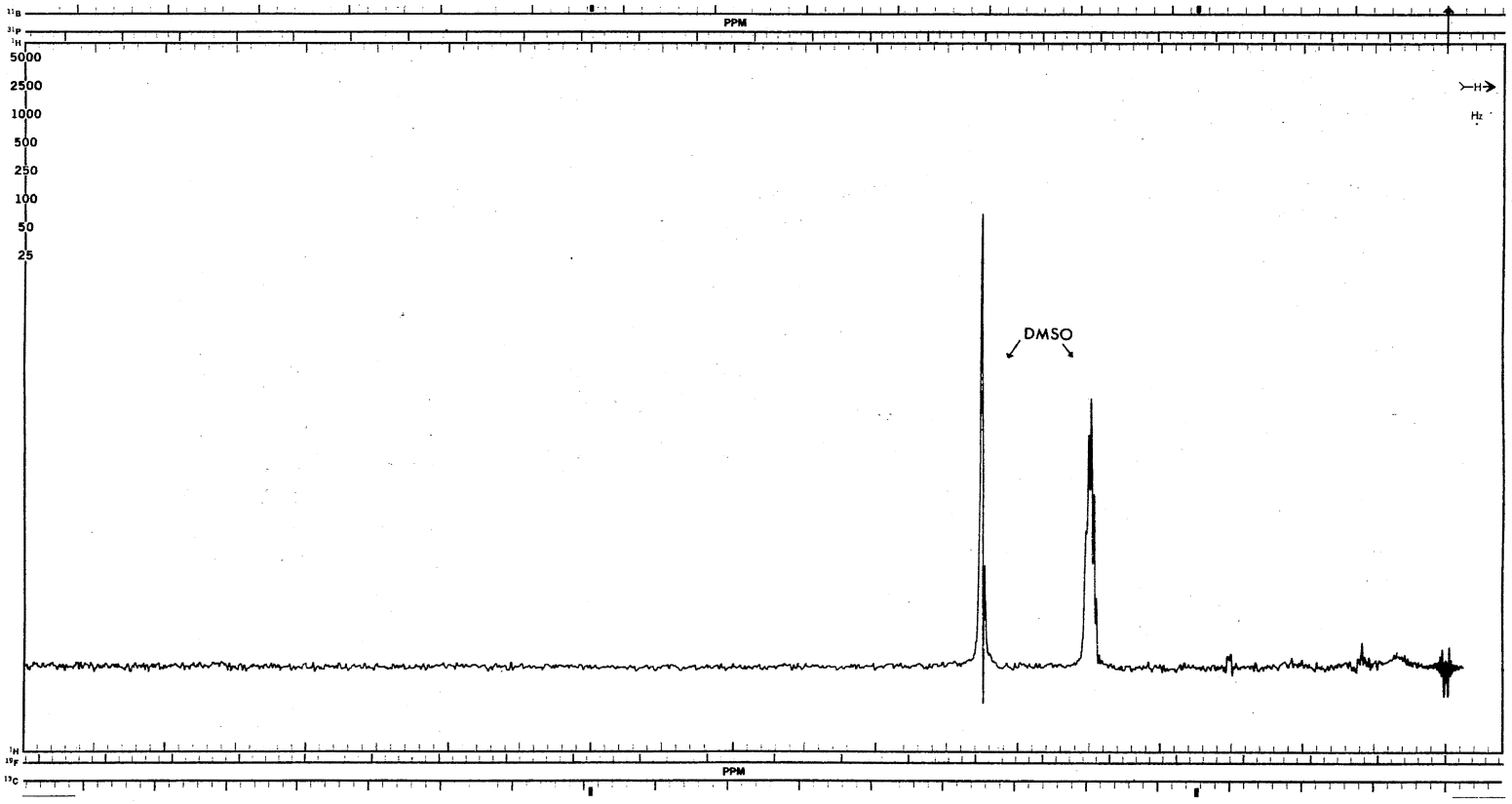
PLATE XVI



5,10-Dihydro-5-methyl-5-phenylacridophosphinium Iodide (46)

Solvent. . . $DCCl_3$ O.F. . . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 73 dB
S.W. . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . .20 Lock. .HOMO

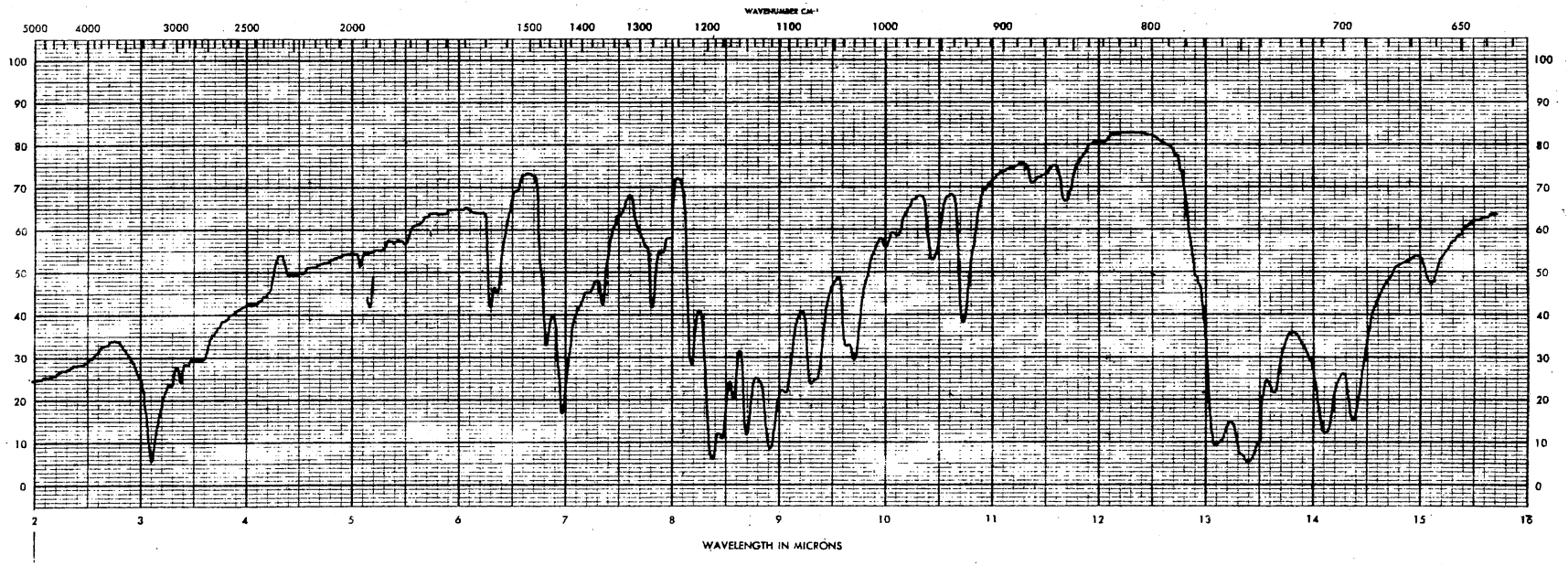
PLATE XVII



DMSO Blank

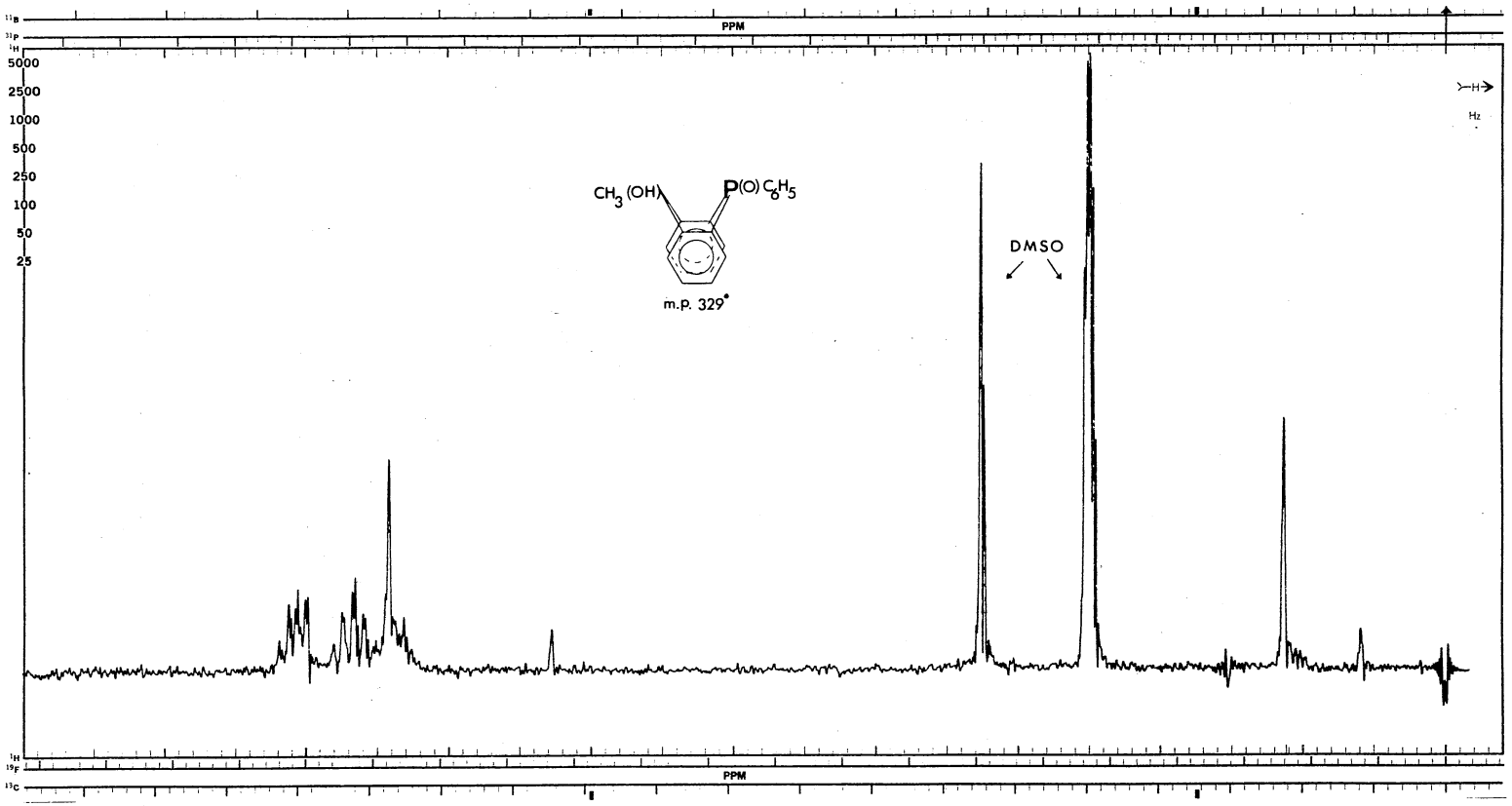
Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 70 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 6.3 Lock. .HOMO

