SYNTHESIS OF PYRROLE DERIVATIVES RELATED TO THE UROPORPHYRINS

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A thesis

by

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The author is deeply indebted to Professor E. Bullock for his supervision throughout this work, and to Memorial University of Newfoundland and the National Research Council for financial support. Thanks are also due to Mr. T. Buckley who ran the n.m.r. spectra.

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Addenda and corrigenda

p.6. 2nd para. A detailed study of decarboxylation of pyrrole carboxylic acids has been made by Chu and Chu, J. Org. Chem. 19, 266 (1955).

p.12. The range of experimental conditions used in this study do not entirely prove that the desulphurization of thiol esters to hydroxymethyl compounds occurs without the formation of an aldehyde intermediate.

p.30. Since completion of this thesis a new paper has appeared on diethyl β-oxoadipate (E.C. Taylor and A. McKillop, Tetrahedron 23, 897 (1967)) reporting a method which gives a much improved yield.

ABSTRACT

The biosynthesis of tetrapyrroles is briefly discussed and the important intermediates for chemical synthesis of these compounds are derived by valuable new methods.

Desulfurization of the pyrrole thiolesters was investigated, and the column reaction was introduced to improve the yield of the products.

Pyrrole aldehydes, hydroxymethyl pyrroles, and methyl pyrroles could be obtained from the corresponding pyrrole thiolesters in fairly good yields.

The hydroxymethyl group on pyrrole ring is easily converted to methyl group through chloromethyl group. Both β-hydroxymethyl pyrroles and β-chloromethyl pyrroles are easily converted to β,β'-dipyrromethanes in acidic medium.

N-H stretching of α-carbethoxydipyrromethanes is very similar to that of α-carbethoxypyrroles, and shows strong intermolecular hydrogen bonding in nonpolar solvents. α,α'-Dipyrromethanes which have adjacent carbethoxy groups show intramolecular hydrogen bonding where as β,β'-dipyrromethanes do not.

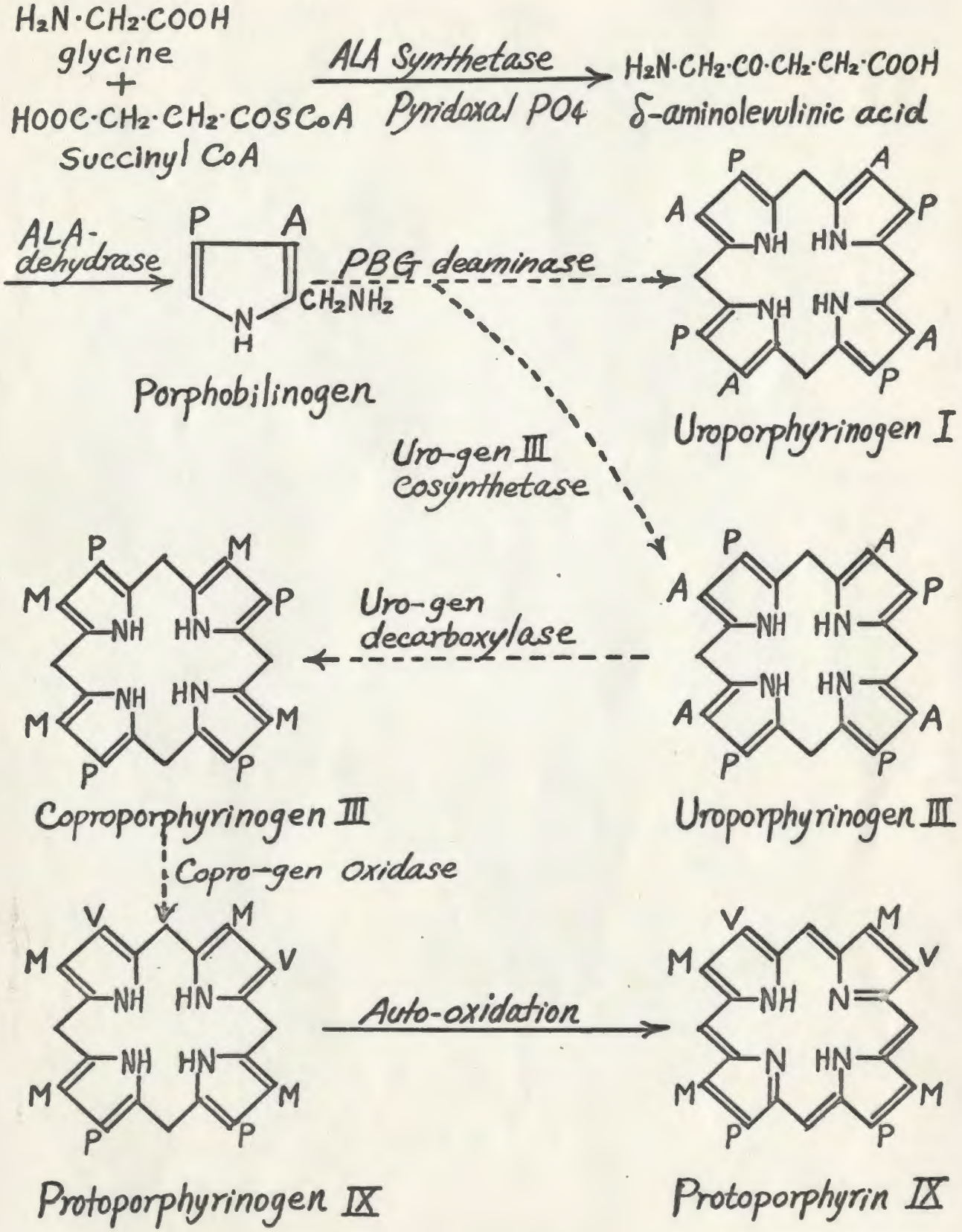
Infrared, ultraviolet and nuclear magnetic resonance spectra are given for all the new compounds.

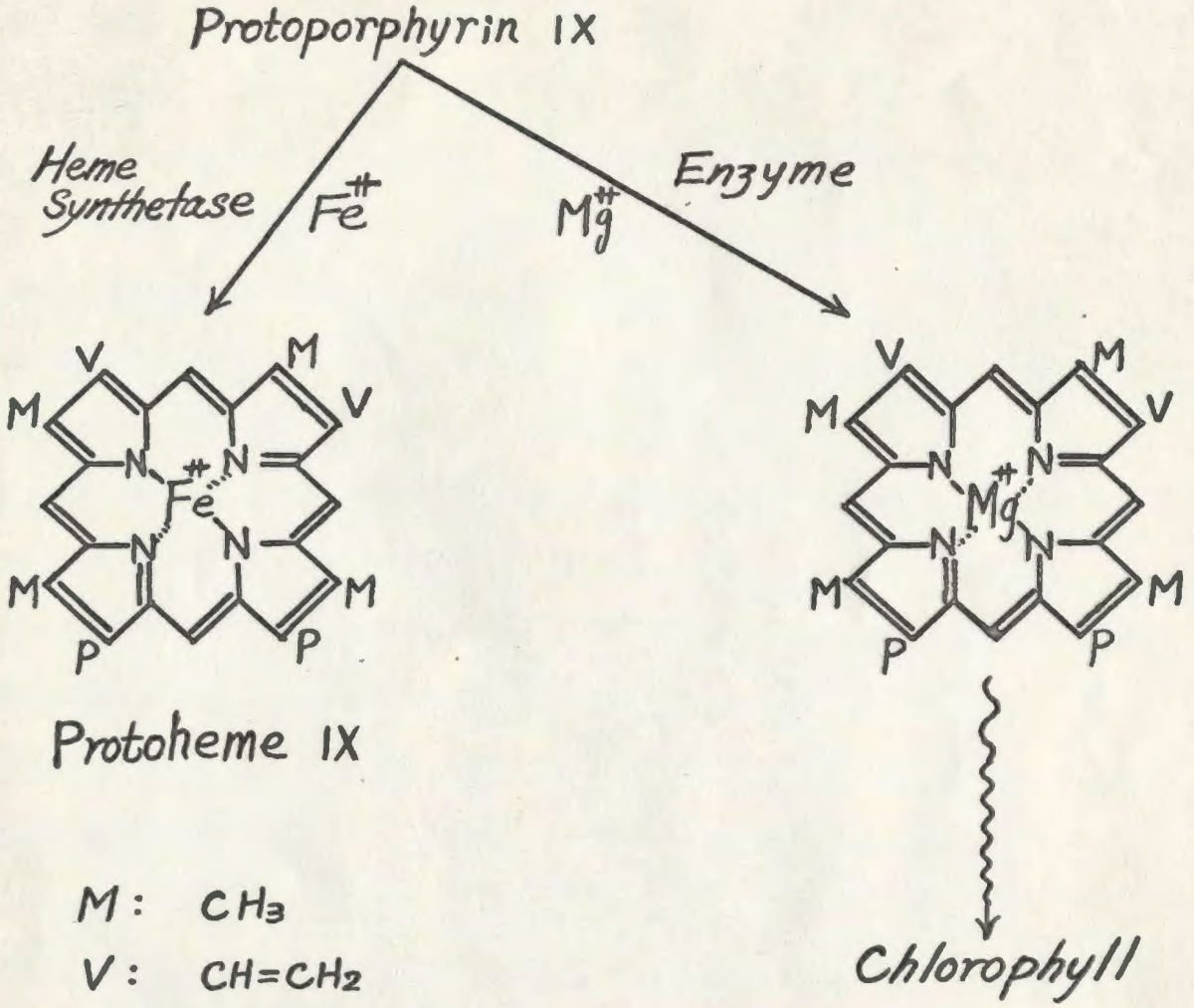
INTRODUCTION

Tetrapyrroles are found conjugated with proteins and widely distributed in most forms of life, ranging from unicellular microorganisms to the higher animals. These compounds function primarily in energy metabolism, as carriers of oxygen (hemoglobin, erythrocruorin, and myoglobin), as electron carriers (the cytochromes in many cells), leghemoglobin[1] in the nitrogen fixing bacteria, (Rhizobium), or as agents for trapping radiant energy (the chlorophyll in plants, phycocyanin and phycoerythrin in red and blue-green algae and the bacteriochlorophyll in some photosynthetic bacteria[2]). The Vitamin B_{12} group represents another type of tetrapyrrole. It acts as a co-factor in transmethylation reactions and nucleic acid synthesis, and probably arises from the same precursors as those of the porphyrins[3].

