This is to certify that the

thesis entitled

Part I: The Synthesis Of Porphyrins
Part II: The Synthesis And Reactions Of Pyrroles

presented by
Dah-Chieh Otto Cheng

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Eugene LeGoff
Major professor

Date 2-22-77

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ABSTRACT

PART I

THE SYNTHESIS OF PORPHYRINS

PART II

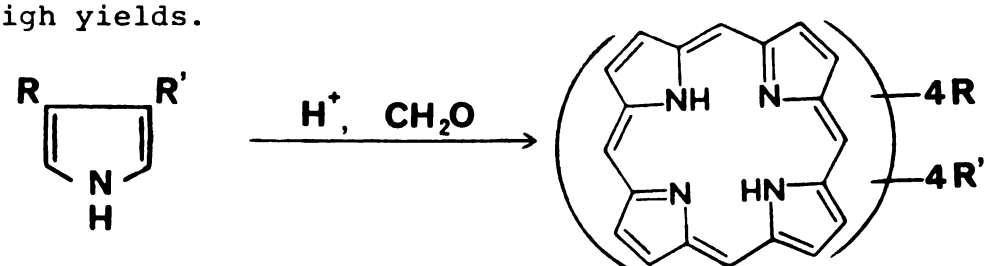
THE SYNTHESIS AND REACTIONS OF PYRROLES

BY

Dah-chieh Otto Cheng

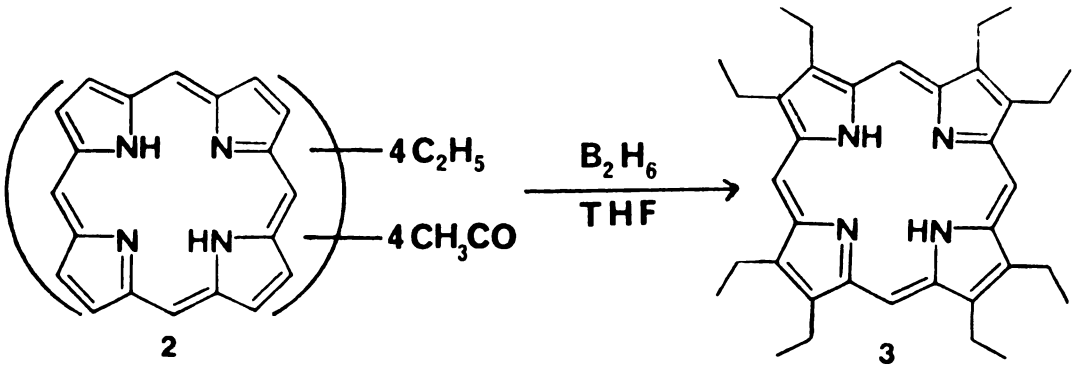
PART I

In the synthesis of the porphyrin macrocycles from pyrrole or a substituted pyrrole yields are usually poor. Thus, a new synthetic route was developed by condensing formaldehyde with 3,4-disubstituted pyrroles (**1**) in the presence of hydrobromic or hydrochloric acid in a large volume of ethanol to give octa-substituted porphyrins (**2**) in high yields.



1 **2**

In the case of R,R'= C_2H_5 or CH_3CO, diborane reduction of **2** gave octaethylporphyrin (**3**) in almost quantitative yield.

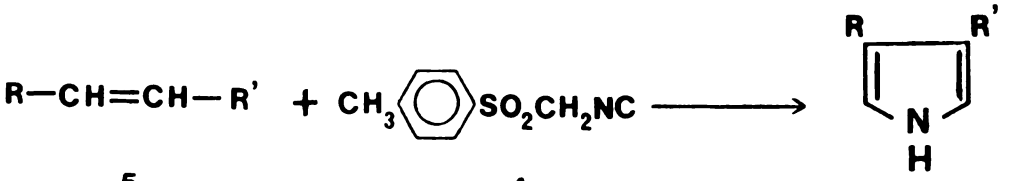


2 3

In the case of R,R'= CH_3 or $CO_2C_2H_5$, base hydrolysis and reesterification with a long chain alkyl iodide yielded an oily porphyrin.

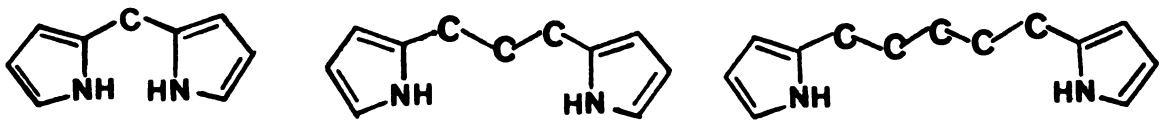
PART II

Various 3,4-disubstituted pyrroles (**1**) were prepared by the reaction of p-toluenesulfonyl methyl isocyanide (**4**) with α,β-unsaturated carbonyl or nitro compounds (**5**).



5 4 1

Two pyrrole molecules were connected by one (**6**), three (**7**) and five (**8**) carbon bridges. The synthesis of their derivatives will also be discussed.



6 7 8

PART I

THE SYNTHESIS OF PORPHYRINS

PART II

THE SYNTHESIS AND REACTIONS OF PYRROLES

By

Dah-chieh Otto Cheng

A DISSERTATION

Submitted to
Michigan State University
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DOCTOR OF PHILOSOPHY

Department of Chemistry

1977

To my wife who has been a
continuing source of
encouragement;

To my parents who have
given me so much.

ACKNOWLEDGEMENTS

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PART I

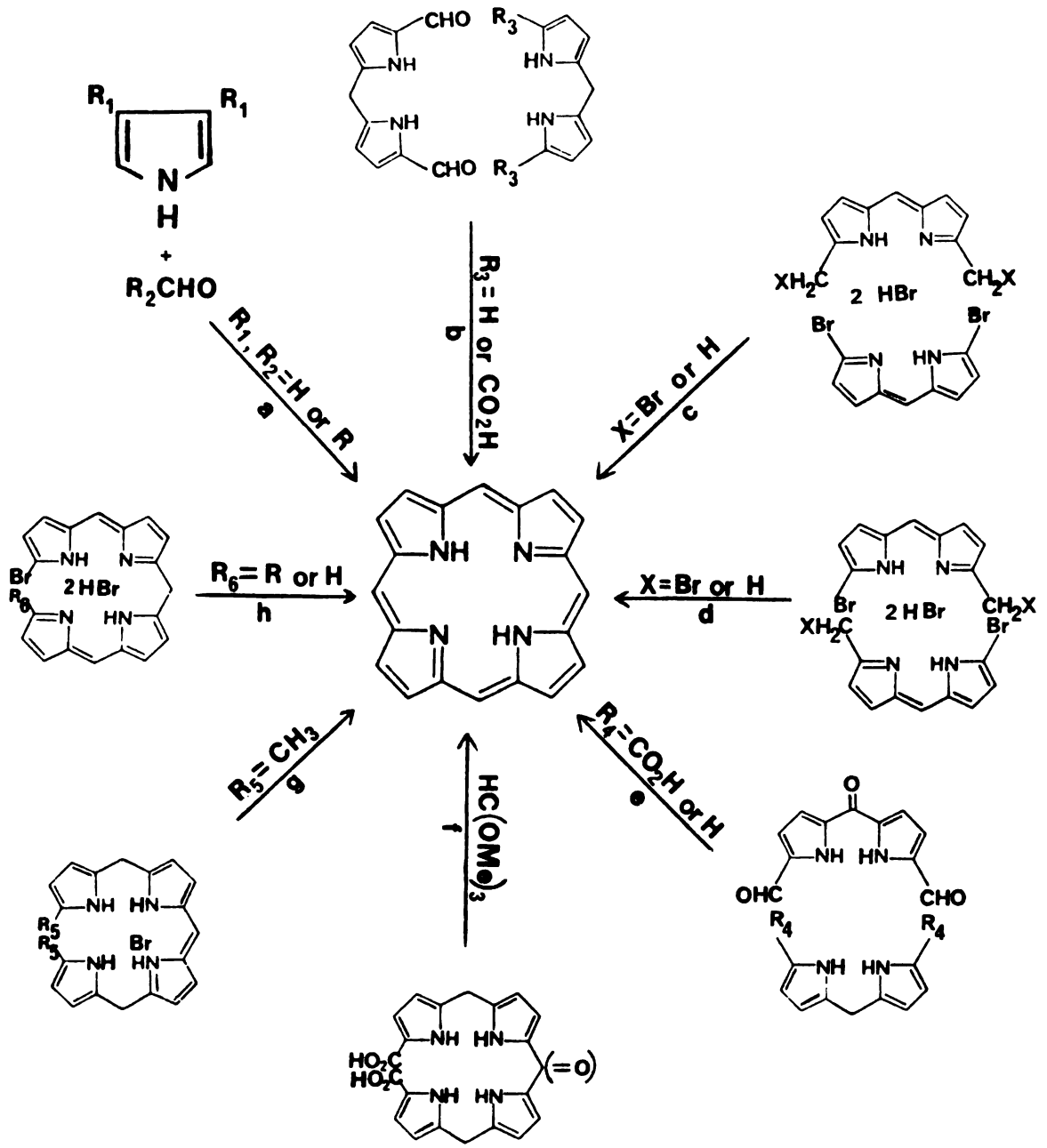
THE SYNTHESIS OF PORPHYRINS

INTRODUCTION

Heme and chlorophylls a and b[10] are the most widespread natural pigments and perform a complementary role in nature, being associated with the oxidative and energy-liberating processes of plant and animal metabolism on the one hand and the reduction and energy-trapping processes of photosynthesis on the other. Massive contributions to our knowledge of the structure and chemistry of porphyrins were accumulated in this century since the classic work of Hans Fischer[1-3] for the synthesis of porphyrins and related compounds.

Various methods[3,5-9] are available for the syntheses of porphyrins from pyrroles (a), dipyrromethanes (b), dipyrromethenes (c and d), dipyrroketones (e), (oxy-)bilanes (f), bilenes (g) or biladienes (h), Scheme 1.

Scheme 1

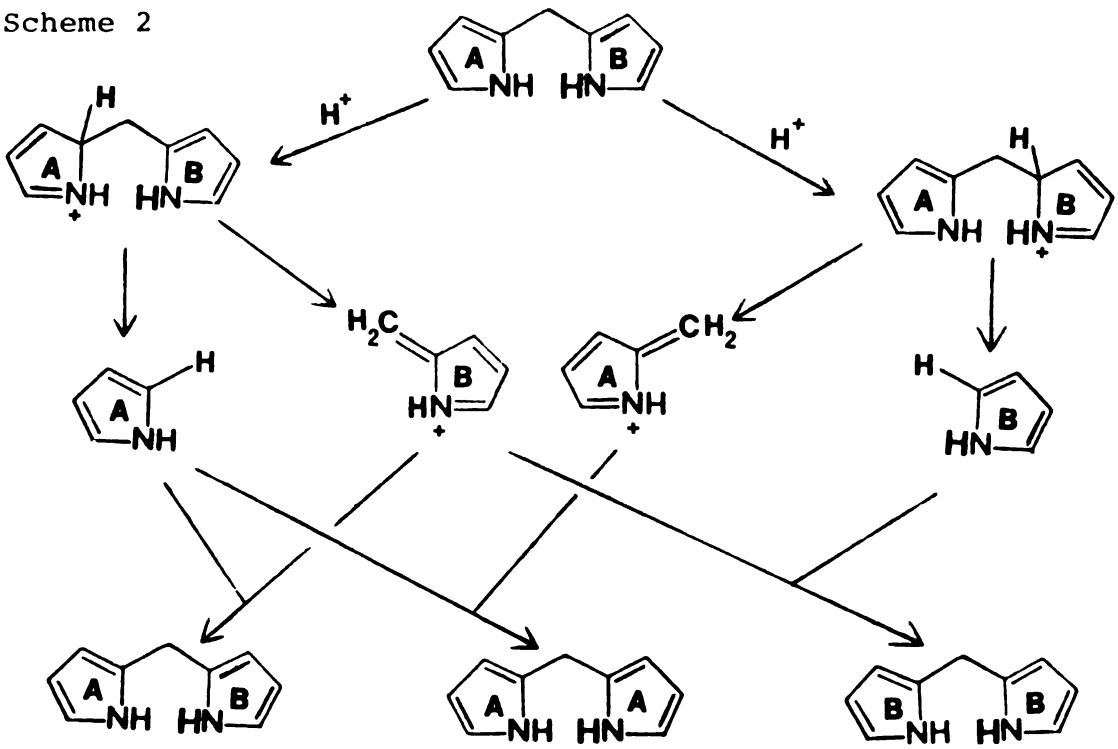

R1 R1
N
H
+
R2CHO
R1, R2=H or R
a
CHO R3
NH HN
NH HN
CHO R3
R3=H or CO2H
b
NH N
XH2C CH2X
2 HBr
Br Br
N HN
X=Br or H
c
NH N
Br
2 HBr
R6
N HN
R6= R or H
h
NH N
N HN
X=Br or H
d
NH N
Br CH2X
2 HBr
XH2C Br
N HN
R5= CH3
g
HC(OMe)3
f
R4=CO2H or H
e
NH HN
R5
R5
NH Br HN
NH HN
HO2C
HO2C
(=O)
NH HN
O
NH HN
OHC CHO
R4 R4
NH HN

The first synthesis of a porphyrin directly from a pyrrole (route a) was the formation of aetioporphyrin from 3-methyl-4-ethylpyrrole (opsopyrrole)[45]. In 1935, Rothemund[46] found that the reaction of pyrrole with aldehyde in the presence of pyridine under pressure and at elevated temperature gave rise to small yields of meso-substituted porphyrins. Thus, acetaldehyde gave rise to meso-tetramethylporphyrin while formaldehyde gave a small yield of parent porphin itself. The best result was found when benzaldehyde was used to give meso-tetraphenylporphyrin[11] in about 20% yield.

Dipyrromethanes were considered as unsuitable intermediates for the synthesis of porphyrins due to their acid lability unless substituted with electron-withdrawing groups. Under the acidic conditions of the reaction (route b), the unsymmetrically substituted dipyrromethanes sometimes resulted in mixtures of porphyrins because cleavage and recombination reactions[47] may occur at the methane bridges, presumably by the mechanism outlined in Scheme 2 on page 5.

A more versatile method introduced by MacDonald and his colleagues[48] is the mild acid-catalyzed condensation of 5,5'-diformyl-dipyrromethane with 5,5'-unsubstituted dipyrromethane or dipyrromethane-5,5'-dicarboxylic acid (route b in Scheme 1). However, MacDonald's method still suffers from the limitation that one of the two dipyrromethanes must be symmetrical , otherwise, two porphyrins could be formed.

Scheme 2



The most widely used porphyrin synthesis to date has been the fusion of two dipyrromethene units[2] in a melt of succinic or tartaric acid at temperature in the range of 160-200°. When different dipyrromethenes are employed in route d, three porphyrins can be formed; one by cross-condensation and two by self-condensation. A logical variation of this method was developed[49] to overcome this shortcoming, a 5,5'-dimethyl or 5,5'-dibromomethyl-dipyrromethene was condensed under similar condition with a 5,5'-dibromodipyrromethene as shown in route c. In this variation one dipyrromethene component supplies both bridge carbon atoms. Unfortunately, this method is also limited in that a single porphyrin can be obtained only if

both of the dipyrromethenes are symmetrically substituted. Apart from symmetry considerations, other limitations to the usefulness of this fusion method are that labile substituents may not survive the drastic experimental conditions, and, moreover, yields may be extremely low.

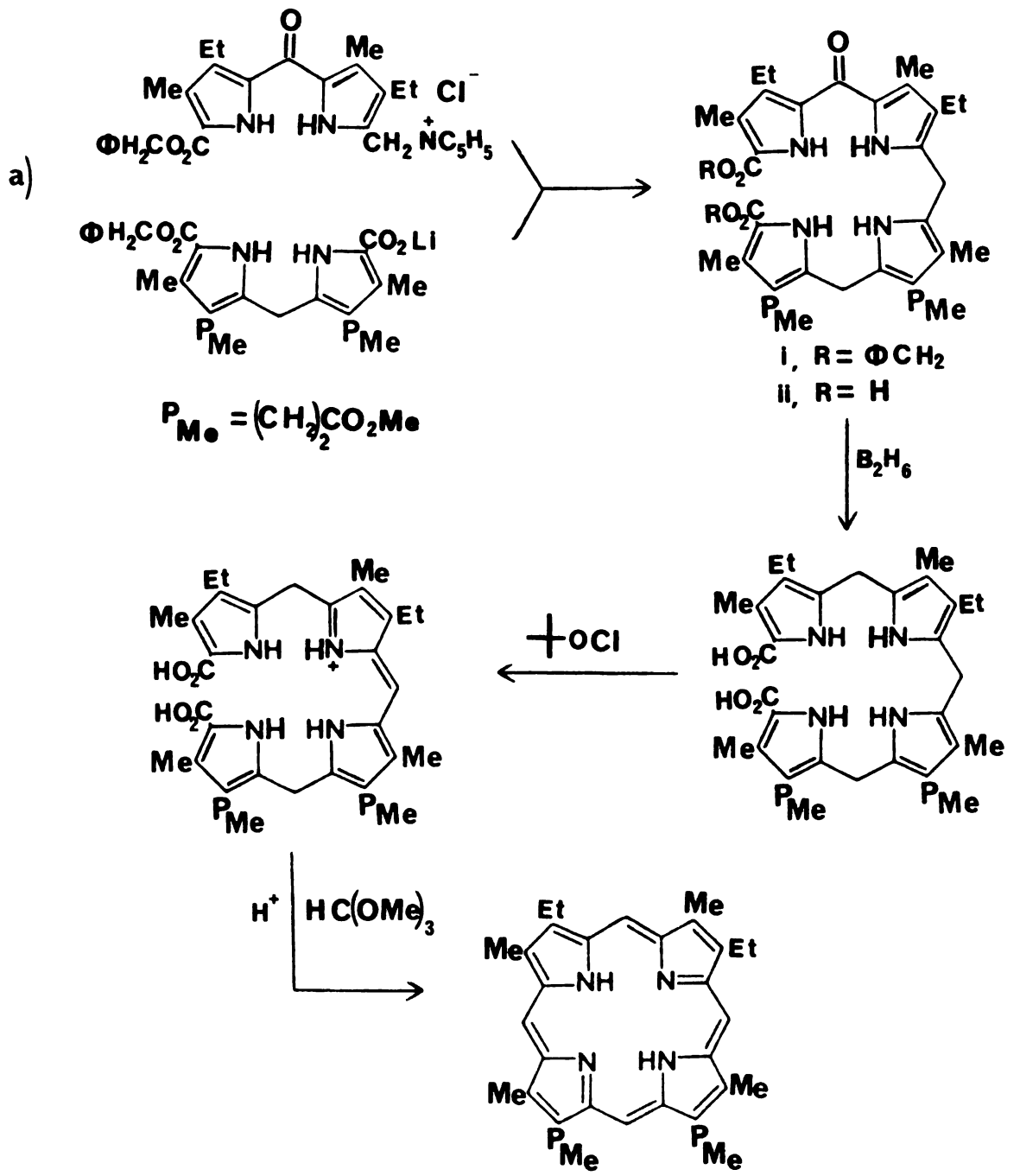
The same symmetry limitations apply to route e as for the syntheses from dipyrromethanes and from dipyrromethenes. An added constraint is that the formyl groups which form the bridging carbon atoms between the two dipyrrolic halves must be sited on the dipyrroketone moiety because the oxo-function in a dipyrroketone deactivates the 5- and 5'-positions toward electrophilic attack[50].

Redistribution reactions during coupling reactions of dipyrromethenes and dipyrromethanes, as well as limitations with regard to symmetry, led to the development of alternatives, particularly designed for the preparations of porphyrins containing unsymmetrically arranged β-substituents. In 1952, Corwin and Coolidge[51] reported the first attempt to synthesize a porphyrin using a discrete open-chain tetrapyrrole as an intermediate (route f). It should be noted that the conditions employed for the final ring closure have been known[47] to cause methane bridge cleavage with the resultant production of more than one porphyrin isomer.

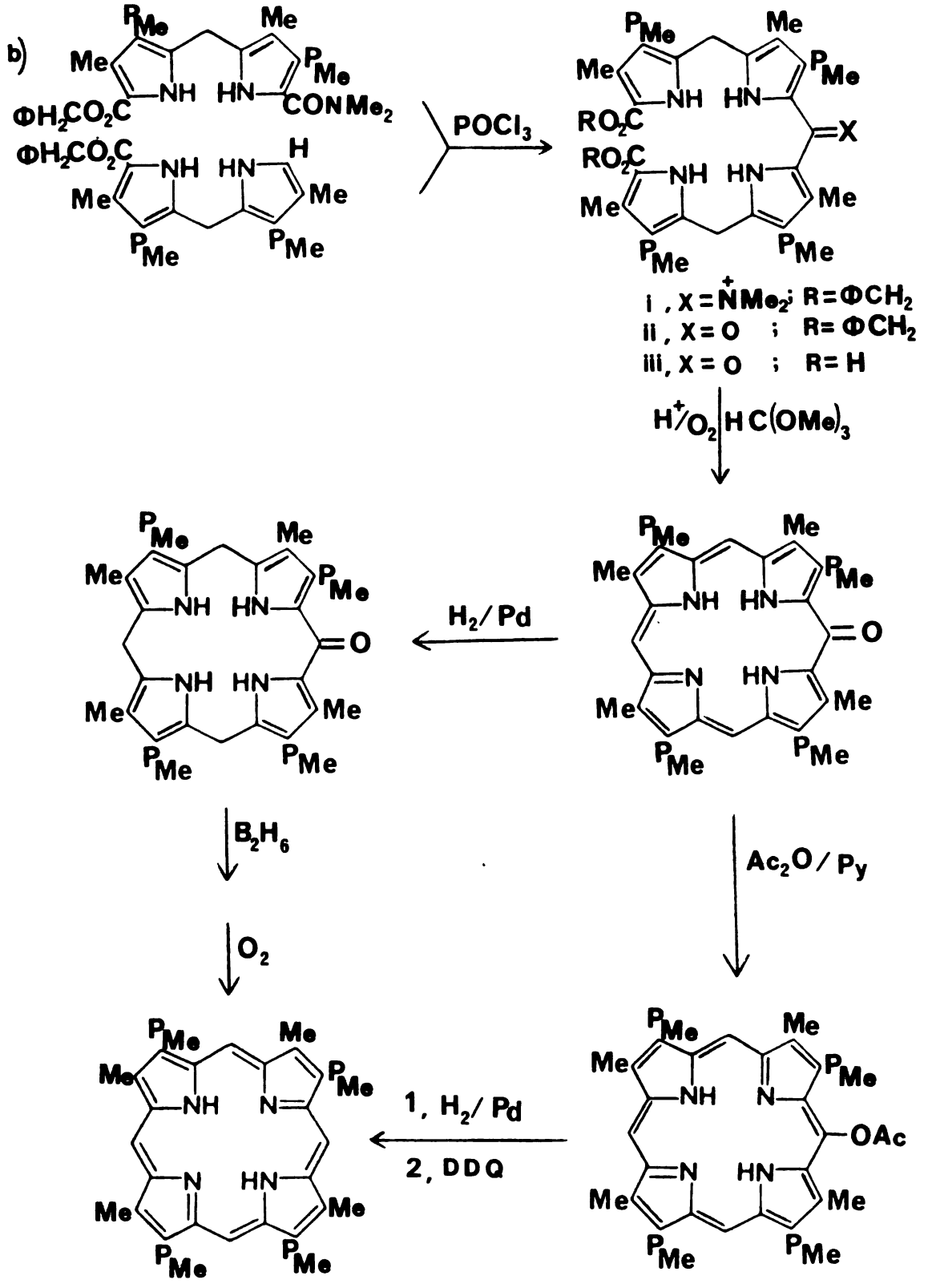
A more sophisticated approach[52,53] is to use a- or b-oxobilanes (Scheme 3a and b) which are considerably more stable

to acid-catalyzed redistribution of the pyrrole rings by virtue of the electron-withdrawing ester functions and the oxo-function.

Scheme 3



Scheme 3 (cont'd)



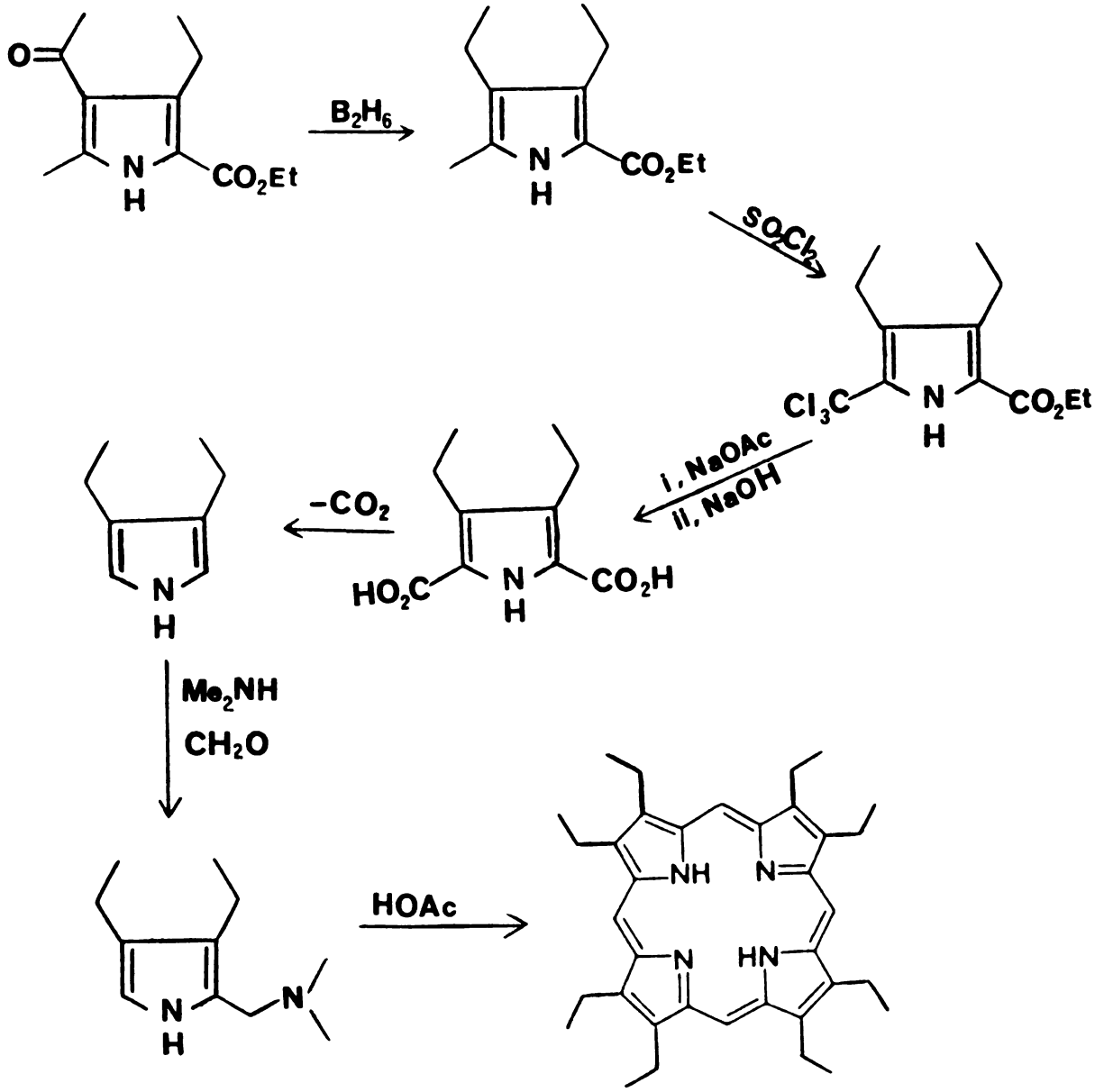
Route h[53] is essentially a two-stage Fischer dipyrromethene condensation in which orientation difficulties of the coupling have been overcome by the isolation of the intermediates. The final cyclization is ususlly achieved by a template method by the use of a copper salt in pyridine or dimethylformamide. However, the dematallation of strongly bound copper from the porphyrin complex requires strong acid such as sulfuric acid in trifluoroacetic acid which sometimes causes difficulties.

Clearly, these methods of using tetrapyrrolic intermediates are limited to the synthesis of porphyrins bearing substituents which are capable of withstanding the conditions of the intermediate steps. In certain cases[54,55], the tetrapyrroles can not be prepared in the laboratory in a completely stepwise fashion; moreover, when prepared in other ways they are not very susceptible to oxidation but readily undergo acid-catalyzed rearrangements, so that attempts at cyclization lead to mixtures of porphyrins. The major drawback of these approaches is after all the complexity of the reaction sequence.

In 1968, Treib and Häberle[11] reported a synthesis of porphyrins unsubstituted in the meso-positions by using the Rothemund reaction conditions which are a 2:1 mixture of acetic acid and pyridine. The yields are from 77% for the preparation of octamethylporphyrin from 3,4-dimethylpyrrole and formaldehyde to 20% for the synthesis of octaphenylporphyrin. However, the work-up procedure was rather tedious; starting from vacuum drying the acetic acid-pyridine solvent, extracting with tetrahydrofuran then boiling o-dichlorobenzene

(bp. 180.4°) to vacuum drying o-dichlorobenzene extracts. To date, the most satisfactory preparation of octaethylporphyrin[12] from 4-acetyl-3-ethyl-5-methylpyrrole-2-carboxylic ethyl ester was reported to give a 40% yield for a multi-step reaction sequence as shown in Scheme 4.

Scheme 4



RESULTS AND DISCUSSION

In order to overcome the difficulties as stated in the introduction and provide a general synthetic route to meso-free porphyrins, simplified procedures have been devised to give high yields of substituted porphyrins. The 3,4-disubstituted pyrroles (preparation in Part II) were chosen mainly because they posses only reactive α-positions, thus preventing reactions at β-positions. In addition the porphyrins formed from them would have a substitution pattern which resembles those which occur naturally.

The study of reaction conditions of porphyrin formation from 3,4-disubstituted pyrrole with formaldehyde was carried out with 3-carbethoxy-4-phenylpyrrole since the starting ethyl cinnamate was readily available. The combination of ethanol and hydrobromic (or hydrochloric) acid was used due to the fact that all the following reaction conditions failed to give porphyrin:

(1) Methanol-hydrobromic (or hydrochloric) acid

(2) Tetrahydrofuran-hydrobromic (or hydrochloric) acid

(3) P-dioxane-hydrobromic (or hydrochloric) acid

(4) Acetic acid

(5) Propionic acid

(6) Acetic acid-pyridine

Thus, the reactions were carried out by refluxing for several hours an ethanolic solution of a 3,4-disubstituted pyrrole with an excess of formaldehyde and a strong acid such as hydrobromic or hydrochloric acid. The reaction mixtures were allowed to stand in a large beaker exposed to the air for periods of a few days to several weeks. Slow air oxidation in this way gave somewhat better yields than procedures involving bubbling air through the reaction mixture.

The following pyrroles were put through the reaction and results are tabulated in Table 1:

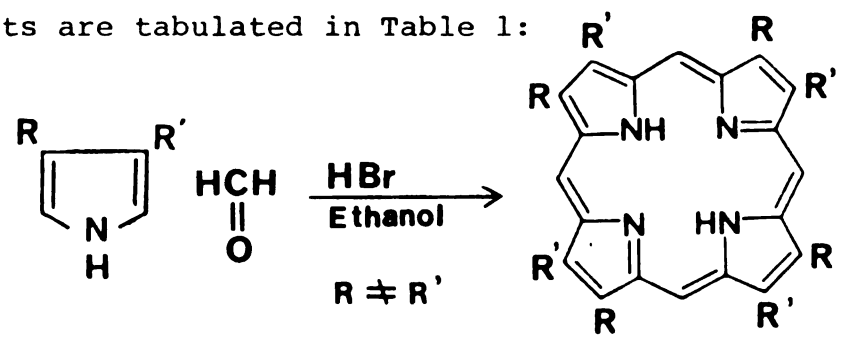


Table 1

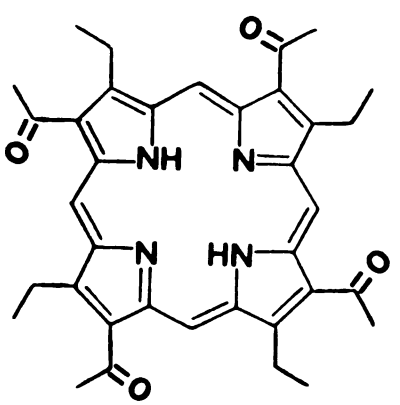
	R	R'	Yield	
1	Ph	$CO_2C_2H_5$	86%	**12**
2	CH_3	$CO_2C_2H_5$	92%	**13**
3	C_2H_5	$COCH_3$	96%	**14**
4	CH_3	$COCH_3$	64%	**15**
5	CH_3	$CO_2n\text{-}C_8H_{17}$	57%	**16**
6	$-CH_2CH_2CH_2CO-$		27%	**17**
7	CH_3	CH_3	65-75%	**18**
8	PhCO	PhCO	0%	
9	Ph	NO_2	0%	
10	Ph	PhCO	0%	
11	$CO_2C_2H_5$	$CO_2C_2H_5$	0%	

For reactions where R=R'= alkyl, symmetrical porphyrins are obtained in comparative yields using this simplified procedure which circumvents the need to prepare aldehyde, aminomethyl or hydroxymethyl pyrrole precursors. Thus,

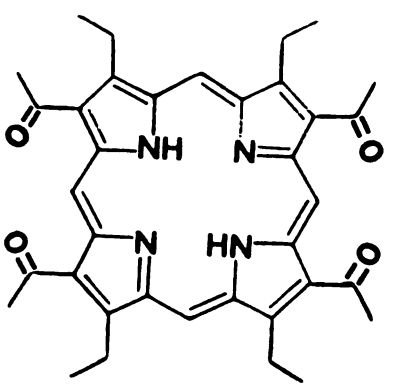
condensing formaldehyde with 3,4-dimethylpyrrole (**7**) gives 2,3,7,8,12,13,17,18-octamethyl-21,23-2H-porphyrin (**18**) in 76% while 3,4-diethylpyrrole gives 2,3,7,8,12,13,17,18-octaethyl-21,23-2H-porphyrin[56] in 65% yields (Nomenclature of porphyrins in Appendix).

For reactions where R≠R', four isomeric porphyrins are possible. In the case of tetraacetyltetraethylporphyrin (**14**), Scheme 5, separation was achieved by High Pressure Liquid Chromatography to give three different bands. Their structures were identified by nmr spectroscopy. The results are summarized in Table 2:

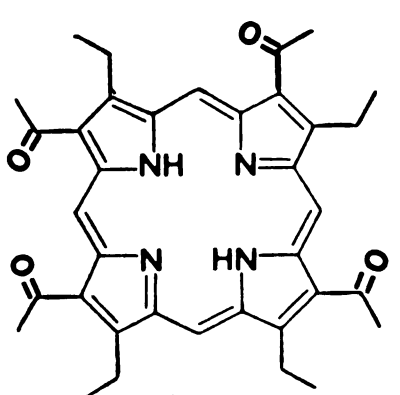
Scheme 5



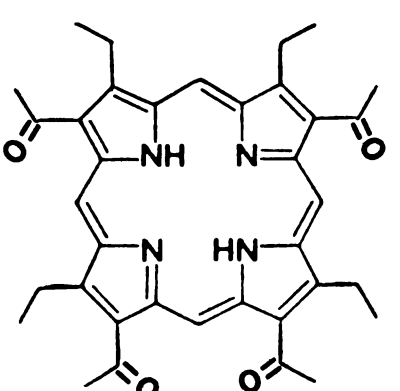
14a (type I)



14b (type II)



14c (type III)



14d (type IV)

Table 2, nmr* Chemical Shifts of **14** (δ values)

	CH_3-------CH_2		CH_3CO	meso-H	N-H
First Band (14.6%)	1.70 (m, 12H)	4.30 (m, 8H)	3.23 (s, 6H) 3.30 (s, 6H)	9.03 (s, 1H) 9.93 (s, 2H) 10.30 (s, 1H)	-4.97 (s, 2H)
Second Band (57.1%)	1.80 (m, 12H)	4.13 (m, 8H)	3.21 (s, 3H) 3.24 (s, 3H) 3.31 (s, 3H) 3.34 (s, 3H)	9.43 (s, 1H) 10.22 (s, 2H) 10.58 (s, 1H)	-4.45 (s, 2H)
Third Band (28.3%)	1.86 (t, 12H)	4.18 (q, 8H)	3.33 (s, 12H)	9.76 (s, 2H) 10.76 (s, 2H)	-4.37 (s, 2H)

* nmr was taken in $CDCl_3$

Thus, the first band is type IV; 2,8,13,17-tetraacetyl-3,7,12,18-tetraethyl-21,23-2H-porphyrin or 1,4,6,7-tetraacetyl-2,3,5,8-tetraethylporphyrin (**14d**).

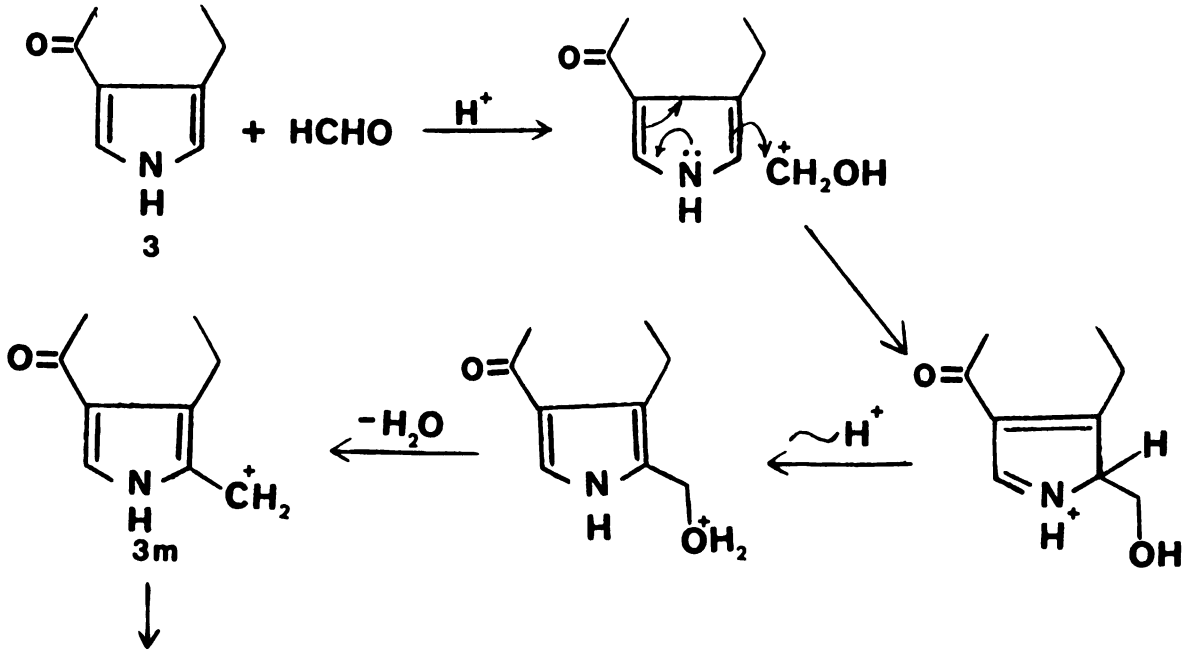
The second band is type III; 2,7,12,18-tetraacetyl-3,8,13,17-tetraethyl-21,23-2H-porphyrin or 1,3,5,8-tetraacetyl-2,4,6,7-tetraethylporphyrin (**14c**).

The third band is type II; 2,8,12,18-tetraacetyl-3,7,13,17-tetraethyl-12,23-2H-porphyrin or 1,4,5,8-tetraacetyl-2,3,6,7-tetraethylporphyrin (**14b**).