PLATE XVIII



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol 5-Oxide (34a), KBr Pellet

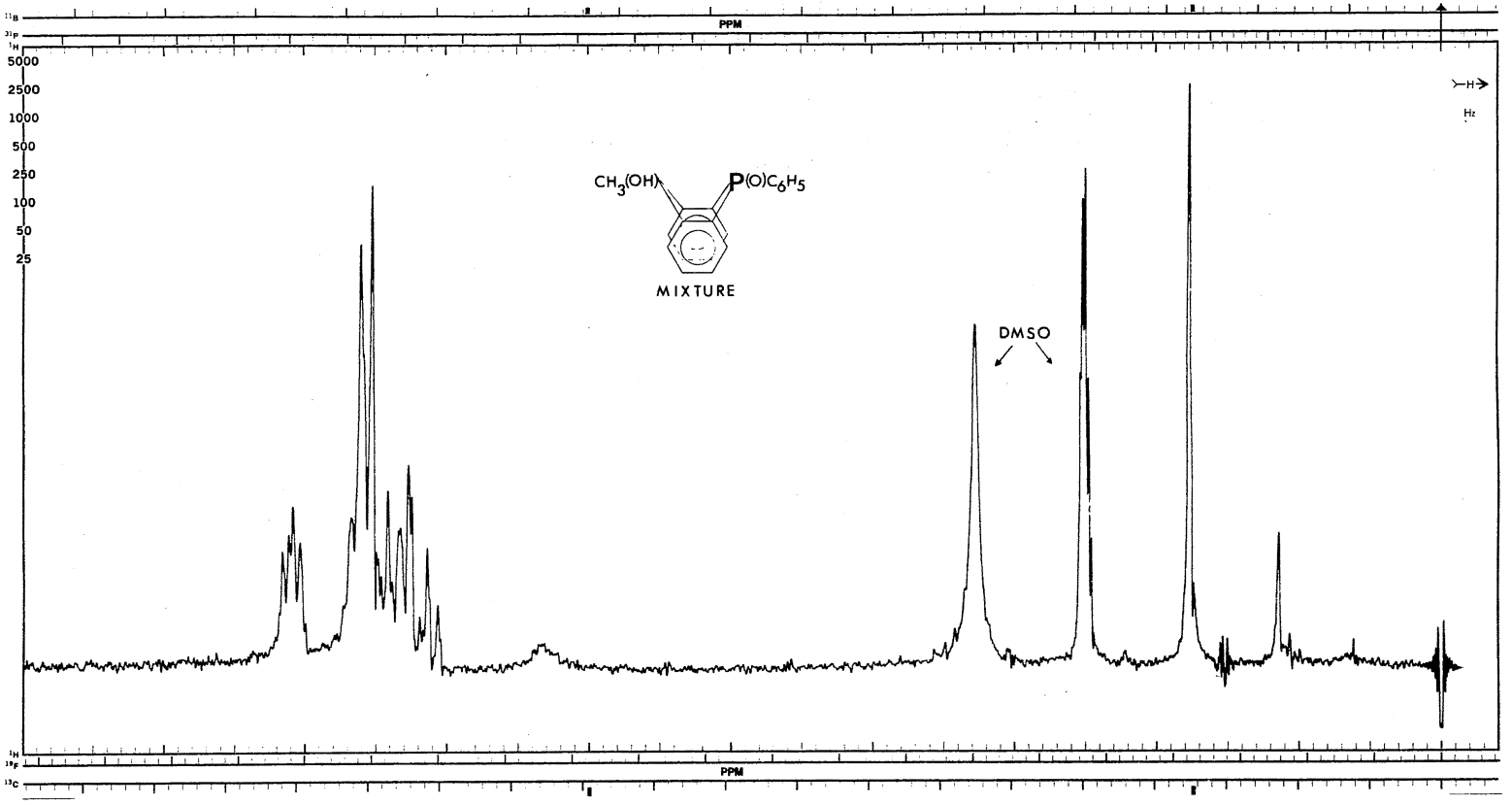
PLATE XIX



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol 5-Oxide (34a)

Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 72 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 8.0 Lock. .HOMO

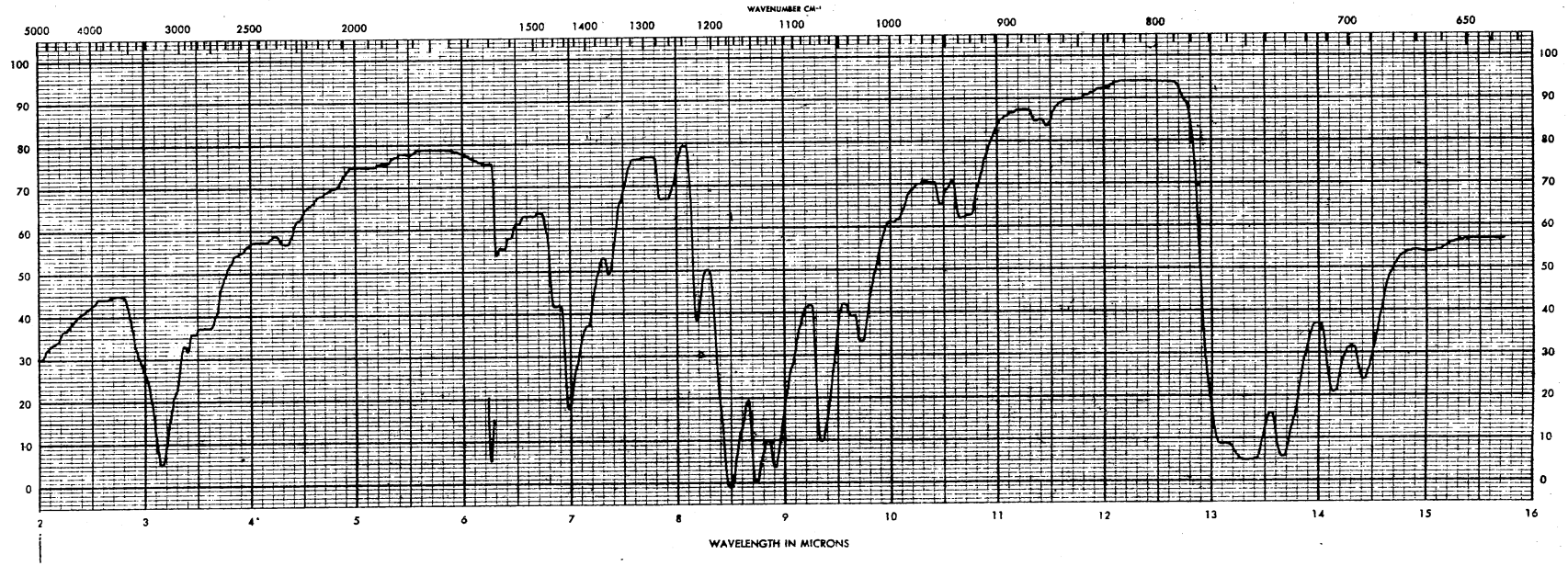
PLATE XX



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol 5-Oxide (34)

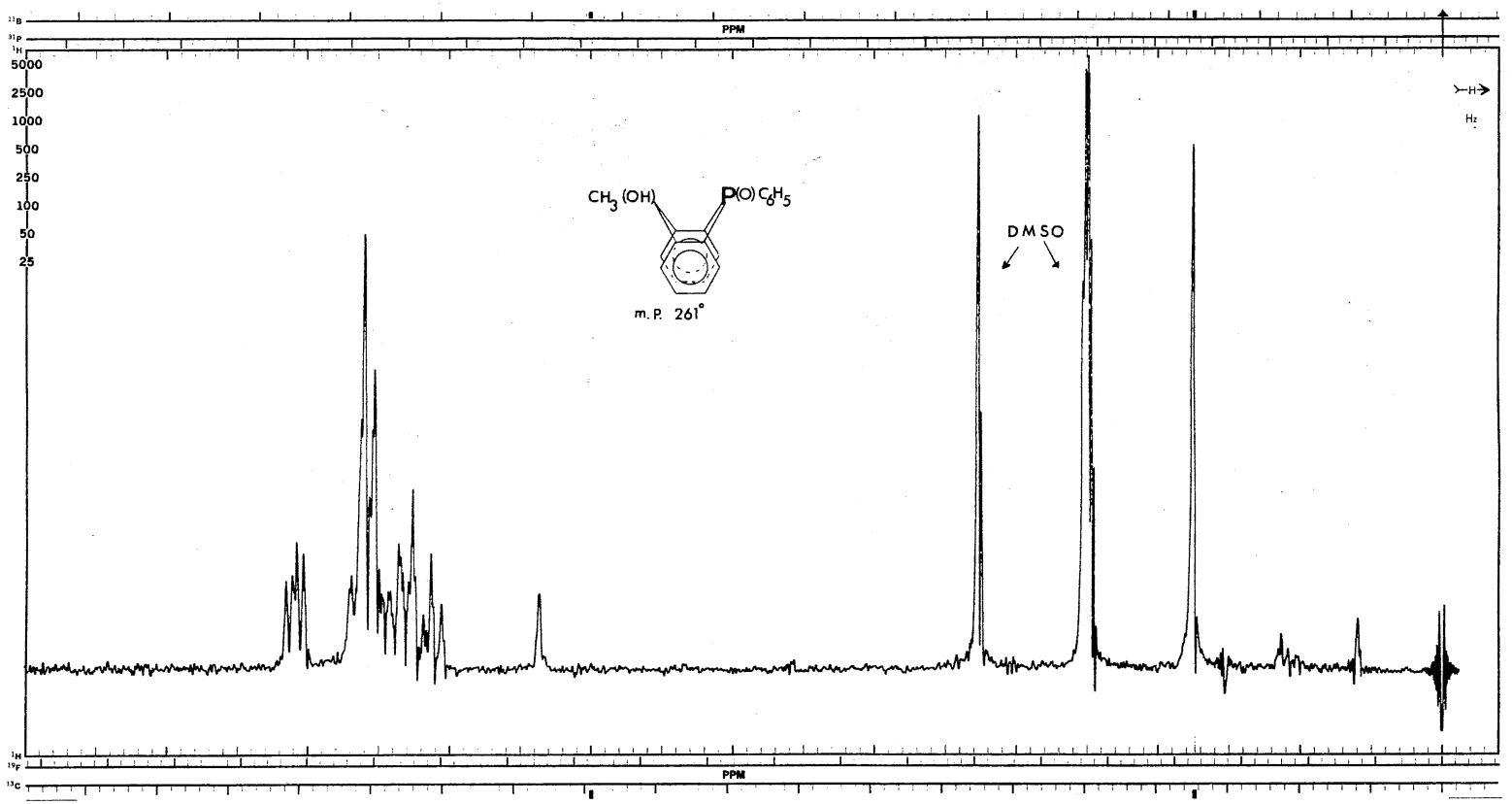
Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 74 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 8.0 Lock. .HOMO

