SYNTHETIC APPROACHES TO PORPHOBILINOGEN AND RELATED MONOPYRROLES

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by

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ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Master of Philosophy

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by Cleanthis C. Froussios

The need for an efficient synthetic route to the porphyrin biogenetic precursor porphobilinogen, provided the initial stimulus for the present work.

The β-ketoaldehyde diethyl β-formyl-γ-oxopimelate was condensed with various primary and secondary amines. The ketoenamine-iminoenol tautomeric equilibria of the condensation products with glycine ethyl ester and diethyl aminomalonate were studied in relation to synthetic models. The ketoenamines resulting from condensation of the above ketoaldehyde with N-benzylglycine esters were successfully cyclized to the corresponding α-proto pyrrole esters, thus establishing an efficient synthetic route to monopyrroles related to porphobilinogen.

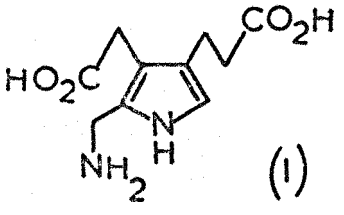
Side chain elaborations were conducted on various α-free pyrrole-2--carboxylates. Thus, 5-iodopyrrole-2-carboxylates were obtained by use of iodine chloride, and the potential of their transformation to the corresponding nitriles using cuprous cyanide was demonstrated. The use of cyanogen bromide for the direct introduction of a nitrile function was also investigated, and a 2-pyrrylnitrile was obtained in this way.

Alternative routes to pyrroles possessing substitution patterns analogous to porphobilinogen were also preliminarily investigated.

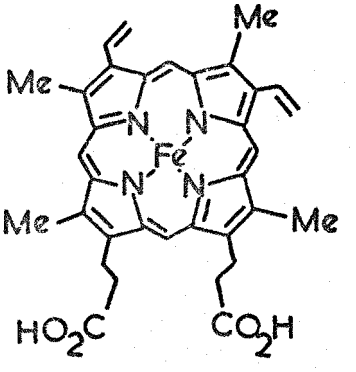
INTRODUCTION

Natural occurrence of pyrroles

One of the main impetus for the study of pyrroles has arisen from the research on the structure of haemin, the blood respiratory pigment, and chlorophyll, the green photosynthetic pigment of plants.[1] Vitamin B12 containing the corrin ring system (4) and many secondary metabolites containing the aromatic pyrrole unit are further examples of the natural occurrence of the pyrrole system. Haem (2), chlorophyll (3) and vitamin B12 have a common biogenetic precursor, porphobilinogen (1), the only aromatic monopyrrole to have a function in fundamental metabolism.



(1)



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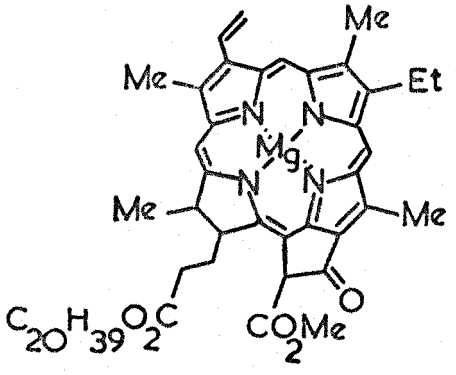

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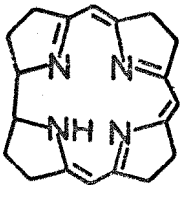
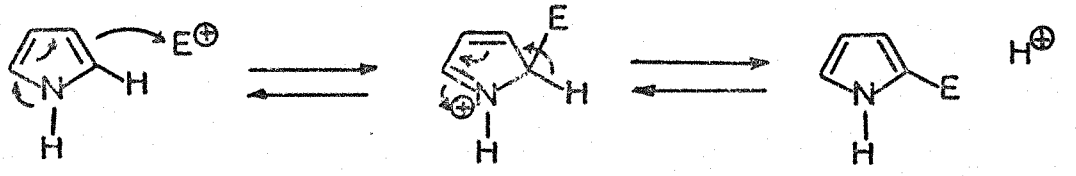


(4)

Chemical properties of pyrroles[2,3,4]

By far the most important chemical feature of the aromatic pyrrole ring system is its marked reactivity towards electrophilic reagents. The effective conjugation between the diene π -system of the carbon

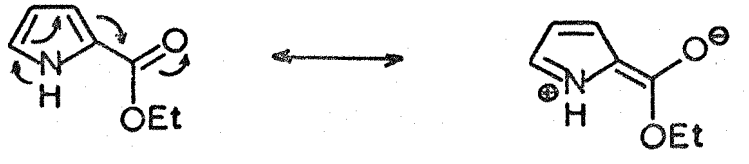
skeleton and the lone pair of nitrogen results in an electron-density transfer from nitrogen to the ring carbon atoms, which thus are able to react with a variety of electrophiles. In simple pyrrole systems, substitution at the 2-position (α) predominates over both 3-substitution (β) and substitution on nitrogen, a situation which is easily rationalized in terms of relative stabilities of the respective transition states involved.



Effect of substitution on nucleophilic reactivity

Alkyl substituted pyrroles exhibit increased nucleophilicity, while substituents bearing polarised unsaturated systems in conjugation with the ring have a greatly depressing effect on the nucleophilicity of the ring through electron withdrawal, e.g. pyrrole-2-carboxylates.

e.g.



Such conjugated esters are more resistant to hydrolysis than their aliphatic counterparts, aldehydes do not give Perkin and Cannizzaro reactions and α-carboxylate esters effectively invert the reactivity

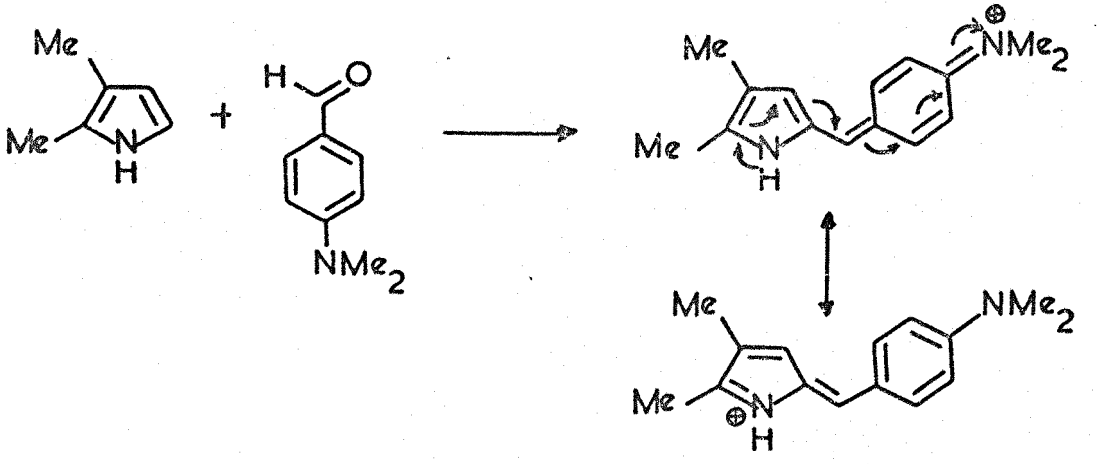
order at α - and β - positions.

Finally, the carboxylic acids themselves are very labile and they easily undergo thermal and acid-catalysed decarboxylation.

The Ehrlich reaction

Pyrrolic compounds having a free nuclear carbon position undergo acid-catalysed condensation with p-dimethylaminobenzaldehyde to give salts which are deeply coloured due to mesomerism. The reaction has enjoyed great utility in the rapid assay of pyrroles.

e.g.



Synthetic approaches to the pyrrole ring

There are three generally important approaches to pyrrolic compounds from non-heterocyclic precursors.

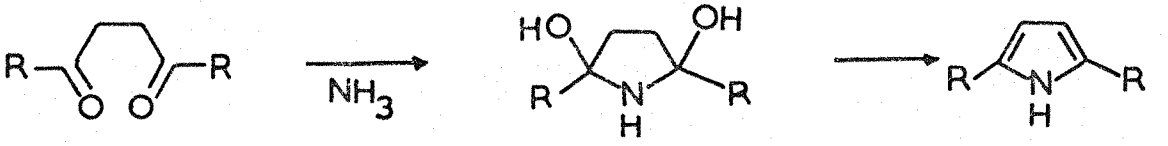
a) 1-4 dicarbonyl compounds react with ammonia or primary amines to produce pyrroles (scheme 1a, page 5).

b) α - aminoketones react with β-dicarbonyl compounds and related derivatives e.g. β - ketoesters (scheme 1b, page 5).

c) α - halocarbonyl comppunds react with β - dicarbonyl compounds (e.g. β - ketoesters) and ammonia (scheme 1c, page 5).

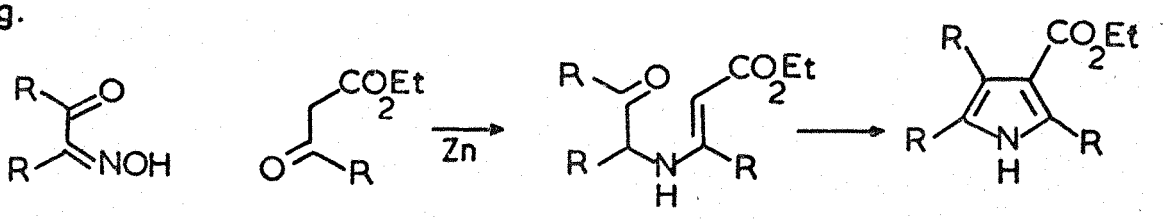
a. PAAL-KNORR SYNTHESIS

e.g.



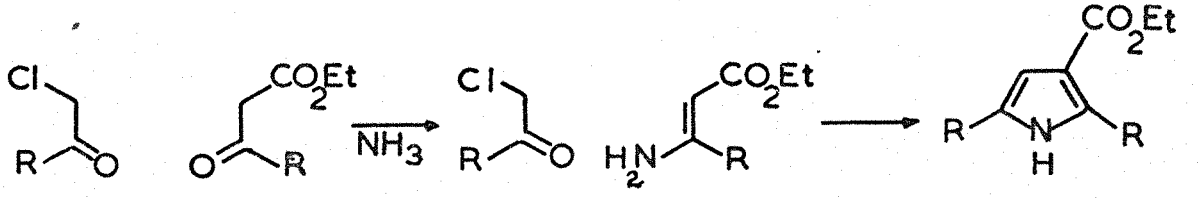
b. KNORR SYNTHESIS

e.g.



c. HANTZSCH SYNTHESIS

e.g.



SCHEME 1

Porphobilinogen and its role in porphyrin biosynthesis

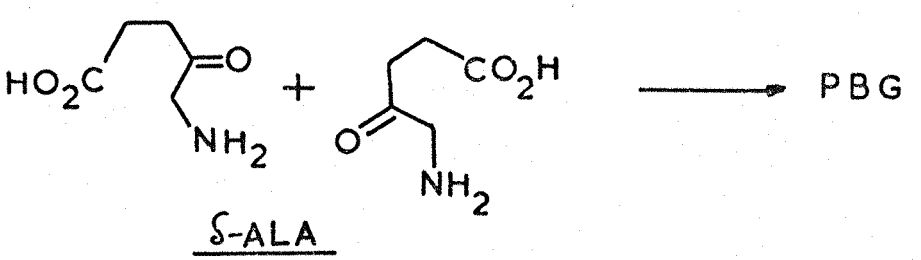
Porphobilinogen (PBG) (1) was first isolated in crystalline form from the urine of patients suffering from acute porphyria; in 1952 by Westall.[5] In 1954 Cookson and Rimington[6,7] established its structure as (1).

This pyrrole proved to be the only direct biosynthetic precursor of uroporphyrinogen III (urogen III) (scheme 2, page 7) in the common biogenetic pathway to haem and chlorophylls.[8]

Under acid catalysis, PBG is tetramerised to a mixture of all four possible urogens[9] but enzymically it produces only the type III isomer, (scheme 2). Such elaboration of the type III isomer is currently an area of intense research activity. Numerous hypotheses have been proposed[10] for the rearrangement necessarily involved, but recently the research of Battersby *et al*[11] has closely limited the number of possibilities.[12,13,14] One viable hypothesis is outlined in scheme 3 (page 8).

Synthetic approaches to Porphobilinogen

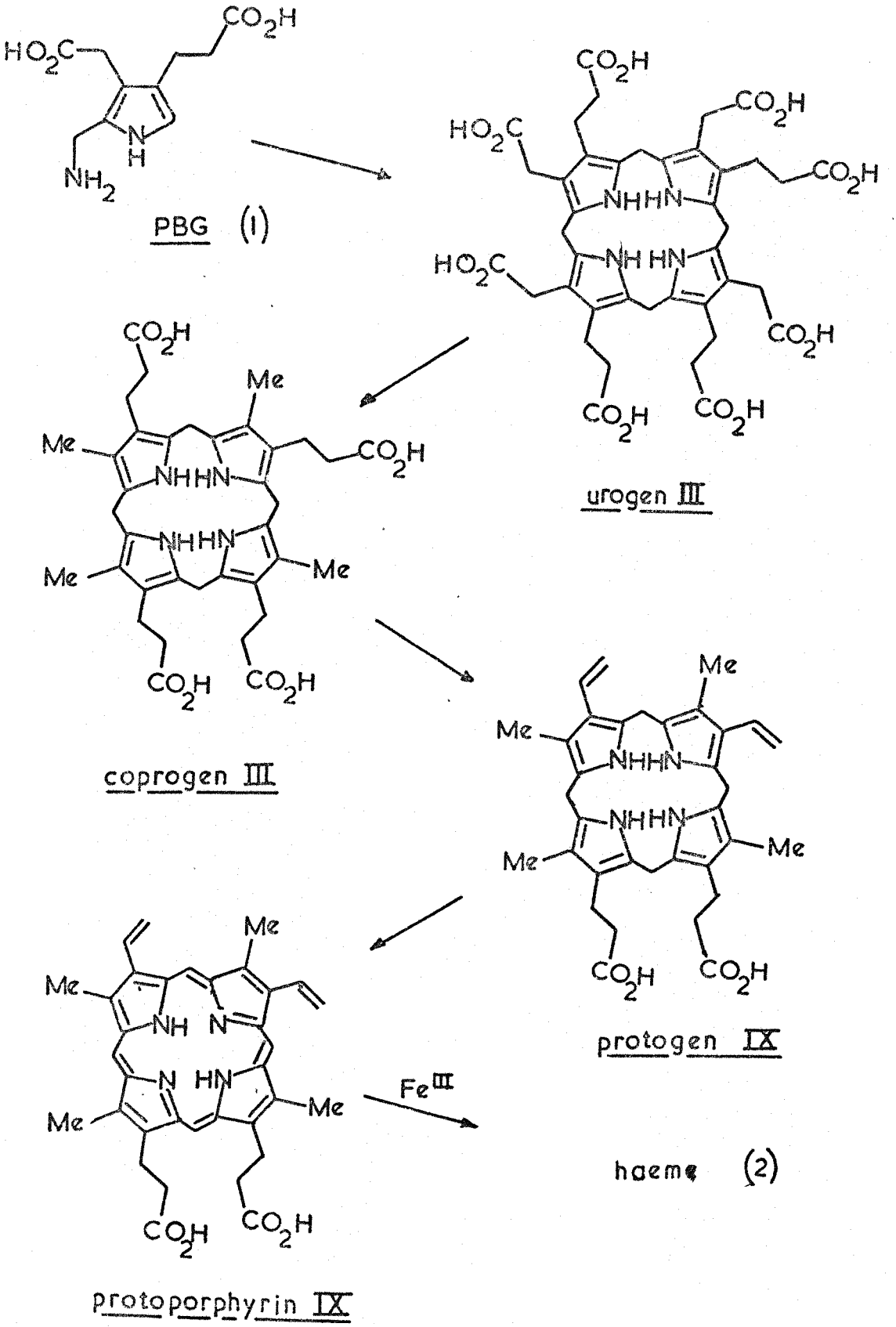
Biosynthetically PBG derives from δ - aminolaevulinic acid (δ - ALA) through a Knorr type condensation. *In vitro* however, this reaction compares very unfavourably with other condensation reactions.[15]



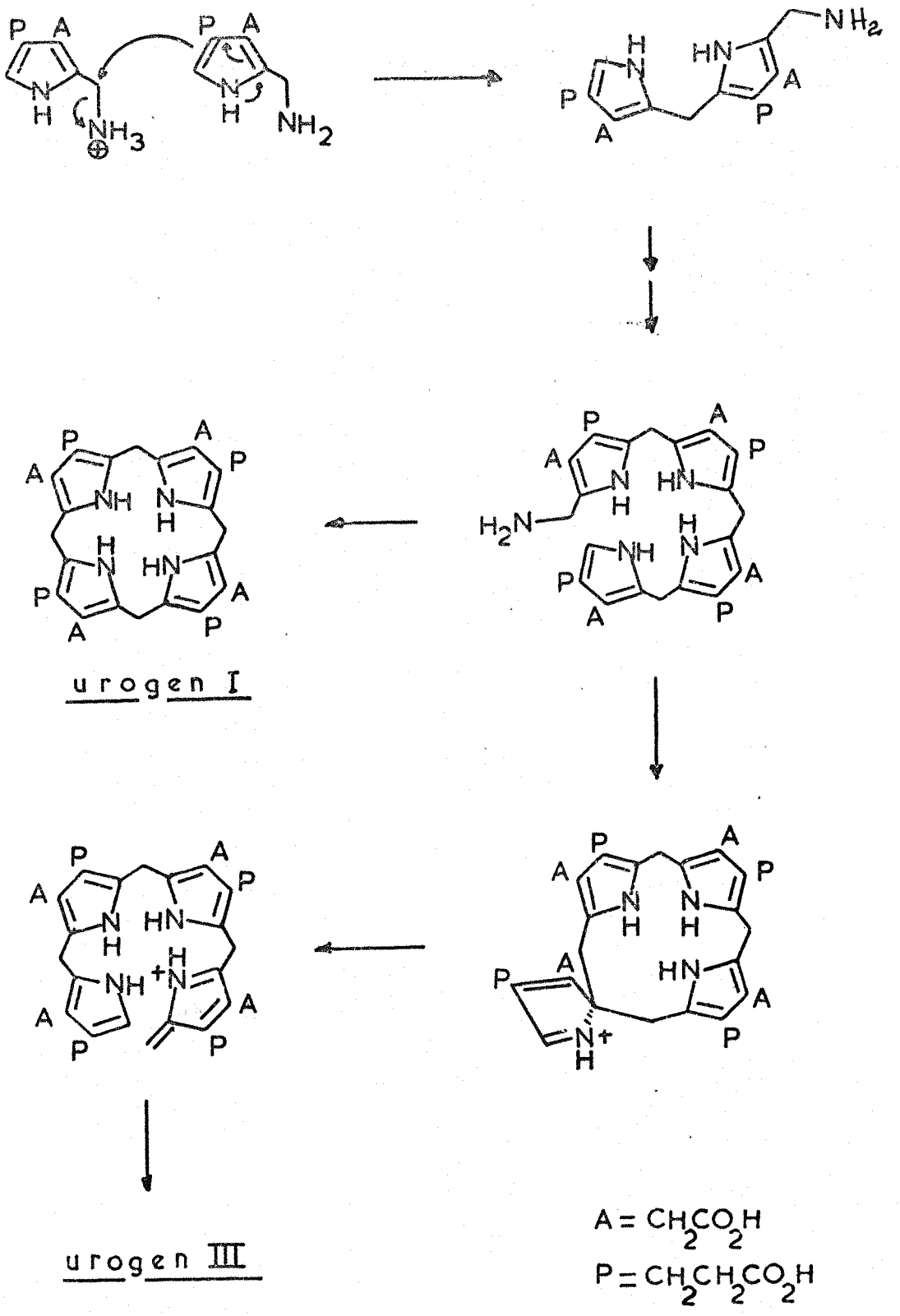
δ-ALA

(1) Synthesis of S.F. McDonald

McDonald synthesised PBG[16,17] using as starting material the


PBG (1)
urogen III
coprogen III
protogen IX
protoporphyrin IX
haeme (2)
Fe III

SCHEME 2



SCHEME 3

pyrrole (5) which has been made available earlier through his modification of the Knorr condensation[19-22] (scheme 4, page 10). Nevertheless the process is long and tedious and leads to overall yields of less than one per cent.

