Pyrroles and Related Compounds. Part XXVI.[1] Pyrrole β-Keto-esters

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Various attempts to synthesise β-keto-esters of pyrroles for use as model compounds, or as intermediates in chlorophyll synthesis, are described. Carboxylation of acetylpyrroles, using dialkyl carbonates or chloroformates, gave a variety of products, including a β-keto-ester and (unexpectedly) *N*-alkyl- as well as *N*-alkoxycarbonyl-pyrroles. Attempts to utilise pyrrylacetylenes were unsuccessful, as were direct acylation reactions with derivatives of malonic ester. The most successful approach involved the coupling of a pyrryl acid chloride with the sodium salts of monoalkyl monobenzyl (or mono-t-butyl) esters of malonic acid; the β-keto-diester thus obtained could then be converted (by hydrogenolysis or treatment with cold trifluoroacetic acid) into the desired β-keto-ester.

CHLOROPHYLLS-*a* (1) and -*b* (2) and bacteriochlorophyll each contain a β-keto-ester grouping associated with the so-called isocyclic ring in these compounds. The mode of formation of this ring has hitherto remained obscure, but Fischer [2] drew attention to the formal possibility that the propionate side-chain at position 6 could be transformed into a β-keto-acid before cyclisation. Jain and Kenner [3] later put forward a scheme for the biosynthesis of the isocyclic ring which involved oxidation of a propionic ester side-chain to give a β-keto-ester at position 6, followed by cyclisation. Model experiments [3] with pyrromethenes provided some support for this suggestion; for example, cyanoacetic ester underwent Michael addition to the central methine carbon atom of the tetramethylpyrromethene (3), and cyclisation onto one of the vacant β-positions, followed by oxidation, gave the tricyclic product (4). Other pyrromethenes also reacted with cyanoacetic ester at the methine carbon atom, but cleavage subsequently occurred, to give monopyrrolic derivatives such as (5).

More recently, we have synthesised porphyrins containing β-keto-ester side-chains and have studied their cyclisation to give analogues of the chlorophylls; [4,5]

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[1] Part XXV, A. H. Jackson, G. W. Kenner, and J. Wass, preceding paper.

[2] H. Fischer and A. Stern, 'Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, vol. IIii, 1940, p. 37.

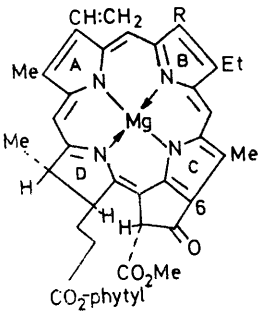
[3] (*a*) A. C. Jain and G. W. Kenner, *J. Chem. Soc.*, 1959, 185; (*b*) A. C. Jain, Ph.D. Thesis, Cambridge, 1957.

[4] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J. Amer. Chem. Soc.*, 1969, **91**, 1232.

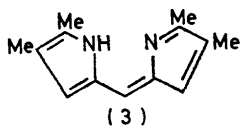
[5] G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Chem. Comm.*, 1972, 844.

these experiments are described in detail in the accompanying papers. This paper is concerned with preliminary experiments related to the synthesis of simple model pyrroles bearing β-keto-ester side-chains, and of fused cyclopentanopyrroles, which it was hoped might be used in the preparation of di- and tetra-pyrroles required for the synthesis of porphyrins related to the chlorophylls-*a* (1) and -*b* (2).

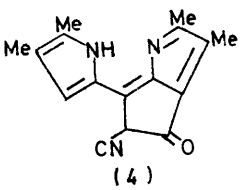
Claisen Condensation and N-*Alkylation of* β-*Acetylpyrroles.*—A number of different approaches to the synthesis of pyrroles with 3-oxopropionate ester side-chains in β-positions were investigated. Initially, the direct acylation of β-acetylpyrroles appeared to be a promising approach, because Dr. A. C. Jain had found that the β-acetylpyrroles (6a and b) condensed readily with diethyl oxalate in dioxan, in the presence of sodamide, to give the corresponding dioxobutyric esters (7a and b).* The structures of the products were confirmed originally by elemental analysis and i.r. spectra, and the u.v. and n.m.r. spectra later showed that they existed largely in the enolic form (8) in chloroform solution. In this connection it is interesting that the α-unsubstituted pyrroles (7a) and (8a) showed a much greater bathochromic shift in their long wavelength band (at 386 nm) in ethanol than the other compounds (7b) and (8b) (321 nm), although all of them manifested a



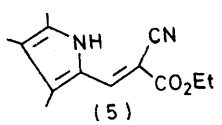
(1) R = Me
(2) R = CHO



(3)



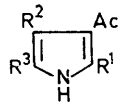
(4)



(5)

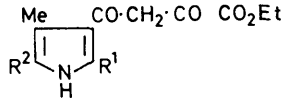
similar short wavelength maximum at 256 nm. The difference is probably attributable to the steric effect of the 2-methyl group in the second pyrrole preventing full conjugation of the enolic system in (8b) with the pyrrole nucleus by inhibiting coplanarity.

Dr. Jain also found that neither of the two acetylpyrroles (6a and b) could be condensed with ethyl formate under the conditions which had been successful with ethyl oxalate. Later, we found that these relatively unreactive β-acetylpyrroles would undergo Claisen-type condensations with diethyl carbonate in the presence of sodium hydride. The first successful experiment with



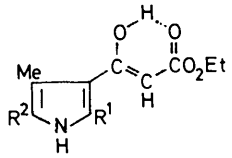
(6)

a; R^1 = H, R^2 = R^3 = Me
b; R^1 = R^2 = R^3 = Me
c; R^1 = R^2 = Me, R^3 = CO_2Et
d; R^1 = R^2 = Me, R^3 = H
e; R^1 = CO_2Et, R^2 = R^3 = Me



(7)

a; R^1 = H, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = Me, R^2 = CO_2Et



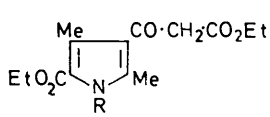
(8)

a; R^1 = H, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = Me, R^2 = CO_2Et

diethyl carbonate utilised the readily available ethyl 3-acetylpyrrole-5-carboxylate (6c), but the product was the triester (10), obtained in good yield, rather than the expected diester (9a). Some difficulty was experienced in obtaining reproducible yields of this triester (10) in later experiments (perhaps owing to differences in the quality of sodium hydride batches) and the products were sometimes tarry and had to be purified by chromatography; at no time was any indication of the diester (9a) apparent.

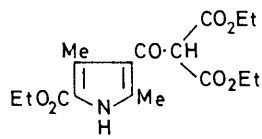
The structure of the triester (10) was proved by its elemental analysis and ^1H n.m.r. spectrum; the latter clearly showed it to be in the keto-form (10), unlike the oxalate condensation products mentioned above. A variety of attempts to effect partial hydrolysis of the triester to the diester (9a) failed, and only tars or starting material were recovered.

Condensations of other acetylpyrroles with diethyl and dimethyl carbonate in the presence of sodium hydride were also investigated. In most cases, mixtures of products



(9)

a; R = H
b; R = Me



(10)

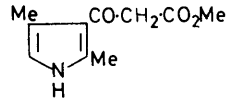
were obtained, and the desired β-keto-esters were not isolated. However, the acetylpyrrole (6d) with dimethyl carbonate did give a moderate yield of the oily keto-ester (11); the acetylpyrrole (6a) with diethyl

* Compound (7a) had previously been prepared by Fischer and Müller[6] by a similar procedure, using sodium ethoxide in ethanol as base, but the product was difficult to purify.