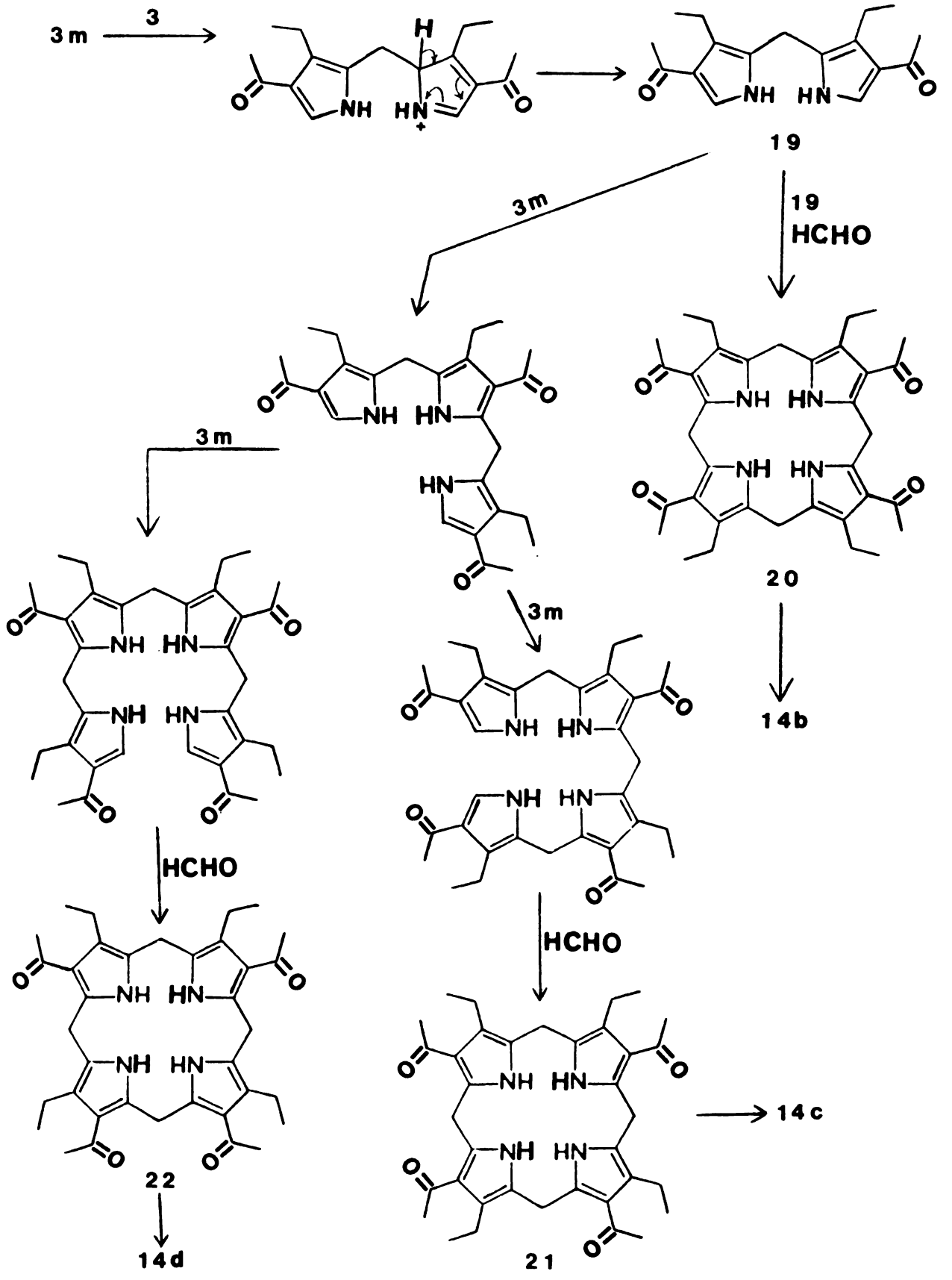
It is interesting that the major isomer is the type III which has the substitution pattern of the naturally occuring porphyrins, but not surprising since the statistical calculation of random formation of porphyrins bearing two sets of different substituents would give the distribution of 1/8type I : 1/8type II : 1/2type III : 1/4type IV.

The absence of type I isomer, 2,7,12,17-tetraacetyl-3,8,13,18-tetraethyl-21,23-2H-porphyrin or 1,3,5,7-tetraacetyl-2,4,6,8-tetraethylporphyrin (**14a**), seems to suggest the possible mechanism of this porphyrin formation reaction as shown in Scheme 6.

Scheme 6



Scheme 6 (cont'd)



Another piece of evidence in support of the porphyrinogens[16] (**20**), (**21**) and (**22**) as intermediates is that a reaction sample after sitting in an UV cell with chloroform showed the following spectral changes (Figure 1).

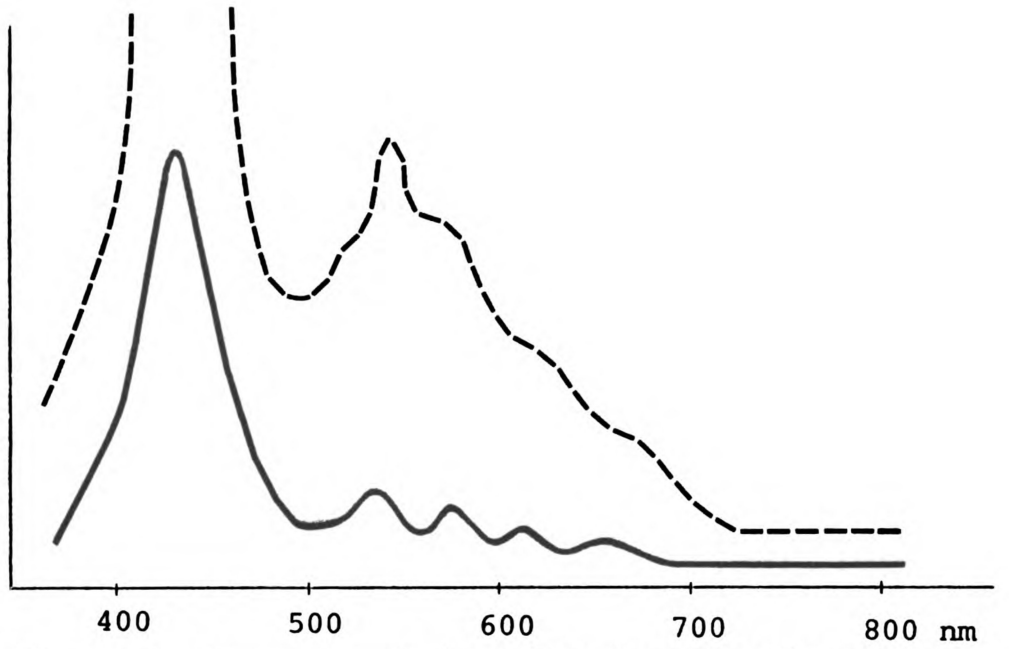
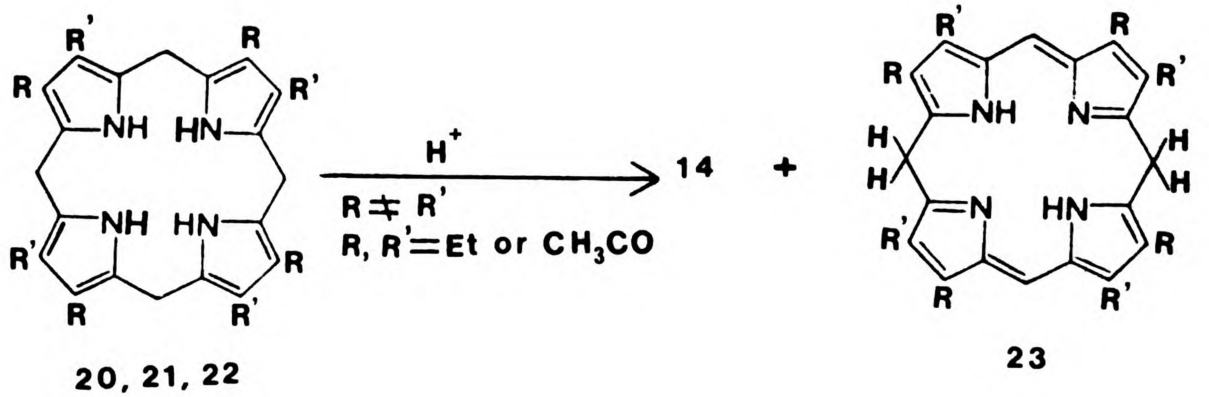


Figure 1, (——————) is taken immediately after sampling; (– – – – – –) is the sample after 10 minutes.

The band at 525 nm is consistant with the formation of porphodimethene[17] (**23**) and the greatly increased Soret band is a strong indication of oxidation of porphyrinogen to porphyrin, Scheme 7.

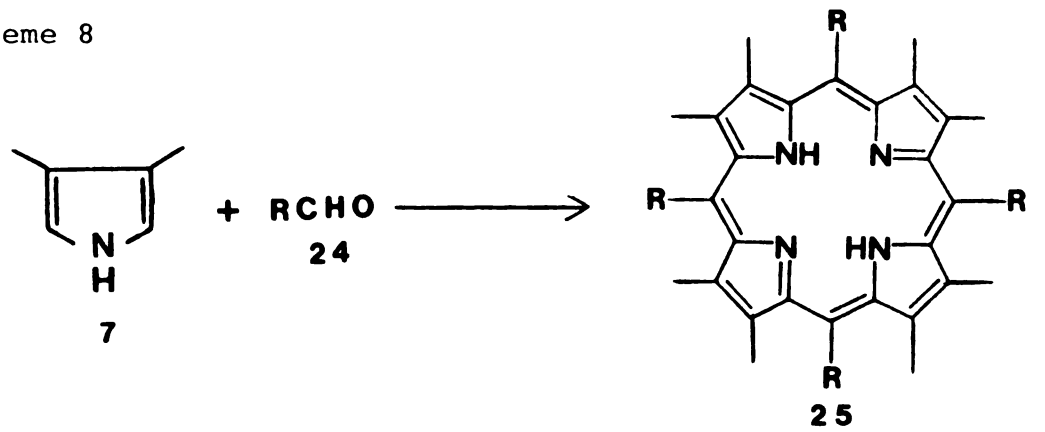
Scheme 7



No porphyrin was obtained when pyrroles **8**, **9**, **10** and **11** were used. This appears to be due to the low nucleophilicity of pyrrole as a result of the lone pair electrons on the pyrrole nitrogen conjugated to a strong electron-withdrawing substituent, i.e., nitro group in **9** and benzoyl group in **10**, and, to two benzoyl groups in **8** and carbethoxy groups in **11**.

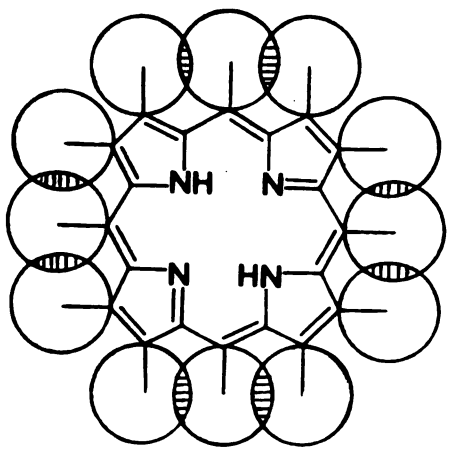
Aldehydes (**24**) other than formaldehyde and 3,4-dimethylpyrrole (**7**) were used in an attempt to prepare dodecasubstituted porphyrin (**25**) as shown in Scheme 8.

Scheme 8

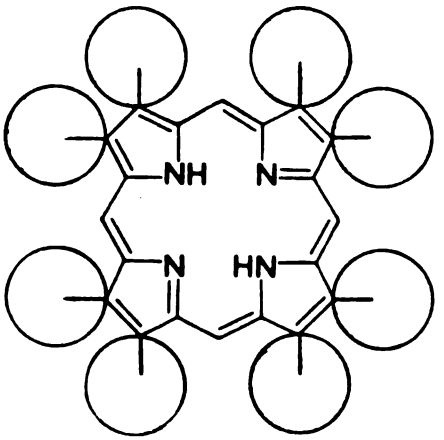


When **24** is acetaldehyde, propionaldehyde, butyraldehyde, 3-cyanopropionaldehyde-diethyl acetal, N,N-dimethylamino-acetaldehyde-dimethyl acetal, bromoacetaldehyde-diethyl acetal or 1,1,3-trimethoxyethane, no **25** was detected. In most cases the reaction stopped at the formation of dipyrromethene salts.

The total failure of the preparation of **25** did not come as a surprise since the introduction of R groups into the meso-positions causes a great deal of strain (see I) wheras in the octasubstituted porphyrin system (II) there is none[22].



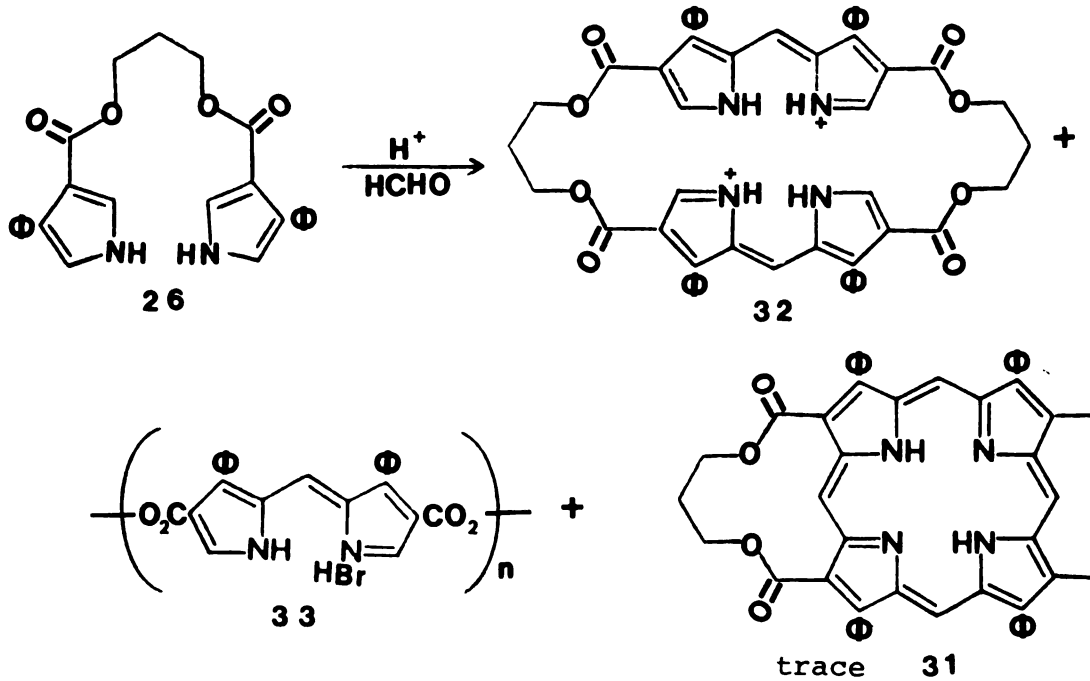
I



II

In an attempt to limit the porphyrin formation to one isomer, 1,3-bis-(4-phenylpyrrole-3-carboxy)-propane (**26**) was prepared and subjected to the same reaction condition. Only a trace amount of porphyrin (**31**) was obtained with dipyrromethenes (**32**) and (**33**) as the major products (Scheme 9). This is best explained by steric interactions that prevent the approach of the protonated formaldehyde to form the carbon bridge between the two pyrrole units of **26**.

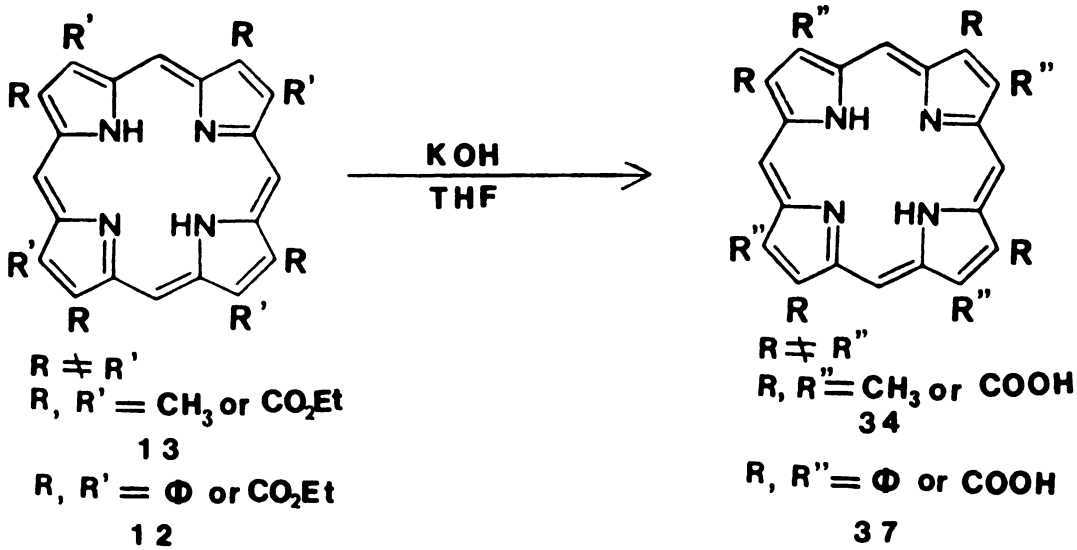
Scheme 9



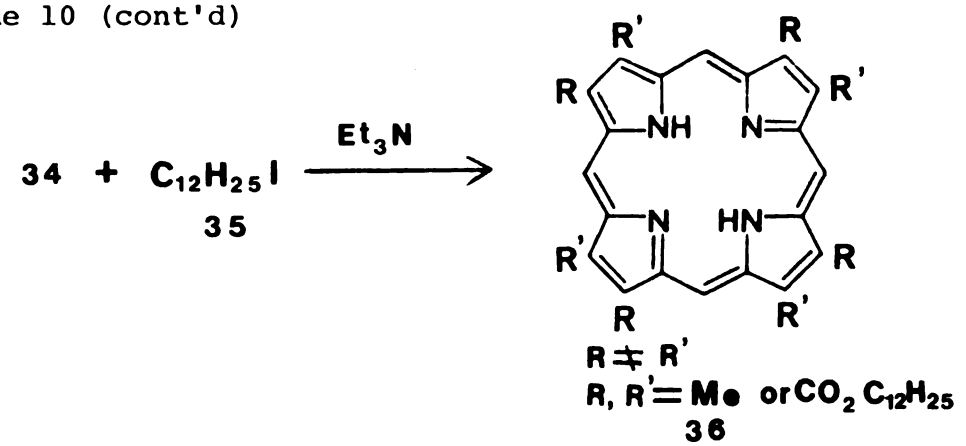
When 3-carboöctoxy-4-methylpyrrole (**5**) was converted to tetracarboöctoxytetramethylporphyrin (**16**), transesterification between the octyl ester and solvent ethanol appeared likely. n-Octanol was employed as the solvent, but after two weeks there was no detectable porphyrin formation. Fortunately, the transesterification was not observed in ethanolic solvent and the resulting porphyrin (**16**) was very soluble in hexanes whereas tetracarbethoxytetramethylporphyrin (**13**) has no solubility in hexanes.

Modification of the porphyrin substituents was carried out on porphyrin esters using a hydrolysis-reesterification sequence. Thus, the long hydrocarbon chain can be put onto the ester functional groups after the formation of porphyrin. One example is to hydrolyze tetracarbethoxytetramethyl-porphyrin (**13**) to tetramethylporphyrin tetracarboxylic acid (**34**), then to esterify with n-iodododecane (**35**) to give tetracarbododecoxytetramethylporphyrin (**36**)[19] as shown in Scheme 10.

Scheme 10



Scheme 10 (cont'd)



The combination of lithium iodide and dimethylformamide[20] gave better results than aqueous potassium hydroxide and tetrahydrofuran[18] in the hydrolysis of tetracarbethoxytetraphenylporphyrin (**12**) to tetraphenylporphyrin tetracarboxylic acid (**37**).

Both tetracarboöctoxytetramethyl (**16**) and tetracarbododecoxytetramethyl (**36**) porphyrins showed aggregation in non-polar solvent and their visible spectra are shown in Figure 2.

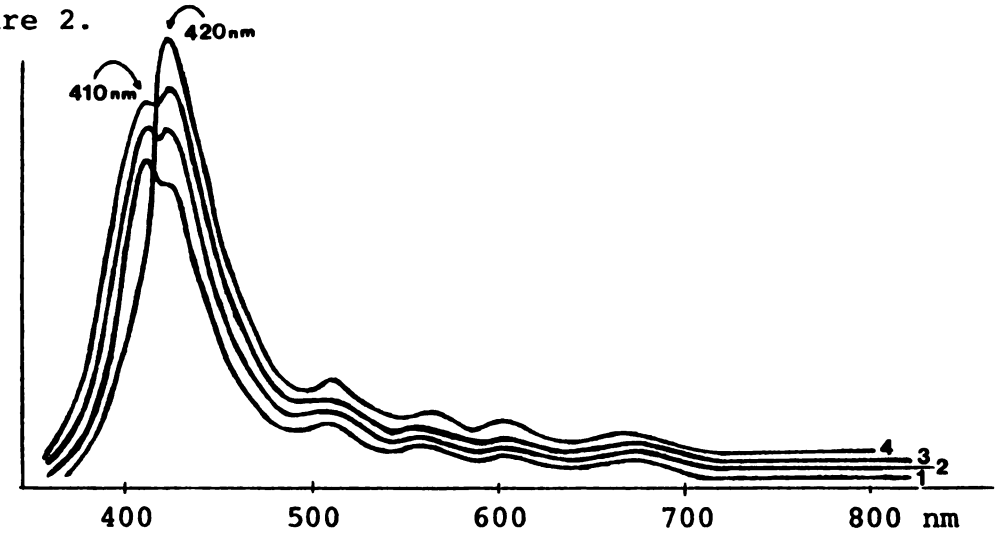
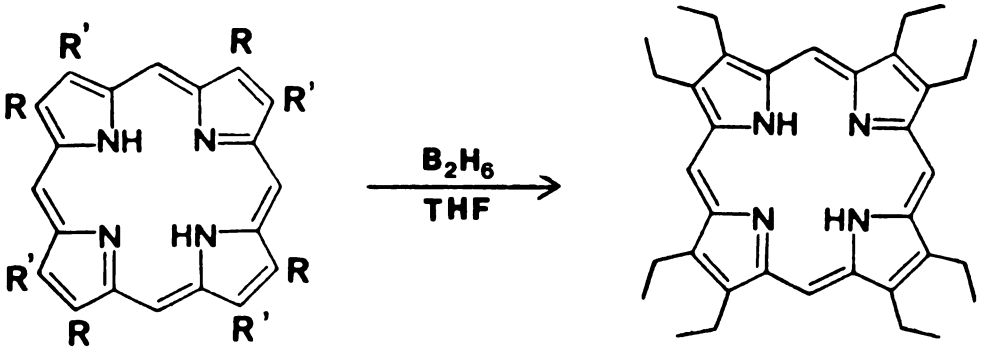


Figure 2, compounds **16** and **36** in hexanes (1) and methylene chloride (4), CH_2Cl_2 concentration increases from (1) ⟶ (4).

When the solvent polarity was increased by adding methylene chloride to hexanes, the peak at ~420 nm increased at the expense of the peak at ~410 nm and finally collapsed to one peak as (4). Presumably, the absorption at shorter wavelength is caused by the aggregation of porphyrins **16** and **36** through the four long hydrocarbon chains on the peripheral positions. While switching solvent to more polar methylene chloride resulted in the dissociation of the aggregates and consequently gave only one Soret band.

Another transformation of the peripheral substituents involving isomeric mixtures proved wholly satisfactory. Thus, diborane reduction of the carbonyl groups of tetraacetyltetraethylporphyrin (**14**) affords octaethylporphyrin (**38**) in 97-100% yield (Scheme 11).

Scheme 11



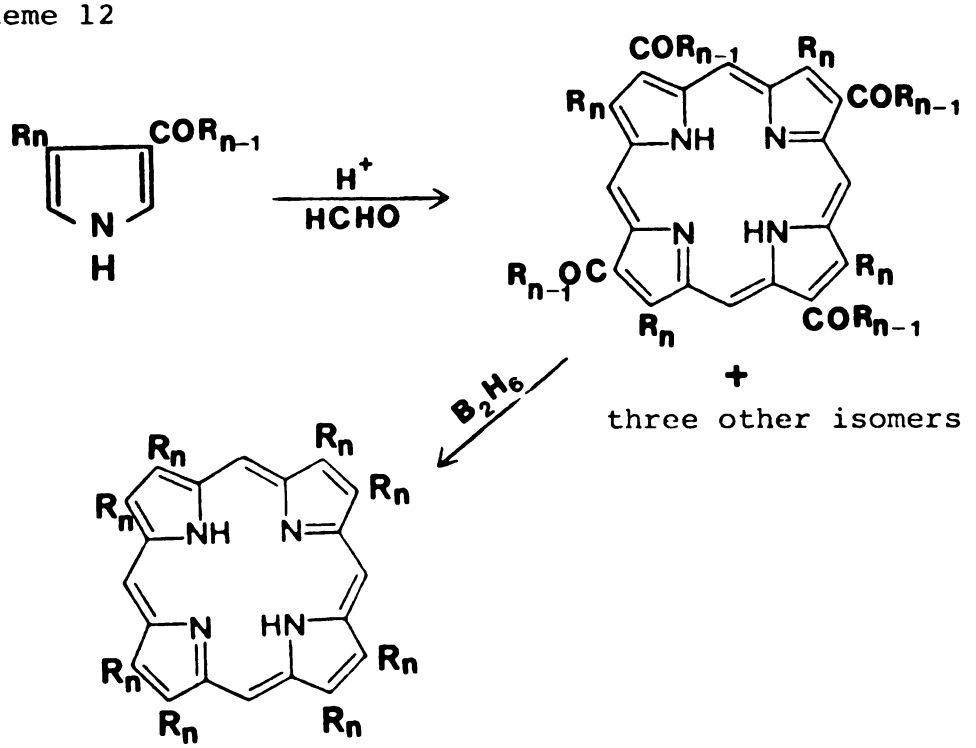
R ≠ R'
R, R' = MeCO or Et

14

38

Therefore, this method is particularly attractive in the syntheses of symmetrical porphyrins as shown in Scheme 12.

Scheme 12

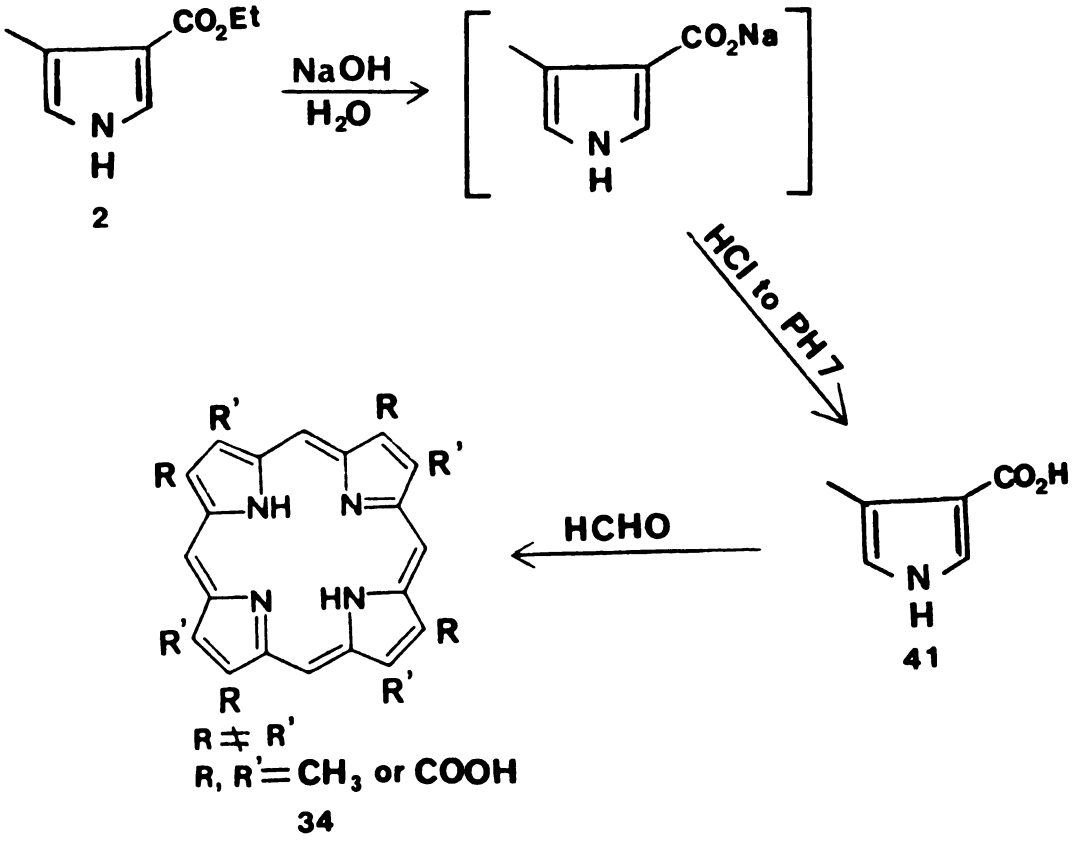


Since 3-nitro-4-phenylpyrrole (**9**) is not reactive toward the reaction conditions of porphyrin formation, **9** was converted to 3-amino-4-phenylpyrrole (**39**) and 3-acetylamino-4-phenylpyrrole (**40**) (transformation of **9**⟶**39** and **40** in Part II). However, when **39** and **40** were subjected to porphyrin formation conditions respectively, still no porphyrin formation could be detected.

A reaction condition was devised to simulate the prebiotic enviroment of porphyrin formation by nature. 3-Carbethoxy-4-methylpyrrole (**2**) was hydrolyzed with sodium hydroxide then carefully neutralized with hydrochloric acid. Upon the addition

of formaldehyde and heating, tetramethylporphyrin tetracarboxylic acid (**34**) was obtained (4.5%) in essentially a "salt" solution (Scheme 13).

Scheme 13



EXPERIMENTAL

General Procedure

The melting points were determined on a Thomas Hoover Uni-melt melting point apparatus and are uncorrected.

The infrared spectra were recorded on a Perkin-Elmer Model 237 B spectrophotometer. The NMR spectra were obtained on a Varian T-60 spectrometer with chemical shifts reported in δ-units measured from tetramethylsilane as the internal standard. The UV and visible spectra were recorded on a Unicam SP-800 spectrophotometer using 1 cm quartz cells. A Hitachi Perkin-Elmer RMU-6 mass spectrometer was used to obtain the mass spectra.

Microanalyses were performed by Spang Microanalysis Laboratory, Ann Arbor, Michigan.

A Waters Associates Prep-HPLC Model 500 was used to separate porphyrin isomers.

Tetracarbethoxytetraphenylporphyrin (12), tetracarbethoxytetramethylporphyrin (13), tetraacetyltetraethylporphyrin (14), tetraacetyltetramethylporphyrin (15), tetracarboöctoxytetramethylporphyrin (16) and tetratrimethylenecarbonylporphyrin (17)

General procedure:

In a flask equipped with a side arm so that a slow stream of air was passing through the flask over the solution throughout the reaction, a solution of 15 mmoles of pyrrole, 60 ml of 40% formaldehyde and 24 ml of 48% hydrobromic acid in 600 ml of ethanol was stirred and refluxed for n hours. Best results were obtained when n=10, in the preparation of **14** and **17**;

n=12, in the preparation of **12**;

n=15, in the preparation of **15**;

n=18, in the preparation of **16**;

n=24, in the preparation of **13**.

The reaction mixture was then allowed to stand at room temperature for one week, except in the case of **16** where one month standing was necessary. The precipitate was collected by filtration. The filtrate was diluted with water and extracted with methylene chloride. The extracts were evaporated to dryness and the residue was chromatographed on a neutral alumina column with 1% methanol in methylene chloride to give another portion of the product. The combined yields are listed in Table 1 on page 12. Spectral characteristics of **12**, **13**, **14**, **15**, **16** and **17** are summarized as below.

Tetracarbethoxytetraphenylporphyrin (**12**)

nmr ($CDCl_3$) δ1.33 (m, 12H, $-CO_2CH_2C\underline{H}_3$), 4.60 (m, 8H, $CO_2C\underline{H}_2CH_3$), 7.67 (m, 20H, phenyl H), 10.67 (s, 1H, meso-H), 11.64 (s, 2H, meso-H), 12.54 (s, 1H, meso-H) and -3.1 (brd s, 2H, N-H); λmax (CH_2Cl_2), 433 nm (ε $3.0X10^5$), 525 nm (ε $1.9X10^4$), 560 nm (ε $7.5X10^3$), 595 nm (ε $7.3X10^3$) and 654 nm (ε $3.0X10^3$)

Anal. Calcd for $C_{56}H_{46}N_4O_8$: C, 74.48; H, 5.15; N, 6.20
Found : C, 74.35; H, 5.09; N, 5.92

Tetracarbethoxytetramethylporphyrin (**13**)

nmr ($CDCl_3$) δ1.77 (m, 12H, $-CO_2CH_2C\underline{H}_3$), 2.87 (m, 12H, $-C\underline{H}_3$), 4.66 (m, 8H, $-CO_2C\underline{H}_2CH_3$), 6.83,7.25,7.52,8.07,8.45,8.69, 9.49,9.78 and 9.94 (9 singlets, 4H, meso-H); λmax (CH_2Cl_2) 425 nm (ε $3.2x10^5$), 521 nm (ε $1.6x10^4$), 556 nm (ε $7.6x10^3$), 595 nm (ε $5.9x10^3$) and 651 nm (ε $2.2x10^3$).

Anal. Calcd for $C_{36}H_{38}N_4O_8$: C, 66.24; H, 5.67; N, 8.58
Found : C, 66.32; H, 5.99; N, 7.57

Tetraacetyltetraethylporphyrin (**14**)

nmr ($CDCl_3$) δ1.75 (m, 12H, $-CH_2C\underline{H}_3$), 3.30 (s, 6H, $-COC\underline{H}_3$), 3.23 (s, 6H, $-COC\underline{H}_3$), 4.08 (m, 8H, $-C\underline{H}_2CH_3$), 9.20 (s, 1H, meso-H), 10.10 (s, 2H, meso-H), 10.40 (s, 1H, meso-H) and -4.75 (s, 2H, N-H); λmax (CH_2Cl_2) in nm, 428 (ε $3.2x10^5$), 524 (ε $2.5x10^4$), 560 (ε $1.1x10^4$), 596 (ε $1.0x10^4$) and 652 (ε $4.5x10^3$).

Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.18; H, 6.50; N, 9.49
Found : C, 72.98; H, 6.76; N, 8.15

Tetraacetyltetramethylporphyrin (**15**)

nmr ($CDCl_3$) δ2.90 (m, 24H, $-C\underline{H}_3$ and $-COC\underline{H}_3$), 7.37,7.55, 8.89,8.90,9.09,9.47,9.56,9.60 (8 singlets, 4H, meso-H) and -8.33 (s, 2H, N-H); λmax (CH_2Cl_2) in nm, 429 (ε $3.1x10^5$), 524 (ε $2.0x10^4$), 561 (ε $9.6x10^3$), 599 (ε $8.1x10^3$) and 654 (ε $3.7x10^3$).

Tetracarboöctoxytetramethylporphyrin (**16**)

nmr ($CDCl_3$) δ0.70-1.85 (3 brd peaks, $-CH_2C_7\underline{H}_{15}$), 2.07 (s, $-C\underline{H}_3$), 3.47,4.10,4.80 (3 brd peaks, $-C\underline{H}_2C_7H_{15}$), 7.42,8.52, 9.42,9.68,9.85,10.75,10.88 (6 singlets, meso-H) and -7.33 (brd s, N-H); λmax (CH_2Cl_2) in nm, 425 (ε $3.1x10^5$), 521 (ε $1.6x10^4$), 556 (ε $7.4x10^3$), 595 (ε $6.0x10^3$) and 652 (ε $2.2 x10^3$).

Anal. Calcd for $C_{76}H_{118}N_4O_8 \cdot H_2O$: C, 71.40; H, 8.79; N, 5.55
Found : C, 71.68; H, 8.91; N, 5.17

Tetratrimethylenecarbonylporphyrin (**17**)

Due to the purification difficulties, only the visible spectrum was taken, λmax (CH_2Cl_2) in nm, 436 (ε $1.8x10^5$), 530 (ε $1.7x10^4$), 570 (ε $1.2x10^4$), 610 (ε $7.0x10^3$) and 665 (ε $3.5x10^3$).

Octamethylporphyrin (**18**)[11]

To a refluxed solution of 3 ml of 40% formaldehyde and 1 ml of 1 N HCl in 250 ml of ethanol was added a solution of 1.9 g (0.02 mol) of 3,4-dimethylpyrrole (**7**) in 200 ml of ethanol. Upon completion of addition oxygen was bubbled through the reaction mixture for two hours. The resulting solution was cooled and allowed to stand for 10 days. The precipitate was collected by filtration, and the filtrate was deposited on neutral alumina and dried in an oven (110^o) for 24 hours. Soxhlet extraction of the alumina with chloroform afforded another portion of **18**. The combined yield was 1.3 g (65%). λmax (CH_2Cl_2):398 (Soret), 491,530,567 and 620.

Tetramethylporphyrin tetracarboxylic acid (**34**)

A mixture of 653 mg (1 mmol) of tetracarbethoxytetramethylporphyrin (**19**) and 45 ml of 1 N KOH solution in 200 ml of oxygen-purged tetrahydrofuran was refluxed in a nitrogen atomsphere for 150 hours. The solvents were removed under reduced pressure. The residue was dissolved in 50 ml of water and acidified with concentrated hydrochloric acid until precipitation occurred (PH=1). The precipitate was centrifuged and repeatly washed with water to free it from traces of acid. The yield was 503 mg (93%).

nmr (5% Na_2CO_3 in D_2O) showed total disappearance of ethyl esters.

λmax (5% Na_2CO_3 in H_2O), 403 nm (ε $2.2x10^5$), 507 nm (ε $1.7x10^4$), 542 nm (ε $1.0x10^4$), 568 nm (ε $8.5x10^3$) and 620 nm (ε $4.2x10^3$).

Anal. Calcd for $C_{28}H_{22}N_4O_8$: C, 61.99; H, 4.09; N, 10.33
Found : C, 62.24; H, 4.98; N, 9.02

Tetraphenylporphyrin tetracarboxylic acid (**37**)

Lithium iodide was finely grounded and vacuum dried at 150 for two days prior to use.

A mixture of 90 mg (0.1 mmol) of tetracarbethoxytetraphenylporphyrin (**15**) and 697 mg (5.2 mmol) of lithium iodide in 25 ml of dimethylformamide (dried over calcium hydride) was stirred and refluxed for 7 days under nitrogen. The reaction mixture was poured into 125 ml of water, acidified with 1 N hydrochloric acid to slightly acidic and extracted with methylene chloride. After the solvent was removed, the

residue was extracted with 10% sodium carbonate solution until no more color in the extract. The combined extracts were then acidified with concentrated hydrochloric acid to PH 1. The fine purple precipitate was filtered and washed with plenty of water to give 67 mg of **37** (The yield was 85%).

nmr (5% Na_2CO_3 in D_2O) showed no ethyl esters.

λmax (in 5% aqueous Na_2CO_3), 414 nm (ε $2.0x10^5$), 514 nm (ε $1.0x10^4$), 550 nm (ε $7.2x10^3$), 565 nm (ε $5.7x10^3$) and 626 nm (ε $2.7x10^3$).

