PYRROLE CHEMISTRY AND THE SYNTHESIS OF SOME PYRROLE THIOLESTERS

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by

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ABSTRACT.

The biogenisis of porphyrins and the problems involved in the chemical synthesis of porphyrins and their biogenetic intermediates are briefly discussed. The direct synthesis from readily available pyrroles is not often possible, because substitution reactions are sometimes blocked by groups already present on the pyrrole ring.

The properties of some pyrrole anilides, thioanilides and esters were investigated, and some unusual reactions were encountered. Several pyrrole thiolesters were successfully synthesised from the thioanilides and from a modified Knorr synthesis with ethyl acetothiolacetate.

The Raney nickel desulphurisation of pyrrole thiolesters was investigated, and it was found that the thiolester group could be converted to a formyl or in some cases a methyl group in this way. The desulphurisation reactions were found to give very good yields and the method represents a useful new route to pyrrole aldehydes.

The acylation of pyrrole esters and thiolesters by perchloric acid/acetic anhydride; silver borofluoride/acetyl chloride; and trifluoroacetic anhydride/carboxylic acid mixtures were investigated. Trifluoroacetic anhydride alone produced good yields of trifluoroacetylated pyrroles all of which were new compounds.

Some examples were found in which carbon disulphide, used as a solvent in Friedel and Crafts reactions with pyrrole

esters, sometimes reacted with the pyrrole to produce derivatives of dithioacids.

Nuclear magnetic resonance spectra are given for many of the compounds prepared in this work.

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ACKNOWLEDGEMENTS

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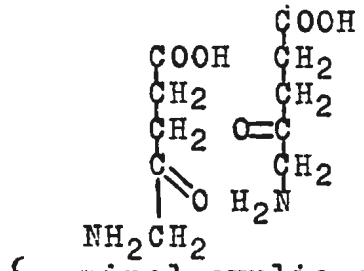
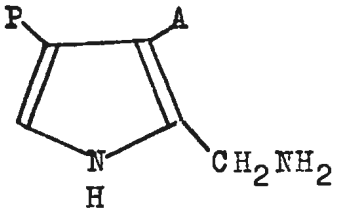
INTRODUCTION.

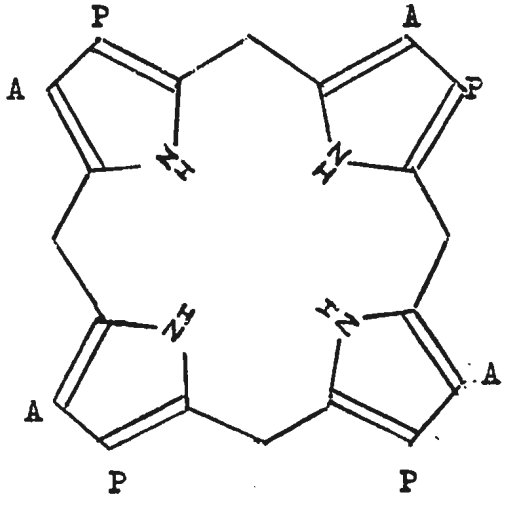
Over many years the synthesis of pyrroles related to the degradation products obtained from haemin has been thoroughly investigated (see particularly the work of Hans Fischer). However the biosynthesis of haemin and the related chlorophyll remains only partially explained[1]. It has been shown that the source of porphyrins *in vivo* is δ-aminolaevulic acid, itself derived from acetic acid and glycine units.[1] δ-Aminolaevulic acid cyclises by enzymic action to yield porphobilinogen[2](I), which is then converted, again by enzymes into üroporphyrin III (II). More detailed work has revealed that at least two enzymes are involved in the cyclisation. One controls the formation of a uroporphyrinogen mixture from porphobilinogen, another causes the formation of uroporphyrinogen III only[3]. The uroporphyrinogen III is then dehydrogenated to yield uroporphyrin III by a normal cell mechanism. (The flow chart containing diagrams I and II illustrates the biosynthesis of uroporphyrin III). There is clearly some 'driving force' for the formation of uroporphyrinogen III even by chemical methods as the table below illustrates:-



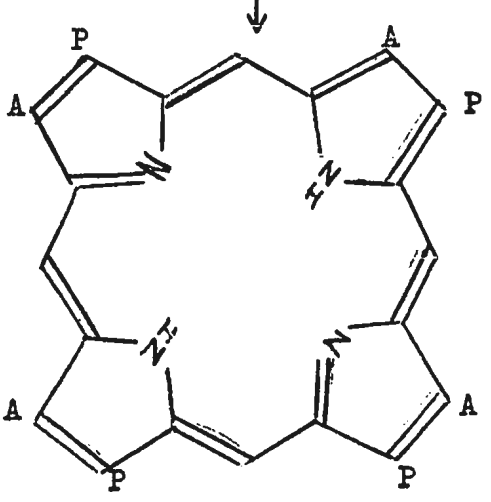
δ-aminolaevulic acid
(two molecules shown)



porphobilinogen
I



Uroporphyrinogen III



Uroporphyrin III

P= CH_2CH_2COOH

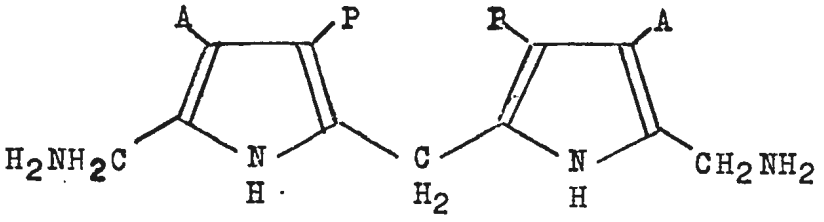
A= CH_2COOH

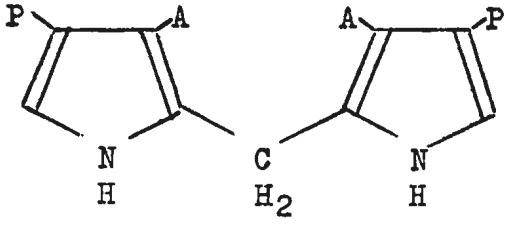
II

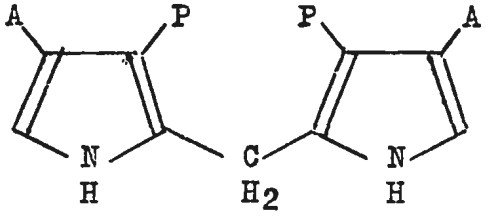
Catalysis	Uroporphyrinogen produced[1] I	II	III	IV
Acid	$\frac{1}{8}$	$\frac{1}{8}$	$\frac{1}{2}$	$\frac{1}{4}$
Base	$\frac{3}{4}$			$\frac{1}{4}$
Neutral	$\frac{1}{2}$			$\frac{1}{2}$

The mechanism of the reaction is not necessarily the same as that *in vivo*[1]. Attempts to identify the intermediates have so far succeeded only in eliminating possibilities, for the compounds shown below (III) have been synthesised and none are intermediates in the formation of uroporphyrinogens *in vivo*[1,4].

The problem of chemical synthesis of possible intermediates in the biosynthesis of uroporphyrin III rests mainly in the synthesis of pyrroles of the type shown in diagram (IV). MacDonald has reviewed the possible routes to these pyrroles and has shown that the Knorr synthesis alone has any practical value[5]. Treibs and Ott were successful in obtaining (IVa) from 2-methyl-5-carbethoxypyrrole by converting it to the 3-propionate (obtained from the 3-aldehyde *via* the 3-acrylate), which was then treated with formaldehyde and piperidine (Mannich type reaction) to yield a 4-piperidinomethylpyrrole. The piperidinomethyl group was converted to a cyanomethyl group (CN^-) which on hydrolysis yielded (IVa)[6]. The other isomer (IVb) has not been obtained



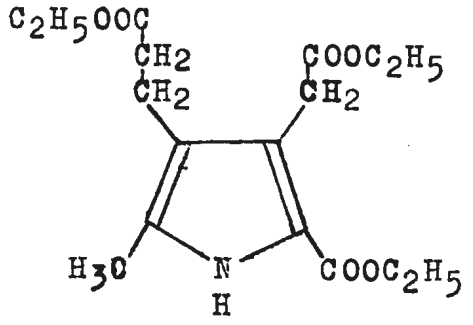




III

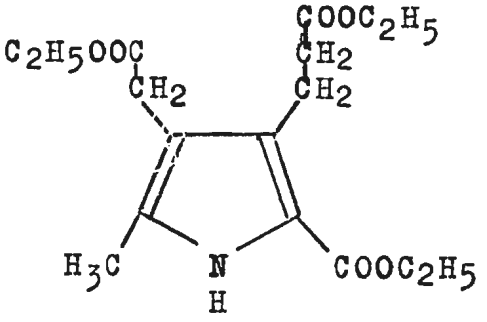
A = CH_2COOH

P = CH_2CH_2COOH

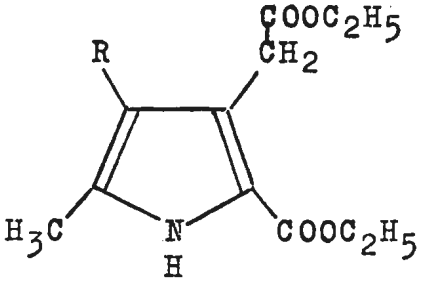


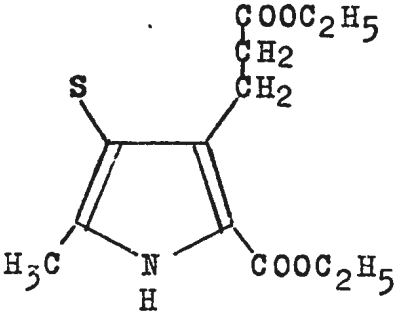
a

IV



b





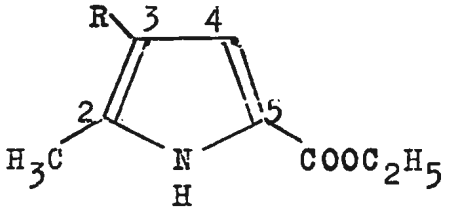
V

a) R = COOH
b) S = COOH

c) R = $CH_2CH_2COOC_2H_5$
d) S = $CH_2COOC_2H_5$

by this route. Slightly earlier work by MacDonald has shown the importance of the Knorr type synthesis for these pyrroles (IV), and his syntheses remain the most valuable[5,7]. Acetone dicarboxylate on nitrosation and reduction reacts with benzyl acetoacetate to yield the benzyl ester of (Va). The benzyl ester of (Vb) was similarly obtained from β-ketoadipic ester and benzyl acetoacetate. Reductive debenzylation afforded the free acids which were thenreadily converted to the required pyrroles (Vc) and (Vd) respectively. The use of the benzyl ester is essential since acid or base hydrolysis (required for most other esters) would de-esterify the other ester groups on the pyrroles, extensive decomposition then follows because the free acids are unstable[5,7]. The pyrroles (Vc) and (Vd) have been converted to porphobilinogen and isoporphobilinogen[4a,8,9] and also a number of pyrromethanes, pyrromethenes and porphyrins[8].

Pyrroles having the substitution pattern (VIa) (e.g 2-methyl-3-propionic acid -5-carbethoxypyrrole) are readily available from pyrrole itself where the group in the 3 position may be almost anything required (e.g. -CN, -CHO, -COCOOR, -CH=CHCOOR). Further reaction at the 4-position is very difficult, presumably due to the electron withdrawing effect and the steric effect of the ortho ester group. Thus (VIb)



VI

a) R = almost any desired group

b) R = $CH_2CH_2COOC_2H_5$

has been brominated[10], acetylated[11], chloracetylated[11] and undergone a Mannich reaction[6], but most reactions fail completely[5]. The usefulness of the pyrroles such as (VIa and VIb) is thus limited by the relative inertness of the free β position ortho to the ester group (∝ nitrile deactivates the adjacent β position[5] in the same way as would be expected for any powerful electron withdrawing group). The ∝ ester group behaves as a directing and protecting group, such a substituent is essential if selective substitution is to be obtained in the β positions. It is possible that there may be other substituents that might exibit similar directing and protecting properties without rendering the adjacent β position so unreactive.

There are many groups which have directing and protecting properties, some examples are; carbanilide[12], thiocarbanilide[13], thiocyanate[14], cyanide, aldehyde and related groups. The anilides and thioanilides are available by very favorable routes in very high yields[12,13] if the parent pyrrole is sufficiently reactive. The anilides have been prepared by reacting the activated pyrrole (e.g. 2-methylpyrrole) with phenyl isocyanate[12]. The thioanilides were prepared in an analogous manner from phenyl isothiocyanate[13]. The anilides were rather insoluble and very stable, however only a few of their reactions have been investigated[12], the only reaction

of interest here was the formylation of 2,4-dimethylpyrrole-5-carbanilide in vacant α position by a Gatterman reaction in very low yield.

The thioanilides were also stable compounds, which could be converted to the corresponding anilides by treatment with alkaline hydrogen peroxide solution, no other chemical properties were recorded[13].

The properties of the more common anilides are better known and are as follows[16]:- They can be hydrolysed to the parent acid and aniline, some undergo the Sönn-Müller reaction to yield aldehydes. They can be N or O methylated according to the method chosen for the reaction and the nature of the anilide. Many anilides have been N halogenated.

The thioanilides behave somewhat similarly, but are far more acidic forming salts by a type of thione-thiol tautomerism (VII) they are also readily S-alkylated by dialkyl sulphates and alkyl halides in base.

$$R\underset{\underset{S}{\|}}{C}NHC_6H_5 \quad + \quad NaOH \quad \longrightarrow \quad R\underset{\underset{S\text{-}Na}{|}}{C}{=}NC_6H_5$$

(VII)

An interesting property of the thioanilides is the ease with which they may be converted to thiolesters, since the S-alkyl thioanilides may be hydrolysed by dilute acid to yield the corresponding thiolester[16], (this reaction has been little used). No thiolesters of pyrrole are recorded in

the literature.