[6] H. Fischer and J. Müller, *Z. physiol. Chem.*, 1924, **132**, 102.

carbonate gave an oily product which was tentatively identified as the *N*-ethylpyrrole keto-ester (12) on the basis of its elemental analysis and i.r. spectrum. (An n.m.r. instrument was not available at the time of its preparation).

The formation of *N*-substituted pyrroles in these reactions was surprising because alkyl carbonates do not normally behave as alkylating agents, but the acetyltrimethylpyrrole (6b) gave the *N*-methyl derivative (13) with dimethyl carbonate and sodium hydride, and the acetyldimethylpyrrole (6d) with diethyl carbonate gave the *N*-ethylpyrrole (14). The structure of the latter was unambiguously confirmed both by its n.m.r. spectrum and by comparison with an authentic sample prepared by alkylation of the parent acetylpyrrole with the more conventional reagent, ethyl iodide, in the presence of potassium t-butoxide.



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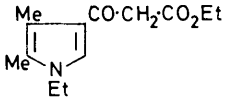

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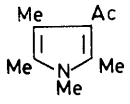

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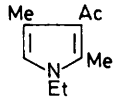
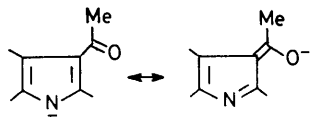


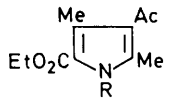
(14)

In view of these results, further studies of the Claisen condensation of β-acetylpyrroles seemed unlikely to be fruitful; the complexity of the products was attributed to the acidity of the pyrrole NH group being comparable to that of the hydrogen atoms of the acetyl group, and the former effect would inhibit acylation of the acetyl group because of the possibility of charge delocalisation of the anion [*e.g.* (15a) ⟷ (15b)]

The 4-acetylpyrrole (6c) was also titrated with the very strong base, sodium methylsulphonylmethanide, in the hope that the dianion might be formed. In the event, only one proton was removed (presumably from nitrogen, because alkylation occurred on nitrogen in the presence of weaker bases; see later) and when 2 equiv.



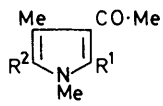
(15a) (15b)



(16)

a; R = CO_2Et
b; R = Me

of sodium methylsulphonylmethanide were added and the mixture treated with ethyl chloroformate, a small amount of the *N*-ethoxycarbonylpyrrole (16a) was obtained (as shown by t.l.c. and i.r. comparison with authentic material; see later). The *N*-methylacetylpyrrole (16b) also behaved as a monoacid upon titration with sodium methylsulphonylmethanide, presumably by removal of a proton from the acetyl group in this case, but after treatment with ethyl chloroformate only starting material was recovered. However, the three *N*-methyl-β-acetylpyrroles (16b), (17a), and (17b) gave the



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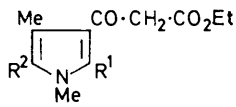
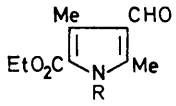


(18)

a; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H

keto-esters (9b), (18a), and (18b) upon treatment with the alkyl carbonate and sodium hydride.

These findings confirmed our supposition regarding the effect of the acidic NH grouping, and we therefore abandoned further work on the Claisen condensation of β-acetylpyrroles. We did, however, extend our studies to the *N*-alkylation of pyrroles, because an attempt to apply the Darzens glycidic ester synthesis (with ethyl bromoacetate and potassium t-butoxide) to the pyrrole aldehyde (19a) had afforded the *N*-acetate (19b). Earlier methods described for *N*-alkylation of pyrroles and indoles generally required the use of solid *N*-potassio-salts, or of sodamide in liquid ammonia, but in the present work, we used potassium t-butoxide in t-butyl



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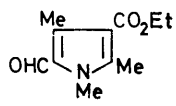
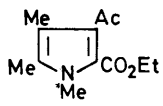


(20)

a; R = H
b; R = $CH_2 \cdot CO_2Et$
c; R = Me



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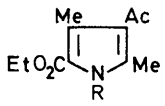


(22)

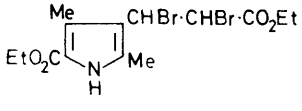
a; R = $CH_2 \cdot CO_2Et$ d; R = Et
b; R = CO_2Et e; R = Me
c; R = CH_2Ph

alcohol at 55—60° during 18—20 h, together with the appropriate alkyl halide.* In this manner, the *N*-methyl derivatives of the acetylpyrroles (6a—d), the *N*-ethyl derivatives of (6c and d), and the *N*-methylpyrroles (20) and (21) were also prepared. The acetylpyrrole (6c) gave the corresponding *N*-ethoxycarbonylmethylpyrrole (22a), *N*-ethoxycarbonylpyrrole (22b), and *N*-benzylpyrrole (22c) upon treatment with potassium t-butoxide and ethyl bromoacetate, ethyl chloroformate, or benzyl chloride, respectively.

* More recently we found that use of sodium methylsulphonylmethanide in dimethylsulphoxide (or dimethyl sulphoxide–tetrahydrofuran) is more convenient for this type of alkylation (A. H. Jackson and G. L. Jones, unpublished work).

Among other methods investigated for the synthesis of pyrrole β-keto-esters were the use of pyrrolylacetylenes, the direct acylation of pyrroles, and the reaction of pyrrole acid chlorides with alkyl malonates; the last of these proved to be the most promising and was later applied to the porphyrin series.

Pyrrolylacetylenes.—The pyrrole dibromoacrylate (23) was prepared in excellent yield by treatment of the parent acrylic ester with pyridine hydrobromide perbromide; this was found to be a much cleaner and more reliable method than the use of bromine in tetrahydrofuran. Fischer and Süs [7] had not been able to dehydrobrominate this compound with sodium hydroxide, nor did we succeed with potassium t-butoxide in t-butyl alcohol or dimethyl sulphoxide. However, with sodamide in liquid ammonia, a low yield of the desired propiolic



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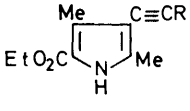
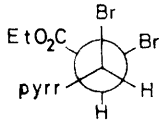
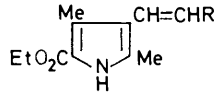


(24)

a; R = CO_2Et
b; R = H



(23a)



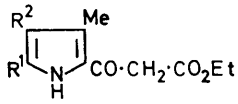
(25)

a; R = CO_2Et
b; R = CO_2H
c; R = Br

ester (24a) was obtained. The difficulty in effecting this reaction is probably due to (*a*) formation of the pyrrole anion through proton abstraction from nitrogen, and (*b*) to steric factors. [The starting acrylic ester (25a) presumably has the *trans*-configuration, and addition of bromine should occur in a *trans*-fashion, with the result that the conformation (23a) required for the usual *trans*-coplanar elimination of hydrogen bromide will be difficult to achieve, owing to the enforced juxtaposition of the four bulky groups.]

Attempts to hydrate the propiolic ester (24) to give the corresponding β-keto-ester (9a) by reaction with dimethylamine or piperidine (as described for the conversion of ethyl phenylpropiolate into the keto-ester) were unsuccessful.