Anal. Calcd for $C_{48}H_{30}N_4O_8 \cdot H_2O$: C, 71.28; H, 3.99; N, 6.93
Found : C, 70.71; H, 4.08; N, 7.08

Tetracarbododecoxytetramethylporphyrin (**36**)

A mixture of 54 mg (0.1 mmol) of tetramethylporphyrin tetracarboxylic acid (**32**) and 150 mg (0.5 mmol) of n-iodo-dodecane in 2 ml of triethylamine was heated in a sealed tube at 140-150° for 20 hours. The reaction mixture was cooled to room temperature and extracted with hexanes. The extracts were then washed with 1% hydrochloric acid, 5% sodium carbonate solution and water. The solvents were removed. The residue (dissolved in hexanes) was chromatographed on a neutral alumina column until 100 ml of hexane were collected then eluted with chloroform. The first purple band was dried to yield 38 mg of **36** (32.3%): nmr ($CDCl_3$), δ0.70-2.50 (3 brd peaks, $-CO_2CH_2C_{11}\underline{H}_{23}$), 3.58 (brd m, $-C\underline{H}_3$), 4.83 (brd m, $-CO_2C\underline{H}_2C_{11}H_{23}$), 8.62, 9.55,9.78,9.95,10.62,10.82 (6 singlets,

meso-H), and -7.03 (brd s, N-H); λmax (CH_2Cl_2), 422 nm (ε $2.8x10^5$), 520 nm (ε $1.7x10^4$), 555 nm (ε $7.2x10^3$), 594 nm (ε $5.7x10^3$) and 651 nm (ε $2.2x10^3$).

Anal. Calcd for $C_{76}H_{118}N_4O_8 \cdot H_2O$: C, 73.98; H, 9.80
Found : C, 74.06; H, 10.18

Octaethylporphyrin (**38**)

To an ice cooled solution of 175 mg (0.3 mmol) of tetraacetyltetraethylporphyrin (**17**) in 60 ml of freshly distilled tetrahydrofuran was added 4 ml (4 mmol) of 1 N borane-tetrahydrofuran solution under nitrogen. Upon completion of addition, the reaction mixture was further stirred for one hour at ice temperature and two hours at room temperature, then cooled to ice temperature. A solution of 5% hydrochloric acid (45 ml) was introduced dropwise to the solution so that the pot temperature remained below 35^o. The resulting solution was added to a separatory funnel containing 50 ml of water and 40 ml of 2 M sodium carbonate solution, and extracted with methylene chloride. Removal of the solvent and chromatography on a neutral alumina column with chloroform yielded 115 mg of **38** (97.1%).

Compound **38** is identified by its visible spectrum, λmax in CH_2Cl_2, 398 nm (ε $1.6x10^5$), 496 nm (ε $1.4x10^4$), 531 nm (ε $1.1x10^4$), 568 nm (ε $6.5x10^3$), 594 nm (ε $1.5x10^3$) and 621 nm (ε $6.0x10^3$).

3-Methylpyrrole-4-carboxylic acid (**41**)

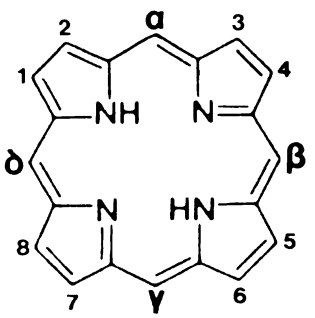
A mixture of 152 mg (1 mmol) of 3-carbethoxy-4-methylpyrrole (**2**) in 20 ml of 5% aqueous sodium hydroxide solution

was refluxed under nitrogen for two hours. The reaction mixture was cooled to room temperature and acidified with 20% hydrochloric acid to PH 1, then refrigerated overnight. The white precipitate was collected by filtration to give 120 mg of **43** (97%); mp. 193-195^{o} (dec.) (lit.[30] mp. 182^{o}); nmr (D_6MSO) δ2.23 (s, 3H, -C$\underline{H}_3$), 6.38 (m, 1H, pyrrolic proton), 7.18 (m, 1H, pyrrolic proton) and 10.26 (brd s, 1H, N-$\underline{H}$).

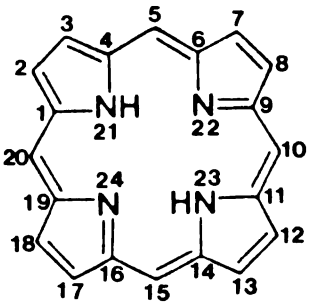
APPENDIX

Nomenclature of porphyrins

Two systems are currently in use; the earlier system devised by Hans Fischer is shown in A and the new system devised by IUPAC Nomenclature Committee[4] is shown in B:

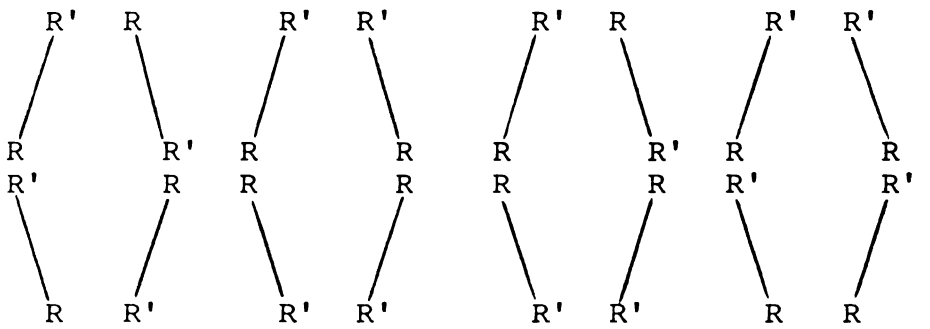


A



B

When each of the four pyrrole rings of a porphyrin bears two different substituents, R and R', in the ß-positions, then four isomers exist:



Type I Type II Type III Type IV

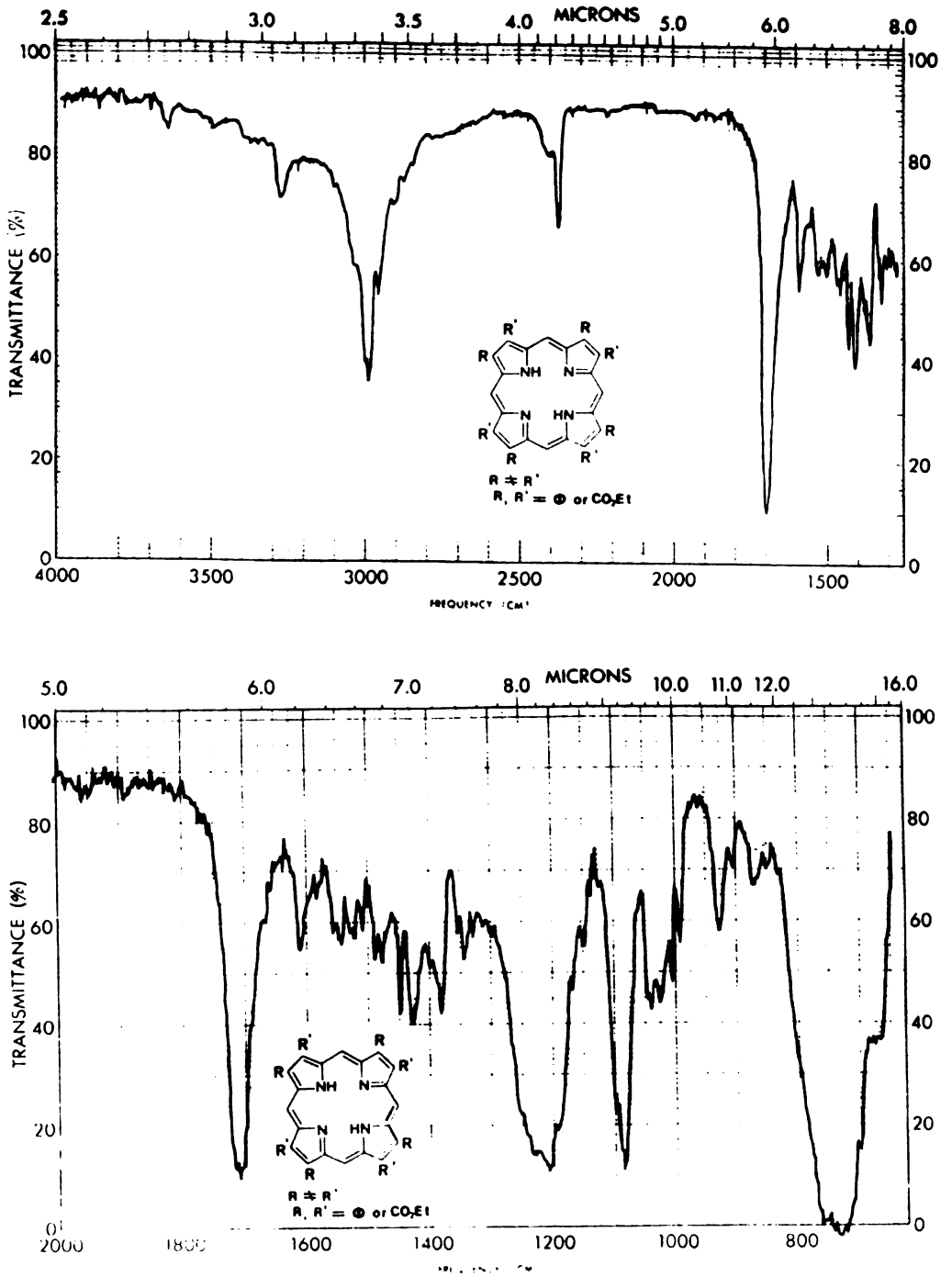


Figure 3, Infrared spectrum of tetracarbethoxy-tetraphenylporphyrin (**12**).

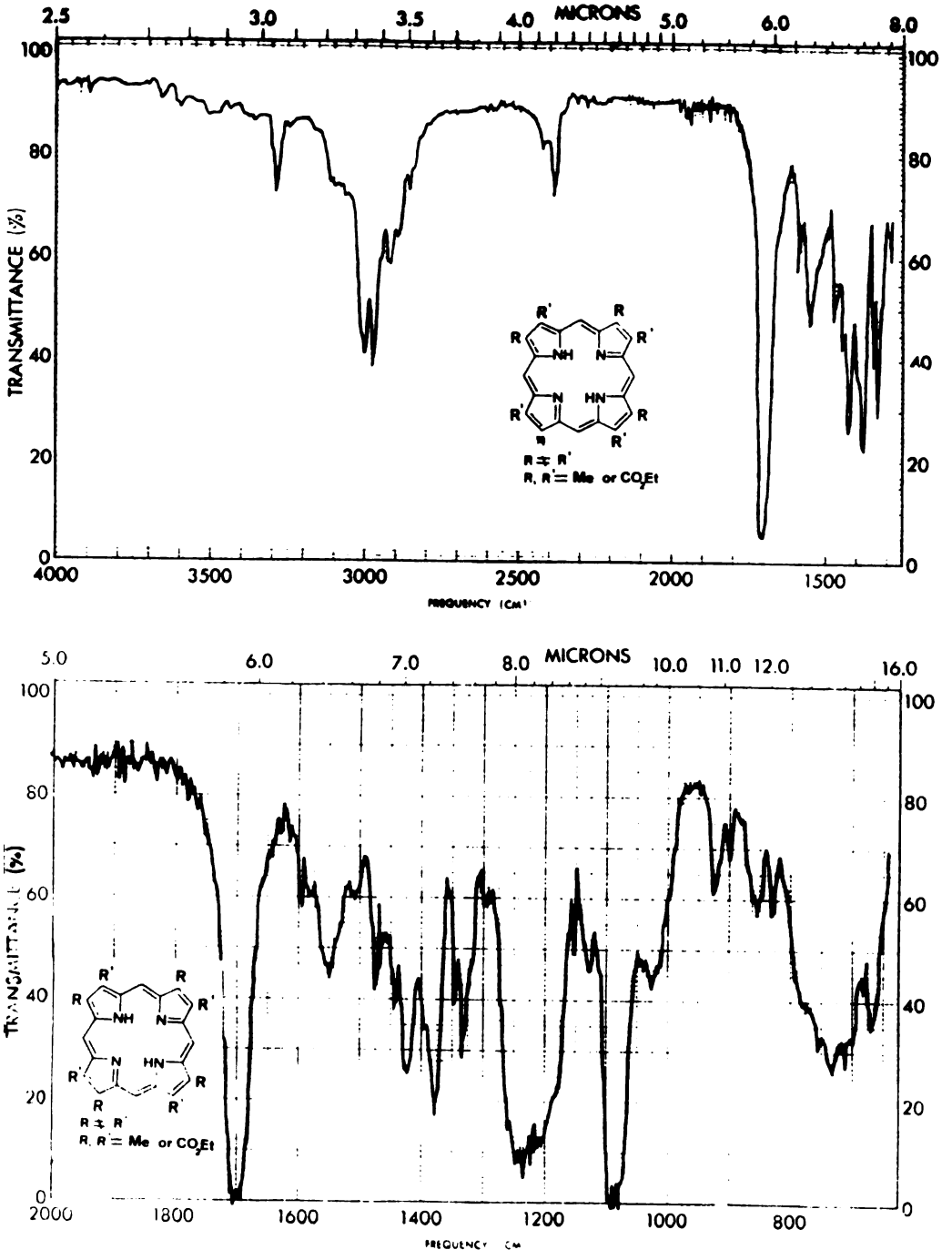


Figure 4, Infrared spectrum of tetracarbethoxy-tetramethylporphyrin (**13**).

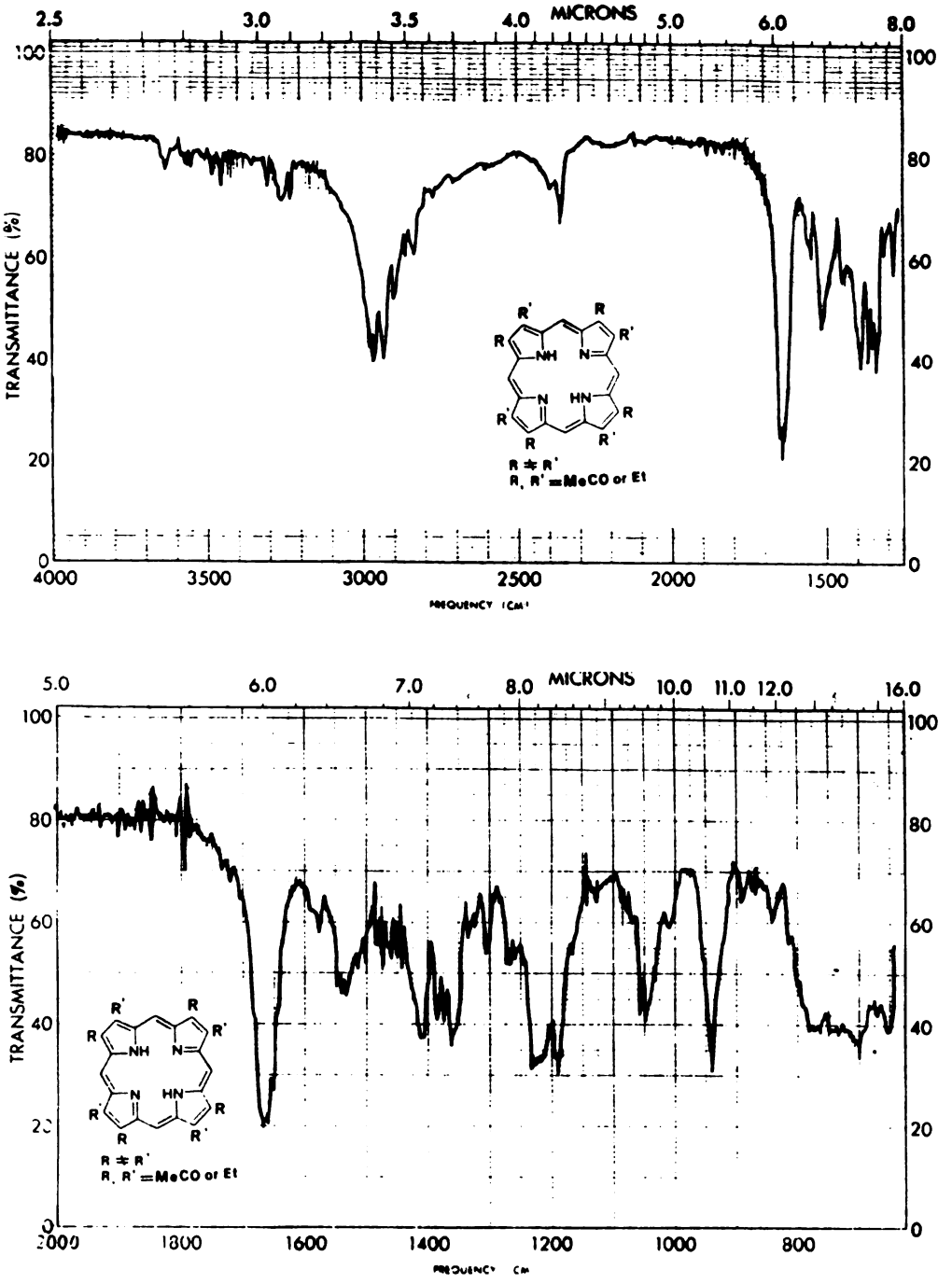


Figure 5, Infrared spectrum of tetraacetyl-tetraethylporphyrin (**14**).

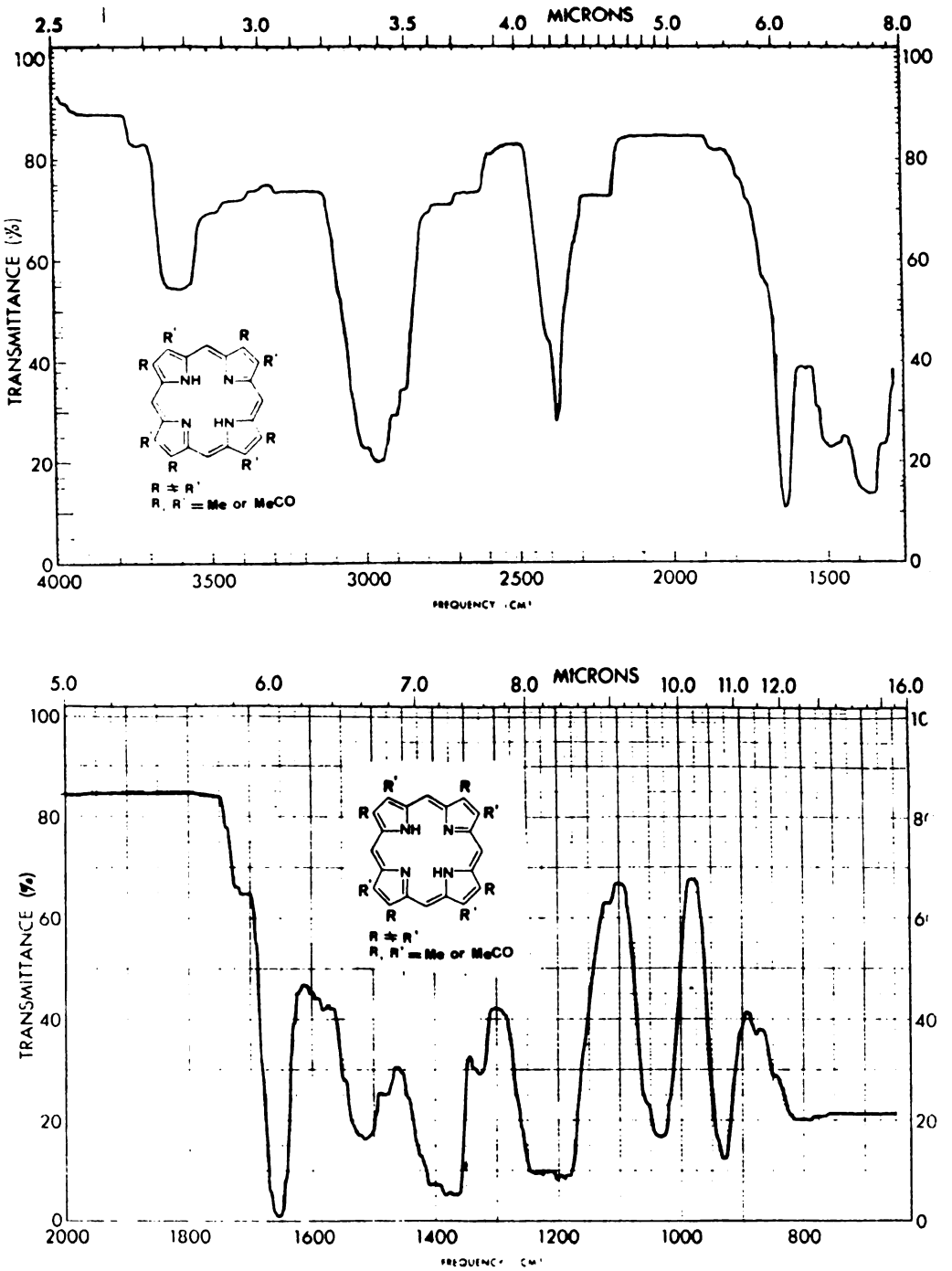


Figure 6, Infrared spectrum of tetraacetyltetramethylporphyrin (**15**).

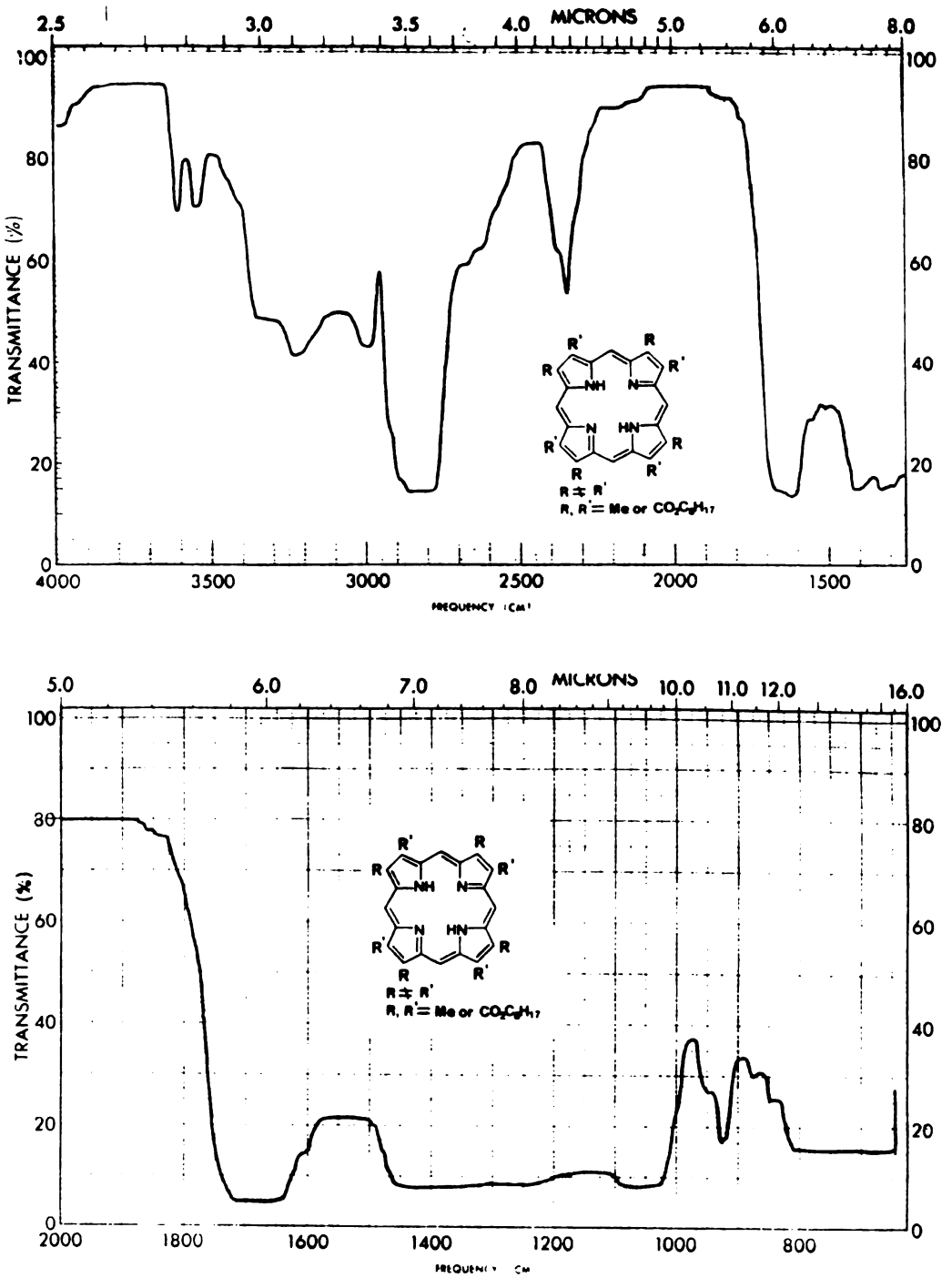


Figure 7, Infrared spectrum of tetracarboöctoxy-tetramethylporphyrin (**16**).

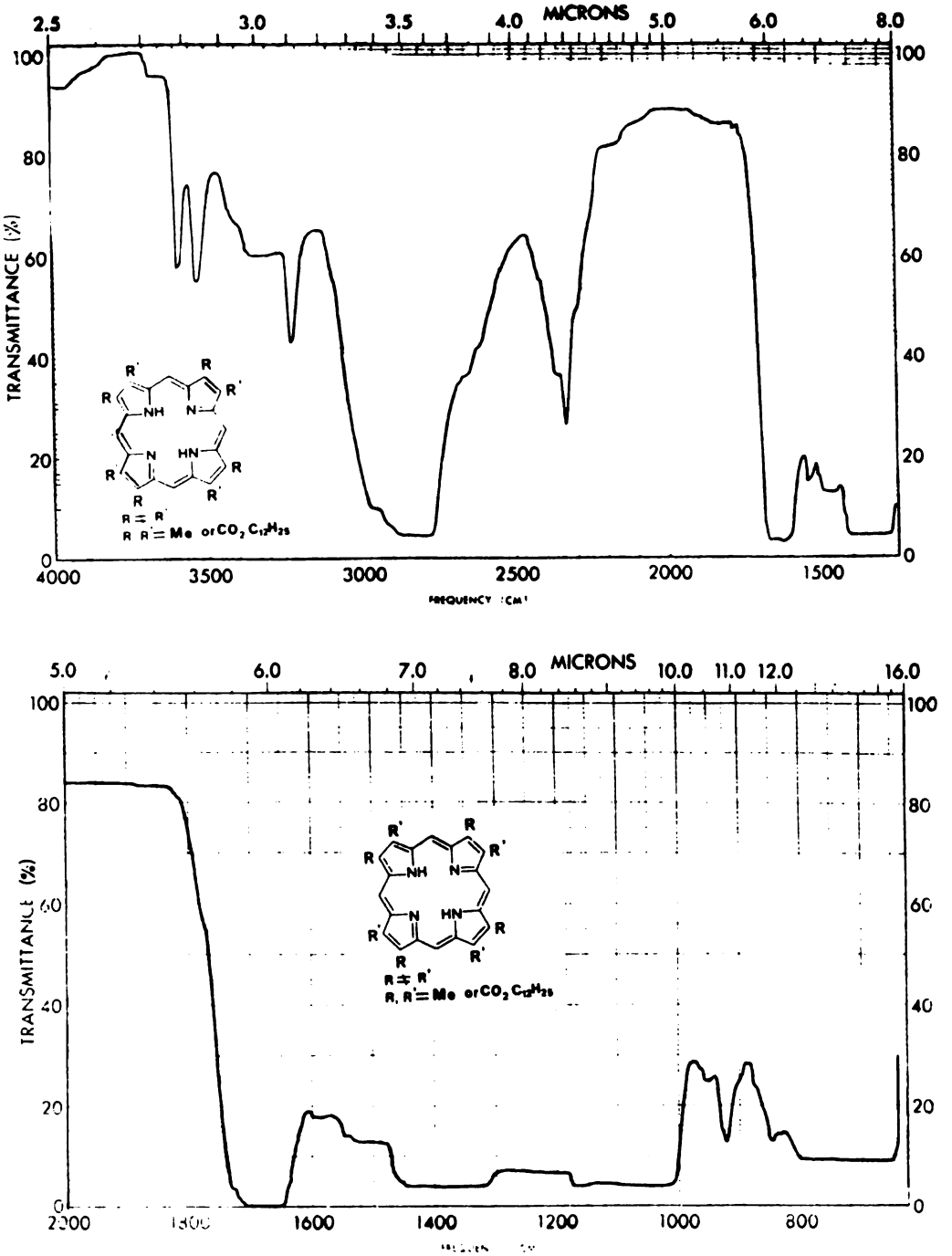


Figure 8, Infrared spectrum of tetracarbo-dodecoxytetramethylporphyrin (**36**).

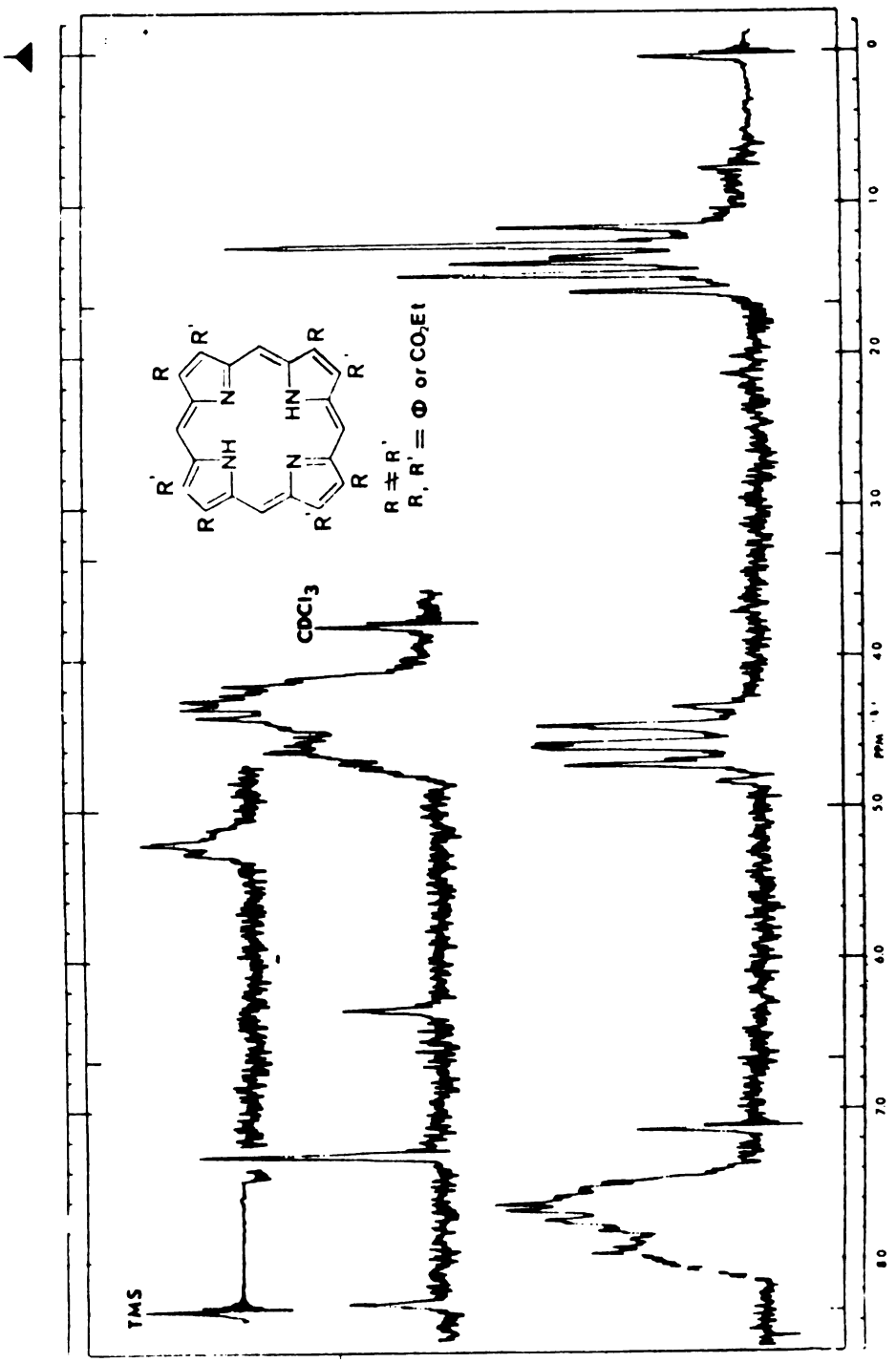


Figure 9, Nmr spectrum of tetracarbethoxytetraphenylporphyrin (**12**).

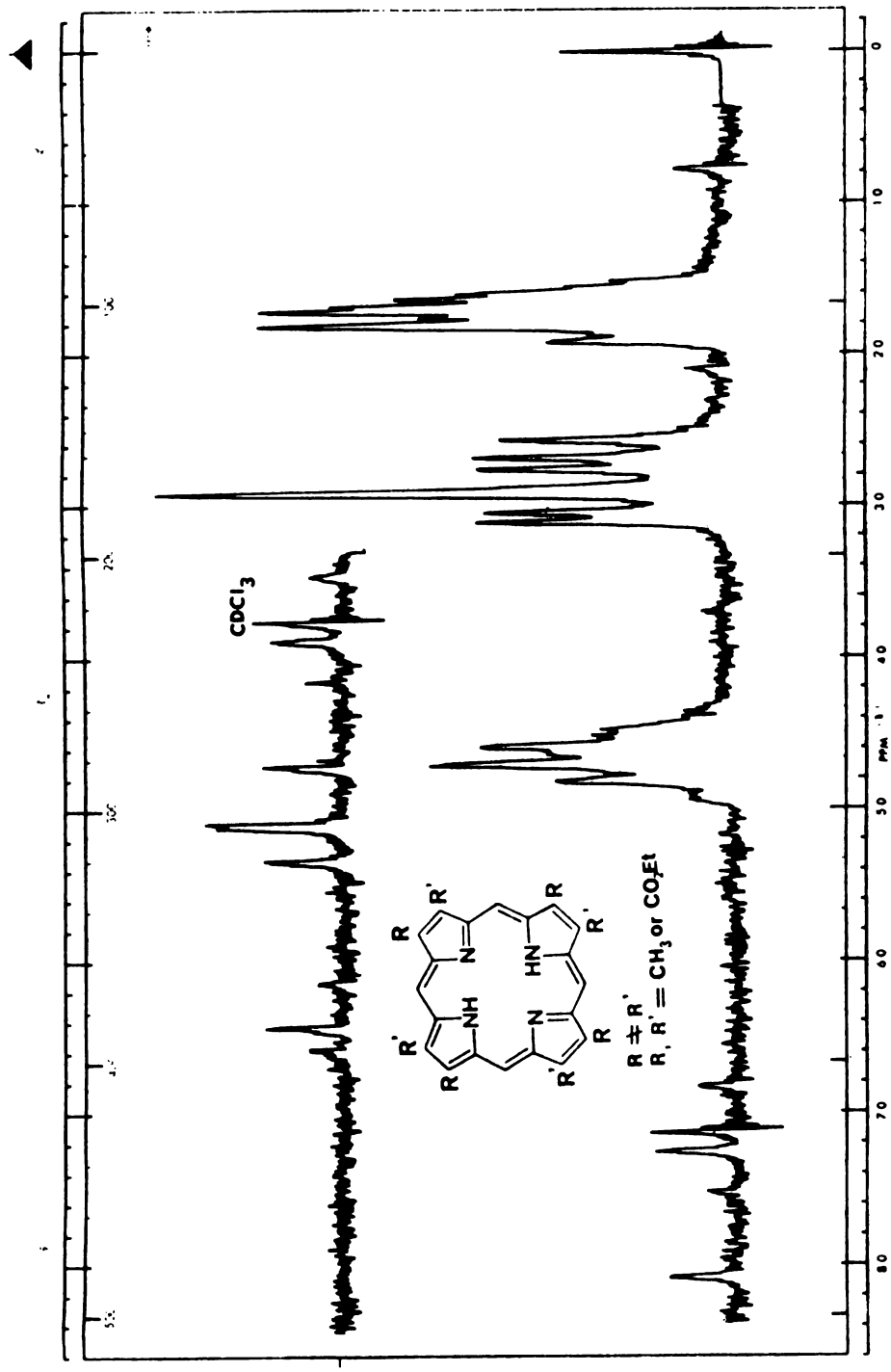


Figure 10, Nmr spectrum of tetracarbethoxytetramethylporphyrin (**13**).

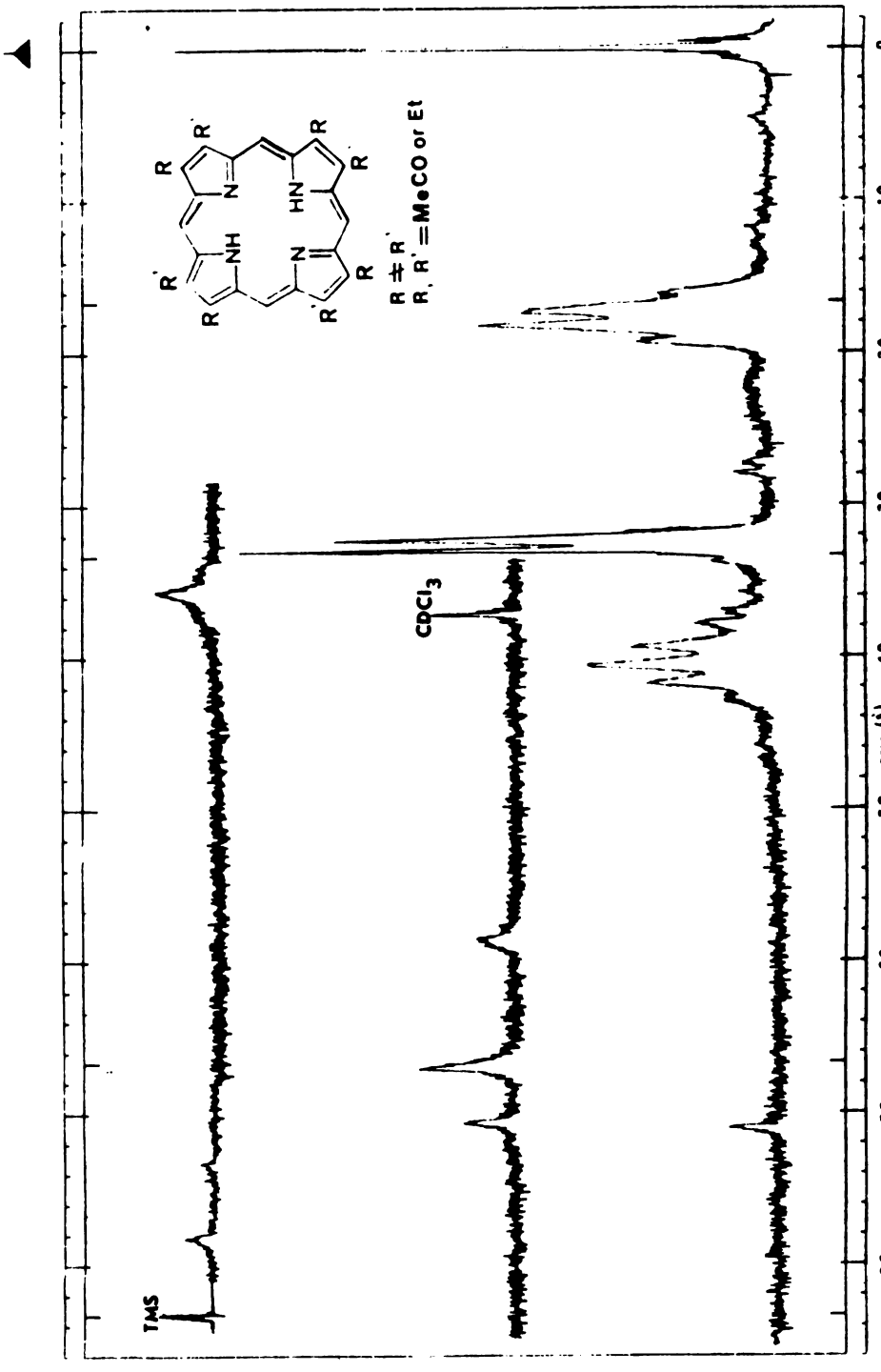


Figure 11, Nmr spectrum of tetraacetyltetraethylporphyrin (14).