Thiolesters have been obtained by a number of methods, from acid chlorides[17], from thioanilides[16], from alkyl thiocyanates by a modified Gatterman-Hoesch reaction[18], to mention the more important. Thiolesters are useful in synthetic chemistry since they provide a fairly stable protecting group which may be converted to a formyl (-CHO), hydroxymethyl ($-CH_2OH$) or even a methyl ($-CH_3$) group by treatment with Raney nickel under fairly mild conditions[19]. Thiolesters have also been reduced to thiols by lithium aluminium hydride[62]. Although thiolesters have been investigated in connection with co-enzyme-A, little recent work has been reported regarding their chemical properties. Several compilations of spectral data have recently been published[21,22,23].

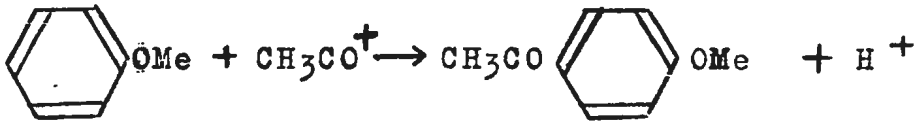
Acylation reactions.

The ease with which pyrroles may be acylated is very much influenced by the nature of other substituents on the ring. Pyrrole itself and alkyl pyrroles may be acetylated merely by heating with acetic anhydride alone[25]. Acetyl chloride and other acyl halides react with pyrroles in the presence of aluminium chloride (Friedel and Crafts reaction)[25]. Satchell[26] has reviewed the available methods of acylation, several of which have not been employed for the acylation

of pyrroles.

Trifluoracetic anhydride has been used successfully to catalyse the acylation of anisole, thiophene, furan and cyclohexene[27,28] (mostly limited to acetylation). The acylation medium consists of a mixture of trifluoracetic anhydride and an acid, an RCO^+ ion is generated which acts as the acylating agent. A typical example is the acetylation of anisole[27]:-

$$(CF_3CO)_2O + RCOOH \longleftrightarrow CF_3COO^- + RCO^+ + CF_3COOH$$



Some of the more important uses of trifluoracetic anhydride have been reviewed[58].

Perchloric acid has been employed industrially as an acetylation catalyst, particularly in the acetylation of cellulose[29] where a zinc chloride/perchloric acid mixture was used. The catalyst has been investigated by Mackenzie and Winter[30] and by Dorofeenko and his co-workers[31]. Dorofeenko has shown that pyrrole itself can be acylated by acyl halide in the presence of magnesium perchlorate, but he did not investigate the acylation of pyrroles with stabilising substituents (electron withdrawing e.g. $-COOCH_3$). The reactions postulated for acetylation by acetic anhydride with a perchloric acid catalyst were:-

$$(CH_3CO)_2O + HClO_4 \longleftrightarrow CH_3\overset{+}{C}O\ \ \overset{-}{ClO_4} + CH_3COOH$$

$$R\text{-}H + CH_3CO^+ \longrightarrow RCOCH_3 + H^+$$

A further catalyst acting in a similar manner to perchloric acid is silver perchlorate[26], it has not proved to be very popular due to the risks involved (explosive). As in the case of perchloric acid/ acetic anhydride (or acetyl chloride) for example, acetyl perchlorate is generated when silver perchlorate reacts with acetyl chloride, silver chloride being precipitated, (the reaction is illustrated below).

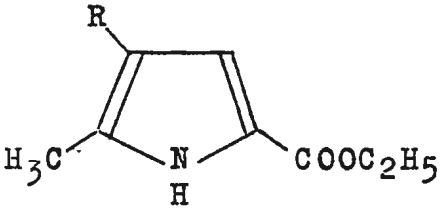
$$AgClO_4 + RCOCl \longrightarrow \overset{+}{RCO}\ \ \overset{-}{ClO_4} + AgCl\downarrow$$

Silver borofluoride may react in a similar manner:-

$$AgBF_4 + CH_3COCl \longrightarrow \overset{+}{RCO}\ \ \overset{-}{BF_4} + AgCl\downarrow$$

Discussion.

The synthesis of pyrroles and porphyrins has been studied in great detail, particularly in connection with the synthesis of haemin and related compounds[59]. It was thus possible to synthesise (VIIIe) and its intermediates by literature methods. 2-Methyl-5-carbethoxypyrrole (VIIIa) was obtained in low yield from 2-methylpyrrole[33]. Attempts to improve the yield by varying the proportions of the reactants were unsuccessful and the maximum yield obtained in any experiment was only about 30% based on the pyrrole used. Treibs[6] obtained the same pyrrole ester by treating 2-methylpyrrole with phosgene to produce the 5-acid chloride, which then reacted with alcohol to give the pyrrole ester in 80-85% yield. Both methods are illustrated in diagramatic



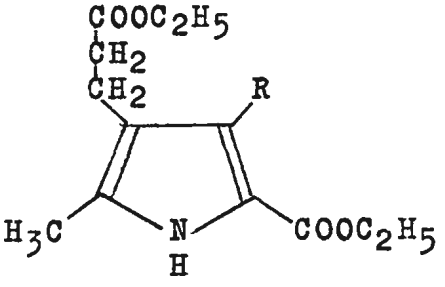
a) R = H

b) R = CHO

d) R = CH=CHCOOC$_2$H$_5$

e) R = CH$_2$CH$_2$COOC$_2$H$_5$

VIII



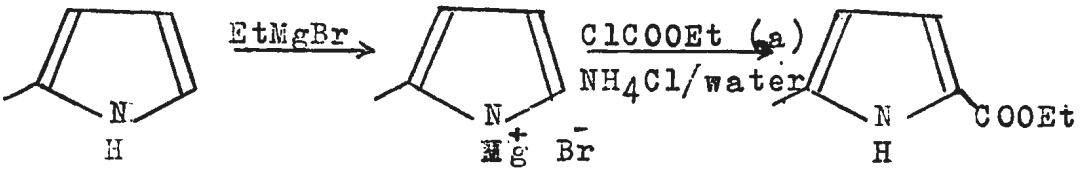
a) R = Br

b) R = COCOOC$_2$H$_5$

c) R = CN

IX

form below:-



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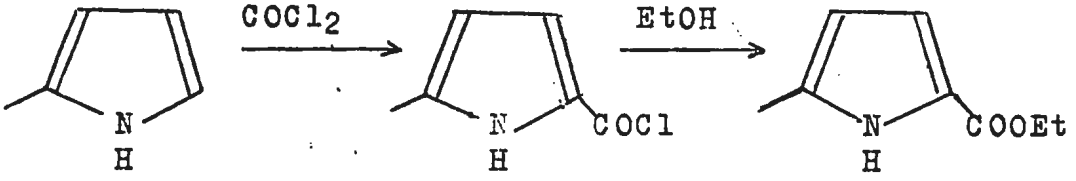

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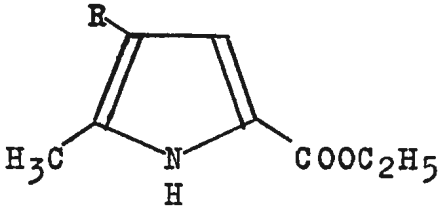
A Vilsmeier formylation reaction under the conditions used by Dezelic[15] (dimethyl formamide/phosphorus oxychloride) yielded 2-methyl-3-formyl-5-carbethoxypyrrole (VIIIb) from (VIIIa). Ethyl hydrogen malonate in pyridine/piperidine solution at 100° [34] reacted with the aldehyde (VIIIb) to form the corresponding acrylate (VIIId), which on catalytic hydrogenation (Adams catalyst, room temperature and 60 pounds pressure in ethanol solution) yielded the propionate (VIIIe).

Investigation of the properties of the free position in (VIIIe) showed that it was easily brominated[10] (IXa), but attempts to form the glyoxalate (IXb) with cyanoformic ester and dry hydrochloric acid gas (Gatterman-Hoesch) failed, even in the presence of a catalyst (aluminium chloride). The pyrrole (VIIIe) would not react with trifluoro-acetic anhydride, perchloric acid/acetic anhydride, or or with dimethyl formamide/phosphorus oxychloride[60](Vilsmeier) under the normal conditions. An attempt was made to obtain (IXc) by an indirect route, the bromopyrrole (IXa) was treated under varied conditions with; i) sodium cyanide in dimethyl sulphoxide[36], cuprous cyanide in dimethyl formamide[35], ii) fused sodium cyanide/potassium cyanide mixture. Neither the solution methods i) nor the salt melt method ii) produced any substitution of cyanide for bromide, (i.e. no nitrile band was detected in the infrared spectrum of the product). It was found that the bromopyrrole (IXa) was sufficiently stable that it could be recovered unchanged from the reaction mixtures, even after several hours exposure to high temperatures. Since the methods tried above for the reaction (i) successfully yield nitriles from the halides of a wide variety of compounds, the bromine atom in (IXa) must be very strongly deactivated or shielded by the ester group.

The reduction of the glyoxalate (Xf) to the acetic acid derivative has proved rather difficult, but it has been reduced with hydrazine in a Wolff-Kishner type reaction[37]. The yield was very low because the product (the sodium salt of the required pyrrylacetic acid) decarboxylates under the reaction conditions. In an attempt to find a more successful route, (Xf) was reduced in acetic acid (to which a little concentrated sulphuric acid had been added) at room-temperature and 60pounds pressure with Adams' catalyst. The only product isolated was rather insoluble in most organic solvents and high melting, properties which were not expected for (Xg). The n.m.r. spectrum was difficult to interpret but indicated three ethyl ester groups and two methyls attached to pyrrole rings (τ7.7), the ring proton was in about the expected position for the ring proton in (Xg) (τ3.1). The infrared spectrum showed intense carbonyl absorption in the 1680-1725cm^{-1} region as would be expected for pyrrole esters[39]. The remainder of the spectrum was rather similar to that of the starting material (Xf), evidence that the product had some similarities to the starting material in structure. The ultra violet spectrum was however quite different to that of the starting material, a hypsochromic shift of about 83mμ being observed in the low frequency band (K)



X

Xf R= $COCOOC_2H_5$

Xg R= $CH_2COOC_2H_5$

and the relative intensities were reversed. This change is that expected for a decrease in conjugation (see table XI). From these observations the structure (XII) was proposed and the analytical results indicate that this is probably correct. The single proton on the bridge was identified in the n.m.r. as a weak resonance at τ5.27, it did not show deuterium exchange when heavy water (D_2O) was added to the solution.

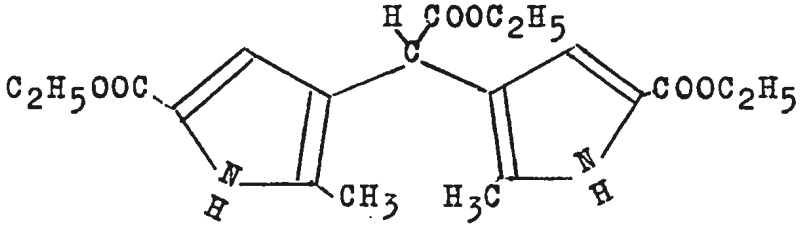
The mechanism of formation of (XII) is interesting in that it requires the displacement of one glyoxalyl group for its production in the reaction. The ease with which the glyoxalyl group may be lost has been noted by MacDonald and Stedman[8]. Thus it is possible that the product (XII) is formed from the glyoxalate (Xf) and 2-methyl-5-carbethoxy-pyrrole (this was not tested experimentally).

Attempted reduction of the glyoxalate (Xf) using a palladium black catalyst with the same conditions as above gave an almost quantitative yield of the alcohol (XIII) in acetic acid solution. The product (XIII) was low melting and easily soluble in organic solvents. It showed hydroxyl(-OH) proton resonance in the n.m.r. which exchangedrapidly when heavy water (D_2O) was added to the solution. The i.r. spectrum also showed a strong hydroxyl band. The remainder of the n.m.r. spectrum was in keeping with this structure.

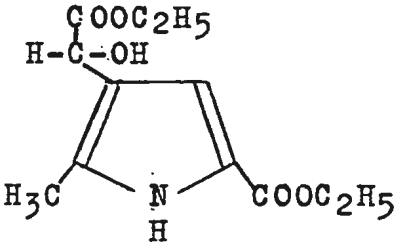
	$\lambda_{max}(\log\varepsilon_{max})$		
2,4-dimethylpyrrole	218(3.67)		
2,4-dimethyl-3-carbethoxypyrrole.	232(3.95)	258(3.72)	
2,4-dicarbethoxy-3-methyl-5-formylpyrrole.	237(4.33)	270(3.88)	308(3.04)

Figures for other pyrroles are given in the tables of spectra. Spectra given above are from reference 54.

Table XI.



XII



XIII

Participation of the solvent in Friedel and Crafts reactions in Carbon Disulphide.

Several attempts were made to introduce acetic ester and propionic ester groups directly on to the pyrrole ring in the free β-positions of 2-methyl-5-carbethoxypyrrole, by Friedel and Crafts reactions. In each case aluminium chloride catalyst was used in carbon disulphide solution. (This mixture had been used successfully by Anderson and Hopkins for isopropylation reactions[39]). The halides used were bromoacetic, chloroacetic and β-bromopropionic esters. Each reaction failed to produce the required products, but in each case some yellow material was formed, which was finally obtained as bright yellow crystals (needles). The compound was fairly soluble in organic solvents and melted without decomposition. The n.m.r. spectrum indicated that an ethyl group had been introduced which was clearly not attached to a carbon atom. The methylene resonance at τ 6.95 showed that a S-ethyl group was more likely than an O-ethyl group. Jörg[38] isolated compounds of the type shown below:

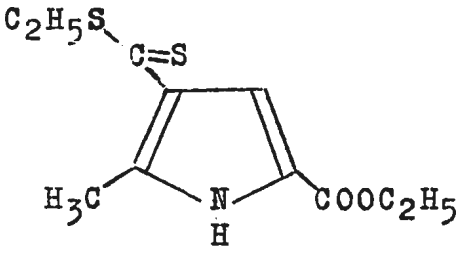
$C_6H_4(OH)C{=}S{\cdot}SH$

$C_6H_4(OH)C{=}S{\cdot}SR$

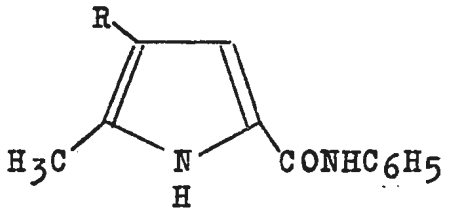
from Friedel and Crafts reactions on phenols[38]. Other workers have found quantities of yellow material among the products from Friedel and Crafts reactions[39,61]. In one of these cases the compound was identified as a complex of aromatic compound, aluminium chloride and alkyl halide. The compound isolated here was clearly not of this type, as the results below will show.