An alternative approach involved bromination of the acrylic acid (25b) with pyridine hydrobromide perbromide in pyridine, but the product was the bromovinylpyrrole (25c) rather than the expected dibromo-derivative, perhaps produced by concomitant dehydrobromination and decarboxylation catalysed by the pyridine solvent. Treatment of the bromovinylpyrrole with sodamide in liquid ammonia then gave the desired pyrrolylacetylene (24b). The overall yields in this process were, however, too low for further elaboration of the side-chain to be considered, and this approach was therefore abandoned.



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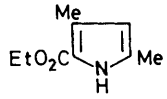

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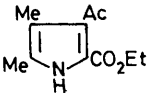


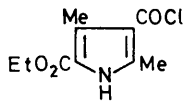
(28)

Acylation of Pyrroles.—Fischer [8a] has described the acylation of two pyrroles at an unsubstituted α-position by a Hoesch-type synthesis with ethyl cyanoacetate, to give keto-esters of structure (26). However, we failed to acylate the β-unsubstituted pyrrole (27) with cyanoacetic ester under the normal conditions of a Hoesch reaction and this may have been due to steric hindrance by the two neighbouring methyl groups.

A more promising reaction involved treatment of ethyl 4,5-dimethylpyrrole-2-carboxylate with the acid chloride of ethyl hydrogen malonate in the presence of boron trifluoride–ether. Apart from starting material, the only other substance isolated was the acylpyrrole (28) obtained in low yield; this must presumably have been formed by hydrolysis and decarboxylation of an intermediate keto-ester.

The first pyrrole β-keto-ester to be described in the literature [9] was prepared by treatment of the pyrrole Grignard reagent with ethyl chloroformylacetate, and application of this reaction to the pyrrole ester (27) gave the desired β-keto-ester (9a) in 10% yield. Use of the cadmium derivative of the pyrrole (in place of the Grignard derivative) gave no improvement in this yield.

Acylation of Malonic Esters.—In early experiments, the pyrrole acid chloride (29) reacted with the sodio-derivative of malonic ester, but not with the ethoxymagnesio-derivative; the product was the diacylpyrrole (30) rather



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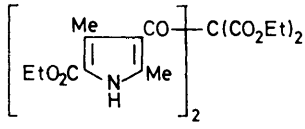

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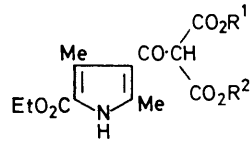
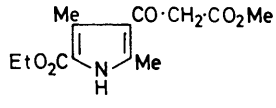
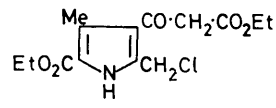


(31)

a; R^1 = Et, R^2 = CH_2Ph
b; R^1 = Me, R^2 = CH_2Ph
c; R^1 = Me, R^2 = Bu^t



(32)



(33)

than the expected keto-triester (10). Further studies showed that by use of an excess of sodiomalonate (5

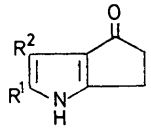
[7] H. Fischer and O. Süs, *Annalen*, 1930, **484**, 119.
[8] (*a*) H. Fischer and K. Schneller, *Z. physiol. Chem.*, 1923, **128**, 247; (*b*) H. Fischer and Z. Czukas, *Annalen*, 1934, **508**, 176.
[9] B. Oddo and A. Moschini, *Gazzetta*, 1912, **42** (II), 267.

equiv.), the undesired reaction was largely suppressed in favour of the desired keto-ester, which was obtained in 35—40% yield. The latter was identical with the material prepared by direct acylation of the acetylpyrrole (6c) with ethyl carbonate.

Acylation of benzyl ethyl, benzyl methyl, and methyl t-butyl malonic esters gave the corresponding pyrrylacyl malonates (31a—c) in comparable yields. By hydrogenation of the benzyl esters or treatment of the t-butyl ester with cold trifluoroacetic acid, the desired keto-esters (9a) and (32) were formed in excellent yield. The n.m.r. spectra of all these keto-esters showed that they existed in the keto-form, but all gave a strong wine-red colouration with iron(III) chloride, and formed salts with alkali. The keto-triesters (31) are, of course, strongly acidic, and this proved useful in separating these compounds from the excess of malonic esters used in their preparation. Both the triesters (31) and the dialkyl malonates form sodium salts, but the latter ones are hydrolysed sufficiently in water to allow the free esters to be extracted into ether preferentially (see Experimental section).

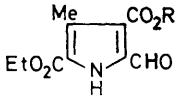
With the eventual aim of preparing pyrromethanes with keto-ester side-chains in mind, chlorination of the 5-methyl group of (9a) was investigated. Use of sulphuryl chloride gave oily products; t-butyl hypochlorite in ether at 2° gave a gummy mixture from which the crystalline chloromethyl derivative (33) was obtained in 17% yield. Further studies were discontinued in view of the low overall yield in the conversion of Knorr's pyrrole into (33), and because work in the porphyrin series was proving more successful.

Bicyclic Pyrrole Ketones.—In connection with the earlier work of Jain and Kenner,[3] reviewed briefly at the beginning of this paper, we also set out to synthesise bicyclic pyrrole ketones of general structure (34), which we hoped might be useful in the synthesis of pyrromethenes related to (4), and hence of porphyrins related to chlorophylls. The aldehyde (35) condensed with malonic acid, diethyl malonate, and ethyl cyanoacetate, to form the pyrryl acrylic acid derivatives (36a), (37a), and (38a), respectively; catalytic hydrogenation of these

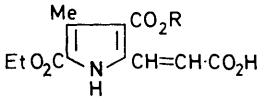


(34)

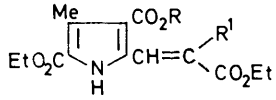
a; R = Et
b; R = CH_2Ph



(35)

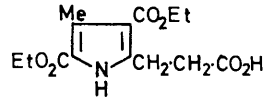


(36)

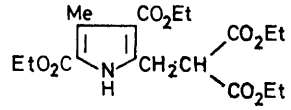


(37) $R^1 = CO_2Et$
(38) $R^1 = CN$

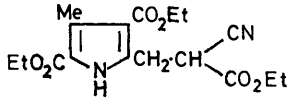
substances gave the corresponding propionic acid derivatives (39)—(41). Alkaline hydrolysis of the cyano-ester (41) and decarboxylation afforded the pyrrylpropionitrile (42). However, attempts to effect Claisen condensation between the 4-ethoxycarbonyl groups of (40)—(42) and the activated methylene group in the side-chain



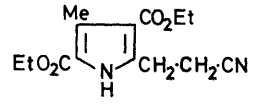
(39)



(40)

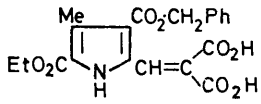


(41)

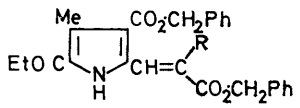


(42)

at the 5-position, failed under a variety of conditions. Steric hindrance to cyclisation is probably the major factor with the more acidic esters (40) and (41). An

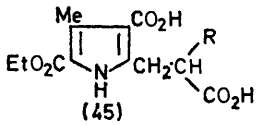


(43)



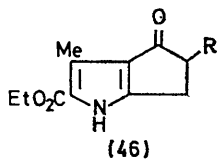
(44)

a; R = CN
b; R = CO_2CH_2Ph



(45)

a; R = CO_2H
b; R = CN



(46)

a; R = H
b; R = CN
c; R = CO_2Et

attempt to cyclise the propionic acid derivative (39) in polyphosphoric acid also failed, but in accord with this it was shown that concentrated sulphuric acid failed to facilitate hydrolysis of the 4-ethoxycarbonyl group in (40); in contrast, the corresponding β-ester group is readily hydrolysed in Knorr's pyrrole, under these conditions.[8b]

Attention was therefore turned to the use of the analogous 4-benzyloxycarbonylpyrroles, the benzyl groups of which could be removed by hydrogenolysis. The formyl benzyl ester (35b) condensed with malonic acid to give the dicarboxylic acid (43) rather than the acrylic acid (36b), but with diethyl malonate, ethyl cyanoacetate, benzyl cyanoacetate, and dibenzyl malonate, it gave the expected products (37b), (38b), (44a), and (44b), respectively.

