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Synthesis of the Tetrapyrrolic Macrocycle
Octaazatetrahydro[1,5,1,5]platyrin

presented by

Eric John Lind

has been accepted towards fulfillment
of the requirements for

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Eugene LeGoff
Major professor

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SYNTHESIS OF THE TETRAPYRROLIC MACROCYCLE OCTAAZATETRAHYDRO[1,5,1,5]PLATYRIN

By

Eric John Lind

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ABSTRACT

SYNTHESIS OF THE TETRAPYRROLIC MACROCYCLE OCTAAZATETRAHYDRO[1,5,1,5]PLATYRIN

By

Eric John Lind

The synthesis of the dihydrobromide salt of octaazatetrahydro[1,5,1,5]platyrin is described. This expanded porphyrin incorporates four pyrrole rings and two pyrazole rings. The condensation of 1-benzyl-3,5-bis(3,4-dimethyl-5-formylpyrrylmethane)pyrazole with 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrrylmethyl)pyrazole yielded the dihydrobromide salt of octaazatetrahydro[1,5,1,5]platyrin. This diprotonated salt was orange-red and exhibited an intense absorption at 469.5 nm in its visible spectrum. Spectral data are presented for the structural proof of the dihydrobromide salt and its precursors. Oxidation of octaazatetrahydro[1,5,1,5]platyrin to the 26π-electron annulene octaaza[1,5,1,5]platyrin was not successful.

To my wife, Donna, and children, Ryan and Colleen.

To my father, the late Leslie A. Lind, Jr.,
and my mother, Patricia K. Lind.

ACKNOWLEDGEMENTS

I would like to thank the Department of Chemistry at Michigan State University for providing financial support in the form of teaching assistantships and Professor Eugene LeGoff for research support during the last three terms. I would also like to express great thanks to Professor Eugene LeGoff for his patience and openness in the multitude of helpful discussions during this learning experience.

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INTRODUCTION

INTRODUCTION

The word "aromatic" was first used in the early nineteenth century to describe the odor of volatile vegetable oils. When it was recognized that these carbon-rich compounds were derivatives of benzene, the term aromatic came to have structural meaning. In 1865, Kekulè suggested the cyclohexatriene structure for benzene.[1] Shortly after this, it was suggested that the concept of aromaticity should encompass compounds of similar reactivity since benzene showed an unusual stability.[2] From this point in time to the present, the term aromaticity has had the possibilities of more than one meaning. Thiele's "residual valency" hypothesis[3] suggested that all cyclic polyenes should have properties similar to benzene. However, when Willstätter synthesized cyclooctatetraene[4], he found it showed the properties of an olefin rather than benzene, thereby disproving Thiele's hypothesis. At the time when cyclooctatetraene was synthesized, none of the theories presented had accounted for the stability of the aromatic sextet.[5] During the 1920's, quantum mechanics was developed, and out of this came theories of chemical bonding which made it possible to account for the difference in stability between benzene and cyclooctatetraene.

In 1927, Heitler and London developed valence bond theory.[6] Valence bond theory uses the idea that an atom retains its individual character in a chemical bond. The concept of resonance was introduced to account for the symmetry of the benzene molecule. The difference between the theoretical energy of a particular resonance structure and the experimentally determined energy is the resonance energy which accounts for the stability of benzene in the ground state. A drawback of the theory is that it predicts a stabilizing resonance energy in cyclooctatetraene which is not observed experimentally.

Molecular orbital theory developed by Hückel[7] uses a linear combination of atomic orbitals to produce molecular orbitals with varying energies. The π-electrons are placed in the lowest energy orbitals first, following Hunds' rule, until all of the electrons have been used. A difference could be seen between the pattern of orbitals in benzene and cyclooctatetraene. Benzene had a closed electronic shell while cyclooctatetraene did not. This observation was the basis for the conception of Hückel's Rule which states that fully conjugated, planar monocyclic polyolefins with $(4n+2)\pi$-electrons where n is an integer will have special aromatic stability.[7] As a corollary, all similar systems with 4n π-electrons will not possess any special aromatic stability. Thus, Hückel molecular orbital theory (HMO) predicted a difference between these (4n+2) and $4n\pi$-electron systems in terms of their electronic configurations. The initial HMO calculations did have the problem of predicting a sizable resonance energy (δ) for cyclooctatetraene (n = number of π electrons) as seen in Figure 1.

In 1965, Dewar[8] derived delocalization energies using a semiempirical molecular orbital method, the Pople-Pariser-Parr (PPP) approximation. They used a new reference system that adopted an acyclic polyene with the same number of single and double bonds as the cyclic polyene. The energies between the (4n+2) and 4nπ-electron systems were found to alternate, with cyclooctatetraene now having a negative delocalization energy (Fig. 1). The plotted Dewar resonance energies shows that, as the ring size increases in the (4n+2)π-electron systems, the resonance energy decreases. Dewar predicts that somewhere between [22] and [26]annulene there will be no delocalization energy and beyond this point the (4n+2)π-electron systems become simple polyolefins. When Schaad and Hess used the new Dewar reference system with the HMO method, they were able to mirror the PPP results (Fig. 2).[9] Dewar has defined aromatic molecules as cyclic systems having a large resonance energy in which all the atoms in the ring take part in a single conjugated system. One problem with this definition is what large actually means. Another problem is that the resonance energies can be difficult to verify experimentally. For example, determination of the heats of hydrogenation or

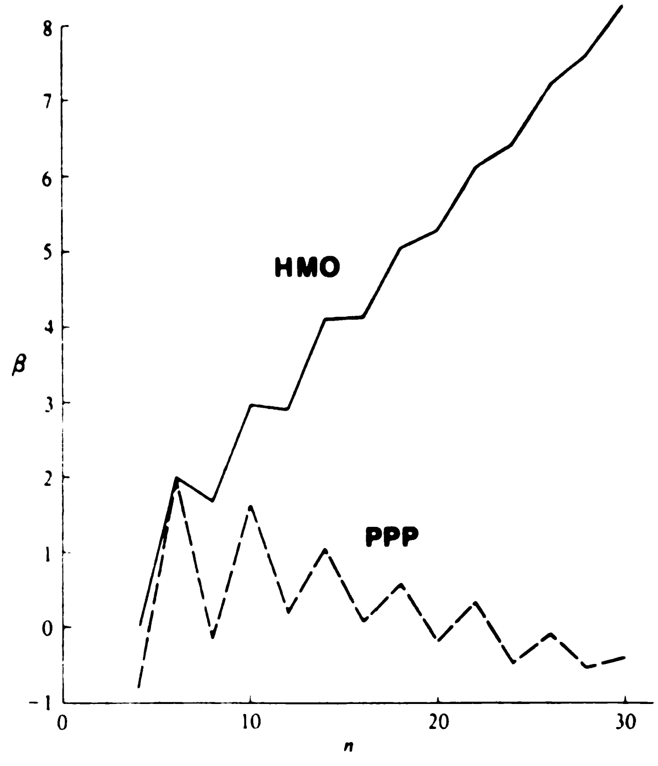


Figure 1

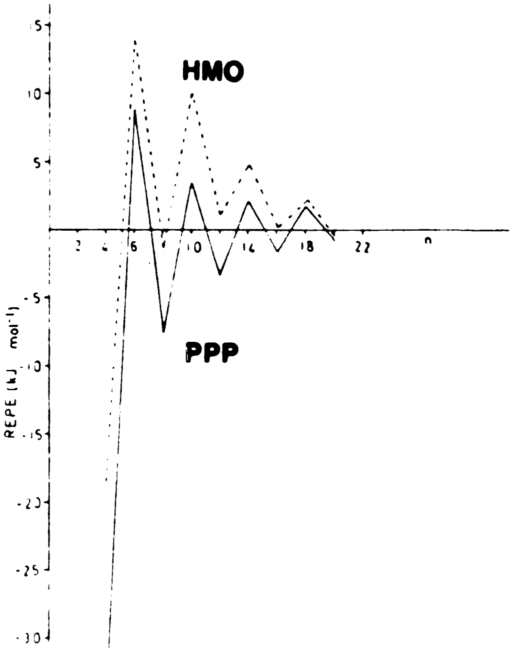


Figure 2

heats of combustion is time consuming and, in some cases, is not feasible.

An easier means of categorizing annulenes is through the measurement of specific spectral data. Electronic spectral data has been used to compare annulenes that are closely related in structure. However, these absorptions correspond to differences in energy between the ground state and excited states and are not a suitable means of distinguishing whether or not a compound is aromatic. The most widely used method in the qualitative determination of aromaticity is the observation of diatropicity[10] in ^1H NMR spectra (Fig. 3).

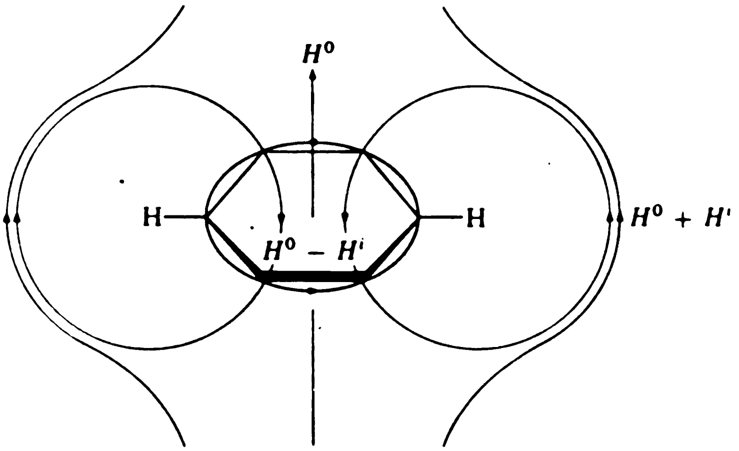


Figure 3

In this model[11], the applied field (H^o) causes the π-electrons to circulate over the six carbon atoms and a magnetic field (H^i) is induced which opposes the applied field. The effect of this induced field is that the apparent field inside the ring is decreased, while the field outside the ring is increased. As a result, protons inside the ring resonate at a higher field than protons not influenced by the induced field, whereas protons outside the ring will resonate at lower field. Systems with (4n+2)π-electrons that exhibit this phenomena are called diatropic. Systems with 4nπ-electrons that exhibit a paramagnetic ring current are called paratropic. In this case, protons inside the ring resonate at a lower field and protons outside the ring resonate at a higher field. Compounds which have no ring current are named atropic. The advantages of using the ^1H NMR as a technique is that it is easy to apply, only small quantities of the compound are needed, and the material can be recovered in many cases. The ring current effects in the ^1H NMR is an excellent qualitative measure of aromaticity.

Haddon[12] has presented a method which uses observed and calculated chemical shifts along with geometrical factors obtained from X-ray structures to obtain ring current values for annulenes. A quantitative measure of aromatic character was determined from a constant k necessary to reproduce this ring current.[13] The constant k relates to the resonance integral and measures bond alteration in the system. Haddon has subsequently presented a unified theory linking resonance energy to the ring current.[14] The resonance energies derived in this way are in good agreement with those observed by the PPP and HMO methods. The study predicts that the ring current increases linearly with N (the number of atoms in the annulene) whereas the resonance energy is inversely proportional to N.

Schaad and Hess[15] have shown that a reaction rate, which was measured by Sondheimer, can be related to the resonance energy of the product system. The calculated resonance energies for these dehydroannulenes were in excellent agreement with the observed reaction rates. Now several experimentally measureable phenomena such as enthalpies of combustion or hydrogenation, proton chemical shifts, geometries, and reaction rates have been correlated to the theoretical resonance energy which begins to establish a theoretical index of aromaticity.

Sondheimer has synthesized several of the larger annuelene rings and used the ring current effects extensively to qualitatively determine whether or not they were aromatic. Dewar predicted these compounds would become simple polyolefins somewhere between [22] and [26] annulene.[8] Sondheimer found [22]annulene[16] to be diatropic and [24]annulene[17] to be paratropic. The [26] and [28] annulene have not been synthesized and, although [30] annulene[18] has been prepared, it was not well characterized and the ^1H NMR was not studied. Monodehydro[26]annulene[19] showed a small diamagnetic ring current effect but does contain an acetylene linkage. A problem that arises with some larger annulenes is that they are conformationally mobile. This can lead to deviations from planarity which reduces the ring current to give structures that have localized bonding.

Ideal molecules for evaluating ring currents are those having rigid planar perimeters as is the case with some heteroannulenes. These are molecules in which one or more carbon atoms in the annulene ring are replaced by a heteroatom. For example, a variety of the familiar porphyrins are stable $(4n+2)\pi$-electron heteroannulenes that show substantial ring current effects. Some of the more recently synthesized $(4n+2)\pi$-electron heteroannulenes which include pyrrole in the ring system are presented along with their ^1H NMR and electronic spectral data in Table 1.

In agreement with Haddons theory, the ring current effects in these $(4n+2)\pi$-electron systems increase linearly with the ring size. This is consistent with the observed ^1H NMR chemical shifts in going from [1,3,1,3]platyrin to [1,5,1,5]platyrin. Haddon also predicted that resonance energy is inversely proportional to N (number of atoms in annulene). The unstable (chemically reactive) [1,5,1,5]platyrin has given some information with regard to

Table 1. (4n+2) π-Electron Hetero-annulenes

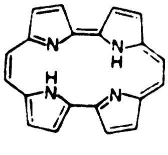
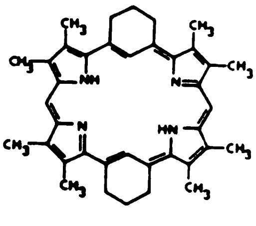
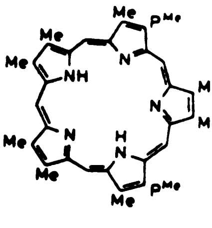
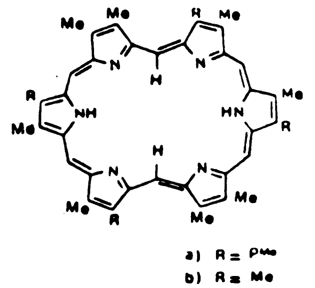
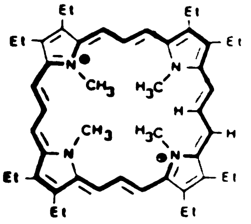
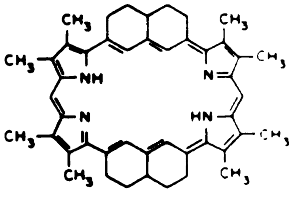
Structure	^{1}H NMR (δ ppm)	U.V. λ max (ε$_M$)	ref.
 Porphycene 18πe, blue solutions	(CDCl$_3$) 3.15 (bs) 2H, NH 9.23 AB 4H 9.67 AB 4H 9.83 (s) 4H	(benzene) 358 (139,200) 370 (106,900) 558 (34,200) 596 (30,400) 630 (51,900)	20
 [1,3,1,3]Platyrin 22πe, dark green	(CF$_3$CO$_2$H/CDCl$_3$) -8.97 2H -5.6 4H, NH 1.0-2.4 12H 4.17 24H 4.22 11.64 2H	(CH$_2$Cl$_2$) 453 sh (60,400) 477 (389,000) 607 (11,800) 469 (9,340) 747 (2,100) 767 sh (1,520) 846 (1,850)	21
 Pentaphyrin 22πe, blue-green	(CF$_3$CO$_2$H/CDCl$_3$) 4.84 4.86 24H 4.88 12.44 (s) 1H 12.46 (s) 2H 12.55 (s) 2H	(CH$_2$Cl$_2$) 367 (5,480) 458 (238,000) 642 (5,990) 695 (3,540)	22

Table 1. CONTINUED.....

Structure	^{1}H NMR (δ ppm)	U.V. λ max (ε_M)	ref.
 a) Hexaphyrin 26πe, violet b) Dodecamethyl-hexaphyrin 26πe	a) (CF_3CO_2D) 1st isomer -7.4 (s) 2H 12.42 (s) 4H 2nd isomer -7.54 (s) 2H 12.19 (s) 2H 12.33 (s) 2H b) (CF_3CO_2D) -7.3 (s) 2H 4.55 (s) 18H 4.60 (s) 18H 12.5 (s) 4H	a) (CF_3CO_2H/CH_2Cl_2) 551 (93,450) b) ---------------	22
 [26] Porphyrin 26πe, deep red-violet	($CF_3CO_2H/CDCl_3$) -11.64 (+) 4H - 9.09 (s) 12H 2.43 (+) 24H 4.99 (q) 16H 13.67 (d) 8H	($CHCl_3$) 547 (909,600)	23
 [1,5,1,5]Platyrin 26πe, dark purple	($DMSO_{d6}/CF_3CO_2H$) -14.26 (s) 4H -10.58 (s) 4H, NH 1.0-2.7 18H 4.43 (s) 12H 4.51 (s) 12H 11.75 (s) 2H	(CH_2Cl_2) 495 (123,000) 536 (144,000) 651 (15,700) 705 (12,300) 718 (13,500) 780 (9,400)	24

the stability of a larger (4n+2)π-electron ring system but not necessarily the resonance energy. A molecule may be resonance stabilized even though it is extremely reactive.

Whether or not these hetero[26]annulenes are considered aromatic depends on what definition of aromaticity is used. If the presence of diamagnetic ring current effects serves as a qualitative criterion of aromaticity, then all of the heteroannulenes in Table 1 could be considered aromatic. However, other definitions of aromaticity include some mention of positive resonance energies. In this case, resonance energies would have to be calculated for these heteroannulenes. The resonance energies could be derived from ring current effects using Haddon's method.[14] As Garratt[25] has pointed out, if the geometrical factors in Haddon's calculations were obtained from models rather than X-ray crystallographic data, more experimentalists would be encouraged to carry out these determinations.

The study of other new heteroannulenes, with 26 or more π-electrons in particular, will continue to give a better understanding of the concept of aromaticity. The compound of interest in the present study is a 26π-electron [1,5,1,5]platyrin (Figure 4). (The word platyrin, which is translated to mean "expanded porphyrin", was coined to simplify the naming of these tetrapyrrolic compounds.[21] The numbers in the bracket indicate the number of methine carbons between each of the pyrrole rings in the macrocycle.) In this macrocycle, two pyrazole rings are incorporated into the system, the nitrogens of which could be endo or exo to the ring (both conformations seen in Figure 4). One conformation has the possibility of forming

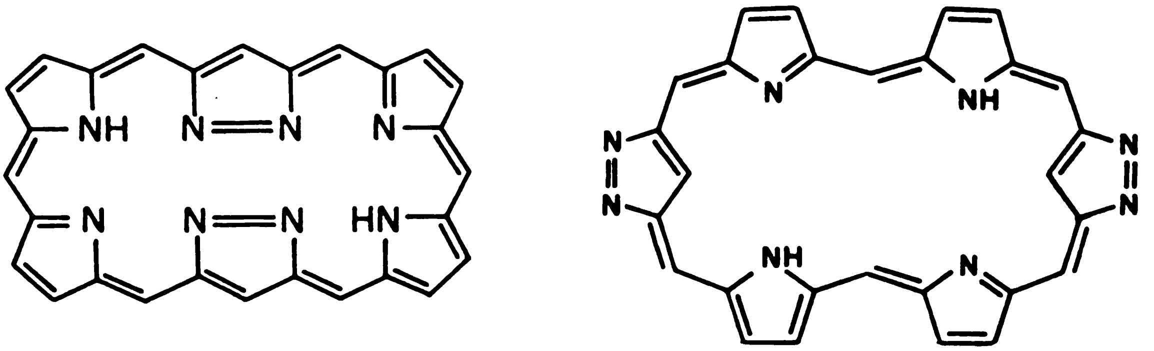


Figure 4

an interesting binucleating ligand where the two metals could sit side by side[26] in each of the porphyrin-like units (Figure 5). Several oxidation states are possible for both the metals and the ligand.

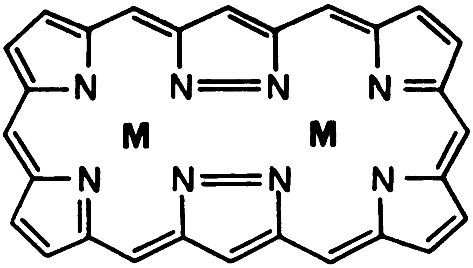


Figure 5

Many binucleating macrocycles have been studied because of their importance in biological systems. For example, bimetallic systems such as cuproproteins[27] play a major role in oxygen transport and oxidase activity. Porphyrins and porphyrin-related ligands are also involved in these processes. The extensive role of metal-metal interactions and porphyrin molecules in many biochemical reactions has led to hybrid porphyrin-like bimetallic systems. Cofacial diporphyrins which have two porphyrin rings that face each other, both of which can coordinate to a metal, were reported by Collman[28] and Chang.[29] Unlike the cofacial diporphyrins, Mertes[30] synthesized a hybrid porphyrin-like bimetallic system that incorporates two metals within one ring system. Various metal complexes of this system were isolated and studied. This model system (Figure 6) was designed with the idea that substrate molecules would have a less-hindered approach to the ligand. The crystal structure of the copper complex has revealed that when n=3, the ligand is folded so that the two dipyrrylmethene portions are facing each other. Hand-held models have shown that the desired [1,5,1,5]platyrin is a planar hybrid porphyrin-like bimetallic system which could also give an unhindered approach to substrate molecules.

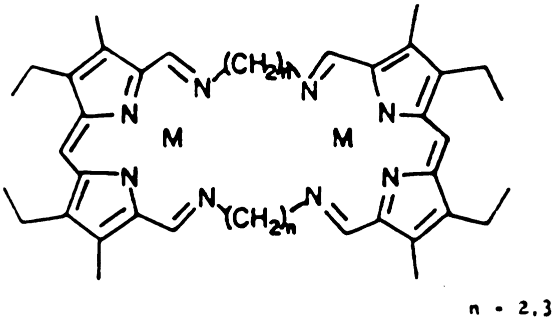


Figure 6

Other related research has involved the use of porphyrin and porphyrin-like metal complexes as conductors.[31,32] It appears that a molecular crystal based on a metal complex can be highly conducting only if it meets two criteria. The metal-ligand molecules must be in a crystallographically similar environment and be essentially planar, so they are arranged (face-to-face) to achieve the intermolecular interactions necessary to generate a conductive pathway. Second, the metal-ligand complex must adopt a nonintegral or partial oxidation state which facilitates movement of charge. The oxidation of nickel phthalocyanine and porphyrin complexes has yielded a number of highly conducting compounds. The desired [1,5,1,5]platyrin has many potentially available oxidation states and appears to be planar, thus the metal complex would have the possibility of exhibiting conducting properties. With the above possibilities in mind, the synthesis of the above-mentioned [1,5,1,5]platyrin was undertaken.

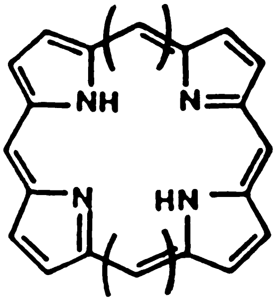
RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

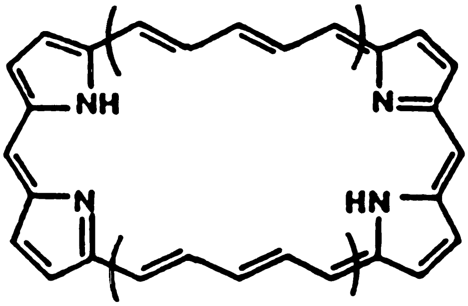
Studies Directed Toward the Synthesis of a Binucleating Octaaza[26]annulene

The octaaza[26]annulene 1 molecule of interest can be described structurally as an expanded porphyrin. Its relation to porphyrin is illustrated in Figure 7. While there is a one-carbon bridge (in parentheses) that separates the dipyrrylmethene units in the tetraaza[18]annulene (porphyrin), there is a five-carbon bridge in both the tetraaza[26]annulene and octaaza[26]annulene ([1,5,1,5]-platyrin) porphyrin vinylogues. The function of the pyrazole rings within these five-carbon bridges in 1 is to give the desired conformationally rigid orientation necessary to obtain a planar macrocycle. The pyrazole rings also serve as good coordinating ligands and metal complexation is another interesting aspect of this molecule.

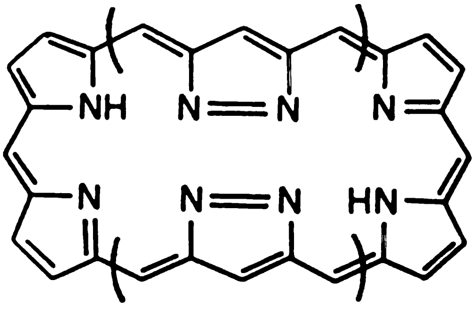
The octaaza[26]annulene could be approached synthetically in a similar way to that of porphyrins. There have been a variety of synthetic methods developed for the synthesis of various porphyrins.[33] Many of these methods take advantage of the fact that the pyrrole rings are susceptible to electrophillic attack at the 2 or α carbon. One route that is used frequently in porphyrin syntheses is



Tetraaza[18]annulene (porphyrin)



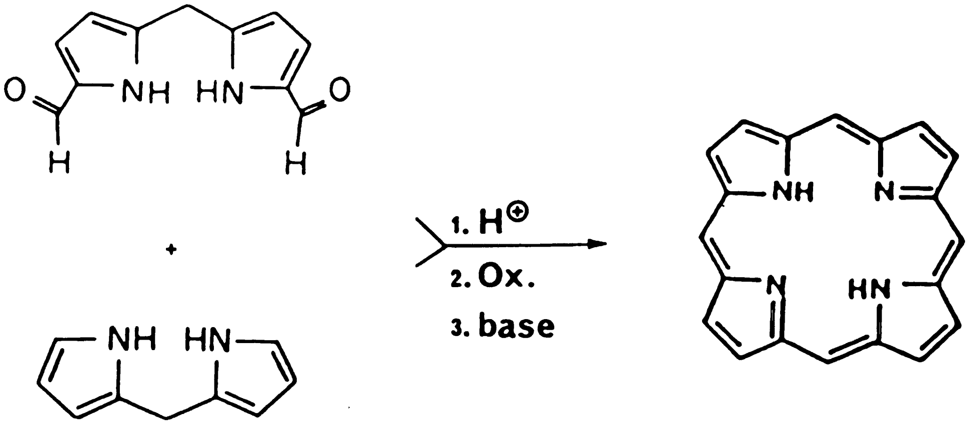
Tetraaza[26]annulene



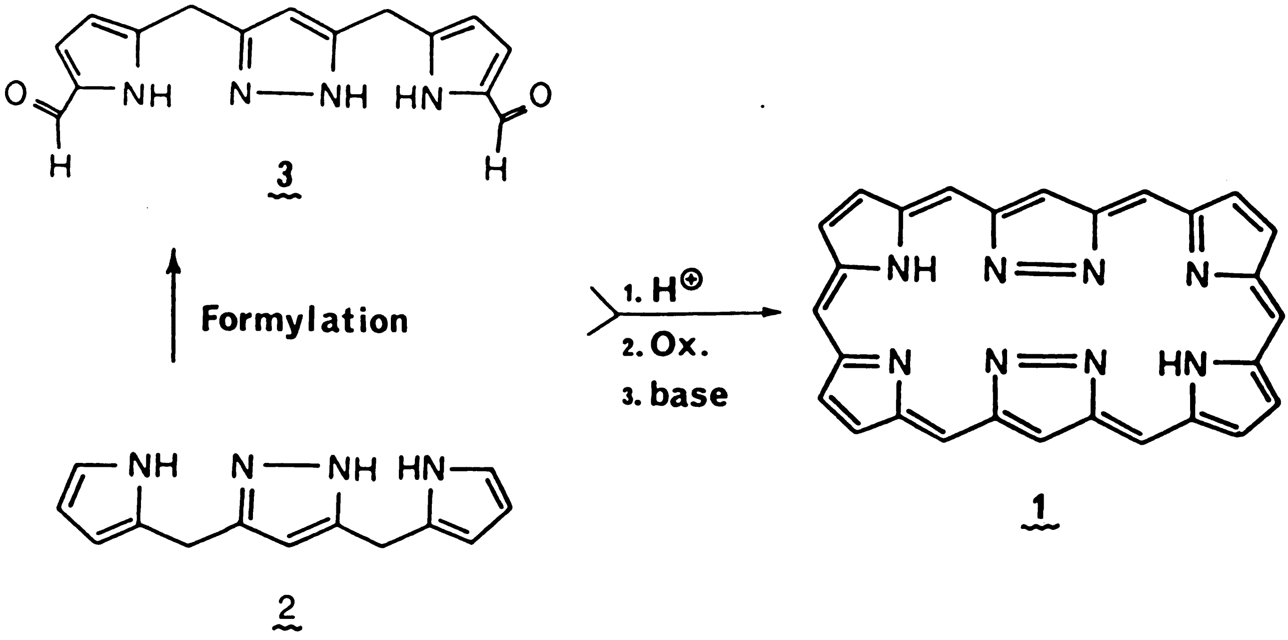
Octaaza[26]annulene 1

Figure 7

the condensation of a bis(α-formyl)dipyrrylmethane with a bis(α-free)dipyrrylmethane under acidic conditions.[34] Subsequent oxidation and treatment with base leads to a porphyrin (Scheme 1). This methodology might be useful in the synthesis of the desired octaaza[26]annulene **1** (Scheme 2). The necessary dialdehyde **3** could be made by formylation of the α-free compound **2**, due to the symmetrical nature of the macrocycle. Thus, the initial compound of synthetic interest was the 3,5-bis(2-pyrrylmethane)pyrazole **2**.