The biosynthetic pathway of these tetrapyrroles remains mostly unexplained[4]. Yet it is clear that the living cell utilizes the glycine and 'active succinate" to form δ-aminolevulinic acid (ALA) with ALA synthetase in the first step[5-7]. Pyridoxal phosphate was found to be a co-factor in this reaction.[6,7] Probably α-amino-β-oxoadipic acid first formed and was then decarboxylated spontaneously[8]. (The flow chart illustrates the biosynthesis of heme and chlorophyll).

BIOSYNTHESIS PATHWAY OF HEME AND CHLOROPHYLL.





M: CH_3

V: $CH=CH_2$

A: $CH_2 \cdot COOH$

P: $CH_2 \cdot CH_2 \cdot COOH$

The dashed arrows indicate the regions of mystery and speculation.

The ALA is then dehydrated by ALA dehydrase to form porphobilinogen (PBG).[9-12] In this reaction it is almost certain that the enzyme acts directly on ALA, and that elimination of both molecules of water occurs at the enzyme surface.[10] The following step is the cyclisation of the PBG to uroporphyrinogen I and III, and the work of Bogorad[13-15] has shown that the conversion of PBG to uroporphyrinogen IIIproceeds in at least two steps catalyzed by PBG deaminase and uroporphyrinogen III cosynthetase. The PBG can also be converted to uroporphyrinogen under acidic, neutral, and basic conditions in vitro, but the uroporphyrinogens are formed as a random mixture of isomers.[16-18] Moreover, the uroporphyrinogens are easily isomerized in hot acidic solution.[19]

acidic, I, 1/8; II, 1/8; III, 1/2; IV, 1/4

neutral, I, 1/2; (III+IV), 1/2,

basic, I, 3/4; (III+IV), 1/4.

But the enzyme, on the other hand, produces uroporphyrinogen III only.[14b] Therefore the above in vitro experiments do not correspond with the results of the biosynthetic reactions and thus cannot completely explain the mechanism of the formation of uroporphyrinogen III.

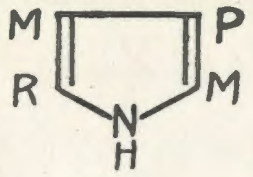
The next step is the decarboxylation of the uroporphyrinogen to coproporphyrinogen catalyzed by uroporphyrinogen decarboxylase, which was isolated from rabbit reticulocytes[20] and found to be active to all the uroporphyrinogen isomers I-IV.[21] Battle and Grinstein found that an intermediate, a heptacarboxylic acid, was isolated when

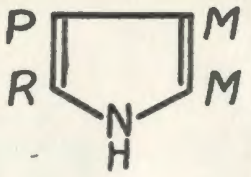
δ-aminolevulinic acid or porphobilinogen was incubated with whole blood or the supernatant liquid from normal rabbits and humans.[22] This heptacarboxylic acid was considered to be a normal intermediate during the decarboxylation of the uroporphyrinogen III.[23] In connection with the side chains of vitamin B_{12} the first step of the decarboxylation clearly occurs at the 5-position, but the order of decarboxylation of the propionic side chains in the other tetrapyrrole systems is still unknown. Coproporphyrinogen III is then further decarboxylated and dehydrogenated to protoporphyrinogen IX by the action of coproporphyrinogen oxidase, and this enzyme is specific for coproporphyrinogen III.[24] The intermediate with one vinyl and three propionic acid groups can be detected in the reaction mixture after short incubations. Protoporphyrinogen IX is dehydrogenated spontaneously to form protoporphyrin IX, which coordinates with ferrous ion and forms protoheme IX by the action of heme synthetase.[25] On the other hand, it reacts with magnesium ion under enzyme-catalysis to form magnesiumprotoporphyrin[26] and proceeds to chlorophylls in plant cells.

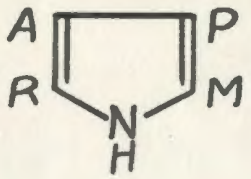
The initial object of the present study was a simplification of the known syntheses of pyrroles with the "uro-" and "copro-" side chains. This will lead ultimately to the preparation of the hepta-, hexa-, penta- and tricarboxylic porphyrins which are the likely intermediates in the biosynthesis of protoporphyrin IX.

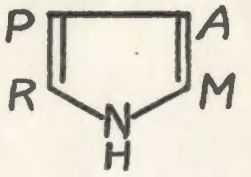
The solution of the unknown portions of the metabolic pathways now mostly depends on the synthesis of possible intermediates. The pyrroles shown in diagram (I), and their α-carbethoxy derivatives, are very important in the synthesis of uroporphyrin and its related compounds. MacDonald reviewed the possible routes to these pyrroles and has shown that the Knorr synthesis alone (with variations) is of practical value.[27] In comparison with the pyrrole IIa, in pyrroles of type IIb it is more difficult to introduce an electrophile into the unsubstituted position[28-30] due to the electron withdrawing effect and the steric effect of the ortho ester group, eg they do not even give a positive Ehrlich's reaction in the cold.[31] On the other hand, pyrroles of type IIa are easily attacked by electrophiles to give for example aldehyde, acetyl, and glyoxylic ester derivatives by the Gattermann-Hoesch reaction.[32] Therefore, the pyrroles (IIa) are advantageous starting materials for the synthesis of pyrroles of formula I.

There are three appropriate ways to prepare IIa. One is Fischer's classical method, which applies the Knorr synthesis, Condensation of acetoacetic ester with oximino acetoacetic ester or available α-oximino-β-keto acid ester forms pyrrole (III,R'=C00Et), which is hydrolysed to III, (R'=C00H), and then through thermal decarboxylation yields IIa[33,34]. MacDonald used benzyl acetoacetate instead of ethyl acetoacetate in the Knorr synthesis and got the corresponding pyrrole (III,R'=$C00CH_2C_6H_5$), which was debenzylated by hydrogenolysis to form III, (R'=C00H) in good yield.[35]







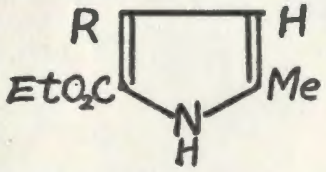


A: $CH_2 \cdot COOH$ (or ester); P: $CH_2 \cdot CH_2 \cdot COOH$ (or ester);

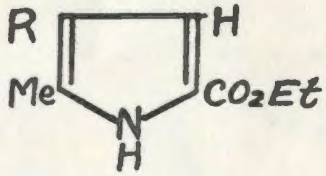
M: CH_3; R: H or $COOEt$

I

a.

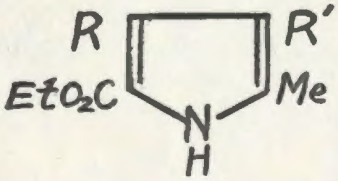


b.