PLATE XXI



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol 5-Oxide (34b), KBr Pellet

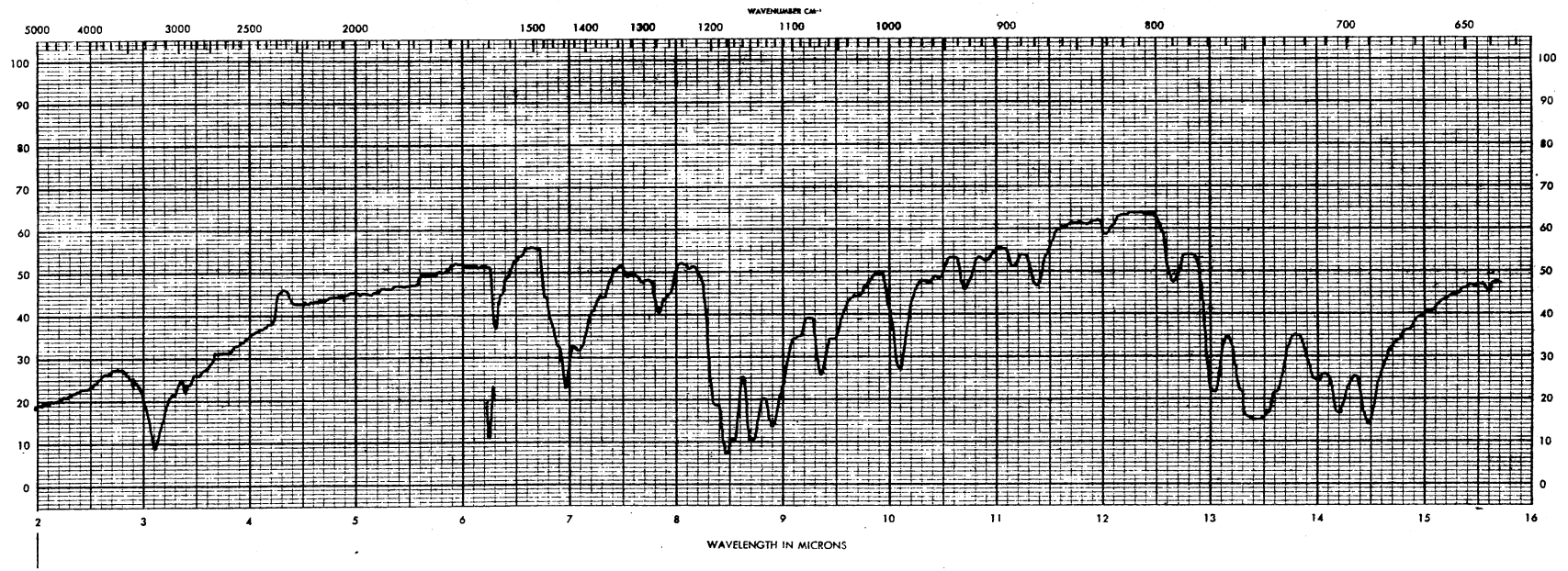
PLATE XXII



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol 5-Oxide (34b)

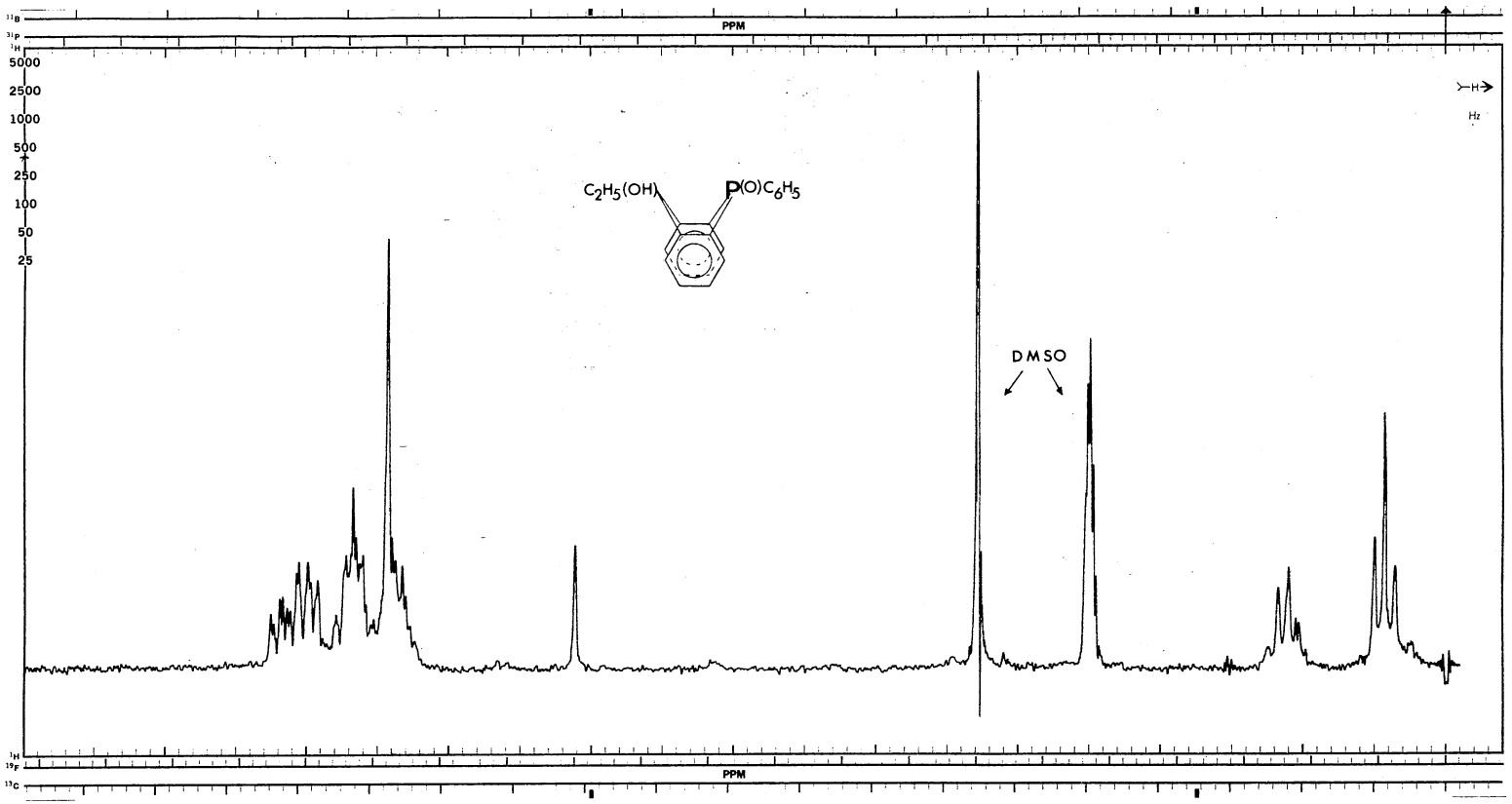
Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 71 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 8.2 Lock. .HOMO

PLATE XXIII



5,10-Dihydro-10-ethyl-5-phenylacridophosphin-10-ol 5-Oxide (47), KBr Pellet

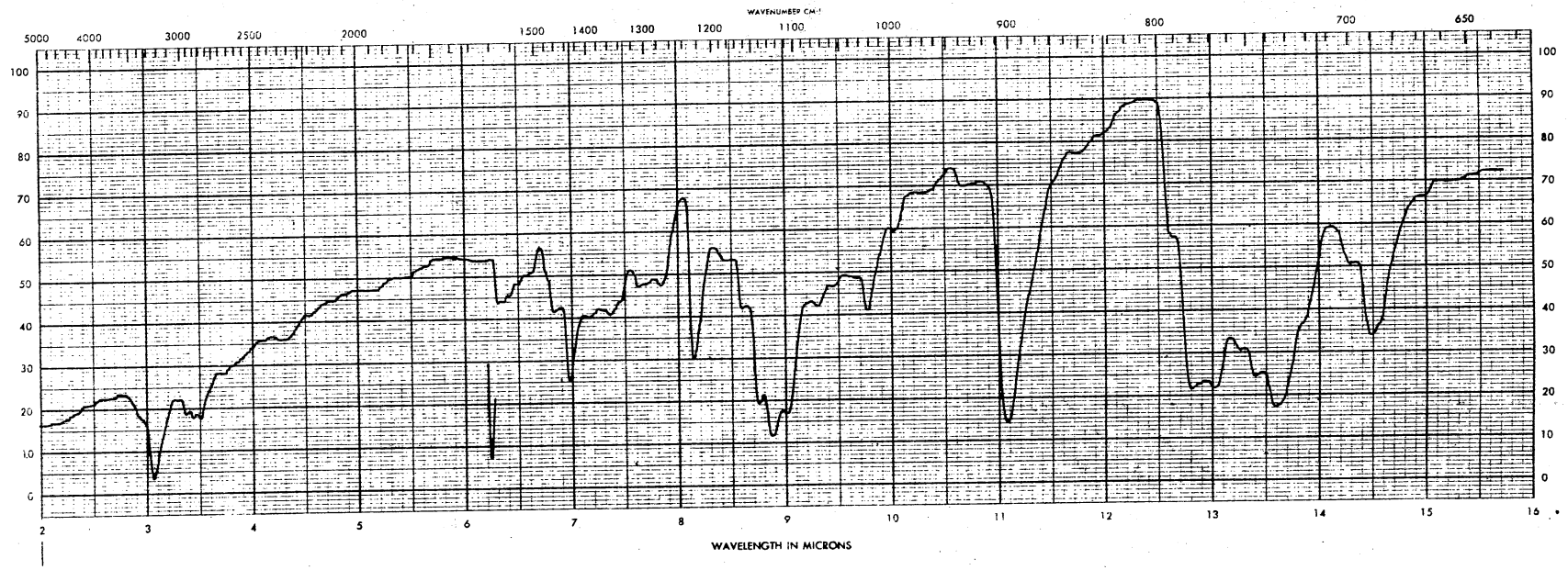
PLATE XXIV



5,10-Dihydro-10-ethyl-5-phenylacridophosphin-10-ol 5-Oxide (47)