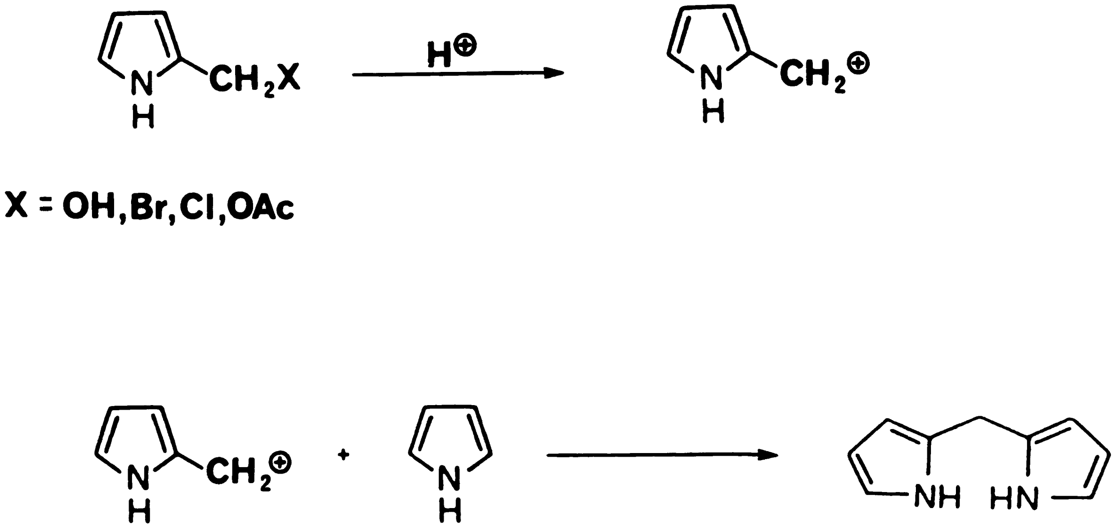
Scheme 1



Scheme 2

I. Electrophillic Substitution Reactions Directed Toward Synthesis of 2.

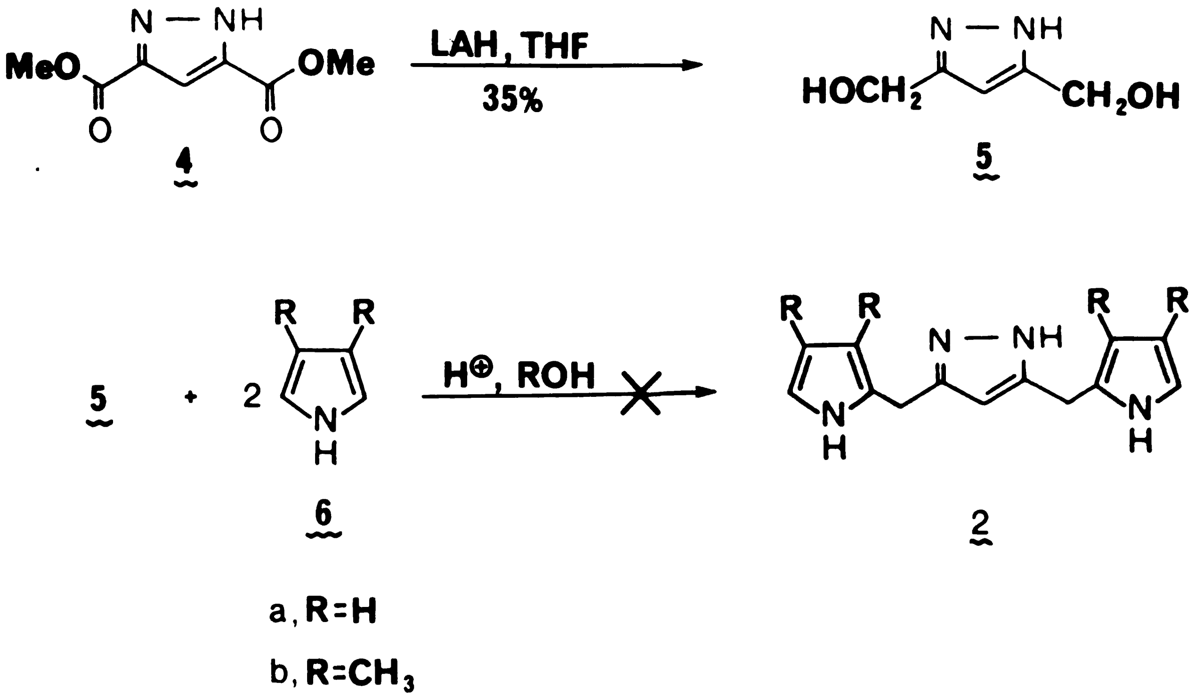
Electrophillic aromatic substitution reactions have been used extensively for the linkage of two pyrroles through a single-carbon bridge in the formation of dipyrrylmethanes, dipyrrylmethenes and dipyrrylketones.[35] For example, dipyrrylmethanes can be made from the reaction of the pyrrylcarbinyl cation and α-free pyrroles under acidic conditions (Scheme 3). This idea was utilized in an effort to synthesize 3,5-bis(2-pyrrylmethane)pyrazole 2. The reactions of some α-free pyrroles with several 3,5-disubstituted pyrazoles were tried. The carbons at the 3



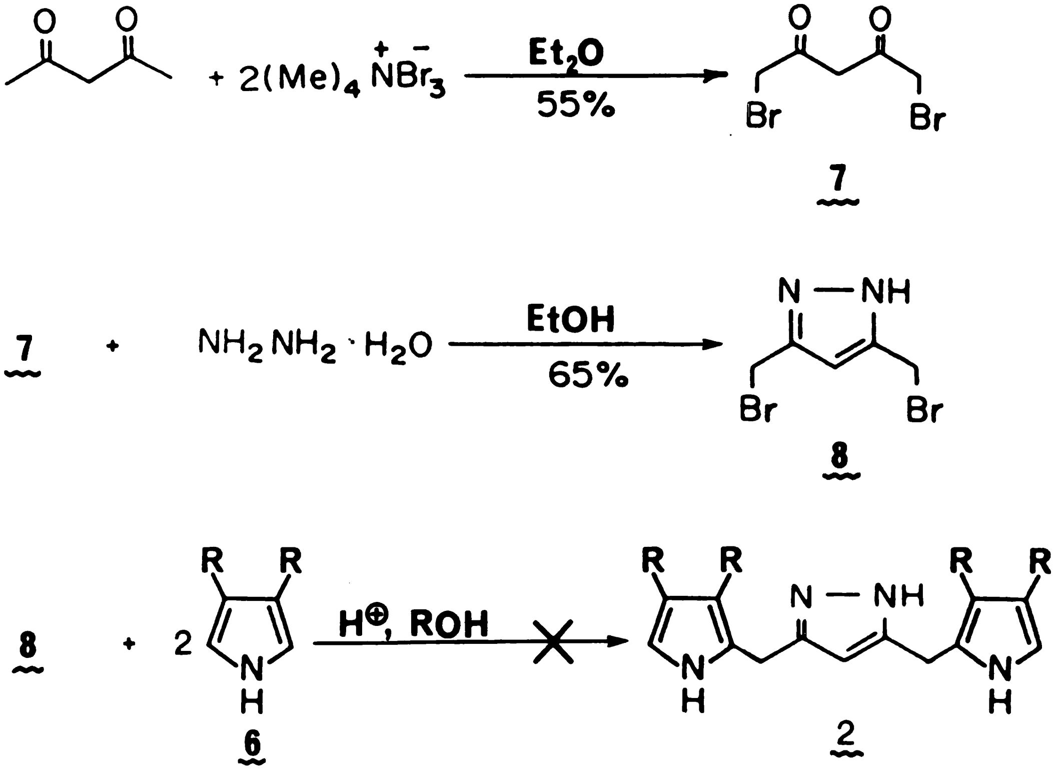
Scheme 3

and 5 positions of these pyrazoles are in the first oxidation state (Schemes 4-7).

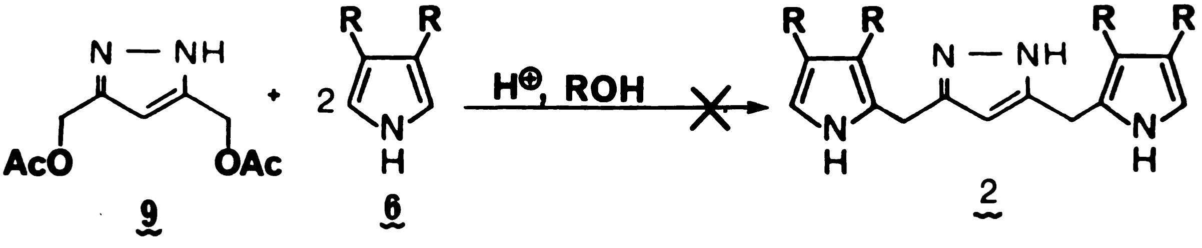
Surprisingly, none of these reactions produced the 3,5-bis(2-pyrrylmethyl)pyrazole. When 3,5-bis(acetoxymethyl)-pyrazole **9** (made *in situ* from 3,5-bis(bromomethyl)pyrazole **8**) was reacted with pyrroles **6a** or **6b**, no product was obtained even though the acetoxypyrroles (X = $OCOCH_3$ in Scheme 3) have worked well in dipyrrylmethane syntheses.[36] In Schemes 4-6, a variety of acids including acetic acid,



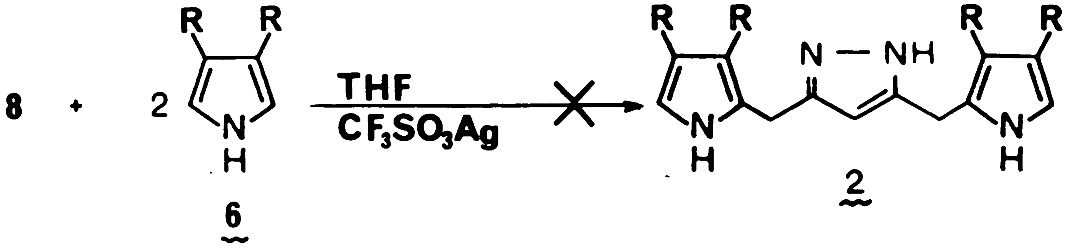
Scheme 4



Scheme 5

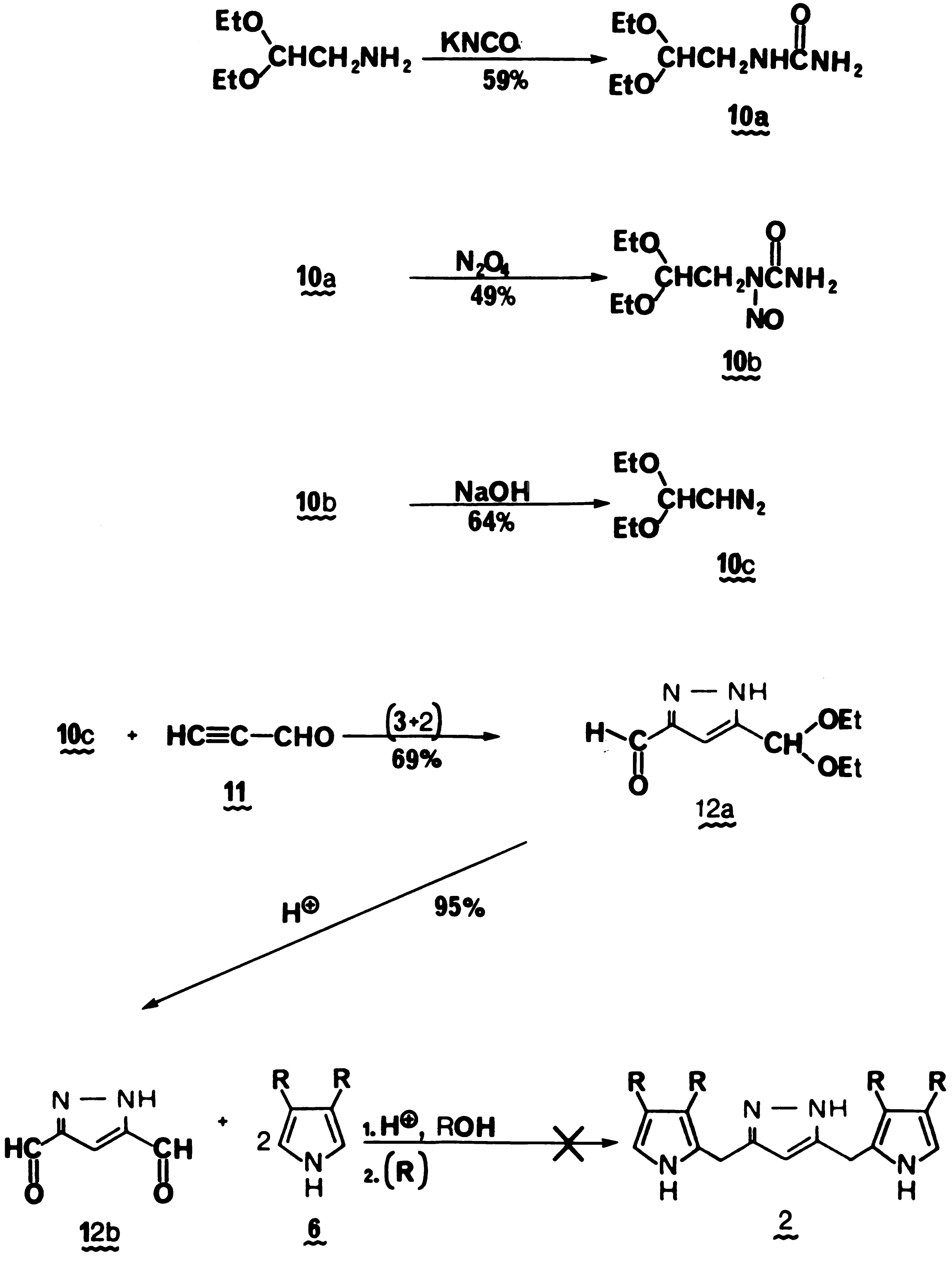


Scheme 6



Scheme 7

toluene sulfonic acid, tetrafluoroboric acid, trifluoroacetic acid, hydrobromic acid and hydrochloric acid in alcohol solvents and Lewis acids including phosphorus oxychloride, zinc iodide, stannic chloride, boron trifluoride etherate, and titanium tetrachloride in dry solvents were tried without success. Only intractable materials were recovered. Among other attempts was the reaction of 3,5 diformylpyrazole **12b** with pyrroles **6a** or **6b** (Scheme 8). The carbons at the 3 and 5 positions of this pyrazole are in the second oxidation state. Reduction of


EtO
CHCH₂NH₂
EtO
KNCO
59%
EtO
CHCH₂NHCNH₂
EtO
O
10a
10a
N₂O₄
49%
EtO
CHCH₂NCNH₂
EtO
O
NO
10b
10b
NaOH
64%
EtO
CHCHN₂
EtO
10c
10c
HC≡C—CHO
11
(3+2)
69%
N — NH
H
C
O
CH
OEt
OEt
12a
H⊕
95%
N — NH
HC
CH
O
O
12b
2
R
R
N
H
6
1. H⊕, ROH
2. (R)
R
R
N — NH
R
R
N
H
N
H
2

Scheme 8

the resulting bis methene salt could give **2**. However, none of the bis methene salt was detected under several different reaction conditions using acids or Lewis acids.

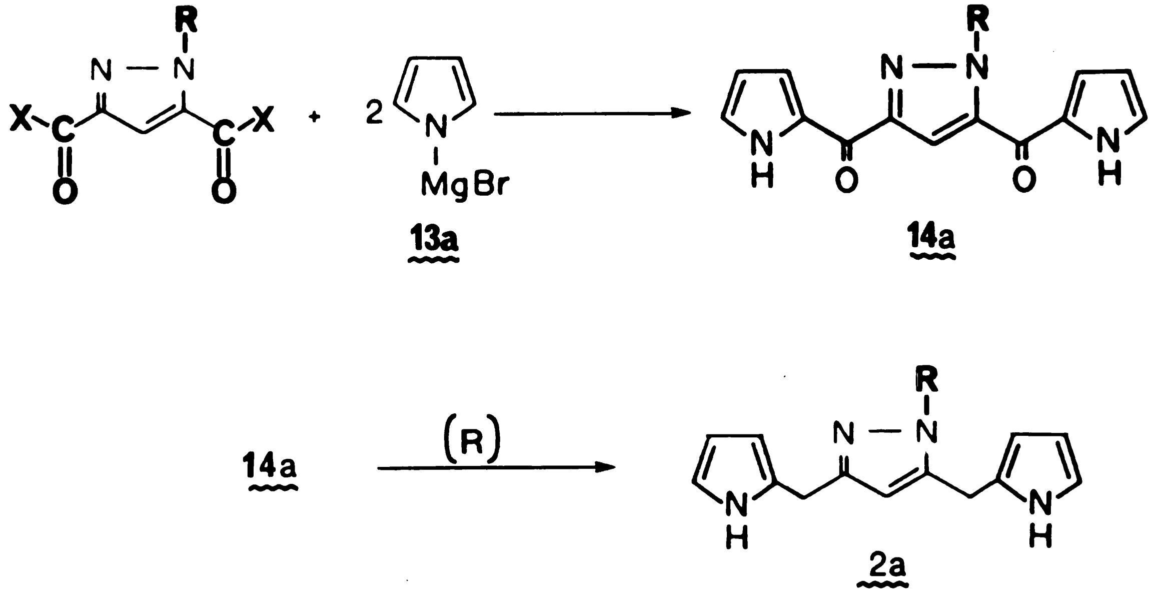
These attempts to synthesize 3,5-bis(2-pyrrylmethyl)-pyrazole **2**, using the electrophillic aromatic substitution routes that worked well in the dipyrrolic syntheses (Scheme 3), were unsuccessful. The problem appears to be the reduced reactivity of the carbons attached to the 3 and 5 positions of pyrazole compared to the carbon attached to the 2 position of pyrrole. This is probably due to the protonation at the second nitrogen of pyrazole which prevents carbocation formation at the carbons attached to the 3 and 5 positions of pyrazole. In view of these results, a different route was needed to synthesize **2**.

II. Anionic Reactions Directed Toward the Synthesis of **2**.

The pyrryl anions are better nucleophiles than pyrrole and could be useful in reactions involving the relatively unreactive pyrazole. Attention was focused on using the ambident anion pyrrylmagnesium bromide since it is possible to control the regioselectivity of electrophillic attack on its carbon or nitrogen. This anion could be well suited for the synthesis of **2** if the desired regioselective α-carbon attack by a selected pyrazole electrophile occurred. Regioselective α-carbon attack would also eliminate the need to protect the pyrrole nitrogen.

Studies have shown that alkylation of pyrrylmagnesium bromide can give total carbon alkylation but isolation of a single alkylation product is not feasible.[37] In contrast to alkylations, the acylation of pyrrylmagnesium bromide has proven to be synthetically useful. Anderson has investigated the acylation of pyrrylmagnesium bromide.[38,39] Among the variables that were studied was the regioselectivity of various acylating agents with respect to their reaction at the nitrogen or carbon of pyrrylmagnesium bromide. It was reported that ethyl carbonate gave predominantly N-acylation (97:3, N/C ratio) when reacted with pyrrylmagnesium bromide in ether. Under the same conditions phosgene or ethyl dithiolcarbonate gave total carbon acylation (0:100, N/C ratio).

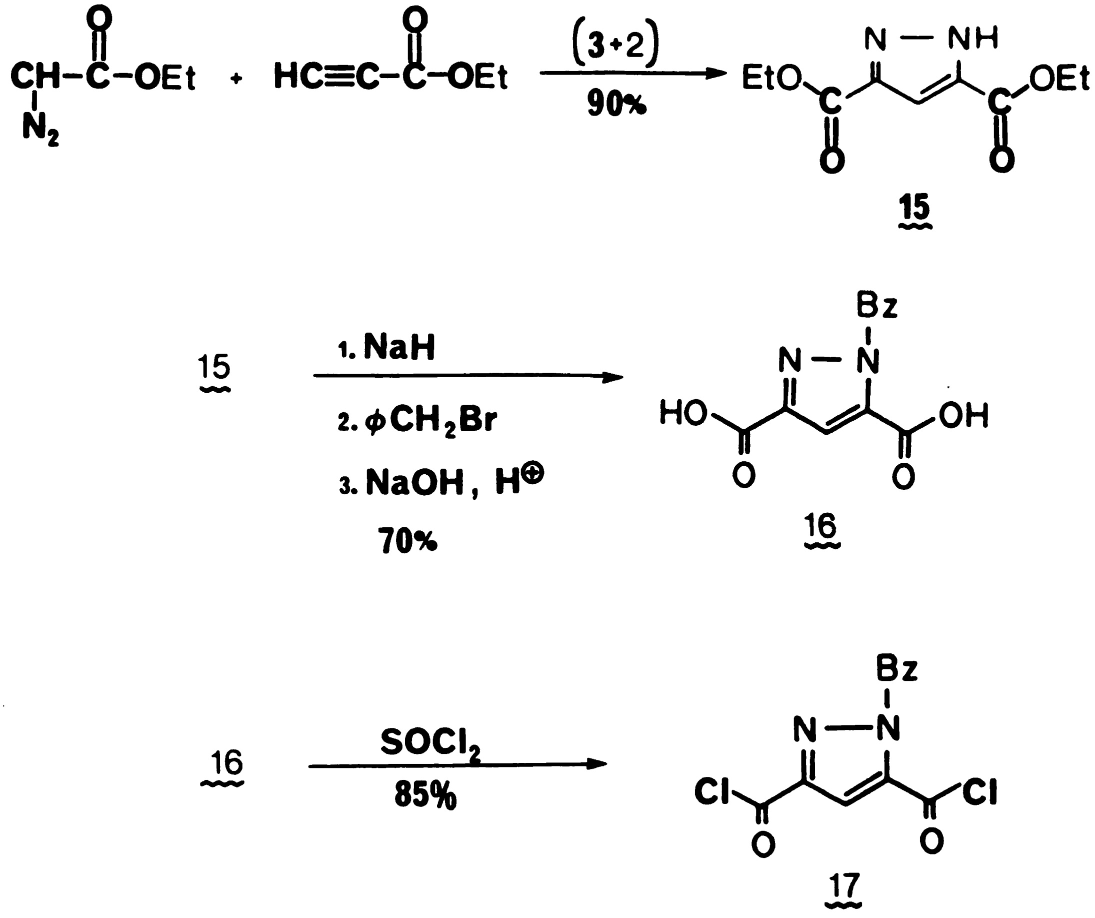
These results were rationalized in terms of the "principle of hard and soft acids and bases".[40] In pyrrylmagnesium bromide the nitrogen is more electronegative, less polarizable, and a harder base than carbon (usually C-2, sometimes C-3) which is less electronegative and more polarizable. Therefore, the hard electrophillic carbon of a carbonyl group such as ethyl carbonate would be expected to and does attack nitrogen. When the carbonyl carbon is softened as in ethyl dithiolcarbonate acylation occurs on the soft carbon. The results establish a trend in the regioselectivity of pyrrylmagnesium bromide acylations that could be used in the synthesis of **2** (Scheme 9). In this Scheme, X represents a selected leaving group of the acylating agent and R is a chosen protecting group. If the regioselectivity can be controlled so that acylation occurs at the α carbon of pyrrylmagnesium bromide, this would lead to the diketone **14a**. Reduction of this diketone would give the compound of interest **2a**, which is equivalent to one half of the macrocycle (see Scheme 2).



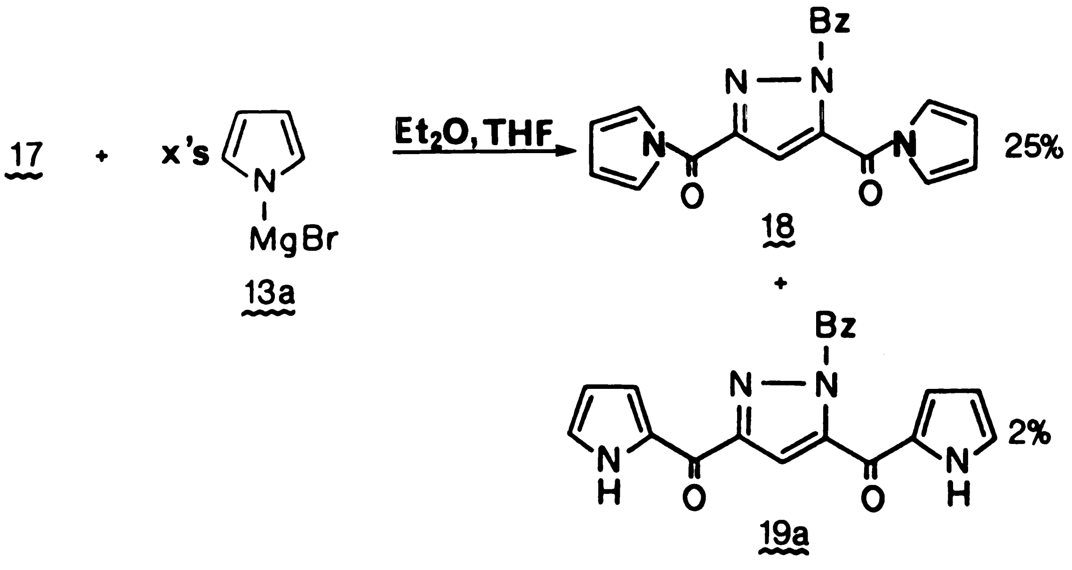
Scheme 9

A suitable protecting group was needed for the pyrazole nitrogen in the above acylation reaction. In addition to being stable under basic conditions, the protecting group would have to be able to survive the acidic conditions used in later reactions. Several possible protecting groups were considered. The [2-(trimethylsilyl)ethoxy]methyl (SEM)[41] protecting group is stable under basic conditions but SEM-imidazole derivatives are deprotected by warming in dilute acid.[42] The benzenesulfonyl and *tert*-butoxycarbonyl groups have been used to protect the pyrrole nitrogen but can be removed under basic conditions.[43] A more suitable choice was the benzyl-protecting group that has been used to protect the pyrazole nitrogen and is stable under both acidic and basic conditions. It is easily introduced on pyrazole but could be difficult to remove. Jones used the harsh Birch conditions to remove the benzyl group from several pyrazole compounds.[44] There are many other possibilities that exist for the removal of the benzyl group. For example, strong acid could remove the benzyl group by taking advantage of the possible isomerization of pyrazole. For the above reasons, the benzyl group was chosen to protect the pyrazole nitrogen.