R: *any desired group*

II



R: CH_3; $CH_2 \cdot CO_2Et$; $CH_2 \cdot CH_2 \cdot CO_2Et$

III

Later, Treibs[36] found that t-Butyl ester acted as a good protecting group in making pyrrole IIa. The corresponding ester III, ($R'=COOCMe_3$) was obtained by means of the Knorr synthesis when t-Butyl acetoacetate was used instead of ethyl acetoacetate, and the pyrrole t-Butyl ester was easily converted to the acid III, ($R'=COOH$) by acidic de-esterification.[36]

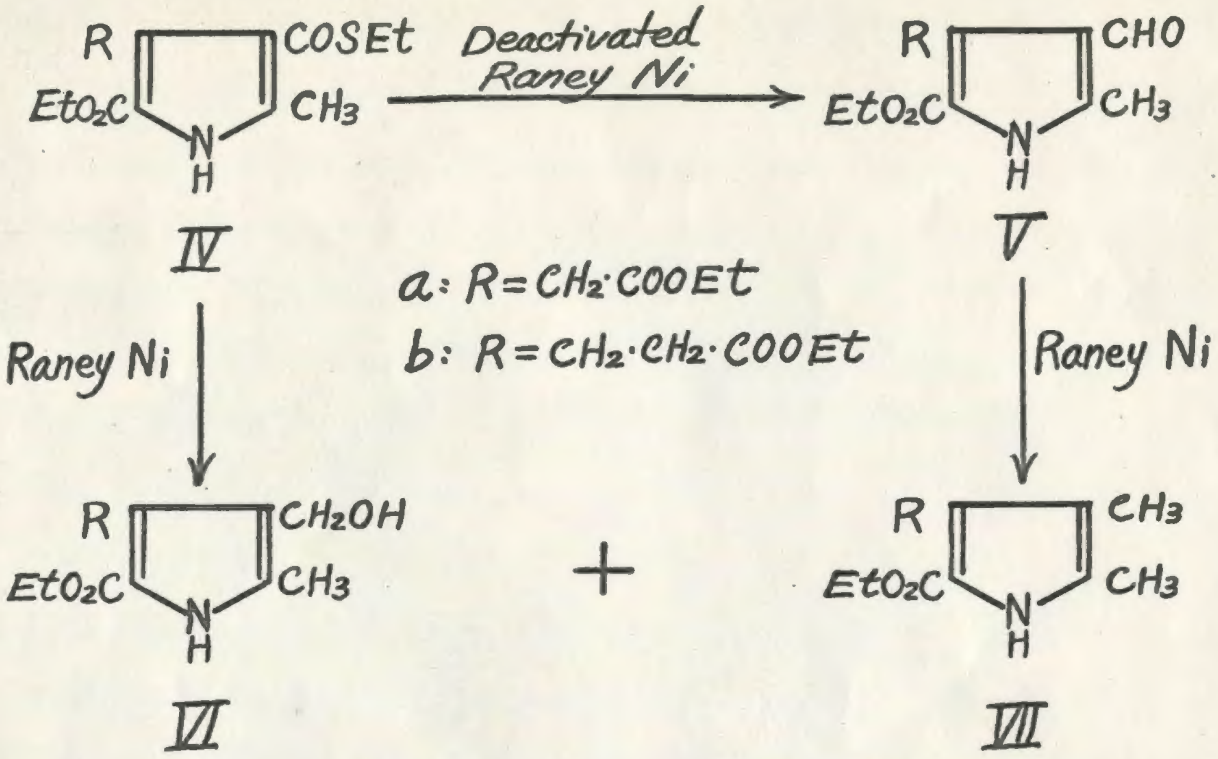
DISCUSSION

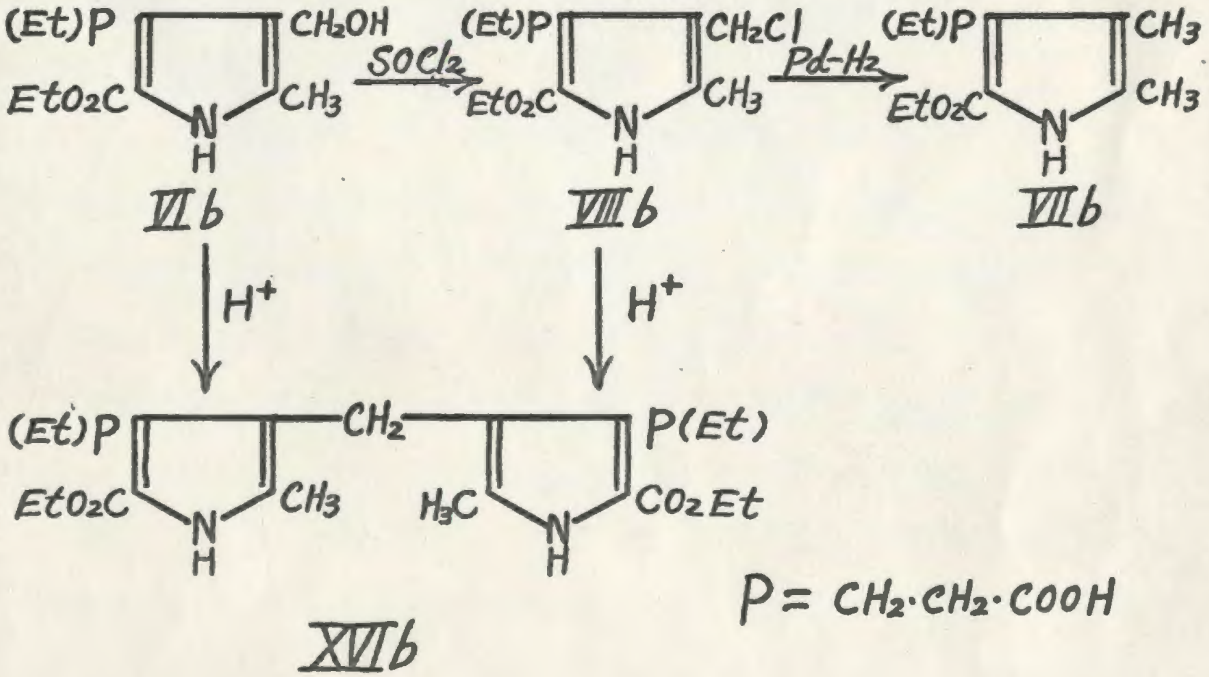
(A) Pyrrole thiolesters and desulfurization.

The pyrroles which have methyl and propionic acid or acetic acid and propionic acid in β,β'-positions are the important intermediates in the synthesis of Uroporphyrins, Coproporphyrins, and related compounds.[35] Fischer,[33,34] MacDonald,[35] and Treibs[36-38] separately introduced efficient methods to obtain the β-free pyrroles IIa. Fisher's classical method used ethyl ester as protecting group, which was easily removed by hydrolysis and thermal decarboxylation. However, it was not a satisfactory method because it sometimes causes the undesirable de-esterification of the other ester group. MacDonald's method and Treib's method were much better for with them selective de-esterification is possible. Recently, Loader[39] has demonstrated that the thiolcarbonyl group was a useful protecting group in the synthesis of pyrroles I, as it may be converted to various groups, such as, formyl-, hydroxymethyl-, and methyl, by treatment with

different grades of Raney nickel.[40,41] Several Knorr type pyrrole thiolesters were synthesized in good yield by the general method and their physical properties and desulfurization reactions were investigated.[39] When oximinoacetonedicarboxylic ester and β-keto-α-oximino-adipic ester were condensed with ethyl acetothiolacetate, the corresponding pyrrole thiolesters (IVa and IVb) were obtained in 50-55% yield.

The desulfurization of steroid thiolesters with Raney nickel has been investigated in detail by McIntosh et al.[42-44] They found that more active Raney nickel (W-4) has a high tendency to convert the thiolcarbonyl group to hydroxymethyl (almost quantitatively) in comparison with W-1, and the reaction easily took place either at room temperature or in refluxing alcohol. If deactivated W-1 was used instead of W-4, the aldehyde was the major product, and very little of hydroxymethyl compound was formed.[42] The desulfurization of steroid thiolcarboxylic acid ethyl-, isopropyl-, and benzyl- esters was also investigated by McIntosh et al,[44] and the ethyl ester gave a much better yield of aldehyde than the others. After modifying the above method, and using deactivated Raney nickel (W-2) in the desulfurization reaction, the pyrrole thiolesters (IVa and IVb) were converted to aldehydes (Va and Vb) in fairly good yield (70-80%), and only small amounts of hydroxymethyl pyrroles (VIa and VIb) were formed as byproducts. Urashibara nickel-B,[45] unflammable nickel catalyst, has almost the same effect as W-2 in this type of reaction.


R
COSEt
EtO2C
CH3
N
H
Deactivated
Raney Ni
R
CHO
EtO2C
CH3
N
H
IV
V
a: R = CH2·COOEt
b: R = CH2·CH2·COOEt
Raney Ni
Raney Ni
R
CH2OH
EtO2C
CH3
N
H
+
R
CH3
EtO2C
CH3
N
H
VI
VII


(Et)P
CH2OH
EtO2C
CH3
N
H
SOCl2
(Et)P
CH2Cl
EtO2C
CH3
N
H
Pd-H2
(Et)P
CH3
EtO2C
CH3
N
H
VIb
VIIIb
VIIb
H+
H+
(Et)P
CH2
P(Et)
EtO2C
CH3
H3C
CO2Et
N
H
N
H
P = CH2·CH2·COOH
XVIb

For large scale reactions, Raney nickel was mixed with deactivated silica gel and packed into a chromatographic column. The pyrrole thiolester was desulfurized when it passed through the column, and the yield of the aldehyde was higher than with the usual procedure.

The thiolcarbonyl group may also be converted to methyl group (VIIa and VIIb) with Raney nickel, but the yield was very low compared to the amount of the corresponding hydroxymethyl pyrroles (VIa and VIb) formed. When the reaction was carried out under hydrogen (55 p.s.i.) and the temperature raised to 70°, the yield of the methyl pyrrole (VIIb) improved. The main product however was still hydroxymethyl pyrrole (VIb) as shown by the n.m.r. spectrum. With the addition of acetone to the above reaction mixture, the desulfurization reaction seems to favour the formation of methyl pyrrole, and the yield of the methylpyrrole is slightly increased by the amount of acetone used.