Hydrogenation of the benzyl esters (43) and (44b) afforded the pyrroletricarboxylic acid (45a) which cyclised and underwent decarboxylation on heating in polyphosphoric acid, to give the cyclic ketone (46a) in low yield. The corresponding cyano-ketone was also prepared in low yield by an essentially similar route from

(44a) or (38b) *via* (45b), but attempts to synthesise the keto-ester (46c) were unsuccessful.

The bicyclic ketone (46a) was a colourless, crystalline compound, which gave a good elemental analysis and showed a carbonyl absorption band at 1710 cm^{-1} (Nujol); this value agrees well with that found [3] (1713 cm^{-1}) for the tricyclic ketopyrromethene (4) and with that ascribed (1700 cm^{-1}) [10] to the isocyclic carbonyl group in chlorophyll-*a*. The n.m.r. spectrum showed a singlet for the two methylene groups, presumably owing to a fortuitous coincidence of their chemical shifts.

Attempts to chlorinate the α-methylene group of the cyclic ketone (46a) gave only a very low yield of an impure derivative, and further experiments aimed at the synthesis of pyrromethanes and pyrromethenes related to (4) were therefore abandoned.

EXPERIMENTAL

N.m.r. spectra were determined on Varian A60 and HA-100 instruments and mass spectra on an A.E.I. MS9 spectrometer. U.v. spectra were measured on a Unicam SP 800 spectrophotometer.

4-Acetyl-2,3-dimethylpyrrole (6a).—This was prepared by condensation of 3-aminobutan-2-one with ethoxalylacetone followed by thermal decarboxylation of the intermediate pyrrole-5-carboxylic acid (m.p. 204°). The latter could also be decarboxylated by treatment with hydrochloric acid. The acetylpyrrole crystallised from ethanol as rods, m.p. 136—137° (lit.,[11] 137°), $\lambda_{max.}$ (EtOH) 282 (log ε 3·58) and 250 nm (4·11), τ ($CDCl_3$) 7·81, 7·73, and 7·58 (3Me), 2·68 (5-H), and *ca.* 0·56 (NH).

4-Acetyl-2,3,5-trimethylpyrrole (6b).—Prepared by reductive condensation of butan-2-one oxime and acetylacetone with zinc and acetic acid, this crystallised from ethanol as needles, m.p. 207—209° (lit.,[12] 207—209°), $\lambda_{max.}$ (EtOH) 298 (log ε 3·61) and 253 nm (4·01), τ ($CF_3{\cdot}CO_2H$) 7·72, 7·67, 7·21, and 7·04 (4Me).

3-Acetyl-2,4-dimethylpyrrole (6d).—Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate (20·9 g) was hydrolysed by heating under reflux for 2 h with methanolic potassium hydroxide (11·4 g in 150 ml of 25% v/v methanol–water). The methanol was removed by distillation and the ice-cold aqueous solution was acidified with sulphur dioxide, giving the 2-carboxylic acid (17 g, 94%) as a white solid. The latter was dissolved in 2-aminoethanol (10·5 g) and heated under reflux for 1 h. The dark brown solution was poured into ice–water (5 l), set aside overnight, and filtered. Recrystallisation from aqueous ethanol gave the pyrrole (11 g, 80%) as a light pink crystalline solid, m.p. 137° (lit.,[13] 137°), τ ($CDCl_3$) 7·44 (2-Me), 7·51 (4-Me), 7·66 (Ac), 3·5 (m, 5-H), and *ca.* 0·1br (NH).

Ethyl 3-Acetyl-4,5-dimethylpyrrole-2-carboxylate (6e).—Ethyl 4,5-dimethylpyrrole-2-carboxylate [14] (50 g) was dissolved in acetic anhydride (180 ml) at 50°, heated to 100° after addition of anhydrous tin(II) chloride (6 g) and stirred at 100° for 2 h. After cooling and storage overnight at 0° the acetylpyrrole (20 g) separated as pink needles and was filtered off and washed free of acetic anhydride with light petroleum (b.p. 60—80°). More (10·2 g) of the pyrrole was obtained by evaporation of the mother liquors followed by chromatography of the residue on alumina in benzene. Recrystallisation from benzene–light petroleum (b.p. 60—80°) gave light pink needles (27 g, 43%), m.p. 136° (lit.,[15] 137°), τ ($CHCl_3$) 5·68 (q) and 8·64 (t) (OEt), 7·99 (Ac), 7·79 (4-Me), 7·42 (5-Me), and 0·15br (NH).

Ethyl 4-(2,3-dimethylpyrrol-4-yl)-2,4-dioxobutyrate (8a).—4-Acetyl-2,3-dimethylpyrrole (3·2 g) in dioxan (50 ml) was added to a stirred suspension of sodamide (1·56 g) in dry dioxan (15 ml) followed by ethyl oxalate (7·8 g), and the mixture was boiled under reflux for 4 h. A voluminous, gelatinous precipitate separated out during this period and the mixture was poured on ice and acidified with acetic acid. The deep yellow precipitate was collected and crystallised from ethanol to give the *pyrrolyldioxobutyrate* (3·1 g) as long lemon prisms, m.p. 180° (lit.,[6] 180°) (Found: C, 60·3; H, 6·2; N, 5·9. Calc. for $C_{12}H_{15}NO_4$; C, 60·7; H, 6·3; N, 5·9%), $\lambda_{max.}$ (EtOH) 254 (log ε 3·73) and 311 nm (4·07).

Ethyl 3-(2,4-Dimethylpyrrol-3-yl)-2,4-dioxobutyrate.—Prepared in the same manner as the foregoing pyrrole, this formed yellow needles, m.p. 178° (lit.,[6] 179°) (Found: C, 60·8; H, 6·5; N, 6·0. Calc. for $C_{12}H_{15}NO_4$: C, 60·75; H, 6·4; N, 5·9%), τ ($CDCl_3$) 7·46 and 7·71 (2Me), 5·67 (q) and 8·62 (t) (OEt), 3·61 (m, 5-H), and 3·30 (CO·CH·CO).

Ethyl 4-(2,3,5-Trimethylpyrrol-4-yl)-2,4-dioxobutyrate (8b) (with Dr. A. C. Jain).—Prepared in the same manner as the foregoing pyrrole, from 4-acetyl-2,3,5-trimethylpyrrole and diethyl oxalate, this formed yellow *needles*, m.p. 179—180° (from ethanol) (Found: C, 62·1; H, 6·95; N, 5·85. $C_{13}H_{17}NO_4$ requires C, 62·15; H, 6·8; N, 5·6%), $\lambda_{max.}$ (EtOH) 255 (log ε 3·48) and 386 nm (4·05), τ ($CDCl_3$) 7·85, 7·79, and 7·47 (3Me), 5·61 (q) and 8·61 (t) (CO_2Et), and 3·26 (CO·CH·CO).