The next step was to decide on what type of acylating agent to use in Scheme 9. As previously mentioned, Anderson reported that both the acid chloride and thiol ester acylated pyrrylmagnesium bromide on carbon. Thus, an obvious first choice was the diacid chloride **17** which was made in the following way (Scheme 10). A [3+2] cycloaddi-



Scheme 10



Scheme 11

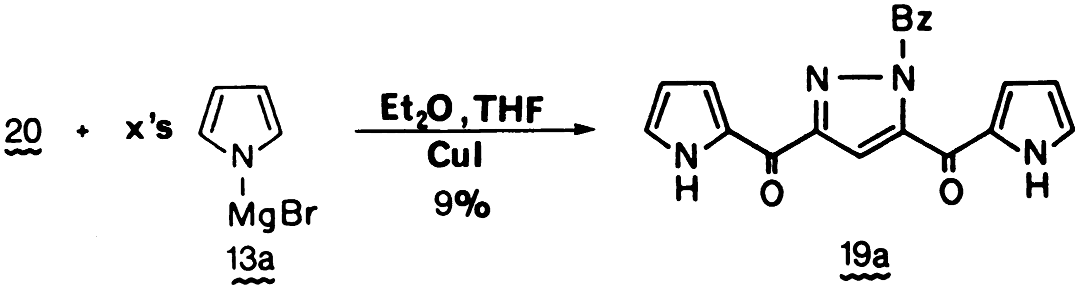
tion involving ethyldiazoacetate and ethyl propiolate led to 3,5-dicarbethoxypyrazole **15** which was benzyl protected then hydrolyzed to 1-benzyl-3,5-dicarboxypyrazole **16** (see experimental for an alternative way to make **16**). Treatment of the diacid with $SOCl_2$ produced the diacid chloride **17**.

The acylation was carried out in dry Et_2O and THF using the protected diacid chloride **17** and excess pyrrylmagnesium bromide (Scheme 11). The major product was the bis(N-acylated) compound **18** with only 2% of the desired bis(C-acylated) compound **19a** being produced. These results differ from Anderson's findings where acylation of pyrrylmagnesium bromide with the acid chloride phosgene gave all C-acylation. This indicates that the particular acid chloride used will also effect the regioselectivity of the acylation.

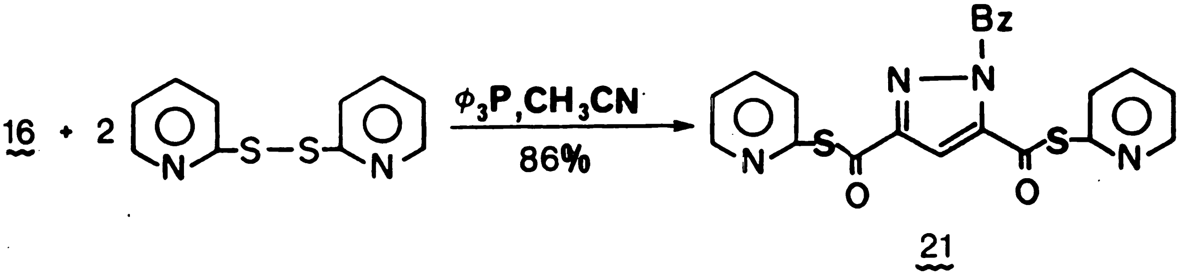
If this acylation is looked at in terms of the "principle of hard and soft acids and bases", then changing the acylating agent from an acid chloride to a softer thiol ester might favor C-acylation. To explore this possibility, the bis(phenylthiol) ester **20** (Scheme 12) was made by reacting the diacid with thiophenol in the presence of 1,1'-carbonyldiimidazole (CDI).[45]

The bis(phenylthiol) ester **20** was treated with an excess of pyrrylmagnesium bromide in the presence of CuI, which had been reported to facilitate this type of reaction presumably through formation of a pyrryl copper complex[46]

Scheme 12



Scheme 13



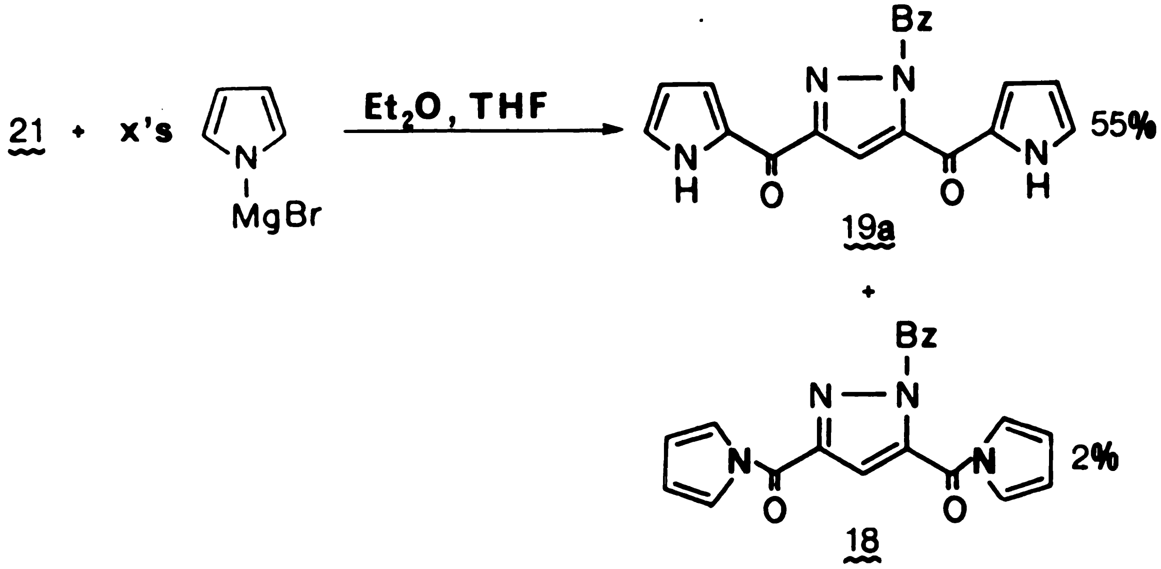
Scheme 14

(Scheme 13). This sluggish reaction yielded 9% of the bis(C-acylated) product **19a** with none of the bis(N-acylated) compound being detected. Even though the regioselectivity of the bis(phenylthiol) ester was an improvement over the acid chloride the yield was low.

Another type of thiol ester which has been used an an acylating agent and proven to give good yields is the pyridylthiol ester. To examine this, the bis(S-2-pyridylthiol) ester **21** was made on a large scale from the reaction of the diacid **16** with 2,2'-dipyridyldisulfide and triphenylphosphine in dry acetonitrile at 25°C[47] (Scheme 14).

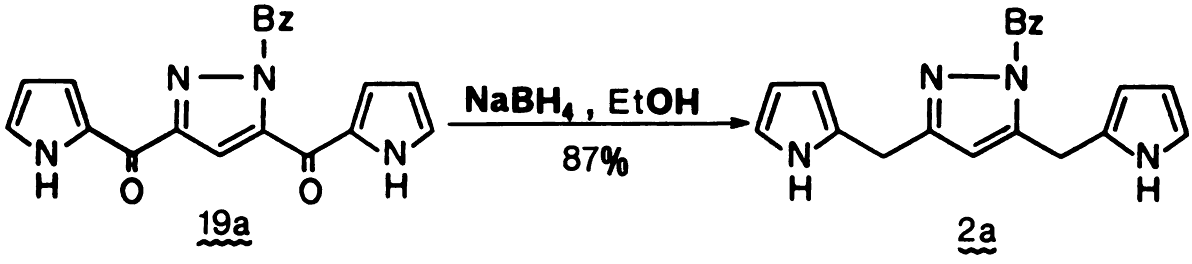
When **21** was treated with an excess of pyrrylmagnesium bromide at 0°C, the desired bis(C-acylated) product **19a** was obtained in 55% yield along with 2% of the bis(N-acylated compound **18** (Scheme 15). Modification of the reaction conditions, including lower and higher temperatures and various reaction media such as Et_2O/toluene, Et_2O, THF, or Et_2O/dioxane, didn't eliminate the small amounts of the bis(N-acylated) compound. However, this by-product **18** was easily separated from **19a** using flash column chromatography. The 1-benzyl-3,5-bis(S-2-pyridylthiol)pyrazolate acylating agent proved to be superior to the other acylating agents (Schemes 11 and 13) that were used in the synthesis of the diketone **19a**.

The next step was the reductive deoxygenation of the diketone **19a**. The first attempt was tried using $NaBH_4$ in refluxing EtOH (Scheme 16). Due to the relatively

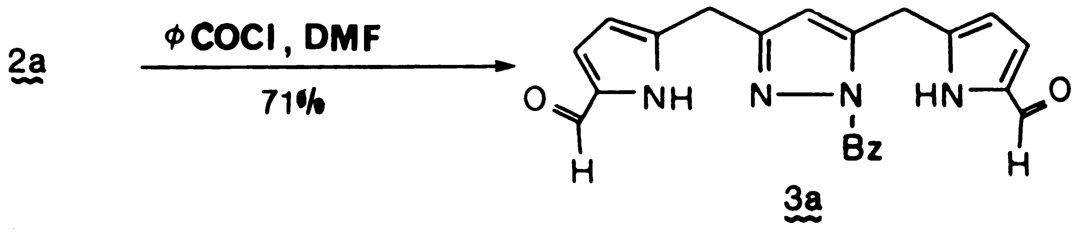


Scheme 15

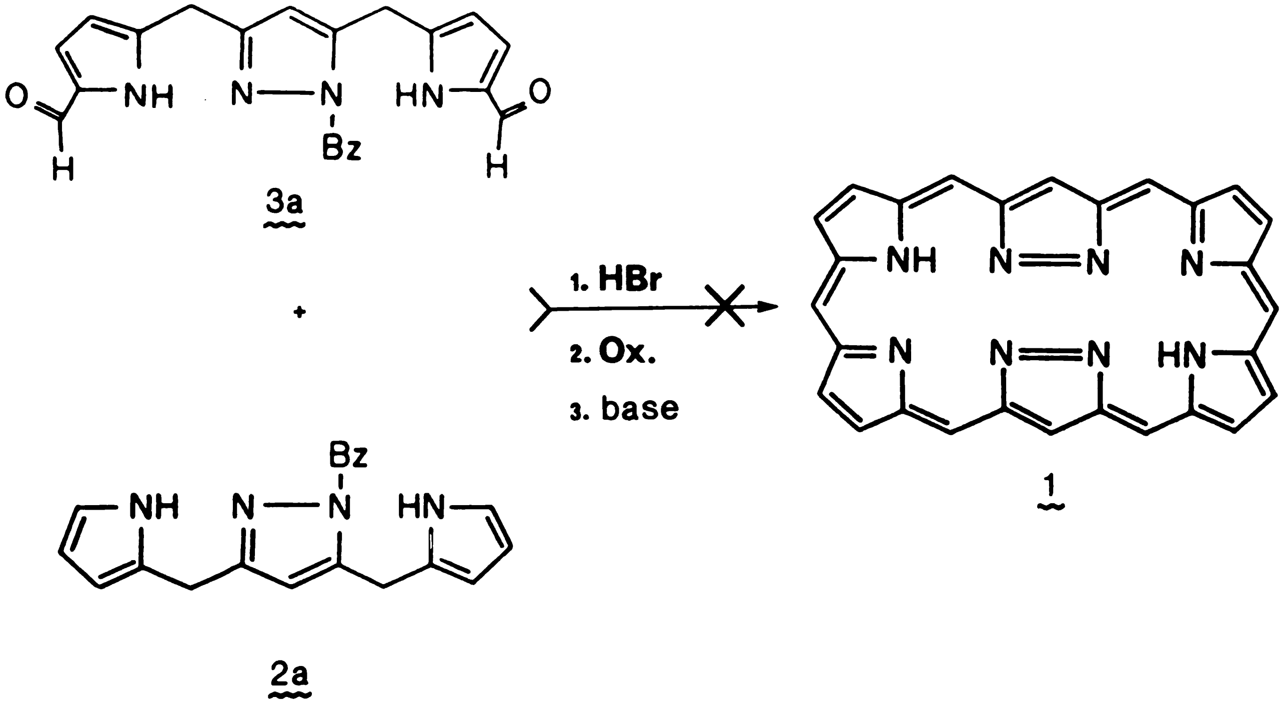
unreactive bis(vinylogous) amide character of each carbonyl group of the diketone, reduction was slow (72 h) but the yields were very good. Another set of conditions using NaCNBH$_3$ and ZnI[51] were tried in an effort to decrease the reaction time but this combination failed to reduce the diketone. Bis formylation of **2a** was accomplished by using a modification of the Vilsmeier-Haack procedure[52] (Scheme 17). The condensation of the bis(α-free) compound **2a** with the dialdehyde **3a** under dilute conditions in the presence of acid was run once without success (Scheme 18).



Scheme 16



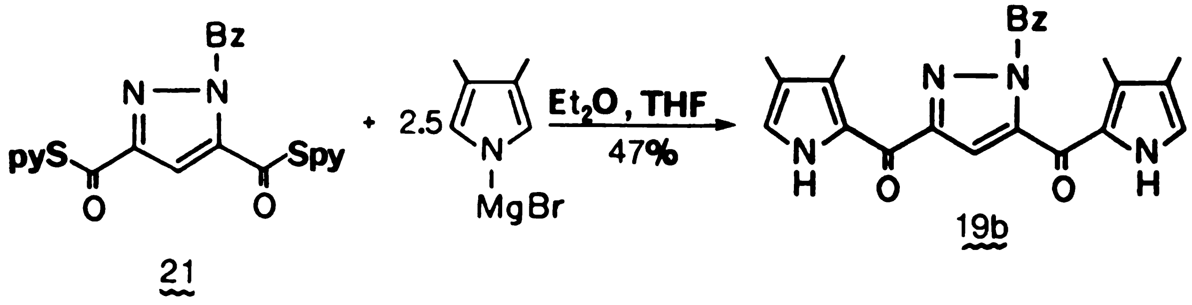
Scheme 17



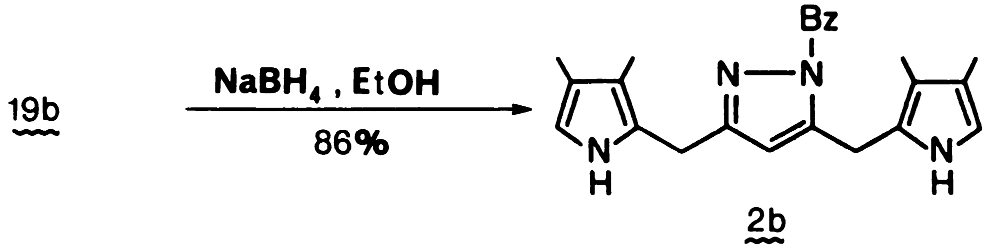
Scheme 18

Rather than repeating this sequence (Scheme 18) again, it was decided to block the β-positions of the pyrrole rings since electrophillic attack at these positions could be interfering with the formation of the macrocycle. This was done by starting with 3,4-dimethylpyrrole,[53] instead of pyrrole, as the precursor to the Grignard reagent used in the acylation reaction. Then a similar reaction sequence using 3,4-dimethylpyrrylmagnesium bromide in place of pyrrylmagnesium bromide was run under modified reaction conditions.

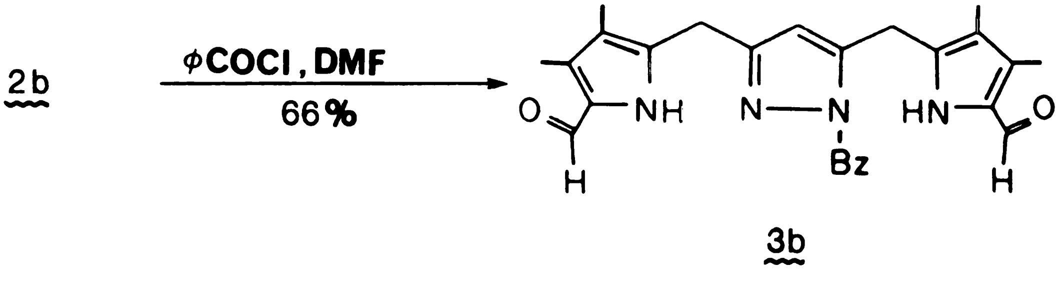
A slight excess of 3,4-dimethylpyrrylmagnesium bromide **13b** reacted with the dithiol ester **21** to give the bis(C-acylated) product with none of the bis(N-acylated) product being detected (Scheme 19). When a larger excess (4-6 equiv.) of **13b** was used, the 3,4-dimethylpyrrole, produced after work-up of the reaction, contaminated the diketone **19b** due to its decomposition on the column during purification. Reduction of **19b** with $NaBH_4$ (Scheme 20) yielded the extremely air- and light-sensitive compound **2b** (**2b** is stable for a limited time under argon in the freezer). Bis-formylation of **2b**, using the modified Vilsmeier-Haack method as before, produced the dialdehyde **3b** (Scheme 21). The desired compounds with the β positions on the pyrrole rings blocked were at hand to try the condensation reaction that could lead to the macrocycle of interest.



Scheme 19



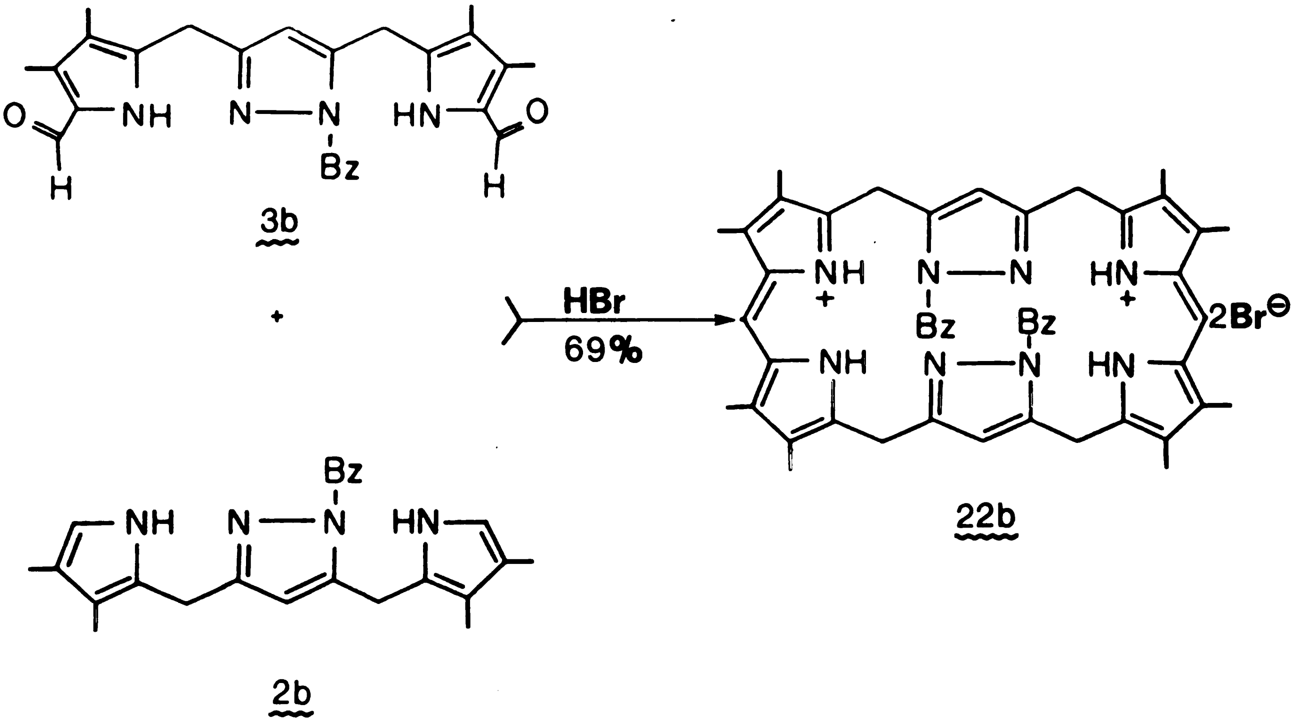
Scheme 20



Scheme 21

III. Synthesis of Octaazatetrahydro[1,5,1,5]platyrin.

Freshly prepared bis(α-free) compound **2b** in MeOH was reacted with the dialdehyde **3b** in MeOH/CH_2Cl_2 under dilute acidic (48% HBr) conditions in the absence of air (Scheme 22). The orange-red tetrahydro[1,5,1,5]platyrin **22b** precipitated out of solution in 69% yield. When this reaction was repeated on the same scale, a 69% yield was obtained again. This compound is consistent with all of its spectral data.



Scheme 22

The 250 MHz ^{1}H NMR of the dihydrobromide salt of tetrahydro[1,5,1,5]platyrin **22b** (Figure A25) was taken in deuterated DMSO with one drop of trifluoroacetic acid to increase its solubility. This spectrum displayed a broad doublet at 12.46 produced by the four (NH and NH$^+$) protons. The peaks at at 7.42 and 7.50 were assigned to the methene protons. The chemical shift of the methene protons in dipyrrylmethene units are generally in the 6.6-7.9 ppm range.[54,55] The phenyl protons of the benzyl group at 7.25 ppm in **22b** are at a similar position to those of compounds **2b** and **3b**, both at 7.20 ppm. The two sharp singlets located at 5.91 and 6.01 ppm were assigned to the aromatic 4H pyrazole protons. The signals of the CH_2 protons of the benzyl group are at 5.46 and 5.48 ppm. The meso CH_2 protons at 4.09, 4.16 and 4.20 are shifted downfield from the meso CH_2 protons of the starting compound **2b**. The eight methyl groups (24H) give peaks that are spread from 1.68-2.31 ppm. The above ^{1}H NMR data could fit the top two or the bottom two configurations seen in Figure 8. For example, either pair could be responsible for the two singlets at 5.91 and 6.01 ppm that were assigned to the 4H pyrazole protons. The 4H pyrazole protons were chosen to illustrate the above structural possibilities because their two peaks cannot be the result of the unsymmetrical nature of the benzyl group

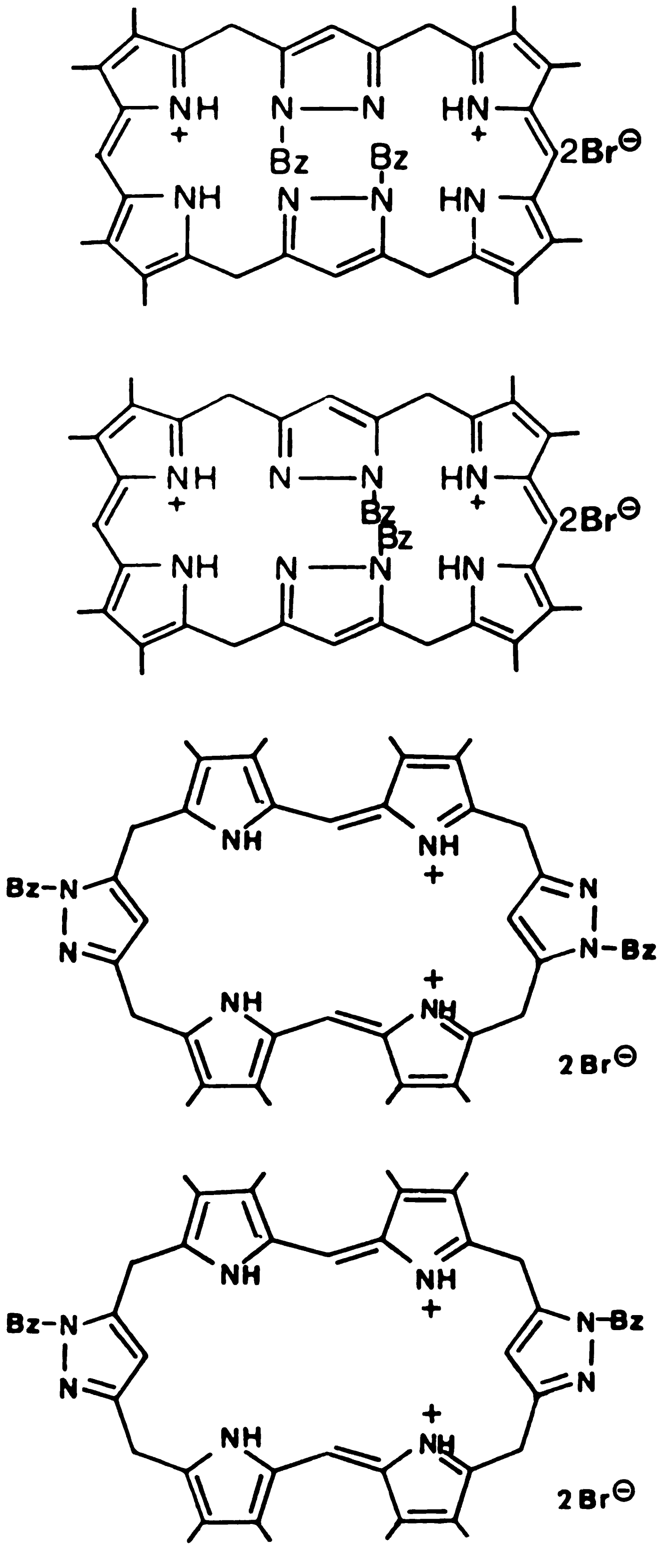


Figure 8

in any one particular structure. The 250 MHz ^1H NMR spectrum of **22b** was also taken in $CDCl_3/CF_3CO_2H$ (Figure A26).

The ^{13}C NMR of **22b** was taken in $CDCl_3/CF_3CO_2H$ and the assignments of the peaks can be found in the experimental section. The methyl carbons, meso CH_2 carbons, benzyl CH_2 carbons, and the pyrazole number 4 carbons could be readily distinguished. The ^{13}C program DEPT (see general methods) assisted in the remaining assignments. DEPT can record a single proton decoupled ^{13}CH, $^{13}CH_2$ or $^{13}CH_3$ spectrum. The DEPT program was used to obtain a ^{13}CH spectrum of **22b** (In Figure A28 the ^{13}C spectrum is on the bottom and the ^{13}CH spectrum is on the top.). The ^{13}CH spectrum led to the assignment of the peaks at 122.69 and 123.18 ppm to the methene carbons. The peaks at 127.68, 129.70, 129.79, and 129.93 ppm are the phenyl carbons of the benzyl groups. Less visible are the signals at 108.96 and 109.31 ppm which had already been assigned to the number 4 carbons of the pyrazole rings. All of the unassigned signals in the 125-150 ppm range of the ^{13}C spectrum could now be assigned to the carbons which had no hydrogens attached.

The fast atom bombardment (FAB) mass spectrum that was taken of **22b** utilized a technique developed for porphyrin analyses.[56] The acidic matrix used (see general methods) will produce monoprotonated compound $(M+H)^+$ ions as the most abundant species in the spectra. The FAB mass spectrum of Tetrahydro[1,5,1,5]platyrin **22b** (Figure A29) reveals a strong $[M+H]^+$ parent ion at m/z 765. Cleavage of the first benzyl group resulted in the signal at m/z 675 and cleavage of the second benzyl group gave the signal at m/z 583. The peaks at the low end of the spectrum are due to the matrix. The signals with higher m/z than the $[M+H]^+$ parent ion are a result of the matrix molecules combining with compound **22b**.