Fischer[46] and Morsingh[47] obtained 2,3,4-trimethyl-5-carbethoxypyrrole and 2,3-dimethyl-4-carbethoxyethyl-5-carbethoxypyrrole from the corresponding pyrrole aldehyde in good yield by hydrogenation in the presence of Raney nickel under high temperature and pressure. The latter compound was obtained only in very low yield in hydrogen (55 p.s.i.) at 70° with Raney nickel and the hydroxymethyl pyrrole (VIb) was the main product. According to these observations, the formation of the hydroxy-

methyl compound and the methyl pyrrole (Vllb) from the thiol ester seem to follow different mechanisms, and the high temperature and high pressure favour the formation of the methyl group. Desulfurization reactions of the pyrrole thiolesters under high temperature and high pressure were not investigated.

(B) Condensation of pyrrole aldehydes and malonic ester.

Pyrrole aldehyde (Va) and ethyl hydrogen malonate were condensed under reflux with piperidine and pyridine, and the resulting vinyl ester (Xll) was hydrogenated quantitatively to pyrrole ester (Xlll) by Adam's catalyst under hydrogen (50 p.s.i.) at room temperature. A byproduct, m.p.160-162°, colorless prisms, was obtained from this condensation. It appears to be the ββ'-dipyrromethane (XVlb) and was probably formed from the hydroxymethyl pyrrole (Vla, as impurity in the aldehyde). The byproduct was identical with the compound obtained by refluxing the hydroxymethylpyrrole (Vla) with acetic acid and anhydrous sodium acetate.

(C) Chloromethyl pyrrole (Vlllb).

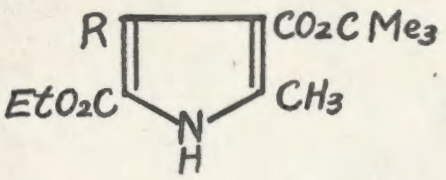
The unexpected hydroxymethylpyrrole (Vlb) from the desulfurization of pyrrole thiolester (IVb) was converted to the chloromethylpyrrole (Vlllb) with thionyl chloride quantitatively at room temperature. The chloromethylpyrrole (Vlllb) was very reactive and easily formed

the β,β'-dipyrromethane (XVIb) by heating or even on recrystallization. The chlorine atom was easily removed by catalytic dehalogenation. This reaction sequence thus offers a simplified method for obtaining the difficult methylpyrrole (VIIb), which is an important intermediate in projected syntheses of the penta, hexa and hepta carboxylic acid porphyrin derivatives.

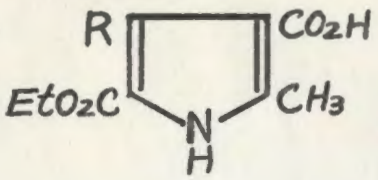
(D) Decarboxylation of t-Butyl pyrrole carboxylate.

t-Butyl ester is a good protecting group in pyrrole synthesis as it is easily removed by acidic deesterification and decarboxylation. When t-Butyl pyrrole carboxylates (IXa and IXb) are refluxed with 80% acetic acid, the corresponding pyrrole carboxylic acids (Xa and Xb) are obtained in nearly quantitative yields, and a trace of p-toluenesulfonic acid in place of acetic acid produced the same results. The latter can also be used to prepare the corresponding β-free pyrroles (XIa and XIb) by heating with the t-Butyl pyrrole carboxylates.[38] However p-toluenesulfonic acid is a strong acid and it will cause some deesterification of the other ester groups. If a small amount of the corresponding pyrrole carboxylic acids (Xa and Xb) is used instead of p-toluenesulfonic acid in the reaction, the β-free pyrroles are obtained in high yield, and the purity is satisfactory for further synthetic reactions. In fact, the pyrrole aldehydes (Va and Vb) were obtained in 46% and 79% directly from the t-Butyl pyrrole carboxylates (IXa and IXb), and the pyrrole glyoxylic ester (XIV) was obtained in 86% from IXb.

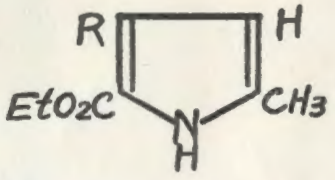
a: R = $CH_2 \cdot COOEt$; b: R = $CH_2 \cdot CH_2 \cdot COOEt$



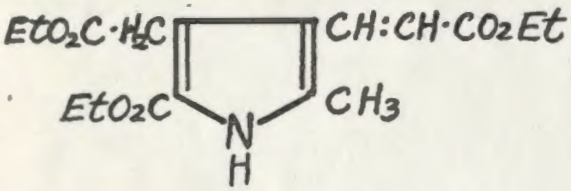
IX



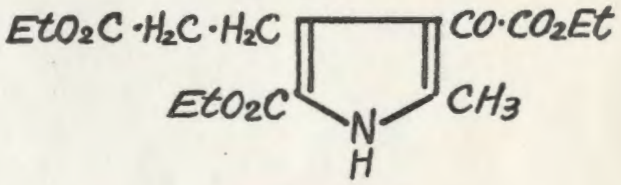
X



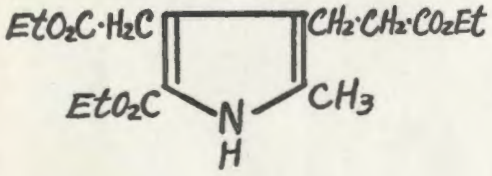
XI



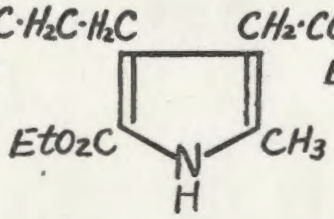
XII



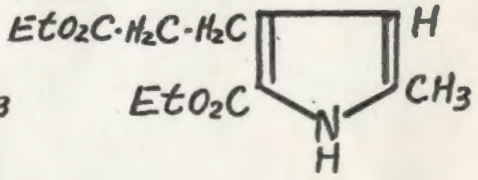
XIV



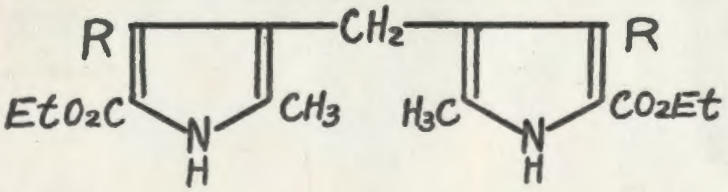
XIII



XV



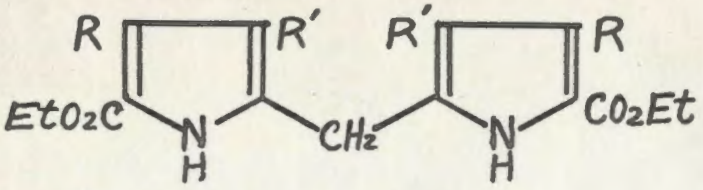
XIX



XVI

a: R = $CH_2 \cdot CO_2Et$

b: R = $CH_2 \cdot CH_2 \cdot CO_2Et$

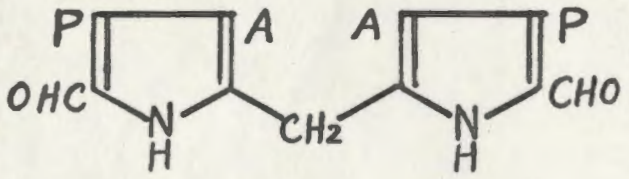


XVII

a: $R = CH_3$
$R' = CH_2 \cdot CH_2 \cdot CO_2Et$

b: $R = CH_2 \cdot CO_2Et$
$R' = CH_2 \cdot CH_2 \cdot CO_2Et$

c: $R = CH_2 \cdot CH_2 \cdot CO_2Et$
$R' = CH_2 \cdot CO_2Et$



XVIII

A: $CH_2 \cdot CO_2CH_3$

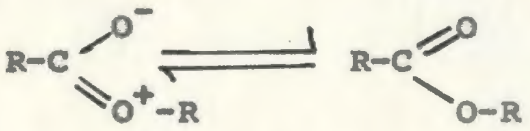
P: $CH_2 \cdot CH_2 \cdot CO_2CH_3$

Infrared Spectra.