Ethyl 4-(2-Ethoxycarbonyl-3,5-dimethylpyrrol-4-yl)-2,4-dioxobutyrate (7c).—Prepared in the same manner as the three related pyrroles above, this crystallised from ethanol as yellow *needles*, m.p. 156—157° (Found: C, 58·2; H, 6·3; N, 4·5. $C_{15}H_{19}NO_6$ requires C, 58·2; H, 6·2; N, 4·5%), τ ($CDCl_3$) 7·42 (2Me), 5·78 (q) and 8·60 (t) ($2CO_2Et$), 3·29 (CO·CH·CO), and *ca.* 0·3br (NH).

Condensation of Acetylpyrroles with Diethyl and Dimethyl Carbonates.—(*a*) Ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate (6c) (5·0 g) was added to a suspension of sodium hydride (1·0 g) in freshly distilled diethyl carbonate (80 ml). A vigorous reaction occurred and the mixture was heated under reflux for 18 h. The solvent was evaporated off *in vacuo* and the oily brown residue treated with aqueous potassium dihydrogen phosphate (50 ml) and extracted with ether (3 × 80 ml). The extracts were dried ($MgSO_4$) and evaporated to dryness and the residual brown oil triturated with light petroleum (b.p. 60—80°). The brown partially crystalline solid formed was crystallised twice from aqueous ethanol and gave *ethyl 4-(bisethoxycarbonylacetyl)-3,5-dimethylpyrrole-2-carboxylate* (10) (3·1 g) as needles, m.p. 104—105° (Found: C, 57·5; H, 6·5; N, 4·0; OEt, 37·6. $C_{17}H_{23}NO_7$ requires C, 57·8; H, 6·6; N, 4·0; OEt, 38·2%), τ ($CDCl_3$) 5·65 (q), 5·72 (q) (2), 8·58 (t), and 8·70 (q) (2) ($3CO_2Et$), 7·44 and 7·46 (2Me), 4·89 (CO·CH), and −0·5 (NH).

In some later experiments difficulty was experienced in crystallising the final product even after chromatography, and t.l.c. showed it to be contaminated with several other

[10] J. W. Weigl and R. Livingstone, *J. Amer. Chem. Soc.*, 1953, **75**, 2173.
[11] O. Piloty and A. Blömer, *Ber.*, 1912, **45**, 3749.
[12] H. Fischer and E. Bartholomäus, *Z. physiol. Chem.*, 1915, **77**, 197.
[13] L. Knorr, *Ber.*, 1901, **35**, 3007.
[14] H. Fischer and E. Fink, *Z. physiol. Chem.*, 1948, **283**, 152.
[15] H. Fischer and W. Kutscher, *Annalen*, 1930, **481**, 201.

compounds including some starting material. With sodium ethoxide as catalyst in place of sodium hydride no reaction occurred and starting material was recovered; use of sodium metal led to intractable gummy products. When sodium hydride was used at lower temperatures or lithium hydride or sodamide at reflux temperature only starting material was recovered. Similar results were obtained with sodium methylsulphonylmethanide (2 equiv. in dimethyl sulphoxide) and diethyl carbonate at 80° for 5 h.

(*b*) 3-Acetyl-2,4-dimethylpyrrole (3·5 g) was added to a stirred suspension of sodium hydride (1·5 g) in diethyl carbonate (35 ml) and the mixture was heated under reflux for 7 h. After work-up as in (*a*) a crystalline product (2·3 g) was obtained, which t.l.c. showed was a mixture of starting material and a faster running compound. The latter was separated by chromatography in benzene on alumina; crystallisation gave 3-*acetyl*-1-*ethyl*-2,4-*dimethylpyrrole* (14) (40 mg) as needles, m.p. 84—86° (after sublimation at 80° and 1 mmHg) (Found: C, 72·6; H, 9·1; N, 8·5. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·2; N, 8·5%), τ ($CDCl_3$) 7·70 (Ac), 7·55 (4-Me), 7·49 (2Me), 6·12 (q) and 8·66 (t) (NEt), and 3·60 (5-H).

The experiment was repeated under a variety of conditions but products were often intractable oils and none of the desired keto-ester was found. The identity of the product was confirmed by its preparation by direct ethylation with ethyl iodide (see later).

(*c*) 4-Acetyl-2,3-dimethylpyrrole (6a) was condensed with diethyl carbonate in the presence of sodium hydride in a similar manner to the foregoing experiments and the product was distilled at 140° and 1 mmHg to give a yellowish oil in low yield tentatively identified as 4-*ethoxycarbonylacetyl*-1-*ethyl*-2,3-*dimethylpyrrole* (12) (Found: C, 66·1; H, 8·3; N, 6·3. $C_{13}H_{19}NO_3$ requires C, 65·8; H, 8·1; N, 5·9%); no NH or CO i.r. bands at 1590 or 1640 cm^{-1}; wine-red colouration with iron(III) chloride.

A similar product was also obtained with dimethyl carbonate (i.r. and t.l.c. evidence, *etc.*) but no further attempts were made to purify it.

(*d*) 3-Acetyl-2,4,5-trimethylpyrrole (6b) showed some evidence of reacting with diethyl carbonate in the presence of sodium hydride (i.r. and t.l.c.) but no pure products were obtained. However, in one experiment with dimethyl carbonate, 3-acetyl-1,2,4,5-tetramethylpyrrole (13) (15%), m.p. 75—76°, was obtained after fractional crystallisation from aqueous methanol and separation from starting material. It was identical with a sample prepared by direct methylation with methyl iodide and potassium t-butoxide (see later).

(*e*) Ethyl 4-acetyl-1,3,5-trimethylpyrrole-2-carboxylate (16b) (4·46 g, 0·02 mol) and sodium hydride (0·60 g, 0·025 mol) were suspended in dry diethyl carbonate (50 ml) and the stirred suspension was heated under reflux for 6 h. After cooling, the excess of diethyl carbonate was removed at 100° and 16 mmHg, and the light yellow residue was acidified with saturated potassium dihydrogen phosphate solution and extracted with ether (2 × 100 ml). The bulked extracts were washed with water and dried ($MgSO_4$). Evaporation, and trituration of the yellow oil with light petroleum (b.p. 60—80°) gave a light yellow amorphous solid which was chromatographed on alumina (Woelm; neutral grade III) (eluant benzene). Evaporation of the eluates gave a light yellow solid (3·9 g), which t.l.c. and n.m.r. showed to be the desired keto-ester contaminated with a small amount of starting material. Sublimation at 120° and 0·05 mmHg afforded the 3-*ethoxycarbonylacetyl*-1,2,4-*trimethylpyrrole* as nearly colourless needles, m.p. 57—59° (Found: C, 61·2; H, 7·1; N, 5·2. $C_{15}H_{21}NO_5$ requires C, 61·0; H, 7·2; N, 4·7%), τ ($CDCl_3$) 5·79 (q) and 8·72 (t) (CO_2Et), 7·79 and 7·54 (2Me), 6·54 (NMe), 6·24 ($CO{\cdot}CH_2{\cdot}CO_2$), and 3·74 (5-H).