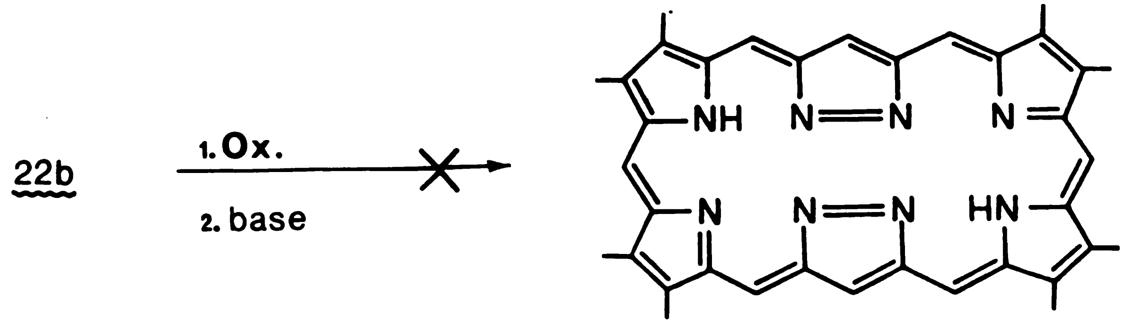
All dipyrrylmethenes show a characteristic absorption at 1600-1680 cm^{-1} in their infrared spectrum. This is called the dipyrrylmethene band.[54] The infrared spectrum of **22b** in nujol has this characteristic absorption at 1615 cm^{-1}.

The UV-visible spectrum of the dihydrobromide salt of tetrahydro[1,5,1,5]platyrin **22b** (Figure A30) in CH_2Cl_2 gave the following data: λ_{max} (ε_M); 469.5 (189,949), 371 (16,114). This data is consistent with that of other bis(dipyrrylmethene) salts. For example, Berger has reported a λ_{max} of 462 nm for a macrocyclic bis(dipyrrylmethene) salt.[57] The extinction coefficient of (189,949) for the major peak of **22b** is in the correct range. The extinction coefficient of this bis(dipyrrylmethene) compound is approximately twice as large as the mono(dipyrrylmethene) compounds.[58] The UV-visible spectrum of the free base of **22b** that was obtained in CH_2Cl_2 and pyridine (Figure A31) gave the following data: λ_{max} (ε_M); 439.0 (56,398), 313.5 (206,161). There was a shift of 30.5 nm in the long wavelength peak when going from the bis salt to the

free base. This agrees with Dolphins' observation that protonated species absorb at about a 20-40 nm longer wavelength than the free base.[59] The short wavelength peak at 313.5 nm is close to the 298 nm peak Mertes observed in a different bis(dipyrrylmethene) macrocycle.[30] When the free base of **22b** was treated with a few drops of trifluoroacetic acid, the longer wavelength peak was regenerated (λ_{max} = 463.5, bis-trifluoroacetate salt).

The stable tetrahydro[1,5,1,5]platyrin bis-hydrobromide salt **22b** could not be oxidized to the 26π-electron annulene (Scheme 23) with any of the following reagents; oxygen, bromine, iodine, chloranil, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, trityltrifluoroacetate[60] or lead tetraacetate. The products obtained from these reactions were unidentifiable by 250 MHz ^1H NMR analyses. The desired [1,5,1,5]platyrin **1b**, being a 26π-electron annulene, would be expected to show distinctive chemical shifts in its ^1H NMR spectrum due to the ring current effects (see Table 1). These characteristic upfield and downfield peaks were not detected in any of the above reaction products. Partially oxidized products could not be identified either.

Removing the benzyl-protecting groups might make the oxidation possible. Strong acid was tried first. Compound **22b** was refluxed in 48% HBr for 24 h. Quantitative amounts of the starting material were recovered. Several other



1b

Scheme 23

attempts including phosphoric acid-phenol,[61] boron trifluoride-methyl sulfide complex, trifluoroacetic acid and 10% Pd/C (ammonium formate as H_2 source[63]) yielded unidentifiable products.

Treatment of the octaazatetrahydro[1,5,1,5]platyrin **22b** with $Zn(OAc)_2$ or $Ni(OAc)_2$ in refluxing dimethylformamide led to unidentifiable products. However, treatment of **22b** with $Cu(OAc)_2$ in DMF at room temperature yielded a product that gave peaks at 506 and 664 nm in its visible spectrum. Treatment of this product with trifluoroacetic acid did not regenerate a peak in the 470 nm range of the starting material .

CONCLUSION

The tetrahydro[1,5,1,5]platyrin dihydrobromide salt **22b** was synthesized in 69% yield. Several attempts to oxidize this compound to the desired [1,5,1,5]platyrin **1b** were not successful. Part of the problem in this last oxidation step could be that the reactant **22b** is a very stable salt while the product **1b** might be an unstable 26π-electron annulene. A previously synthesized 26π-electron tetraazaannulene proved to be relatively unstable (decomposed in a few hours to a few days even at low temperatures).[24] The instability observed in the larger 26π-electron tetraazaannulene could be a result of the decrease in resonance stabilization. Dewar predicted that somewhere between [22] and [26] annulene there would be little delocalization energy.[8] Haddon determined that resonance energy is inversely proportional to the number of π-electrons.[14] More 26π-electron annulenes have to be synthesized and studied to confirm these theories. The possibility of the oxidation of **22b** to the 26π-electron octaazaannulene **1b** still remains. The octaaza[26]annulene would give more experimental information that would lead to a better understanding of these large annulenes.

EXPERIMENTAL

EXPERIMENTAL

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Varian T-60 at 60 MHz or a Bruker WM-250 (^1H NMR at 250 MHz and ^{13}C NMR at 62.9 MHz) instrument in $CDCl_3$ or as noted. The ^{13}C NMR program DEPT (Distortionless Enhancement by Polarization Transfer) developed by R. M. Bendall, D. M. Doddrell and D. T. Pegg can record a single decoupled ^{13}CH, $^{13}CH_2$ or $^{13}CH_3$ spectrum. Ethyl benzene was used to set parameters of this program. The internal standard used was tetramethylsilane (TMS) unless Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) is listed. Electronic absorption spectra were measured on a Shimatzu 160 spectrophotometer using 1 cm matched quartz cells. Mass spectra were obtained on a Finnigan 4000 instrument at 70eV. Fast atom bombardment (FAB) mass spectra were obtained using a Varian-MAT CH5 double-focusing instrument equipped with an Ion Tech fast atom bombardment gun. A matrix of thioglycerol:dithioerythreitol:dithiothreitol (2:1:1) containing 0.1% trifluoroacetic acid previously developed for porphyrin FAB-MASS analyses was used.[56] This acidic matrix will produce monoprotonated compound $(M+H)^+$ ions as the most abundant species in the spectra. Infrared spectra were measured on a Perkin-Elmer 599 spectrophotometer as a Nujol mull for solids or neat for liquids. Elemental analyses were performed by Galbraith Laboratories, Incorporated. Dry ether, benzene, toluene and tetrahydrofuran (THF) were obtained by distillation from potassium benzophenone. Dry methylene chloride (CH_2Cl_2) and acetonitrile were obtained by distillation from calcium hydride. Flash column chromatography refers to the method of Still, Kahn and Mitra[64] using Merck silica gel (0.040-0.063 mm). Thin-layer chromatography (tlc) was performed using Macherey-Nagel "Polygram SIL N-HR/UV_{254}" .1mm pre-coated silica gel plates. Cambridge Isotope Laboratories supplied the following deuterated solvents: chloroform ($CDCl_3$), (acetone$_{d6}$), dimethyl sulfoxide ($DMSO_{d6}$), water (D_2O). All reactions, unless otherwise noted, were carried out under an atmosphere of argon.

<u>3,5-Bis(hydroxymethyl)pyrazole</u> 5.

In a Soxhlet thimble above a refluxing solution of 1.23 g $LiAlH_4$ in 90 mL THF was added 2 g of 3,5-bis(carbomethoxy)pyrazole. After refluxing for 24 h, the resulting solution was cooled to 0°C. To this chilled, stirred solution was added 1.2 mL water, followed by 1.2 mL of 15% NaOH and then 4 mL water. After 1/2 h the solids were filtered from the reaction mixture and extracted with

MeOH. The MeOH layer was decanted and concentrated. There was obtained 0.487 g (35.3% yield) of a waxy white solid: m.p. 230-235°C (dec.); ^1H NMR: (D_2O, DSS) δ 4.61 (4H, s), 6.29 (1H, s); MS: *m/e* 128 (parent), 111, 97, 81 (base).

1,5-Dibromo-2,4-pentanedione 7.[85]

To a stirred mixture of 50 mL ether and 13.2 g of tetramethylammonium tribromide (TMAT) at 25°C was added 2 g of acetylacetone. After about 1 h when all of the bromine has been consumed (orange TMAT goes to white tetramethylammonium bromide, TMAB), the TMAB was filtered from the reaction mixture. The filtrate was washed several times with water. Then the ether layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residual oil was chilled for approximately 36 g to allow the bromine to rearrange. Purification of the resulting oil by flash column chromatography using petroleum ether-ether (85:15) as eluent yielded 2.83 g (55% yield) of a yellow oil: m.p. 6-7°C; ^1H NMR: δ 3.90 (4H, s), 6.04 (1H, s), 12.82 (1H, bs); MS: *m/e* 258 (parent, triplet isotope cluster), 163 (base); IR: cm^{-1} 3445, 1720, 1600.

3,5-Bis(bromomethyl)pyrazole 8.[85]

To a stirred solution of 1,5-dibromo-2,4-pentanedione in 5 mL of 90% EtOH at 0°C was added dropwise 0.281 g of hydrazine hydrate (99%). After 10 min, the solution was chilled. Recrystallization of the resulting solid from EtOH and water afforded 0.93 g (65% yield): m.p. 78-79°C; ^{1}H NMR: δ 4.45 (4H, s), 6.32 (1H, s), 10.8 (1H, s); MS: *m/e* 254 (parent, triplet isotope cluster), 173 (base). *Anal.* Calcd. for $C_5H_6N_2Br_2$: C, 23.62; H, 2.36; N, 11.02; Br, 62.99. Found: C, 23.82; H, 2.52; N, 11.38; Br, 62.27.

Ureidoacetal **10a**.[66]

To a mixture of 49.3 g of aminoacetal and 79 g crushed ice was added 75 mL of cold 5N HCl. Immediately afterwards, a solution of KNCO in 100 mL water was added. This mixture was refluxed for 1 1/2 h. The solvent was evaporated and the resulting mixture was extracted with dry CH_2Cl_2 and filtered. Evaporation of the CH_2Cl_2 afforded 39 g (59% yield) of white solid: m.p. 104-108°C (lit[66] 103-107); ^{1}H NMR: δ 1.22 (6H, t), 3.30 (2H, t), 3.43 (2H, q), 3.42 (2H, q), 4.51 (1H, t), 4.75 (2H, bs), 5.24 (1H, t); MS: *m/e* 131, 47 (base); IR: cm^{-1} 3360, 3200, 1650, 1120.

N-Nitroso-N-[2,2-diethoxyethyl]urea **10b**.[67]

To a stirred suspension of 17.6 g of ureidoacetal and 18 g of anhydrous NaOAc in 200 mL of ether at -10°C was added dropwise a solution of 13.1 g N_2O_4 in 140 mL ether. After 1 h, the ether layer was decanted off. This was treated with 75 mL of a saturated $NaHCO_3$ solution in small portions. The ether phase was separated then dried over anhydrous $MgSO_4$. Evaporation of the ether yielded a yellow oil. Crystallization of the oil from pentane at −78°C afforded 5.7 g (49% yield) of a yellow solid: m.p. 32-35°C (lit[67] m.p. 30-31°C); ^{1}H NMR: δ 1.15 (6H, t), 3.49 (3H, q), 3.64 (3H, q), 4.00 (2H, d), 4.64 (1H, t); MS: *m/e* 103, 46 (base); IR: cm^{-1} 3415, 3330, 3270, 3180, 1735, 1600.

2,2-Diethoxy-1-diazoethane **10c**.[67]

To a stirred solution of 75 mL of 2N NaOH and 20 mL ether at 0°C was added dropwise a solution of 5.7 g of N-nitroso-N-[2,2-diethoxy-ethyl]urea in 20 mL of ether. After 10 h, the ether layer was separated. This ether layer was then dried over KOH and concentrated. The resulting diazo compound was carefully distilled at 25°C under reduced pressure (0.5 mmHg) to yield 2.5 g (64% yield) of a yellow oil: ^{1}H NMR: (benzene d_6) δ 0.75 (6H, t), 3.02 (2H, q), 3.19 (2H, q), 4.4 (1H, t), 4.81 (2H, d); IR: cm^{-1} 2075.

Propargyl aldehyde **11**.[68]

To a 2000 mL three-necked, round-bottom flask was added 120 mL of 95% propargyl alcohol, 135 mL H_2SO_4 and 200 mL of water. This stirred solution was cooled to 0°C and the pressure was reduced to 40 mmHg. A solution of CrO_3 (2.1 moles) in 400 mL of water and 135 mL H_2SO_4 was added dropwise while maintaining a reaction temperature of 2-10°C. As the aldehyde was produced, it was distilled into a series of 3 traps. The first trap was cooled to -15°C and the last two were cooled to -78°C. The distillates were combined and the water layer was separated. The crude aldehyde was dried over anhydrous $MgSO_4$. Redistillation of the resulting liquid yielded 10.8 g (10% yield): b.p. 55-57°C (lit[68] b.p. 55-57°C); ^{1}H NMR: δ 3.5 (1H, s), 9.2 (1H, s).

3-Diethoxymethyl-5-formyl-pyrazole **12a**.

To a stirred solution of 0.114 g of propargyl aldehyde in 2 mL ether at -30°C was added dropwise a solution of 0.257 g of 2,2-diethoxy-1-diazo-ethane in 8 mL ether. After 1 h, this solution was chilled. Recrystallization of the resulting white solid from ether at -10°C afforded 0.242 g (69% yield): m.p. 81-82°C; ^{1}H NMR: δ 1.25 (6H, t), 3.64 (4H, q), 5.70 (1H, s), 6.83 (1H, s), 9.99 (1H, s); MS: *m/e* 199 (M^{+1} parent), 153 (base), 125; IR: cm^{-1} 1715. *Anal.* Calcd. for $C_9H_{14}N_2O_3$: C, 54.55; H, 7.07; N, 14.14; O, 24.24. Found: C, 54.61; H, 6.94; N, 14.08; O, 24.37.

3,5-Diformylpyrazole **12b**.

To a stirred solution of 5 mL of 0.5N HCl was added 0.13 g of 3-diethoxymethyl-5-formyl-pyrazole. This solution was stirred at 25°C for 2 h. Suction filtration of the reaction mixture yielded 0.077 g (95% yield) of the white dialdehyde: m.p. 206-208°C; ^{1}H NMR: (DMSO d_6) δ 7.49 (1H, s), 9.94 (2H, s); MS: m/e 124 (parent), 96, 67, 39 (base); IR: cm^{-1} 1714.

3,5-Dicarboxypyrazole.[69]

To a solution of 22.7 g of 3,5-dimethylpyrazole in 1000 mL water was added 160 g of $KMnO_4$ over 2 h while bubbling in CO_2 continuously. This mixture was stirred for 18 h and then filtered through celite. The filtrate was acidified and the hydrated diacid was collected by suction filtration. The solid was dehydrated by heating overnight at 130°C under reduced pressure to afford 10.4 g (23% yield) of the diacid: m.p. 292-294°C (dec.) (lit.[69] m.p. 289°C); ^1H NMR: (K_2CO_3, D_2O, DSS) δ 6.99 (1H, s); MS: m/e 156 (parent), 112, 67, 44 (base); IR: cm^{-1} 3190, 2440, 1695, 1645.

3,5-Dicarbomethoxypyrazole.

To a solution of 10.4 g of 3,5-dicarboxypyrazole in 50 mL of anhydrous MeOH was bubbled HCl gas. This solution was refluxed for 3 h. Suction filtration yielded 9.5 g (91% yield) of the diester: m.p. 152-154°C (Lit. m.p. 151.5°C); ^1H NMR: δ 3.96 (6H, s), 7.35 (1H, s); MS: m/e 184 (parent), 153 (base), 126, 121; IR: cm^{-1} 3360, 1725, 1700, 1260, 1240.

1-Benzyl-3,5-dicarboxypyrazole **16**.[71]

To a mixture of 11.1 g of the sodium salt of 3,5-dicarbomethoxypyrazole (formed by treating the diester with sodium methoxide) in 50 mL of mesitylene was added 13.8 g of benzyl bromide and 0.94 g of dicyclohexano-18-crown-6. The mixture was refluxed for 2 days. Following this, the solvent was evaporated under reduced pressure to afford a solid. Ethanol (75 mL), water (100 mL) and NaOH (10 g) were added to the solid and this mixture was refluxed overnight. The solvents were evaporated and the resulting solid acidified with an HCl solution. Filtration and recrystallization from EtOH/water yielded 10.8 g (70% yield): m.p. 234-236°C (lit.[71] 234°C); ^{1}H NMR: (K_2CO_3, DMSO, DSS) δ 5.75 (2H, s), 7.35 (5H, m), 7.40 (1H, s); MS: *m/e* 246 (parent), 201, 169, 91 (base); IR: cm^{-1} 2600, 1685, 760, 710, 690.

<u>3,5-Dicarbethoxypyrazole</u> **15**.

To 100 mL of dry THF was added 18.5 g of ethyl propiolate followed by 20 mL of ethyl diazoacetate (10% CH_2Cl_2 solution). The stirred solution was brought to a reflux slowly. After 3 days, 100 mL of a saturated NH_4Cl solution was added at 25°C and stirred for 1/2 h. This solution was extracted with ether. The ether was evaporated and the resulting yellow oil was crystallized from EtOH and water. The water was removed from the product by azetropic distillation from benzene. When the resulting oil was cooled, 35.9 g (90% yield) of product was obtained: m.p. 45-47°C; ^{1}H NMR: (acetone d_6) δ 1.39 (6H, t), 4.40 (4H, q), 7.28 (1H, s); MS: *m/e* 212 (parent), 167, 67 (base); IR: cm^{-1} 3360, 1735, 1260, 1235.

1-Benzyl-3,5-dicarboxypyrazole **16**.

To a 500 mL three-necked, round-bottom flask was added 6.8 g of a 50% mineral oil dispersion of NaH. This was washed several times with pentane. The pentane was decanted and 100 mL of THF was added. After the mixture was cooled to 0°C, 29 g of 3,5-dicarbethoxypyrazole in 25 mL THF was added dropwise over 5 h. Benzyl bromide (26 mL) was added and this mixture was refluxed for 48 h. Hydrolysis was affected by adding a NaOH solution (20 g in 100 mL water) and EtOH (100 mL) then refluxing for 24 h with stirring. The solvents were evaporated and the resulting solid was acidified with an HCl solution. Filtration, then recrystallization at -10°C from EtOH/water, yielded 21.5 g (64% yield) of a white solid: m.p. 233-235°C; ^{1}H NMR: (DMSO d_6, DSS) δ 5.83 (2H, s), 7.25 (1H, s), 7.28 (5H, m), 13.40 (2H, bs); MS: *m/e* 246 (parent), 201, 91 (base); IR: cm^{-1} 2590, 1685, 1450, 1275.

1-Benzylpyrazole-3,5-diacid chloride **17**.

To 2.5 g of 1-benzyl-3,5-dicarboxypyrazole was added 5 mL of $SOCl_2$. The mixture was refluxed for 48 h. Dry toluene (100 mL) was added. This solution was concentrated to afford an oil which was taken up in 80 mL of dry pentane.

Crystallization at -10°C from pentane yielded 2.4 g (85% yield) of white crystals: m.p. 42-43°C (lit.[72] 42-43°C); ^1H NMR: δ 5.75 (2H, s), 7.33 (5H, m), 7.74 (1H, s); MS: *m/e* 284, 282 (parent, doublet isotope cluster), 91 (base); IR: cm^{-1} 1762, 705.

<u>1-Benzyl-3,5-bis(1-pyrryloyl)pyrazole</u> **18** <u>and 1-Benzyl-3,5-bis(2-pyrryloyl)pyrazole</u> **19**.

To a stirred solution of 0.5N pyrrylmagnesium bromide (6 equiv., 4.68 g, prepared from 1 N ethereal ethylmagnesium bromide and excess pyrrole in THF) at -78°C was added a solution of 1-benzylpyrazole-3,5-diacid chloride in 20 mL of THF. After 2 h, the solution was allowed to warm to 0°C and then stirred for 1 h. A saturated NH_4Cl solution (30 mL) was added and the mixture was stirred for 1/2 h. This mixture was suction filtered and the filtrate was extracted with ether. The ethereal extracts were washed first with a 5% aqueous K_2CO_3 solution and then with water and brine. The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a solid that was purified by flash column chromatography using ether-hexane (7:3) as eluent. This reaction yielded 0.307 g (25% yield) of the bis-N-acylated white compound (m.p. 142-144°C) along with 0.028 g (< 2% yield) of the bis-C-acylated off-white compound: m.p. 206-208°C; <u>Bis-N-acyl compound</u>: ^1H NMR: (acetone d_6) δ 5.86 (2H, s), 6.39 (4H, m), 7.40 (10H, m);

MS: *m/e* 344 (parent), 278, 211, 91 (base). IR: no NH peaks; Bis-C-acyl compound: ^{1} NMR: (acetone d_6) δ 5.89 (2H, s), 6.32 (2H, m), 7.40 (10H, m), 11.25 (2H, bs); MS: *m/e* 344 (parent), 250, 156, 91 (base); IR: cm^{-1} 3280, 1590.

1-Benzyl-3,5-bis(phenylthiol)pyrazolate **20**.

To 1-benzyl-3,5-dicarboxypyrazole (1.28 g) in 55 mL DMF at -10°C was added 1,1'-carbonyldiimidazole (1.94 g). This solution was stirred for 2 h then thiophenol (1.2 g) was added. The resulting mixture was stirred for 1 h at -10°C then 3 h at 25°C. Following this, the mixture was poured into water then extracted with ether. The ethereal extracts were washed with water and brine. This ether layer was dried over anhydrous Na_2SO_4 and then evaporated to 20 mL. Crystallization at -10°C yielded 1.07 g (48% yield) of a white solid that was used directly in the next step: m.p. 107-109°C; ^{1}H NMR: (acetone d_6) δ 5.79 (2H, s), 7.32 (5H, m), 7.53 (10H, m), 7.59 (1H, s); MS: *m/e* 430 (parent), 321, 91 (base).

1-Benzyl-3,5-bis(2-pyrryloyl)pyrazole **19** (2nd method).

To a stirred suspension of CuI (3 equiv., 0.710 g) in THF (1 mL) at 0°C was added a solution of 0.5 N pyrrylmagnesium bromide (6 equiv., 1.27 g, freshly prepared from 1 N ethereal ethylmagnesium bromide and excess pyrrole in THF). After 1/2 h, a solution of 1-benzyl-3,5-

bis(phenylthiol)pyrazolate (0.535 g) in THF was added to the suspension. The ice bath was removed and stirring continued for 5 h at 25°C. After cooling to 0°C, a saturated NH_4Cl solution (50 mL) was added to the suspension and stirred for 1/2 h. This mixture was suction filtered through celite and the filtrate extracted with ether. The combined ethereal extracts were washed first with a 5% aqueous K_2CO_3 solution then with water and brine. The ether layer was dried over anhydrous Na_2SO_4 and concentrated to afford a crude product. Purification by flash column chromatography using ether-hexane (7:3) as eluent yielded 0.039 g (9.2% yield) of the product: m.p. 206-208°C; ^1H NMR: (acetone d_6) δ 5.89 (2H, s), 6.32 (2H, m), 7.40 (10H, m), 11.25 (2H, bs); MS: m/e 344 (parent), 250, 156, 91 (base); IR: cm^{-1} 3280, 1590.

1-Benzyl-3,5-bis(S-2-pyridylthiol)pyrazolate 21.

To a mixture of 1-benzyl-3,5-dicarboxypyrazole (6.5 g), triphenylphosphine (13.86 g) and 2,2'-dipyridyldisulfide (11.64 g) was added dry acetonitrile (125 mL) under the exclusion of argon. This mixture was stirred for 4 h at 25°C. The yellow precipitate was suction filtered then rinsed with acetonitrile to yield an initial 6.8 g of product. The filtrate was concentrated to afford a yellow oil. Purification of this crude product by flash column chromatography using CH_2Cl_2-ether (9:1) as eluent yielded an additional 3 g of the dithiolester (86% yield total): m.p. 141-143°C; ^{1}H NMR: (DMSO d_6, DSS) δ 5.80 (2H, s), 7.30 (5H, m), 7.59 (1H, s), 7.5-8.7 (8H, m); MS: *m/e* 432 (parent), 322, 91 (base); IR: cm^{-1} 1670, 1120, 880.

1-Benzyl-3,5-bis(2-pyrryloyl)pyrazole **19** (3rd method).

To a stirred solution of 0.5 N pyrrylmagnesium bromide (6 equiv., 1.75 g, freshly prepared from 1 N ethereal ethylmagnesium bromide and excess pyrrole in THF) at 0°C was added a solution of 1-benzyl-3,5-bis(S-2-pyridylthiol)-pyrazolate (0.739 g) in 25 mL THF. After 3 h, a saturated NH_4Cl solution (50 mL) was added and stirred for 1/2 h. The mixture was suction filtered and the filtrate was extracted with ether. These combined extracts were washed first with a 5% aqueous K_2CO_3 solution then with water and brine. The ether layer was dried over anhydrous Na_2SO_4 and concentrated to afford a crude product. Purification by flash column chromatography using ether-hexane (7:3) as eluent yielded 0.324 g (55% yield) of the bis-C-acylated product (m.p. 206-208°C) along with a small amount 0.035 g (< 2% yield) of the bis-N-acylated by-product: (m.p. 142-144°C); Bis-N-acyl compound: ^{1}H NMR: (acetone d_6) δ 5.89 (2H, s), 6.32 (2H, m), 7.40 (10H, m), 11.25 (2H, bs); MS: *m/e* 344 (parent), 250, 156, 91 (base); IR: cm^{-1} 3280, 1600, 1590. *Anal.* Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.65; N, 16.28. Found: C, 69.46; H, 4.83; N, 15.94.

1-Benzyl-3,5-bis(2-pyrrylmethyl)pyrazole 2a.

A refluxing solution of 0.25 g of 1-benzyl-3,5-bis(2-pyrryloyl)pyrazole in 10 mL of absolute EtOH containing 1/2 mL morpholine was treated with 6 x 0.17 g portions of $NaBH_4$ added at 1 h intervals. Water (1/2 mL) was added 1/2 h after the addition of each portion of $NaBH_4$. During the next 2 days (at approximately 24 h intervals), there were two more $NaBH_4$ (0.17 g)/water (1/2 mL) treatments. After 72 h, the reaction was complete as indicated by tlc. The mixture was cooled to 0°C. A saturated NH_4Cl solution (50 mL) was added and stirred for 1/2 h. This mixture was suction filtered and the filtrate was extracted with ether. The combined extracts were washed with water and brine. The ether layer was dried over K_2CO_3 and concentrated. The crude air and light-sensitive solid was purified immediately by flash column chromatography using ether-hexane (7:3) as eluent. There was obtained 0.198 g (87% yield) of a white solid: m.p. 43-45°C; ^1H NMR: (acetone d_6) δ 3.83 (2H, s), 3.87 (2H, s), 5.23 (2H, s), 5.83 (1H, s), 5.92 (2H, m), 6.62 (2H, m), 7.20 (7H, m), 9.75 (2H, bs); MS: *m/e* 316 (parent and base), 236, 225, 156, 91; IR: cm^{-1} 3390.

1-Benzyl-3,5-bis(5-formyl-2-pyrrylmethyl)pyrazole 3a.

To a stirred solution of 0.317 g of 1-benzyl-3,5-bis(2-pyrrylmethyl)pyrazole in 1.5 mL DMF was added dropwise 1 mL of benzoyl chloride over 10 min at 0°C. After 2 h, the solution was allowed to warm up to 25°C and stirred overnight. To complete precipitation of the diimine salt, 2.5 mL of toluene was added slowly. The mixture was suction filtered. The red diimine salt was collected and washed with toluene. Immediately afterwards, the salt was dissolved in a solution of 0.24 g of Na_2CO_3 in 5 mL of aqueous ethanol (70%). The mixture was refluxed for 15 min then extracted with CH_2Cl_2. These combined extracts were washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford a crude product. Purification by flash column chromatography using CH_2Cl_2-MeOH (98:2) as eluent yielded 0.265 g of an orange solid (71% yield): m.p. 193-194°C; ^1H NMR: (acetone d_6) δ 3.98 (2H, s), 4.06 (2H, s), 5.32 (2H, s), 5.96 (1H, s), 6.02 (1H, d), 6.09 (1H, d), 6.87 (1H, d), 6.88 (1H, d), 7.22 (5H, m), 9.40 (2H, s), 10.9 (2H, bs); MS: *m/e* 372 (parent), 156, 91 (base); IR: cm^{-1} 3230, 1640.