A. Pyrrole thiolesters.

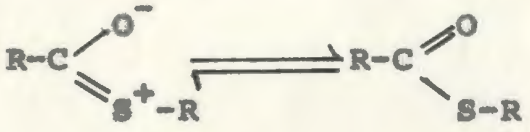
Nyquist and Potts have collected a large amount of infrared data on thiol esters.[48] In simple compounds the thiolesters show carbonyl bands at about 1675 cm^{-1} (e.g. for ethyl thiolacetate 1691 cm^{-1}). The carbonyl bands for the corresponding esters appear at rather higher frequencies, usually at about 1735 cm^{-1}. It is generally accepted that this is a result of a difference in the relative importance of the resonance structure A over B in thiolesters, whereas B predominates in esters:-

Ester,



(A) (B)

Thiolester,



(A) (B)

Recently, Schleppnik and Zienty have obtained spectra of thiolcrotonates and 3-mercaptothiolpropionates[49]. The carbonyl bands of thiolcrotonates are observed in the region 1667-1685 cm^{-1} and the 3-mercaptothiolpropionates at 1685-1697 cm^{-1}. If we accept the value of 1735 cm^{-1} for the carbonyl frequency of normal straight chain esters

and 1690 cm^{-1} for the corresponding thiolesters, the change in frequency is about 45 cm^{-1}. In addition, the α-carbonyl band of the Knorr's pyrrole occurs at 1668 cm^{-1} and the β-carbonyl at 1686 cm^{-1}[50]. From these data, the changes of the α-carbonyl and β-carbonyl from the saturated ester are 67 cm^{-1} and 49 cm^{-1}. Thus, Loader[39] formulated a method of assigning the carbonyl bands of the pyrrole thiolesters as follows:

$\delta\alpha = 45 + 67 = 112\ cm^{-1}$, and $\delta\beta = 45 + 49 = 94\ cm^{-1}$

and found the experimental results quite close to the prediction (α-carbonyl 1626 cm^{-1} and β-carbonyl 1641 cm^{-1} for the thiolesters). The pyrrole thiolesters (IVa and IVb) prepared here showed carbonyl bands at 1631 cm^{-1} and 1639 cm^{-1}. The latter was very close to the prediction 1641 cm^{-1}, and 10 cm^{-1} shift of the former from the prediction is probably due to the electron-withdrawing group, CH_2COOEt.

The thiolesters examined by Nyquist and Potts[48] also showed bands in the 1060-1210 cm^{-1} region which they assigned to -C-C- stretching frequencies and bands in the region 880-1030 cm^{-1} assigned to -C-S- stretching frequencies. The above pyrrole thiolester showed strong bands (IVa at 1073 and 895 cm^{-1}, and IVb at 1078 and 897 cm^{-1}) in these regions.

B. Pyrroles and Dipyrromethanes.

Pyrrole itself shows a large variation in N-H stretching frequency by concentration and solvent polarity. Josien, Fuson et al[51] found that dilute solutions of pyrrole in non-polar solvents show sharp band at 3495 cm^{-1}, whereas concentrated solutions showed broad bands at 3400 cm^{-1} due to hydrogen-bonded molecules. These N-H stretching frequencies are greatly affected by various hydrogen-bond acceptor substituents on the pyrrole rings,[52-54] and the α-substituted pyrrole, such as α-formyl, acyl, carbethoxy-pyrrole, are strongly associated with N-H of another molecule as external hydrogen bonding. The principal species is the dimer (XX) in concentrated non-polar solvents. The intensity and the frequency of N-H are increased with the electron withdrawing power of the group.[55,56]

According to Kuhn and Kleinspehn[57], the poly-substituted pyrroles which do not contain a carbethoxy group (or a group capable of acting as a hydrogen acceptor) in the 5-position, the N-H stretching frequencies are at 3484-3488 $cm.^{-1}$ When there is a carbethoxy group in the 5-position, the N-H band is slightly lowered to 3456 cm^{-1} and has a shoulder at 3485 cm^{-1} indicating the possibility of hydrogen bond, in which the carbethoxy group (in the 5-position) acts as the hydrogen acceptor.

The N-H stretching frequencies of dipyrromethanes are very similar to those of simple pyrroles, and are greatly affected by the substituted group and its positions.[57] If 2,2'-dipyrromethanes contain the carbethoxy

group in the 3-, and 3'- positions, the spectra show only a bonded N-H band. Each N-H is intramolecularly bonded to the carbethoxy group of the other ring (XXl).

When a carbethoxy group is present in the 3-, but not in the 3'-position, the compounds have one free and one bonded (intramolecular) N-H. When neither the 3- nor the 3'- positions have carbethoxy group, only a free N-H band is observed. The 3,3'-dipyrromethanes containing the carbethoxy group in the 4-, and 4'- positions only show N-H free band for it is too far to form an intramolecular hydrogen bond with N-H of the other ring.

The 3,3'-dipyrromethanes (XVIa and XVIb) belong to the last type, and only show a free N-H band. The 2,2'-dipyrromethanes (XVIlC and XVIll) only showed N-H bonded band, and probably the 3,3'-carbethoxymethyl groups act as hydrogen acceptors and form strong intramolecular hydrogen bonds. The 2,2'-dipyrromethanes (XVlla and XVllb) showed free N-H and N-H bonded bands. This indicates either one free N-H and one N-H bonded or both are weakly intramolecularly bonded in this type of compound.

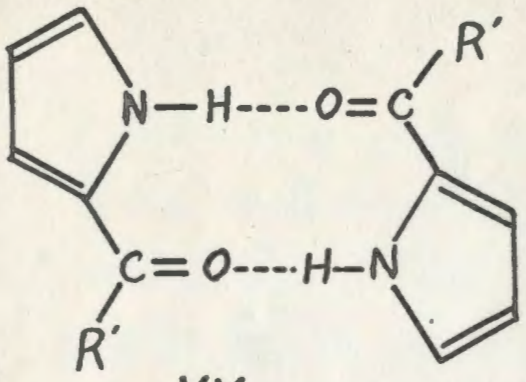
Lord and Miller[58] and Jones[59] have reported the following bands 1527, 1473, 1418 and 1389 cm^{-1} in pyrrole corresponding to the ring stretching frequencies. But only three bands, 1560 ($\pm$ 10), 1468 ($\pm$7) and 1416 ($\pm$ 12) cm^{-1}, were observed in 2-substituted pyrroles.[59] Eisner and Erskine[50] have reported the strong bands at 1565 and 1500 cm^{-1} for polysubstituted pyrroles. But the pyrroles and dipyrromethanes examined here are very complicated and it is difficult to assign the bands in this region.

The hydroxymethyl pyrroles (Vla and Vlb) both showed two sharp peaks at 3450 and 3433 cm^{-1} and weak broad bands at 3500 and 3280 cm^{-1} in the non-polar solvent (CCl_4). The sharp peaks at 3450 and 3433 cm^{-1} do not change on dilution. When chloroform was used as solvent, only one sharp peak at 3433 cm^{-1} was observed. Therefore, the hydroxymethyl pyrroles (Vla and Vlb) form (XXll) strong intramolecular bonds between OH and carbonyl group in the non-polar solvent.

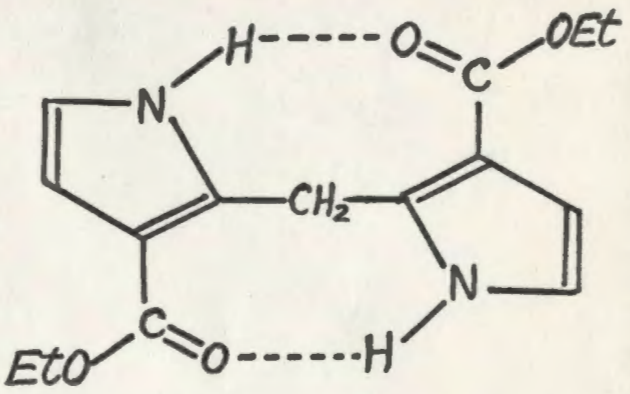
TABLE I

N-H Stretching Frequencies of Dipyrromethanes

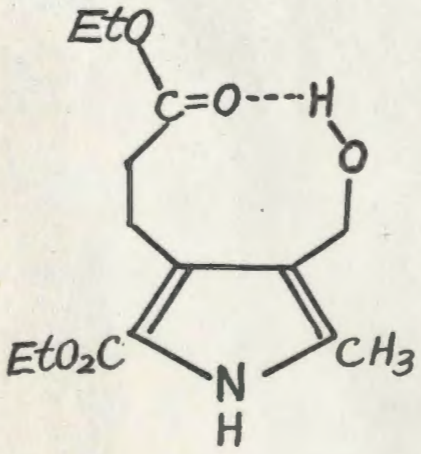
Compounds	Solvent	Free N-H (cm^{-1})	H-bonded N-H(cm^{-1})
5,5′-Dicarboxypyrromethane-4,4′-dimethyl-3,3′-dipropionic acid tetraethyl ester (XVIIa)	CCl_4	3427 (shoulder)	3335 (broad,S)
	$CHCl_3$	3427 (sharp,S)	3342 (broad,M)
5,5′-Dicarboxypyrromethane-4,4′-diacetic acid-3,3′-dipropionic acid hexaethyl ester (XVIIb)	CCl_4	3428 (shoulder)	3333 (broad,S)
	$CHCl_3$	3419 (sharp,S)	3327 (broad,M)
5,5′-Dicarboxypyrromethane-3,3′-diacetic acid-4,4′-dipropionic acid hexaethyl ester (XVIIc)	$CHCl_3$	-	3297 (broad,S)
5,5′-Diformylpyrromethane-3,3′-diacetic acid-4,4′-dipropionic acid tetramethyl ester (XVIII)	$CHCl_3$	-	3283 (broad,S)
5,5′-Dicarboxypyrromethane-2,2′-dimethyl-4,4′-diacetic acid tetraethyl ester (XVIa)	$CHCl_3$	3434 (sharp,S)	3267 (shoulder, W)
5,5′-Dicarboxypyrromethane-2,2′-dimethyl-4,4′-dipropionic acid tetraethyl ester (XVIb)	$CHCl_3$	3434 (sharp,S)	3233 (shoulder, W)

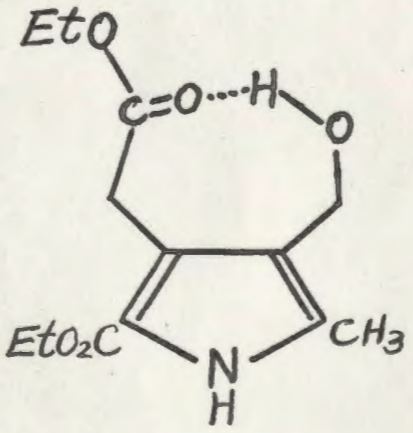


XX



XXI





XXII

EXPERIMENTAL

Melting points (uncorrected) were determined in capillaries. Infrared spectra were recorded by a Perkin-Elmer 237B grating spectrophotometer in chloroform or carbon tetrachloride solution. Ultraviolet were determined on a Perkin-Elmer 202 Ultraviolet spectrophotometer in 95% ethanol as solvent. Nuclear magnetic resonance spectra were recorded on a Varian A-60 analytical spectrometer and all resonance positions are reported on the τ scale.