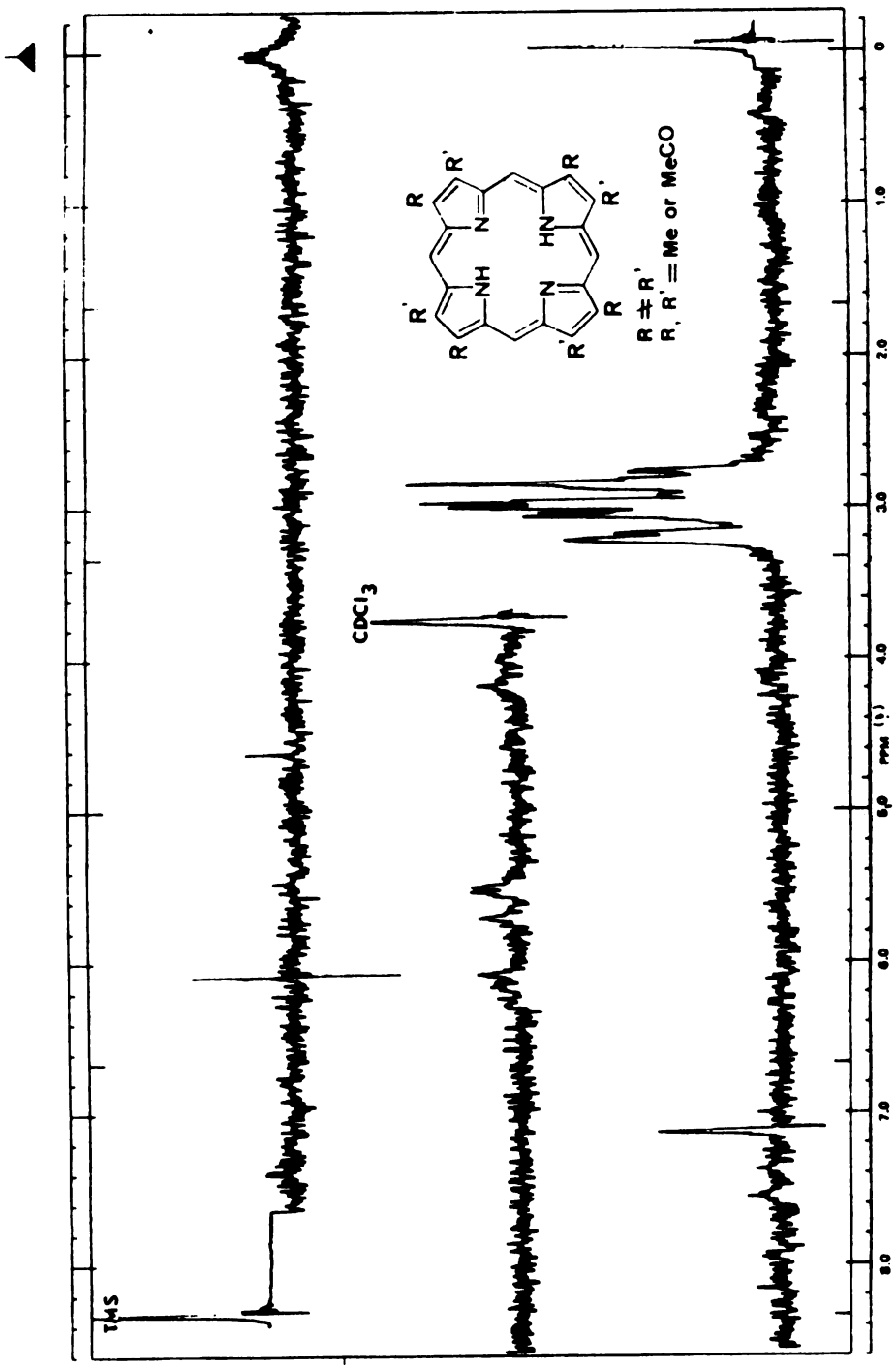


Figure 12, Nmr spectrum of tetraacetyltetramethylporphyrin (**15**).

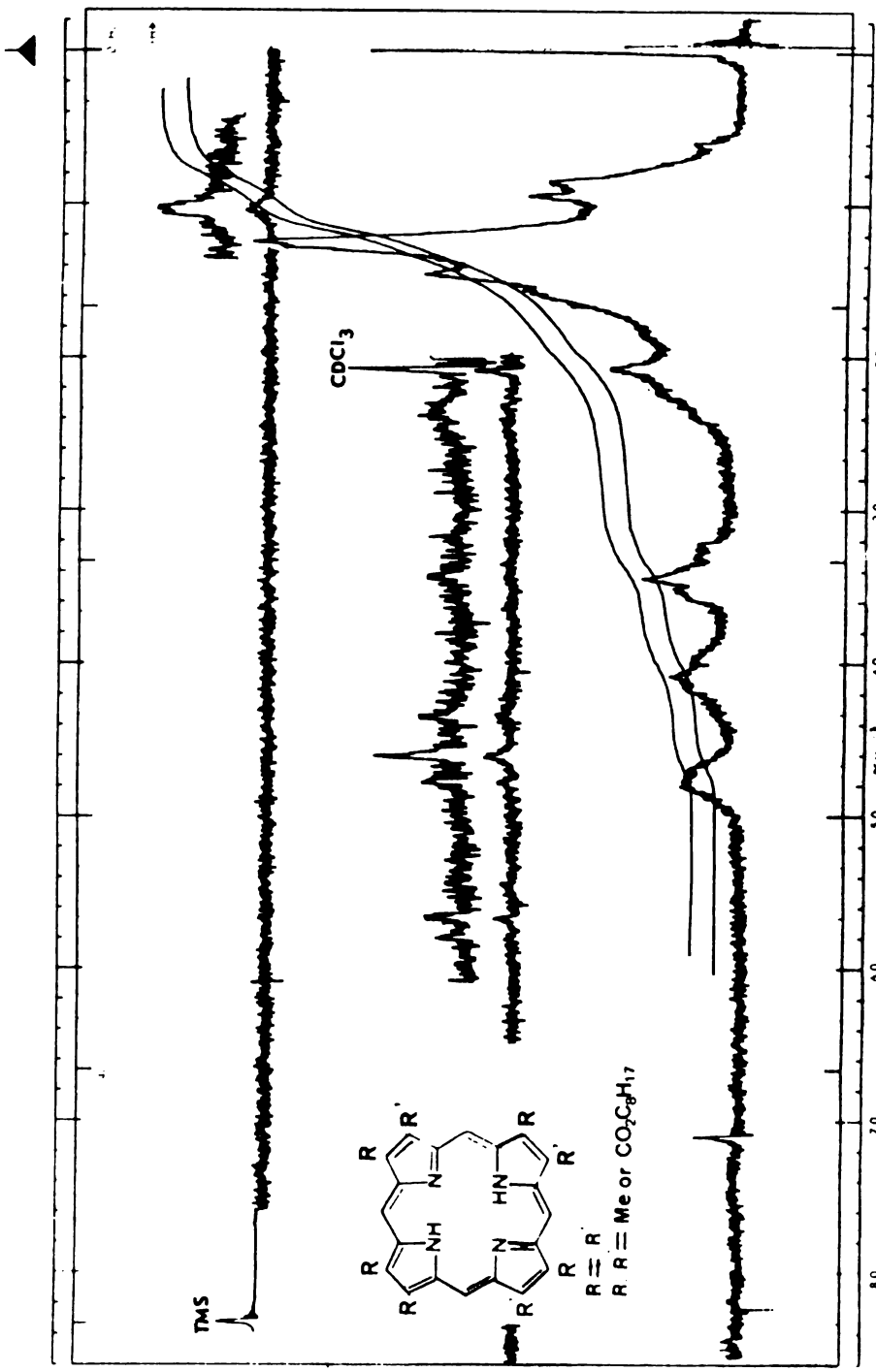


Figure 13, Nmr spectrum of tetracarboöctoxytetramethylporphyrin (16).

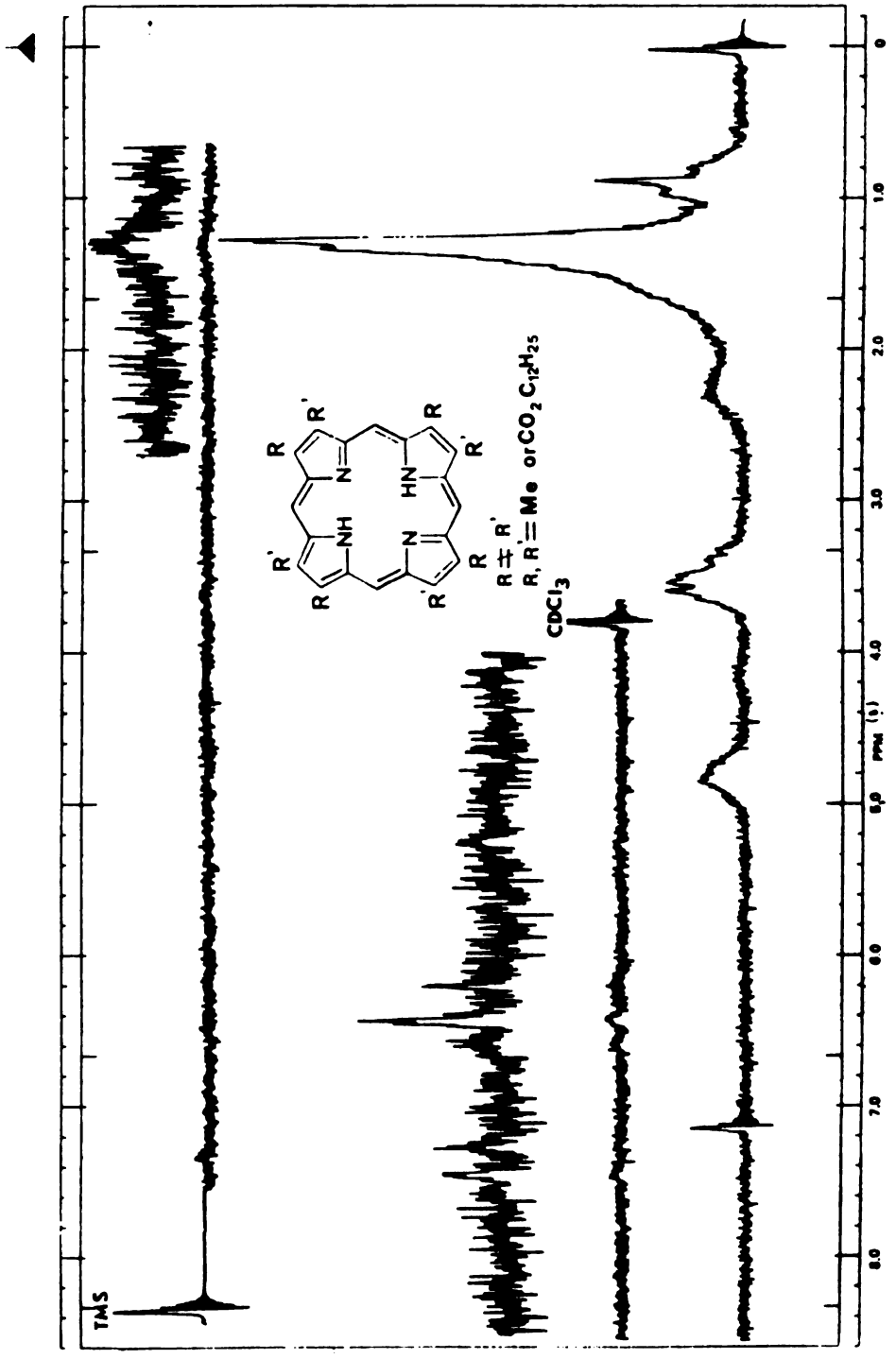


Figure 14, Nmr spectrum of tetracarbododecoxytetramethylporphyrin (**36**).

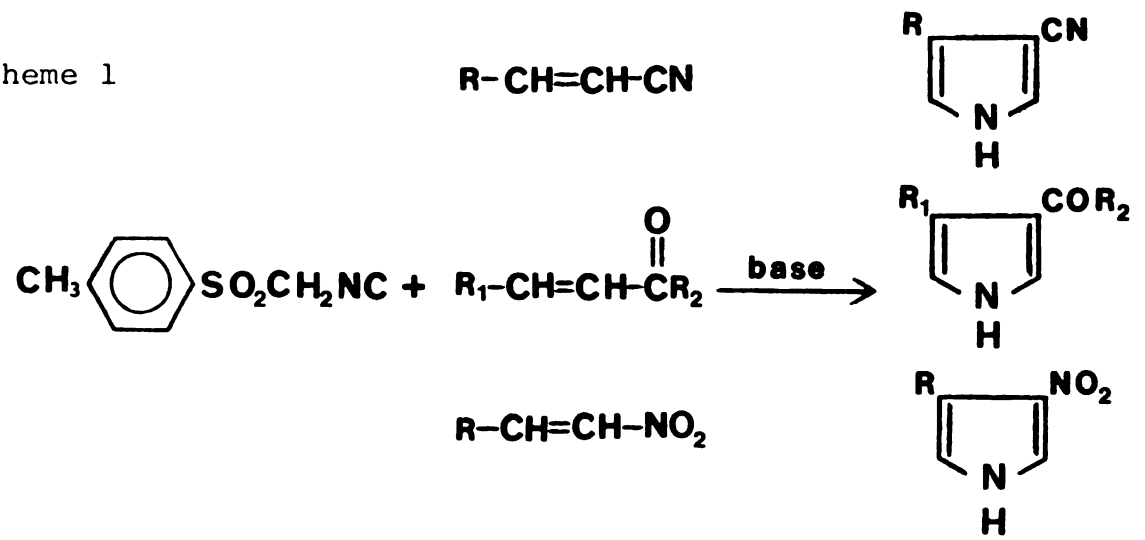
PART II

THE SYNTHESIS AND REACTIONS OF PYRROLES

INTRODUCTION

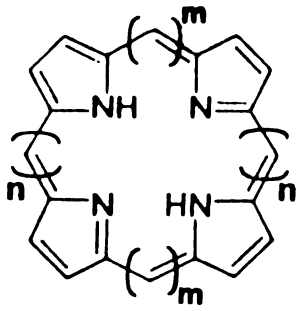
The synthesis of 3,4-disubstituted pyrroles has been known as a multi-step reaction sequence[1,35,57,58] usually involving decarboxylation at N and/or α-carbons in the final stage of the reaction. In 1972, van Leusen, Siederius and Hoogenboom[13] introduced a new synthetic approach from Michael acceptors and p-toluenesulfonyl methyl isocyanide (TosMIC), Scheme 1.

Scheme 1



In this manner eleven pyrroles were prepared according to the needs in the porphyrin synthesis (Part I) and transformation of pyrrole functional groups.

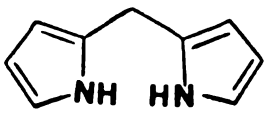
In the investigation of ring-expanded porphyrin (**43**) synthesis[31], several potentially useful dipyrrolic intermediates were synthesized:



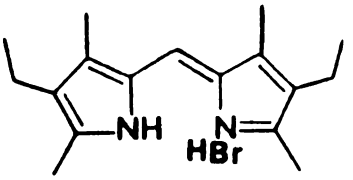
43

n,m = 2k + 1
(k can be any integer)
when k = 0
n = m = 1; a porphyrin

1) Two pyrrole units are connected by one carbon bridge to form dipyrromethane (**44**) and dipyrromethene (**45**).

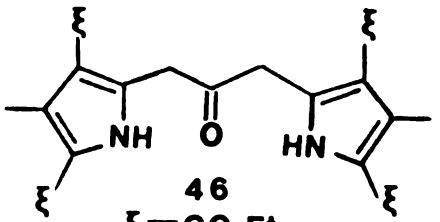


44

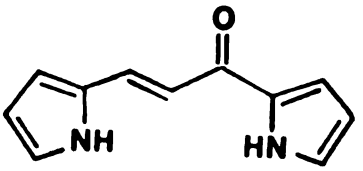


45

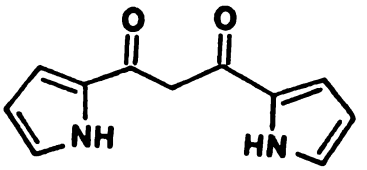
2) Two pyrrole units are connected by three carbon bridge to form dipyrropropanone (**46**), dipyrropropenone (**47**) and dipyrropropanedione (**48**).



46
ξ=CO_2Et

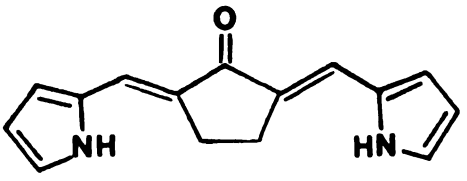


47

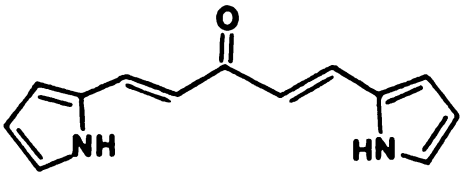


48

3) Two pyrrole units are connected by five carbon bridge to form dipyrropentadienones (**49, 50**).



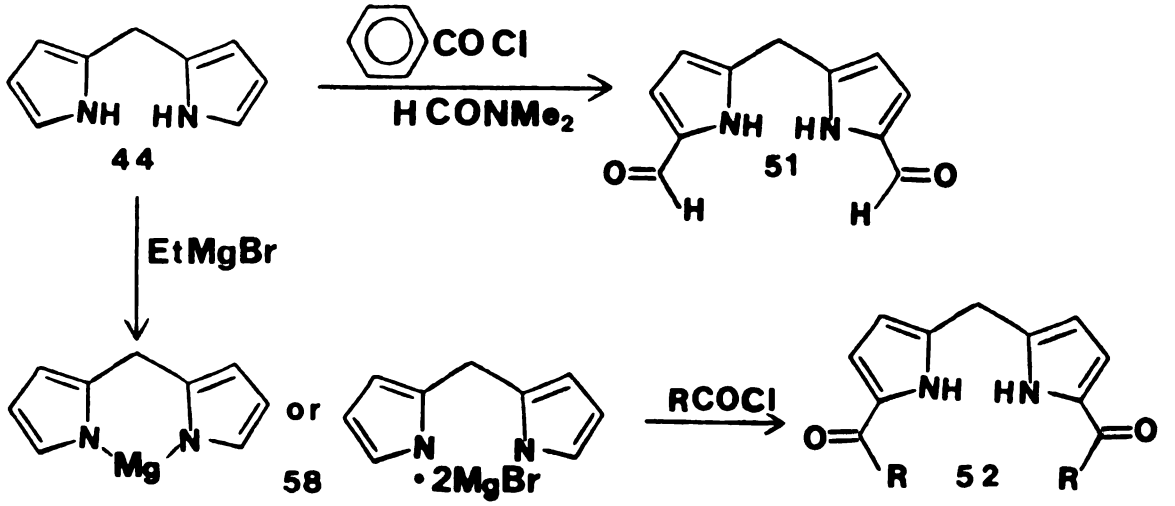
49



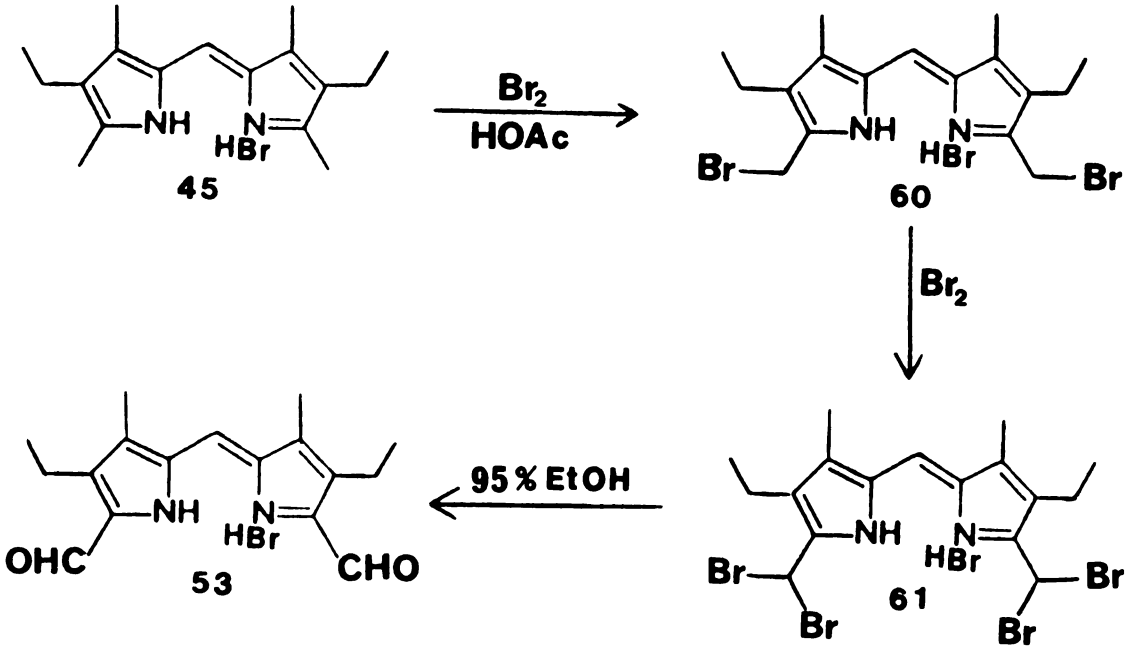
50

Carbonyl functional groups were successfully introduced into compounds **44** and **45** by the processes shown in Schemes 2 and 3 to give dipyrromethane-dialdehyde (**51**), dipyrromethane-diketone (**52**) and dipyrromethene-dialdehyde (**53**).

Scheme 2



Scheme 3



RESULTS AND DISCUSSION

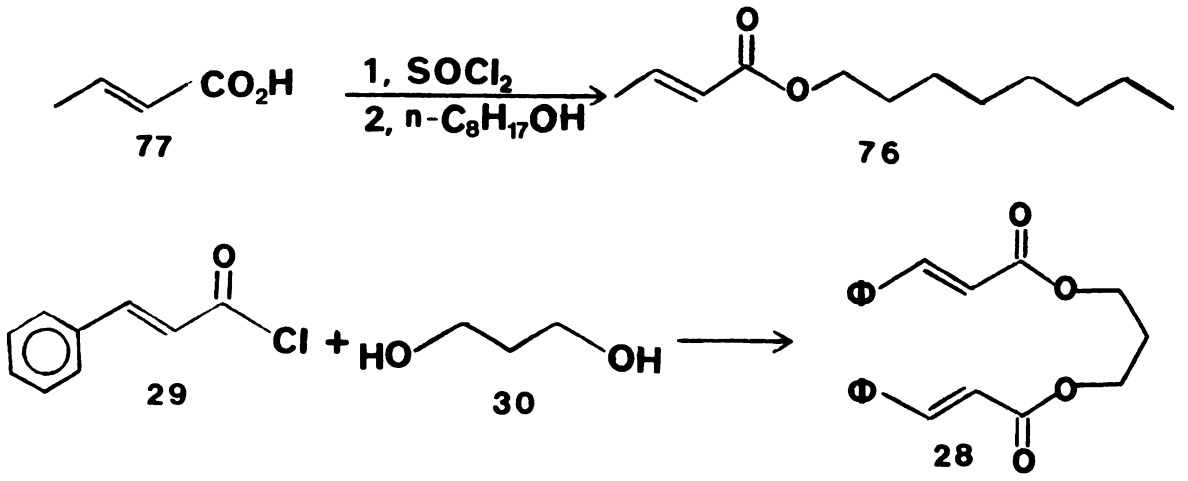
Synthesis of pyrroles

It is fortunate that a variety of α,β-unsaturated carbonyl compounds were readily available, thus the synthesis of pyrroles could be carried out rapidly. However, in special cases the preparation of starting unsaturated carbonyls are necessary such as, in the synthesis of 3-acetyl-4-ethylpyrrole (**3**), 3-hexen-2-one (**73**) was prepared by reacting propionaldehyde (**74**) with acetylmethylene triphenylphosphorane (**75**)[14] as shown in Scheme 4.

Scheme 4

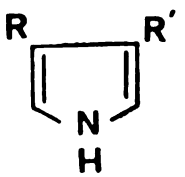
1,3-Bis-(4-phenylpyrrole-3-carboxy)-propane (**26**) and n-octyl crotonate (**76**) were prepared by esterification of acyl chlorides and alcohols as shown in Scheme 5.

Scheme 5



Various 3,4-disubstituted pyrroles were therefore synthesized by reacting TosMIC under basic conditions with α,β-unsaturated ketones, esters or nitro compounds to give, by concomitant loss of p-toluenesulfinic acid, 3-acylpyrroles, pyrrole-3-carboxylates and 3-nitropyrroles respectively, as shown in Scheme 1. The actual experimental results and the purification methods are summarized in Table 1.

Table 1,



	R	R'	Yield	Purification method
1	$CO_2C_2H_5$	Ph	60%	$MeOH/H_2O$
2	$CO_2C_2H_5$	CH_3	65%	100 /0.05 mm
3	$COCH_3$	C_2H_5	91.3%	alumina/ether
4	$COCH_3$	CH_3	84%	boiling pet. ether
5	$CO_2n\text{-}C_8H_{17}$	CH_3	91.4%	alumina/$MeCl_2$
6	$-COCH_2CH_2CH_2-$		80%	alumina/$MeCl_2$
8	COPh	COPh	71%	95% ethanol
9	NO_2	Ph	42%	$EtOH/H_2O$
10	COPh	Ph	70%	$CHCl_3/MeOH$
11	$CO_2C_2H_5$	$CO_2C_2H_5$	56%	$EtOH/H_2O$
26	2 Ph	$-CO_2(CH_2)_3CO_2-$	100%	$EtOH/H_2O$

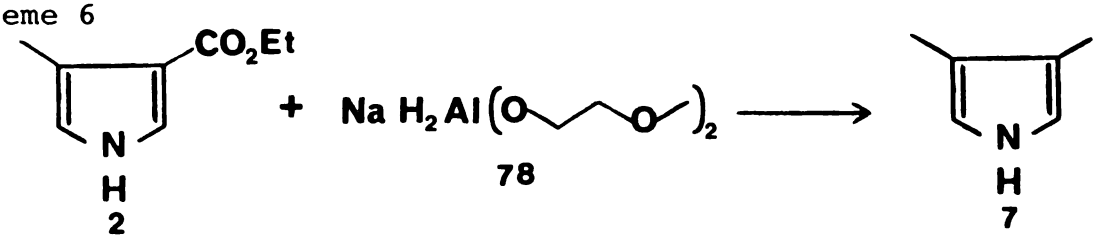
This synthesis provides a simple method for preparing a variety of 2,5-unsubstituted pyrroles which are otherwise relatively inaccessable. This unique approach took a rather convergent pathway by constructing C_2, C_5 and nitrogen atoms of the pyrrole ring in the TosMIC moiety while the vinylic carbon atoms of the Michael acceptors become C_3 and C_4 in the pyrrole ring formation.

Reactions of pyrroles

1) Transformation of functional groups:

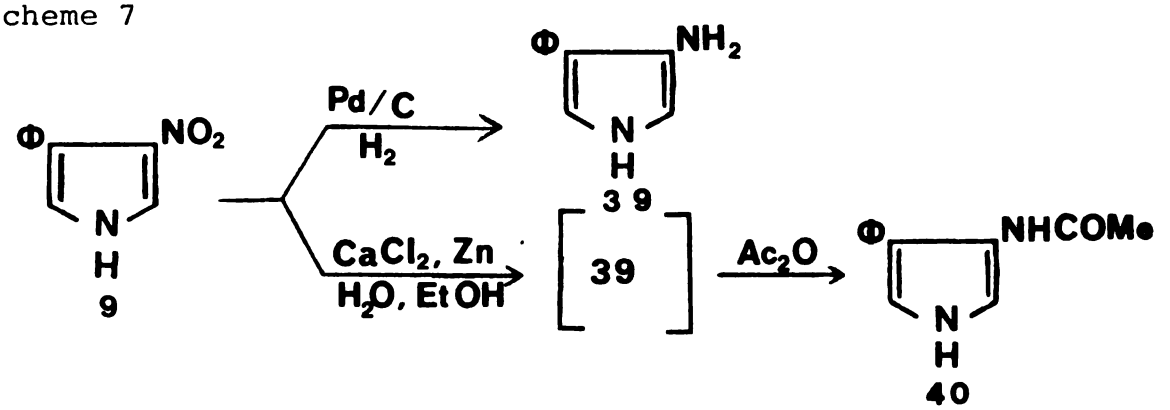
When 3-carbethoxy-4-methylpyrrole (**2**) was treated with sodium dihydro-bis-(2-methoxyethoxy)-aluminate (**78**) in benzene, moderate (44%) yield of 3,4-dimethylpyrrole (**7**) was obtained[15] (Scheme 6). Several other methods[43,44] all involving a multiple step sequence suffered from low overall yields.

Scheme 6



The nitro group of 3-nitro-4-phenylpyrrole (**9**) was converted to amino and acetylamino groups upon hydrogenation and acylation[25] as shown in Scheme 7.

Scheme 7



3-Amino-4-phenylpyrrole (**39**) is very air-sensitive (decomposition took place in 10 minutes) and should be protected by acylation immediately to form 3-acetylamino-4-phenylpyrrole (**40**).

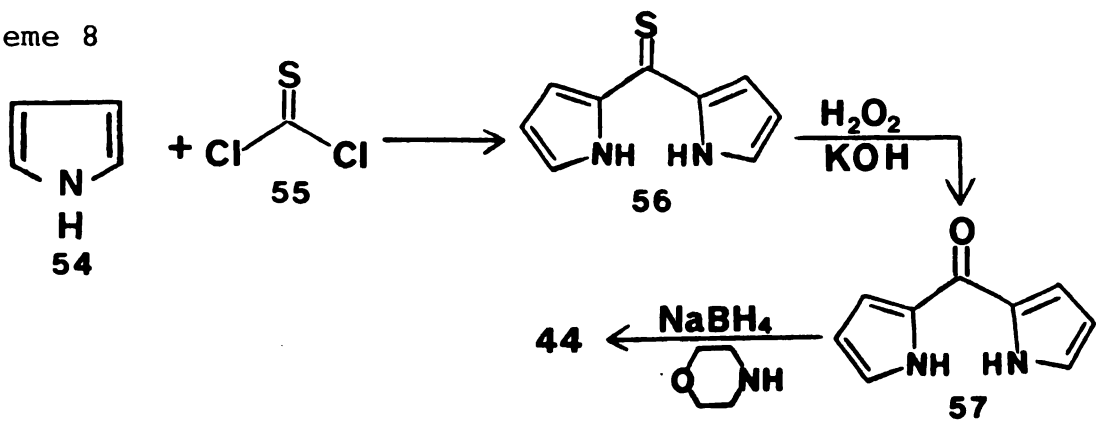
2) Preparation and derivatization of dipyrrolic intermediates:

Much of the synthetic effort in this part of research was directed toward the preparation of dipyrrolic intermediates **44-53** and their derivatives. They are divided into three catagories.

(i) Single carbon bridge:

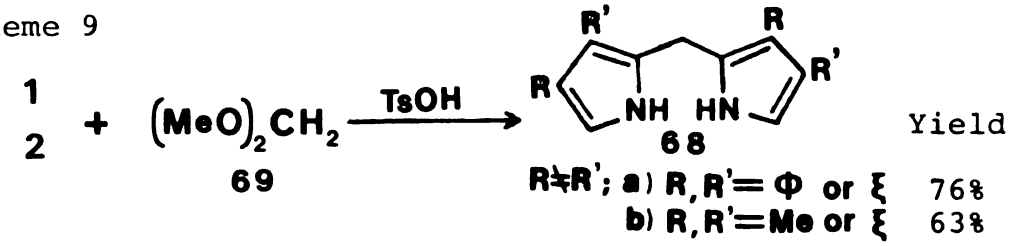
Dipyrromethane (**44**) was prepared according to the procedure of Clezy[32] (Scheme 8). The bridging carbon was introduced by condensing pyrrole (**54**) with thiophosgene (**55**) to form 2,2'-dipyrrothione (**56**) which upon treatment with hydrogen peroxide in a basic ethanolic solution was converted to 2,2'-dipyrroketone (**57**). Reduction of **57** with sodium borohydride afforded dipyrromethane (**44**)[33] in almost quantitative yield.

Scheme 8



In an attempt to differentiate the reactivities between the two α-positions of 3,4-disubstituted pyrroles, **1** and **2** were reacted with dimethoxymethane (**69**) and a catalytic amount of toluenesulfonic acid in methanol, Scheme 9.

Scheme 9



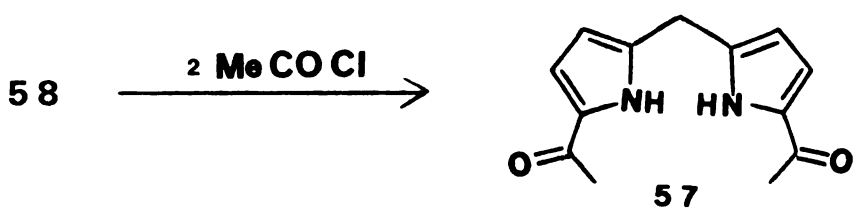
Yield

Good yields of dipyrromethanes (**68a**and **68b**) were obtained, but their nmr spectra (in Appendix) showed that the products were mixtures. Therefore, the two α-positions showed no preference toward electrophiles under these reaction conditions. When pyrrole (**54**) was used, only a 5% yield of **44** was obtained.

Conversion of **44** to 5,5'-diformyl-2,2'-dipyrromethane (**51**)[34] was done under Vilsmeier-Haack formylation condition, i.e., benzoyl chloride-dimethylformamide, as shown in Scheme 2.

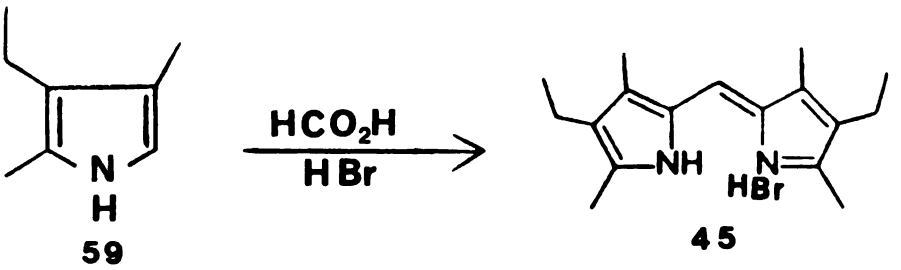
Pyrrole magnesium halides have been frequently used as intermediates in the synthesis of substituted pyrroles[35], therefore the potential is there to make the same use of **44**. Scheme 10 illustrates that 5,5'-diacetyl-2,2'-dipyrromethane (**57**) was prepared in 35-40% yield by reacting two moles of acetyl chloride with one mole of 2,2'-dipyrromethane magnesium salt (**58**). The salt **58** was first prepared from one mole of **44** and two moles of ethyl magnesium bromide (**59**).

Scheme 10



Another way to link two pyrroles together is to unite them with a -CH- to form dipyrromethene such as 3,3'5,5'-tetramethyl-4,4'-diethyl-2,2'-dipyrromethene-HBr (**45**)[36] from 3-ethyl-2,4-dimethylpyrrole (kryptopyrrole) (**59**), Scheme 11.

Scheme 11



59 **45**

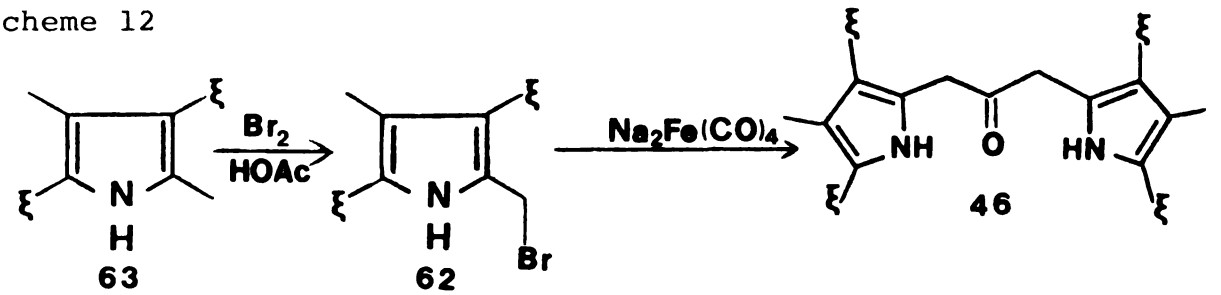
Successful monobromination of 5- and 5'-methyl groups with stoichimetric amount of bromine in acetic acid was reported by Fischer[37] in 1927. Upon repeating his procedure, the yield was found to be very low. However, a simplier procedure was found to give better than 85% yield by adding bromine dropwise to a heated acetic acid solution of **45** until the red 5,5'-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**60**) precipitated out of solution. The nmr spectrum of this precipitate showed no contamination of di- or multi-bromination. Further bromination was carried out in liquid bromine according to the procedure of MacDonald[38] and tetrabrominated product, 5,5'-di-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**61**), was converted to 5,5'-diformyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**53**) by stirring **61** in 95% ethanol overnight (Scheme 3 on page 49).

(ii) Three carbon bridge:

The first route of bringing two pyrrole molecules

together with a three carbon bridge is shown in Scheme 12. 2-Bromomethyl-4-methyl-3,5-dicarbethoxypyrrole (**62**)[39] was first prepared by bromination of 2,4-dimethyl-3,5-dicarbethoxypyrrole (Knorr's pyrrole) (**63**) and then converted to 1,3-bis-(3,5-dicarbethoxy-4-methylpyrr-2-yl)-propan-2-one (**46**) upon carbonylation with disodium tetracarbonylferrate[40] (Collman's reagent).

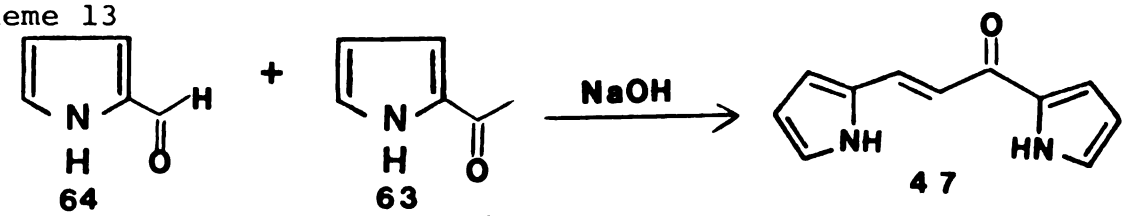
Scheme 12



63 62 46

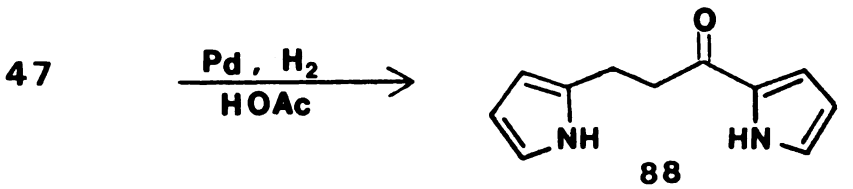
The second method was to condense 1-acetylpyrrole (**63**) and 1-formylpyrrole (**64**) to give 1,3-bis-(2-pyrryl)-1-propen-3-one (**47**)[41], Scheme 13.

Scheme 13



64 63 47

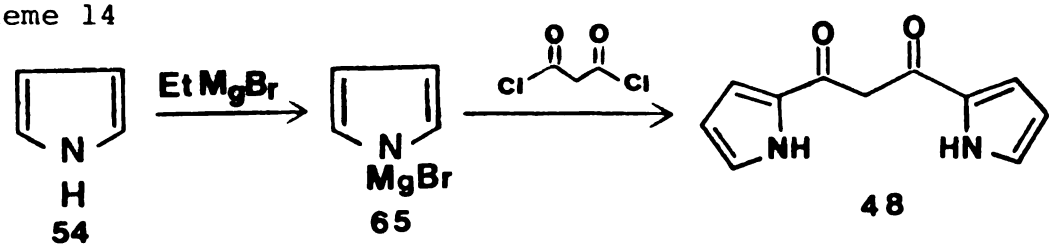
Catalytic hydrogenation[42] with palladium on charcoal in a Paar hydrogenator brought about the reduction of **47** to 1,3-bis-(2-pyrryl)-propan-3-one (**88**).