The compound contained a fairly large amount of sulphur and also nitrogen as shown by a Lassaigne test. Microanalysis favored the formula $C_{11}H_{15}NO_2S_2$. The infrared spectrum showed only one carbonyl absorption at 1681cm^{-1}, within the region expected for pyrrole carboxylic esters[39,50]. Thiocarbonyl stretching frequencies have been assigned to the region 1225-1025cm^{-1} and the carbon-sulphur (C-S) stretching frequency to the region 772-622cm^{-1} [40,41]. The yellow compound obtained here showed bands at 1180, 1200, 1227, 1289 and some weak bands at 1000cm^{-1}. In the 772-622cm^{-1} region bands were observed at 775, 740, 690 and 683cm^{-1}. Two of the bands in the 1225-1025cm^{-1} region are probably due to C-O stretching frequencies from the ester group,(possibly the bands at 1289 and 1227cm^{-1} being the two strongest bands).

The ultraviolet spectrum showed three main absorption bands

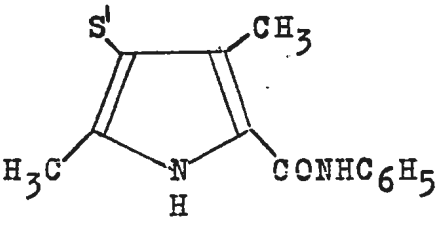


XIV



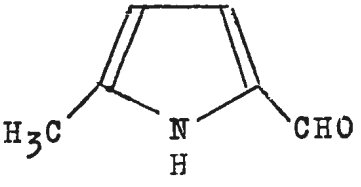
XVa R = H

XVb R = CHO



XVc S' = H

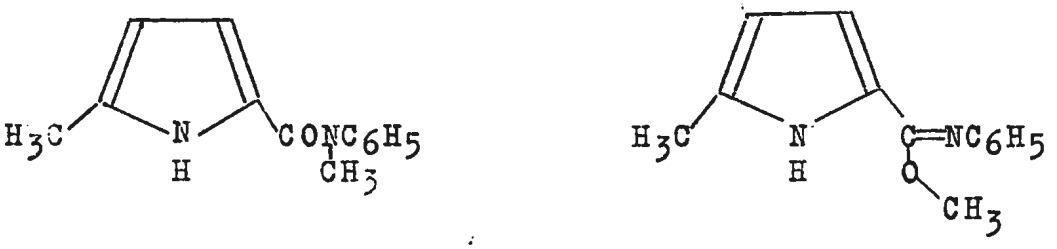
XVd S' = CHO



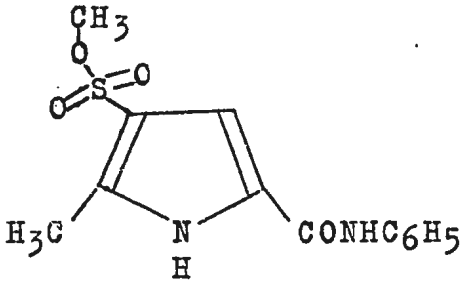
XVI

222, 330, and 349mμ, the low frequency band tailed off into the visible. The thiol esters of pyrrole (pyrrole-COSR) prepared in later work did not show this type of absorption and were not coloured. The yellow compound was thus clearly not a thiolester. The position of the high frequency bandsin the ultraviolet spectrum is similar to that found in 2-methyl-3-acetyl-5-carbomethoxypyrrole (222 and 262μ compared with 224 and 261mμ). On the data so far obtained it is thought that the yellow compound is a dithioester, and has the structure (XIV). Further proof of the structure might have been obtained by desulphurisation in which case 2,3-dimethyl-5-carbethoxypyrrole should be the product (compare Raney nickel desulphurisation reactions below).

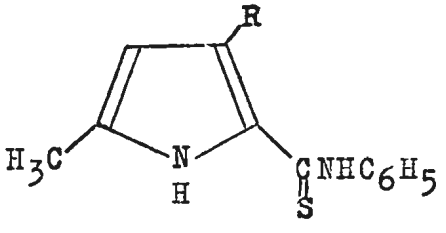
The mechanism of the reaction is probably as follows:-
The carbon disulphide adds to the pyrrole in the first instance producing a dithioacid, which is then esterified at the expense of the haloester present. It was in fact found that some of the yellow compound was obtained when a mixture of the pyrrole ester, ethyl acetate, aluminium chloride and carbon disulphide were heated together. The haloester may behave as a catalyst, since ethyl bromoacetate seemed to produce more of the compound than the other esters. Further work is however required in order to clarify the details of the reaction.



XVII



XVIII



XIX a R= H

b R= CH_3

Pyrrole anilides.

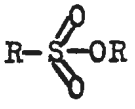
The anilides (XVa and XVc) were prepared in almost quantitative yield by literature methods from 2-methyl and 2,4-dimethylpyrrole respectively[12]. Both were colourless, stable compounds with low solubilities in the common solvents.

The attempted preparation of (XVb) by a modification of the dimethyl formamide/phosphorus oxychloride method[15] gave a product which showed weak aldehydic resonance in the n.m.r., and had a high melting point (270°dec.). Since the compound could not be obtained in the pure state it was not further investigated. (Treibs obtained (XVd) in a very poor yield from a Gatterman reaction (HCN and HCl) on (XVc)).

The Sonn-Müller reaction[42] failed to yield 2-methyl-5-formyl pyrrole from (XVa). This reaction has often failed or given low yields with other anilides[42].

Methylation of 2-methylpyrrole-5-carbanilide (XVa) with neat dimethyl sulphate appeared to proceed rapidly, and solid crystalline material was precipitated from the reaction mixture. However the n.m.r. of the product was inconsistent with the possible methylation products (XVII). Two N-H resonances were present (τ -2.5 pyrrole and 0.09 amidic), and one pyrrole ring proton had been displaced. Two methyl groups were present (τ 7.48 and 7.24), one of which was presumably the ring methyl group present in the starting material. The remaining ring proton was masked

by the aromatic benzenoid resonances of the anilide. Comparison of the n.m.r. spectrum of the anilide (XVa) and that of the dimethyl sulphate product obtained from it, showed that the ring proton was probably at about τ2.53, comparing closely with τ2.41 obtained for the remaining proton in the acetylation product from (XVa). Thus it was clear that substitution had occurred on the pyrrole ring rather than on the nitrogen or oxygen of the anilide. (Note that the pattern of the benzenoid resonance was the same in the anilide (XVa) and in the dimethyl sulphate product indicating that substitution had not taken place on the benzene ring.). The microanalysis of the product was satisfied by $C_{13}H_{14}N_2O_4S$ and on the evidence so far obtained the sulphonate structure (XVIII) was proposed. Bands at 1275 and 1336cm^{-1} might be interpreted as vibrations of the



system[55], the carbonyl band was at 1675cm^{-1}(aromatic amide). The ultraviolet spectrum was similar to that obtained for pyrroles having electron withdrawing groups in the 2 and 4 positions (3 bands A, B and K), in keeping with (XVIII).

The reaction is unusual and apparently results from the attack of

on the pyrrole ring. There has been some investigation of the reactions of alkyl sulphates[44,45]. Both sulphuric acid and alkyl sulphates react in two forms, $H^+ \bar{S}O_4(\bar{H}^+ \bar{S}O_4)$ or as $H_2O{\cdot}SO_3(R_2O{\cdot}SO_3)$. The active form is both temperature and concentration dependant, the ionic form being favored by high dilution, and the sulphur trioxide form by high temperatures and concentrations. In the latter case sulphonation is virtually by sulphur trioxide, an ether being formed as a by-product. Belov and Finkel'shtein[45] found that the sulphur trioxide form was more important in the reactions of dimethyl sulphate than in diethyl sulphate, where the ionic form predominates. Thus the reaction of neat dimethyl sulphate with the anilide may go in two steps; i) the sulphonic acid is first formed by attack by sulphur trioxide, ii) the sulphonic acid formed is methylated by the remaining dimethyl sulphate present in the ionic form. There appear to be no instances in the literature of direct attack by $^+SO_3CH_3$. Methylation of the anilide with hot dimethyl sulphate in base failed to yield product under conditions which succeeded for the thioanilide.

Thioanilides.

Recently the thioanilides of several alkyl pyrroles and pyrrole itself have been prepared[13]. 2-Methylpyrrole-5-thiocarbanilide was obtained in 88% yield from 2-methylpyrrole and phenyl isothiocyanate. The thioanilides are stable crystalline compounds, fairly soluble in organic solvents and normally bright yellow (2,5dimethylpyrrole yielded a colourless 3-thiocarbanilide).

Formylation of the thioanilide(XIXa) by the same method as was used for the anilide yielded a yellow powder which showed only weak aldehydic proton resonance in the n.m.r., most of the material was starting material (XIXa).

Methylation of the thioanilide (XIXa) proceeded rapidly in a mixture of dimethyl sulphate and caustic soda solution. Methylation was also readily obtained by treatment with neat dimethyl sulphate and ethylation by treatment with ethyl bromide in base. In each case the yield of the S-alkyl compound was very good.

The S-alkylated compounds were very pale yellow or colourless (c.f. thiobenzanilide is bright yellow and S-methyl-thiobenzanilide colourless). It was clear from spectra that S-alkylation had taken place (i.e. no thiocarbonyl band in the i.r., no N-H resonance in the n.m.r. for amidic N-H , characteristic S-alkyl resonance in the . .

n.m.r. spectrum). The pyrrole ring proton resonances in the n.m.r. occur to higher field in the S-alkylated thioanilides than in the anilides themselves indicating that the S-alkylation lowers the electronwithdrawing power of the thioanilide.

Attempts to hydrolyse the thioanilide (XIXa) failed both in acid and base, even with boiling, to yield a thioacid. Any thioacid formed probably decomposes rapidly to give 2-methylpyrrole none was however detected.

The ease of formation of the S-alkyl compounds was not entirely unexpected, since the S-alkylation of thiobenzanilide (S=C) proceeds without even heating the reaction mixture. Of the methods available for the S-alkylation of pyrrole thioanilides alkyl halide in base gave the purest product and the best yield, although dimethyl sulphate in base gave the most rapid reaction.

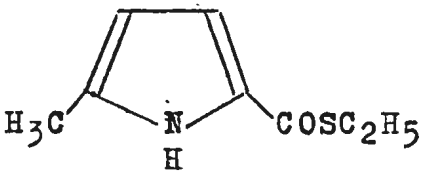
No evidence was found for thiol-thione tautomerism in any of the spectra obtained of the thioanilides (i.r., n.m.r. and u.v.)in agreement May[46] and Rao[23].

Thiolesters.

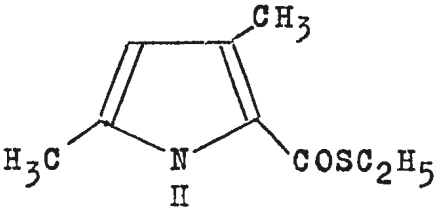
The acid hydrolysis of S-alkyl thioanilides is reputed to yield the corresponding thiolesters and aniline.[16] 2-Methyl- and 2,4-dimethylpyrrole-5-thiocarbanilides were each heated with dilute hydrochloric acid, both yielded the expected pyrrole-5-thioesters, (XX and XXI respectively). Both thiolesters were colourless, crystalline easily sublimable compounds. In general they behaved similarly to the normal esters. They could be acetylated, trifluoroacetylated, formylated, and underwent the Gatterman-Hoesch reaction in the same way, and in similar yields to the corresponding esters. There was slight hydrolysis of the thiolesters during some of the reactions but this did not appear to affect the overall yields. Since the yield of thiolesters from the thioanilides was usually about 80% an exploration of the properties of the thiolesters seemed worthwhile.

Alternative syntheses of thiolesters.

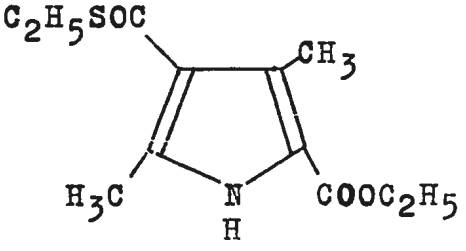
There are several other possible syntheses of thiolesters as was mentioned in the introduction (see page 6). Carbonyl chloride reacts with some pyrroles to yield acid chlorides[6], which in turn would probably react with alkyl thiols to yield thiolesters, this method was not investigated.
The Knorr pyrrole synthesis was modified by the substitution of ethyl acetothiolacetate for ethyl acetoacetate



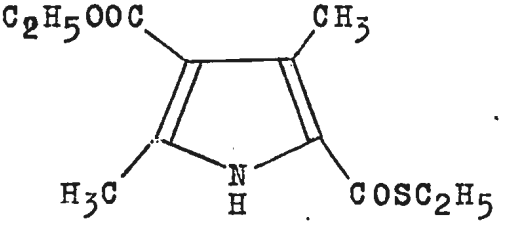
XX



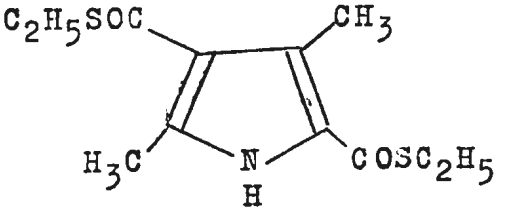
XXI



XXII



XXIII



XXIV

in the usual reactions. Ethyl thiolacetate is fairly readily available from ethane thiol and acetyl chloride[17]. The ethyl thiolacetate can then be converted to ethyl acetothiolacetate[47]. The n.m.r. of the ethyl acetothiolacetate prepared here indicated about 28% of the enol form in the neat liquid at room-temperature (literature[17] 31%) Since ethyl acetoacetate is only about 7%[63] the ∝ hydrogen atoms in ethyl acetothiolacetate are more acidic, and because the nitrosation involves the enolic form it is reasonable to expect differences in the reactivity of the thiol ester and the ester. It might be expected that the ethyl acetothiolacetate would nitrosate and cyclise more readily than ethyl acetoacetate.