3,4-Dimethylpyrrole.

The procedure of Ichikawa and Imamura was followed.[53] To a 2 L three-necked, round-bottom flask, equipped with a mechanical stirrer, a reflux condensor with attached calcium chloride drying tube and two 250 mL equal-pressure dropping funnels, was added 54.2 g ethyl carbamate and 400 mL dry benzene. This solution was cooled to 0°C. With efficient stirring, 100 mL of pyridine and 72.5 g of $SOCl_2$, each in separate dropping funnels, were added dropwise. After 2 h, 50 g of 2,3-dimethylbutadiene was added in one portion. The resulting mixture was refluxed for 2 h then allowed to cool to 25°C and stand overnight. The pyridine hydrochloride was suction filtered and washed with benzene. The filtrate was collected and concentrated at atmospheric pressure to give the crude thiazine oxide. This residue was added slowly to a KOH solution (270 g KOH dissolved in 600 mL MeOH) then refluxed for 2 h. The MeOH was evaporated from the solution at atmospheric pressure. The resulting reaction mixture was steam distilled to give an oily substance. This was extracted with ether. The combined extracts were dried over K_2CO_3 and concentrated. Vacuum distillation of the residue yielded 20.7 g of the air- and light-sensitive 3,4-dimethylpyrrole (36% yield based on ethyl carbamate): b.p. 32-35°C (.3 mmHg); ^1H NMR: δ 2.04 (6H, s), 6.45 (2H, d).

1-Benzyl-3,5-bis(3,4-dimethyl-2-pyrryloyl)pyrazole **19b**.

To a stirred solution of 0.5 N 3,4-dimethylpyrrylmagnesium bromide (2.5 equiv., 3.16 g, the 0.5 N solution was prepared from 1 N ethereal ethylmagnesium bromide and excess 3,4-dimethylpyrrole in THF and was refluxed for 4 h before it was used) was added a solution of 1-benzyl-3,5-bis(S-2-pyridylthiol)pyrazolate (2.76 g) in THF 32 mL). This solution was refluxed for 72 h. After cooling to 0°C, a saturated NH_4Cl solution (50 mL) was added and stirred for 1/2 h. The mixture was suction filtered and the filtrate was extracted with ether. The combined extracts were washed first with a 5% aqueous K_2CO_3 solution then with H_2O and brine. The ether layer was dried over anhydrous Na_2SO_4 and concentrated to afford a crude product. Purification by flash column chromatography using CH_2Cl_2-ether (98:2) as eluent yielded 1.2 g of white solid (47% yield): m.p. 156-157°C; ^1H NMR: (acetone d_6) δ 2.19 (3H, s), 2.38 (3H, s), 5.78 (2H, s), 6.88 (1H, d), 6.96 (1H, d), 7.17 (1H, s), 7.31 (5H, m), 10.55 (1H, bs), 11.45 (1H, bs); MS: *m/e* 400 (parent), 309, 278, 214, 91 (base); IR: cm^{-1} 3375, 3355, 1630, 1600.

1-Benzyl-3,5-bis(3,4-dimethyl-2-pyrrylmethyl)pyrazole **2b**.

A refluxing solution of 0.724 g of 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrryloyl)pyrazole in 25 mL of absolute EtOH containing 1 mL morpholine was treated with 1.5 g $NaBH_4$ and 4 x 1 mL water portions were added periodically. The reaction was complete one week after starting as indicated by tlc. The mixture was cooled to 0°C and a saturated NH_4Cl solution (50 mL) was added and then stirred for 15 min. The resulting solution was suction filtered and the filtrate was extracted with ether. These ether extracts were washed with water and brine. The ehter layer was dried over K_2CO_3 and concentrated. This extremely air- and light-sensitive solid was purified immediately by flash column chromatography using petroleum ether-THF (7:3) as eluent. There was obtained 0.576 g of a white solid (86% yield): m.p. 180-182°C (dec.); ^{1}H NMR: (acetone d_6) δ 1.77 (3H, s), 1.89 (3H, s), 1.90 (3H, s), 1.91 (3H, s), 3.72 (2H, s), 3.76 (2H, s), 5.21 (2H, s), 5.68 (1H, s), 6.32 (1H, d), 4.35 (1H, d), 7.20 (5H, m), 9.13 (2H, bs); MS: *m/e* 372 (parent), 186, 149, 108, 91 (base); IR: cm^{-1} 3395.

1-Benzyl-3,5-bis(3,4-dimethyl-5-formyl-2-pyrrylmethyl)-pyrazole **3b**.

To a stirred solution of 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrrylmethyl)pyrazole (prepared by the reduction of 2 g of 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrroloyl)pyrazole) in 15 mL DMF was added 5 mL benzoyl chloride dropwise over 1 h at 0°C. After 1 h, the solution was allowed to warm up to 25°C and stirred overnight. Ether (50 mL) was added to precipitate the diimine salt. The mixture was suction filtered. The diimine salt was collected and dissolved immediately in 30 mL of absolute EtOH. To this was added a solution of 1.5 g Na_2CO_3 in 10 mL of water. The resulting solution was refluxed for 1/2 h then stirred overnight at 25°C. Water (50 mL) was added and the solution was extracted with CH_2Cl_2. The combined extracts were washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford a crude product. Purification by flash column chromatography using CH_2Cl_2-

MeOH (98:2) as eluent gave a solid. Recrystallization from THF-ether yielded 1.22 g of yellow crystals (66% yield): m.p. 182-183°C; ^{1}H NMR: (acetone d_6) δ 1.76 (3H, s), 1.82 (3H, s), 2.18 (3H, s), 2.21 (3H, s), 3.88 (2H, s), 3.96 (2H, s), 5.32 (2H, s), 5.74 (1H, s), 7.20 (5H, m), 9.52 (2H, s), 10.4 (2H, bs); MS: *m/e* 428 (parent and base), 400, 309, 292, 214, 184, 91; IR: cm^{-1} 3245, 3240, 1650, 1630. *Anal.* Calcd. for $C_{26}H_{28}N_4O_2$: C, 72.90; H, 6.54; N, 13.08. Found: C, 72.41; H, 6.47; N, 12.94.

Dihydrobromide salt of octaazatetrahydro[1,5,1,5]platyrin **22b**.

To a stirred refluxing solution of 550 mL of deaerated MeOH was added 10 mL of HBr (48%). Into the solution was added from separate dropping funnels dropwise over 30 min freshly prepared solutions of 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrrylmethyl)pyrazole in 55 mL deaerated MeOH and 1-benzyl-3,5-bis(3,4-dimethyl-5-formyl-2-pyrrylmethyl)-pyrazole in 20 mL CH_2Cl_2 and 35 mL deaerated MeOH (precipitation of the orange-red condensation product occurred 5 min after addition began. The mixture went from yellow to orange to red within 20 min). After 1 1/2 h, the heat was removed and the mixture allowed to stand overnight at 25°C. Suction filtration of the mixture yielded 0.4105 g (69% yield) of an orange-red solid: m.p. 280-285°C (dec.); ^{1}H NMR: (CF_3CO_2H, DMSO d_6) δ 1.68-2.31 (24H, m), 4.09 (4H, s), 4.16 (2H, s), 4.20 (2H, s), 5.46 (2H, s), 5.48 (2H, s), 5.91 (1H, s), 6.01 (1H, s), 7.25 (10H, m), 7.42 (1H, s), 7.50 (1H, s), 12.46 (4H, d); ^1H NMR: ($CDCl_3$, CF_3CO_2H) δ 1.85-2.27 (24H, m), 4.25 (2H, s), 4.27 (2H, s), 4.37 (4H, s), 5.73 (2H, s), 5.98 (2H, s), 6.18 (2H, s), 6.29 (1H, s), 7.26-7.46 (12H, m), 11.34 (1H, s), 11.60 (1H, s), 11.75 (1H, s), 12.06 (1H, s); ^{13}C NMR ($CDCl_3/CF_3CO_2H$): δ 8.28, 8.47, 8.55, 10.4 (CH_3 carbons): 22.84, 23.01, 23.1 (meso CH_2 carbons): 53.85, 53.95 (benzyl CH_2 carbons): 108.96, 109.31 (pyrazole CH carbons): 122.69, 123.08 (methene CH carbons): 127.68, 129.70, 129.79, 129.93 (phenyl CH carbons): 125.54, 125.86, 126.16, 126.25, 128.27, 128.34, 128.84, 131.25, 131.56, 143.32, 144.52, 144.89, 145.02, 145.32, 146.07, 146.12, 147.22, 148.19, 148.50, 149.34 (aromatic C carbons); ^{13}C NMR ($CDCl_3$, CF_3CO_2H) CH recording only using DEPT program, δ 108.96, 109.31 (pyrazole CH carbons): 122.69, 123.08 (methene CH carbons): 127.68, 129.70, 129.79, 129.93 (phenyl CH carbons); MS: FAB *m/e* 765 (M^{+1} parent), 675, 583; IR: cm^{-1} 3140, 1615, 1270; UV-vis: (CH_2Cl_2) λ_{max} (ε_M) 469.5 (189,949), 371 (16,114); UV-vis: (CH_2Cl_2, pyridine) λ_{max} (ε_M) 439.0 (56,398), 313.5 (206,161). *Anal.* Calcd. for (monohydrate) $C_{50}H_{56}Br_2N_8$: C, 63.56; H, 5.93; N, 11.86. Found: C, 63.58; H, 5.92; N, 11.72.

APPENDIX

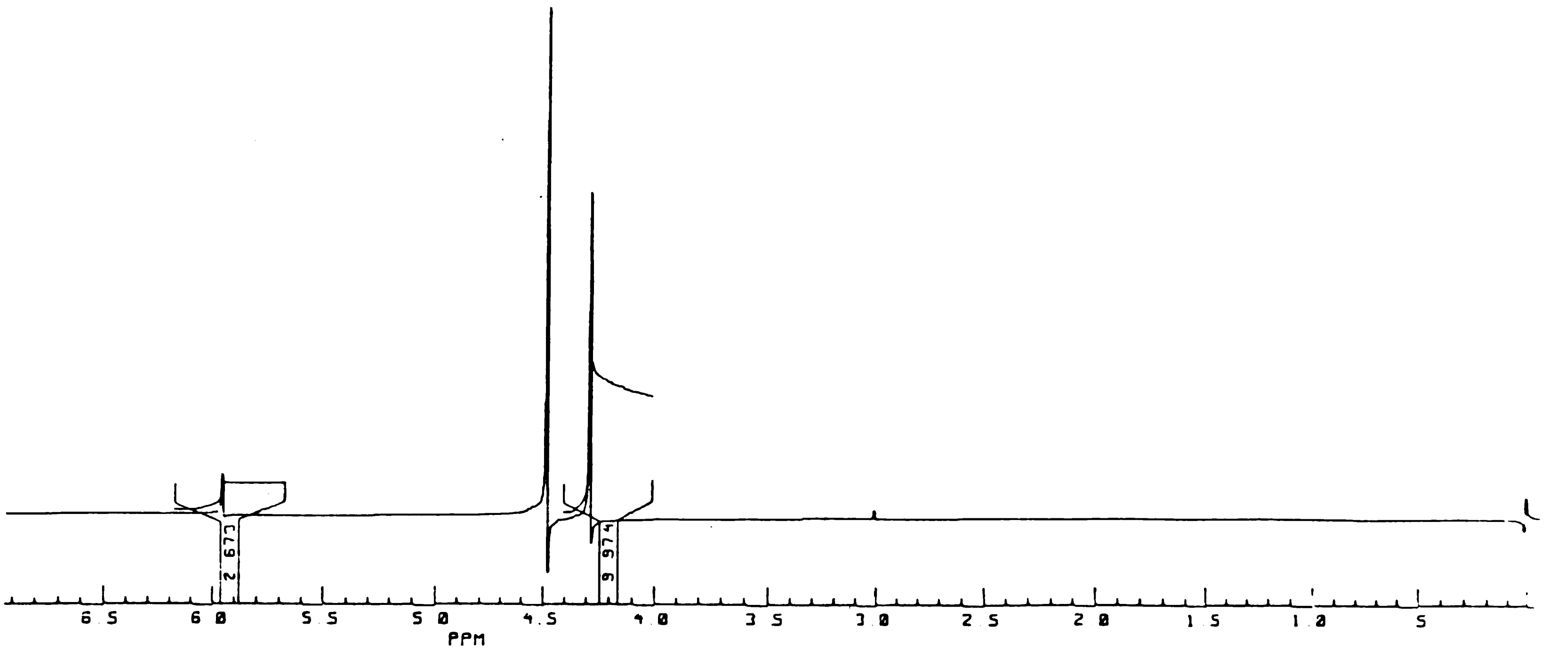


Figure A1. 250 MHz ^{1}H NMR spectrum of 3,5-bis(hydroxymethyl)pyrazole **5**.

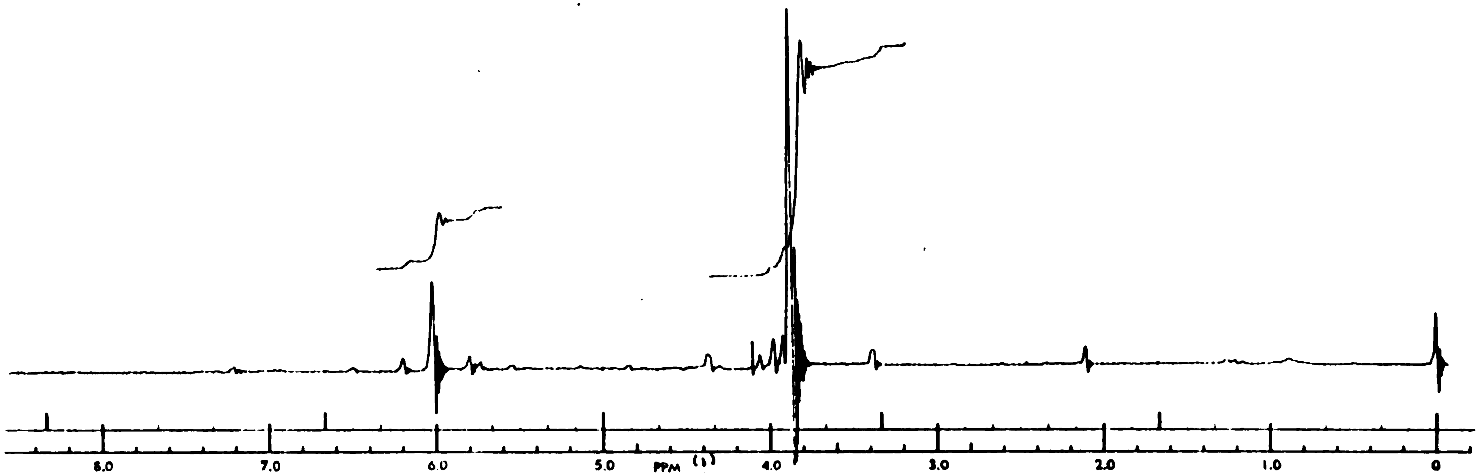


Figure A2. 60 MHz ^1H NMR spectrum of 1,5-dibromo-2,4-pentanedione **7**.

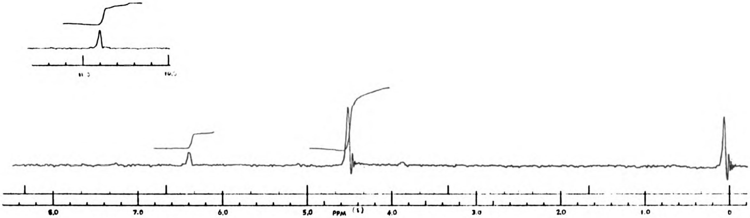


Figure A3. 60 MHz ^{1}H NMR spectrum of 3,5-bis(bromomethyl)pyrazole **8**.

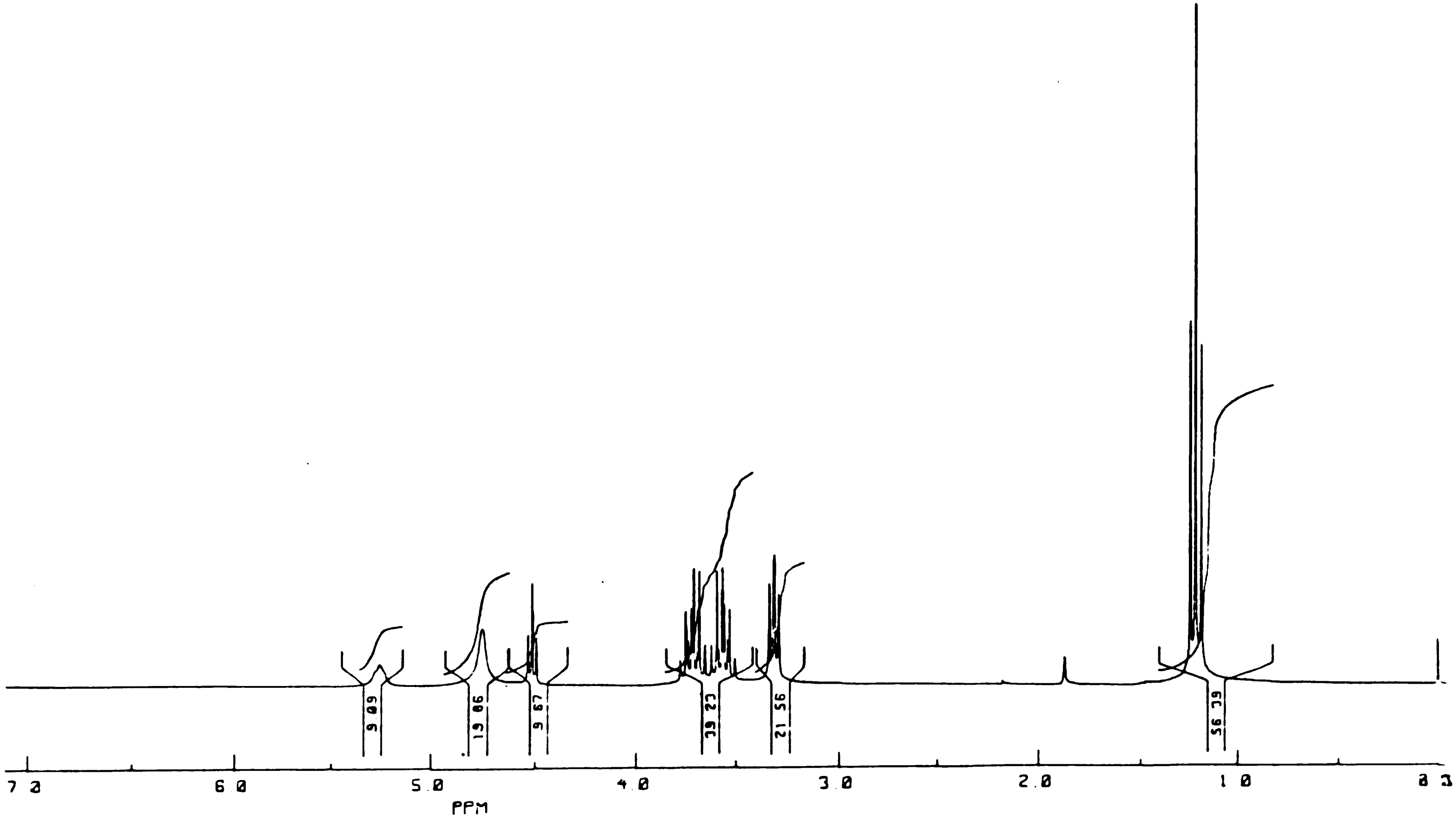


Figure A4. 250 MHz ^{1}H NMR spectrum of ureidoacetal **10a**.

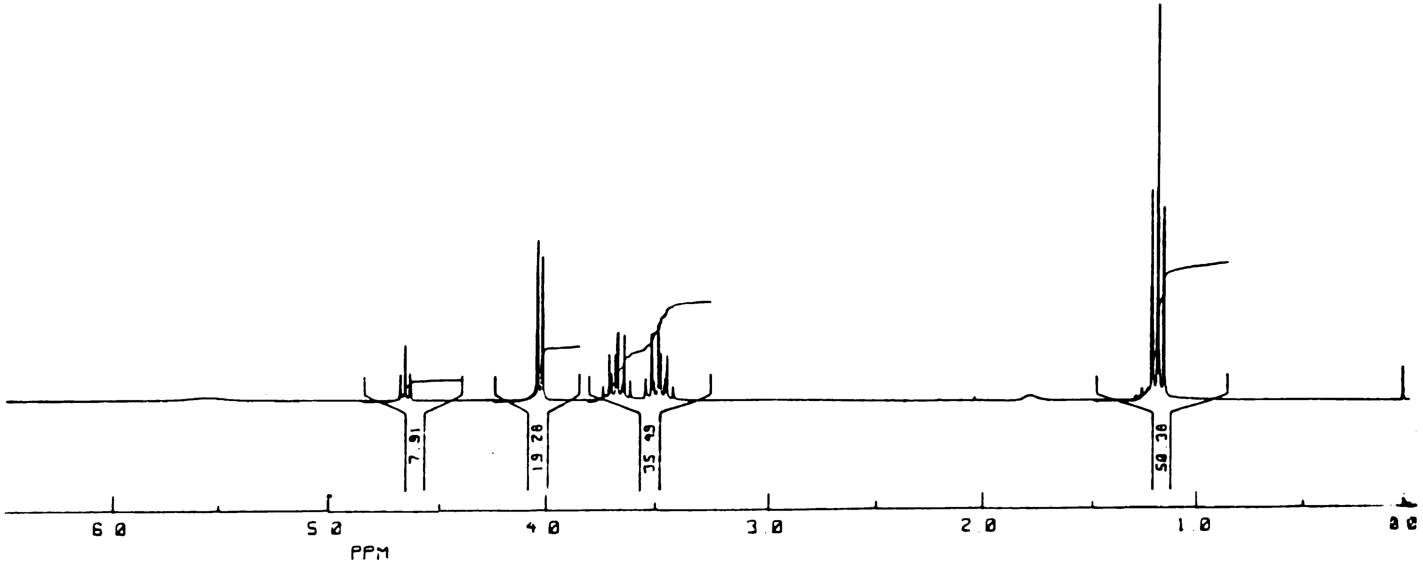


Figure A5. 250 MHz ^1H NMR spectrum of N-nitroso-N-[2,2-diethoxyethyl]urea **10b**.

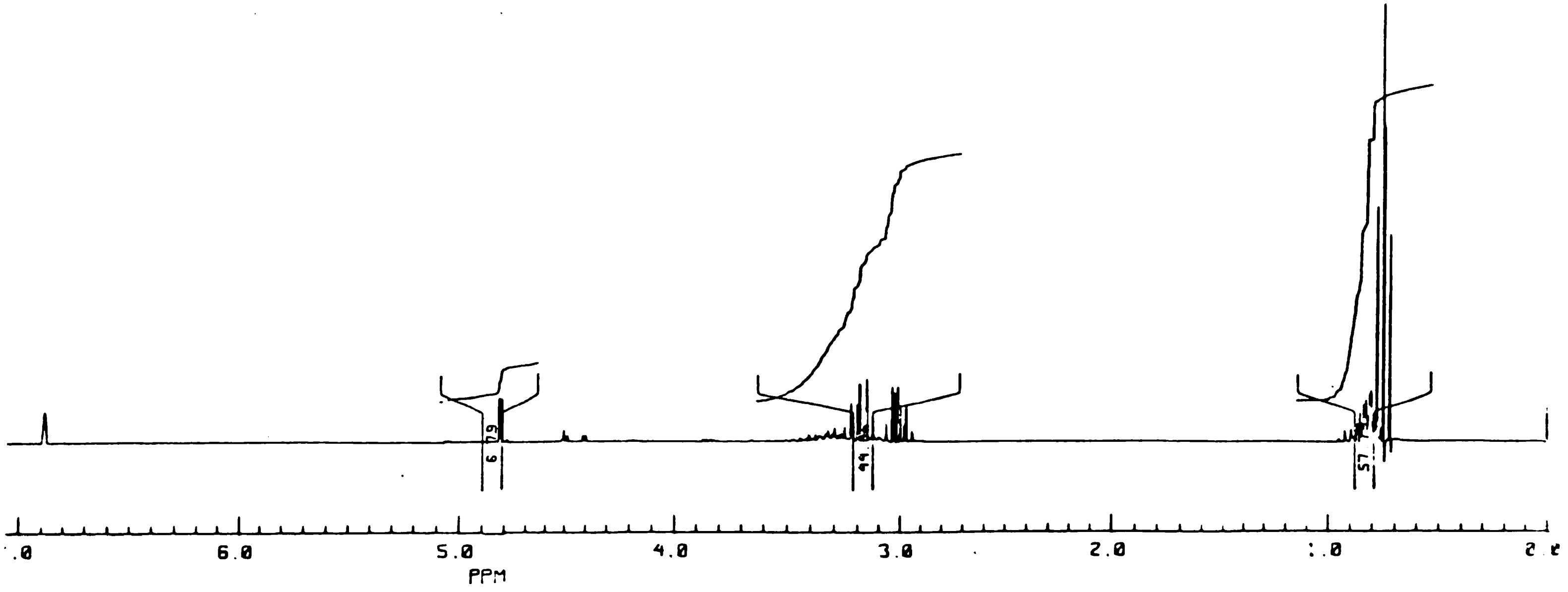


Figure A6. 250 MHz ^1H NMR spectrum of 2,2-diethoxy-1-diazoethane **10c**.

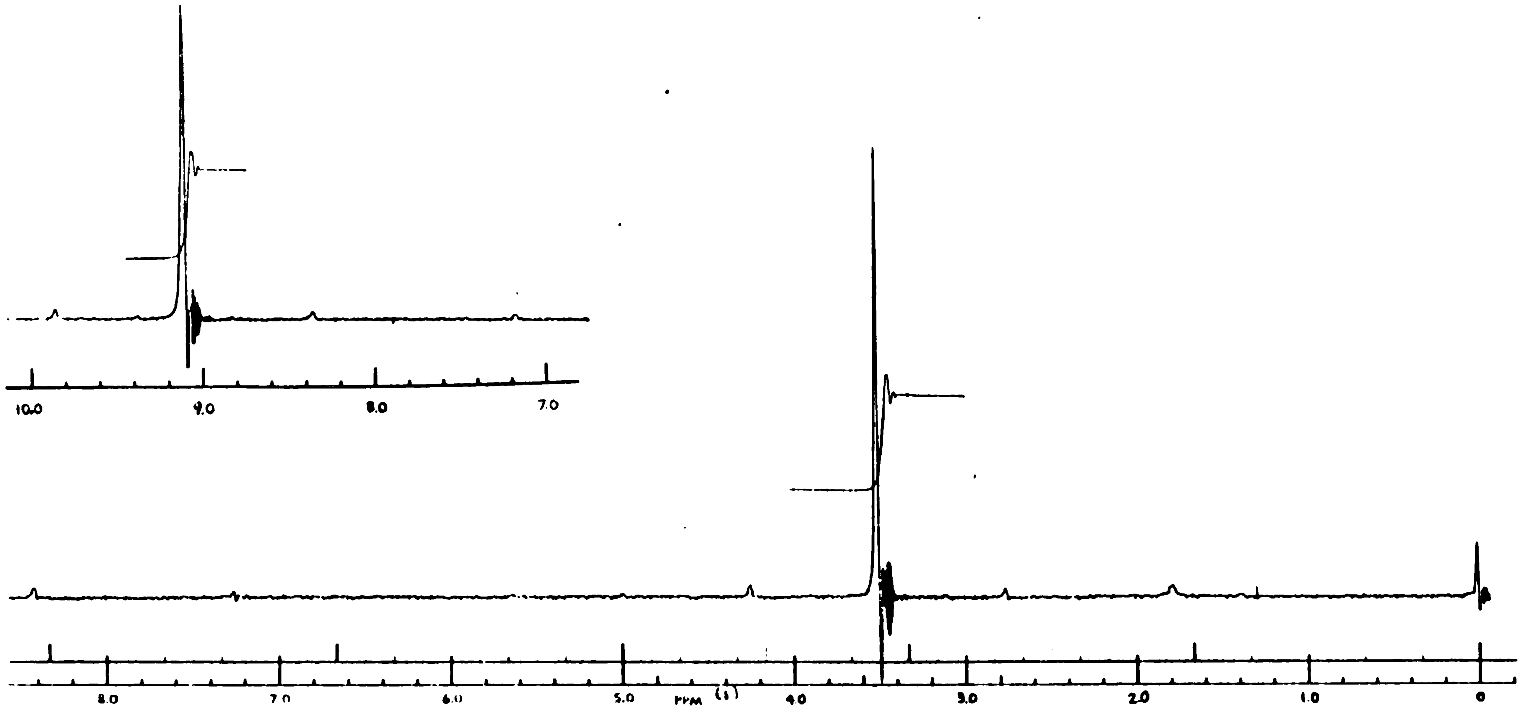


Figure A7. 60 MHz ^{1}H NMR spectrum of propargyl aldehyde 11.