(*f*) 4-Acetyl-1,3,5-trimethylpyrrole (17b) (2·2 g, 1 mol) and diethyl carbonate (30 ml) were treated with sodium hydride (0·8 g, 2·1 mol) in a similar manner to the previous reactions. After work-up and evaporation of the ether a brown oil (3·7 g) was obtained, which slowly solidified. The solid crystallised from light petroleum (b.p. 60—80°)–ether, to give 4-*ethoxycarbonylacetyl*-1,3,5-*trimethylpyrrole* (18b) (2·8 g, 88%). A portion sublimed at 100—105° and 0·03 mmHg gave needles, m.p. 56—58° (Found: C, 64·7; H, 7·7; N, 6·3. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·7; N, 6·3%), τ ($CDCl_3$) 5·79 (q) and 8·72 (t) (CO_2Et), 7·79 and 7·54 (2Me), 6·54 (NMe), 6·24 ($COCH_2$), and 3·74 (5-H).

(*g*) 4-Acetyl-1,2,3-trimethylpyrrole (17a) (5 g), sodium hydride (2 g, 1 mol), and diethyl carbonate (100 ml) were treated as in the foregoing experiment. Evaporation of the ethereal extract gave a brown oil (8·15 g), which was chromatographed on silica; elution with 30% ether–benzene (v/v) gave the 4-*ethoxycarbonylacetyl*-1,2,3-*trimethylpyrrole* (18a) (4·1 g, 55%) as a light yellow oil. A sample distilled at 120° and 1 mmHg (Found: C, 64·7; H, 7·7; N, 6·3. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·7; N, 6·3%) showed τ ($CDCl_3$) 5·85 (q) and 8·76 (t) (OEt), 7·92 and 7·80 (2Me), 6·49 (NMe), 6·35 ($CO{\cdot}CH_2$), and 2·82 (5-H).

N-*Alkylation of Pyrroles in the Presence of Potassium t-Butoxide.*—The pyrrole (0·02 mole) in t-butyl alcohol (50—100 ml) was heated to 60° and treated with a solution of potassium (0·022 g atom) in t-butyl alcohol (100 ml). After stirring for 2 h at 60° to complete formation of the *N*-potassio-salt, the alkyl halide (0·022 mol) was added and the mixture was heated and stirred for a further 18 h at 60°. The solvent was then removed under reduced pressure and the residual oil partitioned between water (200 ml) and ether or chloroform (2 × 200 ml). The organic extracts were washed with water, dried, and evaporated before chromatography on alumina in benzene (if necessary). The *N*-substituted pyrrole was usually the first compound to be eluted in benzene (monitoring by t.l.c.) and was crystallised from light petroleum (b.p. 60—80°) or aqueous ethanol.

The following *N*-substituted pyrroles were prepared from the *N*-unsubstituted analogues by using methyl iodide, ethyl iodide, benzyl chloride, ethyl bromoacetate, or ethyl chloroformate as appropriate.

Ethyl 1-*ethoxycarbonylmethyl*-4-*formyl*-3,5-*dimethylpyrrole*-2-*carboxylate* (19b) (75%) formed needles, m.p. 97° (from aqueous ethanol) and was purified by sublimation at 120° and 1 mmHg (Found: C, 59·9; H, 6·8; N, 5·0. $C_{14}H_{19}NO_5$ requires C, 59·8; H, 6·8; N, 5·0%), τ ($CDCl_3$) 5·67 (4H, q), 8·63 (t), and 8·70 (t) (2OEt), 7·50 and 7·42 (2Me), 4·94 ($N{\cdot}CH_2{\cdot}CO$), and 0·06 (CHO).

Ethyl 4-*acetyl*-1-*ethoxycarbonylmethyl*-3,5-*dimethylpyrrole*-2-*carboxylate* (22a) (46%) crystallised from light petroleum (b.p. 60—80°) as needles, m.p. 99—101° [starting material (30%) was also recovered by chromatography] (Found: C, 61·1; H, 7·4; N, 4·8. $C_{15}H_{21}NO_5$ requires C, 61·0; H, 7·2; N, 4·7%), τ ($CDCl_3$) 5·71 (q), 5·82 (q), 8·66 (t), and 8·72 (t) (2OEt), 7·60, 7·54, and 7·46 (3Me), and 5·03 ($N{\cdot}CH_2{\cdot}O$).

Ethyl 4-*acetyl*-1-*ethoxycarbonyl*-3,5-*dimethylpyrrole*-2-*carboxylate* (22b) (2%) crystallised from light petroleum as needles, m.p. 78—80° (Found: C, 60·0; H, 6·8; N, 5·3.

$C_{14}H_{19}NO_5$ requires C, 59·8; H, 6·8; N, 5·0%). This compound was also isolated in low yield by use of sodium methylsulphonylmethanide in dimethyl sulphoxide instead of potassium t-butoxide in t-butyl alcohol; τ ($CDCl_3$) 5·58 (q), 5·70 (q), 8·53 (t), and 8·66 (t) (2OEt), and 7·56, 7·56, and 7·47 (3Me).

Ethyl 4-formyl-1,3,5-trimethylpyrrole-2-carboxylate (70%) formed needles, m.p. 58—59° (Found: C, 62·9; H, 7·2; N, 7·0. $C_{11}H_{15}NO_3$ requires C, 63·1; H, 7·2; N, 6·7%), τ ($CDCl_3$) 5·69 (q) and 8·61 (t) (OEt), 7·49, 7·46, and 7·46 (3Me), 6·22 (NMe), and 0·10 (CHO).

Ethyl 4-acetyl-1,3,5-trimethylpyrrole-2-carboxylate (63%) formed needles, m.p. 66° (Found: C, 64·9; H, 7·6; N, 6·5. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·7; N, 6·3%), τ ($CDCl_3$) 5·71 (q) and 8·63 (t) (OEt), 7·55, 7·55, and 7·49 (3Me), and 6·26 (NMe).

Ethyl 2-formyl-1,3,5-trimethylpyrrole-4-carboxylate (20) (61%), m.p. 95—96°, was identical with a sample prepared by Corwin's procedure.[16]

Ethyl 3-acetyl-1,4,5-trimethylpyrrole-2-carboxylate (21) (66%), m.p. 46—47° (Found: C, 64·7; H, 7·8; N, 6·5. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·7; N, 6·3%), τ ($CDCl_3$) 5·78 (q) and 8·70 (t) (OEt), 8·05, 7·87, and 7·59 (3Me), and 6·43 (NMe).

Ethyl 4-acetyl-1-ethyl-3,5-dimethylpyrrole-2-carboxylate (58%), m.p. 44—46° (Found: C, 65·9; H, 8·1; N, 6·1. $C_{13}H_{19}NO_3$ requires C, 65·8; H, 8·1; N, 5·9%), τ ($CDCl_3$) 5·62 (q) and 8·63 (t) (OEt), 7·58, 7·55, and 7·50 (3Me), and 5·73 (q) and 8·73 (t) (NEt).

Ethyl 4-acetyl-1-benzyl-3,5-dimethylpyrrole-2-carboxylate (22c) (17%) had m.p. 50—51° (Found: C, 72·5; H, 7·0; N, 4·5. $C_{18}H_{21}NO_3$ requires C, 72·2; H, 7·1; N, 4·7%), τ ($CDCl_3$) 5·79 (q) and 8·78 (t) (OEt), 7·62 and 7·42 (2Me), and 4·46 and *ca.* 3·0 (m) ($PhCH_2$).