(2) Synthesis of Rapoport

Rapoport et. al. published in 1969[23] a totally different approach, based on the observation that PBG is easily and reversibly transformed into its lactam (6). This lactam can be viewed as the 2-piperidone form of a substituted pyrrolo-(2,3,6)-pyridine or 6-azaindole. The starting material 2-methoxy, 5-nitro-γ-picoline, was obtained in 42% yield from 2-amino γ-picoline in four steps.[24] The overall yield was 8% thus offering a distinct advantage over the previous McDonald synthesis. The method, however, is poor for C-labelling, especially at the carbon atoms derived from the pyridine nucleus (scheme 5, page 11).

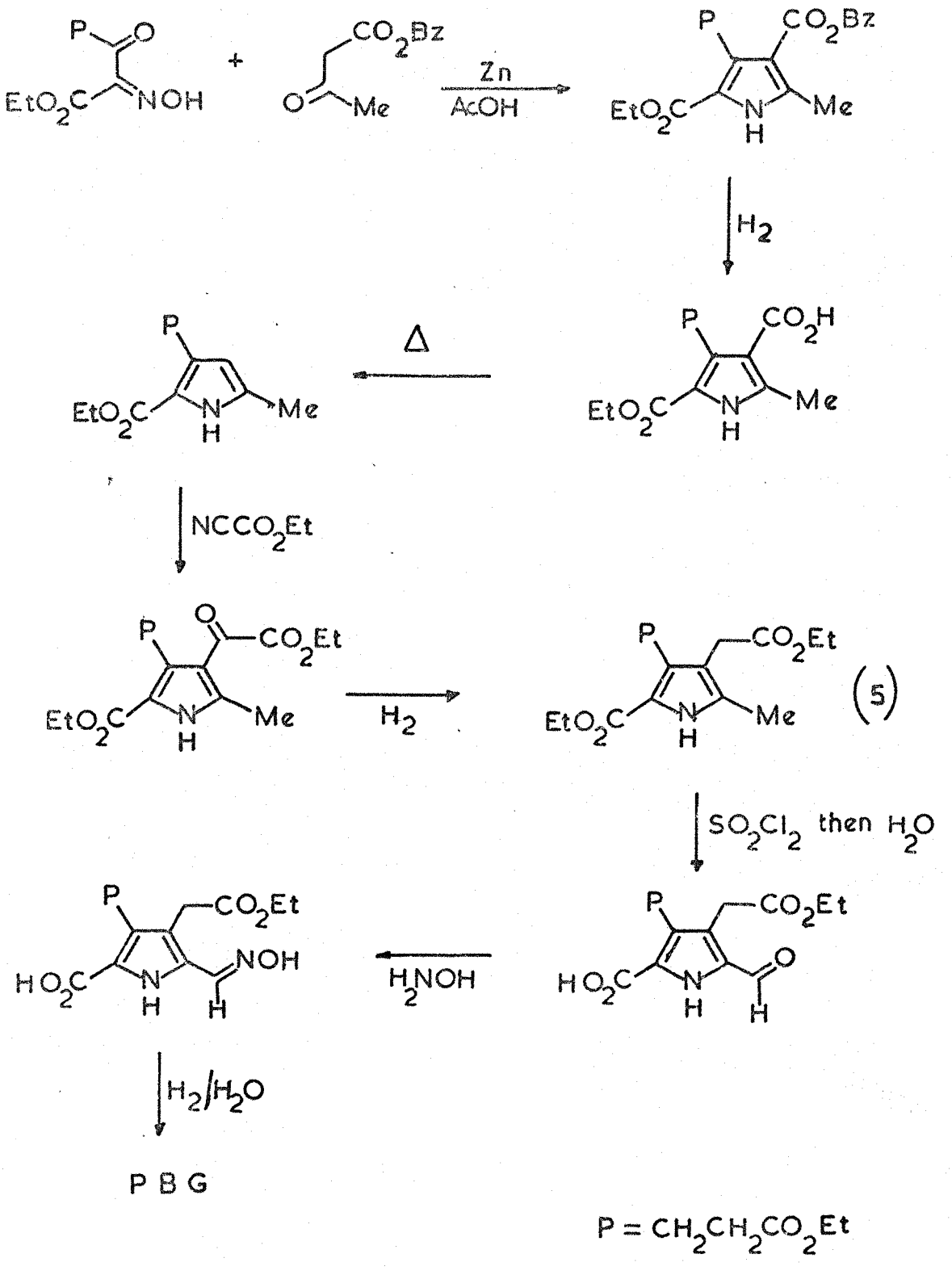
Modification of Battersby[25]

Side-chain elaborations on pyrrole (5) obtainable through the McDonald synthesis lead to PBG lactam through catalytic hydrogenation of the α-azidomethyl analogue. The method involves removal and reintroduction of the α-methyl group thus offering C-labelling at that site, if required (scheme 6(a) page 12).

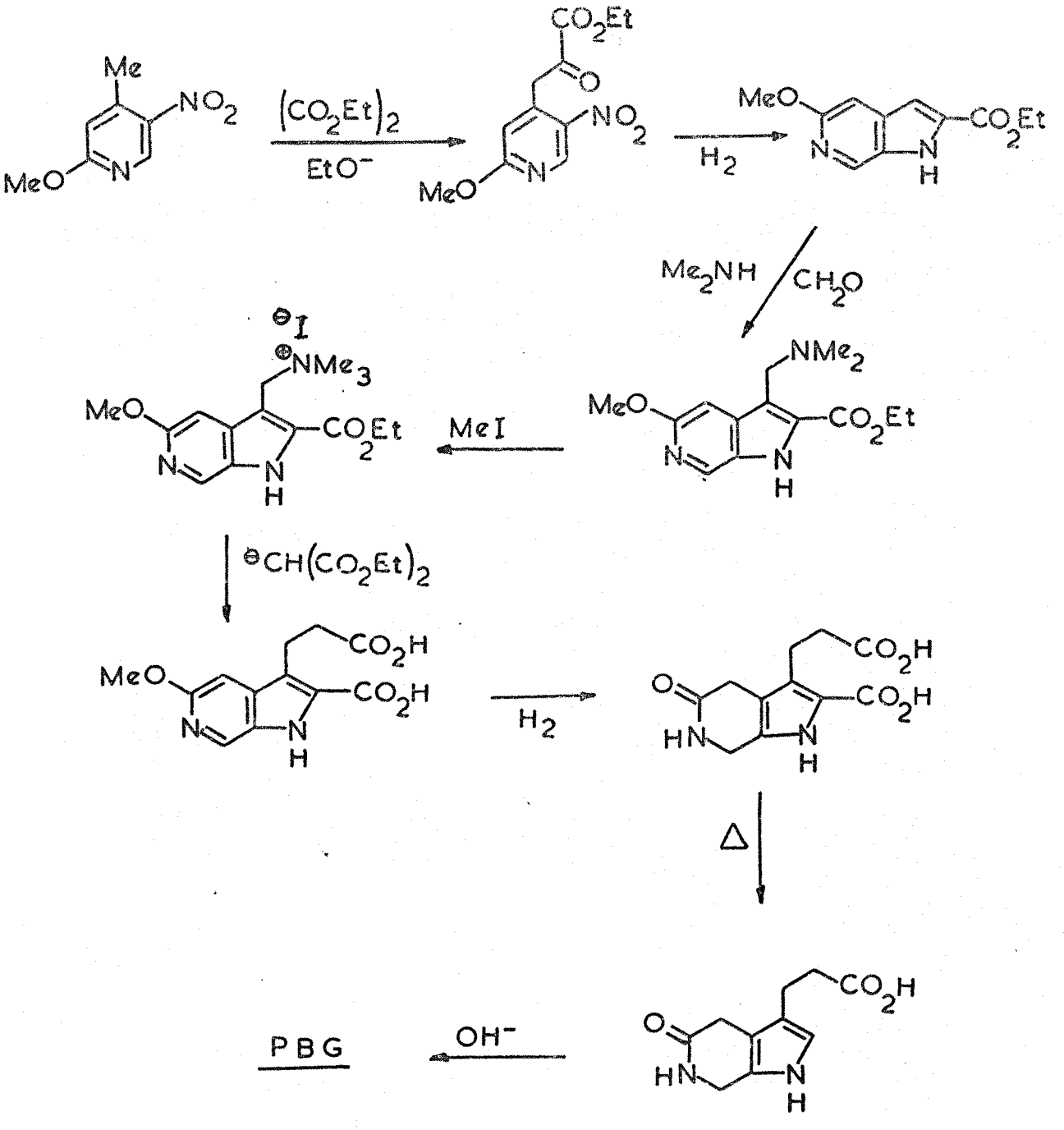
Recently Kenner et. al. reported[26] a novel method of elaboration of the acetate side chain, starting with relatively readily available β- acetylpyrroles (scheme 6(b), page 12).

Present study

As mentioned previously, none of the existing PBG syntheses provide for efficient labelling with ^{13}C or ^{14}C especially at the aminomethyl position. Furthermore the many steps and modest yield of some of them give a rather small turnover in final product.

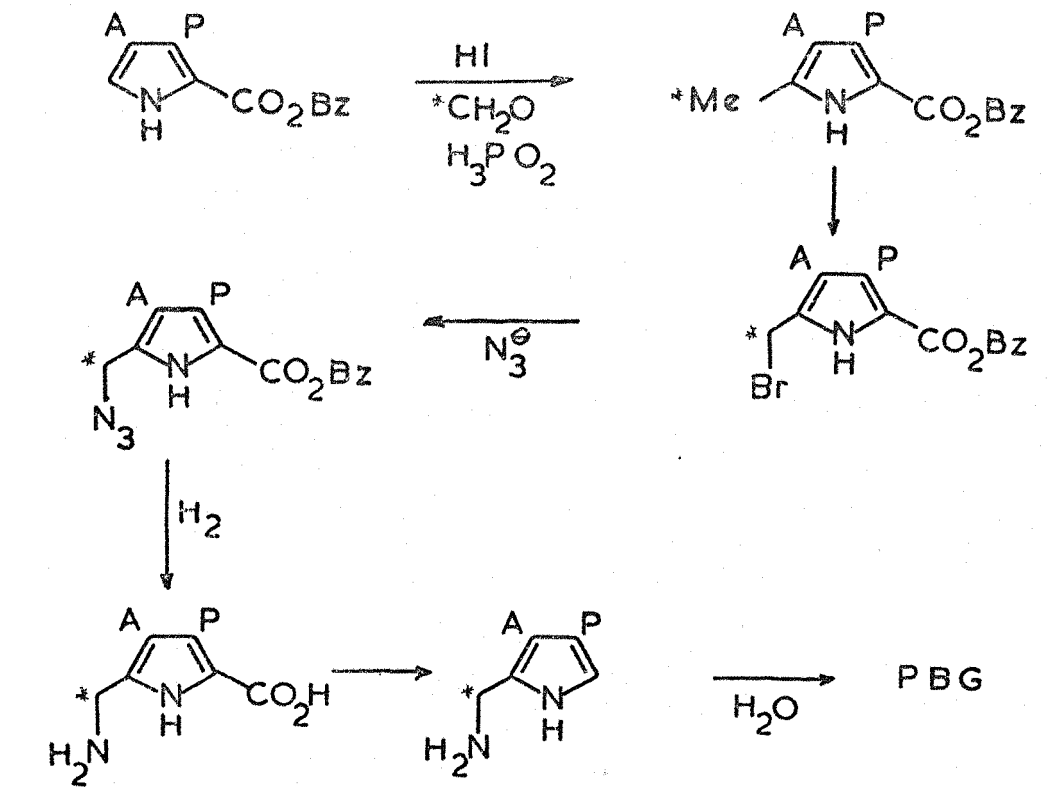

P
O
EtO2C
NOH
+
CO2Bz
O
Me
Zn
AcOH
P
CO2Bz
EtO2C
N
H
Me
H2
P
CO2H
EtO2C
N
H
Me
Δ
P
EtO2C
N
H
Me
NCCO2Et
O
CO2Et
P
EtO2C
N
H
Me
H2
P
CO2Et
EtO2C
N
H
Me
(5)
SO2Cl2 then H2O
P
CO2Et
HO2C
N
H
O
H
H2NOH
P
CO2Et
HO2C
N
H
NOH
H
H2/H2O
P B G
P = CH2CH2CO2Et

S C H E M E 4

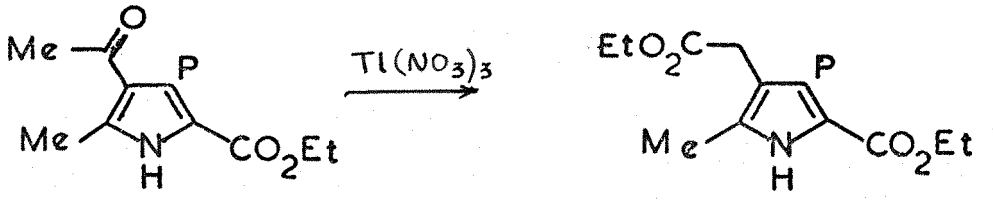


PBG lactam (6)

SCHEME 5



– a –

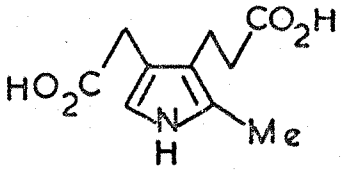


– b –

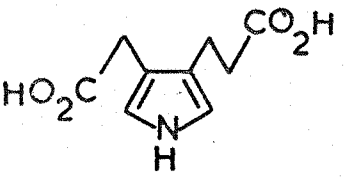
A = CH_2CO_2Et
P = $CH_2CH_2CO_2Et$

SCHEME 6

In view of the above, a more direct approach to α-free 3-carboxymethyl-4-carboxyethylpyrroles would be clearly useful since compounds of that structure can be intermediates in PBG and other related pyrrole syntheses (e.g. cryptopyrrole and opsopyrrole dicarboxylic acids).