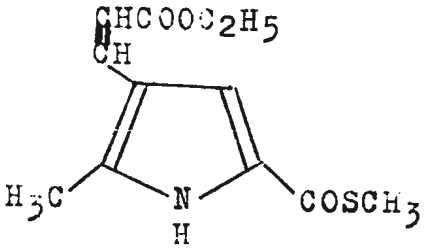
The Knorr synthesis was initially attempted using sodium dithionite as the reducing agent[48] in order to avoid possible reductive desulphurisation by the more usual zinc dust. The pyrrole (XXII) was obtained in about 50% yield from nitrosated ethyl acetoacetate and ethyl acetothiolacetate as shown. However a modification of the Knorr synthesis [5] using a zinc reducing agent was tried and found to give a 60% yield, clearly any reductive desulphurisation was negligable. Samples of the three possible Knorrs' type pyrroles were prepared in good yield from

ethyl acetoacetate and ethyl acetothiolacetate (XXIII, XXII and XXIV). In order to show that the thiolesters obtained by the Knorr method and from the thioanilides were identical, 2,4-dimethyl-3-acetyl-5-ethylthiolcarbonylpyrrole (XXV) was prepared by both methods. Acetylacetone was allowed to react with nirosated ethyl acetothiolacetate as it was reduced in the reaction mixture with zinc dust in a Knorr type synthesis. The product was found to be identical in every way with the product obtained by acetylation of 2,4-dimethyl-5-ethylthiolcarbonylpyrrole which had been obtained from the -5-thiocarbanilide.

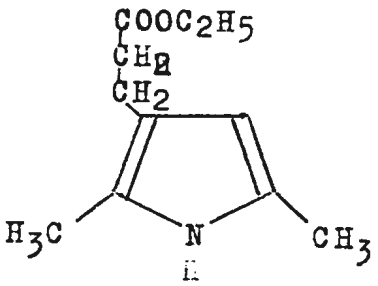
The Knorr type pyrrole thiolesters were characterised by their spectra and from microanalyses, the n.m.r. spectra were particularly characteristic (see tables of spectra, $-S-CH_2-R$ τ 6.9 $-O-CH_2-R$ τ 5.7 for the methylene groups).

A further alternative method for the synthesis of thiolesters is a modified Gatterman reaction with thiocyanates[18]. Thus methyl thiocyanate was allowed to react with 2-methyl-5-carbethoxy pyrrole in the presence of dry hydrochloric acid gas, and the product was heated with water in order to hydrolyse the imine hydrochloride supposedly produced. However the product would not dissolve in the water, and did not appear to hydrolyse, and its properties were quite unlike those of a thiolester. After recrystallisation from water

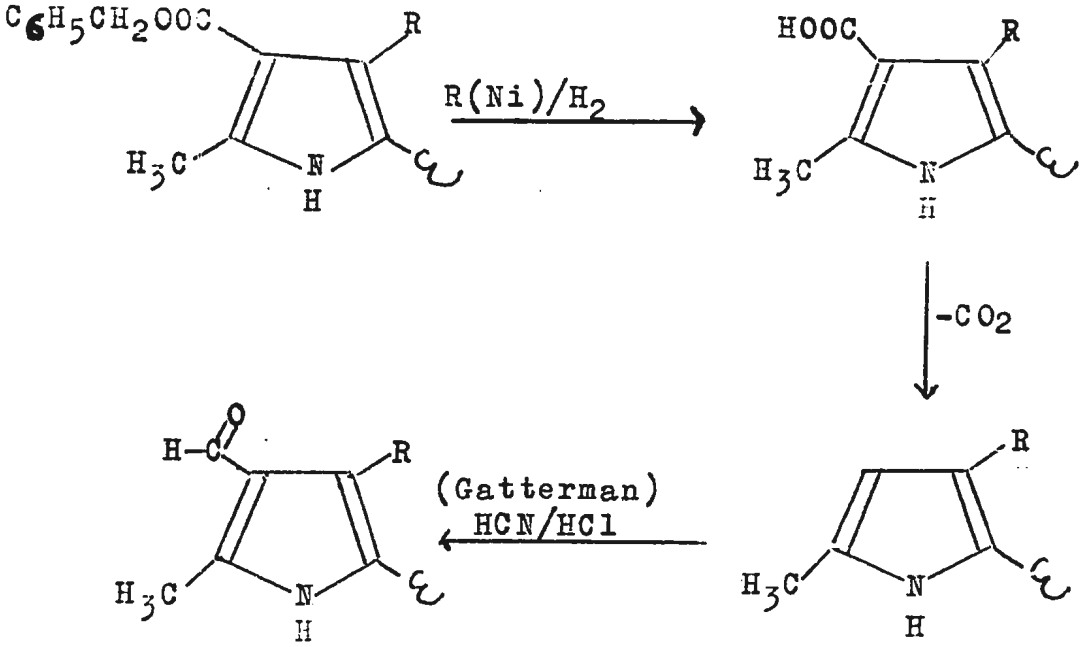
ethanol mixture, a Lassaigne test showed that the product contained chlorine and nitrogen, but no sulphur. The results of a microanalysis indicated a formula $C_{8.9}H_{11.8}Cl_{1.5}N_1O_{1.5}$ which does not appear to fit any compound that could have been expected from the reaction. The n.m.r. spectrum indicated that one pyrrole proton had been removed and that a methyl group had been introduced. The remaining ring proton was at rather high field (τ 3.08) for a 2,4-disubstituted pyrrole where both substituents are ester groups, and indicates that the group which was introduced into the molecule is only weakly electron withdrawing. The methyl group showed proton resonance at τ 8.44 and is almost certainly C-methyl, possibly Cl-C-methyl [55]. The compound did not react with silver nitrate under any conditions, indicating that the chlorine was not ionic and not hydrolysable. It was colourless, crystalline and thermally stable (m.p. 218-219° very slight decomposition took place above 280°). The ultraviolet spectrum was similar to that of the starting material, indicating similar conjugation. The infrared spectrum showed a carbonyl band at 1677cm^{-1} due to the ester group, no bands due to the introduced substituent could be identified. The structure of the methyl thiocyanate/HCl/2-methyl-5-carbethoxypyrrole reaction product could not be deduced from the information available at this time.



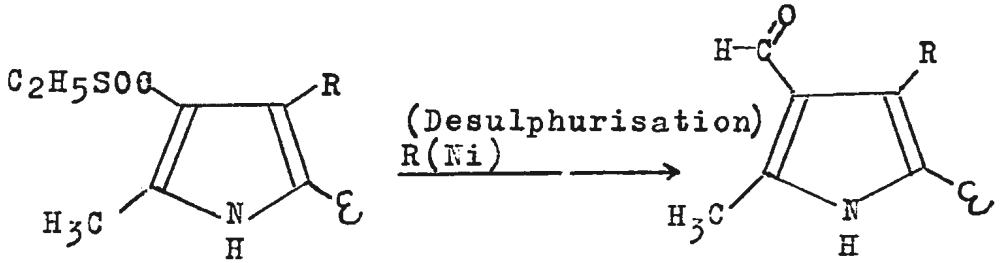
XXVI



XXVII



XXVIII MacDonalds synthesis[5]



XXVIII Synthesis via thiolesters.

($R = CH_2COOC_2H_5$, $\zeta = COOC_2H_5$)

Raney nickel desulphurisation of pyrrole thiolesters.

The pyrrole thiolesters can yield a variety of possible products when desulphurised by Raney nickel (R(Ni)). The grade or activity of the Raney nickel chosen usually governs the nature of the products formed[19]. Initially the desulphurisation of 2-methyl-5-ethylthiolcarbonylpyrrole (and 2-methyl-5-methylthiolcarbonylpyrrole) was attempted using a commercial grade of R(Ni) which had been in store for several years, no reaction at all was detected under any conditions. A fresh sample of W.2. R(Ni) was prepared exactly as described in reference 19, (It was necessary to follow the preparation carefully so that the desulphurisation experiments could be reproduced). Some of the W.2. R(Ni) was deactivated for one hour by refluxing it in acetone, the pyrrole thiolester was then added and the refluxing was continued for a further hour. 2-Methyl-5-formylpyrrole was obtained from the reaction mixture in about 70% yield as colourless plates. The reaction was found to have general applicability to most of the thiolesters prepared in this work, and proved a useful tool in their identification in some cases (e.g. the thiolester analogues of Knorrs' pyrrole). The desulphurisation of the acrylate (XXVI) yielded

mixtures of products which depended upon the reaction conditions chosen. Deactivated R(Ni) (refluxed W.2. R(Ni) 8 hours in acetone) yielded a product which was identified by n.m.r. as mostly 2-methyl-3-carbethoxy(vinyl)-5-formyl pyrrole, this product was not obtained pure. More reactive R(Ni) (W.2. refluxed 1 hour in acetone) resulted in a product which rapidly turned red in air and appeared to be a 2,4-dimethyl pyrrole , the acrylate having been reduced to propionate. When the acrylate (XXVI) was reduced in the presence of an excess of R(Ni) with hydrogen (60pounds pressure/room-temperature), a red oil was obtained which could be distilled under reduced pressure. The distilled oil was colourless, but soon turned red in air. The n.m.r. spectrum indicated that the compound had two methyl groups (τ 6.23 and 6.20), an ethyl ester (methylene τ 5.95), broad resonances for $-CH_2CH_2-(A_2B_2$) and one ring proton at comparitively high field (τ 4.40). The i.r. showed only one carbonyl band and the u.v. spectrum showed absorption at 285 and 203mμ ($\log\varepsilon_{max}$ 2.94 and 3.98). The ultraviolet spectrum probably indicates that the compound is a trialkyl pyrrole, since pyrroles with electron withdrawing substituents all absorb above 203mμ and the intensities of the bands

quite low. 2-Methyl-3-ethyl-4-methylpyrrole absorbs at 214mμ ($\log \varepsilon_{max}$ 3.84), the low frequency band was not detected[54]. With this evidence the structure (XXVII) was proposed, the compound would certainly be unstable in air and probably a liquid. No analysis was obtained for the compound and since it does not appear to have been synthesised before, the structure could not be confirmed at this time.

It is unfortunate that the thiolesters are so easily desulphurised as this results in rapid poisoning of the catalysts, it was therefore impossible to reduce catalytically any group independant of the thiolester. For example the vinyl group in (XXVI) could not be reduced without desulphurisation taking place at the same time.

There is an interesting possibility that compounds which were synthesised by MacDonald by the Knorr method using benzylacetoacetate might be more readily obtained if ethyl acetothiolacetate was used instead. The scheme shown in diagram (XXVIII) illustrates the proposed route, which is several stages shorter than that used by MacDonald.

Acylation reactions.

i)With perchloric acid catalyst.

A mixture of acetic anhydride and acetic acid to which a few drops of perchloric acid had been added was successfully used to acetylate a number of pyrroles. The ionic compound $CH_3\overset{+}{C}O\ \overset{-}{C}lO_4$ is presumably formed, the acetylation being effected by the $CH_3\overset{+}{C}O$ ion. The yields were often very high, and the productswere easily isolated in the pure state. This is probably the most convienient method of acetylating the pyrrole ring, provided the pyrrole is not strongly deactivated. Thus the free β-position next to an α-ester group in (VIb) could not be acetylated by this method. The variety of pyrroles that were acetylated by this method is demonstrated in table (XXIX).

When 2-carbomethoxypyrrole was acetylated with perchloric acid catalyst a mixture of two productswas obtained. These were recognised as the α-and β-acetyl compounds (XXIXc), and were produced in the ratio 51.5% : 48.5% respectively, as estimated from the n.m.r. spectra. No disubstituted (by acetyl) products were detected. The two isomers were easily recognised from the α and β-proton resonances in the n.m.r. because the α-acetyl derivative showed two

	Substituent at position:				Acetylation product:			
	2	3	4	5	2	3	4	5
a.	Me	H	H	COOMe	Me	Ac	H	COOMe
b.	Me	H	H	COSMe	Me	Ac	H	COSMe
c.	H	H	H	COOMe	Ac	H	H	COOMe
					H	Ac	H	COOMe
d.	Me	H	Me	COSEt	Me	Ac	Me	COSEt
e.	Me	H	H	CONHPh	Me	Ac	H	CONHPh

Table XXIX

Ac = $COCH_3$

almost superimposed resonances due to the two β protons, and the acetyl derivative showed two widely separated resonances due to the α and β' protons:-

Pyrrole substituents				Ring proton resonances τ			
2	3	4	5	2	3	4	-
$COCH_3$	H	H	$COOCH_3$	-	3.16	3.20	- (A)
H	$COCH_3$	H	$COOCH_3$	2.63	-	2.39	- (B)

in CCl_4

The assignments were made by comparing the spectra with those of the corresponding trifluoroacetyl analogues, in which the protons adjacent to the acyl group are moved to even lower field (increased deshielding effect). Although compound (A) in the table is known (2-acetyl-5-carbomethoxypyrrole)[65] it was impossible to differentiate between (A) and (B) by melting points alone, because both were almost identical (110-111.5° lit.[65] 113° and 109-110° respectively).

The ultraviolet spectra of (A) and (B) were characteristic in that the 2,5 substituted compound (A) showed two bands and the 2,4 substituted compound (B) showed three (This is also the case for the corresponding trifluoroacetylated compounds, details are included in the ultraviolet spectra tables below).

The reactions illustrate the <u>meta</u> directing effect of the α ester group, which has been noted by many other workers[39].

ii)Acylation reactions with trifluoroacetic anhydride.