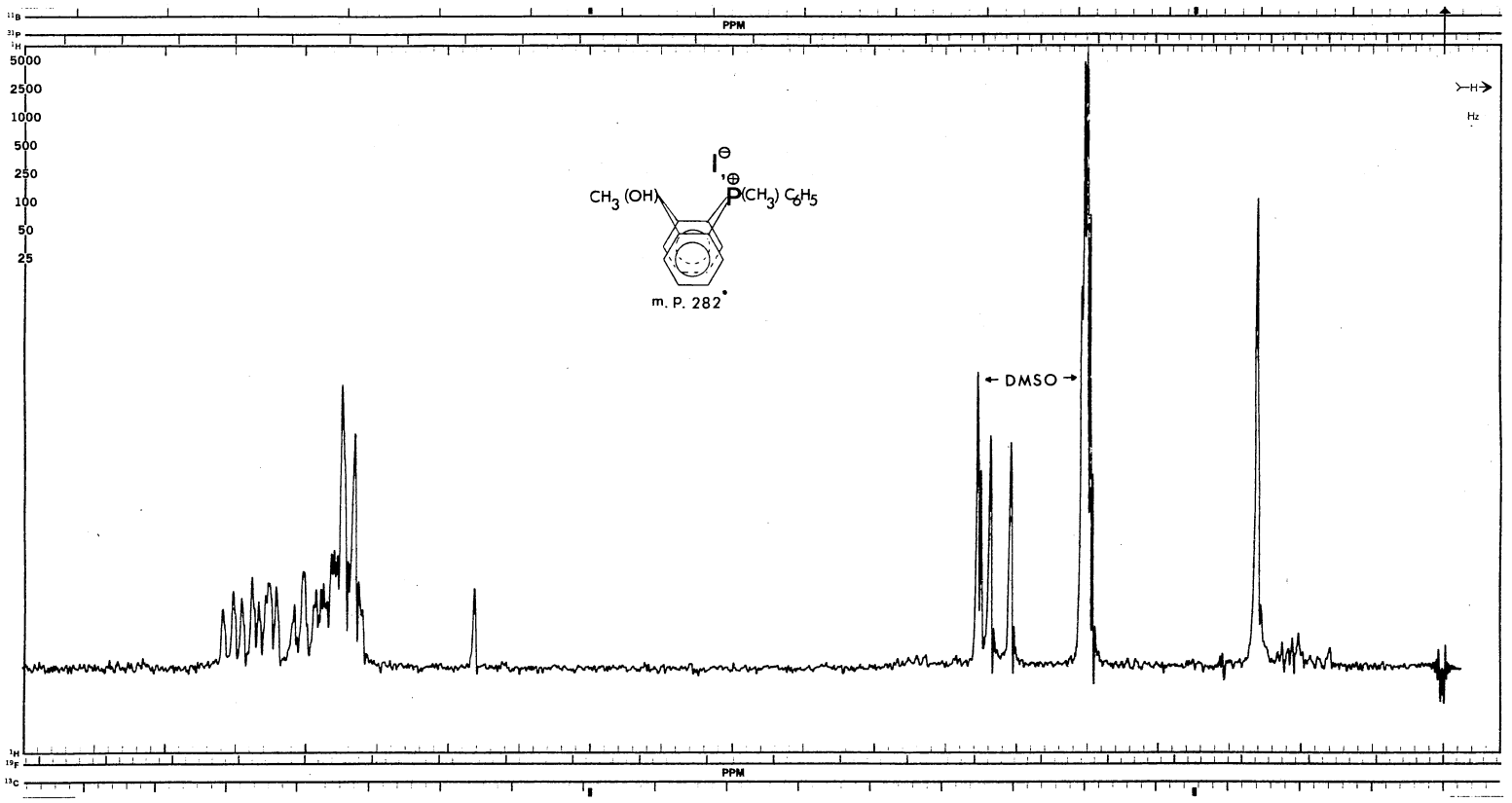
Solvent. . . $DMSO-d_6$ O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 72 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 6.3 Lock. .HOMO

PLATE XXV



5,10-Dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium Iodide (35a), KBr Pellet

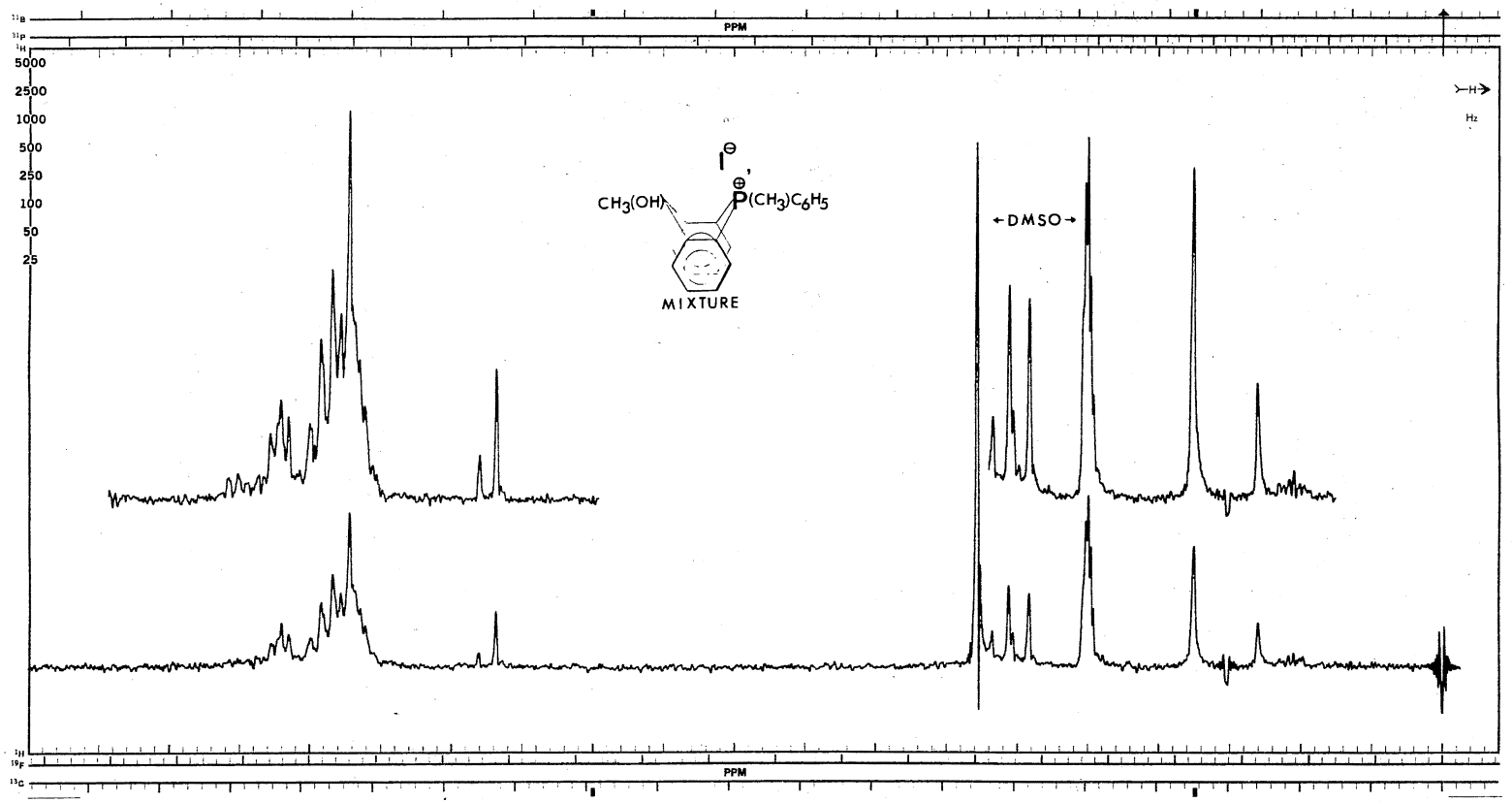
PLATE XXVI



5,10-Dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium Iodide (35a)

Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 72 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 8.0 Lock. .HOMO