cryptopyrrole diacid



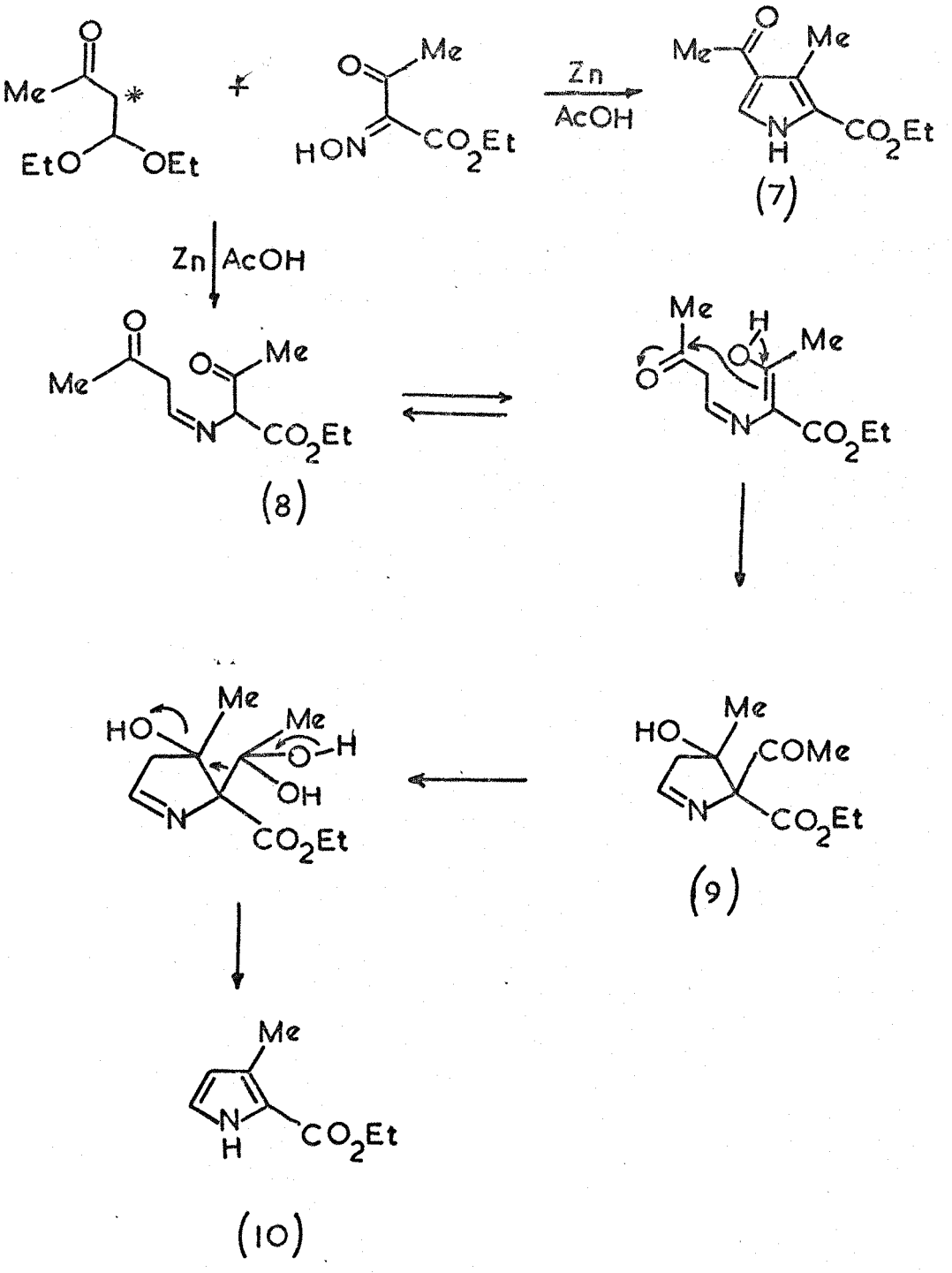
opsopyrrole diacid

Background

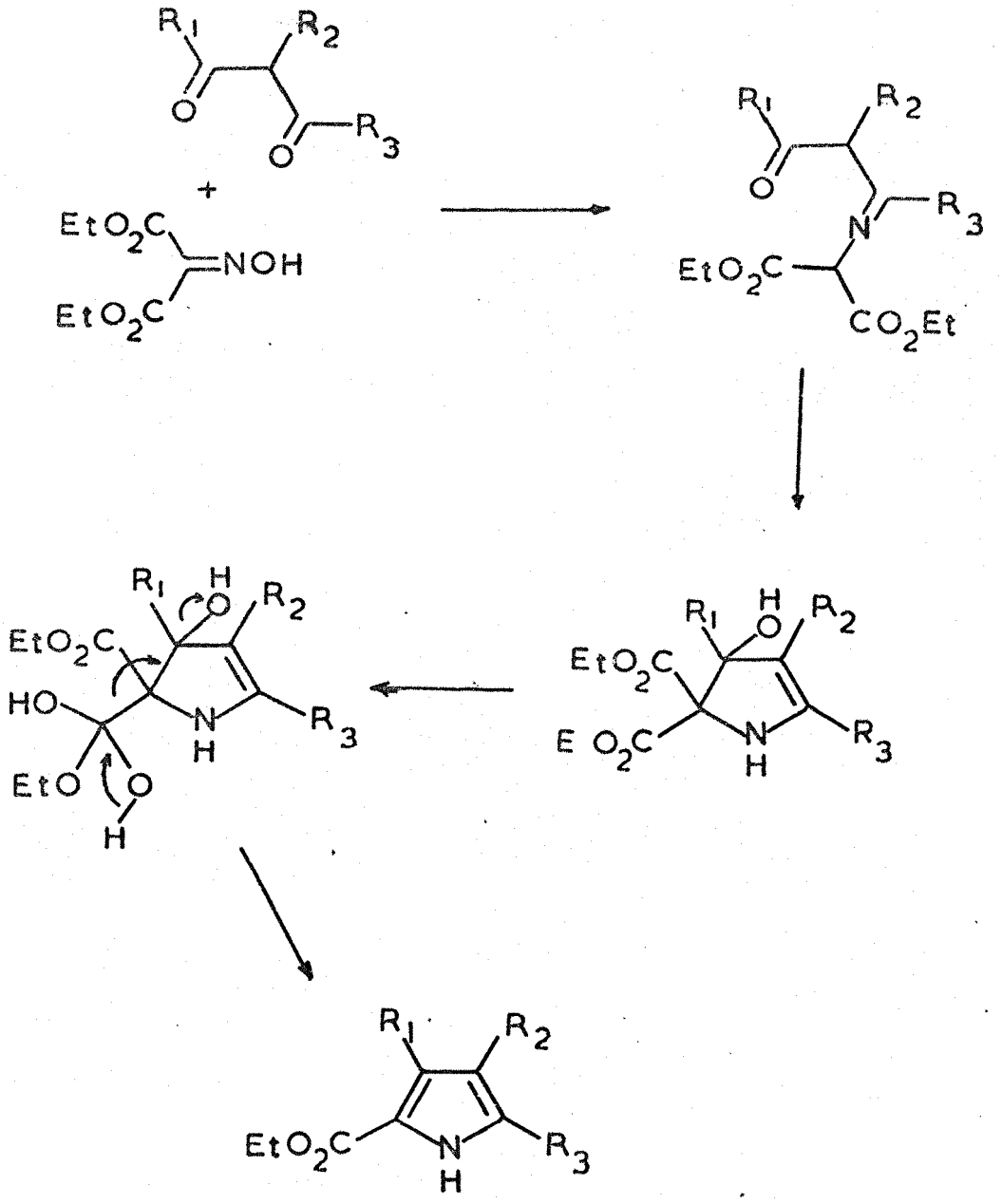
In 1948 Fischer and Fink[27] discovered accidentally a new mode of pyrrole ring cyclization. They attempted the synthesis of pyrrole (7) employing a typical Knorr condensation between ethyl α-oximinoacetoacetate and 3-oxobutyraldehyde (as the ethyl acetal). However they obtained the pyrrole (10) through (8) and (9) (scheme 7, page 14). They also found that this process can compete with the Knorr reaction if the latter is impeded through substitution on the carbon atom labelled (*) of the β-dicarbonyl component (scheme 7).

Work of Kleinspehn

A new improvement was performed by Kleinspehn[28,29] who substituted diethyl oximinomalonate for ethyl oximinoacetoacetate thus eliminating the possibility of Knorr type condensations, (scheme 8, page 15). The obvious advantage of this synthesis of 2-carboethoxypyrroles is that it permits the one step synthesis of pyrroles carrying the desired substituents at the 3,4,5 positions and also that it permits the late generation in the synthesis of the α-free position through a facile



SCHEME 7

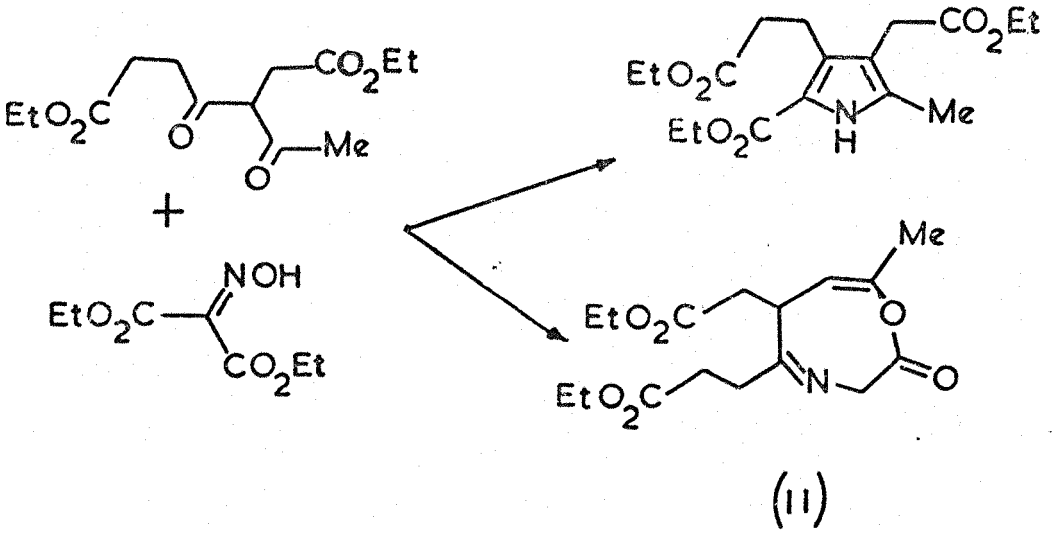


SCHEME 8

decarboxylation reaction.

Work of Plieninger

Plieninger in 1967[30] sought to apply the reaction to the synthesis of the vital PBG precursor (5) (page 10). He used as starting materials the diketone β-acetyloxopimelic diethyl ester and oximinomalonic diethyl ester under standard Knorr conditions as shown below.



(11)

The yield however was average (17% overall) and the azepinone (11) was produced as a by-product in 6% yield. One of the drawbacks of the above method is that the acetyloxopimelate is not prepared directly from oxopimelate thus posing problems if isotopic labelling is required.

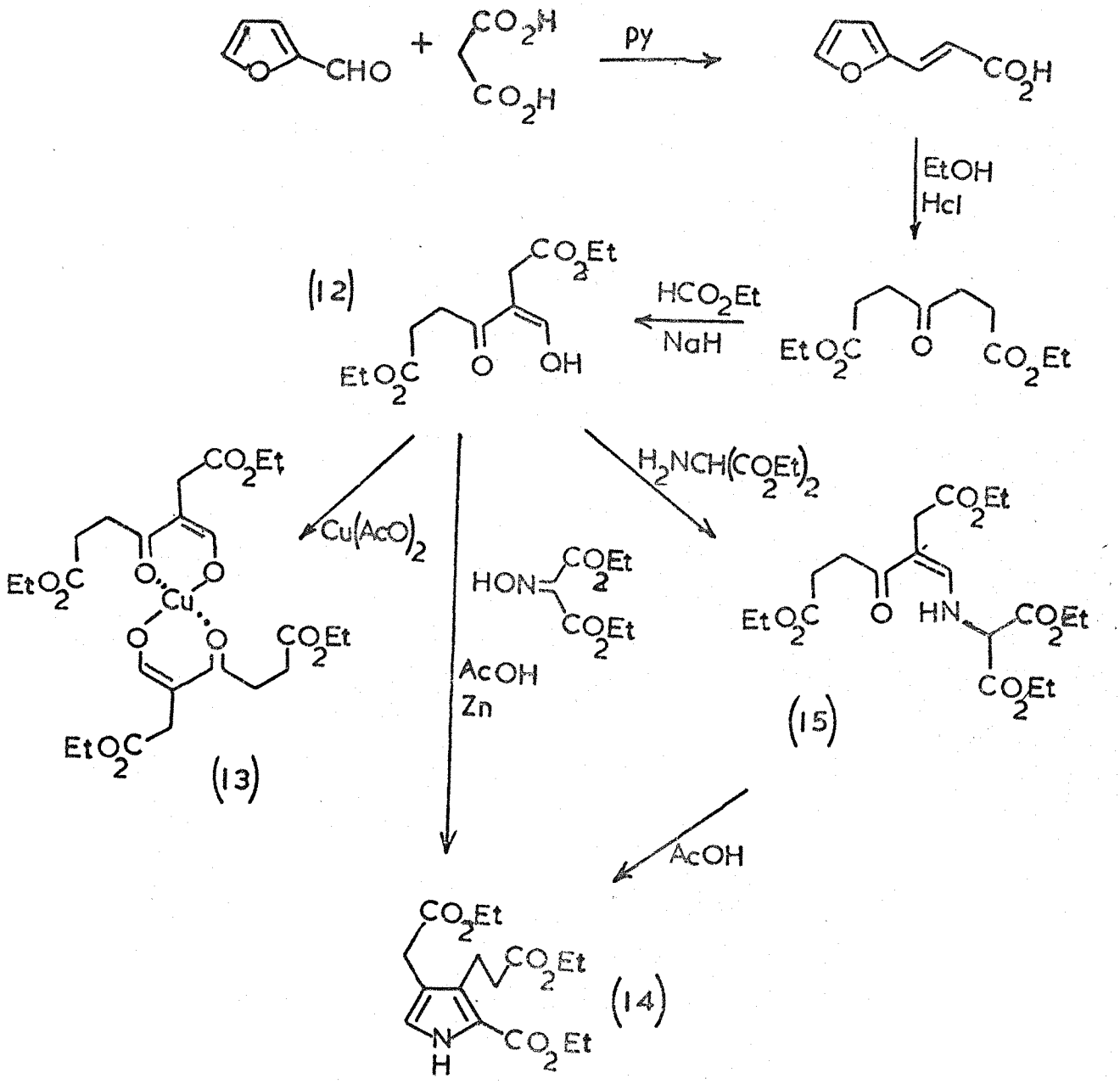
Present work

Due to the need for easier and more efficient synthetic routes to PBG and its derivatives, which are amenable to the introduction of an isotopic label, it was decided to investigate a modification of

Plieninger's route. Other methods of α-H pyrrole synthesis were also studied since these compounds are particularly useful in labelling work due to the ease of introduction of a carbon-label at the α-position by reductive methylation.[31] Furthermore alternative methods of introduction of the aminomethyl side chain were also studied.

DISCUSSION

Scheme 9 below depicts the initial synthetic plan followed in this work.



SCHEME 9

Preparation of the β - ketoaldehyde (12)

Diethyl γ-oxopimelate was prepared in 10% yield in two steps from readily available furfural.[32,33] The dimethyl ester which was subsequently required could not be obtained by direct analogy. An alternative procedure is described in the experimental section.

The diethyl ester was formylated at the β -position (sodium hydride/ethyl formate) to the β-ketoaldehyde (12) which was purified through the crystalline chelate complex with copper (13). Dicarbonyl compounds resulting as side products from intramolecular cyclization of (12) would not be expected to give stable chelates. The chelate (13) on treatment with dilute hydrochloric acid was easily decomposed to the free dicarbonyl compound, thus affording a convenient method of purification of (12).

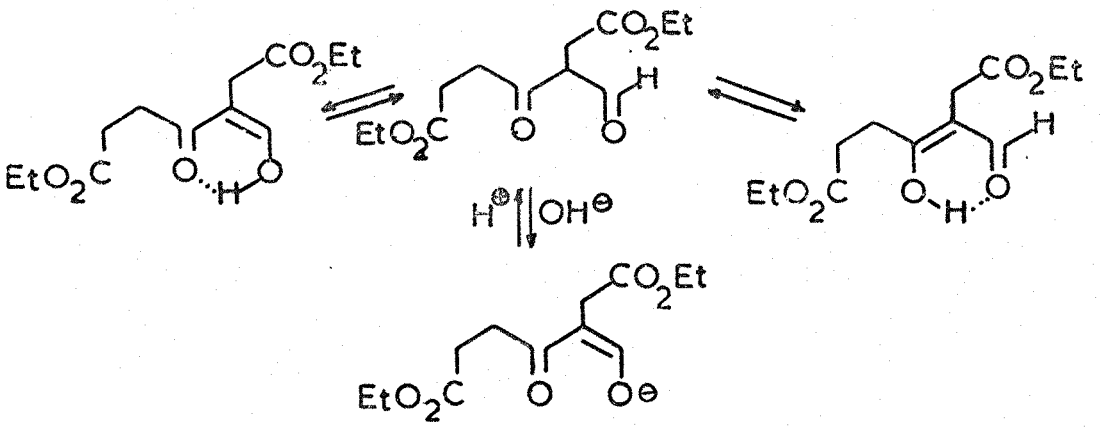
The formylation of ketones to produce β-ketoaldehydes has in the past proved to be a complex problem which has been extensively reviewed.[34,35] In this case yields of up to 60% of purified chelate were obtained with difficulty on occasions but in general yields were variable.[36,37,38] The inconsistency of yields and the relatively large (10-20%) amounts of starting ketopimelate ester which were isolated from the reaction mixture are attributable to the heterogeneity of the reaction mixture and the difficulty of efficient stirring. A tenfold excess of ethyl formate was used in order to trap the enolate before internal cyclization could occur. Excess (two equivalents) of hydride and low temperature (10^{o}) were found helpful.

It was subsequently found possible to use crude product in the synthetic sequence and yields of 80-90% were consistently obtained. Attempts to purify the β-ketoaldehyde (12) otherwise were unsuccessful (e.g. silica gel chromatography, alkaline extraction, nickel chelate, vacuum distillation). Thus in general, exploratory reactions

were conducted on both crude product and β-ketoaldehyde purified via the copper chelate.

Structure of the β-ketoaldehyde (12)

The above dicarbonyl compound showed the expected intense ultraviolet absorption at 253 nm (MeOH) attributable to the chromophore (O=C-C=C-OH) resulting from enolization of one of the carbonyl groups.



In alkaline solution a reversible bathochromic shift of the absorption maximum to 283 nm is attributable to the conversion of the enol to the enolate anion, which is present even in neutral alcoholic solutions (shoulder absorption at 283 nm) but suppressed in the presence of hydrochloric acid. The β-ketoenol is internally hydrogen bonded (chelated six-membered ring) as evidenced by the broad O-H stretching vibration centred at 2,900 cm^{-1} and the carbonyl stretching vibration at 1645 cm^{-1}. [39,40] The NMR spectrum shows an aldehyde hydrogen at 0.25 τ and is interpreted in terms of 75% enolization on the aldehyde site (ratio of aldehydic to olefinic proton 2:7).