Ethyl 4-(2-Ethoxycarbonylvinyl)-3,5-dimethylpyrrole-2-carboxylate (25a).—Ethyl 3,5-dimethyl-4-formylpyrrole-2-carboxylate (12 g) and ethyl hydrogen malonate (11·5 ml) were dissolved in absolute ethanol (50 ml). Piperidine (12·3 ml) was added and the mixture was heated under reflux for 5 h. On removal of the solvents, the yellow mass obtained was acidified with dilute hydrochloric acid and extracted with ether (2 × 250 ml). The bulked extracts were washed with water and dried ($MgSO_4$). The residue obtained by evaporation was dissolved in the minimum quantity of benzene and chromatographed on silica (1 g of product to 30 g silica) [elution with ether–benzene (1 : 4 v/v)]. Evaporation gave the pyrryl acrylate (10·6 g, 68%) as needles, m.p. 138—140° (from ethanol) (lit.,[7] 134°), $\lambda_{max.}$ ($[CH_2]_4O$) 262 and 317 nm, τ ($CDCl_3$) 5·67, 5·76, 8·63, and 8·67 ($2CO_2Et$), 7·60 and 7·55 (2Me), 2·29 (d) and 3·94 (d) (*J* 16 Hz, CH:CH), and *ca.* 0·5 (NH).

Ethyl 4-(1,2-Dibromo-2-ethoxycarbonylethyl)-3,5-dimethylpyrrole-2-carboxylate (23).—The foregoing acrylic ester (4 g) was dissolved in tetrahydrofuran (50 ml) at 0° and treated with pyridine hydrobromide perbromide (4·9 g) in tetrahydrofuran (50 ml) over 5 min. The mixture was stirred at 0° for a further 15 min, and the tetrahydrofuran was removed at 35°. The residual solid was extracted with dry ether (100 ml); evaporation of the extract gave the dibromoacrylate (6·22 g, 97%), m.p. 110—115° (lit.,[7] 121°).

Ethyl (2-Ethoxycarbonyl-3,5-dimethylpyrrol-4-yl)propiolate (24a).—Sodium (0·7 g, 4 mol) was dissolved in liquid ammonia (300 ml) and ethanol (1·8 ml, 4 mol) was added. The crude dibromide (23) (3·0 g) was added and the mixture was stirred for another 4 h. The ammonia was evaporated off at 25—35° and 16 mmHg and the brown residue was extracted with water (200 ml) and ether (200 ml). Evaporation of the washed and dried ($MgSO_4$) ethereal extract gave the dibromide (0·57 g). The aqueous solution was acidified with sulphur dioxide and the precipitated acid filtered off. The acid (0·9 g) was esterified with diazoethane in ether, giving a light yellow solid, which was chromatographed on silica. The solid (0·4 g) obtained crystallised from ethanol–water and sublimed at 130° and 0·1 mmHg to give the *pyrrolylpropiolate* (0·3 g) as needles, m.p. 132—134° (Found: C, 61·7; H, 6·4; N, 5·1. $C_{14}H_{17}NO_4$ requires C, 63·9; H, 6·5; N, 5·3%), $\lambda_{max.}$ ($[CH_2]_4O$), 247 and 296 nm, τ ($CDCl_3$) 5·68, 5·73, 8·73, and 8·75 ($2CO_2Et$), 7·63 (2Me), and *ca.* 0·9 (NH).

Attempts to prepare this propiolic ester by dehydrobromination of the dibromoacrylate with potassium t-butoxide in t-butyl alcohol, sodium methylsulphonylmethanide, sodium ethoxide, *etc.*, gave mixtures of products in which only traces of the desired product were present (t.l.c.).

Ethyl 3-(2-Bromovinyl)-2,4-dimethylpyrrole-5-carboxylate (25c).—To 2-ethoxycarbonyl-3,5-dimethylpyrrole-4-acrylic acid (1·0 g) in pyridine (11 ml) was added pyridine hydrobromide perbromide (1·35 g, 1 equiv.) in pyridine (9 ml) over 15 min. After a further 30 min the solvent was removed *in vacuo* and the residue was treated with 2N-hydrochloric acid (50 ml) and chloroform (100 ml). The chloroform solution was extracted with 0·2N-sodium hydroxide (30 ml), washed with water, and dried ($MgSO_4$). Evaporation *in vacuo* gave the bromovinylpyrrole, which crystallised from aqueous ethanol as prisms (0·51 g, 45%), m.p. 151—153° (decomp.), raised by recrystallisation from aqueous ethanol to 156—157·5° (lit.,[7] 158°) (Found: C, 48·8; H, 5·2; N, 5·0. Calc. for $C_{11}H_{14}BrNO_2$: C, 48·55; H, 5·15; N, 5·15%), τ (pyridine) 5·75 (q) and 8·78 (t) (CO_2Et), 7·71 and 7·46 (2Me), and 3·45 (CH) (other CH obscured by solvent).

Ethyl 3-Ethynyl-2,4-dimethylpyrrole-5-carboxylate (24b).—Sodium (0·5 g, 6 equiv.) was dissolved in liquid ammonia (75 ml) containing a catalytic quantity of iron(III) nitrate. To the grey suspension was added ethyl 3-(2-bromovinyl)-2,4-dimethylpyrrole-5-carboxylate (1·0 g) over 15 min and the mixture was stirred under anhydrous conditions for 7 h. The flask was sealed with cellophane and the ammonia allowed to evaporate overnight at room temperature. Water (150 ml) was carefully added to the residue and the insoluble solid was filtered off, washed with water, and air-dried. The crude product was chromatographed and crystallised from aqueous ethanol to give the *ethynylpyrrole* (0·28 g, 45%) as feathery needles, m.p. 162—163° (Found: C, 68·25; H, 6·9. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85%), τ ($CDCl_3$) 5·68 (q) and 8·64 (t) (CO_2Et), 7·65 (s, 2Me), 6·82 (s, C:CH), and 0·8br (NH), $\nu_{max.}$ ($CHCl_3$) 2090 (C≡C) and 1666 cm^{-1}, $\nu_{max.}$ (Nujol) 2090 and 1656 cm^{-1}, *m/e* 191 (M^+).

Ethyl Chloroformylacetate.—Dry diethyl malonate (210 g) was dissolved in absolute ethanol (800 ml) and stirred during the addition (1 h) of potassium hydroxide (80 g) in absolute ethanol (800 ml). The solution was then stirred for a further 3 h and left at 25° overnight. It was heated to boiling, filtered hot to remove dipotassium salt, and cooled, thus precipitating the monopotassium salt (150 g, 70%) which was filtered off, washed with a little ether, and dried

[16] A. H. Corwin and J. H. Andrews, *J. Amer. Chem. Soc.*, 1936, **58**, 1086.

at 80° and 16 mmHg for 16 h. The potassium salt (106 g, 0·625 mol) was dissolved in water (60 ml), cooled to 0°, acidified with conc. hydrochloric acid (55 ml), and extracted with ether (4 × 250 ml); the bulked extracts were dried ($MgSO_4$). Evaporation gave ethyl hydrogen malonate (53·0 g, 64%) as a colourless liquid, b.p. 96—100° at 5 mmHg.

This acid (62 g) was added dropwise (30 min) to a stirred solution of phthaloyl chloride (150 g) at 100—110° (during the addition there was a vigorous evolution of hydrogen chloride), and stirring and heating were continued for another 2 h. The mixture was then cooled and distilled through a 15 cm Vigreux column at 16 mmHg under nitrogen and the distillate boiling below 75° was collected. This fraction was then redistilled and the acid chloride (70 g, 85%) was obtained as a light yellow oil, b.p. 70—72° at 16 mmHg.