Diethyl Acetonedicarboxylate.

The commercial acid (Eastern Chemical Corp., Pequannock, New Jersey) was esterified with ethanolic hydrogen chloride[60] in very high (81.5%) yield, b.p. 119-124° at 6 mm.

Ethyl Acetothiolacetate.

Two methods of preparation were used. The Claisen condensation[61] of ethyl thiolacetate[62] gave a reasonable yield, but the preparation from diketene is simpler.

(a) Diketene (135 g; T. Schuchardt GMBH, Munich) was added dropwise into a mixture of ethanethiol (100 g) and anhydrous sodium acetate (0.5g) in ligroin (300 ml, b.p. 80-90°) over 4 h. The reagents were protected against

moisture and allowed to stand overnight at room temperature. The solvent was removed under reduced pressure, and the ester was isolated by fractional distillation. The fraction distilling at 92-94° and 12 mm was collected (89 g, 38%). This reaction was accompanied by the formation of a large amount of dehydroacetic acid.

(b) Ethanethiol (15 g) and triethylamine (3 drops) were dissolved in ligroin (100 ml) and treated dropwise with diketene (21 g), with stirring, under gentle reflux. After the solution has been allowed to stand at room temperature overnight, it was poured into ice water. The aqueous layer was separated and washed twice with ether. The combined organic phase were washed with warm (30-35°) sodium bicarbonate solution and then with water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the thiolester (19.5g, 55%) was distilled at 92-94° and 12 mm.

Ethyl 5-carbethoxy-4-carbethoxymethyl-2-methylpyrrole-3-thiolcarboxylate (IVa).

Freshly distilled amyl nitrite (117.5g) was added to a stirred, cooled mixture of ethyl acetonedicarboxylate (202 g) and concentrated hydrochloric acid (1.6 ml) at 20° over 2h. The mixture was allowed to warm up to room temperature spontaneously, and then heated at 40° for 2 h. The mixture was added (over 80 min.) to an ice-cooled, vigorously stirred mixture of ammonium acetate (150 g), glacial acetic acid (800 ml), ethyl acetothiol-

acetate (146 g), and zinc dust (60g). During the addition of the nitroso compound, zinc dust (140 g) was added in small portions. After the initial temperature rise had ceased, the reaction mixture was slowly heated to 90°, with continuous stirring, during 2h. The hot solution was decanted from excess zinc into stirred ice water (12 l). The zinc was washed with a little hot 50% acetic acid, and the washings were added to the aqueous mixture. The precipitate was collected after 2 h, then washed with 50% aqueous ethanol (150 ml), and recrystallized from absolute ethanol to yield colorless flat prisms (167 g, 51%), m.p. 102-103° λmax: 229 and 286 $m\mu$ ($\log\varepsilon$ max 4.31 and 4.24) in 95% ethanol. νmax: 3422 m (N-H), 3239 w (broad, N-H bonded), 1725 S (C=O, CH_2COOEt), 1689S (C=O, COOEt), 1631 S(C=O, COSEt), 1568 m, 1423S, 1367m, 1333m, 1250 ~ 1150 S(broad band), 1073S, 967m, 895S, 875 m, cm^{-1} in chloroform.

The n.m.r. spectrum (CCl_4) showed absorptions at τ-0.27 (broad, NH), 5.73 and 5.88 (quartets, O-CH_2), 5.81 (singlet, -CH_2CO), 7.02 (quartet, S-CH_2), 7.69 (singlet, CH_3), and 8.63, 8.69 and 8.75 (triplets, ester CH_3). Anal. Calcd. for $C_{15}H_{21}NO_5S$: C, 55.04; H, 6.47; N, 4.28; S, 9.79. Found: C,55.11; H, 6.47; N, 4.40; S, 9.68.

Ethyl 2-Methyl-3-formyl-4-carbethoxymethylpyrrole-5-carboxylate (Va).

(a) A mixture of Raney nickel (W-2, 50g) and acetone (150 ml) was heated under reflux for 2 h. with magnetic stirring. A solution of the thiolester (IVa, 3.72 g) in acetone (100 ml) and methanol (50 ml) was added to the mixture and refluxing continued for another 2 h. The catalyst was removed and the filtrate evaporated to dryness in vacuo. The residue was recrystallized from methanol to give colorless needles (2.16 g, 71%), m.p. 153-154.5° (lit. m.p. 154°)[63].

(b) When the foregoing reaction was repeated with thiolester (IVa, 0.75 g) and Urushibara nickel-B(10g,)[45] the aldehyde (Va) was again isolated (0.52g, 85%), m.p. 153-154.5°.

(c) W-2 Raney nickel (65g) and silica gel (100 g) were mixed well and packed into a chromatographic column (25 x 500 mm). Acetone (100 ml) was allowed to percolate through the column at about 2-3 ml/min. The exterior of the column was warmed with a water jacket at 50°, and a solution of the thiolester (IVa, 4.95 g) in methanol (180 ml) and acetone (20 ml) was run through the column at about 2 ml/min. Fractions were collected and the amount of aldehyde present in each fraction was estimated from the n.m.r. spectrum. When the emerging solution showed gross contamination with starting material and a byproduct, the earlier fractions were combined and yielded almost pure aldehyde (3.1 g, 77%) as colorless needles, m.p. 153-154.5°.

(d) A mixture of t-butyl pyrrole-3-carboxylate (IXa, 2.50 g,[37], and the corresponding pyrrole-3-carboxylic acid (Xa, 20 mg,[37]) was heated on an oil bath at 250-260° under nitrogen gas for 25 min. The mixture was cooled, and dissolved in 1,2-dichloroethane (10 ml). Dimethyl-formamide (5 ml) was then added and the mixture was cooled in ice water, while phosphorus oxychloride (1.1 ml) was added, with magnetic stirring. The mixture was heated on a steam bath for 30 min. The solvent was removed in vacuo, and the residue was poured into ice water (40 ml) containing sodium acetate (1g). The mixture was allowed to stand overnight. The crystalline precipitate was collected and washed with water. It was recrystallized from aqueous methanol and decolorized with charcoal to give aldehyde (0.92g, 46%), m.p. 153-154°. The product was identical with an authentic sample prepared by desulfurization of the thiolester (IVa).

2-Methyl-3-hydroxymethyl-4-carbethoxymethyl-5-carbethoxypyrrole (VIa).

A mixture of thiolester (IVa, 4.0 g), Raney nickel (W-2, 30g), and ethanol (100 ml) was shaken at room temperature for 6 h. The catalyst was removed and the filtrate evaporated to dryness in vacuo. The residue was recrystallized from benzene-ligroin to give colorless needles (2.76g, 84%), m.p. 116.5 - 117°. λmax: 210 and 282 mμ (log εmax 3.78 and 4.26) in 95% ethanol. νmax 3432 S (N-H), 1711S (C=O, CH_2COOEt), 1684S (C=O, COOEt), 1584W, 1436S, 1368m,

1333S, 1250 - 1172S (broad band), 1144S, 1093m, 987m cm^{-1} in chloroform. n.m.r. ($CDCl_3$): τ 0.31 (broad, NH), 5.55 (singlet, CH_2OH), 5.70 and 5.84 (quartets, $-OCH_2$), 6.08 (singlet, $-CH_2CO$), 7.12 (broad, OH), 7.72 (singlet, CH_3), and 8.66 and 8.74 (triplets, ester CH_3).
Anal. Calc'd. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N,5.20. Found: C, 57.85; H, 7.12; N, 5.27.

Acetate, m.p. 100-101°, colorless needles, was prepared by the pyridine and acetic anhydride method, and recrystallized from ether-petroleum ether. λmax: 212.5 and 277 mμ (log εmax 3.76 and 4.24) in 95% ethanol. νmax: 3430 m (N-H), 1733S (C=O, $CH_2O.COCH_3$), 1721S (C=O, CH_2.COOEt), 1686S (C=O, COOEt), 1592W, 1439 m, 1372m, 1334m, 1255 - 1175S (broad band), 1150m, 1102S, 1015m, 957 m, cm^{-1} in chloroform. n.m.r. ($CDCl_3$): τ 0.48 (broad, NH), 5.04 (singlet, $CH_2O.CO$), 5.72 and 5.87 (quartets, $-OCH_2$), 6.12 (singlet, $-CH_2CO$), 7.71 (singlet, CH_3), 8.00 (singlet, $O.COCH_3$), and 8.69 and 8.76 (triplets, ester CH_3). Anal. Calc'd. for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.90; H, 6.84; N, 4.49.