Attempted preparation of pyrrole (14)

This elaboration required the condensation of the β-ketoaldehyde (12) with diethyl aminomalonate generated *in situ* by zinc/acetic acid reduction of the oximino-analogue.

Oximinomalonic diethyl ester was prepared[41] by direct nitrosation

of diethyl malonate with sodium nitrite (this product always contained ~ 5% of unreacted malonate).

The β-ketoaldehyde and oximinomalonate failed to produce any pyrrolic compound under Plieninger conditions (acetic acid/sodium acetate/95°-105°). Reaction products were examined by TLC on silica gel and alumina and assayed for pyrrolic products by using a spray of Ehrlich reagent modified as described in experimental section. A sample of authentic (14) was availble (kindly provided by D.A. Evans) and was used for recording reference spectra and conducting comparative TLC.

When the reaction temperature was raised to glacial acetic acid reflux point two minor components of the reaction mixture appeared as Ehrlich positive, one of them essentially identical in Rf with reference compound. The spectral characteristics of that material (less than 1% yield) were those of pyrrole (14) but also suggested that it was a mixture of structurally similar compounds although TLC failed to fully separate any components. Substitution of refluxing propionic acid (as well as butyric, isobutyric, valeric acids) for acetic acid, did not have any marked effect, though the yield after a small increase with propionic acid declined with the increase of boiling point of the reaction medium.

Isolation of the main components of the reaction product revealed the presence of starting materials (β-ketoaldehyde, aminomalonate, oximinomalonate and malonate esters) and a crystalline product which was shown by spectral analysis and melting point to be diethyl acetamidomalonate. The yield of that product was as high as 20% when prolonged refluxing periods were employed.

A further product that was isolated with difficulty was the expected condensation intermediate (15) between the ketoaldehyde and

the amine. The structure of the above intermediate will be discussed later under the chapter "structural possibilities for product (15)."

Finally, when sodium dithionite was used as the reducing agent in the above reaction, no pyrrolic product could again be detected as assayed by Ehrlich test.

The condensation product (15) between the β-ketoaldehyde (12) and diethyl aminomalonate.[42]

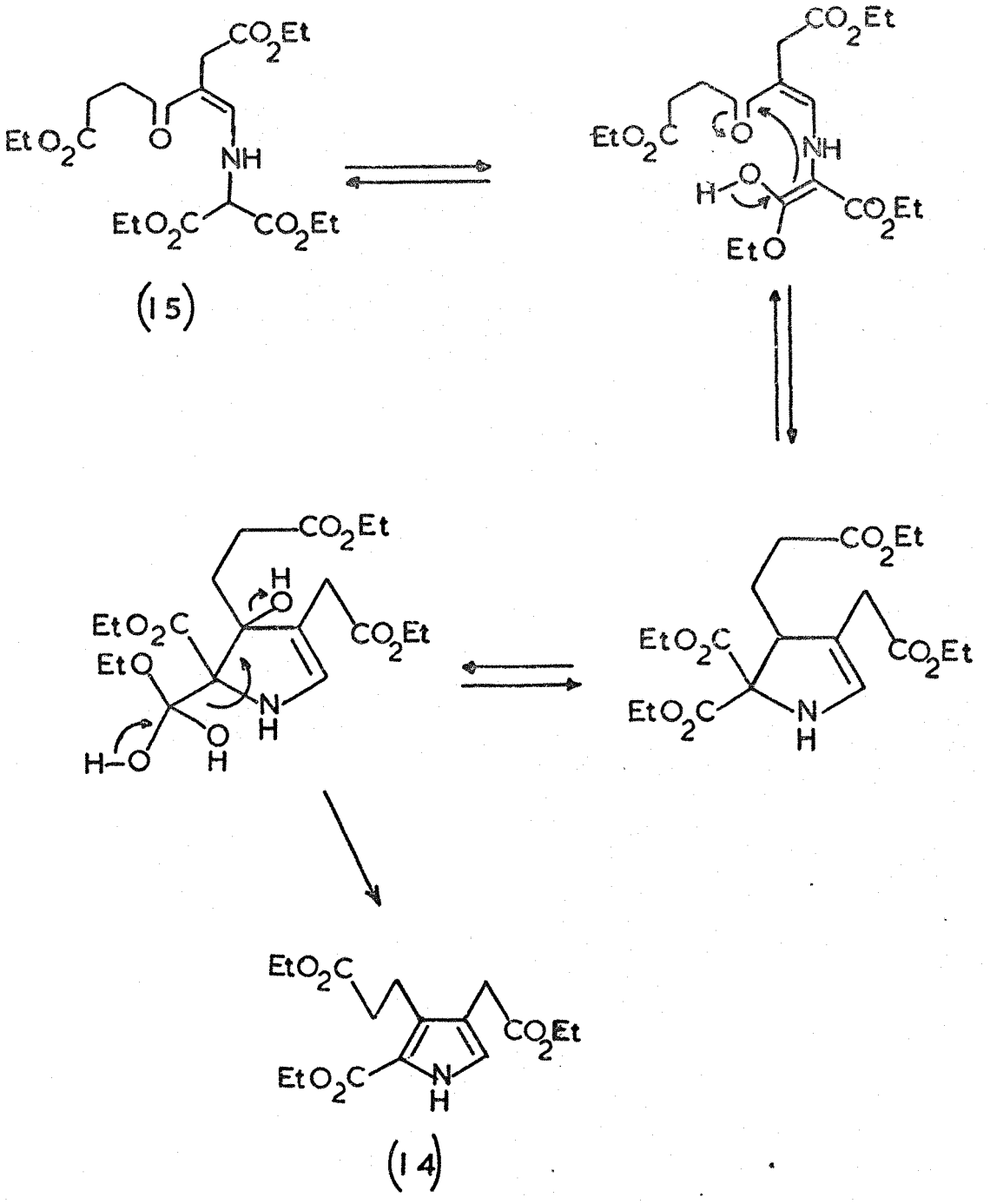
In view of the above it was assumed that the failure of the Knorr condensation was due to the difficulty of the nucleophilic attack on the ketonic carbonyl during the internal cyclization of intermediate (15) or due to the difficulty of the decarboxylation stage necessary for the formation of the pyrrole ring (scheme 10, page 24).

It was therefore decided to prepare the product (15) and attempt its cyclization under strong acid (protonation of ketonic carbonyl) or strong base catalysis (carbanion generation at malonate mesocarbon) (scheme 11, page 25).

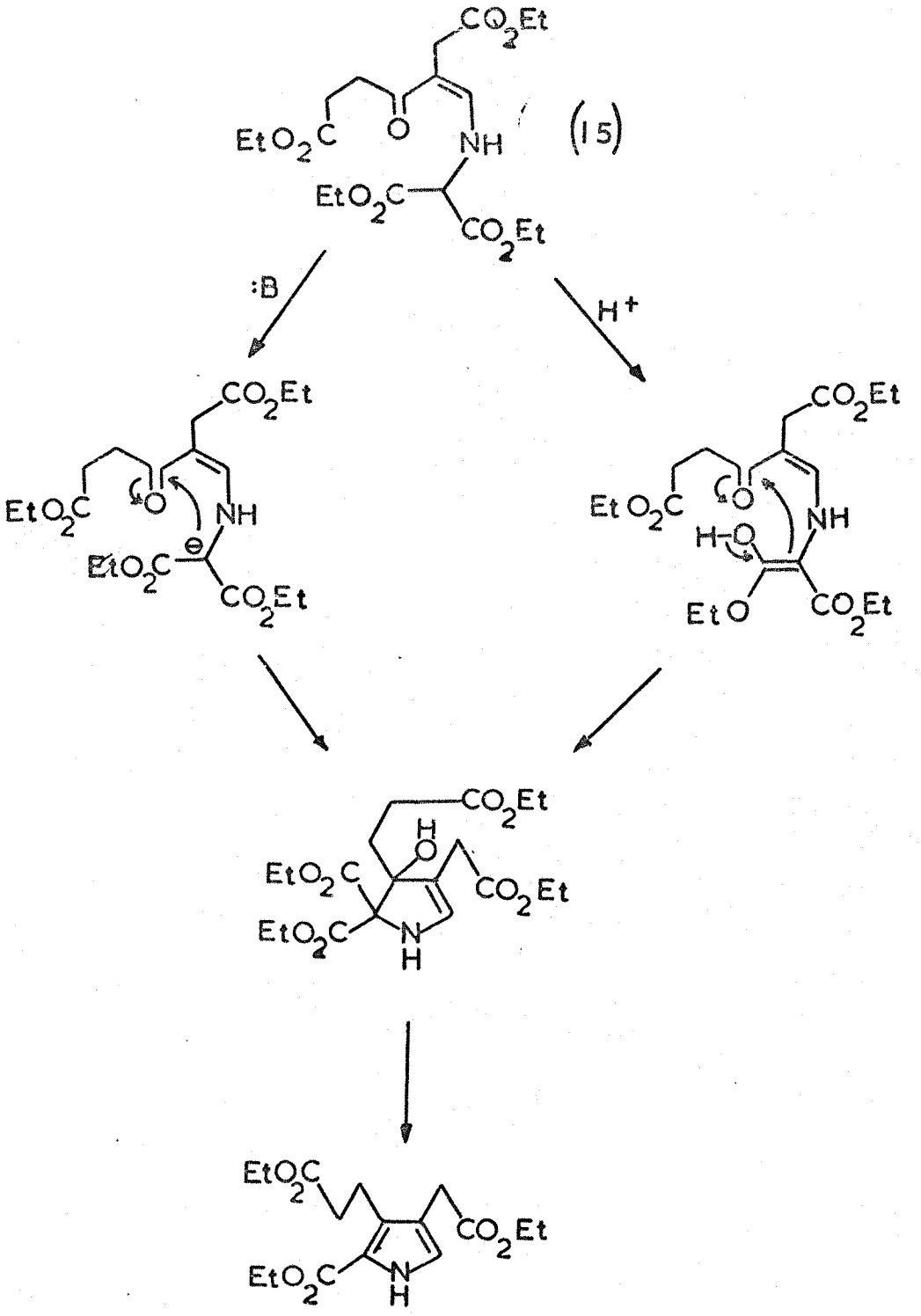
The product (15) was prepared through direct condensation of its constituents in refluxing ethanol and purified with difficulty on silica gel and alumina columns.

Structural possibilities for product (15)

Mass spectrometry of product (15) showed a parent ion consistent with a one to one adduct with loss of one molecule of water between the ketoaldehyde (12) and diethyl aminomalonate. High resolution mass spectrometry suggested the expected formula $C_{19}H_{29}NO_9$. Structurally there are a number of possibilities, involving isomers resulting from condensation of the amine with either the aldehyde or the ketonic carbonyl, tautomers resulting from enolization of the free carbonyl, as well as geometrical isomers around the double bonds in the enolic forms. (Scheme 12, page 27).


CO2Et
EtO2C
O
NH
EtO2C
CO2Et
(15)
CO2Et
EtO2C
O
NH
H
O
CO2Et
EtO
CO2Et
H
O
EtO2C
EtO
N
H
H–O
O
H
CO2Et
EtO2C
CO2Et
EtO2C
N
H
EtO2C
CO2Et
EtO2C
N
H
(14)

SCHEME 10


CO2Et
EtO2C
O
NH
EtO2C
CO2Et
(15)
:B
H+
CO2Et
EtO2C
O
NH
EtO2C
CO2Et
CO2Et
EtO2C
O
NH
H-O
EtO
CO2Et
CO2Et
H
O
EtO2C
EtO2C
N
H
CO2Et
EtOC
CO2Et
EtO2C
N
H

(14)

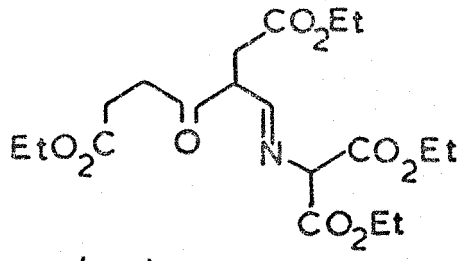
SCHEME II

An intense absorption at 287 nm (MeOH) suggests a rather extensive chromophore (-N-C=C-C=O or -N=C-C=C-OH). The infrared absorption maxima in the region 1600-1700 cm^{-1} as well as a broad absorption at 3200 cm^{-1} attributable to a chelated hydrogen are further evidence in support of such a structural assignment.

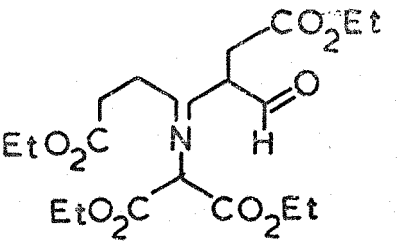
Previous studies[43-46] on the tautomerism of Schiff's bases of β -dicarbonyl compounds indicated that in solution, undetectable amounts of the iminoketone were present and that the compounds almost completely tautomerised to a mixture of the ketonamine and the imino-enol forms. Furthermore, geometrical isomerism in the ketoenamine form has been observed.[43]

The proton magnetic resonance spectrum of product (15) showed two doublets at 2.60 and 3.50 τ respectively, collapsing to singlets on deuterium oxide treatment, and of similar coupling constants (J=13Hz). The above signals are best rationalized in terms of an approximately one to one mixture of the geometrical isomers 15c, 15d although the difference in the chemical shift of the protons labelled * (0.9 τ) is unusually large for this type of structural difference. The remainder of the spectrum of product (15) conforms to this rationale of the presence of a one to one mixture, although the presence of a minor amount of a third component cannot be excluded. Another possible structure which can explain the "olefinic" pattern at 2.6-3.5 τ is (15b') in which the unexpected condensation on the ketone carbonyl has occurred.

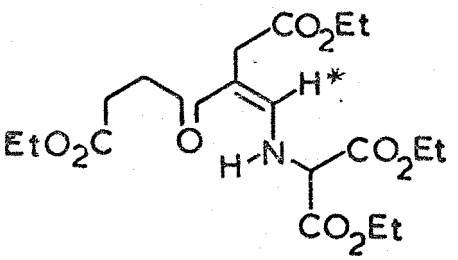
The possibility of rotamers is unlikely since the spectrum does not change appreciably in the range -70° to 55°. Structures (15e), (15f) are also less likely although deuterium exchange experiments in MeOD showed an exchange pattern (15g) that suggests their possibility.



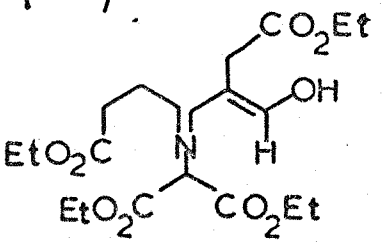
(15a)



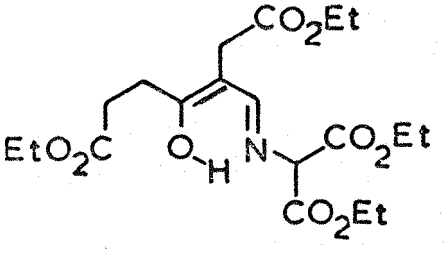
(15d)



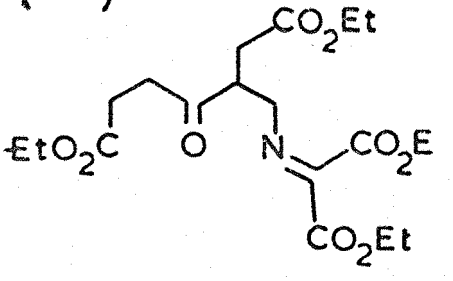
(15c)



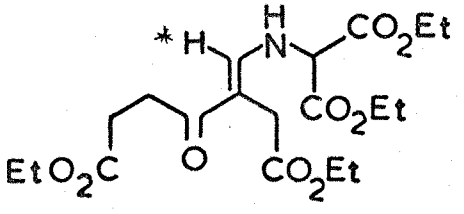
(15b')



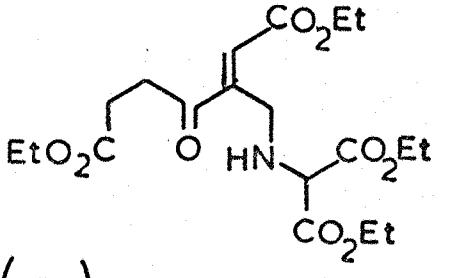
(15b)



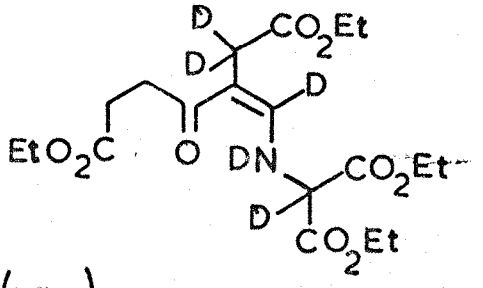
(15e)



(15d)



(15f)



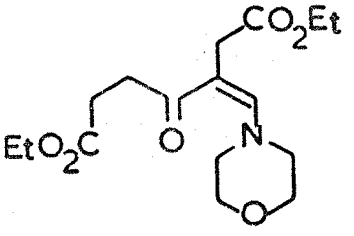
(15g)

SCHEME 12

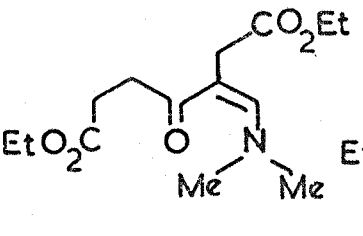
Structures for the condensation products of β-ketoaldehyde (12) with morpholine, dimethylamine and glycine ethylester

In an attempt to clarify the structural problem of condensation product (15), it was decided to synthesize its morpholine and dimethylamine analogues. Both the above mentioned amines being secondary would produce condensation products by necessity having the vinylogous amide (or ketoenamine) structures (16), (17) respectively.