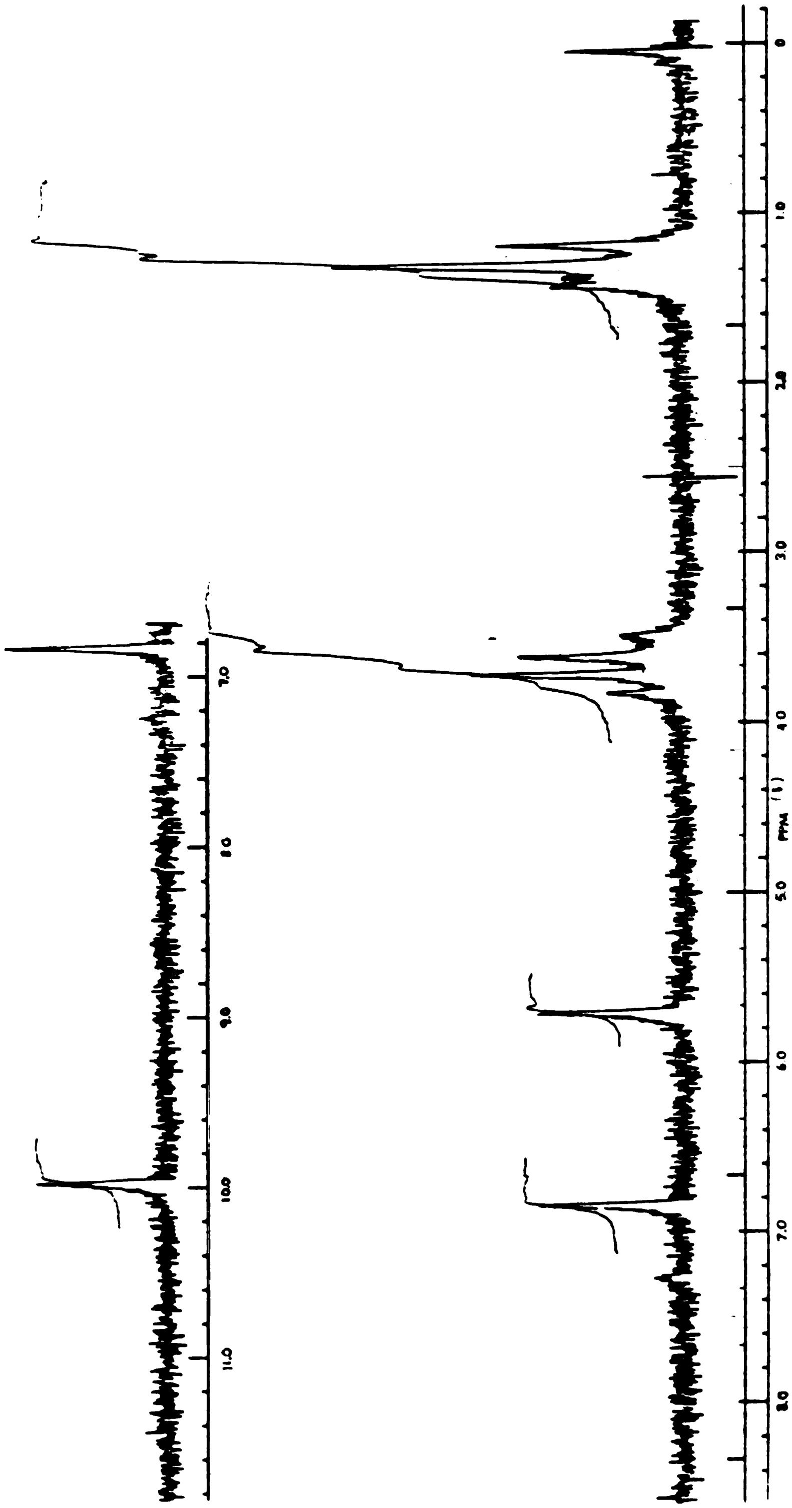


Figure A8. 60 MHz ^{1}H NMR spectrum of 3-diethoxymethyl-5-formylpyrazole 12a.

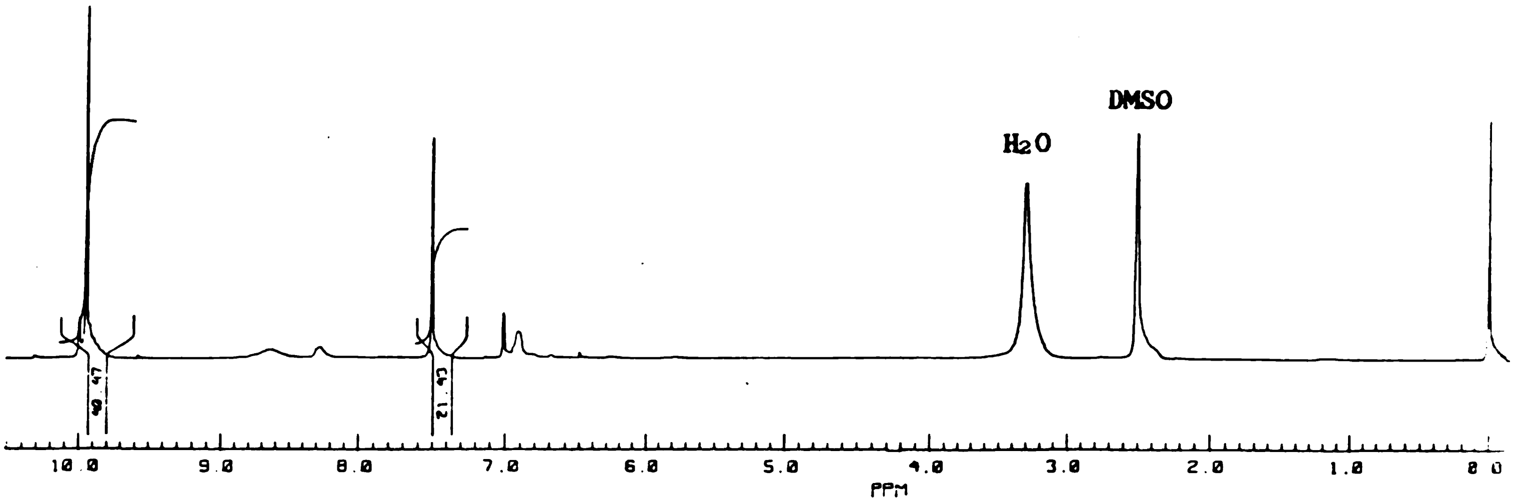


Figure A9. 250 MHz ^1H NMR spectrum of 3,5-diformylpyrazole **12b**.

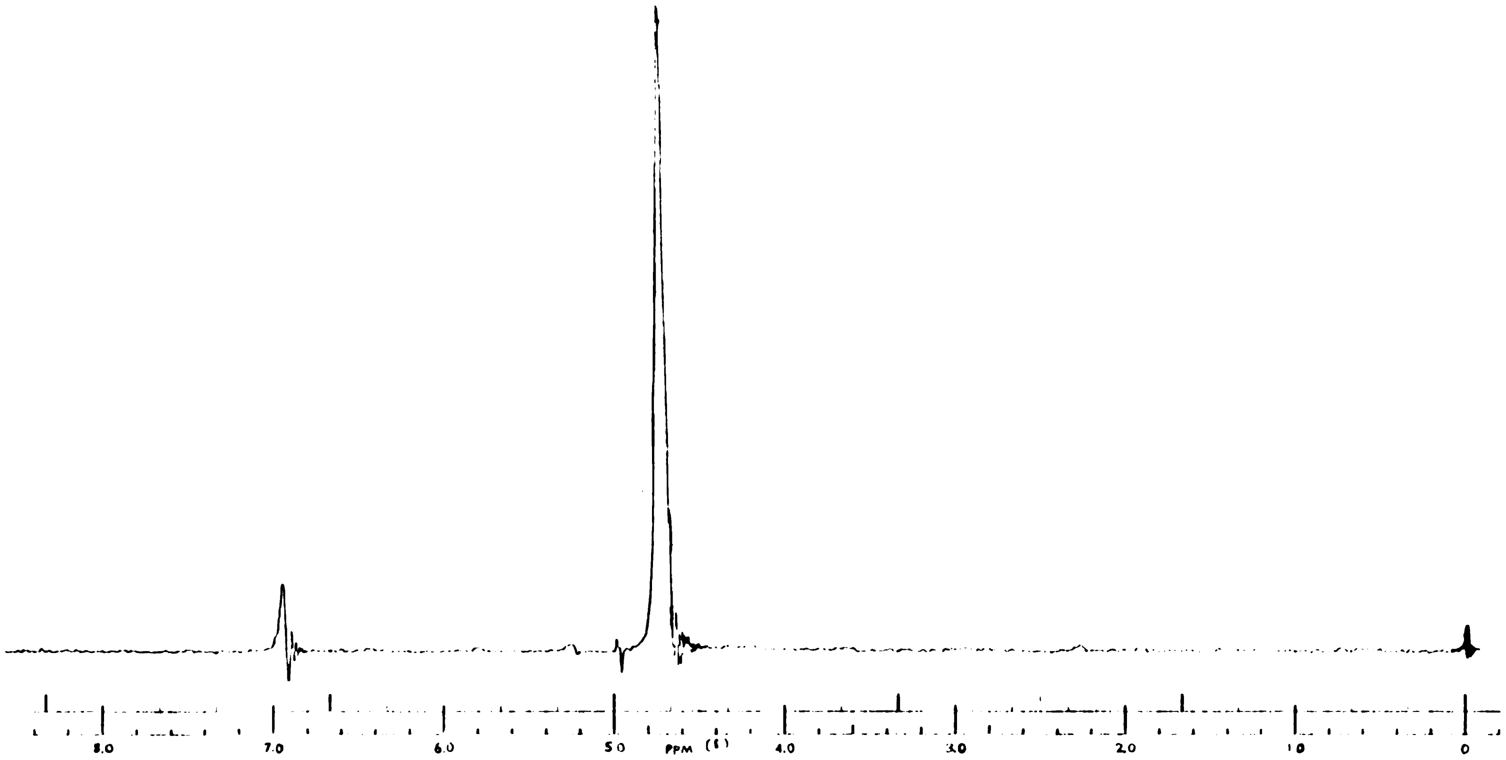


Figure A10. 60 MHz ^{1}H NMR spectrum of 3,5-dicarboxypyrazole.

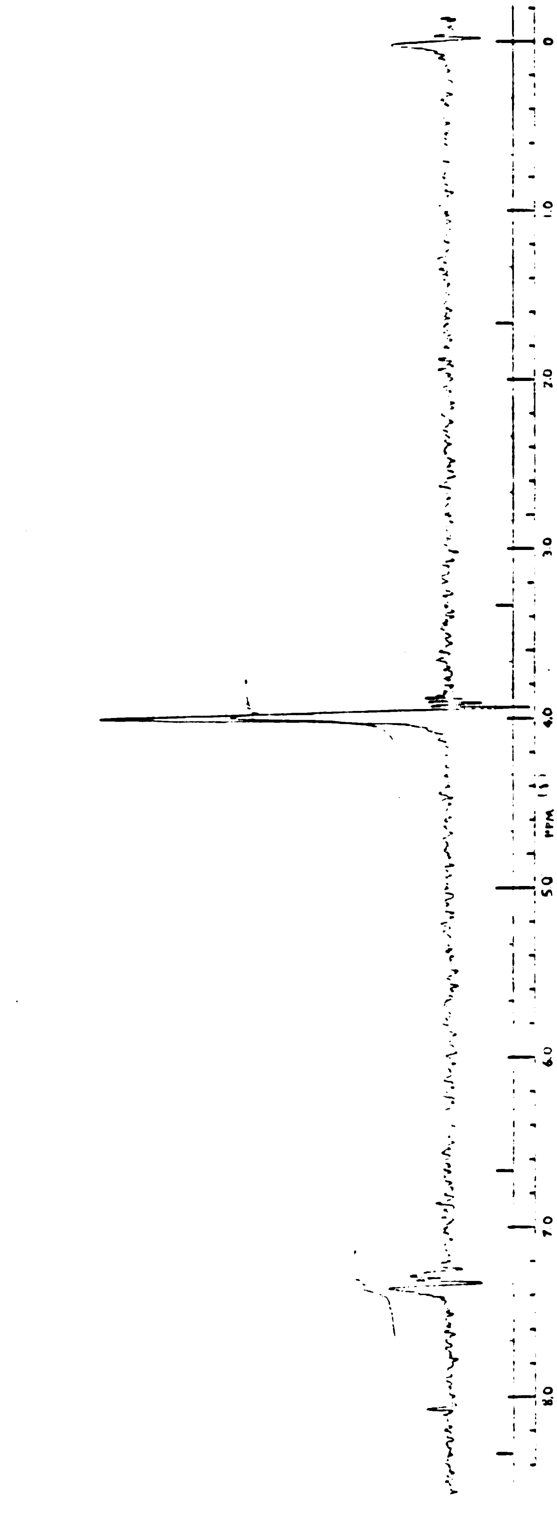


Figure A11. 60 MHz ^{1}H NMR spectrum of 3,5-dicarbomethoxypyrazole.

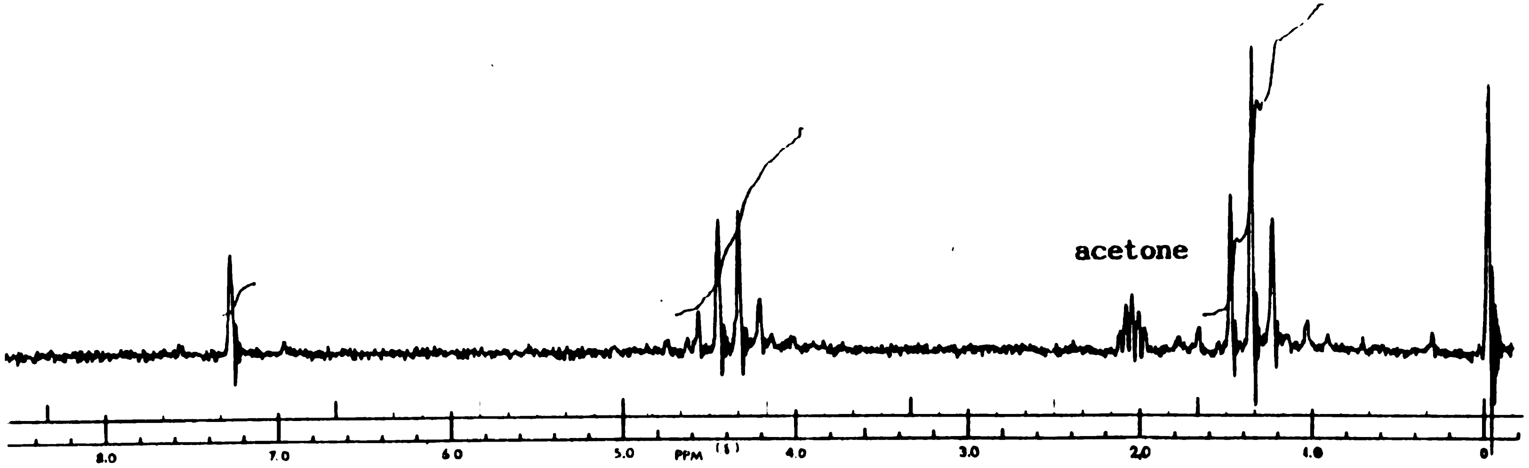


Figure A12. 60 MHz ^1H NMR spectrum of 3,5-dicarbethoxypyrazole **15**.

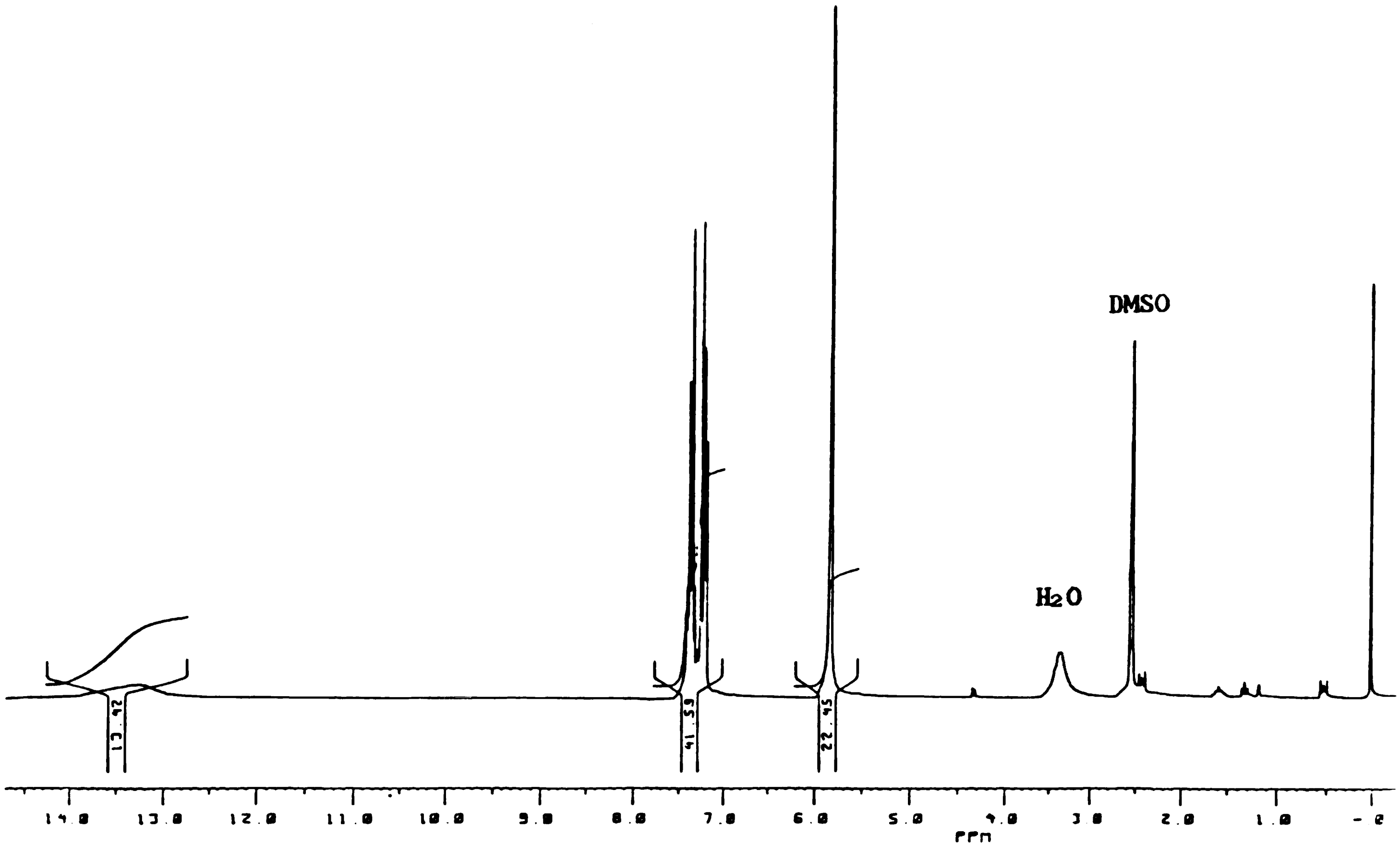


Figure A13. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-dicarboxypyrazole **16.**

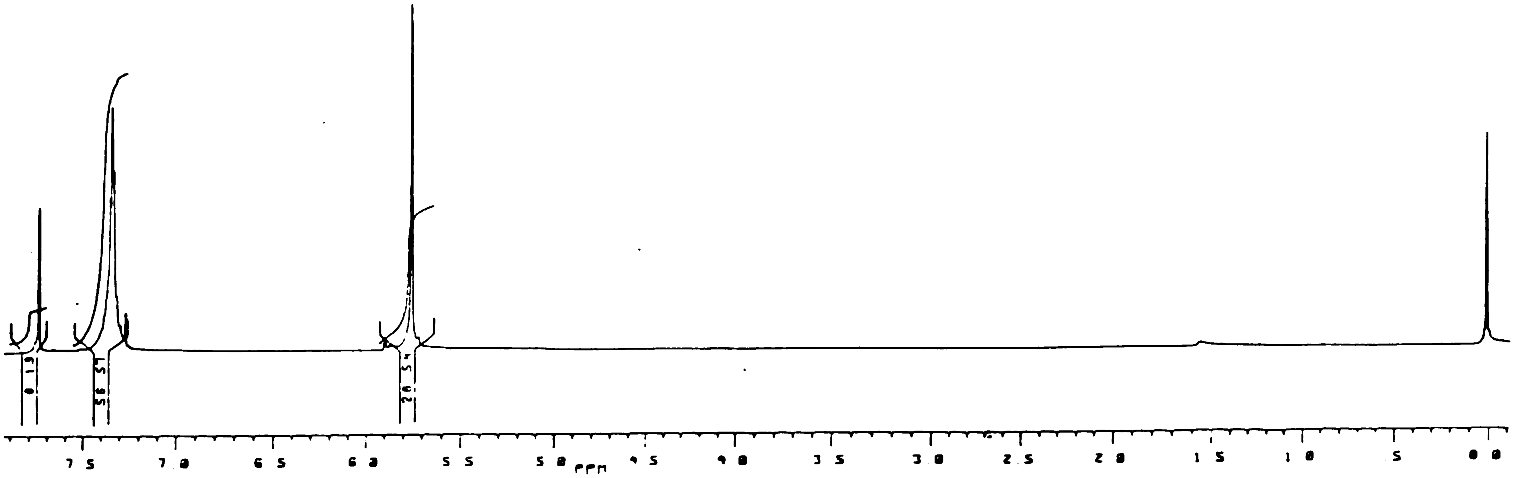


Figure A14. 250 MHz ^1H NMR spectrum of 1-benzylpyrazole-3,5-diacidchloride **17**.

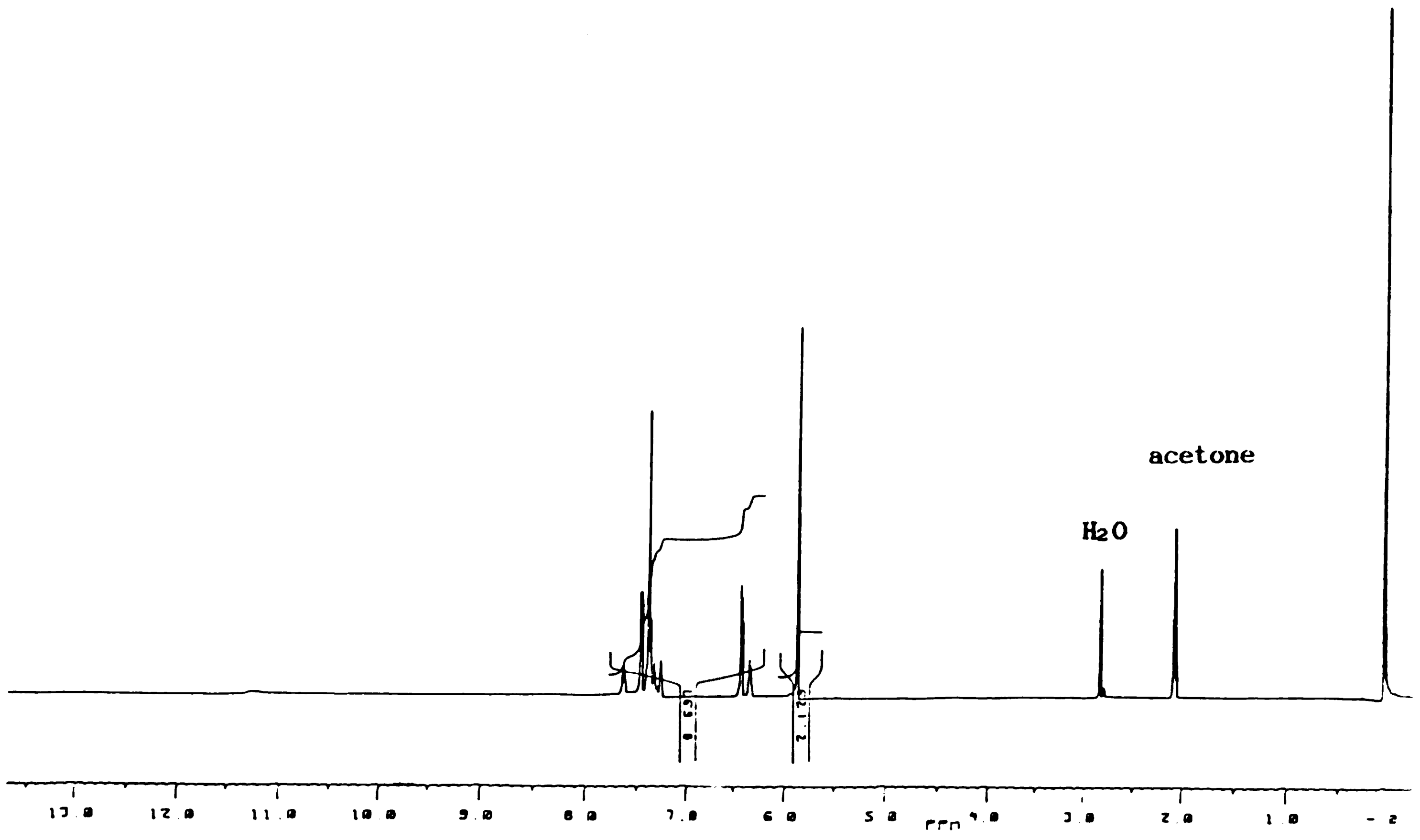


Figure A15. 250 MHz ^1H NMR spectrum of 1-benzyl-3,5-bis(1-pyrryloyl)pyrazole 18.