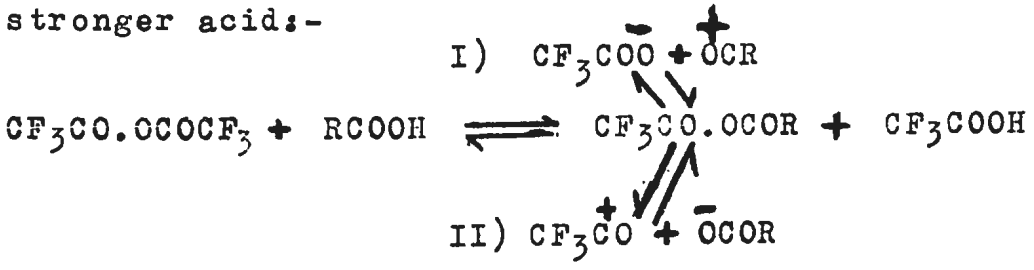
Trifluoroacetic anhydride has been used successfully as a catalyst for acylation reactions[58]. In an attempt to apply the method to pyrroles, reactions between 2-carbomethoxy-pyrrole and trifluoroacetic anhydride/acetic acid mixtures were examined. The reactions were generally fairly slow compared with the perchloric acid catalysed reactions, and the products were much more difficult to isolate.

With acetic acid (3ml.) and trifluoroacetic anhydride (2ml.) for 90 minutes, the product obtained consisted of a mixture of starting material, a little trifluoroacetylated material, and the α and β acetylation products in a ratio of 59% : 41% (as estimated from the n.m.r. spectrum of the reaction mixture). It is interesting that the ratio of the α and β acetylation products is almost the same as was found for the perchloric acid catalysed reactions. This is perhaps not surprising since the acetylating ions are probably the same in both cases ($CH_3\overset{+}{C}O$).

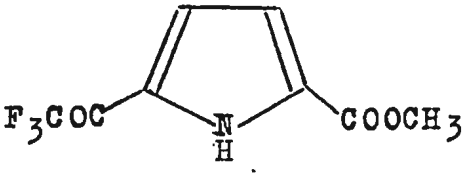
Attempts to use other carboxylic acids in the reaction did not produce the desired results. Ethyl hydrogen oxalate, cyanoacetic acid, chloroacetic acid and ethyl hydrogen malonate were tried and in each case a mixture of products was obtained. The mixtures contained mostly trifluoroacetylated products and only a little other material, from which none of the expected ketones could be isolated.

Though little success was obtained with this method in general acylation reactions, trifluoroacetic anhydride alone gave very good yields of the trifluoroacetylated compounds (XXXa and XXXb). A number of other pyrroles were trifluoroacetylated in this way, some examples are included in the experimental section of this work.

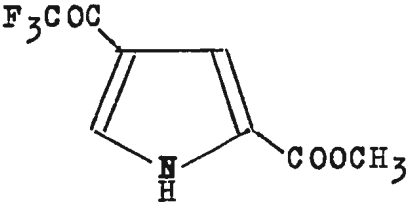
The acylation reactions with trifluoroacetic anhydride/carboxylic acid mixtures probably fail because the mixed anhydride intermediates are not very readily formed for the stronger acid:-



The dissociation of the mixed anhydride will also be influenced by stability of the $R\overset{+}{C}O$ ion , which decreases with increasing acid strength. Since the reactions were carried out in a excess of trifluoroacetic anhydride, dissociation of type II) to give $CF_3\overset{+}{C}O$ might be as favorable as dissociation of type I) to give $R\overset{+}{C}O$, hence resulting in trifluoroacetylation.



XXXa



XXXb

iii)Acylation reactions with silver borofluoride.

$$Ag(BF_4) + RCOCl \longrightarrow AgCl\downarrow + \overset{+}{R}C{=}O \quad (\overset{-}{BF_4})$$

The acylating ion is generated as shown above. Using a similar method to that which had been used for acylations with silver perchlorate catalyst[26] 2-carbomethoxypyrrole was successfully acetylated yielding a mixture of α and β-acetyl derivatives in about the same proportions as were found by methods i) and ii). Since this reaction gave a rather discoloured product which was unpleasant to work with and method i) gave far better yields, this method was abandoned.

SPECTRA.

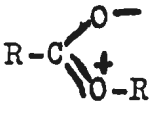
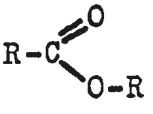
a)Infrared spectra.

Most of the spectra recorded in this work were run as nujol mulls or as potassium chloride discs, a few spectra were obtained as liquid films. The spectra which were run as mulls or discs were not always reproduceable because of variations in crystal structure of the samples.

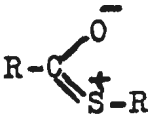
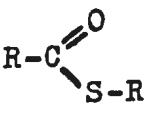
Thiolesters.

Nyquist and Potts have collected a large amount of data on this class of compounds[52]. In simple compounds the thiolesters show carbonyl bands at about 1675cm^{-1} (e.g. for ethyl thiolacetate 1691cm^{-1}). The carbonyl bands for the corresponding esters appear at rather higher frequencies, usually at about 1735cm^{-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)

The thiolesters examined here do not fall immediately into this pattern because they are more complex. Most of the bands fall in the 1650-1590cm^{-1} region.

PYRROLE SUBSTITUTION				CARBONYL FREQUENCIES (cm^{-1})	
2	3	4	5		
Me	COOEt	Me	COSEt	β1675	α1619
Me	COSEt	Me	COSEt	β1650	α1594
Me	COMe	Me	COSEt	β1650	α1590
Me	COOEt	Me	COOEt	α1668	β1686
Me	COSEt	Me	COOEt	β1634	α1669
Me	H	H	COSEt	1616	
Me	H	H	CHO	1650	
Me	H	H	COOEt	1681	

XXXI.

Since all the spectra were run as solids (in mulls or discs), it is possible that some of the shifts may be due to hydrogen bonding in the crystals. Schleppnik and Zienty have obtained spectra of thiolcrotonates and 3-mercaptothiolpropionates. For thiolcrotonates the carbonyl band is observed in the region 1667-1685cm^{-1} and for 3-mercaptothiolpropionates at 1685-1697cm^{-1} (normal saturated esters 1685-1704cm^{-1}) [53].

The absorption frequency of the β-pyrrole thiolesters carbonyl is not unduly low and is similar to that found for thiolbenzoates[52]. The most pronounced effect is seen in the dithiolester analogue of Knorrs' pyrrole (second compound in table XXXI), both carbonyl frequencies are low. In Knorrs' pyrrole the β carbonyl band occurs at 1686cm^{-1} and the α carbonyl at 1668cm^{-1} [50].

If we accept the value of 1735cm^{-1} for the carbonyl frequency of normal straight chain esters, and 1690cm^{-1} for the corresponding thiolesters[52], the change in frequency is about 45cm^{-1}. Comparing the 2,4-dimethyl-3,5-ethylthiol carbonylpyrrole carbonyl frequencies with those of Knorrs' pyrrole, we obtain:-

	Carbonyl frequencies. (cm^{-1})	
Knorrs' Pyrrole	1668	1686
2,4-dimethyl-3,5-ethyl-thiolcarbonylpyrrole.	1594	1650

Thus for Knorrs' pyrrole the change saturated ester to pyrrole ester represents a change in frequency of 67cm^{-1} for the α carbonyl and 49cm^{-1} for the β carbonyl ($\delta\alpha$ and $\delta\beta$ respectively). Thus all other things being equal, it is possible to predict for the thiolesters of pyrrole $\delta\alpha = 67 + 45 = 112\text{cm}^{-1}$ and $\delta\beta = 49 + 45 = 94\text{cm}^{-1}$, for a rough approxamation. This predicts bands at 1623 and 1641cm^{-1} for 2,4-dimethyl-3,5-ethylthiolcarbonylpyrrole, fairly close to the observed frequencies. The large error in the prediction for the α carbonyl absorption indicates a greater interaction with the pyrrole ring than is found in Knorrs' pyrrole (i.e. hyrogen bonding of the carbonyl oxygen with the pyrrole N-H and interaction with the aromatic π electron system). A similar calculation for 2-methyl-5-ethylthiolcarbonylpyrrole predicts the carbonyl absorption at 1635cm^{-1}, the observed figure is 1616cm^{-1}, a shift of about 20cm^{-1} more than predicted.

However compare the alkyl benzoates:-

	Carbonyl(cm^{-1})	
Alkyl benzoates	1725	δ = 10
Alkyl thiolbenzoates	1665	δ = 35

A similar difference in the δ values would bring the carbonyl frequencies of the α thiolesters within the predicted regions for the pyrrole case. Clearly the change in frequency alkyl to aryl ester (aryl-COOR) is less than for the corresponding change in the thiolester series (e.g. benzoates to thiolbenzoates). The infrared spectra show that the environment of the pyrrole α thiolester carbonyl group is very different to that of the β thiolester group. Assignment of the remainder of the infrared bands is complicated by superimposed bands due to the pyrrole ring, and bands due to the thiolester groups. The thiolesters examined by Nyquist and Potts showed bands in the 1060-1210cm^{-1} region which they assigned to -C-$\overset{\overset{O}{\|}}{C}$- stretching frequencies and bands in the region 880-1030cm^{-1} assigned to -$\overset{\overset{O}{\|}}{C}$-S- stretching frequencies. Rao et al[23] have reported bands in the 772-622cm^{-1} region, which they assigned to -C-S-C- asymmetric and symmetric stretching vibrations in certain sulphur compounds. Most of the pyrrole thiolesters showed a band around 870cm^{-1}, but the other

bands could not be located.

Trifluoroacetylated pyrroles.

All the trifluoroacetylated pyrroles showed medium to strong absorption between 1100 and 1400cm^{-1}, overlapping the C-O, C-N and C-C stretching frequency regions. Comparison of the spectra with those of other similarly substituted pyrroles showed that bands at 1190 and 1160cm^{-1} were most likely due to C-F vibrations, but this assignment remains uncertain.

Ultraviolet spectra.

The majority of spectra recorded in the literature of pyrroles show two or three bands.[54] These have been classified in several ways, but the classification of U.Eisner and P.H.Gore[54] is used in the discussion below. The absorption due to A bands is found at usually 200-235mμ , B bands at 250±~25mμ and K bands in a wide range around 280mμ . The K band is probably a conjugation band and is present in all conjugated pyrroles, representing $\pi-\pi^*$ transitions.

All the 2-methyl and 2,4-dimethylpyrroles with a 5-ester, thiolester or formyl substituent showed two absorption bands in the ultraviolet. In all cases the K band was more intense than the B band and the A band was absent. Substitution α ester for a α thiolester group results in a bathochromic shift of both bands and a strong hypsochromic effect. The K band shifts about 32mμ towards the visible and the B band only about 8mμ. The K bands of the α formyl pyrroles lie at about 303mμ, about midway between the corresponding esters and thiolesters, but the B band shows a stronger bathochromic shift than either (

K bands:- ester 277, thiolester 309 and aldehyde 303mμ

B bands:- .. 231, ... 240 .. .. > 240mμ)

When a second electron withdrawing substituent is introduced into the β' position (e.g. 2-methyl-3-acetyl-5-carbethoxy-pyrrole), A, B and K bands may be observed[54]. Almost all such pyrroles examined here showed three bands, but in a few cases the B band was not observed (e.g. Knorrs' pyrrole), perhaps due to swamping by the A and K bands.

The introduction of a trifluoroacetyl group into the 4 position of pyrrole 2-esters (or thiolesters) had a similar effect on the spectrum to that produced by an acetyl group, but slightly more marked. Both the B and the K band showed a bathochromic shift (A bands are absent in the 2-esters), and an A band was observed.

Substitution of an ester group by a thiolester group caused bathochromic shifts in the K type bands, and a large increase in intensity for every case examined. (The B band was observed in too few cases to make any reliable correlations). The effect on the K band was greater for the than for the thiolesters. Surprisingly the same change produced a marked decrease in the intensity of the A band in the case of the Knorr type pyrroles, and only a small bathochromic shift. This effect is presumably connected with differences in the conjugating power of the groups -COOR and -COSR.

To summarise, pyrroles with one α electron withdrawing substituent show two absorption bands in the ultraviolet, a B and a K band. The K band is more intense than the B band and appears at about 270-300mμ . The B band has about one fifth of the intensity of the K band, and appears at 230-250mμ . Pyrroles substituted by α and β' electron withdrawing substituents show three bands; A,B and K type. The A and K bands are usually more intense than the B band but not always, sometimes the B band appears as a shoulder to or is submerged by one of the other bands. The effect of alkyl substituents on the absorption frequencies of the pyrroles is small, usually about 2mμ in the case of the K band and up to 10mμ for the A band. The ultraviolet spectra give a good indication of the substitution pattern on the pyrrole ring for simple compounds, but becomes less reliable for more complex molecules.

Nuclear magnetic resonance (n.m.r.) spectra.

Nuclear magnetic resonance spectra were recorded for almost all the compounds prepared in this work, and were used extensively for identification purposes. The thiolesters produced spectra which could be predicted with some certainty (for simple pyrroles) from the spectra of the corresponding esters. Both ethyl and methyl esters and thiolesters were examined. These contain the groups $-\overset{\overset{O}{\|}}{C}-O-R$ and $-\overset{\overset{O}{\|}}{C}-S-R$ (esters and thiolesters respectively) where R= ethyl or methyl. In 2-methyl-5-carbethoxypyrrole the chemical shift of the methylene group was τ 5.68 and for the corresponding thiolester τ 6.95, a difference of 1.27 parts per million (p.p.m.). Some idea of the shifts to be expected can be obtained from tables of shielding constants. Thus for ethers and thio-ethers the shielding constants for $O-CH_2-$ and for $S-CH_2$ are 2.36 and 1.64 p.p.m. respectively,[55] a difference of 0.72 p.p.m. . A recent paper[56] contains spectra of some compounds containing the S-methyl group. The results contained in the paper indicate that the $S-CH_3$ proton resonance for thiolesters should be expected in the region of τ 7.6 - 7.7 (see table XXXII). For the pyrrole

thiolesters studied here the S-CH_3 proton resonances were observed at about τ 7.5 depending on the other substituents on the ring. Since the methyl protons of the corresponding esters appear at about τ 6.2, the deshielding effect of the oxygen atom is greater than that of the sulphur atom. Since oxygen is more elctronegative than sulphur[51] this effect might have been predicted.

		Chemical shift (τ)	solvent
CH_3COSCH_3		7.76	CCl_4 ref.[56]
CH_3SCN		7.50	
$PhNHCOSCH_3$		7.78	
CH_3SCH_3		8.00	
$(CH_3)C(SCH_3)$		8.05	
Pyrroles:-			
2-methyl-5-ethylthiol-carbonylpyrrole	(methylene)	6.95	CH_2Cl_2
2-methyl-5-methylthiol-carbonylpyrrole		7.58	
2-methyl-3-acetyl-5-methylthiolcarbonylpyrrole		7.51	

From the table above and the main table of n.m.r. spectra below, the following observations can be made:-

The $-S-CH_3$ proton resonances for α thiolesters of pyrrole are found in the region τ 7 to 8.