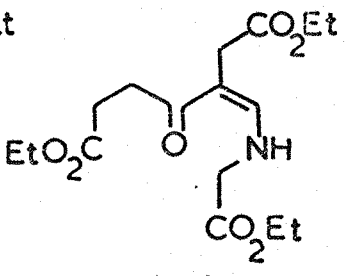
The above products were easily obtained through direct condensation of the components in refluxing ethanol and showed identical ultraviolet absorption maxima (297 nm, MeOH). Their infrared absorption maxima in the 1600-1700 cm^{-1} region were not comparable with those of product (15).



(16)



(17)



(18)

Their proton magnetic resonance spectra were fully interpretable in terms of a vinylogous amide structure (probably trans) showing a one proton singlet at 2.6 τ for the olefinic hydrogen and a two proton singlet at 6.80 for the methylene hydrogens of the ketoaldehyde moiety. Furthermore the adjacent methylenes of the ketoaldehyde moiety showed a clear four proton A_2B_2 multiplet. The above strongly suggests that one component of product (15) has the corresponding vinylogous amide structure.

The next synthetic approach was to condense the β-ketoaldehyde (12) with glycine ethylester, which being a primary amine would be expected

to produce a condensation product (18), this being a close analogue of product (15).

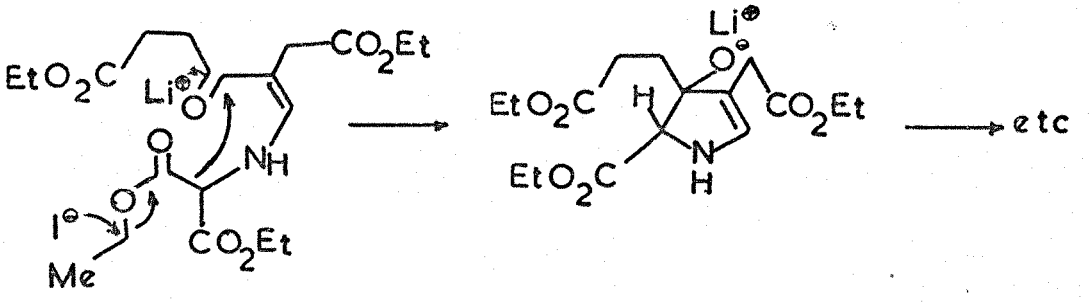
Product (18) was in fact obtained with difficulty by direct condensation of β-ketoaldehyde (25) and glycine ethylester in refluxing ethanol. The ultraviolet absorption maximum (285 nm, MeOH) and infrared maxima in the region 1600 to 1700 cm^{-1} were similar to those of product (15). Proton magnetic resonance spectroscopy revealed the presence of a similar pair of doublets (J=13Hz) at 2.6, 3.5 τ respectively, collapsing to singlets on deuterium oxide treatment and being in a three to four ratio. This suggests an isomeric pair analogous to that observed with product (15).

Attempted cyclization of condensation products (15), (18) of ketoaldehyde (12) with aminomalonate and glycine ethylester

1. Ketoenamine (15)

The ketoenamine (15) failed to produce any pyrrolic product under a variety of both basic (sodium hydride, potasium t-butoxide, sodamide) and acidic catalysts (dry hydrogen chloride, polyphosphoric acid).

In an attempt to facilitate the decarboxylation of the malonate moiety, lithium iodide semihydrate was used in dry pyridine at 80°. Since the reagent would almost certainly hydrolyse all ester groups, the reaction mixture was treated with diazomethane before assaying by TLC. No pyrrolic compound could be detected in the reaction mixture.



However in a refluxing solution of sodium acetate in acetic acid, product (15) gave the pyrrole (14) in less than 1% yield, which could not be improved under a variety of conditions.

2. Ketoenamine (18)

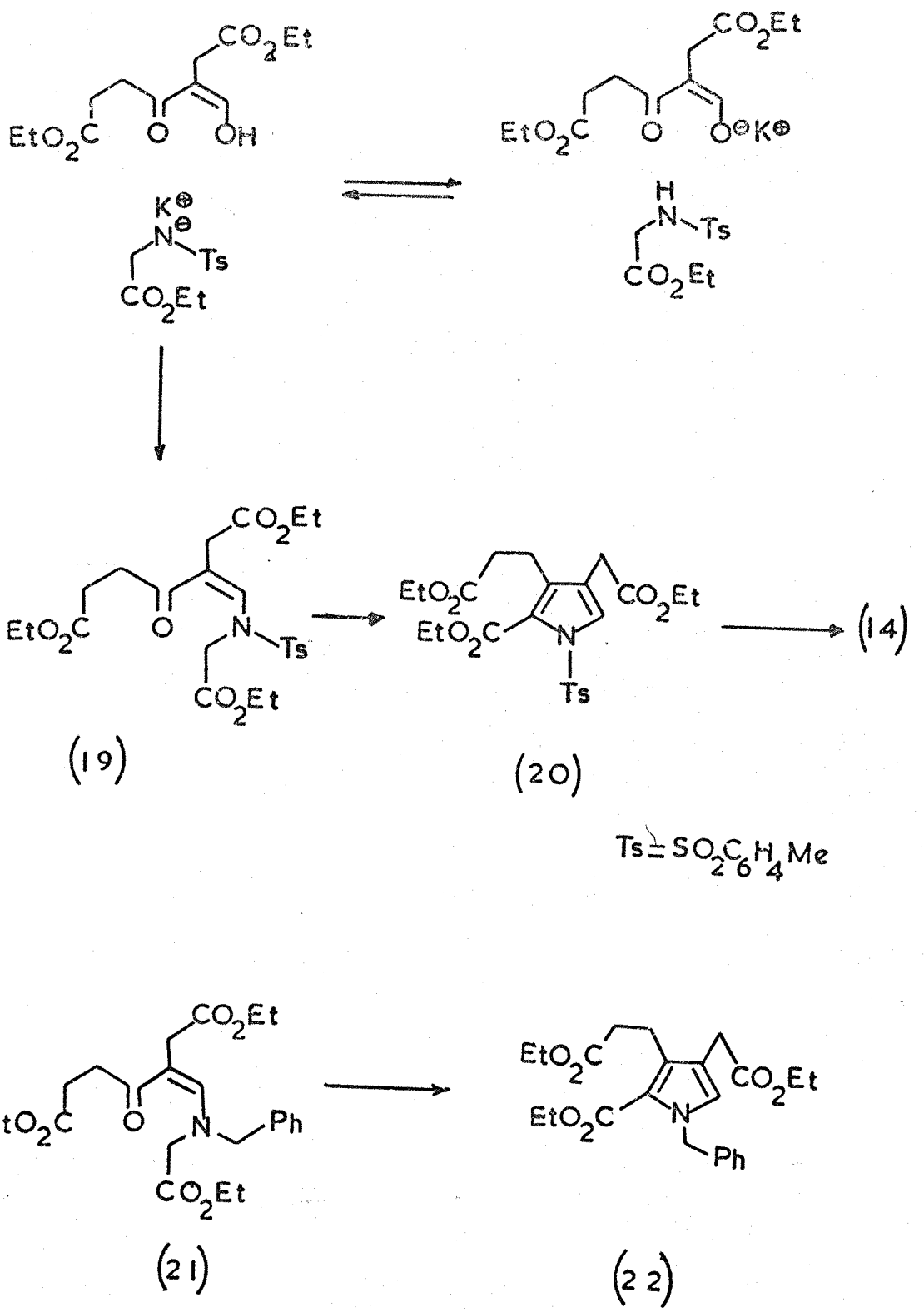
Similar treatment of product (18) from β-ketoaldehyde (12) and glycine ethylester did not produce any pyrrolic product, presumably due to lack of the activating influence of the second ester group and due to the acidity of the N-hydrogen when treated with base. The above reaction mixtures were assayed for pyrrolic products by TLC using a modified Ehrlich spray.

Attempted condensation of β-ketoaldehyde (12) with two N-substituted glycine ethylesters

Since the above failure of cyclization of condensation products (15) and (18) under strong base catalysis was attributed to the acidity of the N-hydrogen, it was next decided to realize the synthetic goal by employing a suitably N-substituted glycine in the condensation with the β-ketoaldehyde. The so produced condensation product would have as the most acidic hydrogens those of the glycine methylene and might thus be expected to be amenable to base catalysed cyclization towards a N-substituted pyrrole which would then have to be converted to the N-free compound.

(1) N-Tosylglycine ethylester

The p-toluenesulphonyl group was selected as the appropriate protective group. That group would be expected to enhance the acidity of the methylene hydrogens α- to the nitrogen in the condensation product (19) (scheme 13, page 31). Furthermore, the resulting N-sulphonyl pyrrole (34) would be sufficiently labile at the S-N bond to allow a mild deprotection stage to pyrrole (14) (scheme 13, page 31).


CO2Et
EtO2C
O
OH
K⊕
N⊖
Ts
CO2Et
O⊖K⊕
H
N
Ts
(19)
(20)
(14)
Ts = SO2C6H4Me

CO2Et
EtO2C
O
N
Ph
CO2Et
(21)
(22)

SCHEME 13

N-tosylglycine ethylester was prepared[47] by action of tosylchloride on glycine in aqueous alkali and esterification of the resulting N-tosylglycine in dry ethanol/hydrochloric acid. It failed however to condense with the ketoaldehyde (12) under a variety of conditions. This almost certainly can be attributed to the decreased nucleophilicity of nitrogen due to strong electron withdrawal by the sulphonyl group. Such reduced nucleophilicity of nitrogen is expressed by the enhanced acidity of the N-hydrogen and N-tosylglycine ethylester gives easily obtainable and stable salts. The potasium salt was prepared but equally failed to condense, presumably due to proton abstraction from the β-ketoaldehyde (scheme 13, page 31).

It was attempted to avoid that complication by employing the ethyl enolether of the β-ketoaldehyde. These experiments are described later (page 40).

(2) N-benzylglycine ethylester

In view of the above, the benzyl group was the obvious choice of protecting group having no appreciable electron-withdrawing properties and furthermore offering the prospect of catalytic removal by a mild hydrogenolytic cleavage of the C-N bond in the resulting N-benzylpyrrole.

N-benzylglycine ethylester was prepared in good yield by the action of benzylamine on an ethanolic solution of ethyl chloroacetate.[48] It easily condensed in refluxing ethanol with the β-ketoaldehyde (12) to give the ketoenamine (21) in very good yield (93%).

High resolution mass spectrometry suggested the expected formula $C_{20}H_{31}O_7N$ for a one to one adduct with loss of water. An intense absorption at 296 nm revealed the presence of the chromophore (O=C-C=C-N-). The infrared spectrum in the 1700-1600 cm^{-1} region is consistent with the above assignment showing a conjugated carbonyl group at 1640 cm^{-1} and a carbon-carbon double bond at 1605 cm^{-1}. The proton

magnetic resonance spectrum is fully interpretable in terms of structure (21), showing a one proton singlet at 2.6 τ for the olefinic hydrogen, a two proton singlet at 6.8 τ for the isolated methylene hydrogens as well as a four proton A_2B_2 multiplet for the two adjacent methylene protons of the β-ketoaldehyde moiety. The benzyl methylene protons appear at 5.5 τ and the glycine methylene protons at 5.85 τ.

Thus the above ketoenamine (21) behaves like the analogues (16), (17) derived from the secondary amines morpholine and dimethylamine respectively, in that no geometrical isomerism can be observed.

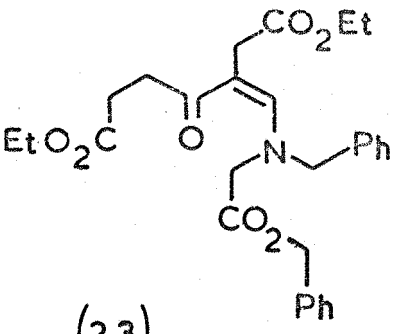
Cyclization of the ketoenamine (21) to pyrrole (22)

The ketoenamine (21) easily cyclized in refluxing acetic acid to afford pyrrole (22) in 73% yield, giving a positive Ehrlich test. High resolution mass spectrometry supported the expected formula $C_{20}H_{29}O_6N$. In the carbonyl region of the infrared spectrum the maxima at 1735 cm^{-1} and 1695 cm^{-1} are attributed to the aliphatic and conjugated ester-carbonyls respectively.

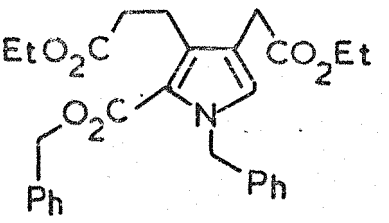
In the proton magnetic resonance spectrum the α-hydrogen appears at 3.20 τ as a one proton singlet, the methylene hydrogens of the acetate residue at 6.80 τ as a two-proton singlet, while at 7.00 to 7.50 τ a four-proton multiplet is due to the adjacent methylenes of the propionic residue. The benzyl methylene hydrogens appear at τ 4.65 as a two-proton singlet.

Condensation of β-ketoaldehyde (12) with N-benzylglycine benzylester to the ketoenamine (23) and cyclization of the latter to pyrrole (24)

It was next decided to investigate the possibility of performing the synthesis using the benzylester analogue of N-benzylglycine instead of the ethylester used before and thus producing the α-carbobenzoxy-pyrrole (24), through the ketoenamine (23).



(23)



(24)

This pyrrole would have an obvious advantage over the α-carboethoxy analogue, in that it would produce in one hydrogenolytic step the N-free-α-carboxypyrrole, thus facilitating the synthesis of PBG by eliminating the need for hydrolysis of the α-ester prior to the decarboxylation stage. Furthermore, side chain elaborations in the final stages of the synthetic route to PBG and related pyrroles, would most probably involve generation of the aminomethyl side chain through a hydrogenation step (reduction of the α-oxime, S.F. McDonald, reduction of the α-methylazide, A.R. Battersby, projected reduction of the α-nitrile in this work). Thus the generation of 1-H-2-carboxy-5-methyl-amino side groupings would be effected in a single mild step.

The ketoenamine (23)

In view of the above, N-benzylglycine benzylester was prepared in two steps from chloroacetic acid through benzylchloroacetate[49] in poor yield due to difficult isolation and considerable amounts of side products e.g. chloroacetobenzamide, $ClCH_2CONHCH_2Ph$, in approximately 30% yield.

N-benzylglycine benzylester easily condensed with β-ketoaldehyde (12) in refluxing ethanol to give the ketoenamine (23) in good yield.

Mass spectrometry supported the expected formula $C_{28}H_{33}O_7N$ for a one to one adduct with loss of one molecule of water. The intense

absorption at 298 nm in the ultraviolet spectrum revealed the chromophore (O=C-C=C-N) and the absorption maxima in the region 1700-1600 cm^{-1} were attributed to aliphatic ester carbonyls (1735 cm^{-1}), conjugated ketone (1640 cm^{-1}) and C-N double bond. The proton magnetic resonance spectrum was fully interpretable in terms of the ketoenamine structure (23), showing a one proton singlet at 2.63 τ, for the olefinic hydrogen and four two proton singlets for the methylene hydrogens of the N-benzyl group, the benzylester group, the glycine and aldehyde moieties at 4.00, 4.50, 6.10 and 6.85 respectively.

Cyclization of the ketoenamine (23) to pyrrole (24)

The ketoenamine (23) easily and in good yield (72%) cyclized in refluxing acetic acid to pyrrole (24), giving a positive Ehrlich test.

High resolution mass spectrometry confirmed the expected formula $C_{28}H_{31}O_6N$. In the carbonyl region of the infrared spectrum the absorption at 1735 and 1690 cm^{-1} are attributed to the aliphatic and conjugated ester carbonyls respectively. In the proton magnetic resonance spectrum the one proton singlet at 3.25 τ is due to the α-hydrogen of the pyrrolic ring while the methylene hydrogens of the N-benzyl, benzylester and carboethoxymethyl side groups appear as two proton singlets at 4.65, 4.90 and 6.60 τ respectively.

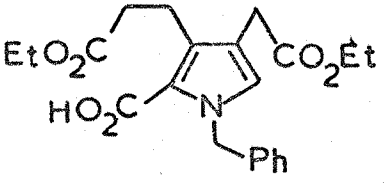
Attempts of removal of the N-benzyl group from pyrroles (22), (24)

The goal of synthesis of a pyrrole with the desired substitution pattern having been successfully realized, it was next necessary to remove the N-benzyl protective group.

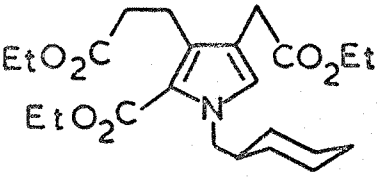
1. Catalytic hydrogenolysis

From hydrogenation over palladized carbon (10%) and 1.1 atm of hydrogen, the N-benzyl-2-carboethoxypyrrole (22) was recovered unchanged. Ethanol or acetic acid were employed as solvents at 20° and 70°.

The 2-carbobenzoxy pyrrole (24), however at 20° in ethanol was quantitatively hydrogenolysed to the 2-carboxylic acid (25).



(25)
(25a) = Me-ester



(26)

Mass spectra of the acid (25) showed a weak peak at $^{m}/_{e}$ 387 for the molecular ion and a strong one at $^{m}/_{e}$ 343 (M-44) for the decarboxylation product. The absorption maximum at 277 nm in the ultraviolet spectrum shows a hypsochromic shift to 267 nm when the acid is treated with dilute alkali. The above 10 nm shift is characteristic of pyrrole-carboxylic acids. The infrared spectrum showed the acidic hydrogen as a broad absorption at 2800 cm^{-1} and the acid carbonyl at 1665 cm^{-1}. The proton magnetic resonance spectrum as compared with that of the starting material (24) lacks the signals associated with the N-benzyl group, viz. the two proton singlet at 4.91 τ of the benzylester methylene protons and the five proton singlet at 2.82 τ of the benzylester phenyl hydrogens. The acid (25) gives a positive Ehrlich test. With diazomethane in ethanol/ether it was converted to the methylester (25a) (m.p. 63°-5°) which showed the expected spectral characteristics and produced a positive Ehrlich test.