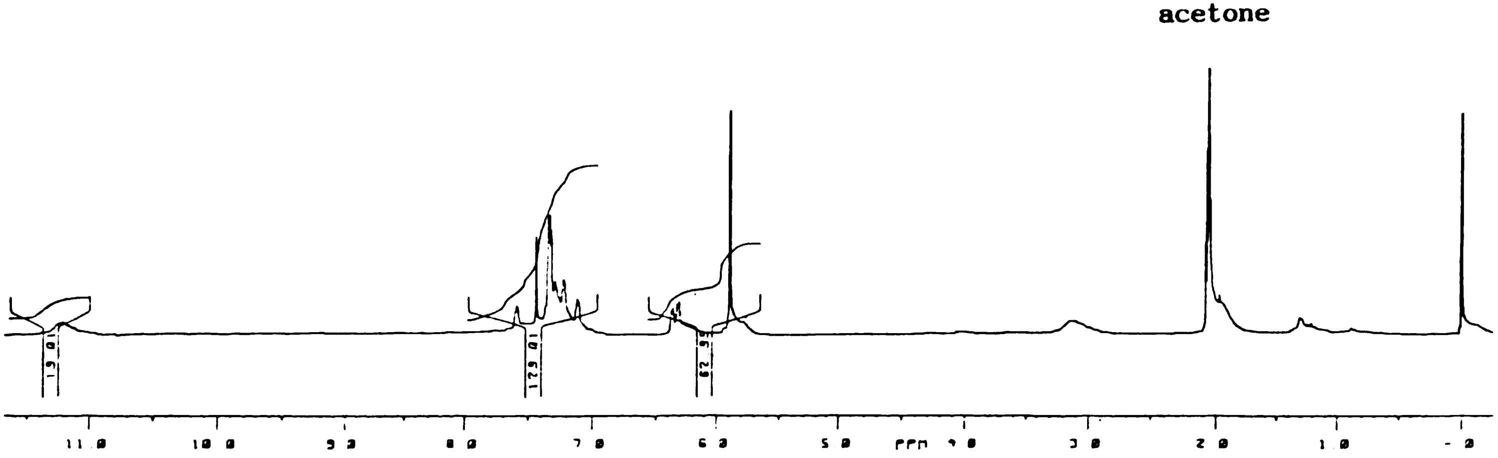


Figure A16. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-bis(2-pyrryloyl)pyrazole **19**.

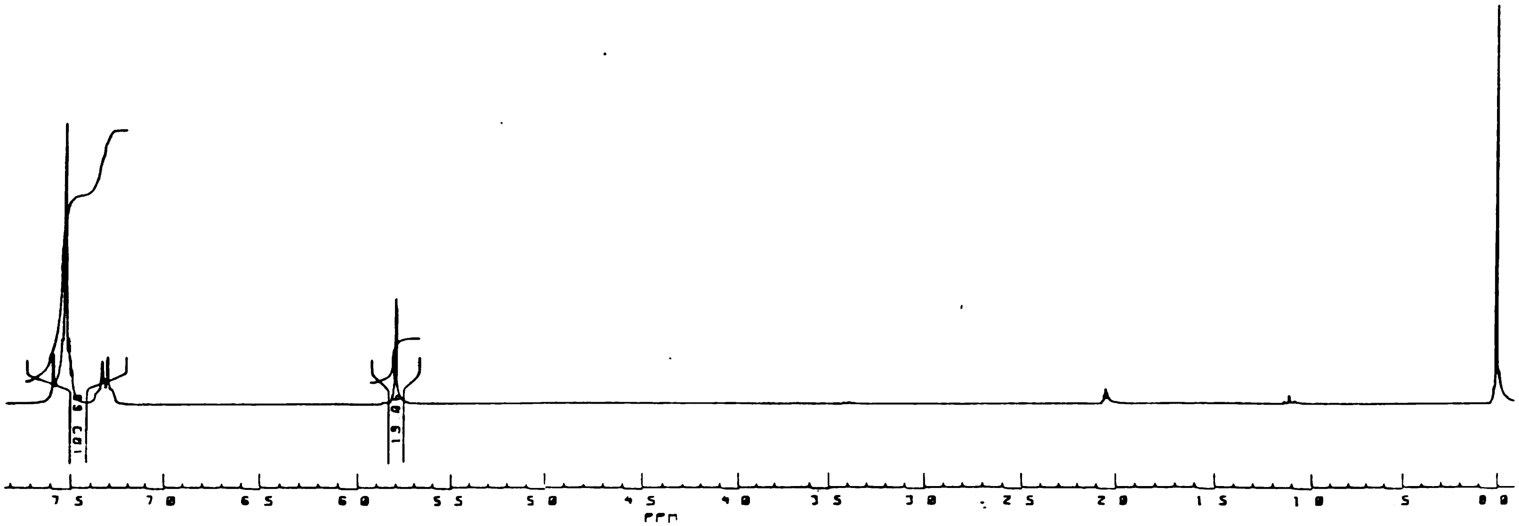


Figure A17. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-bis(phenylthiol)pyrazolate **20**.

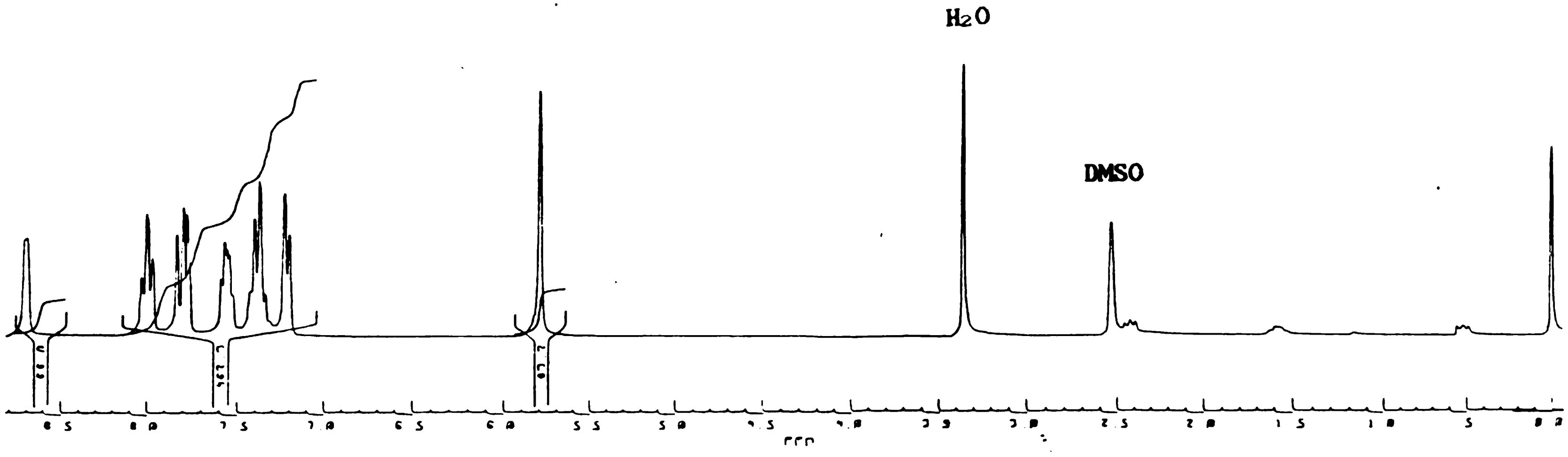


Figure A18. 250 MHz ^1H NMR spectrum of 1-benzyl-3,5-bis(S-2-pyridylthiol)pyrazolate **21**.

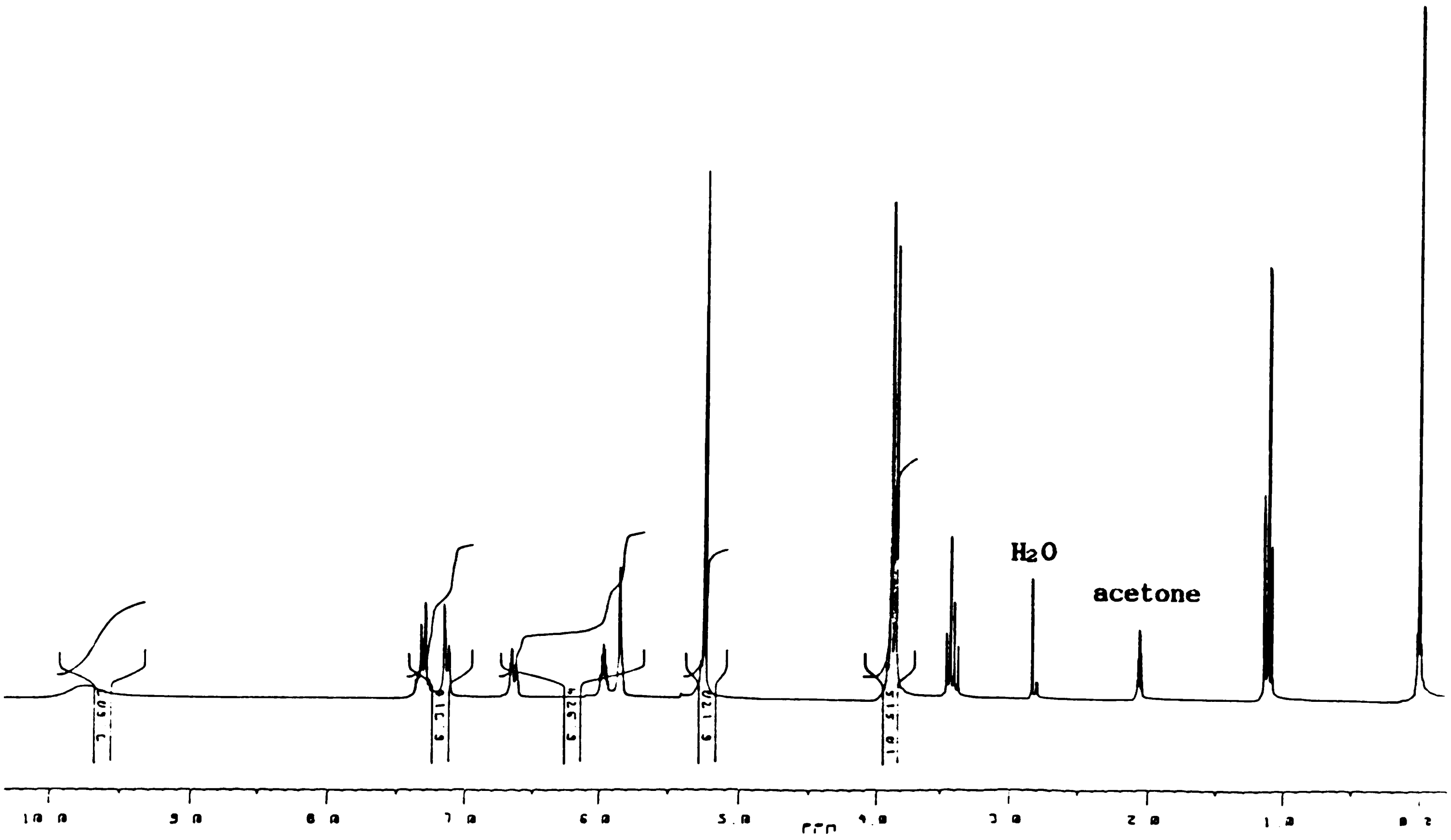


Figure A19. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-bis(2-pyrrylmethyl)pyrazole **2a**.

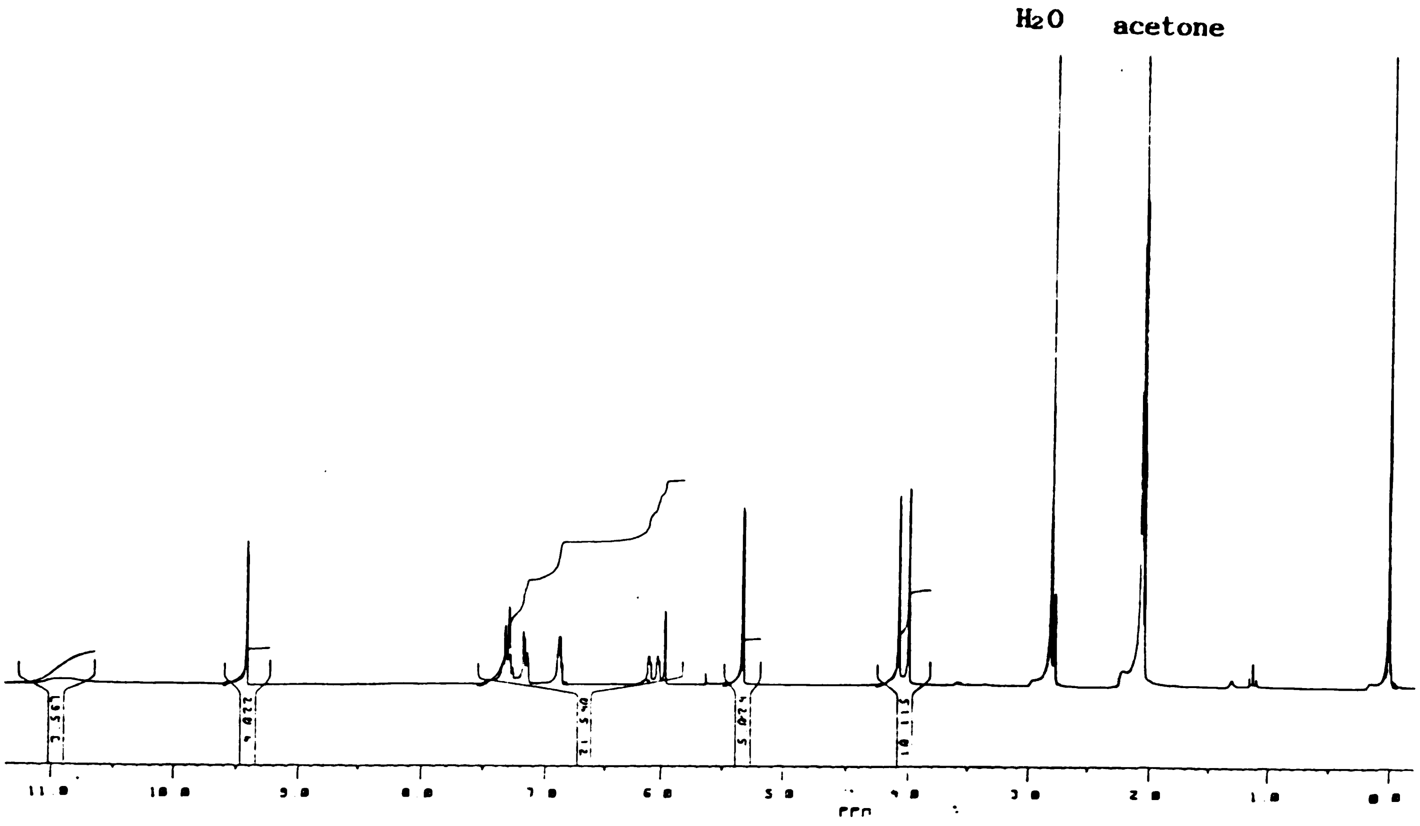


Figure A20. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-bis(5-formyl-2-pyrrylmethyl)pyrazole **3a**.

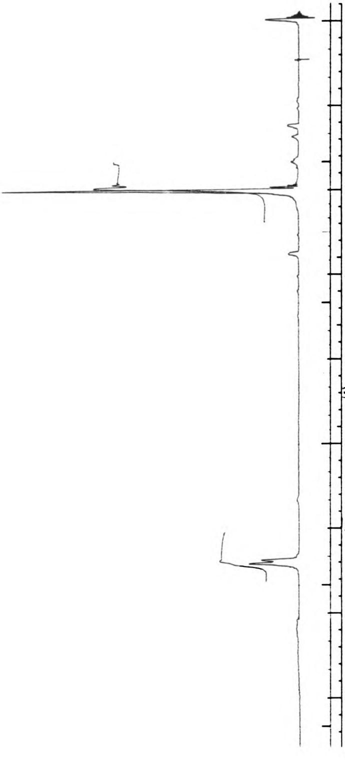


Figure A21. 60 MHz ^1H NMR spectrum of 3,4-dimethylpyrrole.

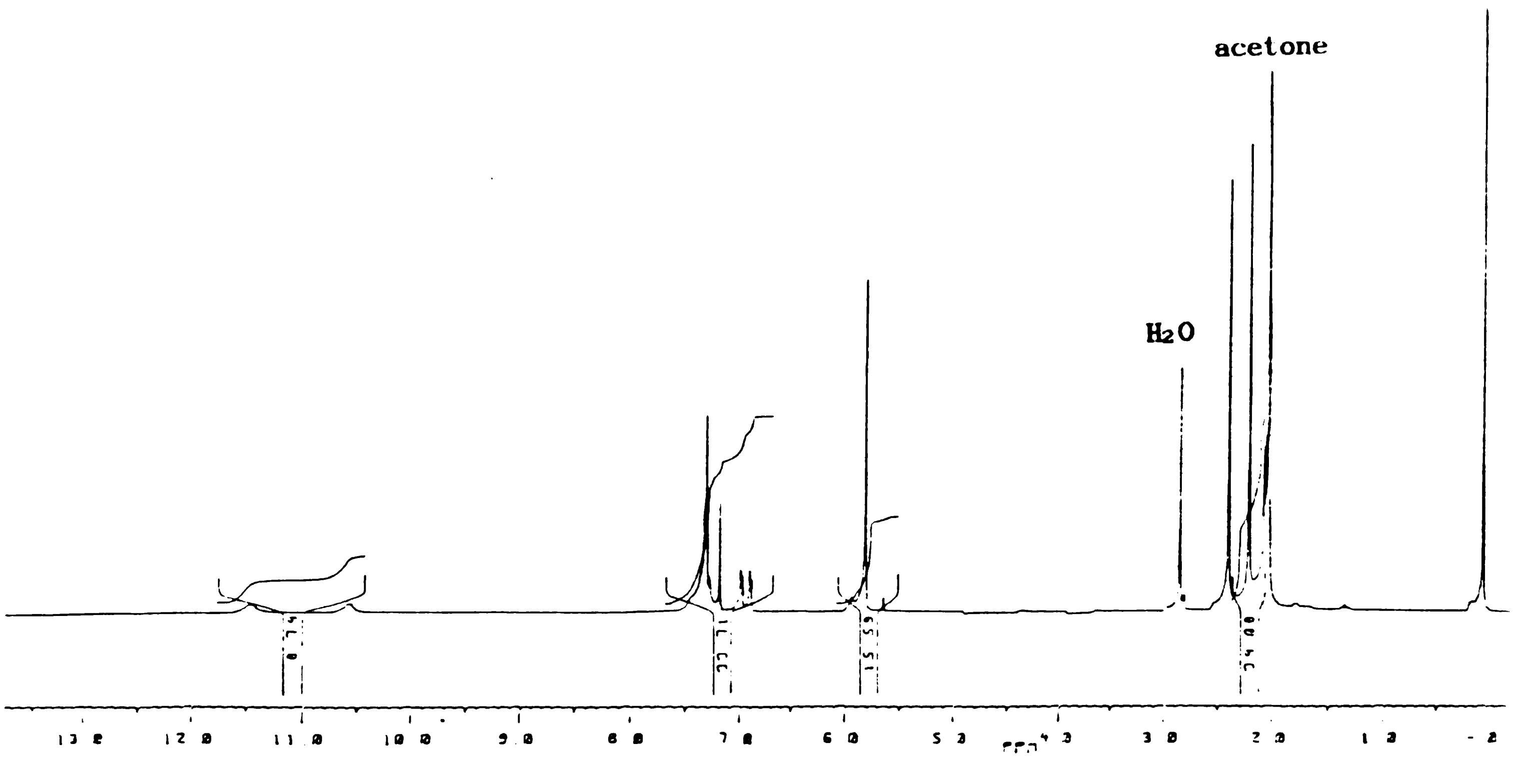


Figure A22. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrryloyl)pyrazole **19b**.

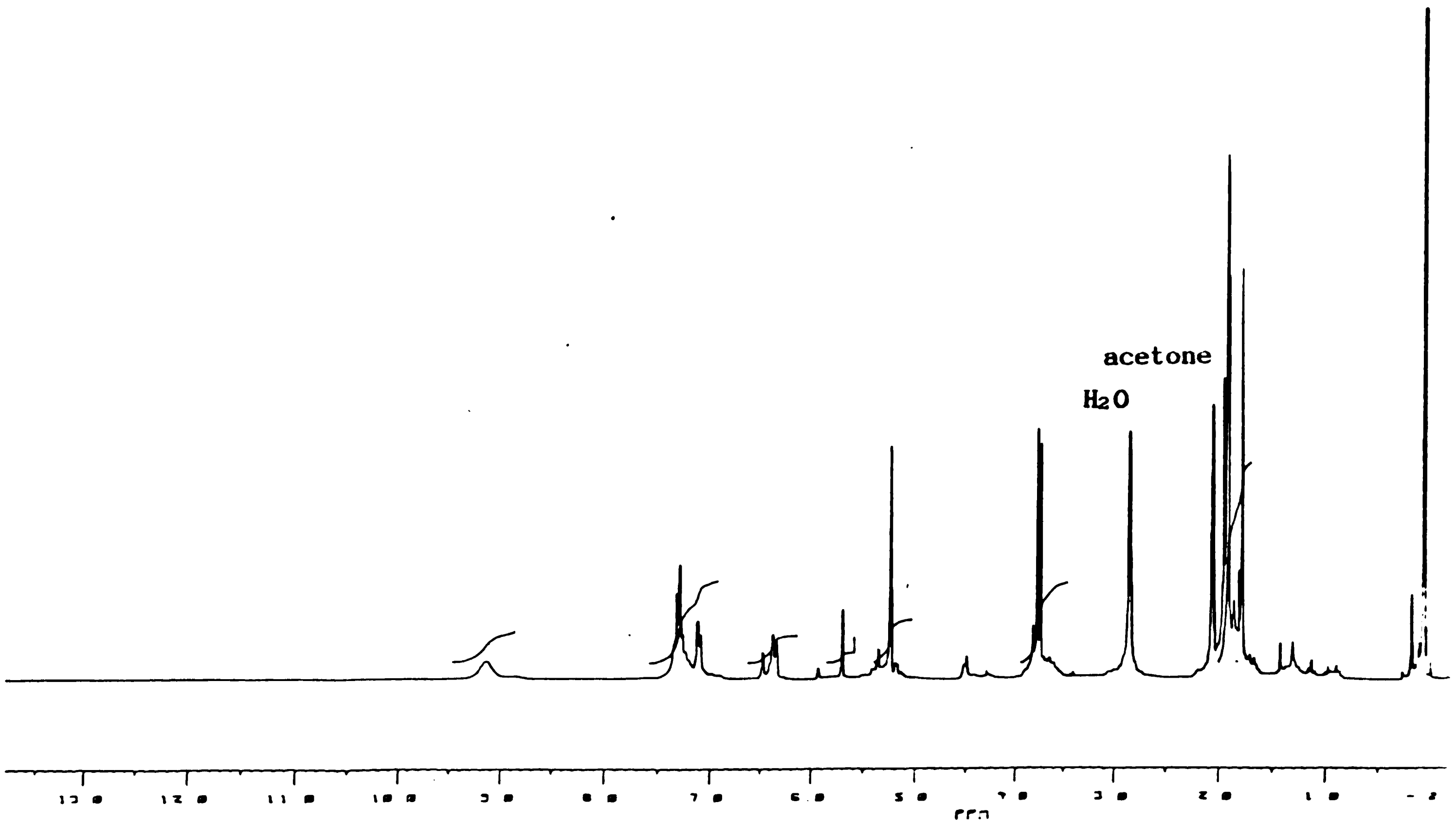


Figure A23. 250 MHz ^1H NMR spectrum of 1-benzyl-3,5-bis(3,4-dimethyl-2-pyrrylmethyl)pyrazole **2b**.

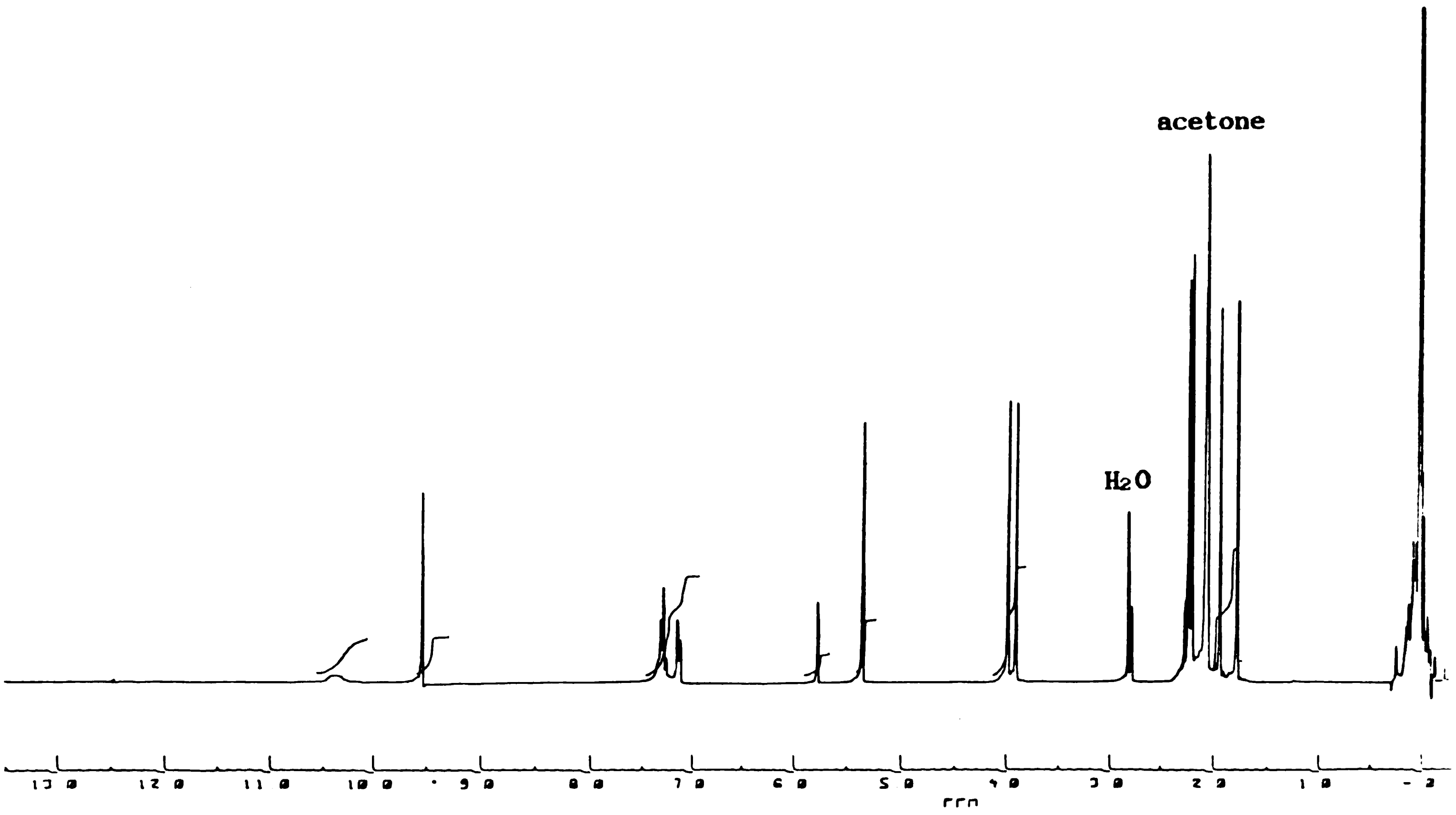


Figure A24. 250 MHz ^{1}H NMR spectrum of 1-benzyl-3,5-bis(3,4-dimethyl-5-formyl-2-pyrrylmethyl)-pyrazole **3b**.