88

The third method (Scheme 14) was first making the pyrrole magnesium bromide (**65**) then reacting it with malonyl dichloride (**66**) to yield 1,3-bis-(pyrr-2-yl)-1,3-propane-dione (**48**)[21].

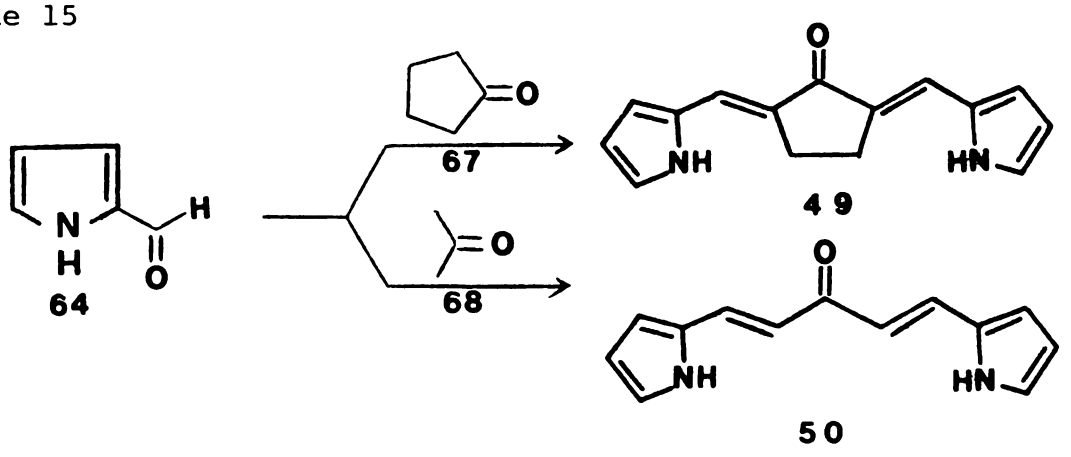
Scheme 14



(iii) Five carbon bridge:

Both 1,3-di-pyrr-2-ylmethylene-2-cyclopentanone (**49**) and 1,5-di-2-pyrryl-1,4-pentadien-3-one (**50**) were synthesized by reacting **64** under Aldol condensation conditions with cyclopentanone (**67**) and acetone (**68**) respectively, Scheme 15.

Scheme 15



EXPERIMENTAL

General

Instruments used are described in Part I.

p-Toluenesulfonyl methyl isocyanide (**27**)

a light brown solid, mp. 111-114°; prepared according to the procedure of van Leusen, Tetrahedron Letters, 5337 (1972).

3-Hexen-2-one (**73**)

Acetylmethylene triphenylphosphorane (**75**) was prepared according to the procedure of Ramirez and Dershowitz[23].

A solution of 31.6 g (0.10 mol) of acetylmethylene triphenylphosphorane (**75**) and 11.0 g (0.19 mol) of propionaldehyde (**74**) in 100 ml of methylene chloride was stirred and refluxed for six hours then allowed to stand overnight under nitrogen. The resulting mixture was condensed to 10-20 ml on a rotatory evaporator and diluted with 500 ml of pentane to precipitate triphenylphosphine oxide. After removal of the precipitate by filtration, the filtrate was again concentrated and distilled under water aspirator pressure. The fraction boiling at 55-56° at 30 mm (lit.[29] 64-70° (57 mm)) was collected as a colorless liquid to give 6.8 g (70%) of **73**.

Compound **73** was also identified by nmr.

n-Octyl crotonate (**76**)

A mixture of 86 g (1 mol) of crotonic acid (**77**) and 119 g (72 ml, 1 mol) of thionyl chloride was placed in a two-neck round bottom flask (500 ml) which was fitted with a condensor and a addition funnel. The mixture was heated and stirred on a steam bath until no further evolution of gas was noted (~1.5 hours) and then allowed to cool, and 130 g (1 mol) of n-octanol was added through the addition funnel. The mixture was again heated on the steam bath until the evolution of hydrogen chloride gas ceased (2 hours).

This reaction mixture after cooling to room temperature was diluted with 200 ml of ether and washed with 10% sodium carbonate solution (3x100 ml) then water (4x100 ml). The ether layer was condensed on a rotatory evaporator and stirred overnight with 20 g of anhydrous calcium chloride and 3 g of charcoal. Filtration of the solids gave 191 g (96%) of **76** as a light brown transparent oil.

Compound **76** was identified by nmr.

1,3-Dicinnamoyl propane (**28**)

A mixture of 16.7 g (0.1 mol) of cinnamyl chloride (**27**) and 3.4 g (>0.05 mol) of 1,3-propanediol was heated to 130-140^{o} under nitrogen until no more hydrochloric gas evolved. Upon cooling the solidified solution was crushed and washed with water and 5% sodium carbonate solution, then chromatographed on a neutral alumina column with benzene to give

14.2 g (85%) of white crystalline diester **26**; mp. 79.5-81°; nmr ($CDCl_3$), δ2.07 (p, 2H, $-OCH_2\underline{C}H_2CH_2O-$), 4.27 (t, 4H, $-OC\underline{H}_2CH_2C\underline{H}_2O-$), 6.13 to 7.67 (ABq, J=16Hz, 4H, vinylic H) and 7.25 (m, 10H, aromatic H); mass (m/e): 336 (parent).

3-Carbethoxy-4-phenylpyrrole (**1**), 3-carbethoxy-4-methylpyrrole (**2**), 3-acetyl-4-ethylpyrrole (**3**), 3-acetyl-4-methylpyrrole (**4**), 3-carboöctoxy-4-methylpyrrole (**5**), 3,4-trimethylenecarbonylpyrrole (**6**), 3,4-dibenzoylpyrrole (**8**), 3-nitro-4-phenylpyrrole (**9**), 3-benzoyl-4-phenylpyrrole (**10**), 3,4-dicarbethoxypyrrole (**11**) and 1,3-bis-(4-phenylpyrrole-3-carboxy)-propane (**26**)

General procedure:

A solution of 5 mmoles of p-toluenesulfonyl methyl isocyanide (TosMIC) and 5 mmoles of α,β-unsaturated carbonyl (or nitro compound) in 25 ml of ether-dimethylsulfoxide (2:1) was added dropwise to a stirred suspension of ca. 1.2 equivalents of sodium hydride in ether (10 ml). The mixture was diluted with water after 15-30 minute further stirring and extracted with ether (3x50 ml). Purification methods and yields are given in Table 1 on page 51.Spectral characteristics for **1**, **2**, **3**, **4**, **5**, **6**, **8**, **9**, **10**, **11** and **26** are given below:

3-Carbethoxy-4-phenylpyrrole (**1**)

mp. 121-123°; ir ($CHCl_3$), 3460 and 3280 cm^{-1} (N-H), 1700 cm^{-1} (C=O), 1525 cm^{-1} (C=C) and 1280 cm^{-1} (C-O); nmr ($CDCl_3$) δ1.23 (t, 3H, $-OCH_2\underline{C}H_3$), 4.15 (q, 2H, $-O\underline{C}H_2CH_3$), 6.50 (m, 1H, pyrrolic proton), 7.25 (m, 6H, phenyl and pyrrolic

protons) and 8.83 (brd s, 1H, N-H); mass (m/e): 215 (parent).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51
Found : C, 72.58; H, 6.07; N, 6.53

3-Carbethoxy-4-methylpyrrole (**2**)

mp. 67-71° (lit.[28] 73°); ir ($CHCl_3$), 3450 and 3290 cm^{-1} (N-H), 1650 cm^{-1} (C=O), 1510 cm^{-1} (C=C) and 1270 cm^{-1} (C-O); nmr ($CDCl_3$), δ1.30 (t, 3H, $-OCH_2C\underline{H}_3$), 2.26 (s, 3H, $-C\underline{H}_3$), 4.18 (q, 2H, $-OC\underline{H}_2CH_3$), 6.38 (m, 1H, pyrrolic proton) and 7.20 (m, 1H, pyrrolic proton).

3-Acetyl-4-ethylpyrrole (**3**)

mp. 60.5-62.5°; ir ($CHCl_3$), 3450 and 3290 cm^{-1} (N-H), 1650 cm^{-1} (C=O) and 1510 cm^{-1} (C=C); nmr ($CDCl_3$), δ1.18 (t, 3H, $-CH_2C\underline{H}_3$), 2.38 (s, 3H, $-COC\underline{H}_3$), 2.75 (q, 2H, $-C\underline{H}_2CH_3$), 6.47 (m, 1H, pyrrolic proton) and 7.27 (m, 1H, pyrrolic proton); mass (m/e) : 137 (parent).

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21
Found : C, 70.08; H, 8.12; N, 10.16

3-Acetyl-4-methylpyrrole (**4**)

mp. 113-114° (lit.[13] 112-114°); nmr ($CDCl_3$), δ2.33 (s, 3H, $-C\underline{H}_3$), 2.42 (s, 3H, $-COC\underline{H}_3$), 6.46 (m, 1H, pyrrolic proton), 7.25 (m, 1H, pyrrolic proton) and 9.58 (brd s, 1H, N-H).

3-Carboöctoxy-4-methylpyrrole (**5**)

a yellow oil freezes at 0-5°; ir ($CHCl_3$), 3455 and 3300 cm^{-1} (N-H), 2900 and 2840 cm^{-1} (C-H), 1680 cm^{-1} (C=O), 1540 cm^{-1} (C=C), 1250 and 1145 cm^{-1} (C-O); nmr ($CDCl_3$), δ0.7-1.8 (3 brd peaks, 15H, $-OCH_2C_7\underline{H}_{15}$), 2.25 (s, 3H, $-C\underline{H}_3$), 4.15 (t,

2H, $-OC\underline{H}_2C_7H_{15}$), 6.40 (m, 1H, pyrrolic proton) and 7.23 (m, 1H, pyrrolic proton); mass (m/e) : 237 (parent).

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90
Found : C, 70.12; H, 9.90; N, 5.32

3,4-Trimethylenecarbonylpyrrole (**6**)

a yellow oil freezes around -10° and turns brown very rapidly at room temperature; its nmr ($CDCl_3$) was taken immediately and showed, δ1.83-2.83 (m, 6H, $-(C\underline{H}_2)_3CO-$), 6.43 (m, 1H, pyrrolic proton), 7.20 (m, 1H, pyrrolic proton) and 9.80 (brd s, 1H, N-H); mass (m/e) : 135 (parent).

3,4-Dibenzoylpyrrole (**8**)

mp. 221-223° (lit.[13] 221-222°); nmr (D_6MSO), δ7.20-7.72 (m, aromatic and pyrrolic protons).

3-Nitro-4-phenylpyrrole (**9**)

mp. 152-153°; nmr (D_6MSO), δ6.62 (m, 1H, pyrrolic H), 7.27 (brd s, 5H, phenyl H), 7.60 (m, 1H, pyrrolic H) and 11.27 (brd s, 1H, N-H); mass (m/e) : 188 (parent).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89
Found : C, 64.83; H, 4.38; N, 14.49

3-Benzoyl-4-phenylpyrrole (**10**)

mp. 228-231° (lit.[13] 229-231 (dec.)); nmr (D_6MSO), δ6.90 (m, 1H, pyrrolic proton), 7.00-7.50 (m, 10H, aromatic protons), 7.73 (m, 1H, pyrrolic proton) and 11.40 (brd s, 1H, N-H).

3,4-Dicarbethoxypyrrole (**11**)

mp. 153-155° (lit.[26] 153-155°); ir ($CHCl_3$), 3450 and

3300 cm^{-1} (N-H), 1725 cm^{-1} (C=O), 1525 cm^{-1} (C=C), 1280 and 1150 cm^{-1} (C-O); nmr ($CDCl_3$), δ1.32 (t, 6H, $-OCH_2\underline{CH_3}$), 4.23 (q, 4H, $-OC\underline{H_2}CH_3$) and 7.27 (d, 2H, pyrrolic protons).

1,3-Bis-(4-phenylpyrrole-3-carboxy)-propane (**26**)

mp. 154-156°; nmr (D_6MSO), δ1.88 (p, 2H, $-OCH_2C\underline{H_2}CH_2O-$), 4.08 (t, 4H, $-OC\underline{H_2}CH_2C\underline{H_2}O-$), 6.62 (m, 2H, pyrrolic protons), 7.27 (m, 12H, aromatic and pyrrolic protons) and 10.59 (brd s, 2H, N-H); mass (m/e) : 414 (parent).

Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76
Found : C, 73.36; H, 5.57; N, 6.39

3,4-Dimethylpyrrole (**7**)

A solution of 5 g (34 mmol) of 3-carbethoxy-4-methylpyrrole (**2**) in 50 ml of benzene was added dropwise to a benzene solution of 23 g (~80 mmol) of sodium dihydro-bis-(2-methoxyethoxy) aluminate (**78**) at 25° under an atomsphere of nitrogen. After the reaction mixture was stirred for 18 hours, 100 ml of water was added. The benzene layer was separated, washed with 2x200 ml of water and dried over anhydrous sodium sulfate. The solvent was removed and the residual oil distilled to give 1.4 g (44%) of **7**[24]; bp. 69-70° (10 torr); nmr ($CDCl_3$), δ2.00 (s, 6H, $-C\underline{H_3}$) and 6.38 (d, 2H, pyrrolic protons).

3-Amino-4-phenylpyrrole (**39**)

A mixture of 188 mg (1 mmol) of 3-nitro-4-phenylpyrrole (**9**) and one-third of a spatula of 10% palladium on charcoal

in 15 ml of 95% ethanol was shaken under 45 psi of hydrogen for 10 minutes. The catalysts were filtered and the filtrate was evaporated under reduced pressure. Since **39** is very air-sensitive, its nmr was taken immediately without further purification; nmr (CCl_4), δ2.87 (brd s, 2H, amino-H), 6.47 (m, 1H, pyrrolic H), 6.82 (m, 1H, pyrrolic H), 7.55 (m, 5H, phenyl H) and 8.10 (brd s, 1H, N-H).

3-Acetylamino-4-phenylpyrrole (**40**)

A mixture of 188 mg (1 mmol) of **9**, 0.1 g of calcium chloride and 3.0 g of zinc dust in 16.4 ml of 95% ethanol and 3.6 ml of water was stirred and refluxed for two hours under nitrogen. The reaction mixture was condensed to 5 ml by distillation under nitrogen. A solution of 102 mg (1 mmol) of acetic anhydride in 5 ml of acetic acid was added and further stirred for 30 minutes. The reaction mixture was then decanted into 50 ml of ether and washed with 5% sodium carbonate solution three times and water twice. Removal of solvent gave 150 mg (75%) of **40** as a grey powder. Its nmr ($CDCl_3$) showed: δ1.93 (s, 3H, $-COCH_3$), 3.92 (s, 1H, amide H), 6.55 (m, 1H, pyrrolic H), 7.10 (brd s, 6H, phenyl and pyrrolic H) and 11.35 (brd s, 1H, N-H).

2,2'-Dipyrromethane (**44**)

The procedure of Clezy[32] was used and the product was purified by crystallization from petroleum ether, mp. 72-73°, Compound **44** is air-sensitive and stored in a refrigerator.

Reactions of **1** and **2** with dimethoxymethane (**69**) in an acidic methanolic solution, dipyrromethanes (**68a**) and (**68b**)

General procedure:

A solution of 1 mmole of pyrrole, 1 ml of dimethoxymethane and 40 mg of toluenesulfonic acid monohydrate in 10 ml of methanol was stirred and refluxed for 24 hours in an atomsphere of nitrogen. The reaction mixture was diluted with water and extracted with methylene chloride. The extracts was evaporated to dryness and extracted with boiling petroleum ether (bp. 60-110^{o}) until only a small amount of residue remained. Removal of petroleum ether gave a white powder and the yields are given on page 54.

nmr of **68a** ($CDCl_3$), δ1.23 (t, 6H, $-OCH_2\underline{C}H_3$), 3.68 (s, 2H, methane-protons), 4.15 (q, 4H, $-OC\underline{H}_2CH_3$), 6.50 (m, 2H, pyrrolic protons) and 7.25 (m, 12H, phenyl and pyrrolic protons).

nmr of **68b** ($CDCl_3$), δ1.30 (t, 6H, $-OCH_2\underline{C}H_3$), 2.26 (3s, 6H, $-C\underline{H}_3$), 3.73 (s, 2H, methane-protons), 4.18 (q, 4H, $-OC\underline{H}_2CH_3$), 6.38 (m, 2H, pyrrolic protons) and 7.20 (m, 2H, pyrrolic protons).

Therefore, both **68a** and **68b** are mixtures of possibly three isomers.

5,5'-Diformyl-2,2'-dipyrromethane (**51**)

Three ml of benzoyl chloride was added dropwise over a period of 10 minutes to a stirred solution of 0.7 g

(4.8 mmol) of 2,2'-dipyrromethane (**44**) in 5 ml of N,N'-dimethylformamide at 0-5° under nitrogen. This solution was further stirred at ice bath temperature for two hours then at room temperature for two hours. Benzene (10 ml) was added and after 30 minutes the crystalline pale yellow imine salt precipitated. The salt was collected by filtration and washed well with benzene but not allowed to dry. The solid was immediately dissolved in 10 ml of 10% sodium acetate solution and slowly warmed to 35-40°, then cooled and allowed to stand overnight. The product **51** precipitated as a pale yellow powder which was collected by filtration to yield 0.8 g (80%); mp. 218-223° (lit.[34] 219-222°); nmr (D_6MSO), δ3.90 (s, 2H, methane-protons), 5.97 (d, 2H, pyrrolic protons), 6.73 (d, 2H, pyrrolic protons) and 9.23 (s, 2H, -CHO).

5,5'-Diacetyl-2,2'-dipyrromethane (**52**)

A solution of 4 ml (4 mmol) of 1 M ethyl magnesium bromide in ether and 292 mg (2 mmol) of 2,2'-dipyrromethane (**44**) in 20 ml of anhydrous ether was stirred and refluxed for two hours under nitrogen. This solution was then added dropwise to an ice chilled solution of 314 mg (4 mmol) of acetyl chloride in 20 ml of ether. After stirring at ice bath temperature for two hours then at room temperature for another two hours, the resulting yellow solution was poured into 130 ml of ice water and 40 ml of saturated aqueous ammonium chloride then

extracted with chloroform. Evaporation of the extracts and crystallization from $CHCl_3$/ether gave 180 mg (39.1%) of **52** as fine white powders; mp. (sealed tube) 234-236° (decomp.); nmr ($CDCl_3$/trace D_6MSO), δ2.33 (s, 6H, $-COCH_3$), 3.90 (s, 2H, methane-protons), 5.93 (m, 2H, pyrrolic H) and 6.67 (m, 2H, pyrrolic protons); mass (m/e) : 230 (parent)

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17
Found : C, 66.48; H, 5.91 N, 12.76

3,3',5,5'-Tetramethyl-4,4'-diethyl-2,2'-dipyrromethene-HBr (**45**)

A mixture of 5.0 g (40.3 mmol) of kryptopyrrole (**59**), 10 ml of 88% formic acid and 8 ml of 48% hydrobromic acid was heated on a steam bath for two hours, then allowed to stand overnight. The shining purple precipitate was filtered and air dried to give 5.8 g (85.4%) of **45**; nmr ($CDCl_3$/CF_3CO_2H), δ1.10 (t, J=6.5 Hz, 6H, $-CH_2CH_3$), 2.30 (s, 6H, $-CH_3$), 2.46 (q, J=6.5 Hz, 4H, $-CH_2CH_3$), 2.53 (s, 6H, $-CH_3$) and 7.08 (s, 1H, methene-H); λmax ($CHCl_3$), 486 nm.

5,5'-Dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**60**)

A solution of 0.92 g (27.3 mmol) of 3,3'5,5'-tetramethyl-4,4'-diethyl-2,2'-dipyrromethene-HBr (**45**) in 35 ml of acetic acid was heated on a steam bath with occasional swirling. Liquid bromine was added dropwise until

precipitation occurred, then two more drops of bromine were introduced. The mixture was cooled to room temperature and filtered. The deep red precipitate after air drying, gave 1.15 g (85.2%) of **60**; nmr ($CDCl_3/CF_3CO_2H$), δ1.17 (t, J=6.5 Hz, 6H, $-CH_2C\underline{H}_3$), 2.32 (s, 6H, $-C\underline{H}_3$), 2.52 (q, J=6.5 Hz, 4H, $-C\underline{H}_2CH_3$), 4.68 (s, 4H, Br-$C\underline{H}_2$-) and 7.20 (s, 1H, methene-H); λmax ($CHCl_3$), 509 nm.

5,5'-Di-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**61**)

A solution of 4.50 g (9.1 mmol) of 5,5'-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**60**) in 30 ml of liquid bromine was stirred at room temperature for one hour. Bromine was removed under reduced pressure and 60 ml of acetone was introduced. The acetone solution was refluxed for 30 minutes then cooled to room temperature and refrigerated overnight. The red precipitate was filtered, washed with cold acetone and dried to give 5.28 g (90%) of **61** as a red powder; nmr ($CDCl_3/CF_3CO_2H$), δ1.27 (t, J=7 Hz, 6H, $-CH_2C\underline{H}_3$), 2.37 (s, 6H, $-C\underline{H}_3$), 2.80 (q, J=7 Hz, 4H, $-C\underline{H}_2CH_3$), 7.13 (s, 2H, $Br_2C\underline{H}$-) and 7.42 (s, 1H, methene-H); λmax ($CHCl_3$), 514 nm (lit.[38] 519 nm).

5,5'-Diformyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**53**)

A solution of 1.0 g (1.53 mmol) of 5,5'-di-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr

(**61**) in 50 ml of 95% ethanol was stirred at room temperature for 17 hours. The resulting solution was diluted with 170 ml of water and refrigerated. A dark precipitate was collected and dried to give 0.4 g (72%) of **53**; mp. 220-222° (decomp.); nmr ($CDCl_3$), δ1.15 (t, J=6.5 Hz, 6H, $-CH_2\underline{CH}_3$), 3.28 (s, 6H, $-\underline{CH}_3$), 2.58 (q, J=6.5 Hz, 4H, $-\underline{CH}_2CH_3$), 5.53 (s, 1H, methene-H) and 9.46 (s, 2H, -CHO); λmax ($CHCl_3$), 507 nm, 575 nm and 615 nm.

1,3-Bis-(3,5-dicarbethoxy-4-methylpyrr-2-yl)-propan-2-one (**46**)

A solution of 3.27 g (10.3 mmol) of 2-bromomethyl-4-methyl-3,5-dicarbethoxypyrrole (**62**) in 5 ml of N-methyl-2-pyrrolidone was added to a stirred solution of 3.84 g (11.1 mmol) of $Na_2Fe(CO)_4 \cdot 3/2$dioxane in 30 ml of N-methyl-2-pyrrolidone in a nitrogen atomsphere. Bubbling occurred immediately. After the reaction mixture was stirred for one hour, 9.81 g (30.9 mmol) of **62** in 15 ml of N-methyl-2-pyrrolidone was added and stirred for an additional 24 hours. Ether (150 ml) was added and the diluted solution was washed with saturated sodium chloride solution three times. During the third washing white solids precipitated, 50 ml of methylene chloride was introduced to dissolve the precipitate. The combined ether-methylene chloride layer was evaporated to dryness and crystallization from ethanol-water gave 4.30 g (41.75%) of **46** as a fluffy white solid; mp. 185-187°; nmr ($CDCl_3$), δ1.35 (2 overlapping triplets,

J=7 Hz, 12H, $-CO_2CH_2\underline{CH_3}$), 2.58 (s, 6H, $-\underline{CH_3}$), 4.18 (s, 4H, $\underline{CH_2}$ α to -CO-) and 4.27 (2 overlapping quartets, J=7 Hz, 8H, $-CO_2\underline{CH_2}CH_3$); mass (m/e) : 504 (parent).

Anal. Calcd for $C_{25}H_{32}N_2O_9$: C, 59.50; H, 6.41; N, 5.55
Found : C, 59.56; H, 6.34; N, 5.44

1,3-Bis-(2-pyrryl)-1-propen-3-one (**47**)

A solution of 1.09 g (0.01 mol) of 2-acetylpyrrole (**63**), 0.95 g (0.01 mol) of 2-formylpyrrole (**64**), 7 ml of ethanol, 5 ml of water and 2 ml of 15% NaOH was stirred for 5 hours then allowed to stand for 12 hours. Dilution with water and refrigeration resulted in a golden flaky precipitate. This product after recrystallization from ethanol and water gave 0.60 g (32%) of **47**; mp. 157-160° (decomp. at 120°, lit.[41] 174°); λmax ($CHCl_3$), 382 nm; nmr ($CDCl_3/D_6MSO$), δ6.13 (m, 2H, pyrrolic protons), 6.42 (m, 1H, pyrrolic proton), 6.78 (m, 1H, pyrrolic proton), 6.92 (m, 2H, pyrrolic protons), 6.93-7.68 (ABq, J=15 Hz, 2H, vinylic protons) and 10.72 (s, 2H, N-$\underline{H}$).

1,3-Bis-(2-pyrryl)-propan-3-one (**88**)

A solution of 93 mg (0.5 mmol) of 1,3-bis-(2-pyrryl)-1-propen-3-one (**47**) in 5 ml of acetic acid was hydrogenated at 30 psi over a small amount of 10% palladium on charcoal for 45 minutes. The catalyst was filtered immediately, and the filtrate was diluted with 5% sodium carbonate solution and extracted with chloroform. Evaporation of the extracts and crystallization from chloroform/cyclohexane gave 80 mg

(89%) of **88** as a pale yellow solid which is acid and air sensitive; nmr ($CDCl_3$), δ3.00 (t, J=3 Hz, 4H, $-COCH_2CH_2-$), 5.83 (m, 1H, pyrrolic proton), 5.97 (m, 1H, pyrrolic H), 6.13 (m, 1H, pyrrolic H), 6.50 (m, 1H, pyrrolic proton), 6.83 (m, 2H, pyrrolic protons), 8.40 (brd s, 1H, N-H) and 9.80 (brd s, 1H, N-H).

1,3-Bis-(pyrr-2-yl)-1,3-propanedione (**48**)

A solution of 10.0 ml (10 mmol) of 1 M ethyl magnesium bromide in ether and 670 mg (10 mmol) of pyrrole in 50 ml of ether was stirred and refluxed for two hours under N_2. This solution was then added to a stirred solution of 705 mg (5 mmol) of malonyl dichloride in 50 ml of ether at dry ice and ethanol temperature. The resulting yellow solution after two hour stirring at dry ice temperature was poured into 200 ml of water and 50 ml of saturated ammonium chloride, extracted with ether then the ether extracts was evaporated to dryness. The residue after crystallizing from ethanol and water gave 354 mg (35%) of **48** as a pale yellow powder; nmr ($CDCl_3/D_6MSO$), δ4.13 (s, 2H, $-COCH_2CO-$), 6.13 (m, 2H, pyrrolic protons), 6.93 (m, 4H, pyrrolic protons) and 11.01 (brd s, 2H, N-H).

1,3-Di-pyrr-2-ylmethylene-2-cyclopentanone (**49**)
and 1,5-di-2-pyrryl-1,4-pentadien-3-one (**50**)

To a stirred mixture of 480 mg (0.5 mmol) of 2-formyl-pyrrole (**64**), 4 ml of 15% NaOH, 10 ml of water and 14 ml of

ethanol was added 210 mg (0.25 mmol) of cyclopentanone (or 120 mg of acetone) at room temperature under nitrogen. After completion of addition, the mixture was stirred for two hours then allowed to stand overnight. The orange precipitate was collected by filtration to yield 526 mg (90%) of **49** (or after crystallizing from ethanol/water to give 32 mg (15%) of **50**).

Compound **49** showed nmr (D_6MSO) absorptions at : δ2.83 (s, 4H, cyclopentanone-protons), 6.20 (m, 2H, pyrrolic protons), 6.43 (m, 2H, pyrrolic protons), 6.96 (m, 2H, pyrrolic protons), 7.27 (s, 2H, vinylic protons) and 11.20 (brd s, 2H, N-H).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76
Found : C, 74.22; H, 5.86; N, 11.31

Compound **50** showed nmr (D_6MSO) absorptions at : δ6.10 (m, 2H, pyrrolic protons), 6.43 (m, 2H, pyrrolic protons), 6.80 (m, 2H, pyrrolic protons), 6.57-7.60 (ABq, J=15 Hz, 4H, vinylic protons) and 10.77 (brd s, 2H, N-H).

APPENDIX

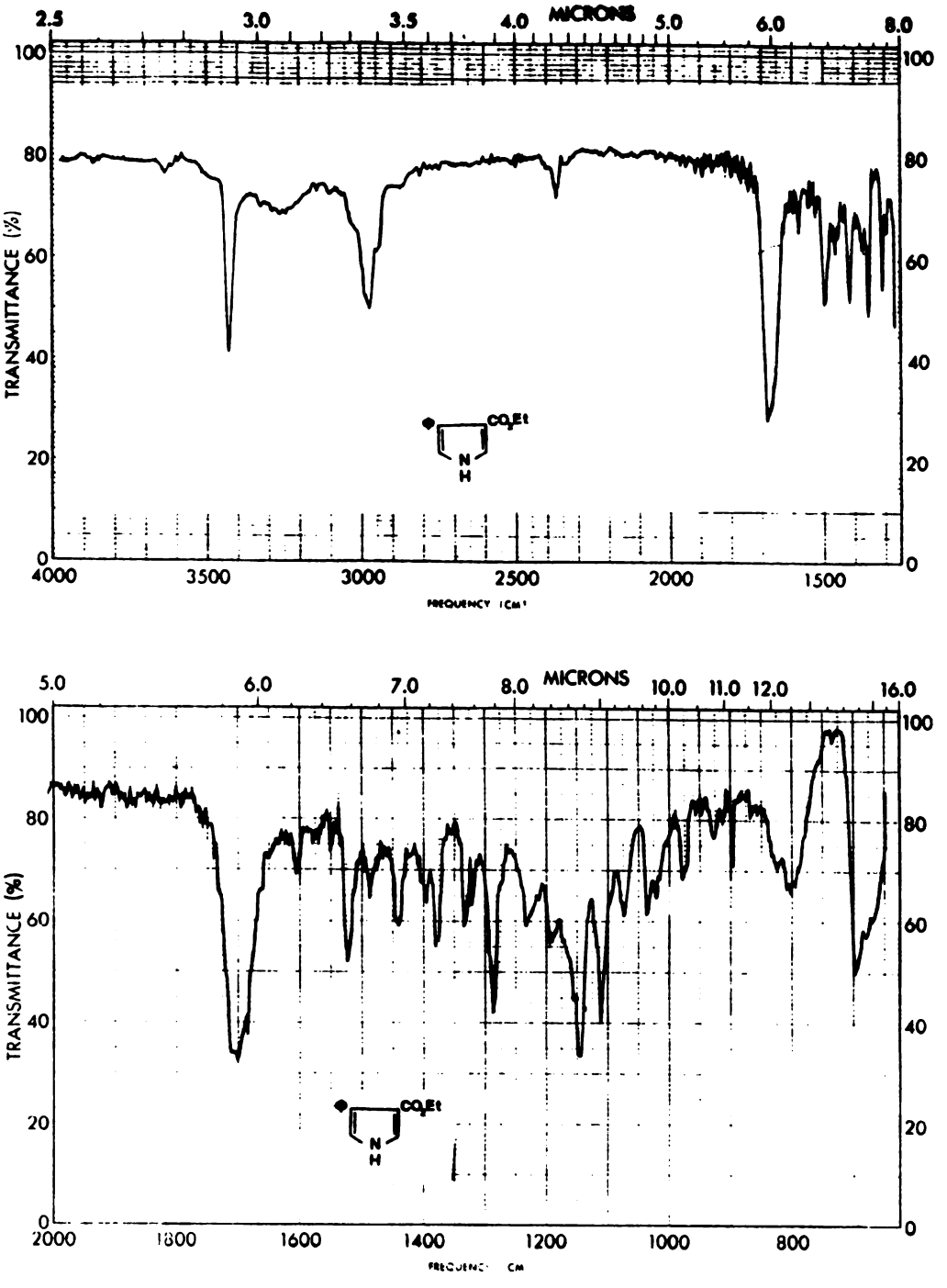


Figure 15, Infrared spectrum of 3-carbethoxy-4-phenylpyrrole (1).

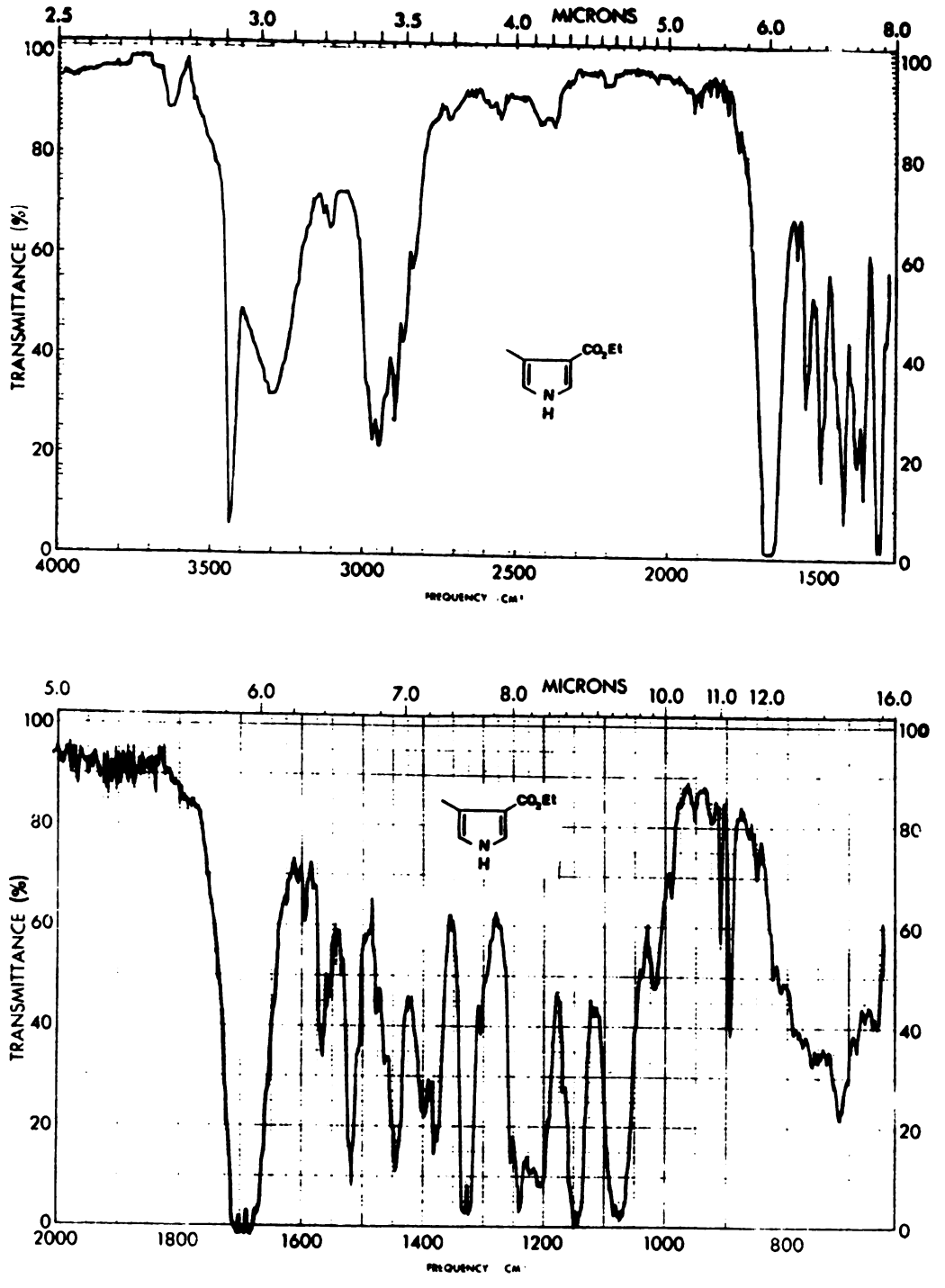


Figure 16, Infrared spectrum of 3-carbethoxy-4-methylpyrrole (**2**).

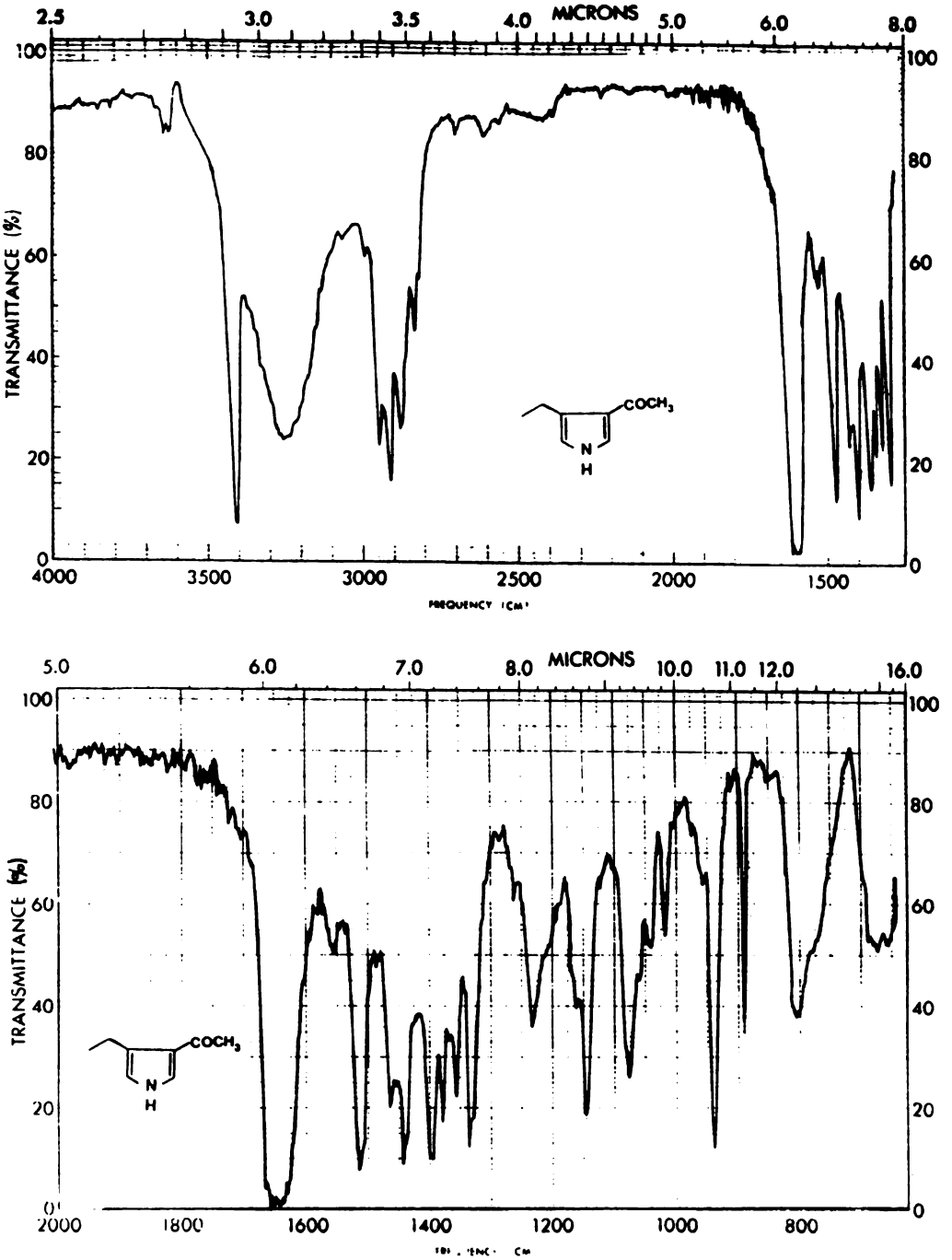


Figure 17, Infrared spectrum of 3-acetyl-4-ethylpyrrole (**3**).