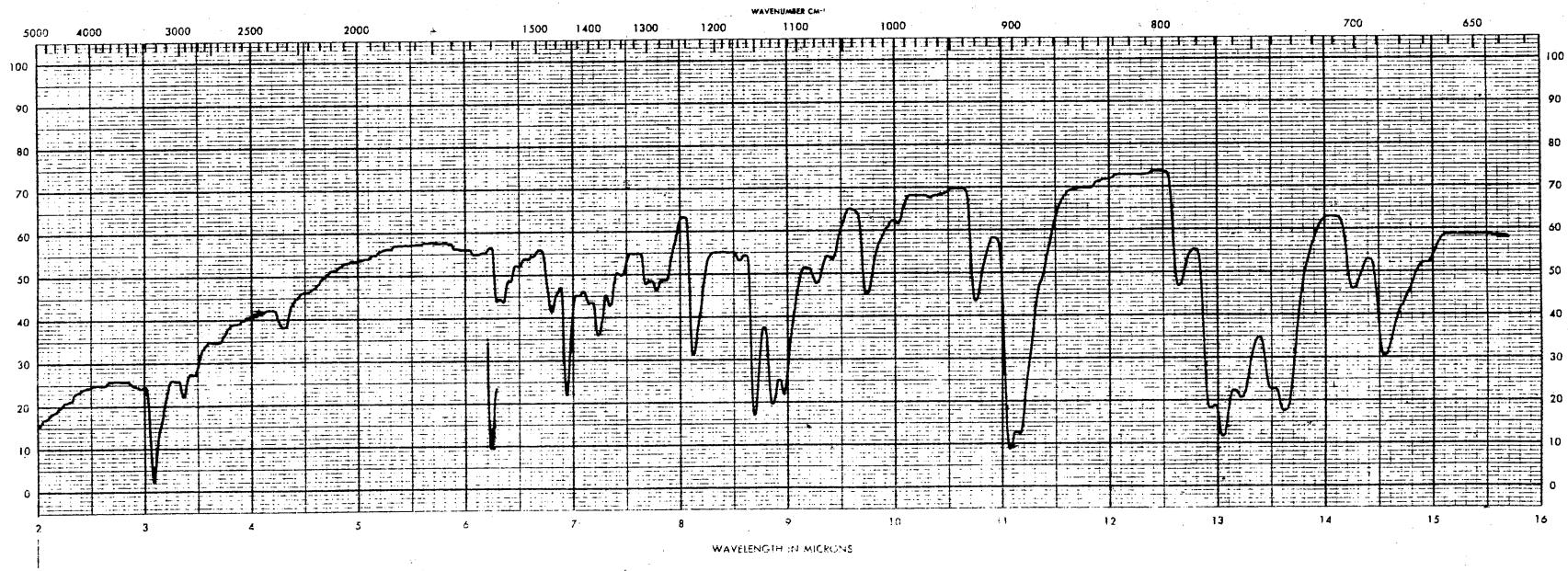
PLATE XXVII



5,10-Dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium Iodide (35)

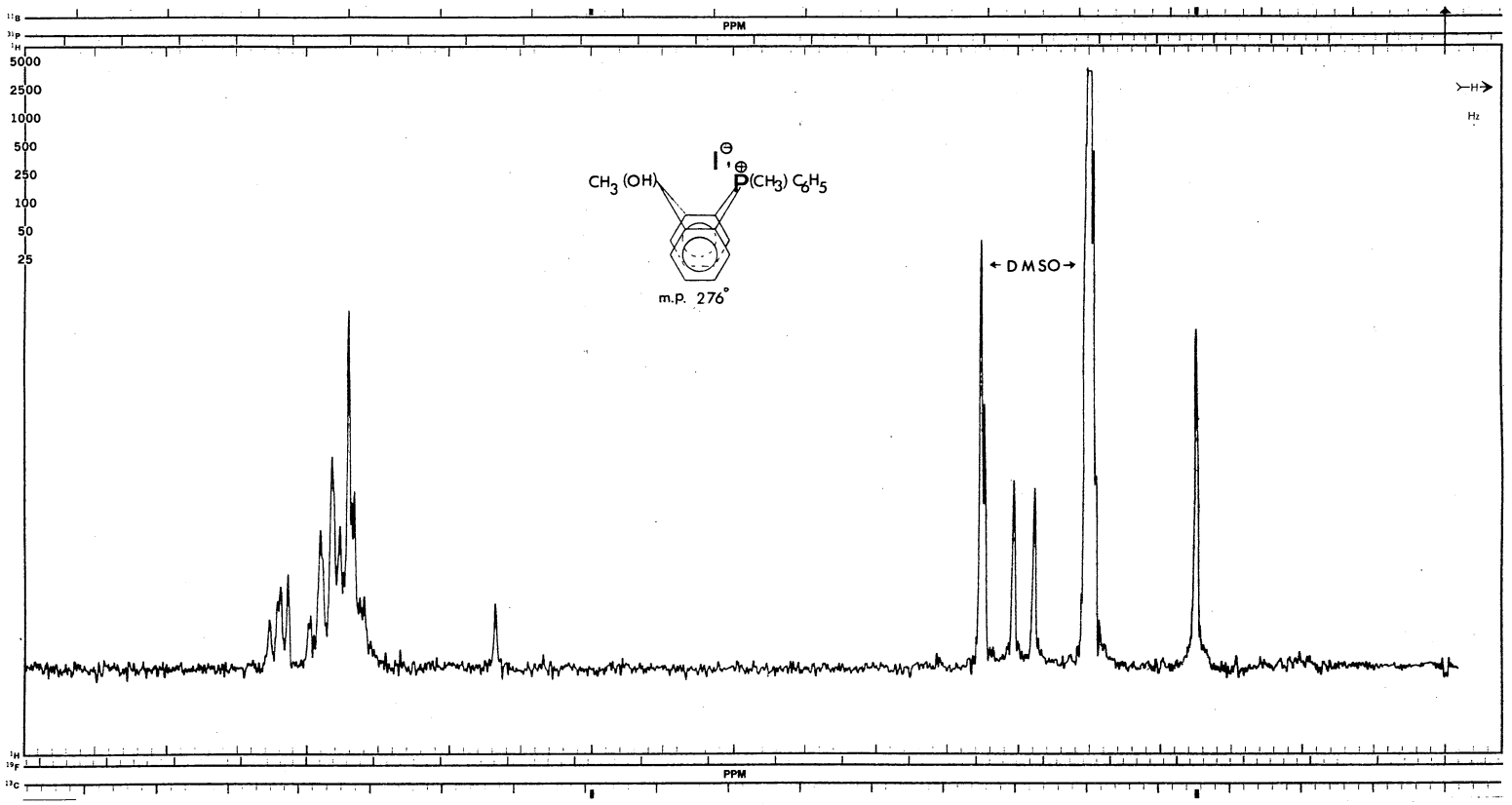
Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 67 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 6.3 Lock. .HOMO

PLATE XXVIII



5,10-Dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium Iodide (35b), KBr Pellet

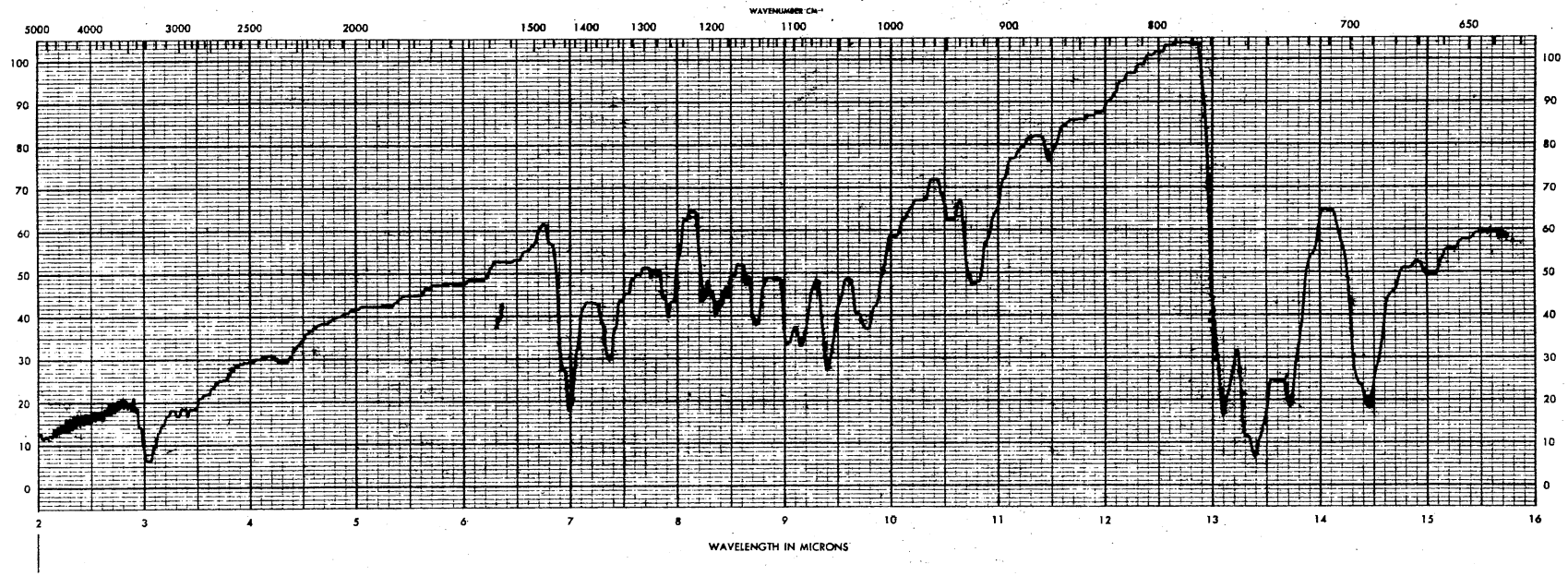
PLATE XXIX



5,10-Dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium Iodide (35b)