When platinum oxide was employed as the catalyst the N-benzyl-2-carboethoxypyrrole (22) was converted to pyrrole (26) by reduction of the phenyl ring to the cyclohexyl analogue.

High resolution mass spectrometry supported the formula $C_{20}H_{35}O_6N$ and revealed a fragmentation pattern characteristic of N-alkylpyrroles.

The absorption maximum at 273 nm is attributable to the pyrrolic ring chromophore, while the proton magnetic resonance spectrum as compared with that of the starting compound (22) lacks the signals associated with the N-benzyl group, viz. the five proton multiplet at 2.95 τ of the phenyl hydrogens and the two proton singlet at 4.61 τ of the benzyl methylene hydrogens. Furthermore it shows a two proton signal in the area 5.70 - 6.10 τ (obscured by the ethylester quartets) and an eleven proton unresolved signal at 8.5 to 9.0 τ attributable to the methylene protons adjacent to nitrogen and the cyclohexyl moiety respectively. The above pyrrole (26) gives a positive Ehrlich test.

2. Attempted cleavage with dissolving metal

The N-benzylpyrrole (22) on treatment with sodium in liquid ammonia, sodium in hexamethylphosphoramide, was recovered largely unchanged.

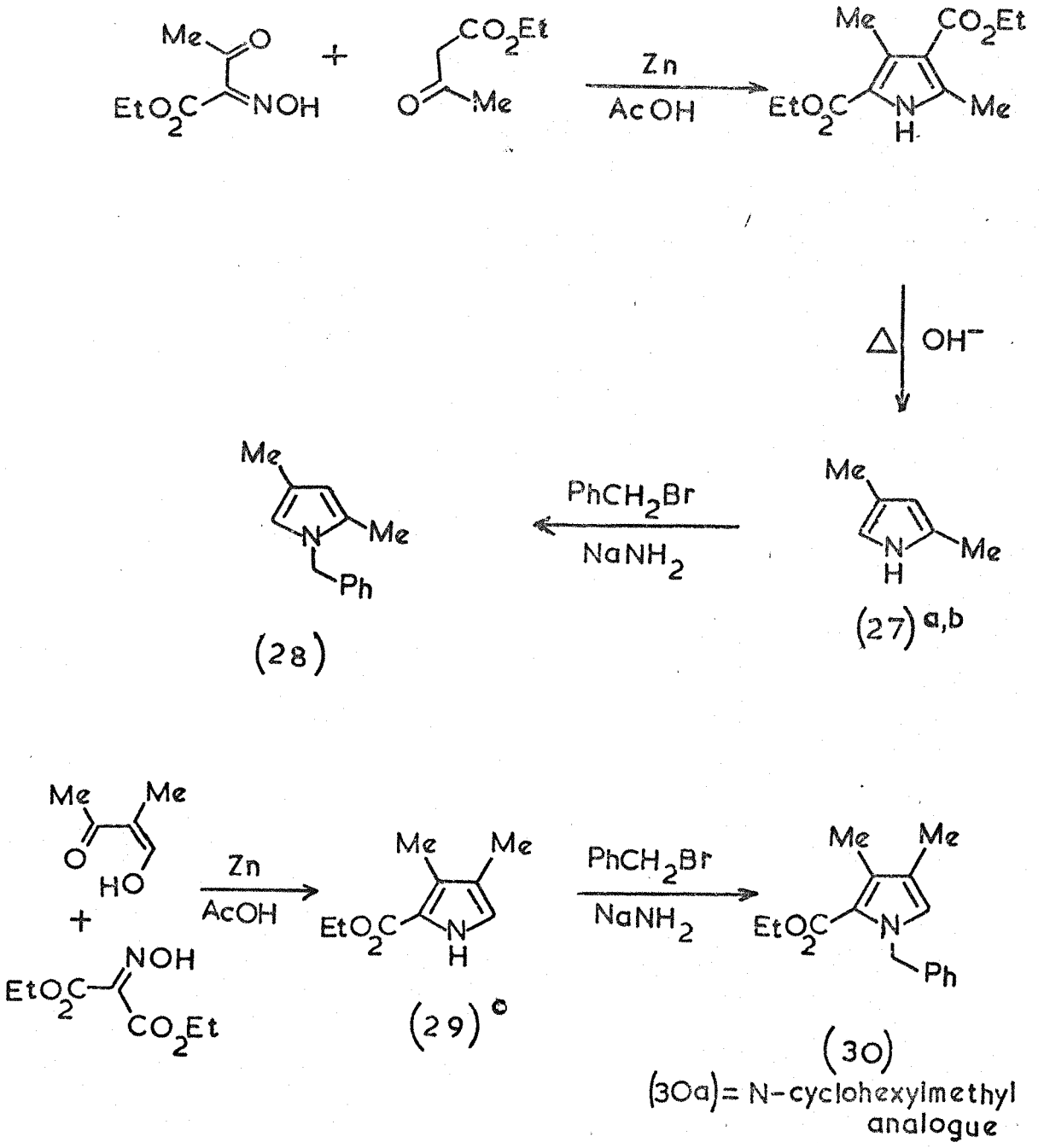
3. Attempted cleavage with hydrogen bromide

The N-benzylpyrrole (22) was similarly recovered after treatment with a solution of dry hydrogen bromide (2N) in glacial acetic acid for up to 24 hours at room temperature. Elevation of temperature to 45° reduced the amount of starting material recovered but did not produce any other pyrrolic compound. Similar results were obtained when dimethylformamide was employed as a solvent.

Thus α-H pyrroles were successfully synthesized from the β-ketoaldehyde (12) and suitably N-substituted glycine esters. However a method for converting those N-substituted pyrroles to their N-H analogues has yet to be found. Conditions different to those employed in the present work or even alternative blocking groups might well provide the answer to the above problem.

Attempted debenzylation of model N-benzylpyrroles

In view of the above unsuccessful attempts of debenzylation of



SCHEME 14

a - H. Fischer, Org. Syn. 1969, 2, 217.

b - H. Fischer, Org. Syn. 1969, 2, 202.

c - G.G. Kleinspehn, J. Amer. Chem. Soc. 1955, 77, 1546.

pyrroles (22), (24), it was decided to investigate these findings with a series of model pyrrole compounds which were relatively easy to synthesize. The pyrroles (28), (30) were chosen and synthesized as shown in scheme 14 (page 38).

The pyrrole (30)

The N-benzylpyrrole ester (30) behaved similarly to pyrrole (22), being recovered unaffected after sodium ammonia, or sodium hexamethylphosphoramide treatment and converted to the N-cyclohexylmethyl analogue (30a) on platinum catalyzed hydrogenation. This pyrrole produced a positive Ehrlich test and high resolution mass spectrometry supported the formula $C_{16}H_{25}NO_2$. The absorption maximum at 274 nm and the infrared maximum at 1695 cm^{-1} are consistent with the above structural assignment. Furthermore the proton magnetic resonance spectrum as compared with that of the starting material (29), lacked the signals associated with the benzyl group (five proton multiplet at 2.95 τ of the phenyl hydrogens, and two proton singlet at 4.95 τ of the benzyl methylene hydrogens) while it showed the signals of a cyclohexylmethyl side chain (two proton doublet at 5.95 τ of the next-to-nitrogen methylene protons and unresolved signal at 8.6 - 9.0 τ of the cyclohexyl moiety).

The pyrrole (28)

The pyrrole (28) similarly resisted debenzylation when treated with sodium in ammonia or hydrogenated over palladized carbon, but the experiments on hydrogenation over platinum oxide although producing no 2,4-dimethylpyrrole nevertheless produced a complex mixture of products.

Thus it appears that N-benzylpyrrole esters are not amenable to conversion to the N-H analogues by hydrogenolytic removal of the benzyl group.

Alternative approaches to the pyrrole triester (14)

In view of the failure of the crucial debenzylation step in the present synthetic route, it was decided to investigate the possibility of synthesizing the pyrrole (14) through an alternative scheme, still employing the β-ketoaldehyde (12) as the key starting material (scheme 15, page 41).

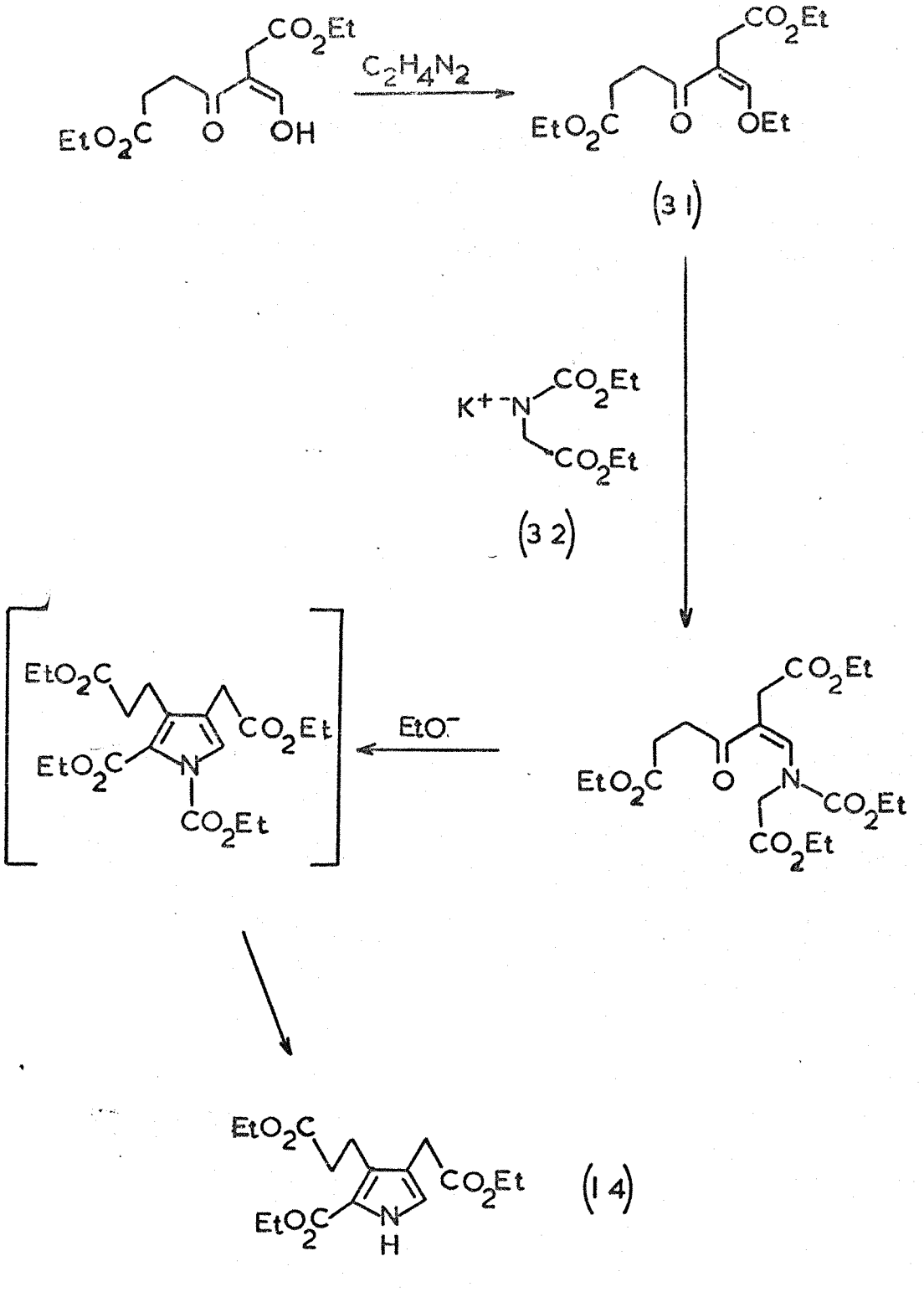
The enol ether (31) was synthesized from the β-ketoaldehyde (12) by action of diazo-ethane in ether. Spectral characteristics confirm the above structural assignment thus: high resolution mass spectrometry supported the expected formula $C_{14}H_{22}O_6$. The absorption maximum at 251 nm is attributed to the chromophore (O=C-C=C-O-) and the maxima at 1640 and 1605 cm^{-1} in the infrared spectrum to the carbonyl and C-C double bond of the same system respectively. The proton magnetic resonance spectrum shows a one-proton singlet at 2.65 τ for the olefinic hydrogen, a two-proton singlet at 6.95 τ for the isolated methylene hydrogens and a four proton A_2B_2 multiplet for the vicinal methylene hydrogens at 7.1-7.5 τ.

Enol ether (31) failed to produce any pyrrolic product on treatment with either potasium ethyl tosylglycinate (33) or potasium ethyl carboethoxyglycinate (32)[50] under a variety of conditions. Instead the enol ether (31) was recovered unchanged in yields of 50 to 70%. This is somehow surprising in view of the successful condensation of carbethoxy-glycinate (32) with a similar enol ether carried out during the prodigiosin synthesis of Rapoport.[51]

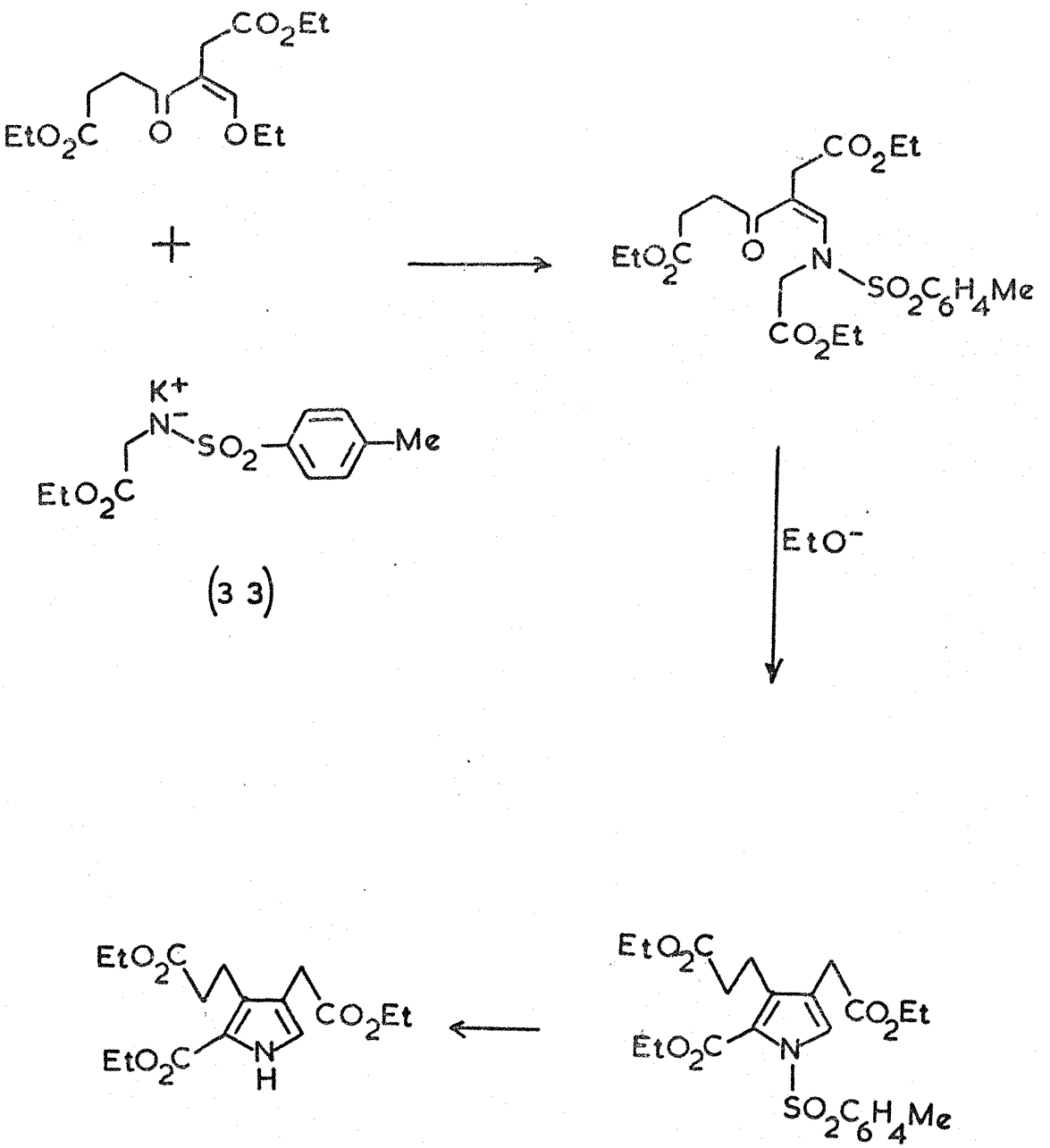
Side chain elaborations

Attempted synthesis of α-carbonitriles as intermediates in α-aminomethyl side chain generation

Simultaneously with the attempts of debenzylation of N-benzyl pyrroles, it was decided to investigate the possibility of direct



SCHEME 15a


CO2Et
EtO2C
O
OEt
+
K+
N−
SO2
Me
EtO2C
(33)
CO2Et
EtO2C
O
N
SO2C6H4Me
CO2Et
EtO−
EtO2C
CO2Et
EtO2C
N
H
(14)
EtO2C
CO2Et
EtO2C
N
SO2C6H4Me

SCHEME 15b

introduction of a cyano group in an α-free position of a pyrrole ring and the subsequent catalytic reduction of this group to the aminomethyl analogue.

This introduction of the cyano group might be accomplished either directly, employing a nucleophilic attack of the pyrrole on a cyanogen halide[52] (e.g. cyanogen bromide) or via the α-halocompound (preferably the α-iodocompound) by the action of cuprous cyanide (scheme 16a, page 44).