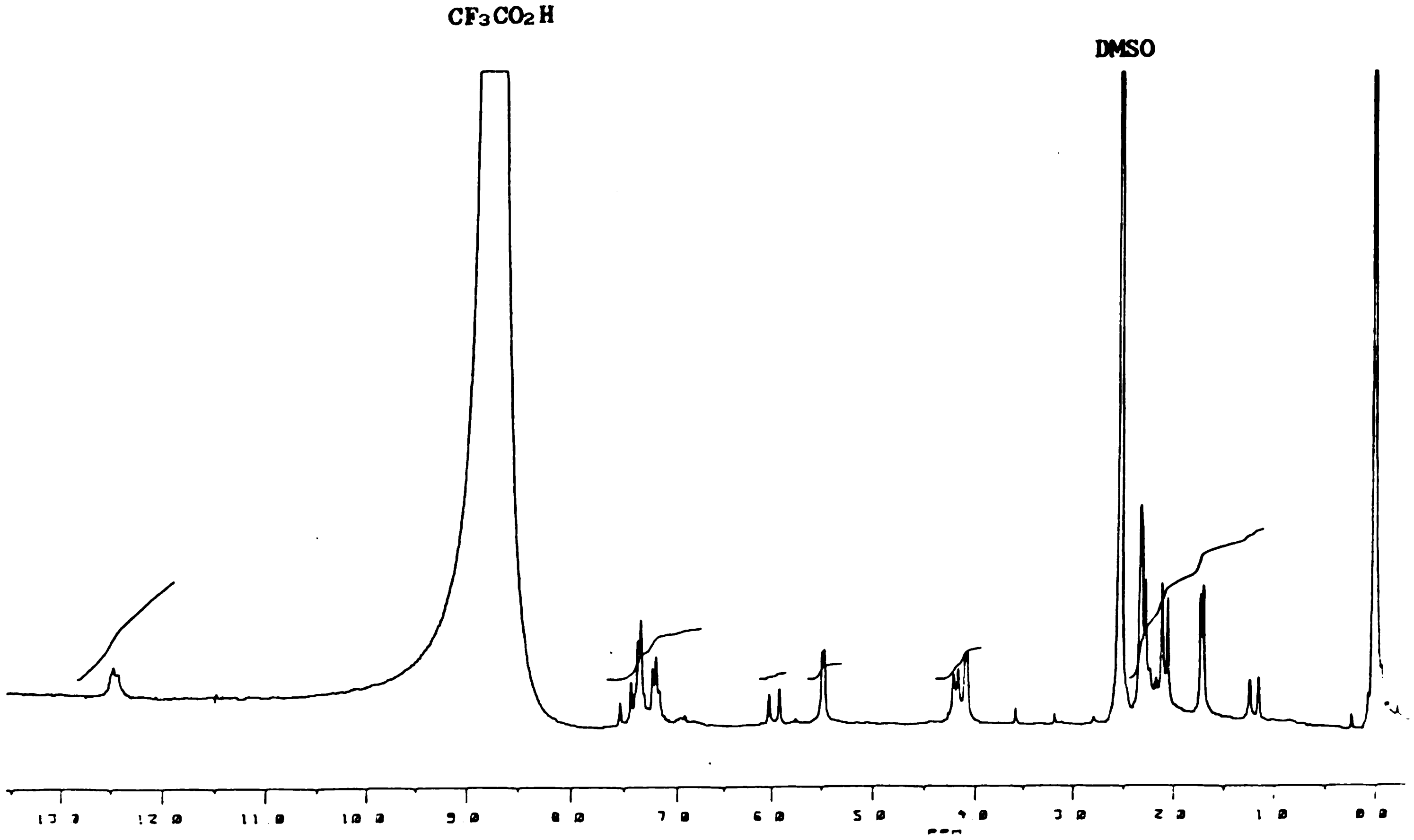


Figure A25. 250 MHz ^1H NMR spectrum of octaazatetrahydro[1,5,1,5]platyrin **22b** in DMSOd$_6$/CF$_3$CO$_2$H.

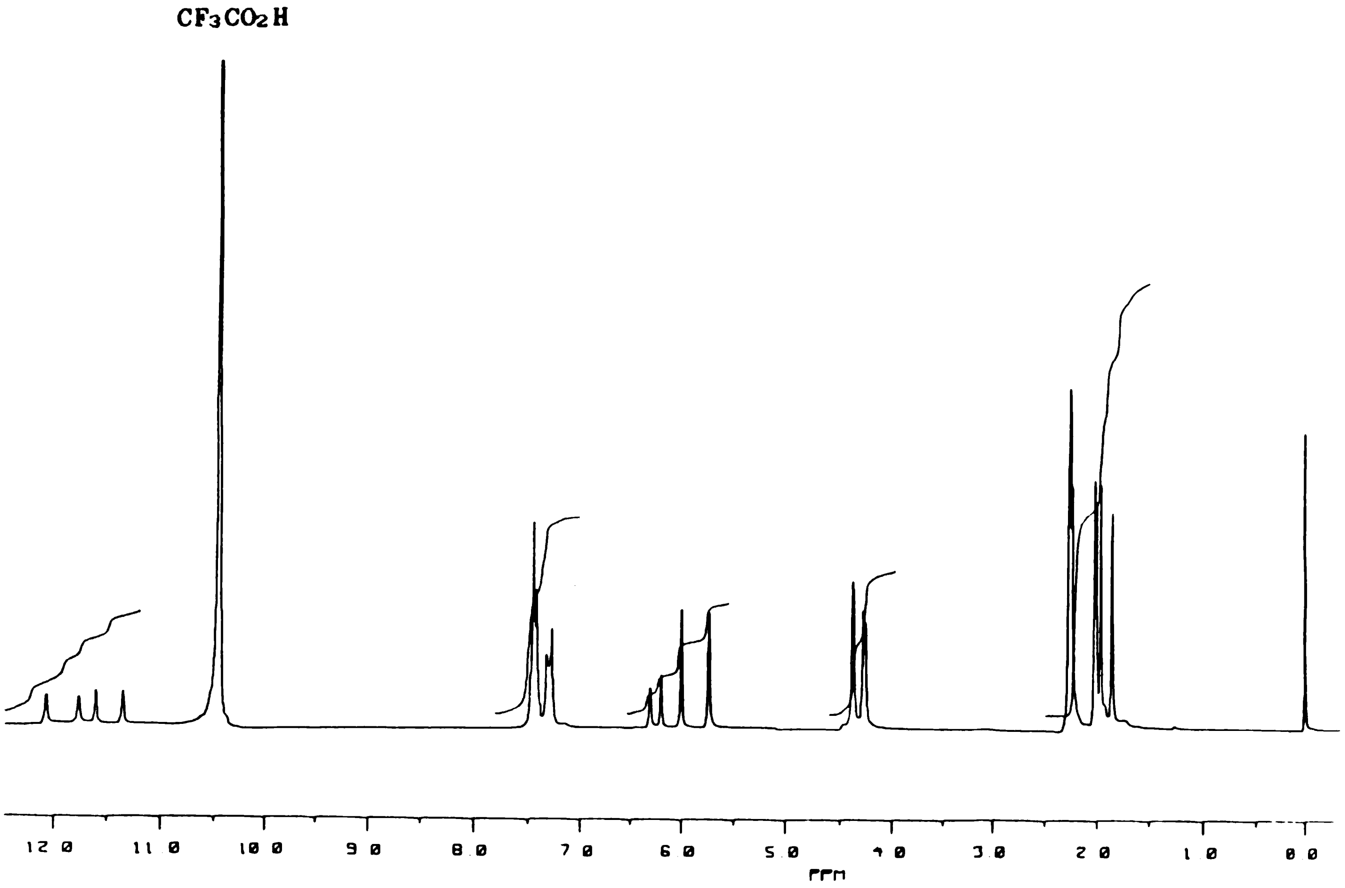


Figure A26. 250 MHz ^1H NMR spectrum of octaazatetrahydro[1,5,1,5]platyrin **22b** in $CDCl_3/CF_3CO_2H$.

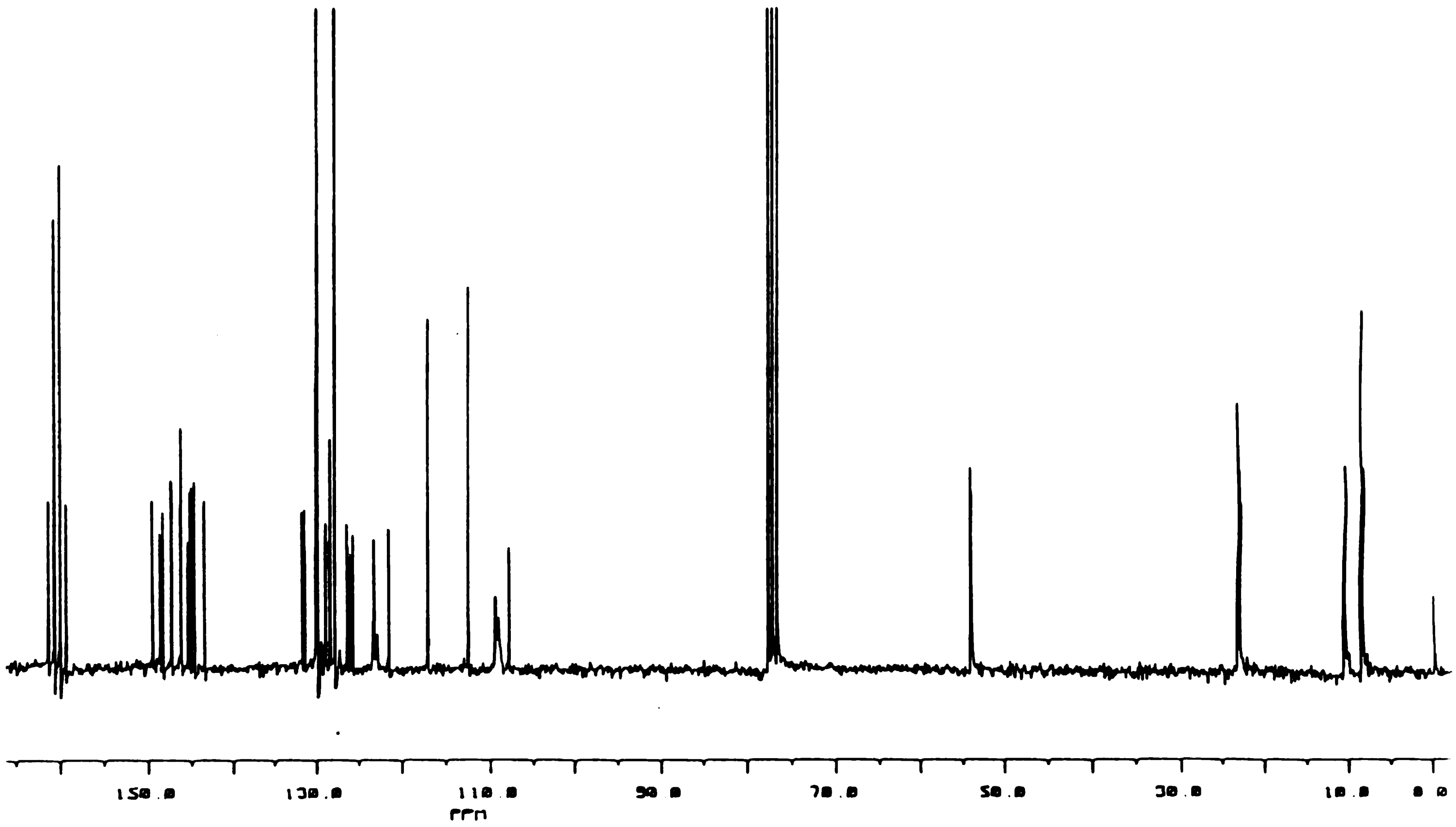


Figure A27. 62.9 MHz ^{13}C NMR spectrum of octaazatetrahydro[1,5,1,5]platyrin **22b** in $CDCl_3/CF_3CO_2H$.

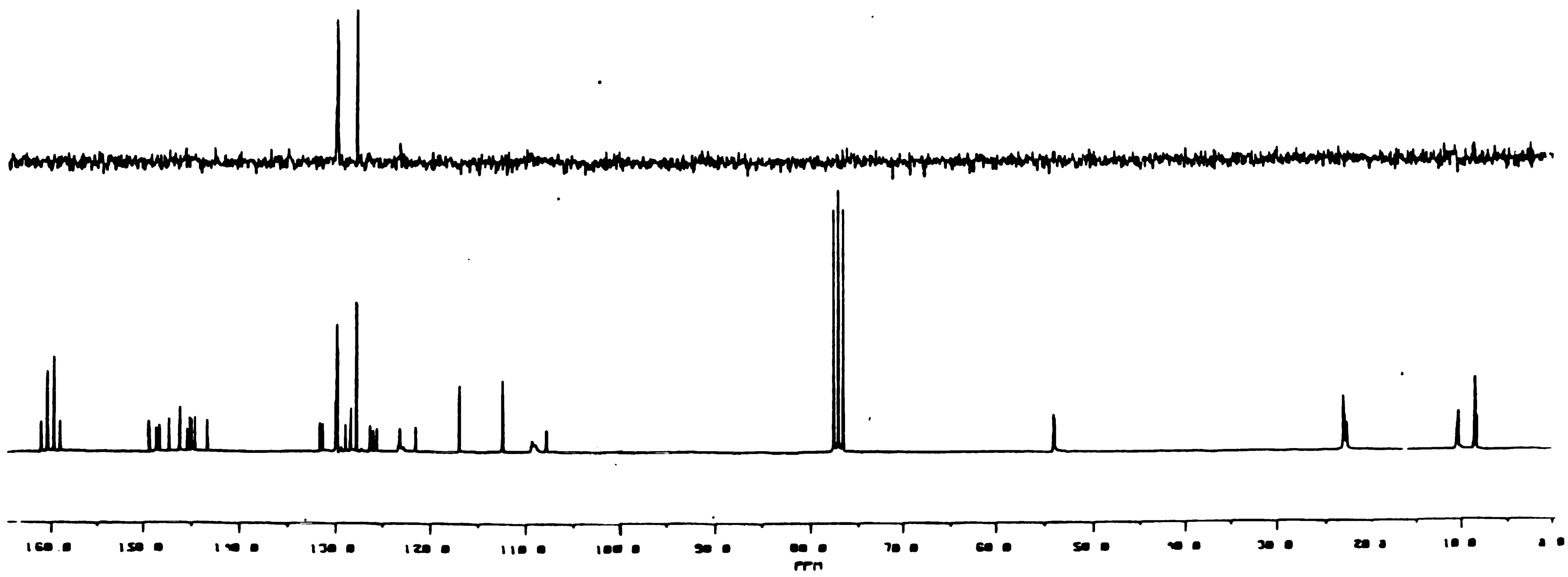


Figure A28. 62.9 MHz ^{13}CH recording using DEPT program of octaazatetrahydro[1,5,1,5]platyrin **22b** in $CDCl_3/CF_3CO_2H$.

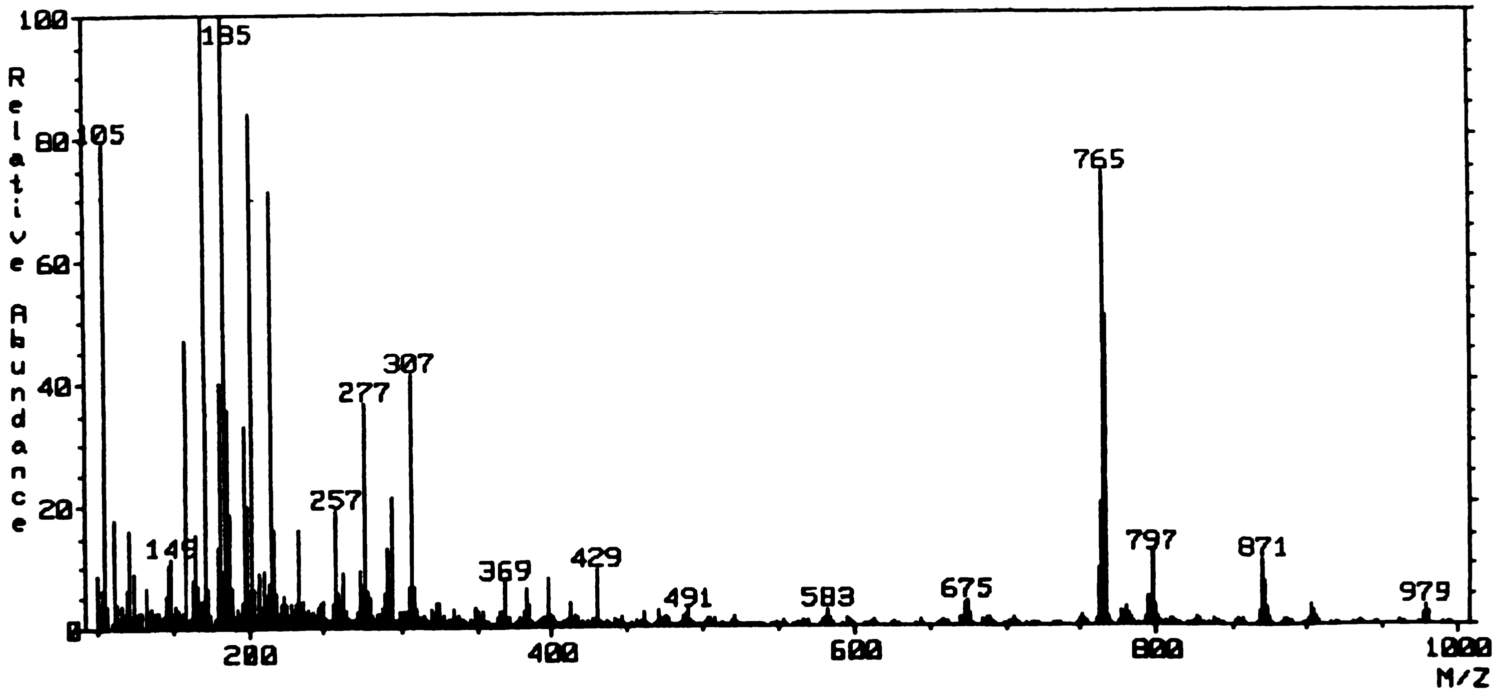


Figure A29. FAB mass spectrum (see general methods for matrix) of octaazatetrahydro[1,5,1,5]-platyrin **22b**.

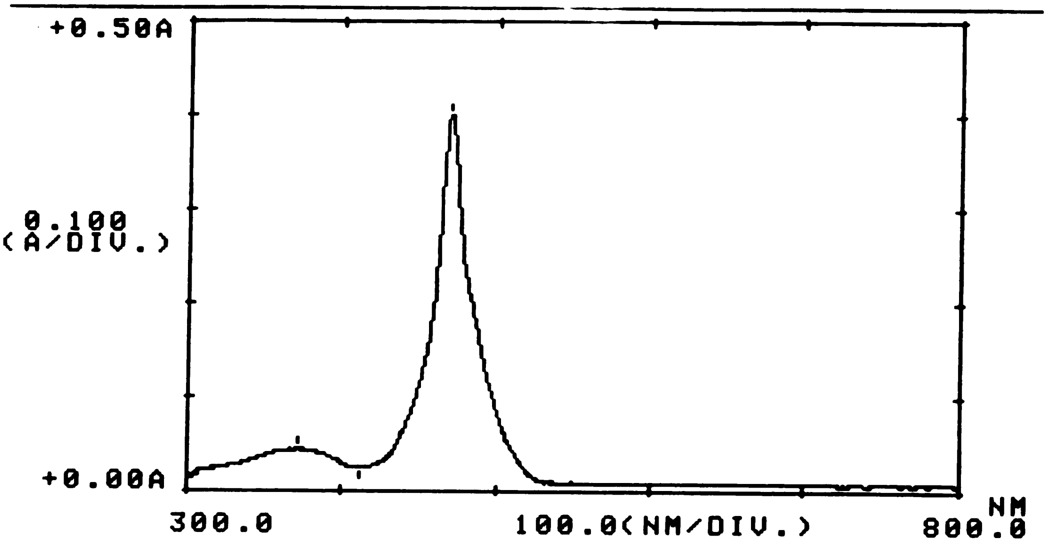


Figure A30. UV-visible spectrum (CH_2Cl_2) of octaazatetrahydro-[1,5,1,5]platyrin **22b** (dihydrobromide salt).

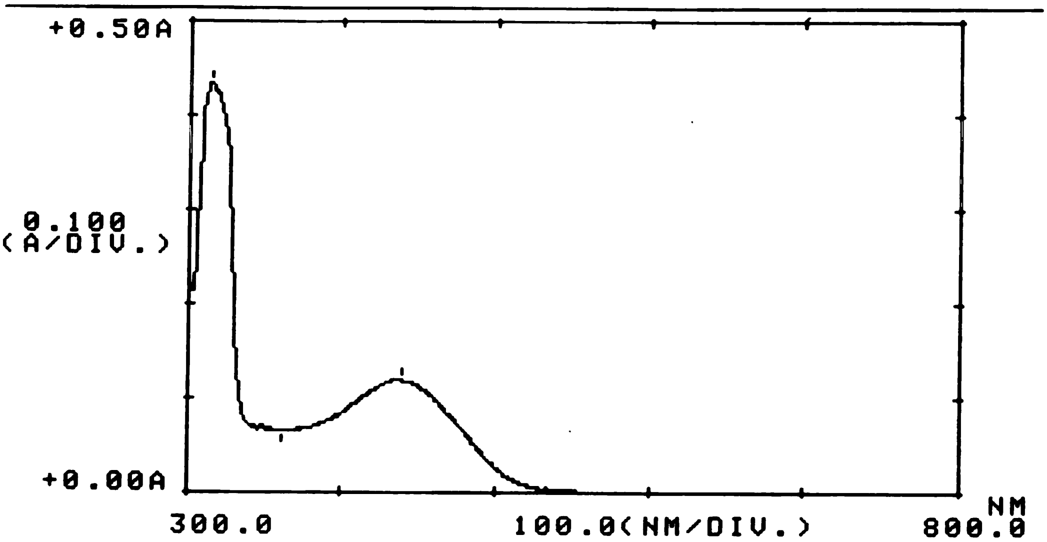


Figure A31. UV-visible spectrum (CH_2Cl_2, pyridine) of octaaza-tetrahydro[1,5,1,5]platyrin **22b** (free base).

LIST OF REFERENCES

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1. Kekulè, F. A. *Bull. Soc. Chim. France* **1865**, *3*, 98.
2. Erlenmeyer, E. *Ann.* **1866**, *137*, 1866.
3. Thiele, J. *Ann.* **1899**, *306*, 87.
4. Willstäter, R.; Wasser, E. *Ber.* **1911**, *44*, 3423.
5. Armit, J. W.; Robinson, R. *J. Chem. Soc.* **1925**, *127*, 1604.
6. Heitler, H.; London, F. *Z. Phys.* **1927**, *44*, 455.
7. Hückel, E.; *Z. Physik* **1931**, *70*, 204; **1931**, *72*, 310.
8. Dewar, M. J. S.; Gleicher, G. J. *J. Am. Chem. Soc.* **1965**, *87*, 685.
9. Schaad, L. J.; Hess, B. A. *J. Chem. Educ.* **1974**, *51*, 640.
10. Pauling, L. *J. Chem. Phys.* **1936**, *4*, 673.
11. Pople, J. A. *J. Chem. Phys.* **1956**, *24*, 1111.
12. Haddon, R. C. *Tetrahedron* **1972**, *28*, 3613.
13. Haddon, R. C. *Tetrahedron* **1972**, *28*, 3635.
14. Haddon, R. C. *J. Am. Chem. Soc.* **1979**, *101*, 1722.
15. Schaad, L. J.; Hess, A. B. *J. Chem. Soc. Chem. Commun.* **1977**, 243.
16. Sondheimer, F.; Metcalf, B. W.; McQuilkin, R. M. *Chem. Commun.* **1971**, 338.
17. Sondheimer, F. *Chem. Commun.* **1966**, 904.
18. Sondheimer, F.; Gaoni, Y. *J. Am. Chem. Soc.* **1962**, *84*, 3520.

19. Sondheimer, F.; Metcalf, B. W. *J. Am. Chem. Soc.* **1971**, *93*, 5271.

20. Vogel, E.; Kocher, M.; Schmickler, H.; Lex, J. *Angew. Chem. Int. Ed. Eng.* **1986**, *25*, 257.

21. LeGoff, E.; Berger, R. A. *Tetrahedron Lett.* **1978**, *44*, 4225.

22. Gossauer, A. *Chimia* **1983**, *37*, 341.

23. Franck, B.; Gosmann, M. *Angew. Chem. Int. Ed. Eng.* **1986**, *25*, 1100.

24. LeGoff, E.; Weaver, O. G. *J. Org. Chem.* **1987**, *52*, 710.

25. Garratt, P. J. *Aromaticity*, Wiley, New York, **1986**, p. 294.

26. Lehn, J. M. *Science* **1985**, *227*, 849.

27. Spiro, T. G. *Copper Proteins*, Wiley, New York, **1981**.

28. Collman, J. P.; Elliot, C. M.; Halbert, T. R.; Tovrog, B. S. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 18.

29. Chang, C. K. *J. Chem. Soc. Chem. Commun.* **1977**, 800.

30. Mertes, K. B.; Takusagawa, F.; Acholla, F. V. *J. Am. Chem. Soc.* **1985**, *107*, 6902.

31. Hoffman, B. M.; Ibers, J. A. *Acc. Chem. Res.* **1983**, *16*, 15.

32. Hoffman, B. M.; Ibers, J. A.; Stanton, J. L.; Palmer, S. M. *Inorg. Chem.* **1986**, *25*, 2296.

33. Dolphin, D., Ed., "The Porphyrins"; Academic Press: New York, **1978**; Vols. I-VII.

34. Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384.

35. Dolphin, D., Ed., "The Porphyrins", Vol. 1, pg. 167; Academic Press: New York, **1978**.

36. Cavaleiro, J. A. S.; Gonsalves, A. R.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc. Perkin Trans. I* **1973**, 2471.

37. Wang, N. C.; Teo, K. E.; Anderson, H. J. *Can. J. Chem.* **1977**, *55*, 4112.

38. Wang, N. C.; Anderson, H. J. *Can. J. Chem.* **1977**, *55*, 4103.

39. Loader, C. E.; Anderson, H. J. *Can. J. Chem.* **1971**, *49*, 45.

40. Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 581.

41. Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503.

42. Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891.

43. Hasan, I.; Marinelli, E. R.; Lin, L. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.

44. Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 3994.

45. Gais, H. J. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 244.

46. Nakahara, Y.; Fujita, A.; Ogawa, T. *Agric. Biol. Chem.* **1985**, *49*, 1491.

47. Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.

48. Mukaiyama, T.; Araki, M.; Sakata, S.; Takei, H. *Bull. Chem. Soc. Japan* **1974**, *47*, 1777.

49. Nicolaou, K. C.; Clareman, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *46*, 4647.

50. Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3761.

51. Lau, C. K.; Dufresne, C.; Belanger, P. C.; Pietre, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038.

52. Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *2*, 229.

53. Ichimura, K.; Ichikawa, S.; Imamura, K. *Bull. Chem. Soc. Japan* **1976**, *49*, 1157.

54. Dolphin, D., Ed., "The Porphyrins"; Academic Press: New York, **1978**; Vol. II, pg. 223.

55. Cheng. D. O.; Ph.D. Thesis, Michigan State University, **1977**, pgs. 67-68.

56. Musselman, B. D.; Watson, J. T.; Chang, C. K. *Org. Mass Spectrum* **1986**, *21*, 215.

57. Berger, R. A.; Ph.D. Thesis, Michigan State University, **1978**, pg. 51.

58. Guy, R. W.; Jones, A. R. *Aust. J. Chem.* **1965**, *18*, 363.

59. Dolphin, D., Ed., "The Porphyrins"; Academic Press: New York, **1978**; Vol. II, pg. 222.

60. Fu, P. P.; Harvey, R. G. *Tetrahedron Lett.* **1974**, 3217.

61. Field, G. F.; Zally, J. W.; Sternbach, L. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3853.

62. Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662.

63. Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, 515.

64. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

65. Lind, E. J.; Masters Thesis, Michigan State University, **1984**.

66. Duschinsky, R.; Dolan, A. L. *J. Am. Chem. Soc.* **1946**, *68*, 2350.

67. Kirmse, W.; Buschhoff, M. *Chem. Ber.* **1967**, *100*, 1491.

68. Sauer, J. C. *Org. Syn.* **1963**, *4*, 813.

69. Knorr, L.; MacDonald, J. *Ann.* **1894**, *279*, 217.

70. Buchner, E.; Papendieck, A. *Ann.* **1893**, *273*, 232.

71. MacDonald, J. E.; Masters Thesis, Michigan State University, **1976**.

72. Eidebenz, E.; Koulen, K. *Archive Der Pharmazie* **1943**, *28*, 171.