<u>Ethyl 3-carbethoxymethyl-4-(2'-carbethoxyvinyl)-5-methyl-pyrrole-2-carboxylate (XII)</u>.

A mixture of the foregoing aldehyde (Va,3.0g), ethyl hydrogen malonate (1.8g), pyridine (10 ml), and piperidine (8 drops) was heated at 90° for 6 h, and then refluxed for further 3h. After cooling, it was poured into ice water and neutralized with dilute hydrochloric acid. After 3 h the precipitate was collected, washed with water, and recry-

stallized from aqueous methanol and then cyclohexane to give colorless prisms, m.p. 88-89°(2.3 g). The filtrate and mother liquors were combined and extracted with ether to give a further crop of the vinyl ester (0.5 g, total yield 74%). λmax: 258 and 319 mμ (log εmax 4.27 and 4.37) in 95% ethanol. νmax: 3422 m (N-H), 1729S (C=O, CH_2.COOEt), 1692S (C=O, COOEt and CH=CH.COOEt), 1640S (C=C), 1577 m, 1439m, 1373m, 1337 m, 1305S, 1263 ~1188S (broad band), 1173S, 1095m, 985m, cm^{-1} in chloroform. n.m.r. (CCl_4): τ-0.26 (broad, NH), 2.43 and 4.07 (AB quartet, τ=16.5 c.p.s., olefinic CH), 5.77 (quartet, -OCH_2), 6.01 (singlet, -CH_2CO), 7.71 (singlet, CH_3), and 8.68 (triplet, ester CH_3). The ester signals were not resolved in the spectrum of this compound and the signals for the O-CH_2-CH_3 groups are broad. Integrated areas for all the peaks are in accord with structure XII.
Anal. Calc'd. for $C_{17}H_{23}NO_6$:C, 60.52; H, 6.87; N, 4.15.
Found: C, 60.45; H, 6.85; N, 4.14.
The final mother liquors was left to stand for several days, the volatile solvent evaporated spontaneously and a small amount of crystal formed on the bottom. It was collected and recrystallized from methanol to give colorless prisms (27 mg), m.p. 160-162°, and was identified with an authentic sample, β,β'-dipyrromethane (XVIa).

Ethyl 3-carbethoxymethyl-4-(2'-carbethoxyethyl)-5-methyl-pyrrole-2-carboxylate (XIII)

A solution of the vinyl ester (XII, 2.0g) in 95% ethanol (50 ml) was shaken for 1 h with Adams' catalyst

(50 mg) under hydrogen (50 p.s.i.) at room temperature. The platinum was removed and the solvent distilled off in vacuo. The residue was recrystallized from cyclohexane to give colorless needles (1.91 g, 95%), m.p. 63-64° (lit. m.p. 63.5°.[63]

Ethyl 4-carbethoxyethyl-5-carbethoxy-2-methylpyrrole-3-thiolcarboxylate (IVb).

(a) A solution of diethyl β-oxoadipate (21.6g[64]) in glacial acetic acid (30 ml) was cooled in an ice bath, while sodium nitrite (6.9g, saturated in water) was added with stirring, the temperature being kept below 20°. After standing at room temperature for 3 h. the solution was dropped into a mixture of ethyl acetothiolacetate (14.6g), glacial acetic acid (45 ml), and zinc dust (6g). Temperature was kept near 70° with the addition of zinc dust (15 g). The solution was then heated to 80° for 1 h, then poured into 2 l ice water, and allowed to stand for 4 h. The precipitate was collected and recrystallized from ethanol to give colorless prisms (16.8 g, 49%), m.p. 94-95°. λmax: 231 and 285 mμ (log εmax 4.33 and 4.22) in 95% ethanol. νmax: 3419 m (N-H), 3239W (broad, N-H bonded), 1725S (C=O, CH_2CH_2.COOEt), 1682S (C=O, COOEt), 1639S (C=O, COSEt), 1561 m, 1422S, 1372m, 1298m, 1255-1180S (broad band), 1146m, 1078m, 897m, cm^{-1} in chloroform. n.m.r. (CCl_4): τ -0.50 (broad, NH), 5.68 and 5.89 (quartets, $-OCH_2$), 7.01 (quartet, $-SCH_2$), 6.68 and 7.49 (A_2B_2 multiplet, $-CH_2CH_2CO$), 7.42 (singlet, CH_3), and 8.62, 8.68 and 8.75 (triplets, ester CH_3). Anal. Calc'd for: $C_{16}H_{23}NO_5S$: C,56.30; H, 6.79; N, 4.10; S, 9.39. Found:C,56.47; H, 6.75; N, 4.27; S, 9.45.

(b) This compound (IVb), m.p. 94-95°, was prepared with a yield of 54% by the procedure analogous to that used for IVa.

2-Methyl-4-carbethoxyethyl-5-carbethoxypyrrole ((XIX).

A mixture of t-butyl pyrrole-3-carboxylate (IXb, 6g,[37]), and the corresponding pyrrole 3-carboxylic acid (Xb, 50 mg,[37]) was heated on an oil bath at 250° under nitrogen gas for 40 min. It was cooled, and the petroleum ether was added to dissolve the decarboxylated product (XIX). The solid was filtered off and washed with petroleum ether to recover the pyrrole carboxylic acid (0.25 g, 5%). The filtrate and the washings were combined and the solvent was removed in vacuo. A pale yellow crystalline material (4.1g) was obtained, which was recrystallized from petroleum ether to give colorless needles (3.81g, 87%), m.p. 65-66° (lit.m.p. 66°[37]).

2-Methyl-3-formyl-4-carbethoxyethyl-5-carbethoxypyrrole(Vb).

(a) This compound, m.p. 121-122°, colorless prisms, (lit. m.p. 122°,[35]) was prepared with a yield of 81% by refluxing the corresponding thiolester (IVb, 2.0 g) with deactivated Raney nickel (W-2, 30g) in acetone (60 ml) and methanol (30 ml), following the procedure for Va.

(b) The t-butyl pyrrole-3-carboxylate (IXb, 4.0 g) and the corresponding pyrrole 3-carboxylic acid (Xb, 20 mg) were decarboxylated as above, and the 3-free pyrrole was dissolved in dimethylformamide (7 ml) without purification. The mixture was cooled in icewater, while phosphorus oxychloride

(1.8 ml) was added dropwise with stirring. After heating on the steam bath for 20 min. the mixture was cooled, and poured into ice water (60 ml) containing sodium acetate (12 g), then refrigerated overnight. The crystalline precipitate was collected and washed with water. It was recrystallized from aqueous ethanol and decolorized with charcoal to give pale grey flat plates (2.54 g, 79%), m.p. 121-122°, identical by mixed melting point and n.m.r. spectrum with an authentic sample prepared by desulfurization of the thiolester (IVb).

2-Methyl-3-carbethoxycarbonyl-4-carbethoxyethyl-5-carbethoxy pyrrole (XIV).

A mixture of t-butyl pyrrole-3-carboxylate (IXb, 40g) and the corresponding pyrrole 3-carboxylic acid (Xb, 200 mg) was decarboxylated as above, and the crude 3-free pyrrole was dissolved in dry ether (100 ml), and chloroform (35 ml, dry and ethanol free). Ethyl cyanoformate (30 ml) was then added. The mixture was treated according to the method of MacDonald[65] to give colorless needles (34.7g, 86%), m.p. 78°. (lit. m.p. 78.5-79°[65].

2-Methyl-3-carbethoxymethyl-4-carbethoxyethyl-5-carbethoxy-pyrrole (XV).

The glyoxylic ester (XIV, 24g) in glacial acetic acid (100 ml) and concentrated sulfuric acid (3.6 ml) was shaken for 2 h with palladium black (1.2g, freshly prepared[66] under hydrogen (55 p.s.i.) at 25°. The resulting solution was

then treated according to the procedure of MacDonald[65]. Three reductions, using 72g of glyoxylic ester, were worked up together to give the ester (XV, 57.2g, 82.5%) as long colorless needles, m.p. 63-64°(lit. m.p. 63-64°[65].

Preparation of Palladium black[66]

A stirred solution of sodium borohydride (10g) in distilled water (400 ml) was cooled in cold water, while palladium chloride (2.0 g) was added portion by portion. After the vigorous reaction had ceased, another part of sodium borohydride (4g in 100 ml of water) was added dropwise. Stirring was continued for 3 h. The upper clear solution was decanted out and the black solid washed with distilled water five times and then with glacial acetic acid. Thus palladium black (1.2 g) was obtained.

2,3-Dimethyl-4-carbethoxyethyl-5-carbethoxypyrrole (VIIb) and 2-Methyl-3-hydroxymethyl-4-carbethoxyethyl-5-carbethoxy pyrrole (VIb).