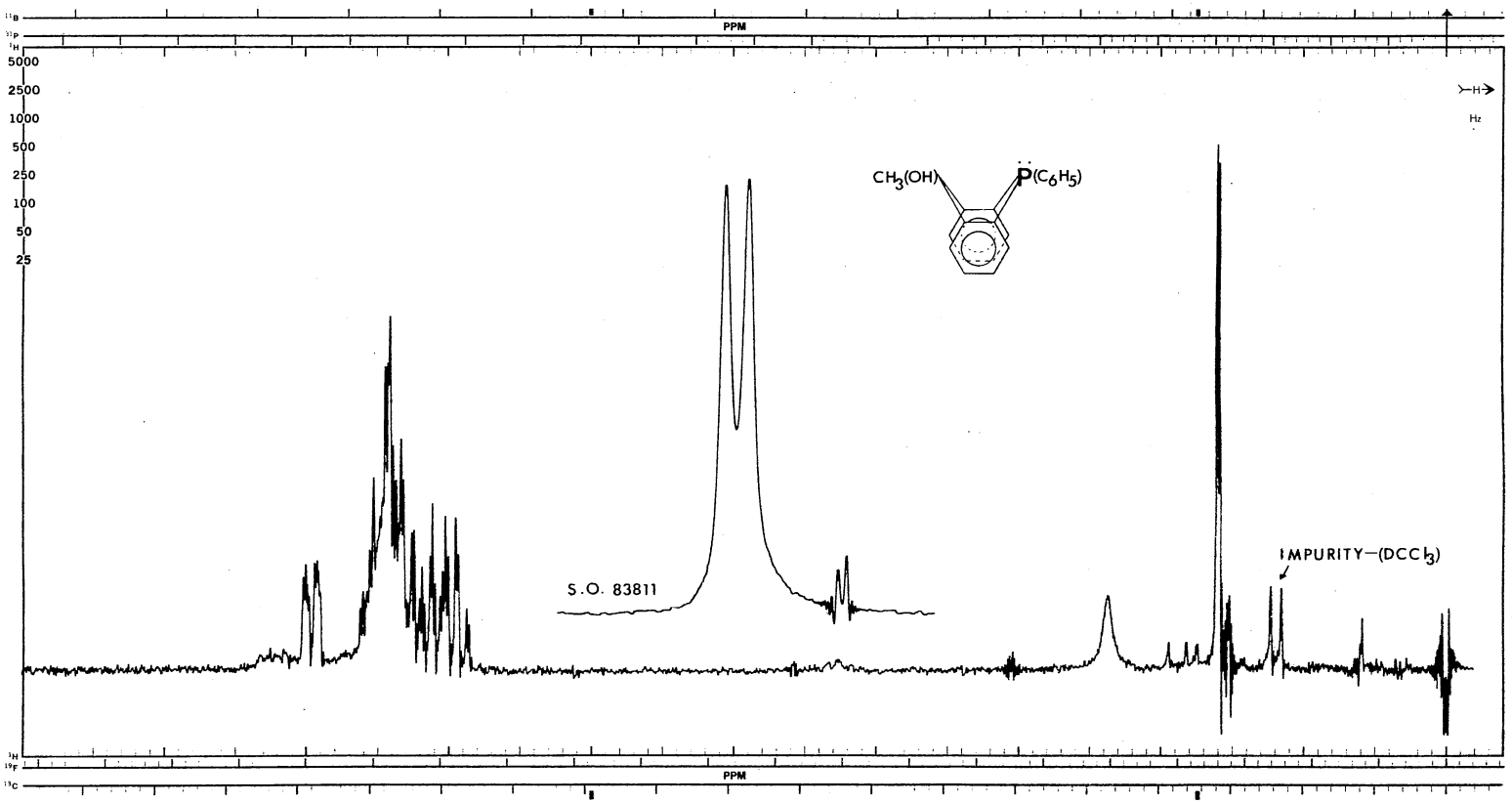
Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 70 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 12.5 Lock. .HOMO

PLATE XXX



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol (30), KBr Pellet

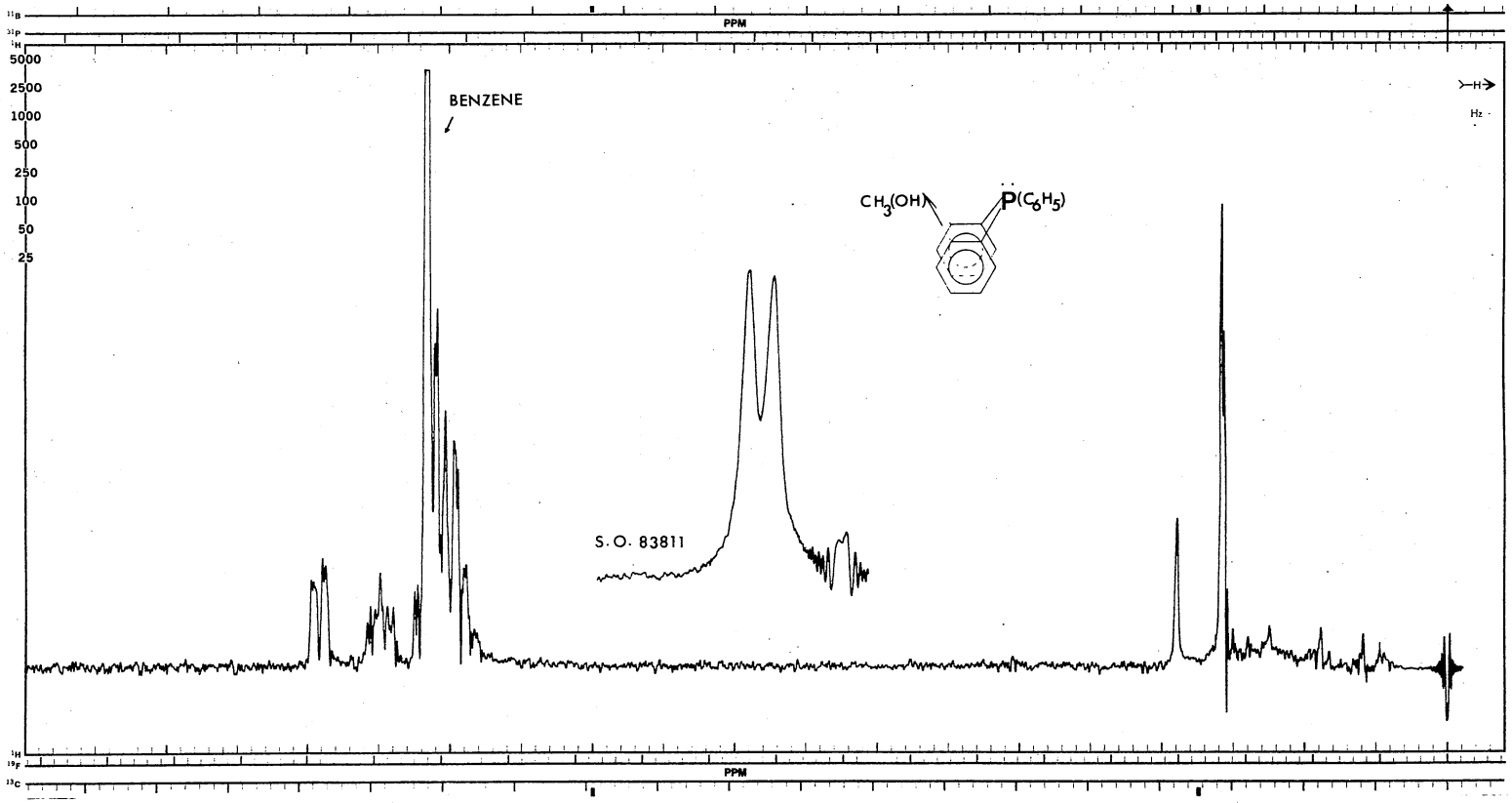
PLATE XXXI



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol (30)

Solvent. . . $DCCl_3$	O.F. . . . 100.1 MHz	F.B. . . . . 2 Hz	R.F. . . . 70 dB	
S.W. . . . 1000 Hz	S.T. . . . . 250 sec	S.O. . . 83701 Hz	S.A. 6.3	Lock. .HOMO

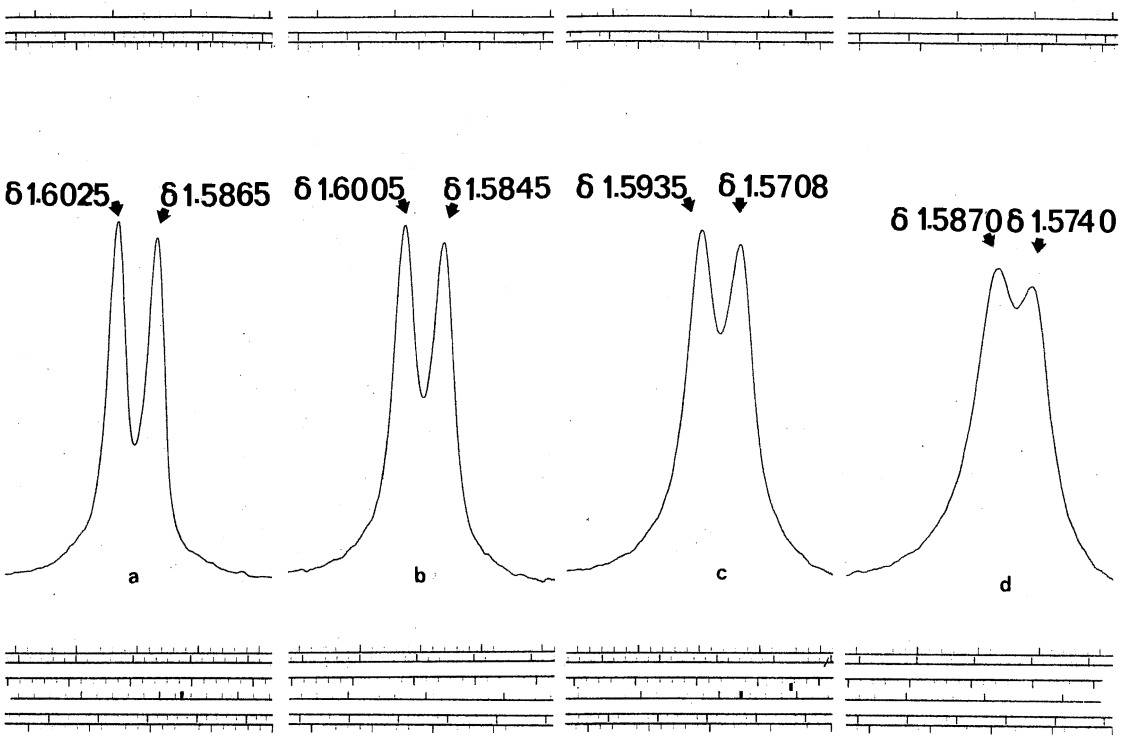
PLATE XXXII

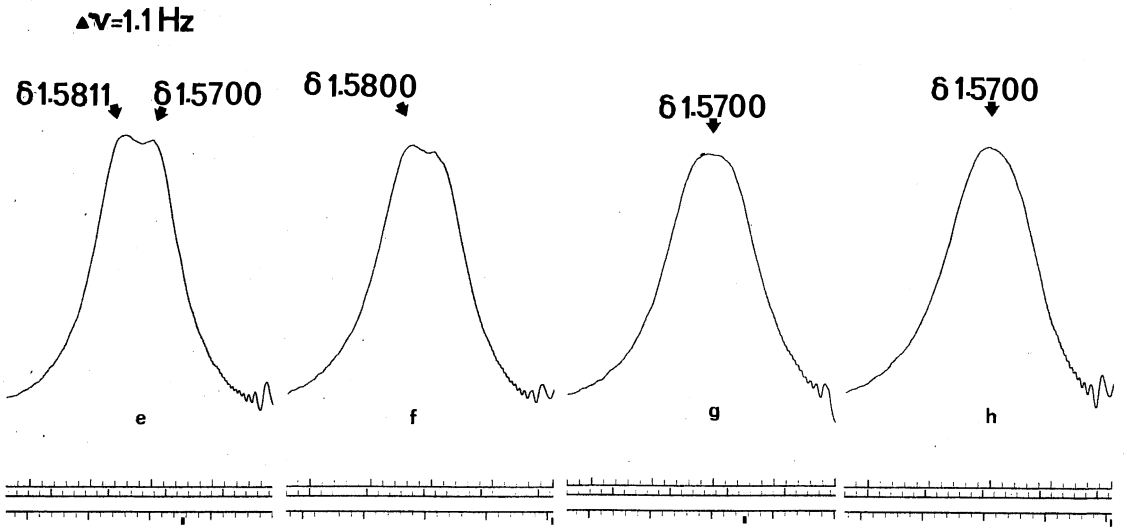


5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol (30)