The $-S-CH_2CH_3$ methylene resonances for α and β ethyl pyrrole thiolesters are found in the region τ 6 to 7.

The exact positions are influenced slightly by the deshielding effects of the substituents on the pyrrole ring.

The pyrrole ring protons are affected by deshielding due to substituents on the ring. This may be roughly summarised as as follows:-

	Ring proton resonances (τ)		
	3	4	5
2 substituted only with a 5-methyl group.	3.2	4.1	-
2,4 disubstituted	2.4	-	2.6
2,5 disubstituted	3.2	3.2	-

Where the substituents are carbalkoxy, trifluoroacetyl, acetyl, thioester group or formyl. The trifluoroacetyl group exibited the greatest deshielding effect of all the groups investigated.

Experimental.

Melting points (uncorrected) were determined in capillaries. Infrared spectra were recorded by a Perkin-Elmer 237B grating spectrophotometer as potassium chloride discs (2mg. sample in 200mg. KCl) or nujol mulls. Ultraviolet were determined on a Beckman DK-2A recording spectrophotometer in 95% ethanol, or methanol 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.

S-Methylation of 2-methylpyrrole-5-thiocarbanilide.

The pyrrole thioanilide (12g.) was warmed on a steam bath with sodium hydroxide (24ml. 3N.) and dimethyl sulphate (7ml.), with rapid stirring for 10 minutes. The mixture formed two layers, the lower layer colourless and the upper layer brownish yellow. The mixture was then cooled and ammonia solution (30ml. 6N.) was added in order to hydrolyse the excess dimethyl sulphate. After 30 minutes the mixture was extracted with ether, the ether extracts were washed with water, dried (Na_2SO_4) and the ether was evaporated. The yellow oily residue of 2-methylpyrrole-5-(S-methyl)thiocarbanilide would not crystallise, but was sufficiently pure for the preparation 2-methyl-5-methylthiolcarbonylpyrrole (below). The n.m.r. spectrum, apart from benzenoid resonances (τ 3.2), showed two doublets τ 3.44 and 4.23 due to the 3 and 4 ring protons, and a singlet τ 7.90 due to the ring methyl and S-methyl groups.

2-Methyl-5-methylthiolcarbonylpyrrole.

2-Methylpyrrole-5-(S-methyl)thiocarbanilide (~12g. from the preceeding experiment) was added to hydrochloric acid (240ml., 1N.) and heated on a steam bath for 2 hours. Yellow crystals were slowly formed in the solution. The mixture was then cooled in ice and the crystals were filtered off. The filtrate was again heated until no more crystals were deposited. A total yield of 6.5g. (75% based on

2-methylpyrrole-5-thiocarbanilide) of almost pure crystalline material was obtained, and was recrystallised from chloroform/petrol (60-80°b.p.) and sublimed (100°/15mm). The colourless crystals of 2-methyl-5-methylthiolcarbonylpyrrole had m.p. 126-7°.

Anal. Calc. for C_7H_9NOS: C, 54.17; H, 5.81; N, 9.02; S, 20.66%
Found: C, 54.19; H, 5.90; N, 9.20; S, 20.57%.

n.m.r. (CH_2Cl_2) 3.02 and 4.15 triplets (ring protons), 7.58 and 7.67 singlets (S-methyl and ring methyl).

λ_{max} 311.5 and 283mμ ($\log \varepsilon_{max}$ 4.34 and 3.67) in ethanol(95%)

ν_{max} 1620s, 1263s, 1200s, 1048m, 862m, cm^{-1}(nujol) main bands only.

2-Methyl-3-formyl-5-methylthiolcarbonylpyrrole.

2-Methyl-5-methylthiolcarbonylpyrrole (2.8g.) was added to a cooled mixture of dimethylformamide (6g.) and phosphorus oxychloride (2ml.) keeping the temperature below 0°. The red solution was warmed on an oil bath at 35° for 30 minutes, (the imine hydrochloride slowly crystallised), and then cooled and added to ice cold caustic soda solution (NaOH 4g. and water 8ml.). After 10 minutes cold dilute hydrochloric acid (3N.) was stirred into the mixture until pH6, and after a further 10 minutes the pinkish brown precipitate was filtered off and recrystallised from ethanol/water mixture (decolourising charcoal failed to remove the colour even after boiling the solution)

yielding slightly 'off white' needles of 2-methyl-3-formyl-5-methylthiolcarbonylpyrrole (2.78g., 85%). Further recrystallisation gave colourless needles, m.p. 179-81°. Anal. Calc. for $C_8H_9NO_2S$: C, 52.50; H, 4.96; Found : C, 52.25; H, 4.98%. λ_{max} 307, 272.5 and 229mμ ($\log\varepsilon_{max}$ 4.26, 4.04 and 4.30).

Raney nickel desulphurisation of 2-methyl-5-methylthiol-carbonylpyrrole.

Raney nickel (2.8g. W.2 grade, see Org. Synth. Coll. Vol. III page 181) was deactivated by refluxing in acetone (6ml.) for 1 hour. 2-Methyl-5-methylthiolcarbonylpyrrole (0.25g.) was then added to the refluxing solution followed by acetone (2ml.) and water (2ml.). The mixture was refluxed for a further hour, cooled and filtered through diatomite. The solvent was removed from the filtrate under vacuum, and the oily residue crystallised on adding a drop of methanol. The crystalline product was sublimed (100°/15mm) yielding colourless plates of 2-methyl-5-formylpyrrole, m.p. 68.5-69.5°, oxime 151-2° (lit.[64] 68°, oxime 153°).
n.m.r.(CCl_4): 0.69 singlet (formyl), 7.57 singlet (ring methyl), and complex triplets due to ring protons at 3.13 and 3.98. λ_{max} 248 and 302mμ ($\log\varepsilon_{max}$ 3.56 and 4.25). ν_{max} 3250m, 1650s, 1570m, 1492m, 1270m, 1190m, 1046m, 805m, cm^{-1}(nujol).

2-Methyl-3-(glyoxalic)-5-carboxypyrrole diethyl ester.

Dry hydrochloric acid gas was bubbled into a mixture of 2-methyl-5-carbethoxypyrrole (10.5g.), dry ether (45ml.), dry spectrograde chloroform (15ml.) and ethyl cyanoformate (15ml) cooled in an ice salt bath, for 3 hours. The gas flow was then stopped and the ice bath removed. Most of the solvent was blown off with a stream of dry air, leaving a solid residue of the ketimine hydrochloride. The residue was added to iced water (1 litre), in which it at first dissolved to give a clear yellow solution, but after about 1 minute a precipitate of pale yellow crystals began to form. The mixture was allowed to stand in a cold room over night (0°). The crystals were then filtered off, washed with water, and finally recrystallised from an ethanol/water mixture, (15g., 87%). The glyoxalate formed yellow needles m.p. 158-9° (lit.[10] 160°). The product gave a positive Erlich's reaction when warmed.

ν_{max} 3264s, 1642s, 1684s, 1667s, 1569m, 1516m, 1383m, 1367w, 1307m, 1281m, 1216s, 1191s, 1032m, 1000w, 969w, 784w, 721w, 675w, cm^{-1}(nujol).

2-Methyl-3-(glyoxalic acid)-5-thiolcarbonylpyrrole 3-ethyl ester, 5-methyl ester.

The same method was used as for the preparation of the corresponding ester (above). The glyoxalate was obtained as yellow needles m.p. 167.5-169°. The product gave an Erlich's reaction slowly in the warm.

2-methyl-3-carbethoxy(vinyl)-5-methylthiolcarbonylpyrrole.

2-Methyl-3-formyl-5-methylthiolcarbonylpyrrole (0.25g.) was added to a mixture of pyridine (1.3ml.), piperidine (0.03ml.) and ethyl hydrogen malonate (0.2g.), and the resulting solution was warmed on a water bath for 90 minutes. The mixture darkened and carbon dioxide was given off. The mixture was then cooled and poured into ice cold hydrochloric acid (3N.) (sufficient to form the pyridine salt). The precipitate of brown crystals was filtered off and recrystallised from chloroform/petrol (60-80°b.p.),as brownish needles. The crystals were sublimed yielding 0.16g. of the required acrylate, m.p. 156.5-157.5°, as colourless needles. n.m.r. (Dimethyl sulphoxide) 2.44 and 3.75 (doublets of an AB system due to the vinyl protons), also visible were a doublet at 2.65 (pyrrole ring proton) and a quartet at 5.80 (ethyl ester). The remainder of the spectrum was obscured by solvent bands

Reduction of 2-methyl-3-(glyoxalic acid)-5-carbethoxypyrrole ethyl ester.

The glyoxalate (2g.) was dissolved in acetic acid and sulphuric acid (0.3ml.) was added. The mixture was hydrogenated at 60lbs pressure at room temperature in the presence of Adams catalyst (100mg.) for 30 hours. The catalyst was then filtered off, and the filtrate was poured into water (250ml.). The aqueous solution was extracted with ether, the ether extracts were washed with sodium carbonate, with water and then dried (Na_2SO_4). The ether was evaporated and the residue was chromatographed on acid alumina (Fischer). Elution with benzene/petrol (60-80°b.p.) yielded a crystalline product (0.76g.), which was decolourised with charcoal and recrystallised from acetone/water mixture. The product formed colourless needles m.p. 201-203°, and gave an Erlich's reaction when warmed.

Calc. for $C_{20}H_{26}N_2O_6$: C, 61.32; H, 6.66; N, 7.31%

Found: C, 61.52; H, 6.71; N, 7.18%. The ultraviolet spectrum showed a weak band at 213mμ and a strong band at 281mμ. ν_{max} 3316s (N-H), 1725s, 1700s, 1680s, 1518w 1372m, 1320m, 1271s, 1252s, 1220s, 1192s, 1142m, 1119m, 1104m, 1033s, 992m, 850w (doublet), 773s (doublet), 667w, cm^{-1} (nujol).

Note/ A repeat of this experiment using the same method but omitting the sulphuric acid and using palladium black catalyst, yielded a different product. The infrared spectrum showed bands at 3487 (O-H), 3300(N-H), 1745s, 1688s, 1593w, 1511s, 1429m, 1392s 1358m, 1275s, 1212s, 1147s, 1087m, 1040s, 995s, 860s, 780s cm^{-1} (liquid film). The structure of this compound was not fully investigated in the time available, but is discussed in the discussion.

n.m.r. ($CHCl_3$) 3.10 (pyrrole ring proton), 4.80 (diffuse, sharp when D_2O was added), ~5.7 (multiplets due to methylenes of ethyl esters), ~6.15 (diffuse, absent when D_2O was added), 7.66(ring methyl group) and 8.69 (methyl groups of ethyl esters as almost superimposed triplets).

Acylation reactions.

i) With perchloric acid catalyst.(Acetylations.)

The pyrrole (0.25g.) was dissolved in a mixture of acetic acid (2ml.) and acetic anhydride (1ml. excess for the pyrroles acetylated here), perchloric acid (5 drops) was added and the solution was cooled under a tap. After about 15 minutes the reddish brown solution was poured into iced water. After some time the solid product was filtered off or extracted into ether. The product was recrystallised from ethanol/water mixture and then $CHCl_3$/petrol (60-80°b.p.). The yield was in most cases almost quantitative.

Spectra for these product are recorded in the tables of spectra.

Analyses.(Two compounds only).

2-Methyl-3-acetyl-5-carbomethoxypyrrole. m.p. 179-80°

Calc. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73%

Found: C, 59.54; H, 6.08; N, 7.89%.

2,4-Dimethyl-3-acetyl-5-ethylthiolcarbonylpyrrole. m.p. 123-4°

Calc. for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.48; N, 6.22; S, 14.23%

Found: C, 59.54; H, 6.75; N, 6.41; S, 14.14%.

ii)With trifluoroacetic anhydride catalyst.

The pyrrole (1 mole) was dissolved in trifluoroacetic anhydride (2 moles) and the carboxylic acid from which the acylinium ion was to be derived (1 mole) was added. The solution rapidly turned dark red and it was advisable to cool the reaction mixture. The reaction mixture was allowed to stand at room temperature for 90 minutes and then poured into a strong solution of sodium bicarbonate (excess). The mixture obtained was extracted with ether, the red ether extracts were washed with water and dried (Na_2SO_4). Evaporation of the ether yielded a gum, which sometimes crystallised. The products were isolated by alumina chromatography or, where possible, by recrystallisation. The reaction was only successful when acetic acid was used, other acids gave mostly trifluoroacetylated products.

Analysis.

2-carbomethoxy-5-acetylpyrrole. m.p. 109-110°.

Calc. for $C_9H_{11}NO_3$: C, 58.48; H,5.43; N, 8.38%

Found: C, 58.41; H, 5.52; N, 8.51%.

The acetylation products obtained by both methods i) and ii) were identical in physical properties. Since the physical properties are given in tables below it will not be repeated here. All but the acetylation products from 2-carbomethoxypyrrole and 2-methyl-5-carbomethoxypyrrole (prepared by both methods) were obtained by the perchloric

acid catalysed method.

iii)With silver borofluoride catalyst.

This experiment was only attempted on 2-carbomethoxypyrrole. 2-Carbomethoxypyrrole (1 mole) was dissolved in nitromethane and added to silver borofluoride (1 mole). Acetyl chloride (1 mole) was then added to the cooled (0°) solution over about 15 minutes, stirring throughout. The dark red mixture was then allowed to stand for 1 hour, at 0°. The mixture was poured on to ice, extracted into ether, the ether extracts were washed (water), dried (Na_2SO_4) and the ether was evaporated. The gummy residue was chromatographed on alumina (Fischer acid alumina) with a petrol(60-80°b.p.)/ether solvent system. Moderate yields of 4-acetyl and 5-acetyl-2-carbomethoxypyrrole were obtained (~70%), which proved to be identical with the products obtained by methods i) and ii).