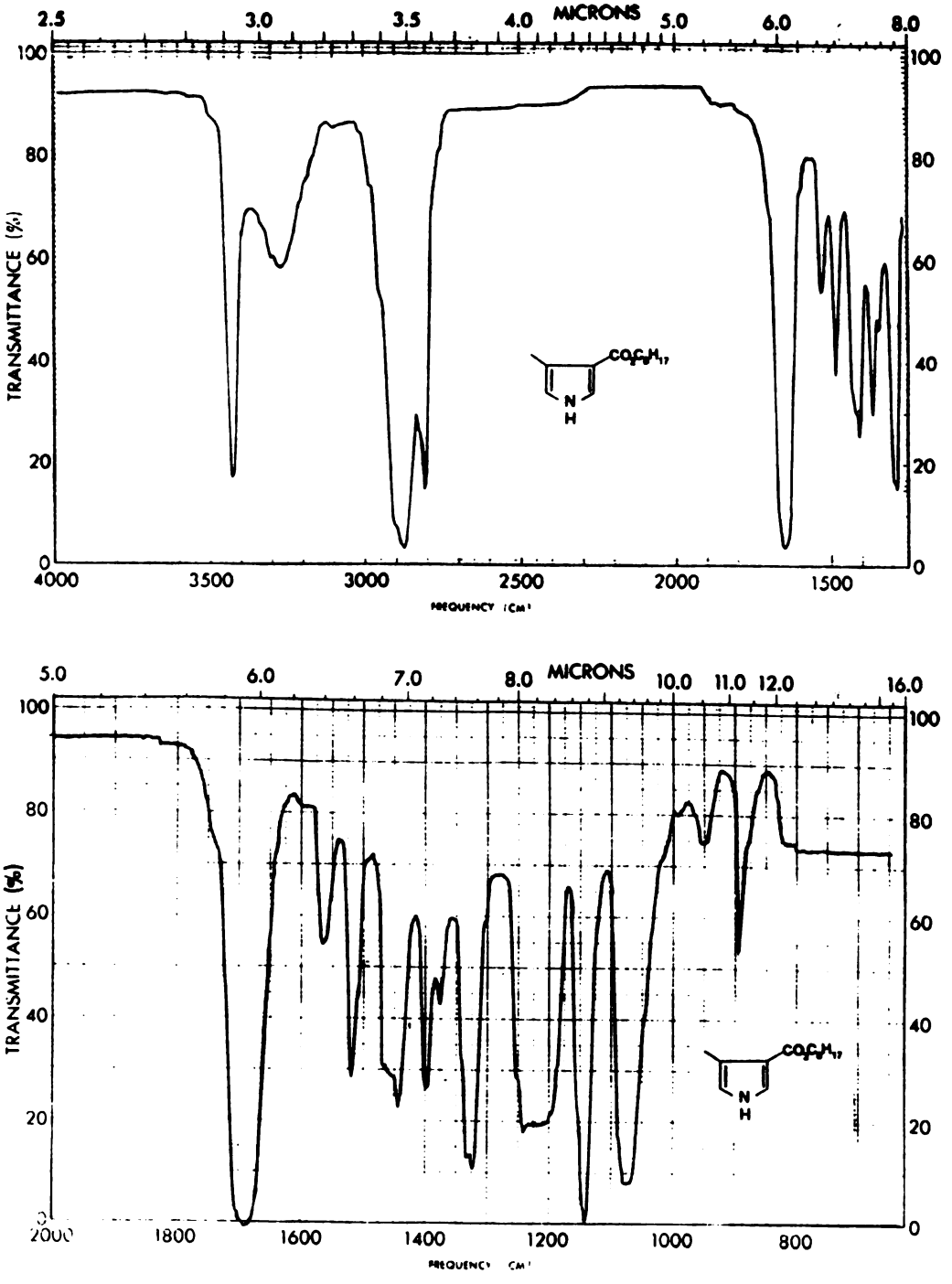


Figure 18, Infrared spectrum of 3-carboöctoxy-4-methylpyrrole (**5**).

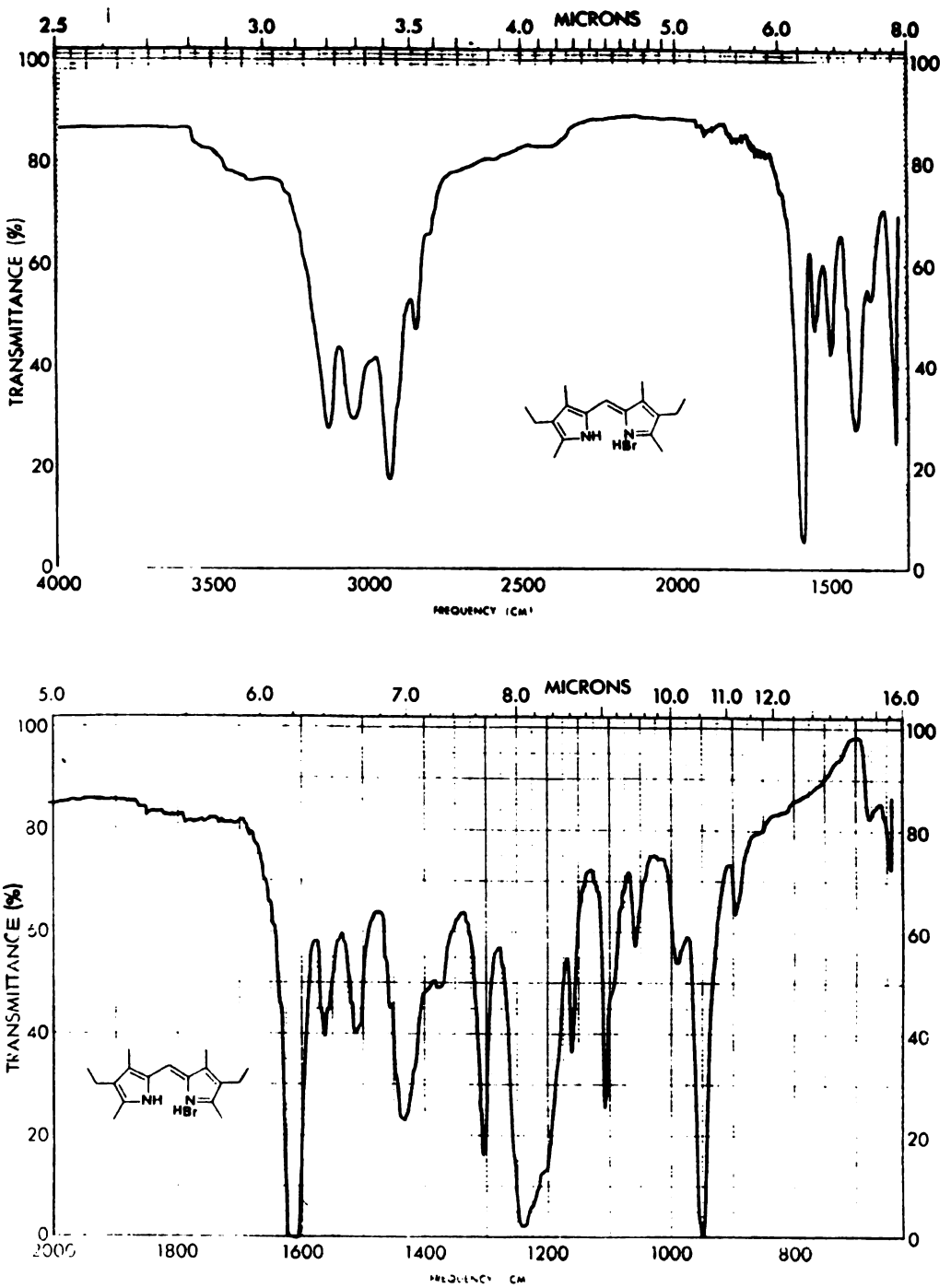


Figure 19, Infrared spectrum of 3,3',5,5'-tetramethyl-4,4'-diethyl-2,2'-dipyrromethene-HBr (**45**).

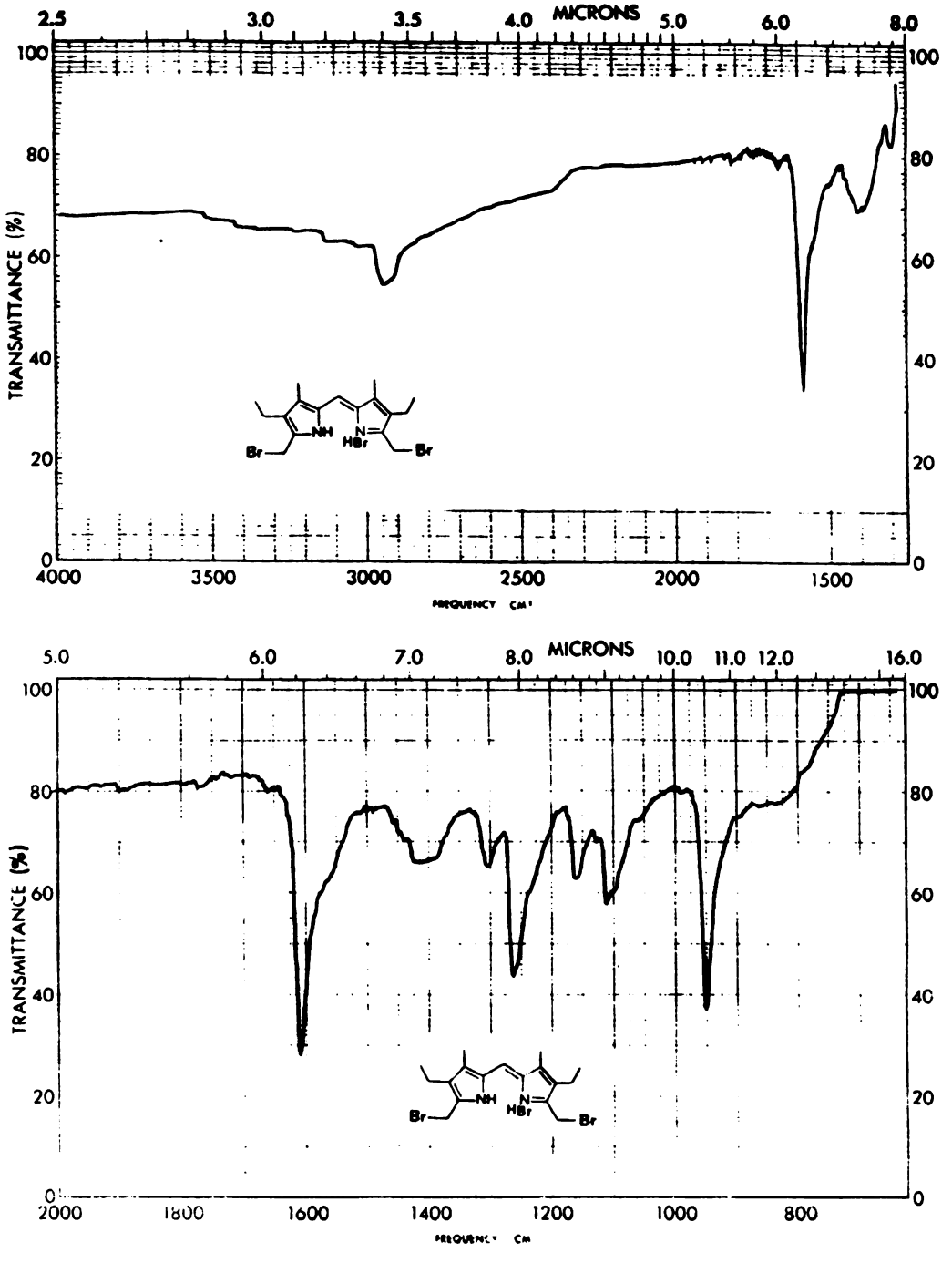


Figure 20, Infrared spectrum of 5,5'-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**60**).

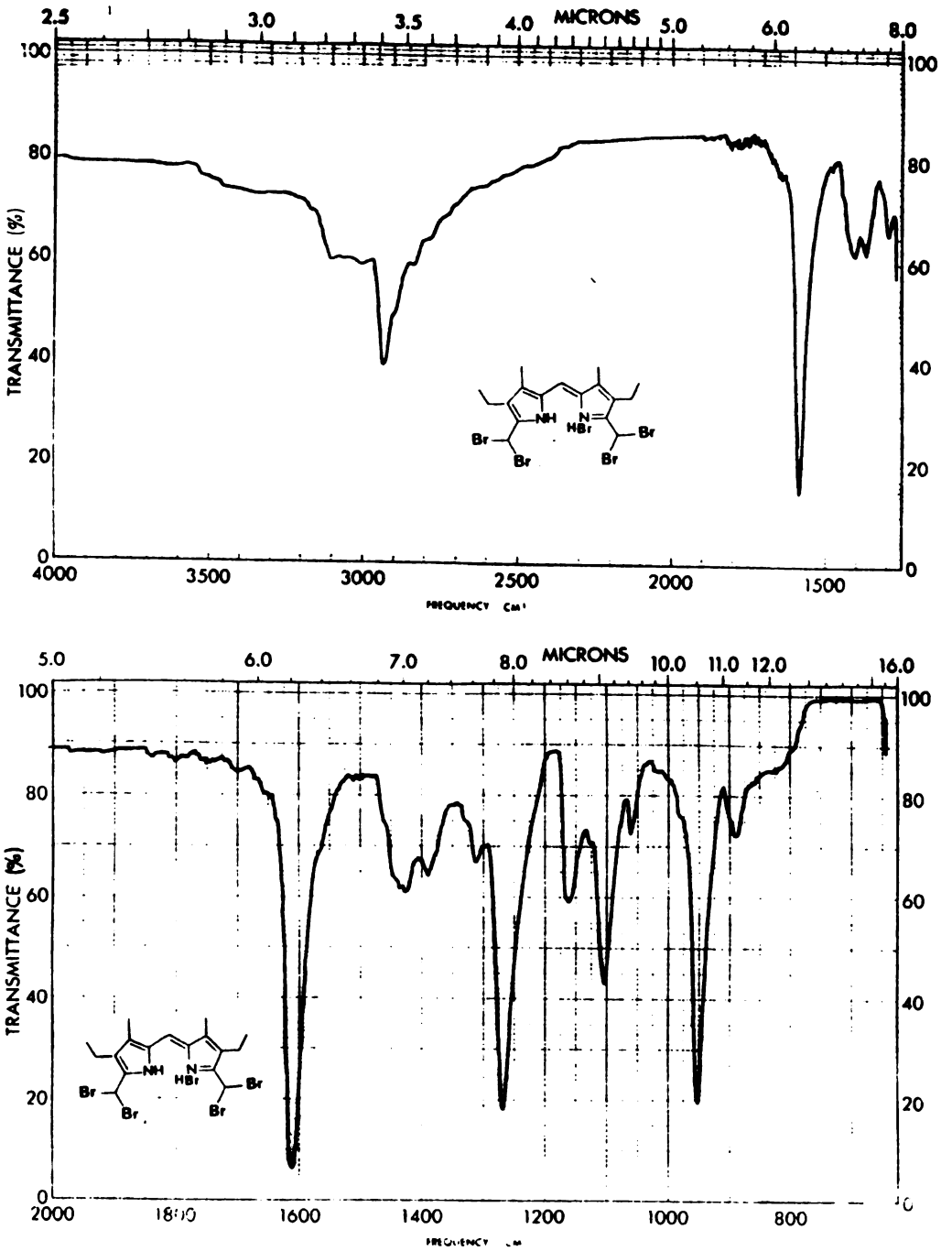


Figure 21, Infrared spectrum of 5,5'-di-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**61**).

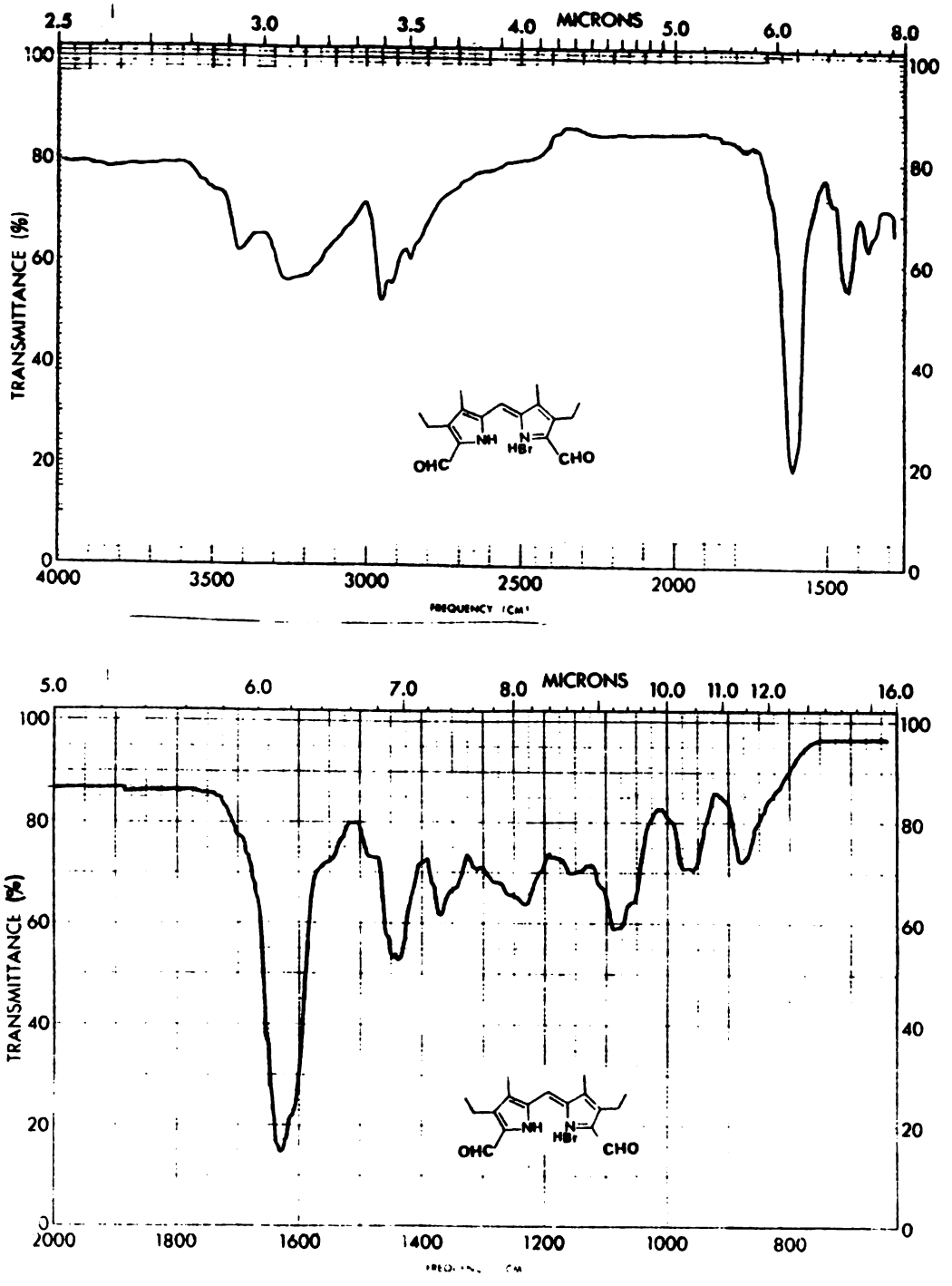


Figure 22, Infrared spectrum of 5,5'-diformyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**53**).

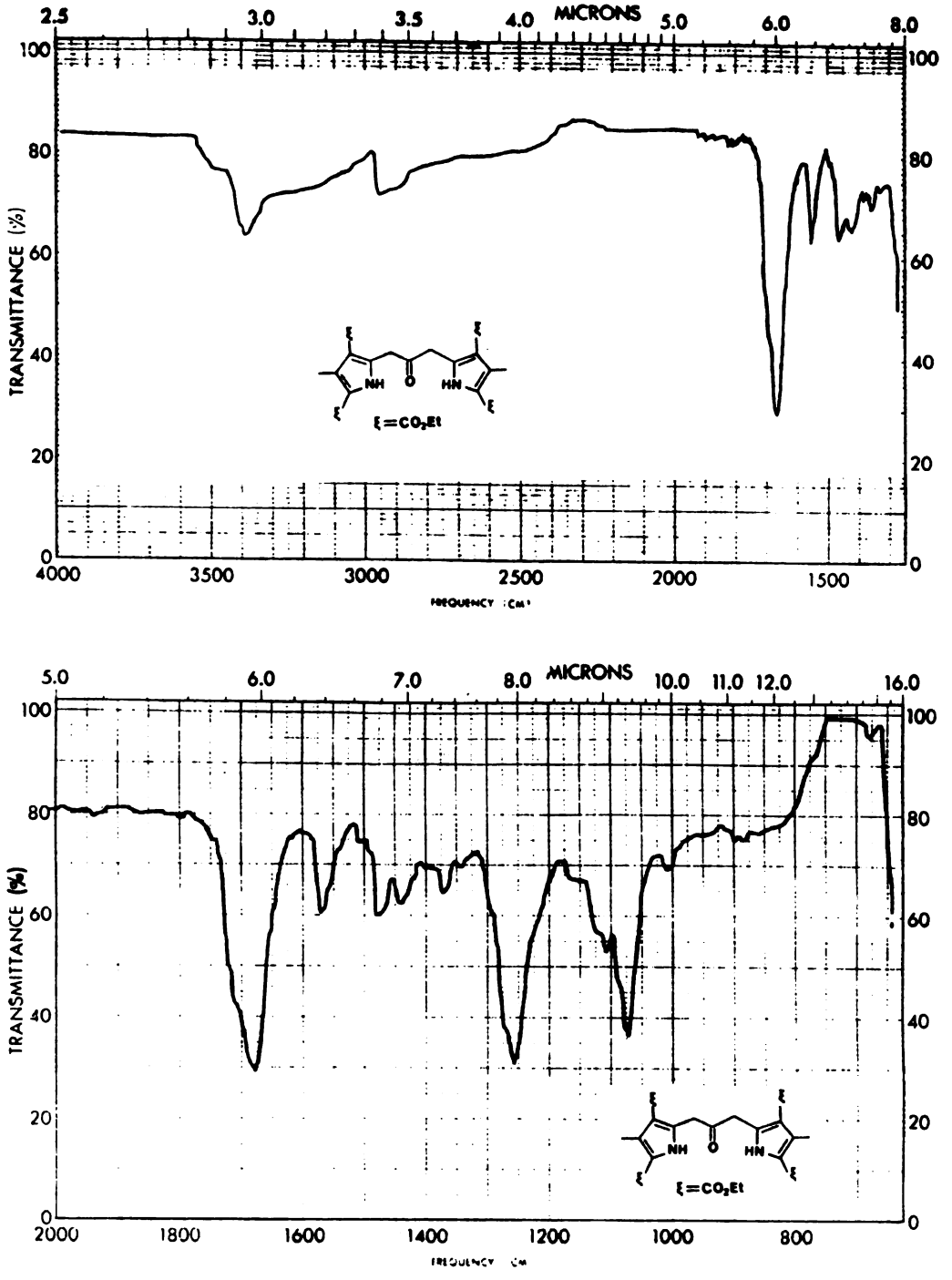


Figure 23, Infrared spectrum of 1,3-bis-(3,5-dicarbethoxy-4-methylpyrr-2-yl)-propan-2-one (**46**).

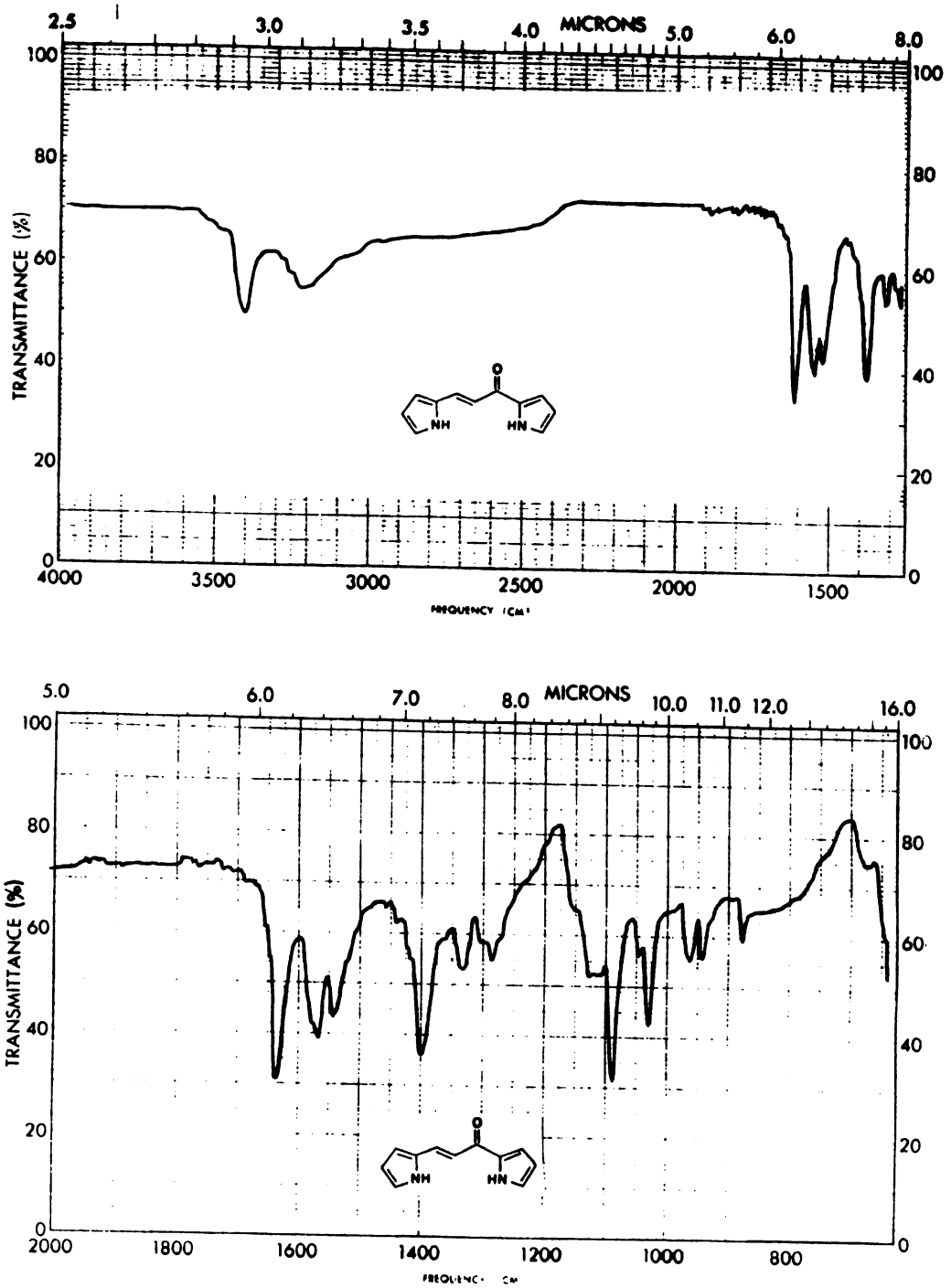


Figure 24, Infrared spectrum of 1,3-bis-(2-pyrryl)-1-propen-3-one (**47**).

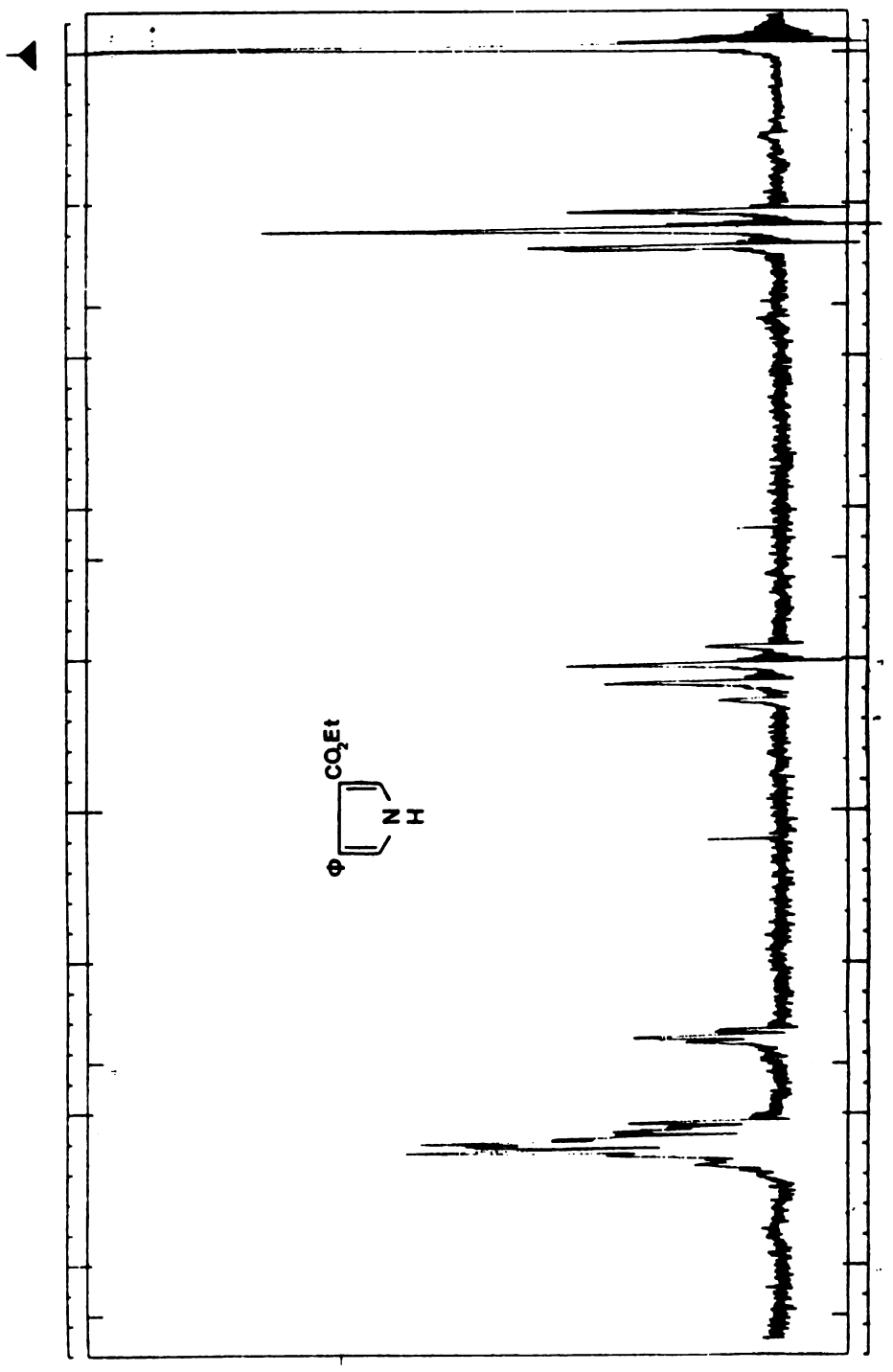


Figure 25, Nmr spectrum of 3-carbethoxy-4-phenylpyrrole (1).

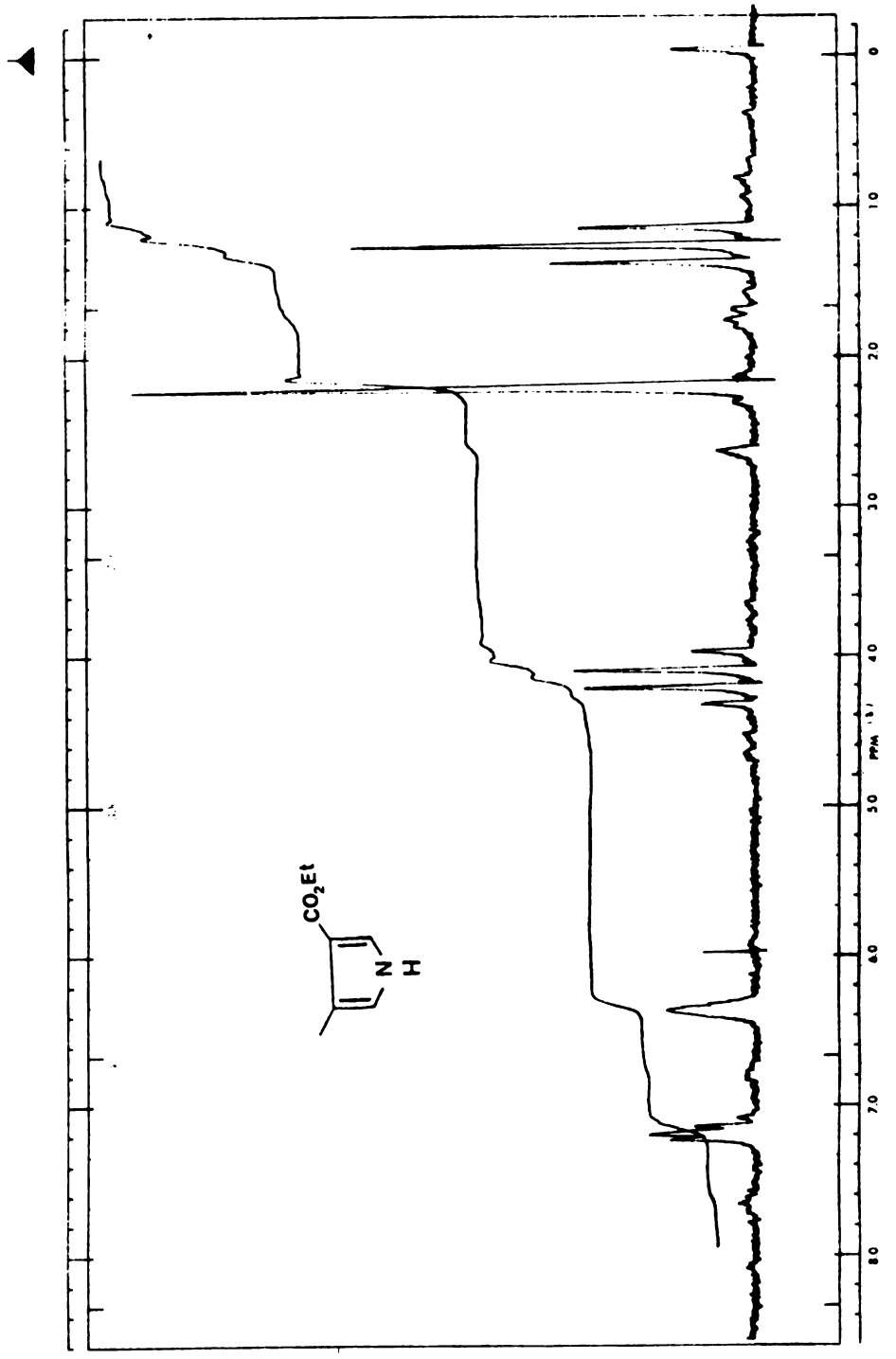


Figure 26, Nmr spectrum of 3-carbethoxy-4-methylpyrrole (**2**).

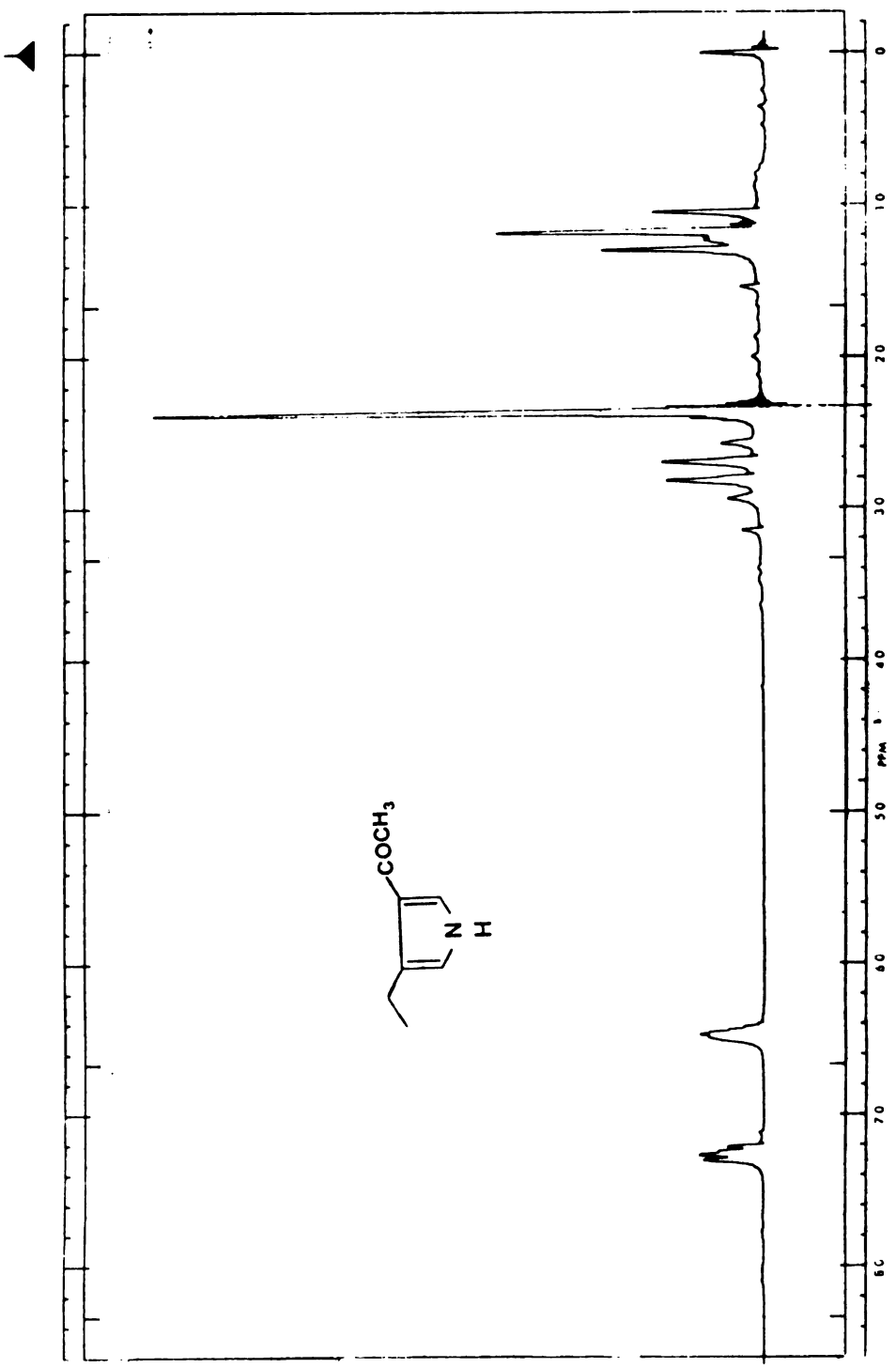


Figure 27, Nmr spectrum of 3-acetyl-4-ethylpyrrole (**3**).