Solvent. . BENZENE-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . 73 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . 8.0 Lock. .HOMO

PLATE XXXIII

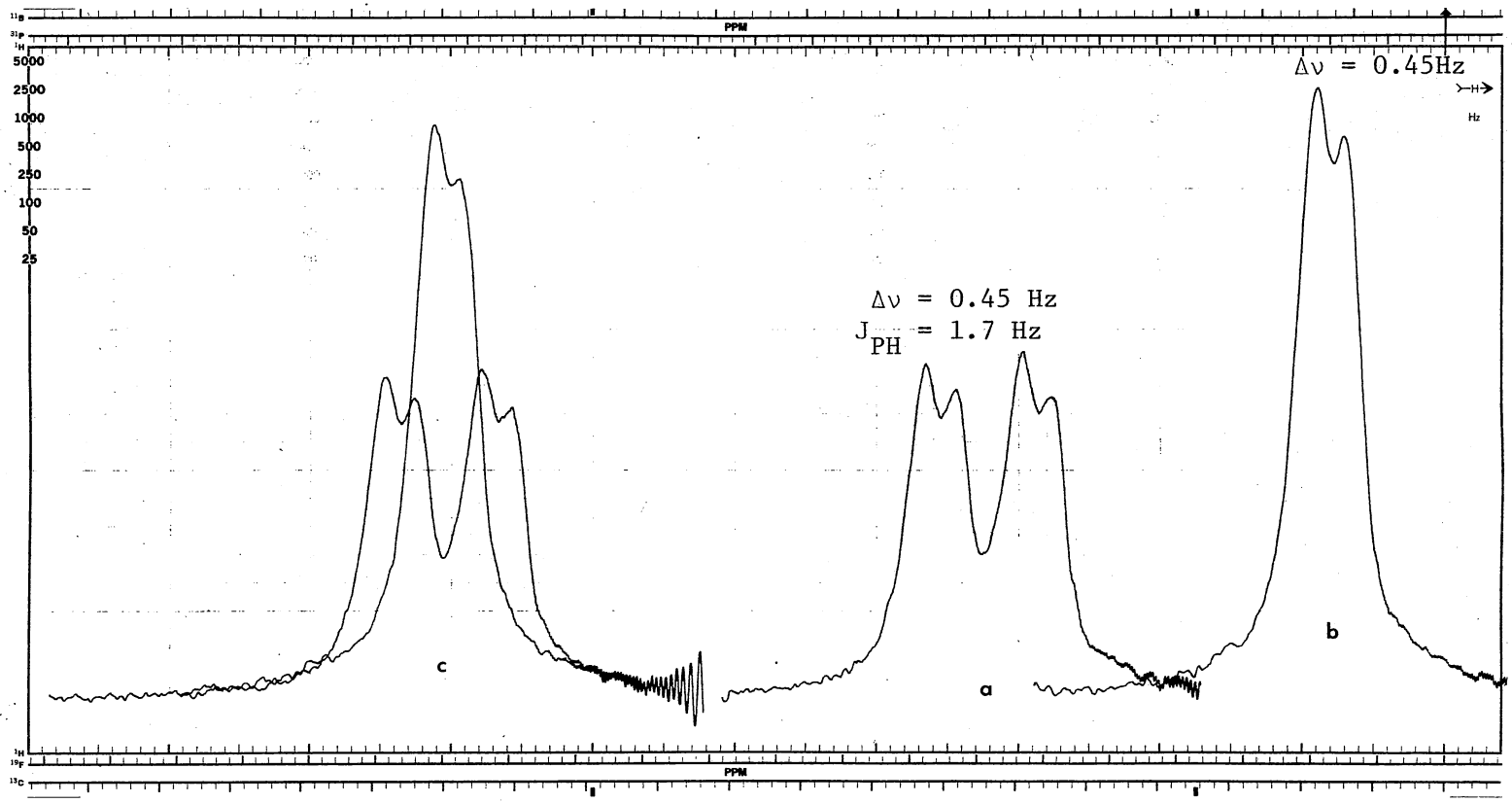




5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol (30), Methyl Protons

Solvent. . . $DCCl_3$ S.W. . . 50 Hz S.T. . . 250 sec S.A. . . 6.3
R.F. . . . . 69 dB Temperature (°C) a. 30 b. 10 c. 0 d. -10
e.-18 f.-19 g.-20 h. -30