5-acetyl-2-carbomethoxypyrrole. ν_{max} (Unicam SP200 spectrophotometer) 1729s, 1658s, 1578s, 1466s, 1401m, 1296s, 1231s, 1153s, 999w, 941m, 853w, 777m (KCl disc) cm^{-1}

4-acetyl-2-carbomethoxypyrrole. ν_{max} 1713s, 1646s, 1573s, 1283s, 1226s, 1182m, 1152s, 1000w, 988w, 946m, 854m, 785m, 654m (nujol) cm^{-1}.

Alternative synthesis of pyrrole thiolesters.

2-Methylpyrrole-5-(S—ethyl)thiocarbanilide.

2-Methylpyrrole-5-thiocarbanilide (6g.) was added to a mixture of sodium hydroxide (24ml., 3N.) and ethyl bromide (4ml.). The mixture was refluxed for four hours on a steam bath, then cooled and extracted with ether. The ether extracts were washed with water, dried (Na_2SO_4) and the ether was evaporated. The residue, a yellow-green oil, slowly crystallised. The product was recrystallised from ethanol/water mixture and then chloroform/petrol(60-80°b.p.). The S-ethyl thiocarbanilide formed pale yellow chunky plates, m.p. 49.5-51°, and gave an Erlich's reaction in the cold. The yield of the crude product was quantitative, and the unpurified material was suitable for the preparation of 2-methyl-5-ethylthiolcarbonylpyrrole, (below).

2-Methyl-5-ethylthiolcarbonylpyrrole.

2-Methylpyrrole-5-(S-ethyl)thiocarbanilide (3g.) was added to dilute hydrochloric acid (60ml., 1N.) and heated on a water bath for several hours until crystals had filled the liquid. The crystals were filtered off, and the filtrate was again heated. Several crops of crystals were obtined in this way,

and were recrystallised from $CHCl_3$/petrol (60-80°b.p.), (1.8g. 84% theor. from 2-methylpyrrole-5-thiocarbanilide). The thiolester formed colourless needles, m.p. 88-90°.

ν_{max} 3280s (N-H), 1616s, 1562w, 1265m, 1201s, 1048m, 977w, 866s, 795m, 725s, 615w, 659w, cm^{-1} (nujol).

n.m.r. (CH_2Cl_2) 3.05 and 4.00, triplets due to the pyrrole protons; 6.95, quartet due to the methylene group of the ester; 7.66, singlet due to ring methyl; 7.01, triplet methyl group of ester.

2,4-Dimethyl-5-ethylthiolcarbonylpyrrole.

The previous two experiments were repeated using 2,4-dimethyl pyrrole-5-thiocarbanilide. The 2,4-dimethylpyrrole-5-(S-ethyl)thiocarbanilide was sufficiently high melting to allow easy purification, m.p. 69.5-70.5°(from ethanol/water).

Anal. Calc. for $C_{15}H_{18}N_2S$: C, 69.73;H, 7.02; N, 10.84; S, 12.41%. Found: C, 69.80; H, 7.13; N, 11.00; S, 12.33%.

ν_{max} 3420m(N-H), 2973s, 2921m, 2860m, 1583s, 1588s, 1481s, 1382m, 1266m, 1220w, 1183s, 1168s, 1120w, 1075w, 1048s, 976w, 910m, 884s, 774s, 701s, cm^{-1}(liquid film).

n.m.r. ($CHCl_3$) 4.28 singlet(pyrrole ring proton), 7.35 quartet (methylene), 7.82 (two superimposed methyl singlets) and 8.87 (methyl protons of ethyl group).

The S-ethyl conpound was then converted to the thiolester by heating it with dilute acid as before. The 2,4-dimethyl-5-ethylthiolcarbonylpyrrole was recrystallised from chloroform/petrol(60-80°b.p.), m.p. 111.5-113°. The analysis gave a poor result: Calc. for $C_5H_{13}NOS$; C, 58.95; H, 7.15; N, 7.64; S, 17.49%. Found; C, 57.81; H, 7.11; N, 8.10; S, 18.07%. ν_{max} 1618s, 1578s, 1562s, 1242s, 1174m, 1014w, 920s, 810m, 759m, 724s, 689w, cm^{-1}(nujol).
n.m.r. (CH_2Cl_2), 4.21 (pyrrole ring proton), 7.36 quartet (methylene), 7.61 and 7.72 singlets (ring methyl groups), and 8.67 triplet (methyl group of ethyl ester). The compound gave an Erlich's test in the cold.

Raney nickel desulphurisation experiments.

W.2 Raney nickel[49] was used in these experiments. It was essential that the nickel was prepared exactly as described in the reference.

Desulphurisation of 2-methyl-3-carbethoxy(vinyl)-5-methylthiolcarbonylpyrrole.

Method i) Raney nickel (~ 6g.) was deactivated by refluxing with acetone (18ml.) for 8 hours, and then allowed to stand overnight at room temperature. The 2-methyl-3-carbethoxy (vinyl)-5-methylthiolcarbonylpyrrole (0.25g.) was added in acetone (2ml.), followed by water (2ml.). The mixture was

then refluxed for a further 3 hours, and finally cooled. The Raney nickel was filtered off, and the solvent was removed in a rotary evaporator at about 60°. The pale yellow gummy residue crystallised on scratching with a glass rod, but darkened in colour rapidly. The n.m.r. spectrum showed the product to be mostly 2-methyl-3-carbethoxy(vinyl)-5-formyl-pyrrole, but none of this product was isolated in the pure state.

Method ii. The Raney nickel was deactivated for 1 hour only, otherwise the method was identical to method i. The product did not crystallise and decomposed more rapidly than the product from i. The n.m.r. showed that the product was a mixture, but mostly 2,5-dimethyl-3-carbethoxy(ethyl)pyrrole, the side chain and the ester having been reduced.

Method iii. 2-Methyl-3-carbethoxy(vinyl)-5-methylthiolcarbonyl-pyrrole (0.5g.) was dissolved in methanol (50ml.) and Raney nickel (~2.5g.) was added. The mixture was hydrogenated at room temperature and 60 pounds pressure for 2 hours. The nickel was then removed by filtration and the solvent was evaporated on a rotary evaporator at about 60°. The oily residue would not crystallise and the n.m.r. indicated that the product was a trialkyl pyrrole. The oil was there-fore distilled, b.p. ~120°/15mm., a pale yellow oil was obtained which became rapidly redder in air.

After two more distillations a colourless product was obtained, which remained colourless if stored in a sealed tube in a refrigerator, b.p. ~120°/15mm. Hg.

ν_{max} 3370s(N-H), 2958s, 2920s, 2858m, 1770s, 1708w, 1725w, 1440m, 1374m, 1300m, 1362m, 1175s, 1117m, 1042m, 944w, 857w, 790w, cm^{-1}(liquid film).

n.m.r.(CH_2Cl_2), 4.44 doublet(ring proton), 5.93 quartet (methylene of ethyl ester), 7.47 multiplet ($-CH_2CH_2-$), 6.23 and 6.20 singlets(due to ring methyl groups), 8.83 triplet (methyl group of ethyl ester).

No analytical data was obtained, but on the above evidence and from the ultraviolet spectrum (see tables), the compound was almost certainly 2,5-dimethyl-6-carbethoxy(ethyl)pyrrole.

<u>2,4-Dimethyl-5-formylpyrrole.</u>

2,4-Dimethyl-5-ethylthiolcarbonylpyrrole (0.25g.) was desulphurised by the same method as described for the desulphurisation of 2-methyl-5-methylthiolcarbonylpyrrole, (above). 2,4-Dimethyl-5-formylpyrroles was obtained as colourless needles after recrystallisation from chloroform/petrol(60-80°b.p.), m.p. 89-90° (0.124g., 73%). Ref. gives m.p. 90° from water. λ_{max} 304 and 270mμ(log ε_{max} 4.33 and 3.71) lit λ_{max} 297 and 264mμ (log ε_{max} 4.36 and 3.71) both in 95% ethanol.

Investigation of the properties of 2-methylpyrrole-5-carbanilide.

Attempted preparation of 2-methyl-3-formylpyrrole-5-carbanilide.

2-Methylpyrrole-5-carbanilide (10g.) was dissolved in a mixture of ether (150ml.) and dimethyl formamide (15ml.), contained in a 500ml. flask fitted with a magnetic stirrer and cooled in an ice bath. When the solution had cooled to 0° a solution of phosphorus oxychloride (5ml.) in ether (180ml.) was added dropwise over about 1 hour. The solution slowly turned yellow, and a yellow oil began to separate. After a further 20 minutes the ether layer (A) was collected, and the yellow oil remaining was poured into an iced caustic soda solution (300ml., 3N.). After two hours the alkaline solution was acidified to pH 6 with cold dilute hydrochloric acid, and after a further hour the yellow powdery precipitate was filtered off. The product was washed with water and dried in a desiccator (silica gel); yield 6g. crude material. The product was exceedingly insoluble in most solvents, but a small sample was successfully recrystallised from a pyridine/ethanol mixture, m.p. 250°decomp. (darkens at 250°). The supposed aldehyde was obtained as a white powder.

The ether layer (A): The solvent was removed from (A) under reduced pressure, and iced caustic soda solution was added to the red gummy residue. The alkaline solution was treated as described for the yellow oil above. The final product

was obtained as a red powder, (about 3g.).
The n.m.r.(dimethyl sulphoxide) spectrum showed aldehydic proton resonances, but since the material was rather insoluble only a poor spectrum was obtained. Other reactions attempted on the anilide were:- The Sonn-Müller reaction[42], acetylation with acetic anhydride/perchloric acid mixtures, the Gatterman-Hoesch reaction, and hydrolysis by acid and base. The only reaction in which a recognisable product was obtained was the acetylation, which yielded a product having the expected n.m.r. for 2-methyl-3-acetylpyrrole-5-carbanilide, and m.p. 239-242°.

Attempted O-methylation of 2-methylpyrrole-5-carbanilide.

The anilide (3g.) was heated on a water bath with dimethyl sulphate (3.4ml.) for 90 minutes. The anilide dissolved, the reaction mixture became slowly yellower, and crystalline material was precipitated. The reaction mixture was cooled and poured into strong ammonia solution (6N.). The yellow brown precipitate was filtered off, washed with water and recrystallised from ethanol as brown crystals m.p. 212-214°. Decolourisation with charcoal yielded colourless crystals,(1.1g) m.p. 217-220°(bubbled and turned black above 180°).
Anal. Calc. for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.66% . Found: C, 53.08; H, 4.75; N, 9.65; S, 10.66%.

ν_{max} 1658s, 1595s, 1565m, 1534s, 1481m, 1448s, 1400m, 1377m, 1336s, 1300m, 1271m, 1240s, 1167s, 1092m, 991s, 910w, 871w, 841m, 761s, 695s, 635w, cm^{-1}(KCl disc).

n.m.r.(pyridine) -2.5 and 0.09 (pyrrole N-H and amidic N-H), 7.24 and 7.48 (two methyl groups).

The possible structure of this compound is considered in the discussion.

Modified Knorr pyrrole synthesis using ethyl acetothiolacetate.

Ethyl acetothiolacetate.

Ethyl thiolacetate was prepared by the method of Baker and Reid[17], and converted to ethyl acetothiolacetate by the method of Cronyn et al [47]. The n.m.r. spectrum of the neat β-ketothiolester showed that about 28% of the enol form was present.

2,4-Dimethyl-3-ethylthiolcarbonyl-5-ethoxycarbonylpyrrole.

a) By a modified Knorr method as described by Treibs et al[48]. Ethyl acetoacetate (1.3g.) was dissolved in acetic acid (1.2ml.) and sodium nitrite (0.7g.) in water (minimum for solution) was slowly added with stirring. Stirring was continued for a further 4 hours at room temperature. The mixture was then neutralised with 20% sodium hydroxide solution, and ethyl acetothiolacetate (1.4g.) was added followed by sodium dithionite (2.6g.) in small portions, keeping the mixture at about 40° and neutral with 20% sodium hydroxide solution. The mixture was stirred at 40° for 1 hour and then made alkaline to phenolphthalein. After 12 hours crystals had separated out. The mixture was diluted with water and extracted with ether, the ether extracts were washed with water and dried (Na_2SO_4). Evaporation of the ether yielded a pale yellow gum which slowly crystallised.

The crystals were purified by recrystallisation from ethanol/water mixture, and were obtained a colourless needles (0.85g.,40%), m.p. 112-113°. This product was later found to be identical with that obtained where a zinc dust reducing agent was used (below), and which was identified as 2,4-dimethyl-3-ethylthiolcarbonyl-5-ethoxycarbonylpyrrole.

b) By a modified Knorr synthesis, and using a zinc dust reducing agent.

Ethyl acetoacetate (0.4g.) in acetic acid (0.9ml.) was treated slowly with sodium nitrite (0.22g.) in water (0.3ml.) at 5° with constant stirring. The pale yellow solution was allowed to stand for 1 hour, and then added dropwise to a stirred mixture of ethyl acetothiolacetate (0.41g.), acetic acid (1.4ml.) and zinc dust (0.6g.) at 60° rising to 100°. The yellow mixture was stirred at 100° for 90 minutes and then allowed to stand over night. It was then diluted with water and extracted with ether. The ether extracts were washed with sodium bicarbonate solution and water, dried ($MgSO_4$) and the ether was evaporated. The crystalline residue was recrystallised from chloroform/petrol (60-80° b.p.) yielding colourless needles of 2,4-dimethyl-3-ethyl-thiolcarbonyl-5-ethoxycarbonylpyrrole, (0.45g., 57%) m.p. 112-113°. Some of the product was sublimed (same m.p.) for analysis (100°/15mm.)

Anal. Calc. for $C_{12}H_{17}NO_3S$; C, 56.44; H, 6.71; N, 5.49;

S, 12.59%. Found: C, 56.14; H, 6.65; N, 5.37; S, 12.34%.

2,4-Dimethyl-3-ethyoxycarbonyl-5-ethylthiolcarbonylpyrrole.

The compound was made by method b) above, on the same scale. Here the ethyl aceto thiolacetate was nitrosated, and added to a mixture ethyl acetoacetate, acetic acid and zinc dust. The required pyrrole was obtained as very pale yellow needles from chloroform/petrol (60-80°b.p.), (0.51g., 60%). After sublimation (100°/15mm.) the product was obtained as colourless needles, m.p. 143-44°.