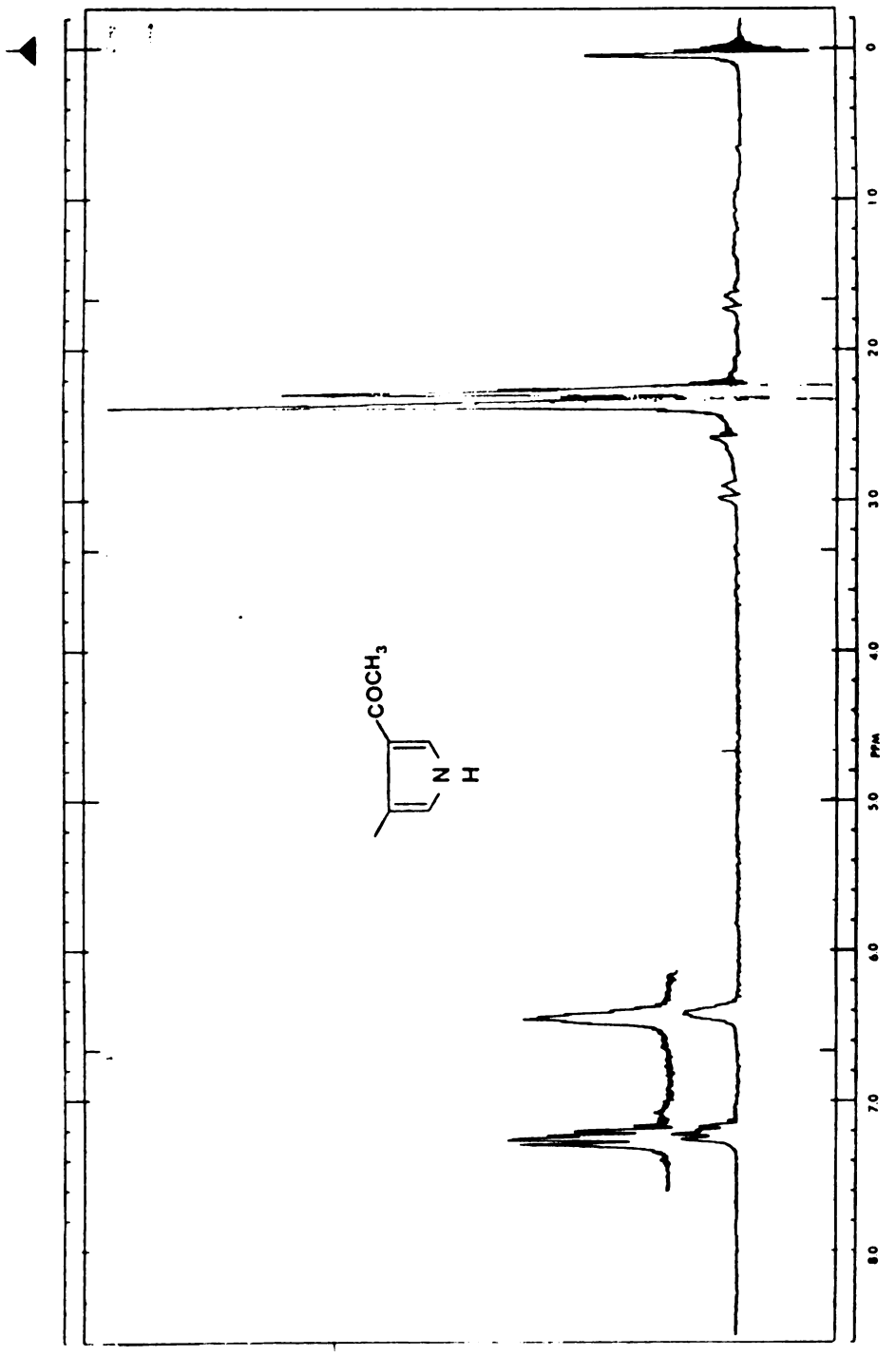


Figure 28, Nmr spectrum of 3-acetyl-4-methylpyrrole (4).

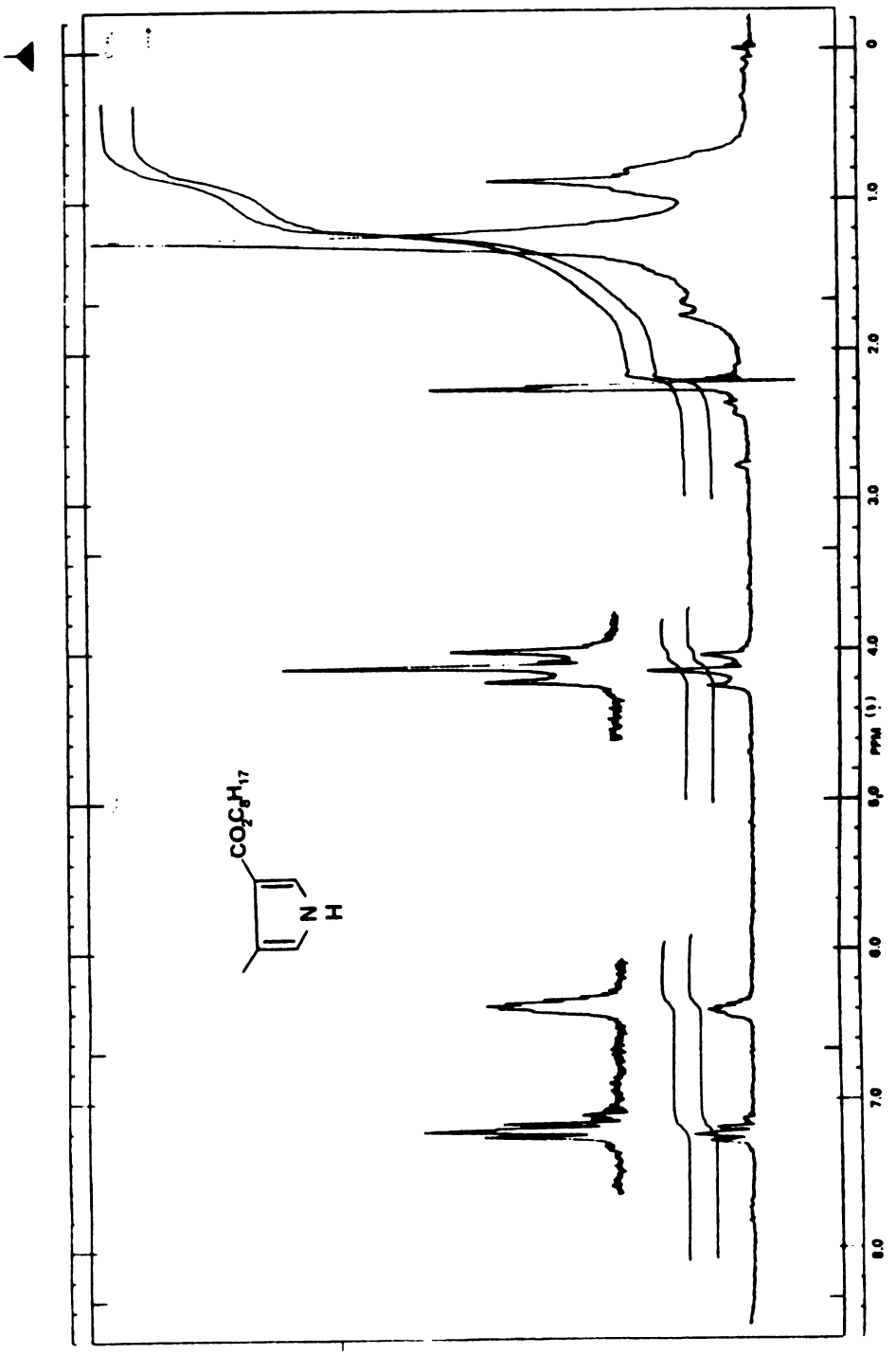


Figure 29, Nmr spectrum of 3-carboöctoxy-4-methylpyrrole (5).

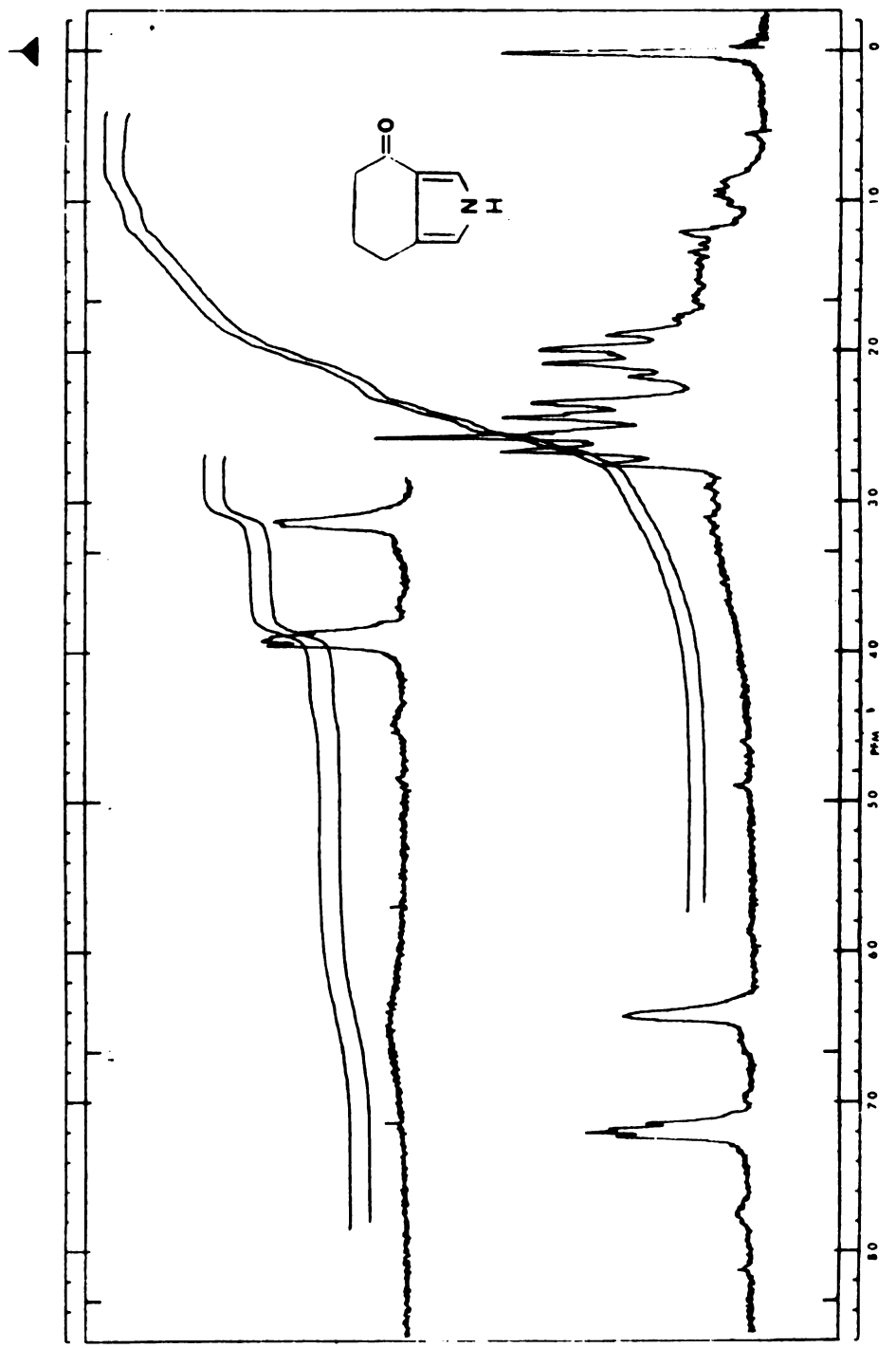


Figure 30, Nmr spectrum of 3,4-trimethylenecarbonylpyrrole (**6**).

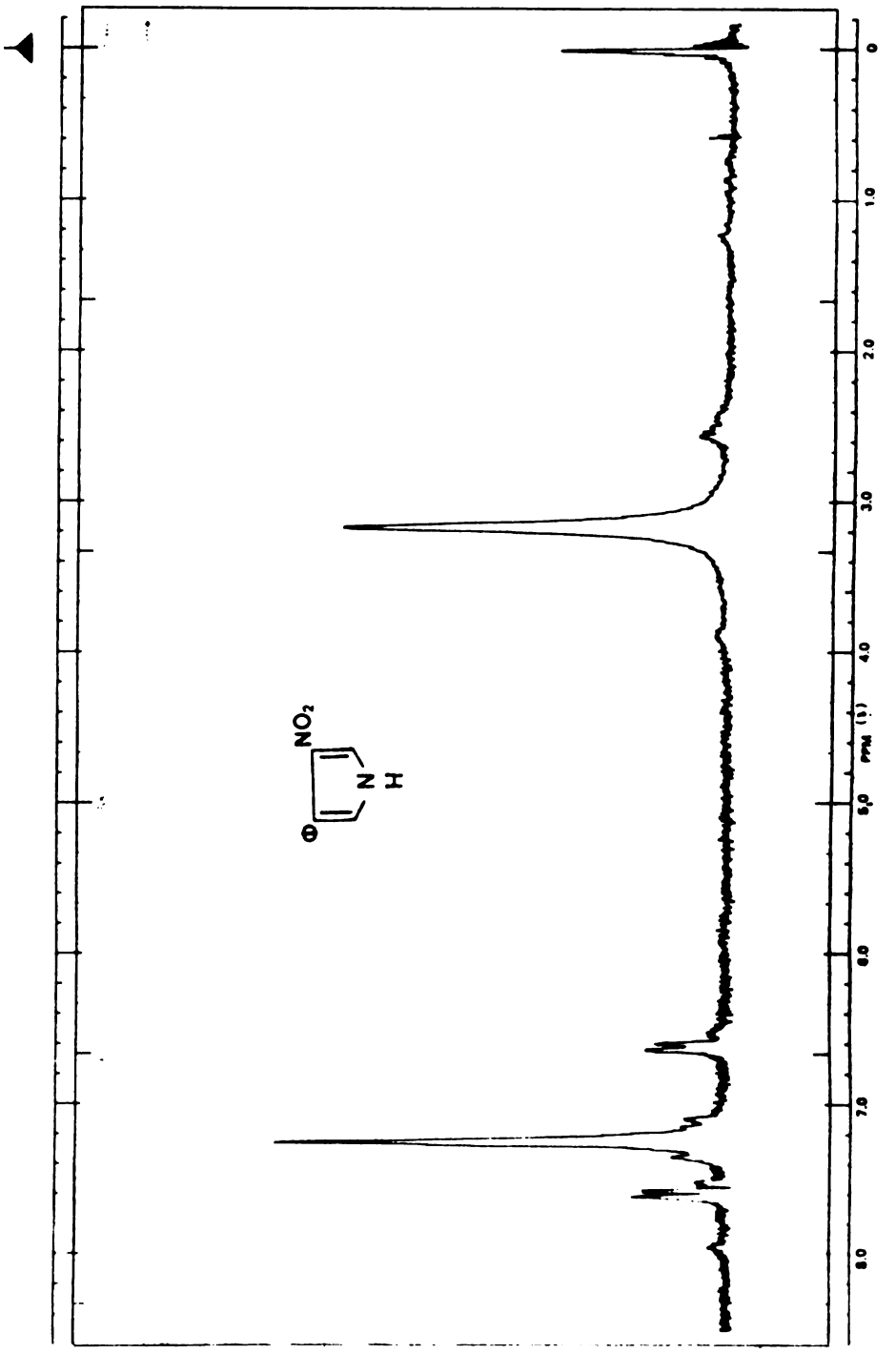


Figure 31, Nmr spectrum of 3-nitro-4-phenylpyrrole (**9**).

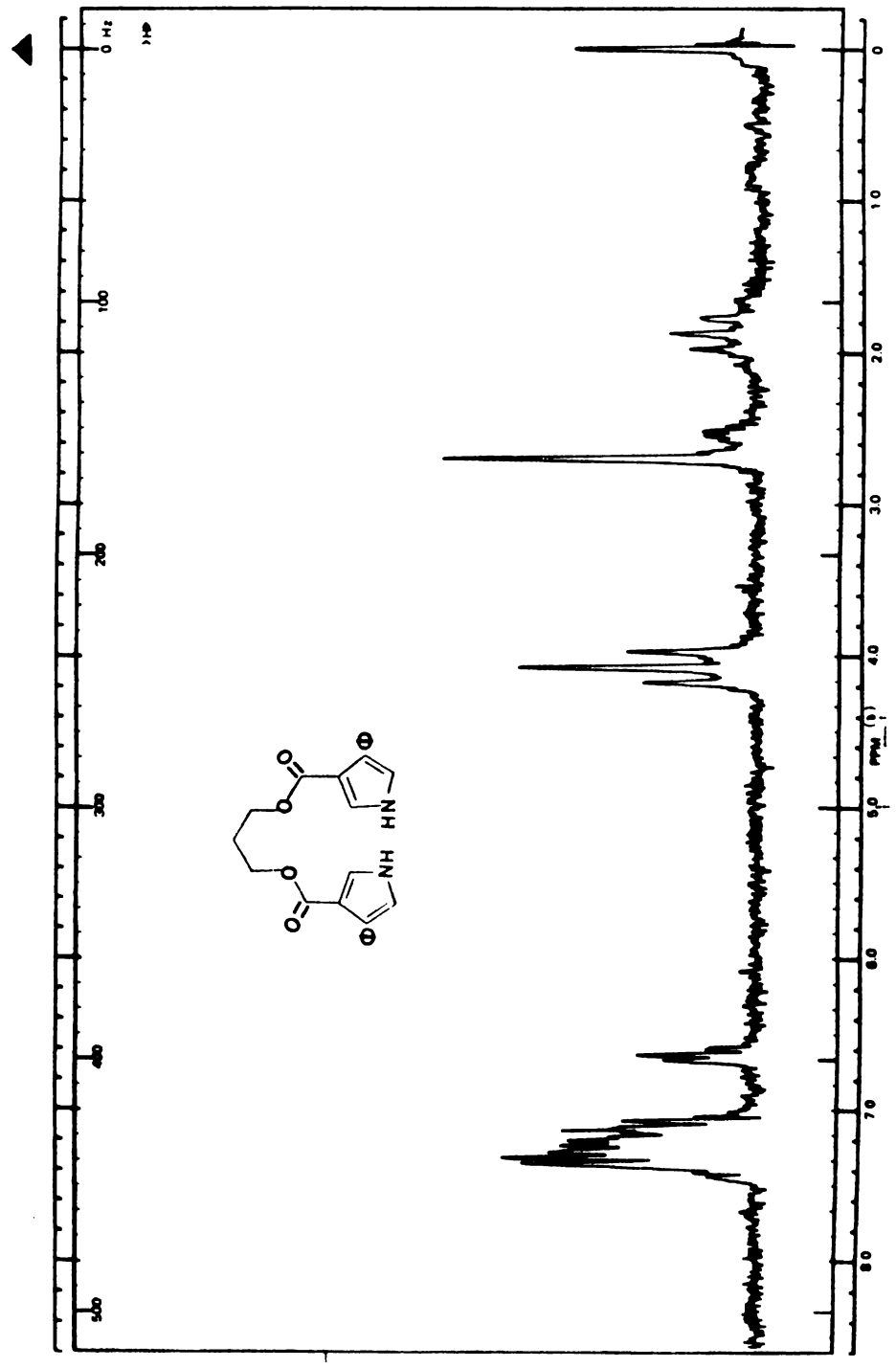


Figure 32, Nmr spectrum of 1,3-bis-(4-phenylpyrrole-3-carboxy)-propane (**26**).

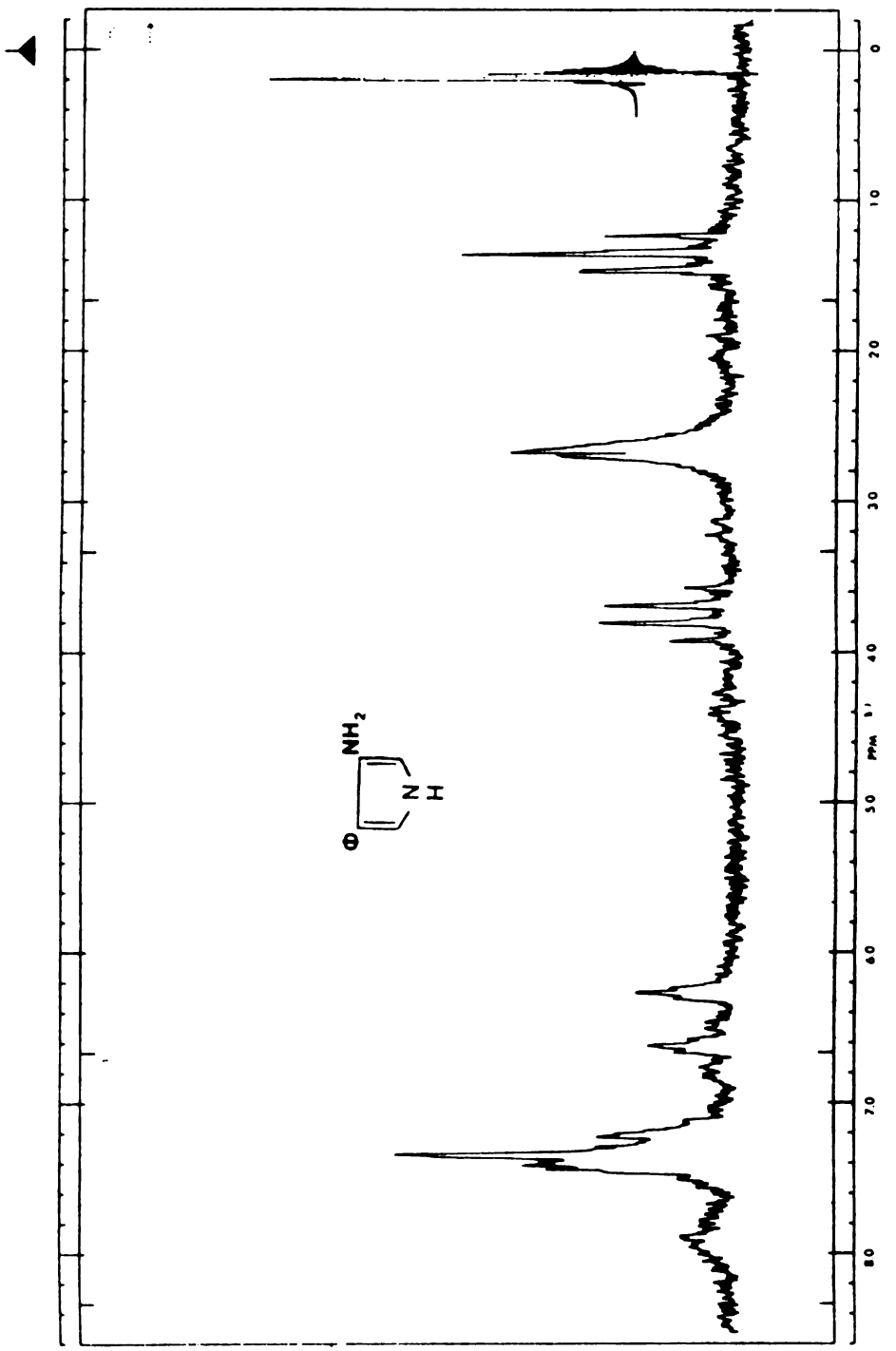


Figure 33, Nmr spectrum of 3-amino-4-phenylpyrrole (**39**).

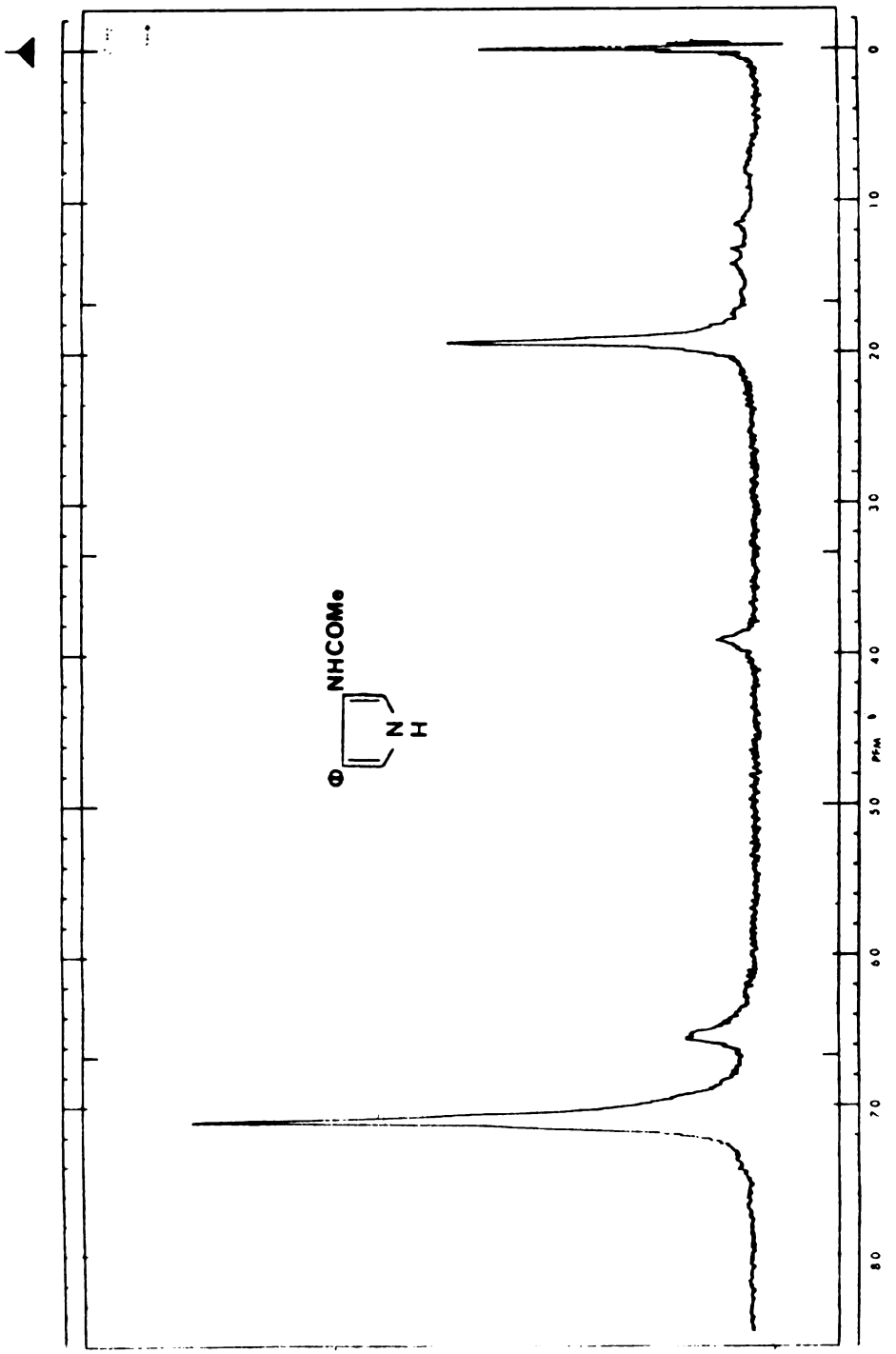


Figure 34, Nmr spectrum of 3-acetylamino-4-phenylpyrrole (**40**).

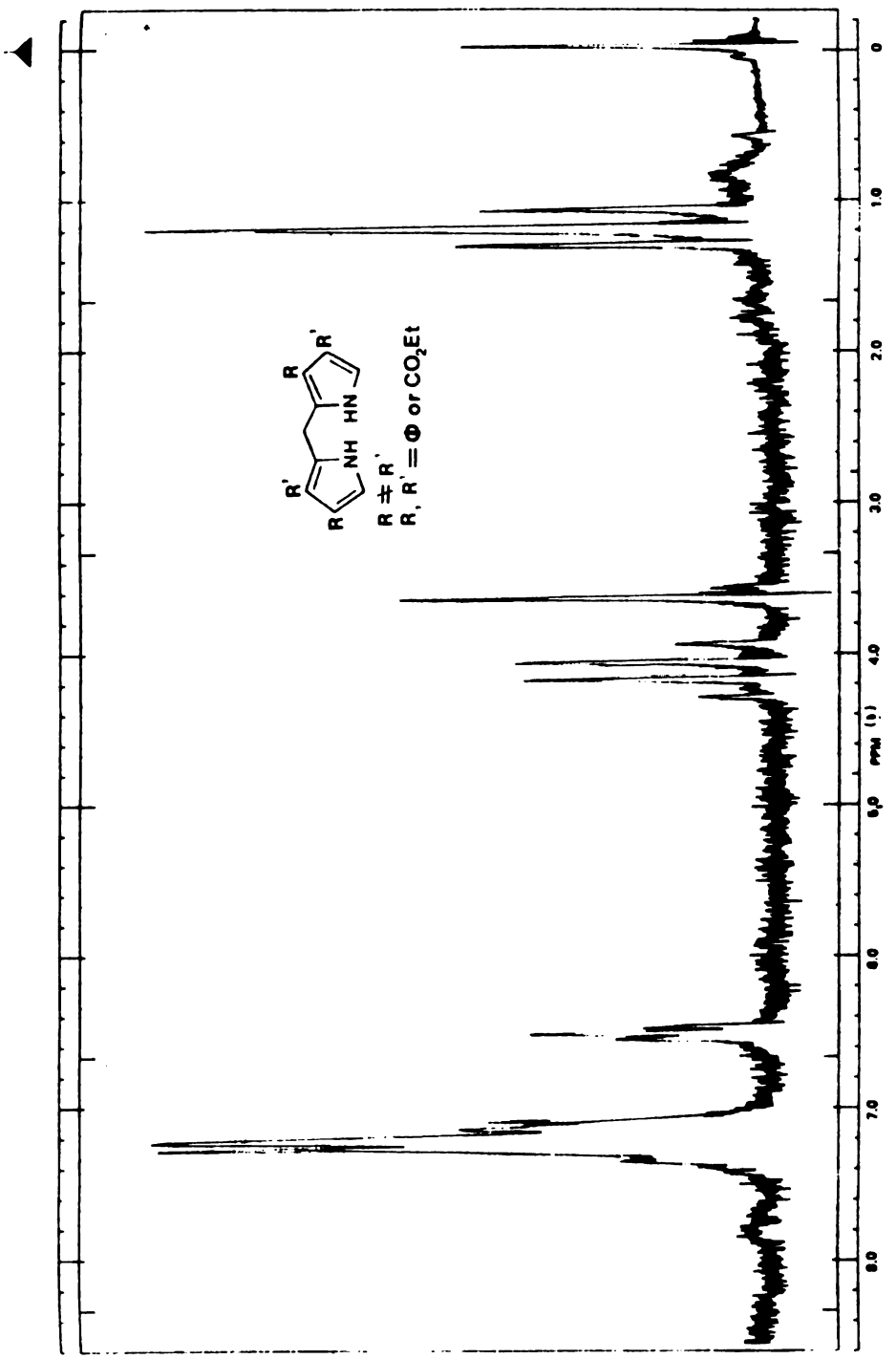


Figure 35, Nmr spectrum of 3,3',4,4'-dicarbethoxydiphenyl-2,2'-dipyrromethane (68a).

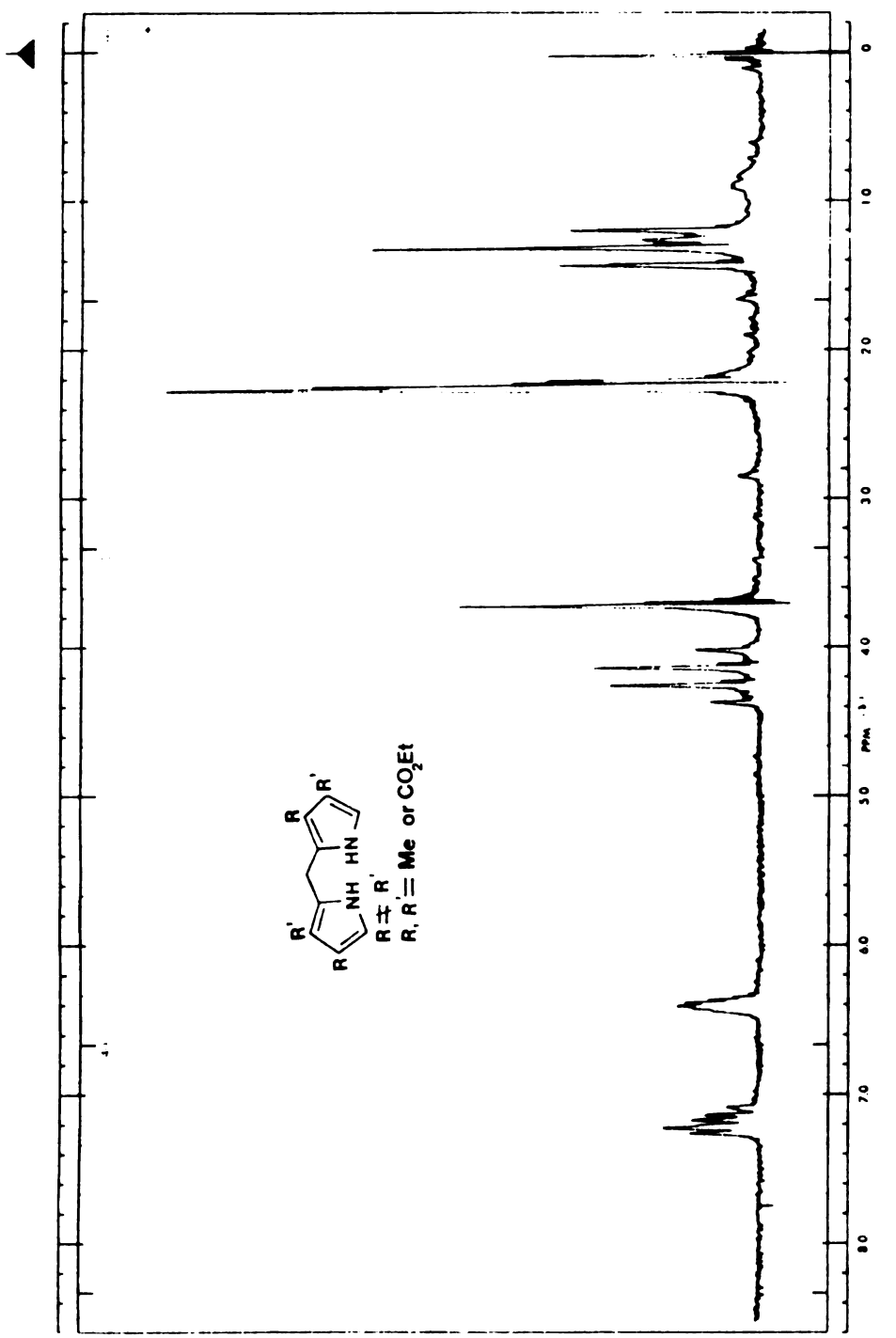


Figure 36, Nmr spectrum of 3,3'4,4'-dicarbethoxydimethyl-2,2'-dipyrromethane (**68b**).

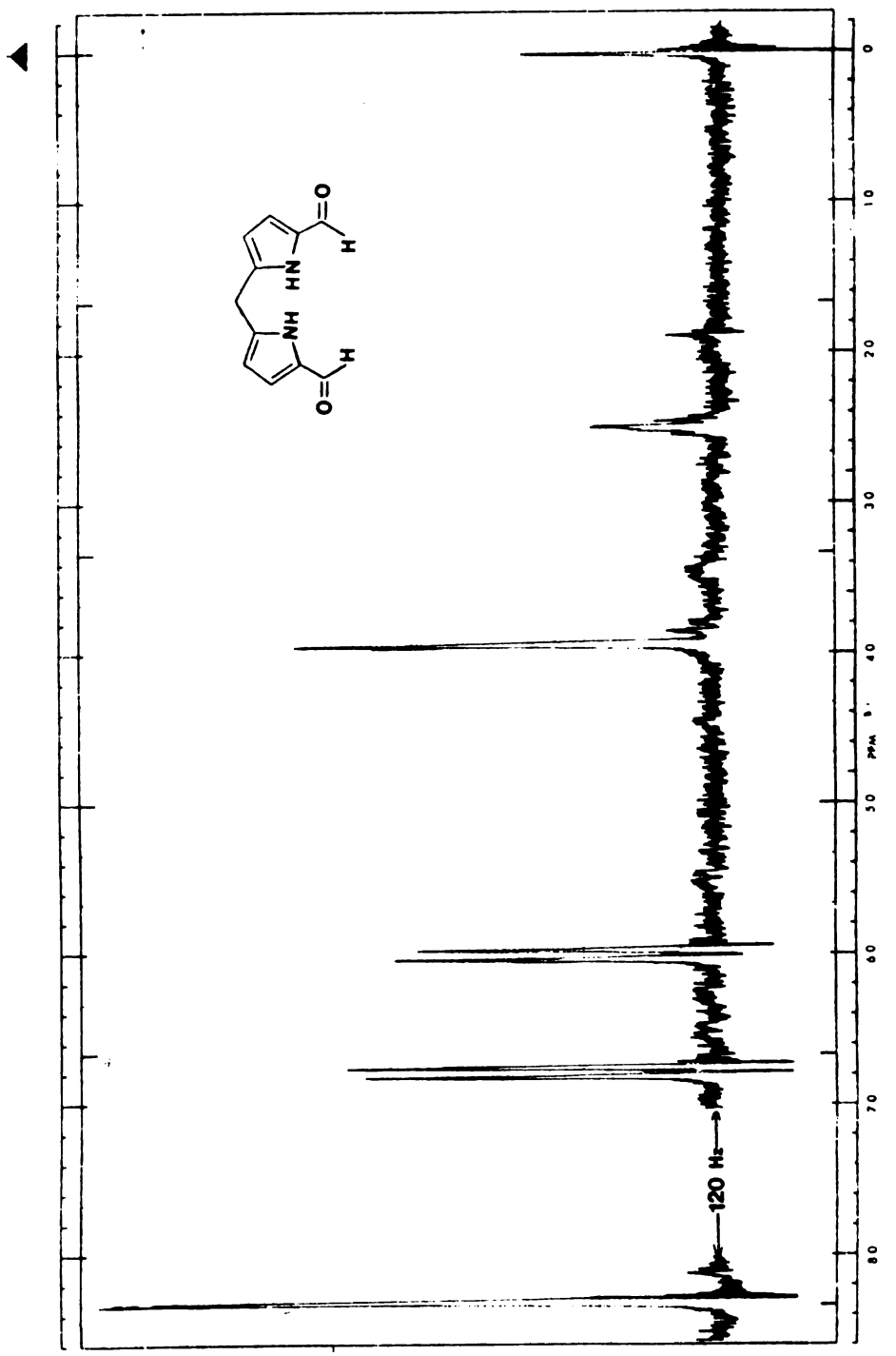


Figure 37, Nmr spectrum of 5,5'-diformyl-2,2'-dipyrromethane (**51**).

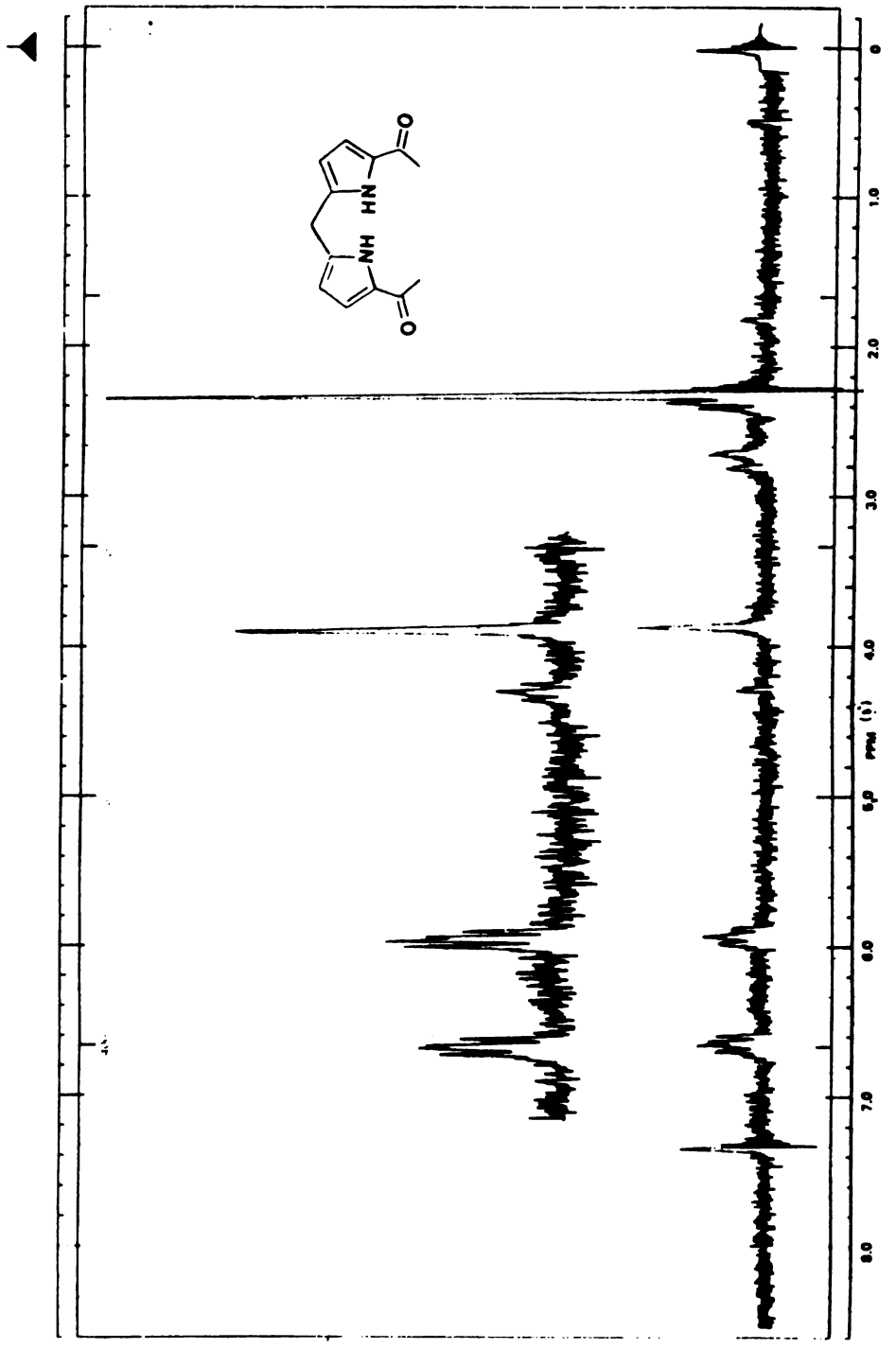


Figure 38, Nmr spectrum of 5,5'-diacetyl-2,2'-dipyrromethane (**52**).