(a) A mixture of thiolesters(IVb, 20g), Raney nickel (W-2, 80g), acetone (30 ml), and ethanol (100 ml) was shaken under hydrogen (55 p.s.i.) at 70° for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from aqueous methanol to give colorless prisms (VIIb, 6.8 g, 43%), m.p. 88° (lit. m.p. 88-89°[47]. The mother liquors and the washings were combined and evaporated to dryness in vacuo. The residue was then recrystallized from benzene-

ligroin to give colorless needles (VIb, 7.85g, 47%), m.p. 94-95.5°. λmax: 210 and 282 mμ (log εmax 3.89 and 4.29) in 95% ethanol. νmax: 3431S (N-H 1720S (C=O, $CH_2.CH_2.COOEt$), 1683S (C=O, COOEt), 1582W, 1439S, 1377m, 1350m, 1300m, 1256 - 1180S (broad band), 1142m, 1094S, 990m, 944m, cm^{-1} in chloroform. n.m.r. ($CDCl_3$): τ 0.50 (broad, NH), 5.50 (singlet, CH_2OH), 5.69 and 5.91 (quartets, $-OCH_2$), 6.96 and 7.29 (A_2B_2 multiplets, $-CH_2.CH_2.CO$), 7.22 (singlet, OH), 7.71 (singlet, CH_3), and 8.65 and 8.80 (triplets, ester CH_3). Anal. Calc'd. for $C_{14}H_{21}NO_5$: C, 59.36; H, 7.47; N, 4.95. Found: C, 59.18; H, 7.30; N, 4.75. Acetate, m.p. 126-127°, colorless needles was prepared by the acetic anhydride and pyridine method, and recrystallized from ether. λ max: 212 and 279 mμ (log εmax 3.94 and 4.25) in 95% ethanol. ν max: 3426 m (N-H), 1723S (C=O, $CH_2O.COCH_3$ and $CH_2.CH_2.COOEt$), 1675S (C=O, COOEt), 1597W, 1433m, 1370m, 1294m, 1250 - 1174S (broad band), 1138 m, 1097S, 1011m, 939m, cm^{-1} in chloroform. n.m.r. ($CDCl_3$): 0.55 (broad, NH), 5.00 (singlet, $-CH_2O.CO$), 5.67 and 5.86 (quartets, $-OCH_2$), 6.94 and 7.43 (A_2B_2 multiplets, $-CH_2.CH_2CO$), 7.69 (singlet, CH_3), 7.97 (singlet, $-O.CO.CH_3$), and 8.64 and 8.75 (triplets, ester CH_3). Anal. Calc'd for $C_{16}H_{23}NO_6$: C, 59.08; H, 7.12; N, 4.31. Found C, 59.38; H, 7.22; N, 4.23.

The details of reductions are shown in Table II.

(b) The mixture of chloromethylpyrrole (VIIIb, 6.0g) palladium black (300 mg), glacial acetic acid (40 ml), and sodium acetate (1.7g) was shaken under hydrogen 55 (p.s.i.) at 50-60° for 3 h. The reaction mixture was poured into 400 ml of ice water, and the precipitate was collected and washed

with water. It was recrystallized from aqueous methanol to give colorless prisms (5.2 g, 92%), m.p. 87-88°, identical by mixed melting point and n.m.r. spectrum with an authentic sample prepared by reduction of thiolester (IVb).

(c) A mixture of aldehyde (Vb, 0.2g), Raney nickel (W-2, 5g), and ethanol (30 ml) was shaken under hydrogen (55 p.s.i.) at 70° for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in chloroform and filtered. After removal of the solvent, the crude material was used for n.m.r. analysis directly. The spectrum shows that the aldehyde was mostly (90%) reduced to hydroxymethyl (VIb), and only 10% was reduced to methyl (VIIb).

2-Methyl-3-chloromethyl-4-carbethoxyethyl-5-carbethoxypyrrole (VIIIb).

Thionyl chloride (8 ml) was added dropwise to a cooled solution of hydroxymethylpyrrole (VIb, 15g) in dry ether (100 ml) with stirring. Stirring was continued for 30 min. The solvent and excess thionyl chloride were removed in vacuo below 20°, and three 50 ml portions of dry ether successively added and removed in the same way. The final solid was then recrystallized from dry ether-petroleum ether to give nearly colorless needles (15.6g, 94%), m.p. 126-129°. The n.m.r. spectrum ($CDCl_3$) showed absorptions at τ -0.04 (broad, NH), 5.36 (singlet, CH_2Cl), 5.26 and 5.81 (quartets, $-OCH_2$), 6.90 and 7.34 (A_2B_2 multiplets, $-CH_2CH_2CO$), 7.66 (singlet, CH_3), and 8.62 and 8.74

TABLE II

Reduction of Thiolester

Thiolester used (g)	Raney Ni used (g)	Treatment of Raney Ni	P lb/in^2	Temp. °C	Time h.	Products %			
						Thiolester IVb $-COSet$	Aldehyde Vb $-CHO$	Hydroxymethy $-CH_2OH$ VIb	Methyl- VIIb $-CH_3$
0.5	5	No	55	25	3	+	-	> 95	trace
0.5	5	No	55	70	3	-	-	84	16
0.5	1	No	55	70	3	45	40	14	trace
0.5	2.5	No	55	70	3	-	-	67	33
0.5	5	+ 1 ml Me_2CO	55	70	3	-	-	55	45
0.5	5	+ 3 ml Me_2CO	55	70	3	-	-	53	47
0.5	5	Deactivated with Me_2CO at R.T. 3h.	55	70	3	-	-	64	36
0.5	5	Deactivated with Me_2CO (reflux 1h.)	55	70	3	-	75	21	4

(triplets, ester CH_3).

5,5'-Diformyl-3,3'-dicarbomethoxymethyl-4,4'-dicarbomethoxyethyl-2,2'-dipyrromethane (XVIII).

A mixture of pyrromethane-3,3'-diacetic acid-4,4'-dipropionic acid tetramethyl ester (3.0g[67]), and dimethylformamide (7 ml, distilled over P_2O_5) was cooled in ice water, while phosphorus oxychloride (1.7 ml) was added with magnetic stirring. The mixture was heated in an oil bath at 80° for 30 min. After cooling, it was poured into ice water (60 ml) containing sodium acetate (12g), and then allowed to stand in a refrigerator for several days. The precipitate was collected and recrystallized from ethanol to give colorless prisms (2.1g), m.p. 203-204°. (lit. m.p. 207-208°[67]; 203°[68]). The filtrate and washings were combined and extracted with chloroform to give another crop of diformylpyrromethane (XVIII), 0.69, total yield 80%).

2,2'-Dimethyl-4,4'dicarbethoxymethyl-5,5'-dicarbethoxy-3,3'-pyrromethane (XVIa).

A mixture of the 3-hydroxymethyl pyrrole (VIa, 200 mg), glacial acetic acid (15 ml), anhydrous sodium acetate (1g) was refluxed for 3 h. The solution was poured into ice water and extracted with ether. Ether solution was washed with water and dried over anhydrous sodium sulfate. The solvent was removed and the residue recrystallized from aqueous methanol to give colorless prisms (96 mg,53%), m.p. 160-162°. λ max: 247 and 289 mμ (log εmax 3.98 and 4.54)

in 95% ethanol. ν max: 3433S (N-H), 3274W (broad, N-H bonded), 1730S (C=O, CH_2COOEt), 1678S (C=O, COOEt), 1584W, 1436S, 1370m, 1335m, 1256 ∿1172S (broad band), 1144m, 1083m, (broad), 1028m, cm^{-1} in chloroform. n.m.r. ($CDCl_3$): τ 0.26 (broad, NH), 5.70 and 5.90 (quartets, $-OCH_2$), 6.29 (singlet, $-CH_2CO$), 6.43 (singlet, meso $-CH_2-$) 7.90 (singlet), CH_3), and 8.68 and 8.79 (triplets, ester CH_3). Anal. Calc'd. for $C_{25}H_{34}N_2O_8$: C, 61.21; H, 6.99; N, 5.71; Mol. Wt. 490.56. Found: C, 61.32; H, 7.03; N, 5.68; Mol. Wt. (Rast method) 473.

2,2'-Dimethyl-4,4'-dicarbethoxyethyl-5,5'-dicarbethoxy-pyrromethane (XVIb).

This compound (XVIb), m.p. 152-153°, colorless prisms, was prepared with a yield of 58% by the procedure analogous to that used for (XVIa). λmax: 252 and 287 mμ + (log εmax 4.08 and 4.57) in 95% ethanol. νmax: 3433m (N-H), 1725S (C=O, $CH_2.CH_2.COOEt$), 1675S (C=O, COOEt), 1435S, 1370m, 1331W, 1295M, 1250∿1168S (broad band) 1136m, 1088S, 1070S. n.m.r. ($CDCl_3$):τ 0.82 (broad, NH), 5.72 and 5.91 (quartets, $-OCH_2$), 6.46 (singlet, meso CH_2), 7.09 and 7.82 (A_2B_2 multiplets, $-CH_2CH_2CO$), 7.86 (singlet, CH_3), and 8.68 and 8.79 (triplets, ester CH_3). Anal. Calc'd. for $C_{27}H_{38}N_2O_8$: C, 62.53; H, 7.39; N, 5.40; Mol. Wt. 518.61. Found: C, 62.52; H, 7.55; N, 5.49; Mol. Wt. 520.

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