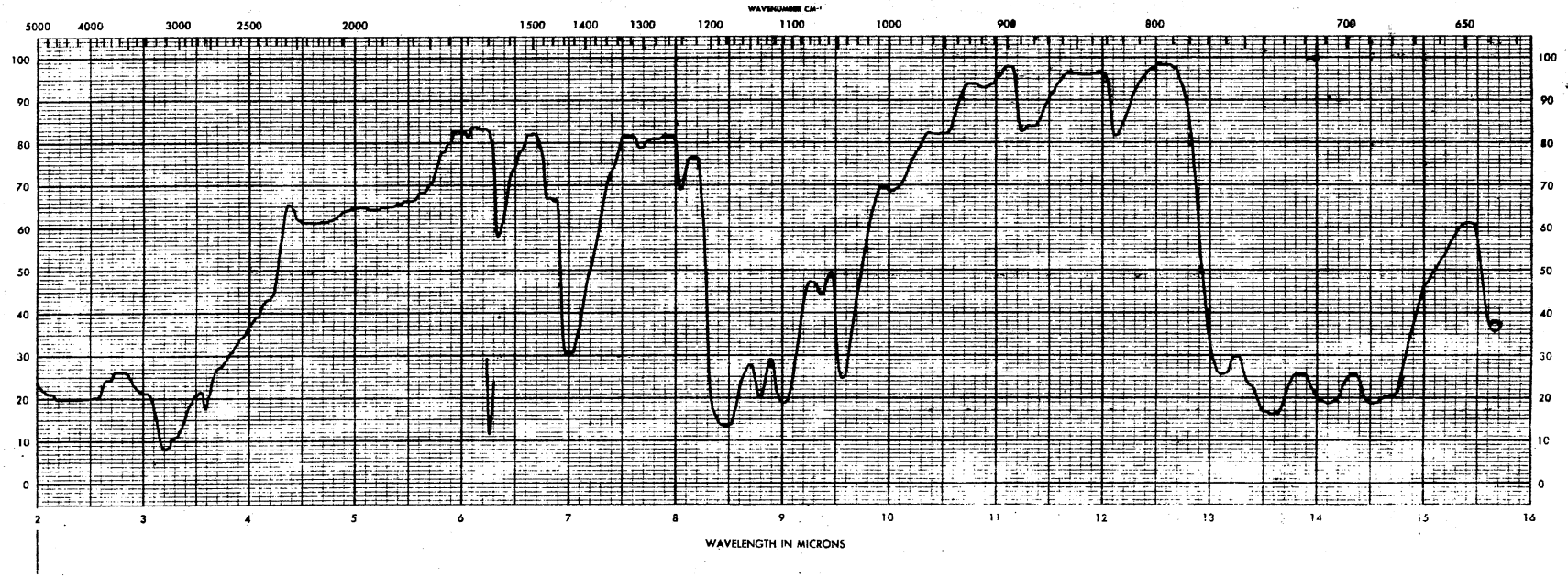
PLATE XXXIV



5,10-Dihydro-10-methyl-5-phenylacridophosphin-10-ol (30), Methyl Protons

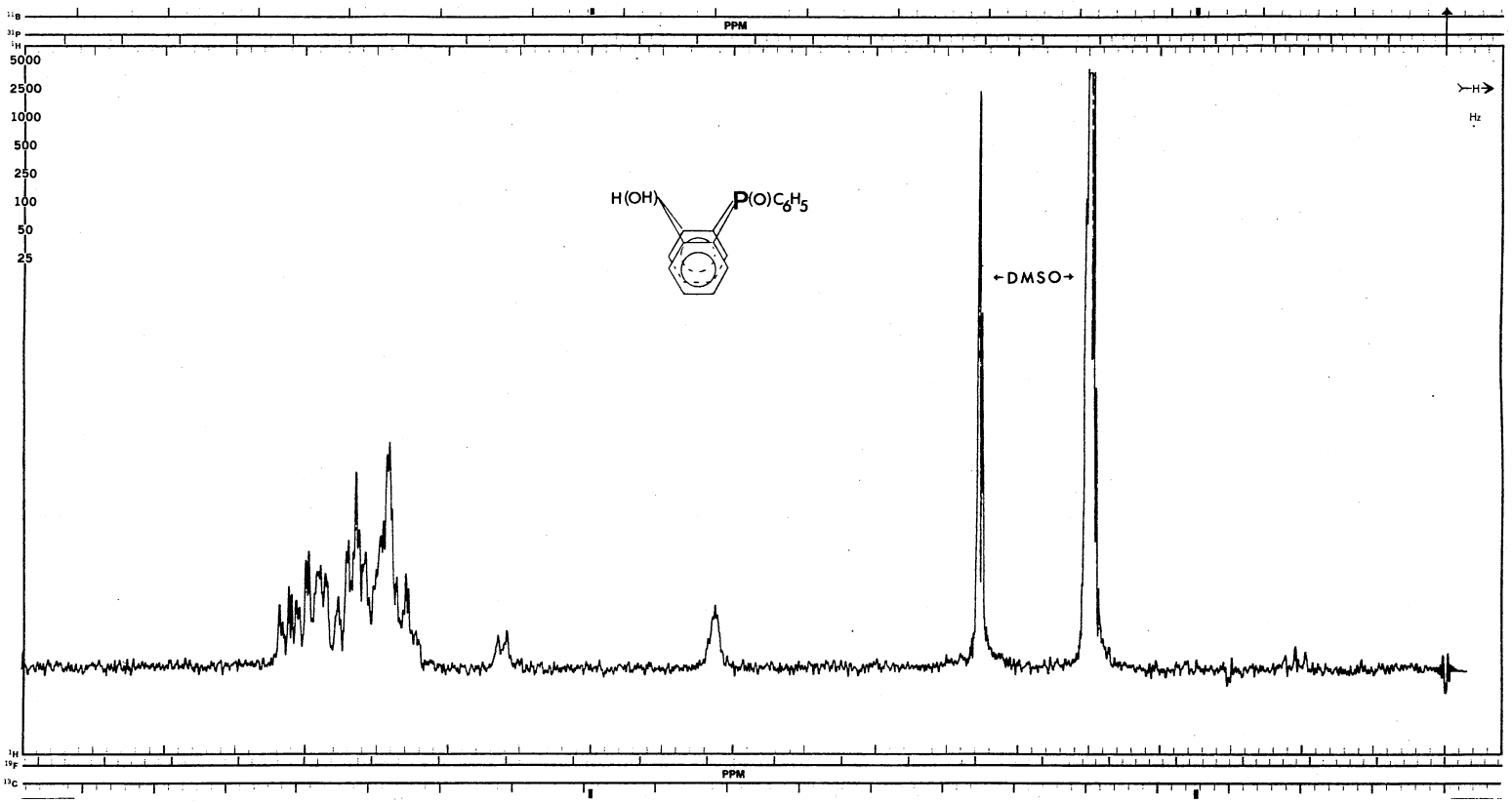
Solvent. . . BENZENE-d_6 S.W. . . . 25 Hz S.T. . . . 250 sec S.A. . . 20
Temperature. . . . R.M. a) Before ^{31}P spin-decoupling b) After ^{31}P spin-decoupling
c) Superimpose of a. and b. signal

PLATE XXXV



5,10-Dihydro-5-phenylacridophosphin-10-ol 5-Oxide (33), KBr Pellet

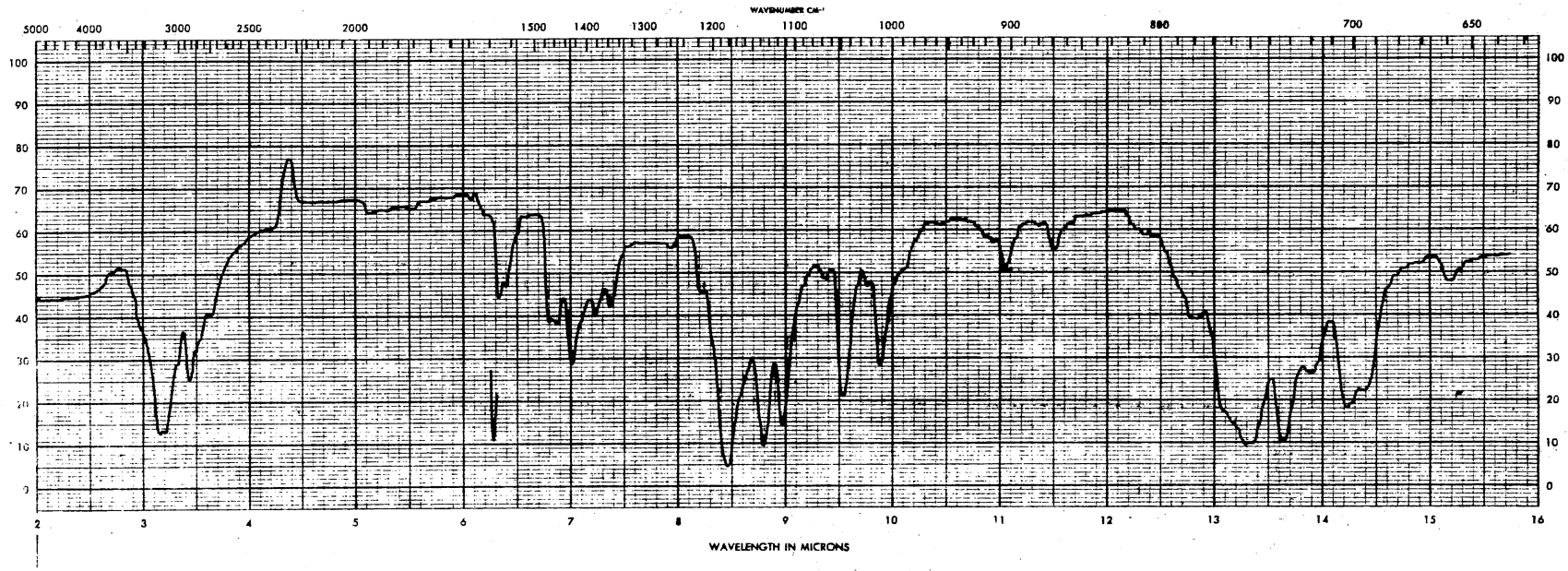
PLATE XXXVI



5,10-Dihydro-5-phenylacridophosphin-10-ol 5-Oxide (33)

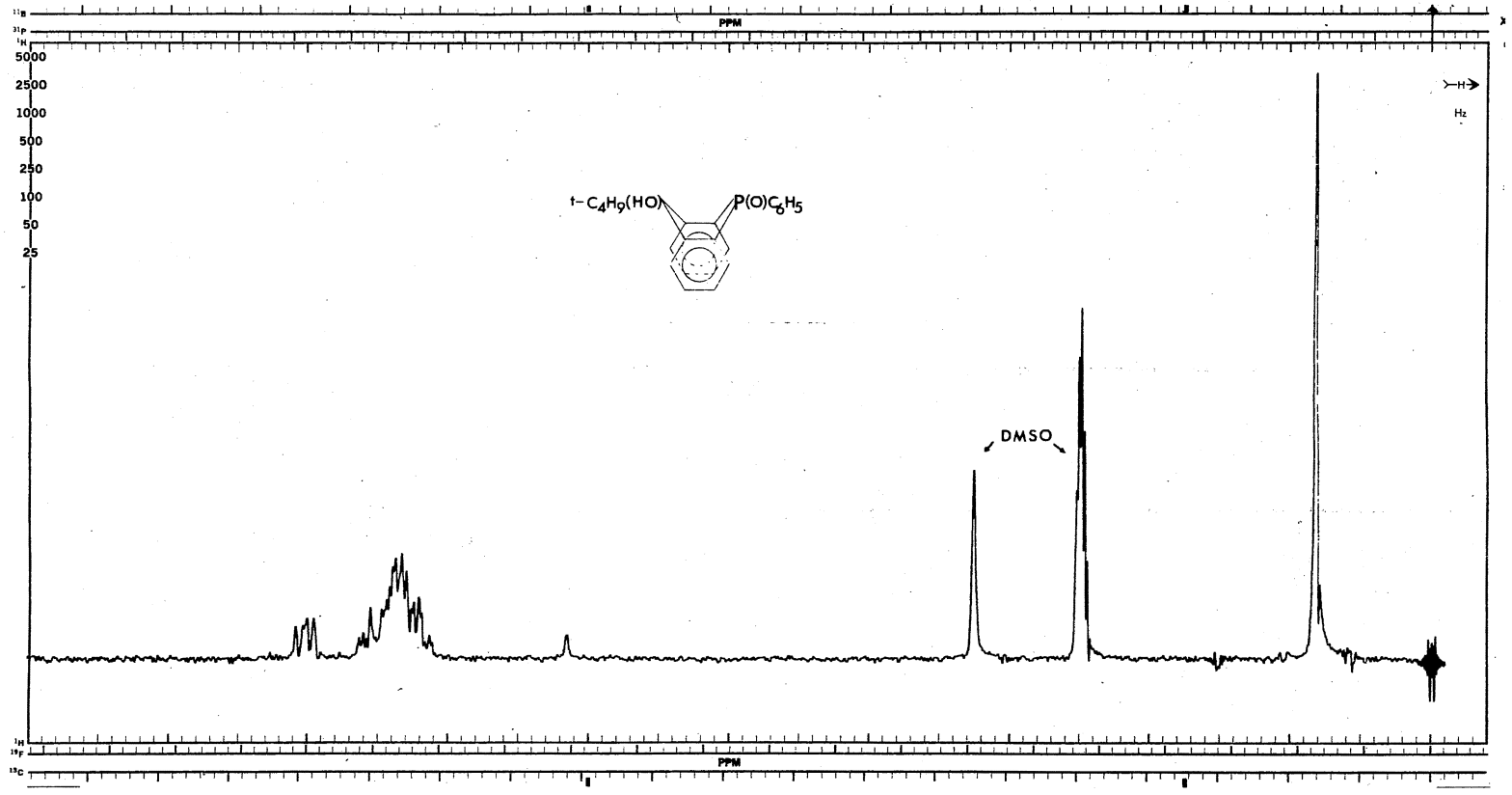
Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . . 73 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 10.0 Lock. .HOMO

PLATE XXXVII



5,10-Dihydro-10-tert-butyl-5-phenylacridophosphin-10-ol 5-Oxide (31a), KBr Pellet

PLATE XXXVIII



5,10-Dihydro-10-tert-butyl-5-phenylacridophosphin-10-ol 5-Oxide (31a)

Solvent. . . DMSO-d_6 O.F. . . . 100.1 MHz F.B. . . . . 2 Hz R.F. . . . 71 dB
S.W. . . . . 1000 Hz S.T. . . . . 250 sec S.O. . . 83701 Hz S.A. . . . . 5.0 Lock. .HOMO

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Thesis: DERIVATIVES OF 5,10-DIHYDRO-5-PHENYLACRIDOPHOSPHIN-10-ONE— SYNTHESIS AND NMR ANALYSIS OF THESE "BUTTERFLY" COMPOUNDS

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