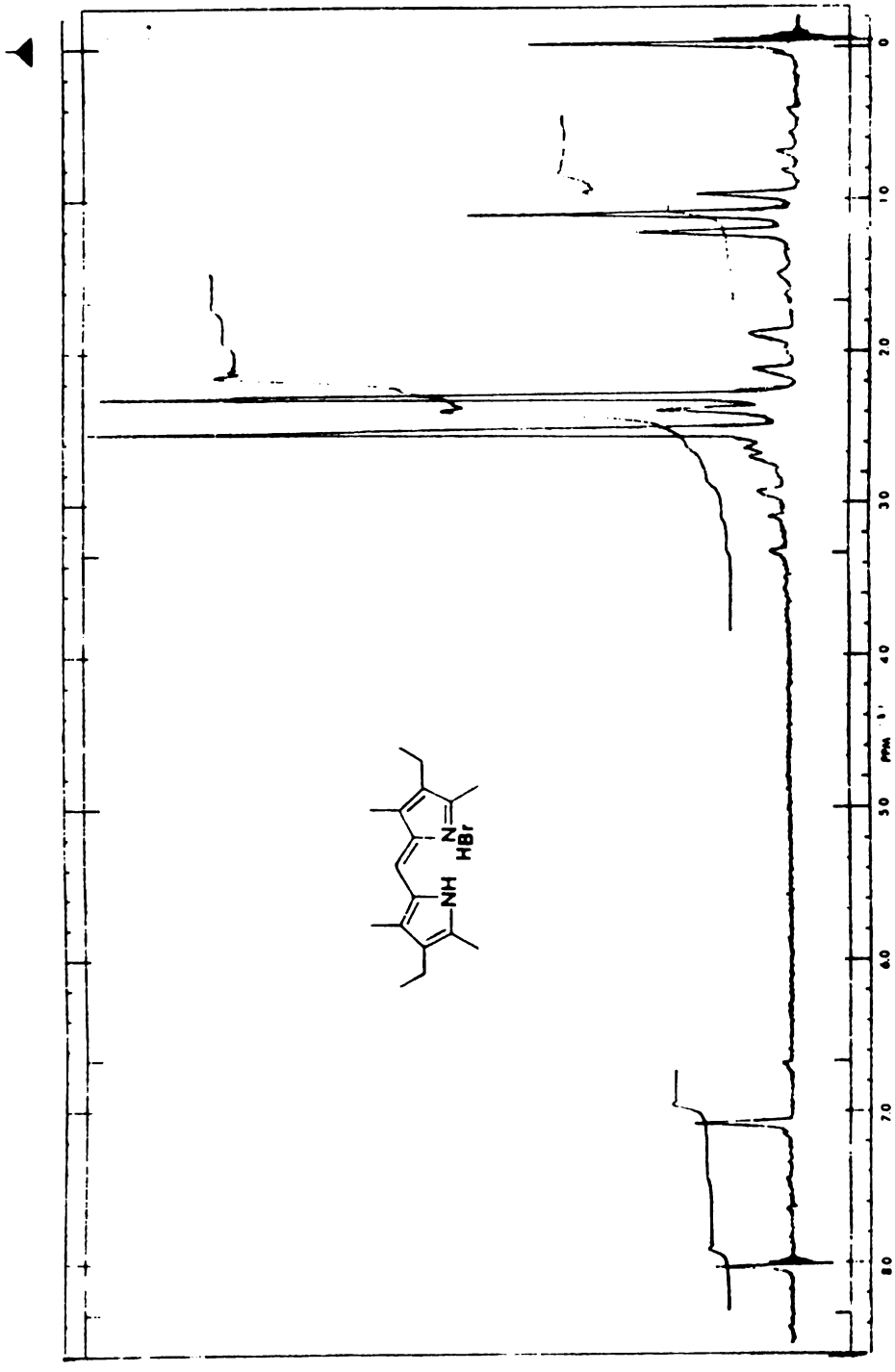


Figure 39, Nmr spectrum of 3,3',5,5'-tetramethyl-4,4'-diethyl-2,2'-dipyrromethene-HBr (**45**).

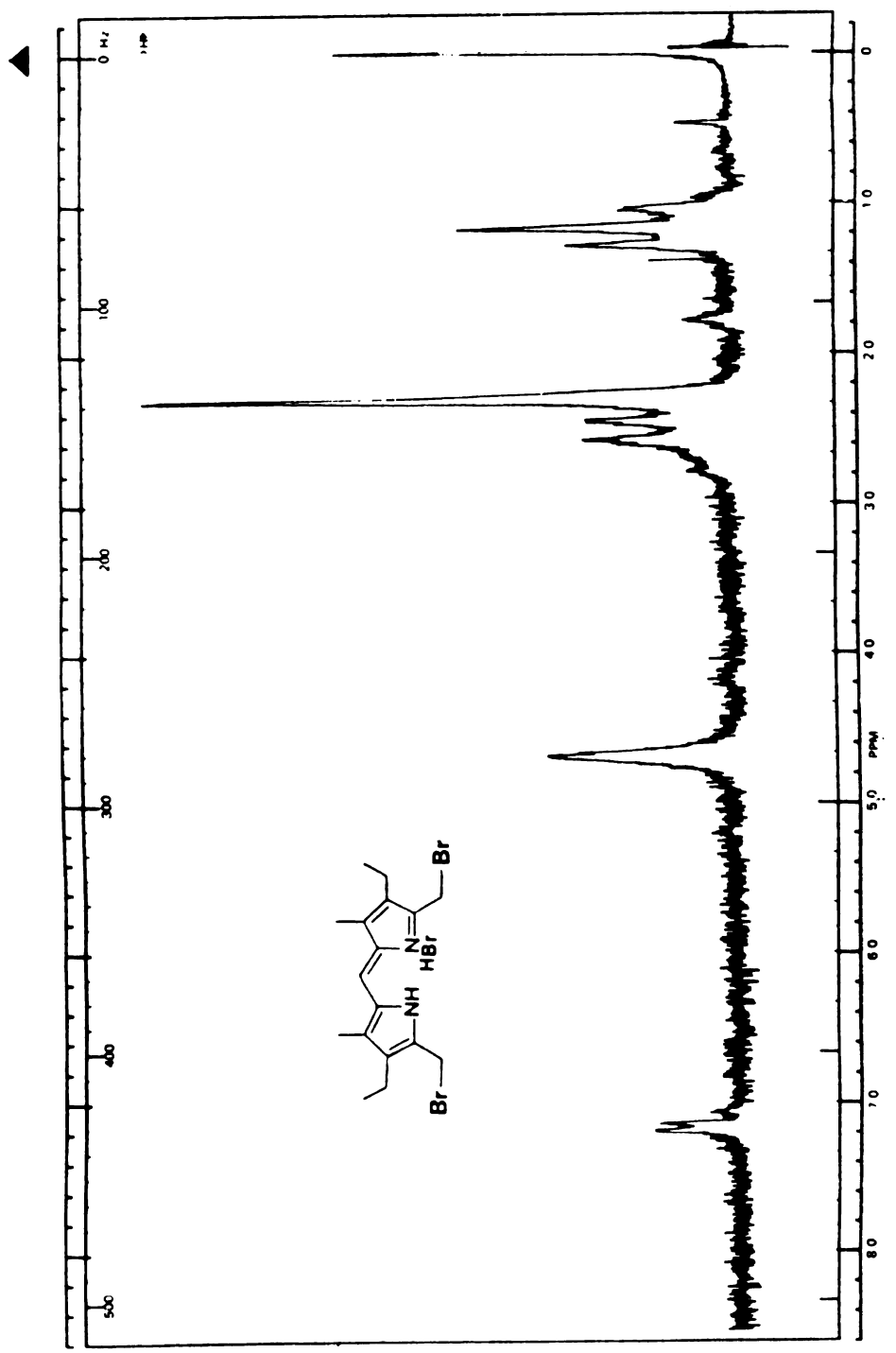


Figure 40, Nmr spectrum of 5,5'-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**60**).

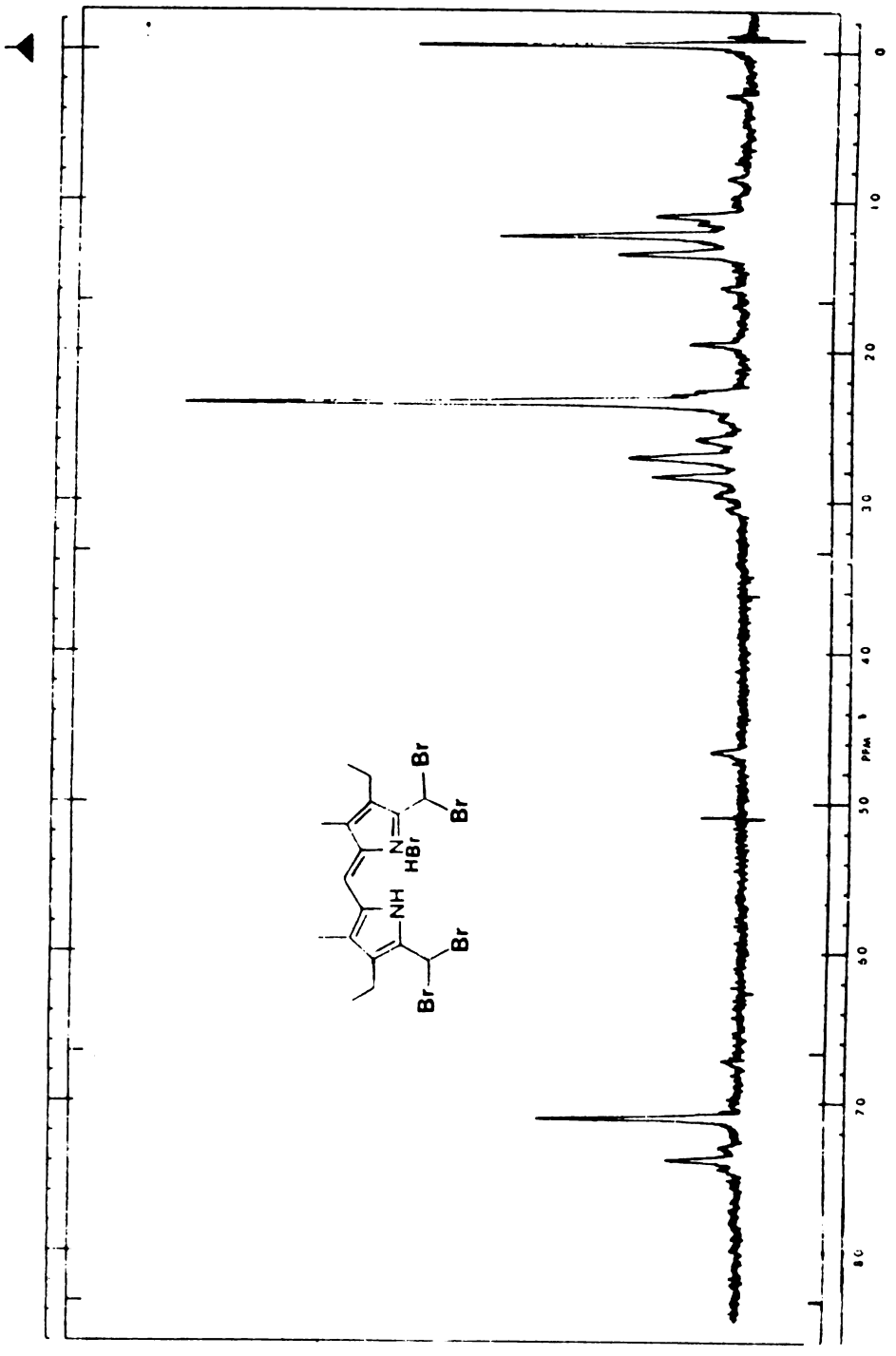


Figure 41, Nmr spectrum of 5,5'-di-dibromomethyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**61**).

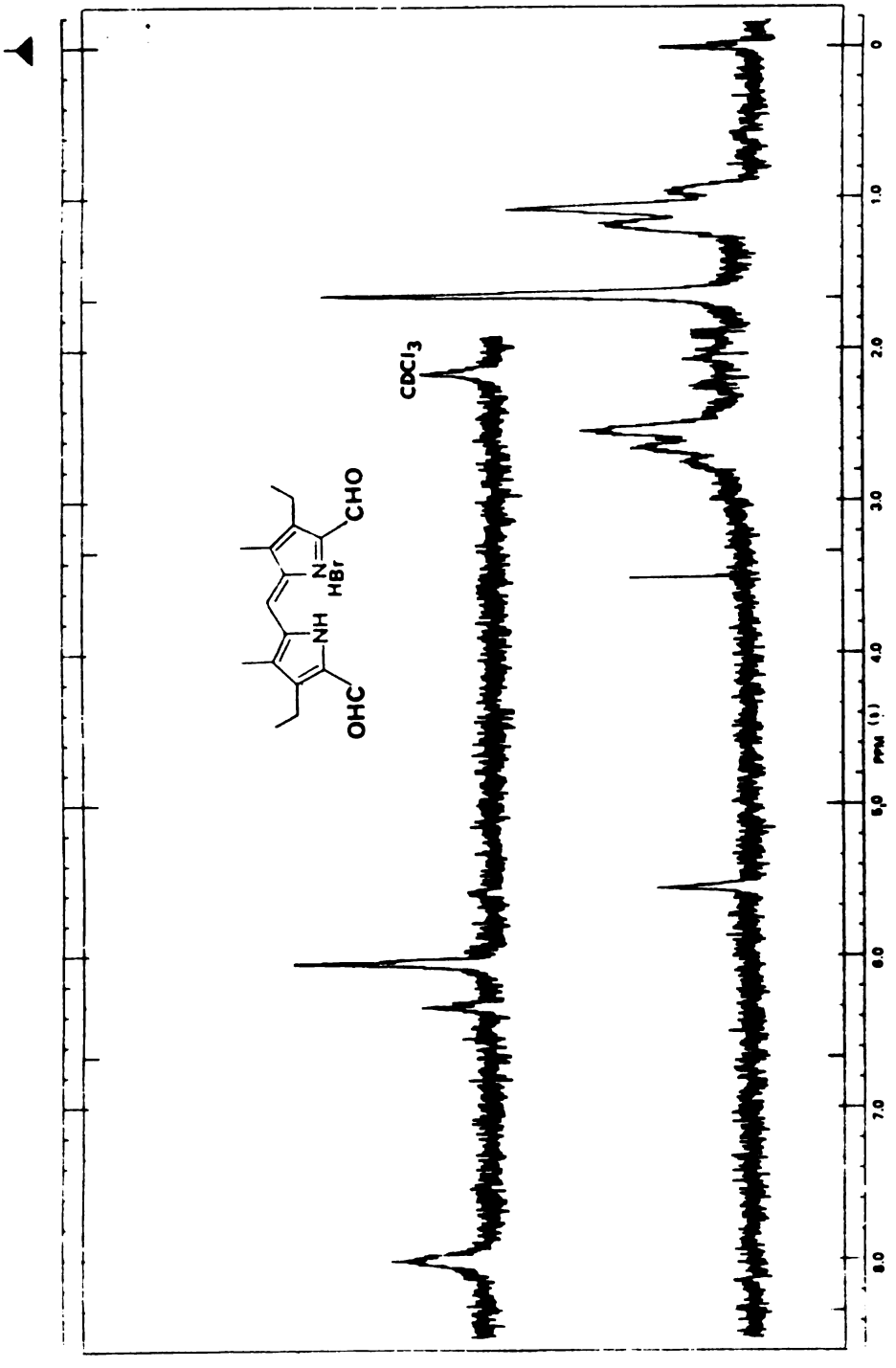


Figure 42, Nmr spectrum of 5,5'-diformyl-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrromethene-HBr (**53**).

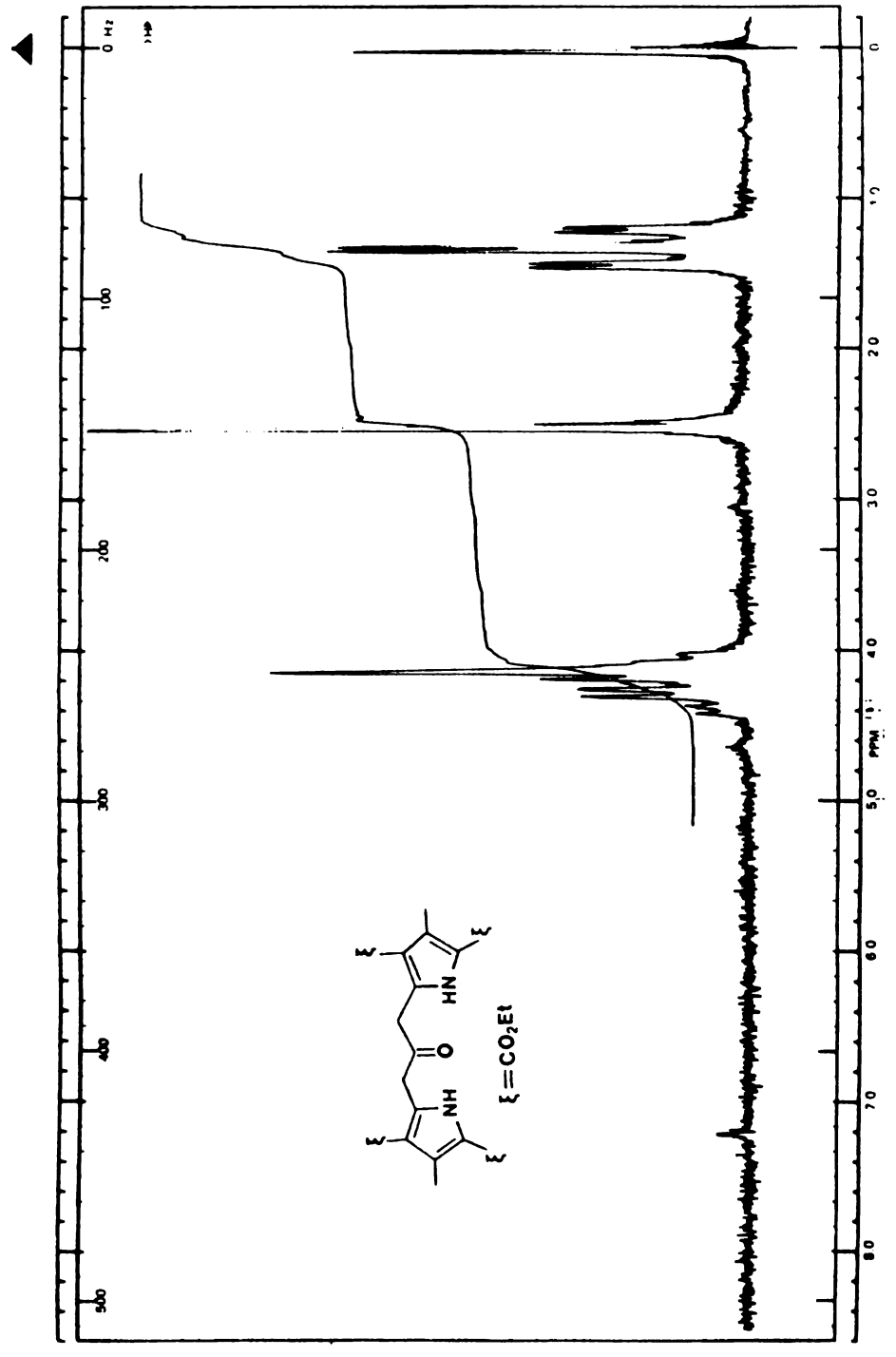


Figure 43, Nmr spectrum of 1,3-bis-(3,5-dicarbethoxy-4-methyl-pyrr-2-yl)-propan-2-one (**46**).

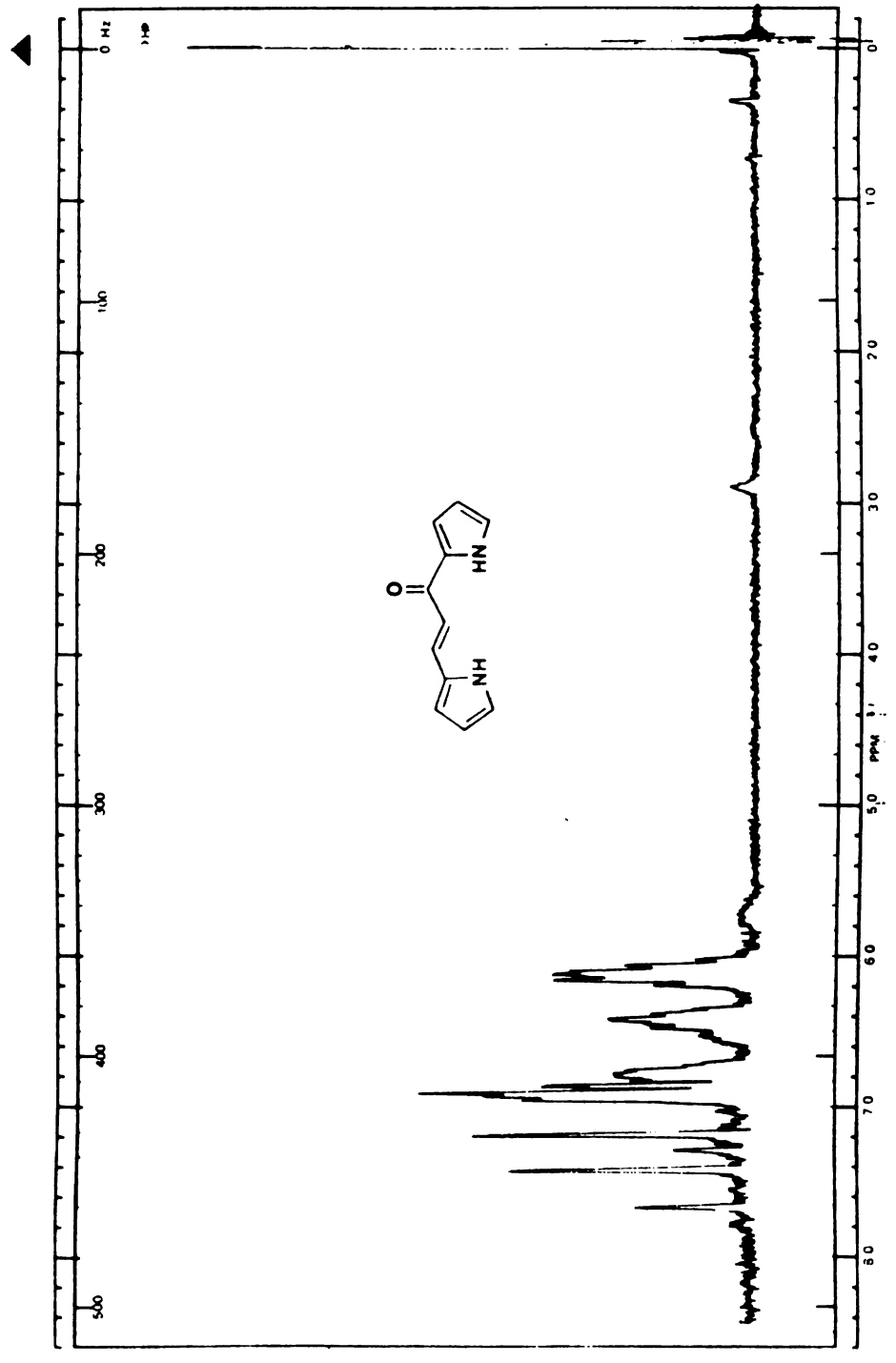


Figure 44, Nmr spectrum of 1,3-bis-(2-pyrryl)-1-propen-3-one (**47**).

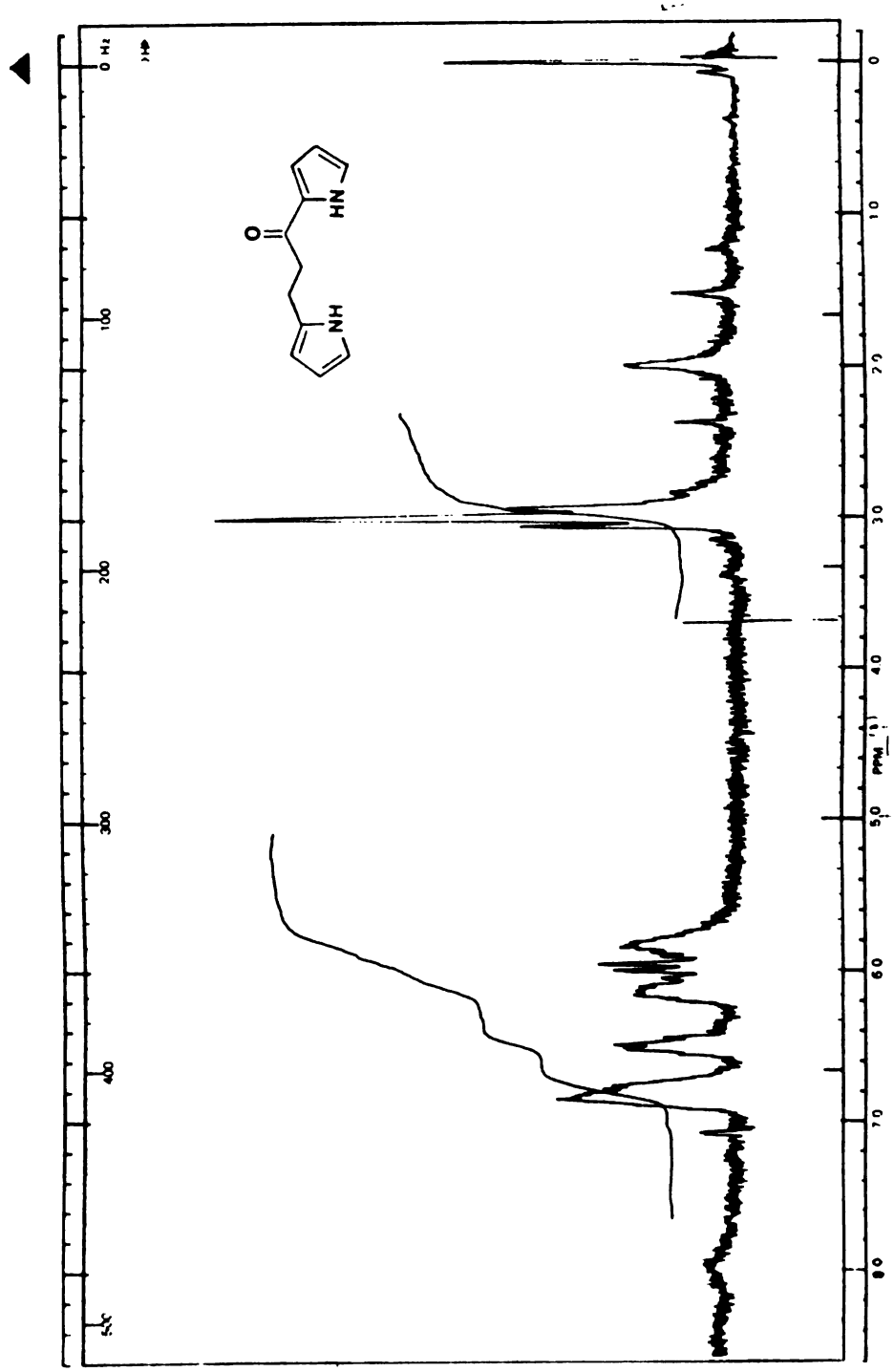


Figure 45, Nmr spectrum of 1,3-bis-2-pyrryl-propan-3-one (**88**).

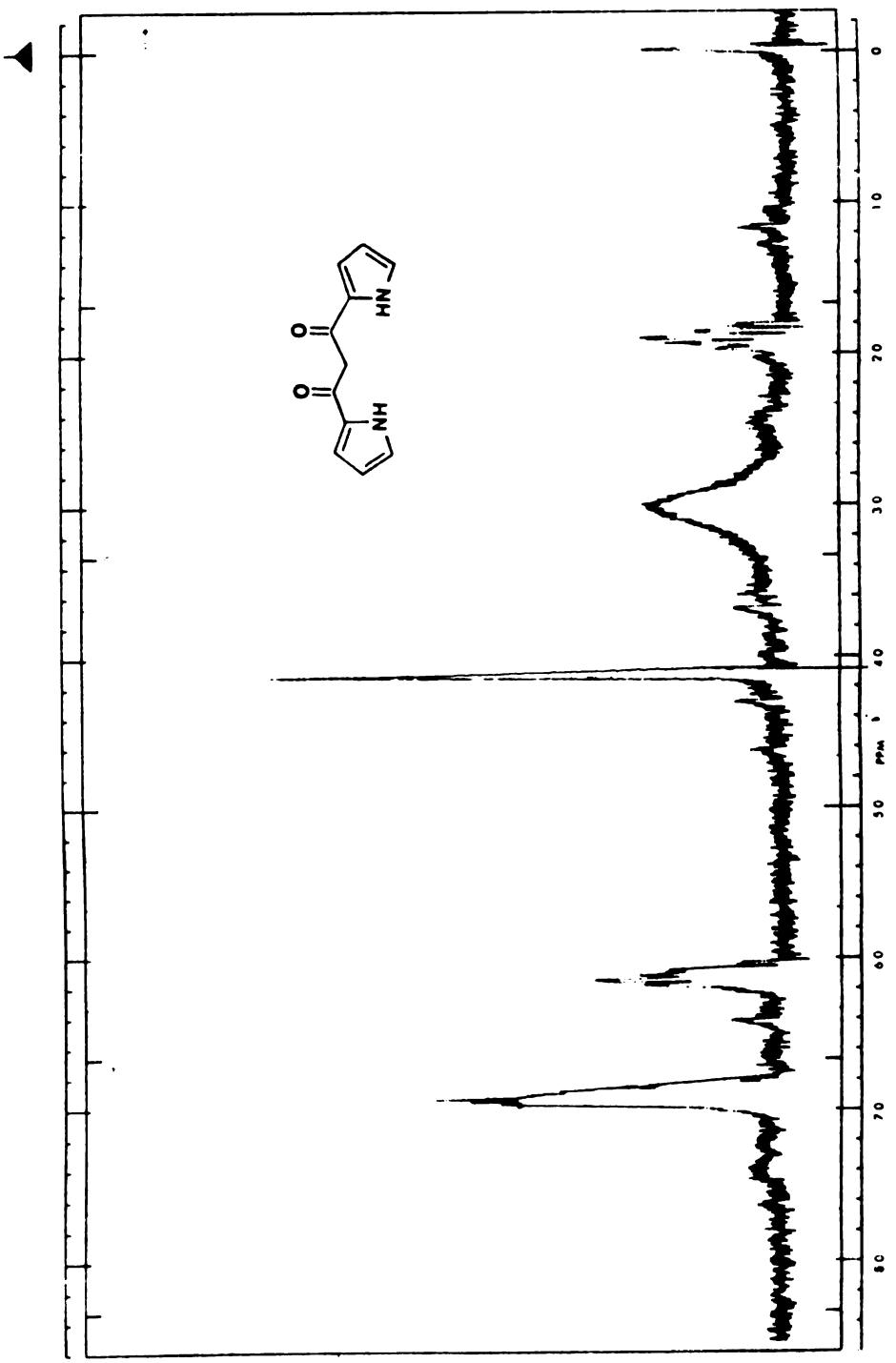


Figure 46, Nmr spectrum of 1,3-bis-(pyrr-2-yl)-1,3-propanedione (48).

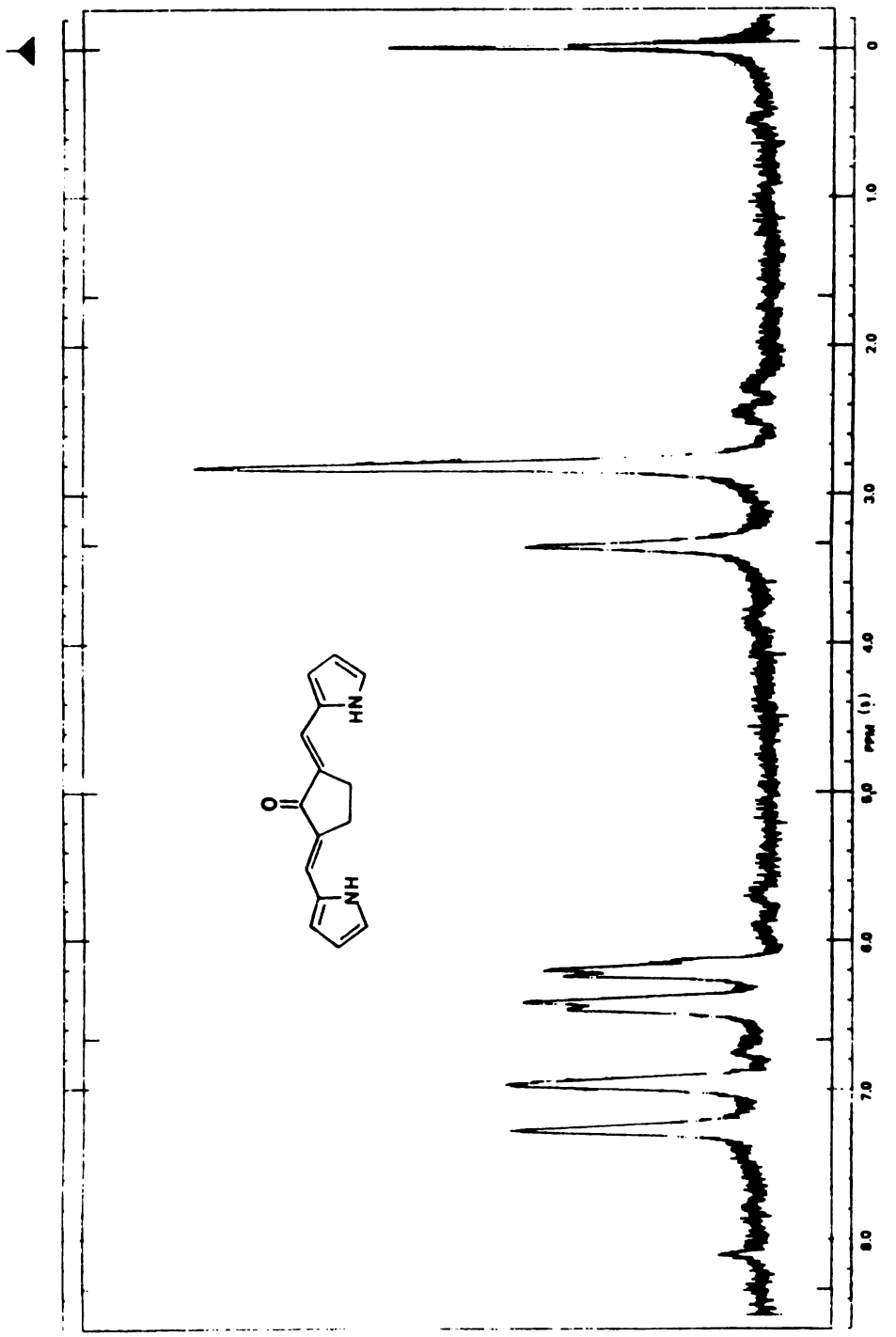


Figure 47, Nmr spectrum of 1,3-di-pyrr-2-ylmethylene-2-cyclopentanone (**49**).

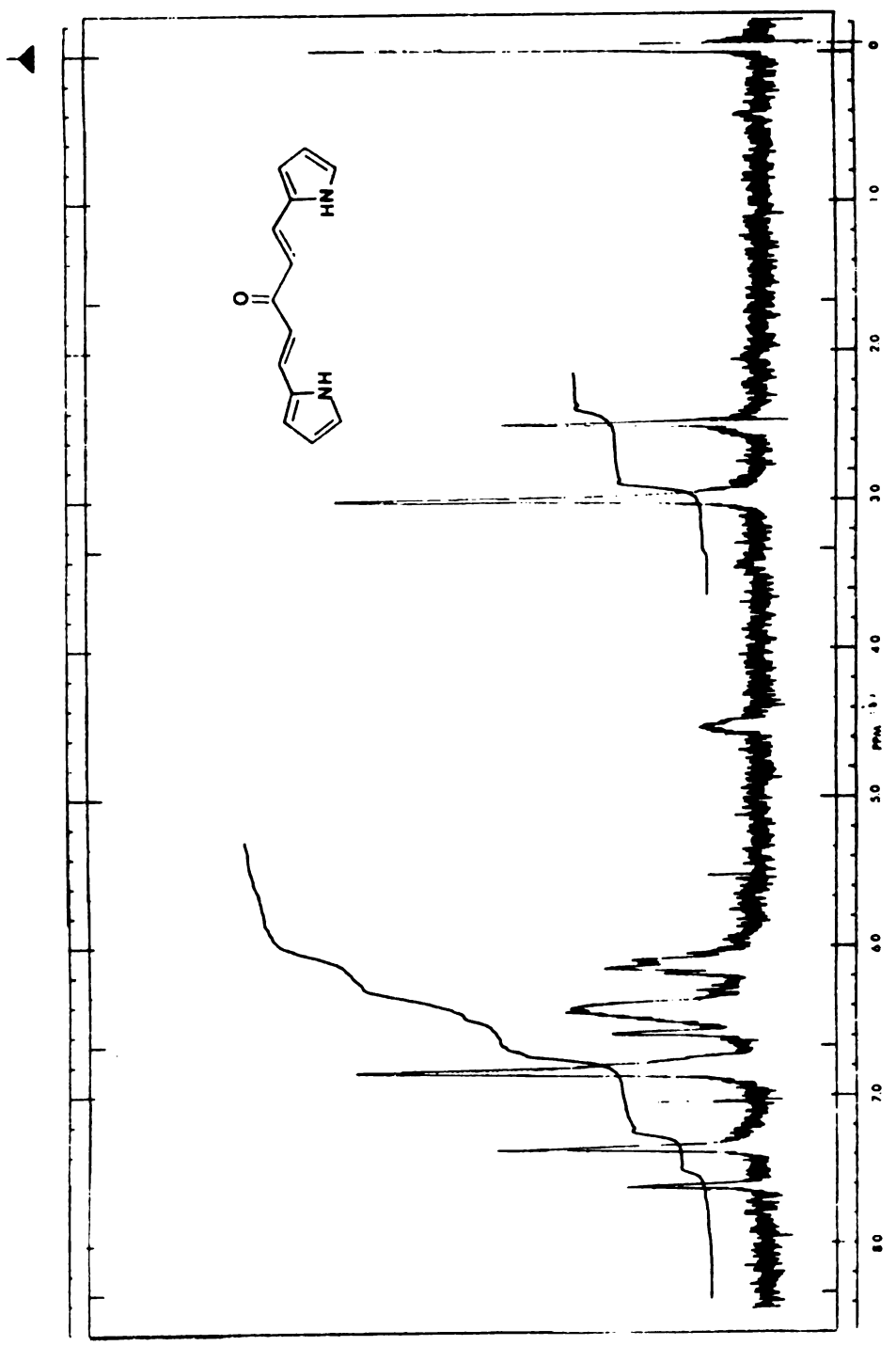


Figure 48, Nmr spectrum of 1,5-di-2-pyrryl-1,4-pentadien-3-one (**50**).

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