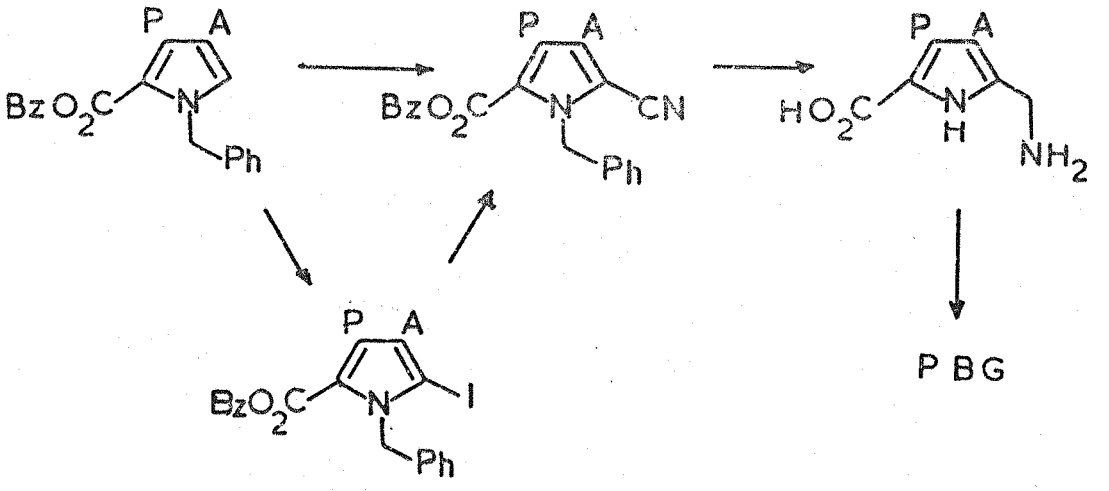
Both pyrroles (22) and (24) however failed to react with cyanogen bromide under a variety of conditions of solvent and temperature, including silver salt catalysis and heating in dry pyridine. They equally failed to react with iodine but pyrrole (22) when refluxed with excess of iodine chloride in ethanol in presence of sodium carbonate produced a low yield of the α-iodocompound, (34) (scheme 16b, page 44) as evidenced by high resolution mass spectrometry, supporting the formula $C_{13}H_{22}INO_6$.

Action of cyanogen bromide on model pyrrole compounds

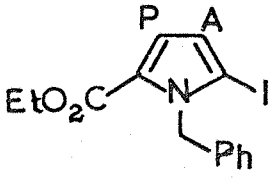
In view of the above unsuccessful attempts to establish an effective method for the synthesis of α-carboxypyrryl-α'-nitriles and α-carboxypyrryl-α'-iodides, it was decided to investigate these findings with some model pyrrole compounds which were available through scheme 14 (page 38).

(1) Action of cyanogen bromide on 2,4-dimethylpyrrole

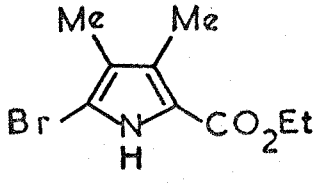
2,4-Dimethylpyrrole reacted smoothly with cyanogen bromide in refluxing ethanol in presence of sodium carbonate to produce the α-carbo-nitrile (35) mp 73°-5° (lit 75°-6°). Compound (35) shows an intense absorption at 255 nm and in the infrared region a sharp absorption at 2220 cm^{-1} of the nitrile group. The proton magnetic resonance



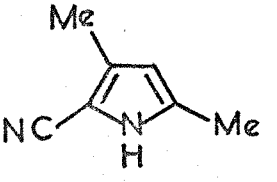
a



(34)



(36)



(35)

b

SCHEME 16

spectrum as compared with that of 2,4-dimethyl pyrrole lacks the α-hydrogen signal, as expected.

(2) Action of cyanogen bromide on pyrrole esters (29), (30)

Both pyrrole esters (29) and (30) (page 38) failed to react with cyanogen bromide under various conditions of solvent and temperature. Under forcing conditions however (dimethylformamide 120°), pyrrole (29) produced the α-bromide (36) (mp 131°-3°, lit 134°) in approximately 10% yield as evidenced by mass spectroscopy (p.61) and proton magnetic resonance spectra which compared with those of (29) lack the α-H signal at 3.25 τ .

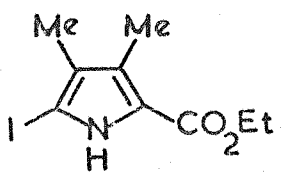
Thus it appears that α-pyrrole esters are not sufficiently nucleophilic to react with cyanogen bromide, while the non-deactivated alkyl pyrrole (27) easily does so. This method holds great promise as a general route to cyanopyrroles.

Action of iodine chloride on model pyrrole compounds

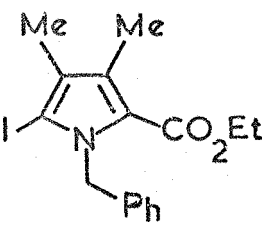
The α-pyrrole ester (29) with iodine chloride in refluxing ethanol and in presence of sodium carbonate smoothly produced in 64% yield the α'-iodopyrrole (37), which showed an intense absorption maximum at 277 nm^{-1} and an absorption at 1690 cm^{-1} in the infrared region. The proton magnetic resonance spectrum as compared with that of the pyrrole ester (29) lacks the α-H signal at 3.25 τ . High resolution mass spectrometry supported the formula $C_9H_{12}INO_2$.

The N-benzylpyrrole ester (30) similarly produced the α-iodocompound (38) in 34% yield. The proton magnetic resonance spectrum of compound (38) as compared with that of compound (30) lacks the α -H signal at 3.15 τ . High resolution mass spectrometry supported the formula $C_{10}H_{18}INO_2$.

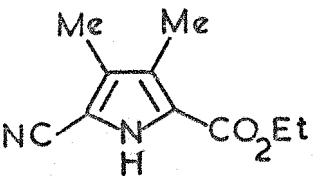
Iodine itself failed to react with either of the above pyrrole esters (29), (30).



(37)



(38)



(39)

The α-iodide (37) was subsequently converted to the α-carboxynitrile (39) by the action of cuprous cyanide in pyridine, in low yield (16%).

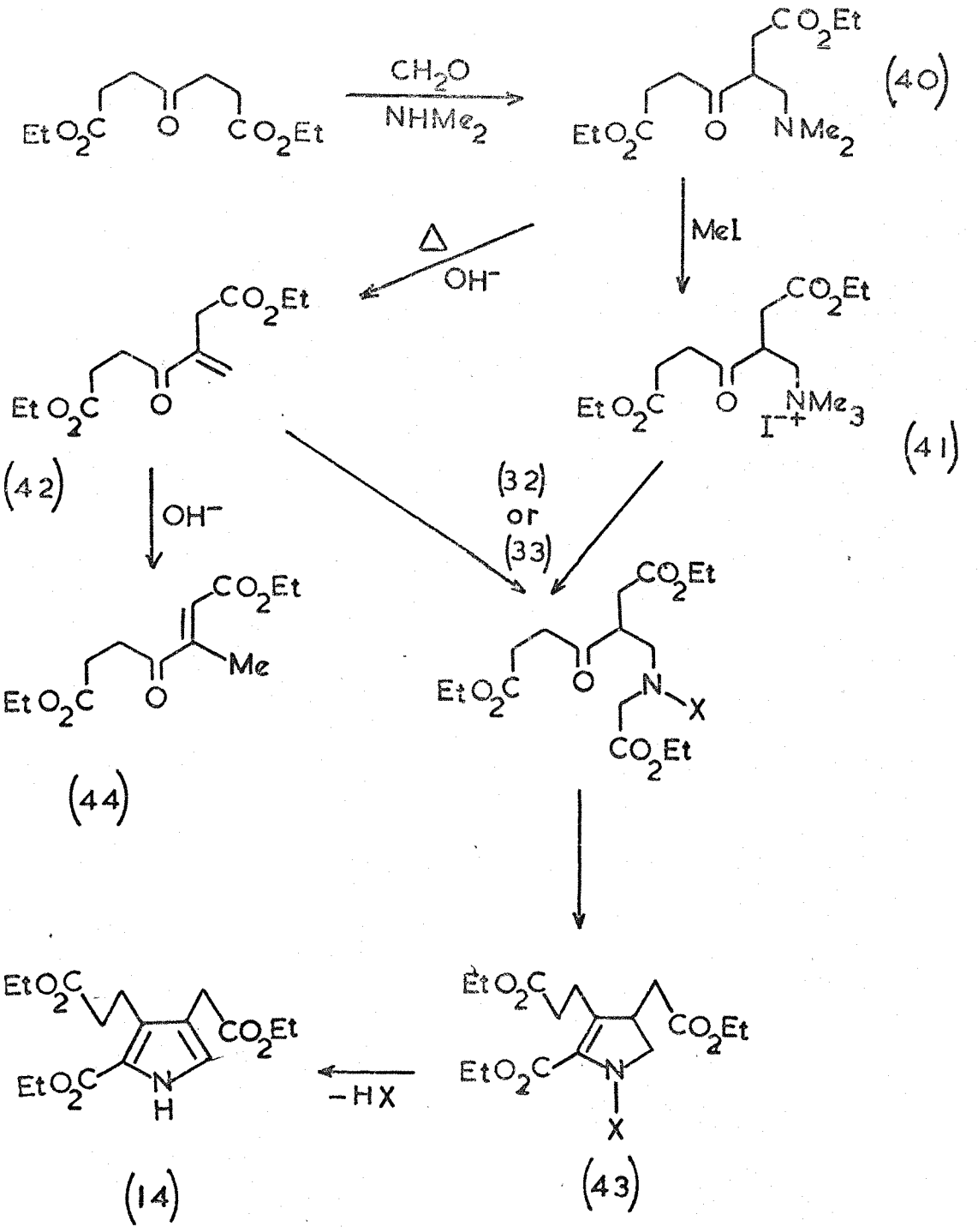
The above nitrile (39) showed an intense absorption at 277 nm and in the infrared region the sharp nitrile band at 2210 cm^{-1} and the ester carbonyl absorption at 1695 cm^{-1}. High resolution mass spectrometry supported the formula $C_{10}H_{12}N_2O_2$.

Other routes under consideration

The possibility of using γ-oxopimelic diethylester to synthesize the dimethylamine Mannich base (40) was considered. By the action of ethyl tosylglycinate or ethyl carboethoxyglycinate salts on the above Mannich base or its quaternary salt (41) it might be possible to accomplish the synthesis of pyrrole (14) as shown in scheme 17 (page 47).

Alternatively, the β-methylidene compound (42) might be obtained through thermal deamination of the Mannich base. Similarly, action of ethyl glycinate salts on the above $\alpha\beta$-unsaturated ketone could result (through a Michael type condensation) in the formation of N-substituted pyrrolines (43) similarly to the "Kenner" synthesis of pyrroles.[53]

One possible drawback of the proposed use of the $\alpha\beta$-unsaturated ketone (42) might well arise in the isomerisation to the ketone (44)



SCHEME 17

in which the double bond has shifted in conjugation with the ester. The above transformation would be very likely if strongly alkaline conditions were employed for the reaction.

Preliminary experiments were carried out employing γ-oxopimelate and morpholine or dimethylamine under Mannich base formation conditions. With dimethylamine a 7% yield of the Mannich base (40) was obtained while 80% of the ketone was recoverable.

Conclusion

Although the projected synthesis of PBG was not successfully realized, some useful contributions to this area of chemistry have been made. An investigation of condensation products between various primary and secondary amines and the β-ketoaldehyde (12) have been made. α-H pyrroles were successfully synthesized although a different protective group is required for continuance to PBG synthesis; α-pyrrylnitriles were synthesized through the use of cyanogen bromide; one-step iodinations of α-pyrrole carboxylates were realized and the potential of conversion of those α-iodides to the corresponding α-carboxypyrryl-α′-nitriles has been demonstrated.

EXPERIMENTAL

Methods and Materials

Melting points were taken on a Kofler micro hot-stage and are uncorrected.

Ultraviolet spectra were recorded on Unicam SP 800 and Perkin Elmer 402 spectrophotometers.

Infrared spectra were recorded on a Perkin Elmer 157 G instrument and are related in wavelength to a polystyrene standard. 1 mm path cells were used for solution spectra.

Nuclear magnetic resonance spectra were determined on deuteriochloroform solutions (unless otherwise stated), using a Perkin Elmer R 12, or a Varian HA 100 instrument and are related to an internal tetramethylsilane standard.

Mass spectra were recorded on a A1-MS12 spectrometer.

Preparative TLC was conducted on Kieselgel GF_{254} (Typ 60) Merck, and Aluminium oxid GF_{254} (Typ E) Merck. Visualization was effected by ultraviolet fluorescence, and iodine vapour, chromic acid or Ehrlich reagent on non-preparative runs. Solvent system A = 20% ethylacetate in cyclohexane.

Preparation of β-formyl-γ-oxopimelic diethyl ester (12)

In a stirred (Herschberg) suspension of sodium hydride (5.0 g. 10% dispersion in oil) in 50 ml of dry ether containing 2 drops of absolute ethanol, a solution of γ-oxopimelate (11.5 gr) in ethyl formate* (78 ml) was added over a period of 30 minutes with exclusion of moisture under cooling (ice bath). Stirring was continued for 15 more minutes and the reaction mixture was brought to pH 4 with hydrochloric acid (3N). The organic layer was dried (Na_2SO_4) and evaporated ($< 50^{\circ}$) to a red oil containing mainly the ketoaldehyde (60-80%) and some γ-oxopimelate.

Preparation of the copper chelate complex of β-formyl-γ-oxopimelic diethylester (12)

A warm (50°) saturated aqu. solution of copper acetate (15ml) was added to a stirred solution of crude β-formyl-γ-oxopimelic diethylester (4 gr) in ethanol (10 ml). The green gum that separated on standing was washed with water (2 x 10 ml) and dissolved in 15 ml of boiling acetone. On standing under refrigeration the chelate precipitated as green leaflets (grey when dried) 1.7 - 2.2 g. mp 126°-32°. Second crystallization (400 mg) from ethanol/ether 3:1 (4 ml) afforded 320 mg (m.p. 130°-132°).

ν_{max} (CCl_4) 1735, 1605 cm^{-1}

λ_{max} (MeOH) 243 nm ε12 200 296 nm 16 600

$^m/_e$ 577(M^+) 500, 321, 292, 258, 230, 213, 212, 184, 167, 156, 139, 138, 129, 111(b).

requires C 49.92% H 5.94%

found C 49.59% H 6.07%

* - distilled over P_2O_5

Generation of the β-ketoaldehyde from its copper chelate complex (13)

Copper chelate (13), (200 mg) was added to a stirred mixture of IN hydrochloric acid (1 ml) and ether (2 ml). Stirring was continued until complete dissolution of the chelate. The combined organic phase and washings (1 ml ether) were dried (Na_2SO_4) and evaporated to a pale yellow oil (170 mg 93%).

ν_{max} (CCl_4) 1735, 1695, 1645, 1605 cm^{-1}

λ_{max} (E+OH) 253 nm ε 8,000

τ 0.20 (0.2H, s, -CHO), 2.35 (1H, d(J=10Hz), -C=CH)

5.95 (4H, m, $-OCH_2Me$), 6.80 (2H, s, $=C-CH_2-CO_2Et$)

7.30 (4.5H, m, $-CH_2CH_2-$ and $-CH-CH_2-$) 8.75 (6H, 2t, $-OCH_2CH_3$)

m/e 258(M^+), 213(M-45), 185(M-73), 171(M-87), 157(M-101).

Preparation of Ketoenamine (15)

Ketoaldehyde (12) (170 mg) and aminomalonic diethylester (115 mg) were refluxed in absolute ethanol (1 ml) for 2 hours, and subsequently evaporated at 60°. 1 ml of chloroform was added and similarly evaporated to a brown oily residue. TLC purification (system A, two developments, Rf 0.65) afforded the ketoenamine (15) (210 mg, 77%) as a yellowish oil.

ν_{max} (CCl_4) 1735, 1635, 1660 cm^{-1}

λ_{max} (EtOH) 286 nm ε 8000

τ 2.60 (0.5H, d, =C-H), 3.50 (0.5H, d, -N=C-H)

5.92 (7H, m, $-OCH_2Me$), 6.80 (1H, s, $=C-CH_2-CO_2Et$),

7.00 (1H, s, $=C-CH_2-CO_2Et$), 7.25-7.50 (5H, m, $-CH_2CH_2-$)

8.85 (9H, m, $-OCH_2CH_3$).

m/e 415(M^+), 370(M-45), 342(M-73), 338(M-87), 314(M-101),

256(M-159).

Calculated mass for $C_{19}H_{29}NO_9$ 415.16171

found 415.16181

Preparation of ketoenamine (17)

Ketoaldehyde (12) (300 mg) and a solution (4 ml) of 0.5 N dimethylamine in absolute ethanol were refluxed for 30 minutes and allowed to evaporate. 1 ml of chloroform was added and similarly evaporated to an oily residue. TLC purification (system A) afforded the ketoenamine (17) (315 mg. 96%) as a transparent oil.

ν_{max} (CCl_4) 1725, 1600 cm^{-1}

λ_{max} (EtOH) 297 nm ε 8,500

τ 2.61 (1H,s,-C=C-H), 5.75-6.00 (4H,2q,-OCH_2Me),
6.81 (2H,s,=C-CH_2-CO_2Et), 7.25-7.50 (4H,A_2B_2,-CH_2CH_2-)
7.15 (6H,s,-NMe_2), 8.75-8.95 (6H,2t,-OCH_2CH_3)

m/e 285(M^+), 240(M-45), 212(M-73),
198(M-87), 184(M-101).

Preparation of Ketoenamine (21)

Ketoaldehyde (12) (130 mg) and benzylglycine ethylester (100 mg) were refluxed in absolute ethanol (1 ml) for 30 minutes. The solvent was allowed to evaporate to a yellow residue which was purified by TLC (system A, Rf 0.65) to afford the ketoenamine (204 mg 92%) as a transparent oil.