Anal. Calc. for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71, N, 5.49; S, 12.59% . Found: C, 56.26; H, 6.53; N, 5.60; S, 12.45%.

2,4-Dimethyl-3,5-diethylthiolcarbonylpyrrole.

This compound was obtained by method b) above, on the same scale. Ethyl acetothiolacetate was nitrosated and added to a mixture of ethyl acetothiolacetate, acetic acid and zinc dust. The pyrrole was obtained as pale yellow needles from chloroform/petrol (60-80° b.p.), (0.59g.,66%). After sublimation the product was obtained as colourless needles, m.p. 107-108°.

Anal. Calc. for $C_{12}H_{17}NO_2S$: C, 53.10; H, 6.32; N, 5.16% Found: C, 53.05; H, 6.23; N, 5.30%.

Desulphurisation of the thiolester analogues of Knorrs pyrrole.

2,4-Dimethyl-3-formyl-5-carbethoxypyrrole.

2,4-Dimethyl-3-ethylthiolcarbonyl-5-carbethoxypyrrole (56.7mg.) was desulphurised by the same method as was used for the desulphurisation of 2,4-dimethyl-5-ethylthiolcarbonylpyrrole, (see page 60). The 2,4-dimethyl-3-formyl-5-carbethoxypyrrole was obtained as colourless crystals m.p. 143-5°, lit.[67] 145° (40mg., 87%). The infrared spectrum was identical and the ultraviolet spectrum was similar to those published for 2,4-dimethyl-3-formyl-5-carbethoxypyrrole[50,54].

λ_{max} 240 and 279mμ (log ε_{max} 4.27 and 4.00), lit.[54]
λ_{max} 240 and 288mμ (log ε_{max} 4.35 and 4.00).

2,4-Dimethyl-3-carbethoxy-5-formylpyrrole.

2,4-Dimethyl-3-carbethoxy-5-formylpyrrole was desulphurised as in the previous experiment. The aldehyde was obtained as colourless crystals m.p. 164-5° (lit.[68] 165°). The product was identical in the infrared spectrum and similar in the ultraviolet spectrum to spectra published for 2,4-dimethyl-3-carbethoxy-5-formylpyrrole.

λ_{max} 299.5, 230 and 219mμ (log ε_{max} 4.32, 4.15 and 4.18)
lit.[68] λ_{max} 297, 228 and 220mμ (log ε_{max} 4.32, 4.15 and 4.19)

Attempted desulphurisation of 2,4-dimethyl-3,5-diethylthiolcarbonylpyrrole.

2,4-Dimethyl-3,5-diethylthiolcarbonylpyrrole was desulphurised by the same method as was used for the two previous experiments. The product obtained was however a mixture (as shown by n.m.r.) of desulphurisation products and possibly other further reduced compounds.

2,4-Dimethyl-3-acetyl-5-ethylthiolcarbonylpyrrole.

Ethyl acetothiolacetate was nitrosated and added to a mixture of acetylacetone, zinc dust and acetic acid by the method described on page 65. The product was isolated and recrystallised for ethanol/water mixture as colourless needles m.p. 121-122°. This compound was found to be identical in every way with that prepared by acetylation of 2,4-dimethyl-5-ethylthiolcarbonylpyrrole.

ν_{max} 3280s, 1666s, 1594s, 1562m, 1514m, 1257s, 1166m, 1090m, 1052w, 1016m, 982m, 951m, 786m, 770s cm^{-1}(nujol).

Trifluoroacetylation reactions.

All the trifluoroacetylation reactions were performed by the same method. The pyrrole was dissolved in trifluoroacetic anhydride and allowed to stand for 30 minutes. The red solution was then poured on to iced water, and the mixture extracted with ether. The ether extracts were washed with sodium bicarbonate solution and water. The extracts were then dried ($MgSO_4$) and the ether was evaporated, the residue was recrystallised from chloroform/petrol (60-80°b.p.). The trifluoroacetylated products were colourless, stable, crystalline compounds.

2-Methyl-3-trifluoroacetyl-5-ethoxycarbonylpyrrole. (m.p. 191-2°)

Anal. Calc. for $C_{10}H_{10}F_3NO_3$: C, 48.19; H, 4.04; N, 5.62; F, 22.88%. Found: C, 47.82; H, 3.97; N, 6.12; F, 20.70%.

2,4-Dimethyl-3-trifluoroacetyl-5-ethylthiolcarbonylpyrrole.

(m.p. 131-2°).

Anal. Calc. for $C_{11}H_{15}F_3NO_2S$: C, 47.31; H, 4.33; N, 5.02%

Found: C, 47.53; H, 4.30; N, 5.21%.

The products from the trifluoroacetylation of 2-carbomethoxy-pyrrole were: 2-trifluoroacetyl-5-carbethoxypyrrole m.p.118-9.5° and 2-carbethoxy-3-trifluoroacetylpyrrole m.p. 117-118°.

2,4-Dimethyl-3-formyl-5-ethylthiolcarbonylpyrrole.

2,4-Dimethyl-5-ethylthiolcarbonylpyrrole (1.67g.) was slowly added to an ice cold mixture of phosphorus oxychloride (1.56g.) and dimethyl formamide (4ml.). The red mixture was allowed to stand for one hour in ice and for two hours at room temperature. The dark red liquid was then added slowly to an ice cold sodium hydroxide solution (5N.). Most of the oil dissolved to give a red solution from which crystals soon began to separate. After about 5 minutes hydrochloric acid (5N.) was added to bring the solution to pH6. After a further 30 minutes the precipitate of creamy brown crystals was filtered off, washed with water and dried (silica gel). The 2,4-dimethyl-3-formyl-5-ethylthiolcarbonylpyrrole was recrystallised from chloroform/petrol (60-80°b.p.), colourless crystals m.p. 145-6.° (The corresponding methyl ester melted at 181-2°, and was prepared by the same method.)

$\tilde{\nu}_{max}$ 1676s, 1605s, 1560w, 1249s 1213w, 1126m, 1046w, 1000m, 958m, 829m, 779s, 725s cm^{-1}(nujol).

λ_{max} 308, 278, 238mμ (log ε_{max} 4.28, 4.07, 4.33)

Friedel and Crafts reactions,(In carbon disulphide).

The Friedel and Crafts reactions mentioned in the discussion were all performed using the same general method: 2-Methyl-5-carbethoxypyrrole (0.26g.) was dissolved in carbon disulphide (2ml.), and aluminium chloride (0.75g.) was added slowly with stirring and cooling. Ethyl chloroacetate (0.25g.) was added, the mixture boiled for a few moments, and then boiling was continued on a water bath for 30 minutes. Two layers were present in the mixture, one yellow (lower), and the other colourless. The reaction mixture was finally poured on to ice. The mixture was extracted with ether, the ether extracts were washed with water, dried ($MgSO_4$) and the ether was evaporated. The residue was chromatographed on acid alumina (Fischer), and most of the material proved to be 2-methyl-5-carbethoxypyrrole, however a little yellow crystalline material was sometimes obtained which contained sulphur (Lassaigne test).

The yellow compound was recrystallised from ethanol/water mixture, m.p. 167-8°. The compound also sublimed readily as yellow needles with the same melting point.

Anal. Calc. for $C_{11}H_{15}NO_2S_2$: C, 51.32; H, 5.87; N, 5.44%

Found ; C, 51.30; H, 5.77; N, 5.60%

2-Methyl-5-carbomethoxypyrrole also yielded a similar product m.p. 163-4°. Some spectra of these compounds are recorded in the spectra table below.

A Modified Gatterman-Hoesch reaction between methyl thiocyanate and 2-methyl-5-carbethoxypyrrole.

The method described on page 49 was repeated, substituting methyl thiocyanate for cyanoacetic ester. The residue obtained after most of the solvent had been blown off would not dissolve in water, but was successfully crystallised from an ethanol/water mixture. The product was obtained as colourless needles from chloroform m.p. 218-219°.

A Lassaigne test showed that the compound contained nitrogen and chlorine but no sulphur.

Anal. Found: C, 49.99; H, 5.65; N, 6.70; S, 0.22; Cl, 25.81%

n.m.r. (CH_2Cl_2) 3.08 doublet (ring proton), 5.80 quartet (methylene), 8.16 singlet (methyl), 8.44 singlet (methyl), 8.66 triplet (of methyl of ethyl ester).

λ_{max} 292 and 237mμ

The possible structure of this compound is discussed in the discussion.

Ultraviolet Spectra.

All spectra were run in methanolic solution unless otherwise indicated. Spectra indicated thus * were run in 95% ethanol. All spectra are recorded in mμ, and the figures enclosed in brackets refer to $\log \varepsilon_{max}$ for the absorption bands.

Substituent at position:				Band.		
2	3	4	5	B		K
Me	-	Me	C=NPh SEt	218(4.17)		320(4.13)
Me	-	Me	COSEt	247(3.71)		308(4.42)
Me	-	Me	COOEt	240(3.70)		276(4.29)
Me	-	Me	CHO	270(3.71)		304(4.34)
Me	-	-	COOEt	231(3.54)		277.5(4.30) *
Me	-	-	COSMe	238(3.67)		311.5(4.34) *
Me	-	-	COSEt	238(3.70)		310(4.39)
Me	-	-	CHO	248(3.55)		302(4.27)*
				A	B	K
$COCF_3$	-	-	COOMe	230		308
-	$COCF_3$	-	COOMe	225(4.46)	269(4.08)	297(4.16)
COMe	-	-	COOMe	219(4.07)		292(4.37)
-	COMe	-	COOMe	224(4.07)	244(4.04)	274(4.09)

Substituent at position:				Band			
2	3	4	5	A	B	K	
Me	COSEt	Me	COOEt	231(4.28)	247(4.16)	285.5(4.14)	
Me	COOEt	Me	COSEt	232(4.27)		302(4.35)	
Me	COSEt	Me	COSEt	237(4.26)		308(4.38)	
Me	COOEt	Me	COOEt	221(4.40)		273(4.21)	ref. 54*
Me	$COCF_3$	Me	COSEt	255(4.14)	281(4.14)	308(4.14)	
Me	CHO	Me	COSEt	238(4.33)	278(4.01)	308(4.28)	
Me	CHO	Me	COOEt	240(4.35)		288(4.00)	ref. 54*
Me	CHO	Me	COOEt	240(4.27)		279(4.00)	found*
Me	COOEt	Me	CHO	219(4.18)	230(4.15)	299.5(4.32)	found
Me	COOEt	Me	CHO	220(4.19)	228(4.15)	297(4.32)	ref. 54*
Me	COMe	Me	COOEt	235(4.36)	255(4.08)	283(4.07)	ref. 54*

m.p°	Substituent at position: 2	3	4	5	Band A	B		K
191-2	Me	$COCF_3$	-	COOEt	237(4.44)	255(4.10)		297(3.94)
194-5	Me	$COCF_3$	-	COSMe	241(4.22)	282.5(4.15)		307(4.20)
	Me	CHO	-	COOMe	232(4.29)	250(4.02)		286(4.08)*
	Me	CHO	-	COSMe	229(4.30)	272.5(4.04)		307(4.25)*
	Me	$CH=CHCOOC_2H_5$		COOEt	237(4.17)	274(4.11)	283(4.10)	323(4.38)*
	Me	.. ..		COSMe	243(4.18)	284(4.23)	293(4.22)	340(4.18)
	Me	COCOOEt	-	COOMe	239(4.27)			296(3.86)*
	Me	COCOOEt	-	COSMe	238(4.02)	288(4.07)		316(4.13)
	Me	COMe	-	COOMe	224(4.36)	261(4.05)		282(4.16)
168-9	Me	COMe	-	COSMe	228(4.36)	274(4.00)		305.5(4.33)
167-8	Me	CSSEt	-	COOEt	222	262		331

Melting points not included above are to be found in the experimental section, or are in the literature (ref. 59 particularly).

Nuclear Magnetic Resonance Spectra.

All spectra are recorded on the τ scale with a tetramethyl silane internal standard. The solvents are indicated as follows:-

A.....CH_2Cl_2

B.....$CHCl_3$

C.....$CDCl_3$

D.....CCl_4

E.....Pyridine

Where ethyl ester groups were present in the compound only the resonances of the methylene groups have been recorded.

	Substituent at position:				Proton resonance.			
	2	3	4	5	2	3	4	5
D	Me	H	H	COSMe	7.67	4.16	3.02	7.58
A	Me	H	H	COSEt	7.66	4.00	3.05	6.95(CH_2)
D	Me	H	H	C=NPh SMe	7.90	4.23	3.44	7.90
A	Me	$COCF_3$	H	COSMe	7.22	-	2.25	7.42
A	Me	COMe	H	COSMe	7.55	7.36	2.57	7.51
C	Me	COCOOEt	H	COOEt	7.29	5.51	2.44	5.59
E	Me	SO_3Me	H	CONHPh	7.48	7.24	-	-
A	Me	H	Me	C=NPh SEt	7.82	4.28	7.82	7.35
A	Me	COOEt	Me	COOEt	7.47	5.75	7.43	5.65
A	Me	COOEt	Me	COSEt	7.35	5.69	7.44	6.91
A	Me	COSEt	Me	COSEt	7.34	6.98	7.42	6.94
A	Me	COSEt	Me	COOEt	7.41	6.97	7.44	5.64
C	Me	CHO	H	COCMe	7.38	0.08	2.73	6.10
D	Me	H	H	COOMe	7.66	4.13	3.27	6.16
A	Me	$COCF_3$	H	COOEt	7.24	-	2.36	5.44
C	$COCF_3$	H	H	COOMe	-	2.98	3.15	6.15
C	H	$COCF_3$	H	COOMe	2.54	-	2.21	6.06
A	H	COMe	H	COOMe	2.67	7.56	2.39	6.10
A	COMe	H	H	COOMe	7.54	3.16	3.20	6.09
B	Me	COCOOEt	H	COOMe	7.34	5.58	2.50	6.10
C	Me	H	H	COOEt	7.68	4.05	3.16	5.68
A	Me	H	Me	COSEt	7.72	4.12	7.61	6.93
A	Me	CHO	Me	COSEt	7.43	0.00	7.34	6.90

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