ν_{max} (CCl_4) 1735, 1640 cm^{-1}

λ_{max} (EtOH) 296 nm ε 9,500

τ 2.55 (1H,s,=CH-N), 2.70(5H,s,Ph),
5.45(2H,s,-NCH_2Ph), 6.00(2H,s,-NCH_2CO_2Et),
5.95(6H,3q,-OCH_2Me), 6.75(2H,s,-C=CCH_2CO_2Et),
7.35(4H,m,-CH_2CH_2-), 8.75(9H,3t,-OCH_2CH_3).

m/e 433(M^+), 360(M-73), 332(M-101),
279, 206, 192(M-241),

Calculated mass for $C_{23}H_{29}NO_6$ 415.19995

found 415.1992

Preparation of ketoenamine (23)

Ketoaldehyde (12) (86 mg) and N-benzylglycine benzylester (95 mg) were refluxed in absolute ethanol (1 ml) for 1 hour. The solvent allowed to evaporate afforded a brown oil which was TLC purified (alumina, ether/petroleum ether 40°-60° 1:1, Rf 0.3) to afford the ketoenamine (23) as a transparent oil (123 mg. 64%).

ν_{max} (CCl_4) 1735, 1645 cm^{-1}

λ_{max} (EtOH) 298 nm, ϵ 10,800

τ 2.60(1H,s,C=CHN), 2.80(10H,m,Ph)

4.95(2H,s,$-OCH_2Ph$), 5.55 (2H,s,$-NCH_2Ph$)

6.05(4H,29,$-OCH_2Me$), 6.85(2H,s,$-CCH_2CO_2Et$),

7.45(4H,m,$-CH_2CH_2CO_2Et$), 8.85(6H,2t,$-OCH_2CH_3$)

$m/_e$ 433(M^+), 360(M-73), 328, 302, 279, 211, 206, 192.

Preparation of N-benzylglycine benzylester

Benzylchloroacetate (300 mg)[49] and benzylamine (350 mg) were heated in benzyl alcohol (2 ml) to 120° for 45 minutes. The cooled reaction mixture was diluted with ether (3 ml), filtered and extracted with IN hydrochloric acid (3 x 2 ml). The combined extracts were neutralized with IN sodium hydroxide and extracted with ether (3 x 2 ml). The ether phase was dried (Na_2SO_4) and evaporated. TLC separation (Silica gel GT_{230}, 10% AcOEt in cyclohexane, two developments) afforded N-benzylglycine benzylester, as a transparent oil (180 mg, 43%) at Rf 0.55.

(Four bands develop: Rf = 0.45, 0.55, 0.75, 0.80).

ν_{max} (CCl_4) 3600, 1735 cm^{-1}

λ_{max} (EtOH) 255 nm

τ 2.75(5H,s,Ph), 2.95(5H,s,Ph), 4.97(2H,s,$-OCH_2Ph$),

6.35(2H,s,$-NCH_2Ph$), 6.75(2H,s,$-NCH_2CO_2Et$), 8.01(1H,s,-NH).

Preparation of ketoenamine (18)

A solution of potasium hydroxide (60 mg) in absolute ethanol (2 ml) was added to a solution of glycine ethylester hydrochloride (140 mg) in absolute ethanol (2 ml) followed by 255 mg of the -ketoaldehyde (12) and reflux was maintained for 30 minutes. The solvent was evaporated and the residue was treated with chloroform (2 ml), filtered from NaCl and evaporated to a yellow oil which was purified by TLC (system A, Rf 0.6) to afford the ketoenamine (18) (264 mg, 75%) as a yellowish oil.

ν_{max} (CCl_4) 3400, 1735, 1645, 1610 cm^{-1}

λ_{max} (EtOH) 285 nm ε 8000

τ 2.55(0.5H,d,(J=13Hz)-C=C-H), 3.50(0.5H,d,(J=13Hz)-N=C-H),
5.80-6.05(8H,m,-OCH_2Me and -N-CH_2CO_2Et),
6.75(1H,s,-C=C-CH_2-CO_2Et), 6.95(1H,s,C=C-CH_2-CO_2Et),
7.20-7.45(5H,m,-CH_2CH_2-), 8.80-9.00(9H,m,OCH_2CH_3).

$m/_e$ 343(M^+), 298(M-45), 270(M-73), 256(M-87), 242(M-101).

Preparation of 1-benzyl-2-carboethoxy-3-(2-carboethoxyethyl)-4-carboethoxymethyl pyrrole

Ketoenamine (21) (100 mg) was refluxed for 3 hours with a solution of sodium acetate (100 mg) in acetic acid (1 ml). The solution was then neutralized with aqueous sodium hydroxide (10%) and extracted with ether (2 x 2 ml). Evaporation of the ether phase afforded a red oil which was purified by TLC (system A, Rf 0.8) to afford pyrrole (22), 71 mg (73%), as an Ehrlich positive transparent oil. (At Rf 0.65 ketoenamine (21) (13 mg, 14%) can be recovered).

ν_{max} (CCl_4) 1736, 1732, 1690 cm^{-1}

λ_{max} (EtOH) 276 nm ε 7,500

τ 3.95(5H,m,Ph), 3.30(1H,s,H^5), 4.65(2H,s,-NCH_2Ph),
5.95(6H,2q,-OCH_2Me), 6.65(2H,-CH_2CO_2Et), 7.35(4H,m,-$CH_2CH_2CO_2$Et),
8.80(9H,3t,-OCH_2CH_3).

$^{m}/_{e}$ 415(M^{+}), 387(M-28), 370(M-45, 342(M-73), 324(M-91).

Calculated mass for $C_{23}H_{29}NO_6$ 415.1995

measured 415.1992.

Preparation of 1-benzyl-2-carbobenzoxy-3-(2-carbethoxyethyl)-4-carbethoxy-methyl pyrrole

Ketoenamine (23) (52 mg) was refluxed with sodium acetate (50 mg) in acetic acid (0.5 ml) for 1 hr, diluted with water (3 ml) treated with sodium carbonate solid (800 mg) and extracted with ether (2 x 2 ml). The ether phase was dried (Na_2SO_4) and evaporated to a yellow oil. TLC purification (alumina, petroleum ether 40°-60°/ether 1:2 Rf 0.75) afforded the pyrrole (34) as a transparent oil (36 mg, 72%). (At Rf 0.6, starting Schiff's base can be recovered (8 mg)).

ν_{max} (CCl_4) 1735, 1695 cm^{-1}

λ_{max} (EtOH) 277 nm ε 10,100

τ 3.00(10H,m,2Ph), 4.65(2H,s,$-NCH_2Ph$), 4.90(2H,s,$-OCH_2Ph$),
6.00(4H,2q,$-OCH_2Me$), 6.70(2H,s,$-CH_2CO_2Et$),
7.35(4H,m,$-CH_2CH_2CO_2Et$), 8.90(6H,2t,$-OCH_2CH_3$).

$^{m}/_{e}$ 477(M^{+}), 431(M-46), 404(M-73), 386(M-91), 340.

Calculated mass for $C_{28}H_{31}NO_6$ 477.2151

found 477.2161.

Preparation of 1-benzyl-2-carboxy-3-(2-carboethoxyethyl)-4-carboethoxy-methyl pyrrole

Benzyl ester(34), (35 mg) in ethanol (1 ml) was hydrogenated over palladized carbon (2 mg, 1 at 20°) for 4 hours. The solvent was evaporated after filtration of the catalyst and the residue was left for one hour at 45° under vacuo. The white crystals of the acid (29 mg 98%) melted 117°-9°.

ν_{max} (nujol mull) 1735, 1660 cm^{-1}

λ_{max} (MeOH) 269 nm ε 7,500

CD_3OD 2.95(5H,m,Ph), 3.15(1H,s,H^5), 4.55(2H,s,CH_2Ph), 5.95(4H,2q,--OCH_2Me), 6.60(-CH_2CO_2Et), 7.30(4H,2m,-CH_2CH_2-), 8.85(6H,2t,-OCH_2CH_3).

$m/_e$ 343(M-44), 287, 257, 242.

Preparation of 1-cyclohexylmethyl-2-carbethoxy-3-(2-carboethoxyethyl)-4-carboethoxymethylpyrrole

The N-benzylpyrrole(22), (40mg) in acetic acid (0.5 ml) was hydrogenated over PtO_2 (1 at, RT) for six hours and the catalyst was removed by filtration. The filtrate was diluted with water (5 ml) neutralized with sodium carbonate and extracted with ether (2 x 2 ml). The extract was dried (Na_2SO_4) and evaporated. The residue was TLC purified (silica gel GT_{230}, 10% ethyl acetate in cyclohexane Rf 0.6) to a transparent oil (40 mg, 97%).

ν_{max} (CCl_4) 1730, 1700 cm^{-1}

λ_{max} (EtOH) 273 nm ε 5,400

τ 3.43(1H,s,H^5), 5.95(8H,m,-OCH_2Me,-N-CH_2-), 6.61(2H,s,-CH_2CO_2Et), 7.42(4H,m,-$CH_2CH_2CO_2Et$). 8.8(9H,3t,OCH_2CH_3).

$m/_e$ 421(M^+), 393(M-28), 376(M-45), 348(M-73), 338(M-C_6H_{11}), 334, 302, 274.

Calculated mass for $C_{23}H_{35}NO_6$ 421.2464

found 421.2470

Preparation of 1-benzyl-2-carbomethoxy-3-(2-carboethoxyethyl)-4-carboethoxymethylpyrrole

The pyrrolecarboxylic acid (39) (2 mg) was dissolved in methanol (0.5 ml) and was treated with excess of ethereal diazomethane.

Evaporation of the solvent afforded white crystals of the methylester (2mg, mp 61°-4°). Recrystallization from ether (1 ml) afforded product mp 63-5°.

$^{m}/_{e}$ 401(M^+), 376(M-31), 356(M-45), 342(M-59), 328(M-73), 311(M-91).

ν_{max} (CCl_4) 1735, 1690 cm^{-1}

λ_{max} (MeOH) 272 nm ε 7,600.

Preparation of 2 carboethoxy-3,4-dimethyl-5-iodopyrrole

2-Carboethoxy-3,4-dimethylpyrrole (200 mg) was refluxed with iodine chloride (600 mg, (three equivalents) and sodium carbonate (400 mg) in absolute ethanol (5 ml) under stirring for 3 hours. The cooled reaction mixture was filtered and evaporated in vacuo at 30° until most of the iodine chloride was removed. TLC purification (system A, Rf 0.55) afforded the iodide (210 mg, 64%, mp 127°-9°. Recrystallization from 95% ethanol afforded material melting 127°-9°.

ν_{max} (CCl_4) 3550, 1695 cm^{-1}

λ_{max} (EtOH) 282 nm ε 16500

τ 0.8 br(1H,s,pyrrNH), 5.65(2H,q,$-OCH_2Me$), 7.70(3H,s,Me), 8.00(3H,s,Me), 8.60(3H,t,$-OCH_2CH_3$)

$^{m}/_{e}$ 293(M^+), 265(M-28), 248(M-45), 247(M-46), 220(M-73), 166(M-127)

Calculated mass for $C_9H_{12}INO_2$ 292.9914

measured. 292.9908

Preparation of 1-benzyl-2-carboethoxy-3,4-di-methylpyrrole

2-Carboethoxy-3,4-dimethylpyrrole (200 mg) was dissolved in a suspension of sodium hydride (50 mg) in liquid ammonia and stirred for 30 minutes. A solution of benzylbromide (200 mg) in ether (3 ml) was then added over a period of 10 mins. and stirring continued for 20

more min The solvent was allowed to evaporate and the residue was extracted with ether (4 x 1 ml). The extract was evaporated to a brown oil, which was TLC separated (silica gel GT_{230}, 10% ethyl acetate in cyclohexane) to three components (Rf 0.45, 0.50, 0.65). The band Rf 0.5 affords the N-benzylpyrrole (92 mg, 34%, mp 61°-3°).

ν_{max} (CCl_4) 1690 cm^{-1}

λ_{max} (EtOH) 273 nm ε 8,200

τ 2.76(5H,m,Ph), 3.20(1H,s,H^5), 4.60(2H,s,$-CH_2Ph$),
5.86(2H,q,$-OCH_2Me$), 7.82(3H,s,Me), 7.98(3H,s,CH_3),
8.81(3H,t,$-OCH_2CH_3$)

m/e 257(M^+), 212(M-45), 184(M-73), 166(M-91)

Calculated mass for $C_{13}H_{19}NO_2$

measured

Preparation of 1-benzyl-2-carboethoxy-3,4-dimethyl-5-iodopyrrole

1-Benzyl-2carboethoxy-3,4-dimethylpyrrole (8 mg) was refluxed for 48 hrs in ethanol (1 ml) with iodine chloride (approximately 100 mg, one drop) and pyridine (0.5 ml). The solution was then neutralized with 3N hydrochloric acid, and extracted with chloroform (3 x 1 ml). Evaporation of chloroform, and most of the excess iodine chloride at reduced pressure was followed by TLC separation. (Silica gel GT_{230}, 30% ether in cyclohexane). The band at Rf 0.7 afforded the iodide (4 mg, 32%) as a transparent oil.

ν_{max} (CCl_4) 1690 cm^{-1}

λ_{max} (MeOH) 278 nm ε 18,700

τ 2.77(5H,m,Ph), 4.51(2H,s,CH_2Ph), 5.87(2H,q,$-OCH_2Me$),
7.75(3H,s,CH_3), 7.92(3H,s,CH_3), 8.81(3H,t,OCH_2CH_3)

m/e 383(M^+), 338(M-45), 310(M-73), 234(M-91), 256(M-127), 242, 225
210, 182

Preparation of pyrrole 2-carbethoxy-3,4-dimethyl-5-carbonitrile

2-Carboethoxy-3,4-dimethyl-5-iodopyrrole (35 mg) was heated to 80° for 24 hours under nitrogen in a solution of Cu_2CN_2 (30 mg) in dry pyridine (0.5 ml). It was then neutralized with 3N hydrochloric acid (2 ml) and extracted with ether (3 x 1 ml). The combined extracts were dried (Na_2SO_4) and evaporated to a brown gum. TLC purification (silica gel GT_{230}, 15% ethyl acetate in cyclohexane, Rf 0.75) afforded the nitrile (7 mg, 16%) as white crystals mp. 116°-7°. Ehrlich negative.

ν_{max} (CCl_4) 3440, 3250(br), 2220, 1695 cm^{-1}

λ_{max} (MeOH) 277 nm ε 18,700

τ 5.75(2H,q,$-OCH_2Me$), 7.90(3H,s,Me), 7.95(3H,s,Me),
8.70(3H,t,$-OCH_2CH_3$)

m/e 192(M^+), 164(M-28), 147(M-45), 146(M-46), 119(M-73), 90.

Calculated mass for $C_{10}H_{12}N_2O_2$

measured

Preparation of 1-cyclohexylmethyl-2-carbethoxy-3,4-dimethyl pyrrole

From 20 mg of N-benzyl product the N-cyclohexylmethyl compound (12mg, 61%) was obtained through a procedure similar to that described in page 57 for the pyrrole (22).

ν_{max} (CCl_4) 1690 cm^{-1}

λ_{max} (MeOH) 273 nm ε5,800

τ 3.7(1H,s,H^5), 5.85(2H,q,$-OCH_2Me$), 6.15(2H,d(J=7Hz),$-NCH_2-$),
7.92(3H,s,Me), 8.15(3H,s,Me), 8.75(3H,t,$-OCH_2Me$).

m/e 263(M^+) 218(M-45) 190(M-73) 180(M-C_6H_{11})

Calculated mass for $C_{16}H_{25}NO_2$ 263.1885

found 263.1883

Formation of 2-carboethoxy-3,4-dimethyl-5-bromopyrrole

2-Carboethoxy-3,4-dimethyl pyrrole (17 mg) was heated for 24 hours at 80° in dimethylformamide (1 ml) with cyanogen bromide (15 mg). The solution was then diluted with H_2O (2 ml) and extracted with ether (3 x 1 ml). The evaporated extract (brown oil) was TLC separated (system A) to three bands (Rf 0.4, 0.5, 0.55). The band Rf 0.5 afforded the bromide (2.5 mg, 10%) as white crystals (mp 132°-4°, lit 134°).

ν_{max} (CCl_4) 1690 cm^{-1}

λ_{max} (MeOH) 278 nm ε 15,200

τ 1.2(1H,b,pyrrNH), 5.79(2H,q,$-OCH_2Me$), 7.75(3H,s,CH_3), 7.95(3H,s,Me), 8.78(3H,t,$-OCH_2CH_3$).

$^m/_e$ 247(M^+, ^{81}Br), 245(M^+, ^{79}Br), 218, 210, 202, 201, 200, 199

Preparation of enol ether (31)

β-Ketoaldehyde (12) (85 mg) was treated with ethereal diazoethane (excess) at ambient temperature. The solution was allowed to evaporate to afford a yellow oil which was purified by TLC (silica gel GT_{230}, 10% ACOEt in cyclohexane, Rf 0.65) to afford the ethyl enolether (61 mg, 64%) as a transparent oil.

ν_{max} (CCl_4) 1735, 1645, 1610 cm^{-1}

λ_{max} (MeOH) 251 nm ε 3,000

τ 2.55(1H,s,=CH-OEt), 5.90(6H,m,$-OCH_2Me$), 6.85(2H,s,$-CH_2CO_2Et$), 7.35(4H,m,$-CH_2CH_2-$), 8.75(9H,m,$-OCH_2CH_3$)

$^m/_e$ 286(M^+), 258(M-28), 241(M-45), 213(M-73), 185(M-101), 157, 139, 101.

Calculated mass for $C_{14}H_{12}O_6$

measured

Preparation of modified Ehrlich reagent

p-Dimethylaminobenzaldehyde (1.25 g) was dissolved in glacial acetic acid (600 ml). Concentrated orthophosphoric acid was then added (100 ml) followed by concentrated hydrochloric acid (30 ml) and dilution (water) to one litre. It can be stored as such for considerable period of time. For use, a spray of the reagent on TL plates is followed by gentle heating.

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