Friedel–Crafts Reaction between Ethyl Chloroformylacetate and Ethyl 2,3-Dimethylpyrrole-5-carboxylate.—The pyrrole (4·2 g) was dissolved in methylene chloride (150 ml), a solution of the acid chloride (3·8 g) in methylene chloride (10 ml) was then added, and the whole was heated under reflux for 10 min. Boron trifluoride–diethyl ether (3·5 ml) in methylene chloride (50 ml) was then added over 30 min and the mixture was heated under reflux for a further 3 h. The solution was taken nearly to dryness, 95% ethanol (25 ml) was added, and the mixture was heated under reflux for 90 min, cooled, and extracted with ether (2 × 250 ml). The extracts were washed with water, dried ($MgSO_4$), and evaporated to leave a dark brown oil (4·0 g) which solidified. Chromatography on alumina (Woelm neutral; grade III), showed that this was a mixture of the starting pyrrole, some unidentifiable material, and a small amount (600 mg) of a light yellow crystalline compound, m.p. 138°. I.r. and n.m.r. spectra and a mixed m.p. determination showed that this was ethyl 4-acetyl-2,3-dimethylpyrrole-5-carboxylate.

Ethyl 3-(Ethoxycarbonylacetyl)-2,4-dimethylpyrrole-5-carboxylate (9a).—(*a*) Dry magnesium turnings (0·77 g, 1·1 equiv.) were suspended in dry ether (150 ml; distilled from lithium aluminium hydride) and a small crystal of iodine was added. Ethyl bromide (3·13 g, 1 equiv.) was added and after the initial reaction had subsided the mixture was heated under reflux for 30 min. Ethyl 3,5-dimethylpyrrole-2-carboxylate (4·8 g, 1 equiv.) was added in portions (after each addition a brisk effervescence occurred). The resultant clear solution was heated under reflux for 30 min. Ethyl chloroformylacetate (5·0 g, 1·15 equiv.) was then added over 15 min, during which time a solid separated, and the mixture was heated under reflux for 2 h. Water (150 ml) was added and the mixture was shaken until all the solid had dissolved. The ethereal solution was washed successively with aqueous 10% sodium hydrogen carbonate (3 × 100 ml) and water (100 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give a buff solid (4·8 g), which was chromatographed on alumina. Elution with benzene gave the starting pyrrole (3·8 g, 79%) and finally the *keto-ester* as an oil. The latter crystallised from benzene–light petroleum (b.p. 60—80°) to give feathery needles (0·75 g, 9%), m.p. 108—109° (Found: C, 59·7; H, 6·8; N, 5·1. $C_{14}H_{19}NO_5$ requires C, 59·8; H, 6·8; N, 5·0%), τ ($CDCl_3$) 5·78 (q), 5·63 (q), 8·72 (t), and 8·62 (t) (2OEt), 7·54 (s) and 7·52 (s) (2Me), 6·18 (s, $CO{\cdot}CH_2{\cdot}CO$), and 0·13br (NH), $\nu_{max.}$ ($CHCl_3$) 1730, 1680, and 1655 cm^{-1}, $\nu_{max.}$ (Nujol) 1730, 1670, and 1645 cm^{-1}, $\lambda_{max.}$ (MeOH) 238 (ε 25,300) and 285 nm (14,300), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 290 nm (31,400), *m/e* 209 [β-acetylpyrrole (6c)] (no M^+).

(*b*) Ethylmagnesium bromide was prepared as above from ethyl bromide (3·26 g) and magnesium (0·8 g) and dry benzene (200 ml; freshly distilled from phenylmagnesium bromide) was added. The ether was distilled off and ethyl 2,4-dimethylpyrrole-5-carboxylate (5·0 g) was added during 15 min. The resultant clear solution was heated under reflux for 1 h, then cooled; cadmium chloride (2·74 g) was added and the mixture was heated under reflux for 1 h. The cooled solution was decanted from the white solid and added to ethyl chloroformylacetate (4·6 g) in dry benzene (25 ml) over 15 min. After heating under reflux for 3 h, the mixture was worked up as above to give the keto-ester (0·7 g, 8·4%), m.p. 108—109°, and starting pyrrole (4·2 g, 84%).

(*c*) Ethyl 3-[benzyloxycarbonyl(ethoxycarbonyl)acetyl]-2,4-dimethylpyrrole-5-carboxylate (0·5 g) (see later) was dissolved in ethanol (30 ml) and 10% palladium–charcoal (0·05 g) and triethylamine (1 drop) were added. The solution was hydrogenated at room temperature and atmospheric pressure for 1 h. Filtration, evaporation, and crystallisation of the residue from benzene–light petroleum (b.p. 60—80°) gave feathery needles (0·29 g, 86%), m.p. 108—109°, identical (t.l.c. and spectra) with the product prepared by the previous methods.

Ethyl 3-Acetyl-2,4-dimethylpyrrole-5-carboxylate.—The cadmium derivative of ethyl 2,4-dimethylpyrrole-5-carboxylate (5·0 g) in dry benzene (200 ml), prepared as above, was added to acetyl chloride (2·5 g) in dry benzene (75 ml) over 10 min. The mixture was stirred and heated under reflux for 2 h, cooled, treated with 2N-hydrochloric acid (150 ml), and shaken vigorously. The benzene layer was separated and washed with aqueous 10% sodium hydrogen carbonate (100 ml) and water (2 × 100 ml), and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a buff solid mixture of the required product and the starting pyrrole (t.l.c.). These were separated by fractional crystallisation from methylene chloride to give the β-acetylpyrrole (3·05 g, 48%), m.p. 140—142° (lit.,[17] 143°), identical (t.l.c. and i.r.) with an authentic sample, and the starting pyrrole (1·98 g, 40%).

Acylation of Diethyl Malonate with Ethyl 4-Chlorocarbonyl-3,5-dimethylpyrrole-2-carboxylate.—(a) *Ethoxymagnesiomalonate in tetrahydrofuran.* Magnesium turnings (0·25 g) were washed with a little carbon tetrachloride and treated with dry ethanol (0·3 ml); the reaction was allowed to continue for 5 min at 25° and then dry tetrahydrofuran (10 ml) was added. The mixture was heated to its b.p., a mixture of ethanol (1 ml) and diethyl malonate (1·8 ml) in tetrahydrofuran (5 ml) was added, and the resulting mixture was heated under reflux until a clear solution was obtained. The solution was evaporated under reduced pressure, and dry benzene was added and then distilled off to remove the excess of ethanol and any water. The residual solid was dissolved in tetrahydrofuran (25 ml).

A solution of the chlorocarbonylpyrrole (29) (2·85 g) in tetrahydrofuran (40 ml) was then added and the mixture was heated under reflux for 1 h, cooled, acidified with dilute sulphuric acid, and extracted with ether (2 × 100 ml). The extract was washed with sodium carbonate solution and water, dried ($MgSO_4$) and evaporated to leave a brown amorphous solid (2·1 g), recrystallisation of which from light petroleum (b.p. 60—80°) gave diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate, m.p. and mixed m.p. 138°.

[17] H. Fischer, E. Baumann, and H. J. Riedl, *Annalen*, 1929, **475**, 238.

(b) *Diethyl Sodiomalonate* (2 *mol. equiv.*) *in tetrahydrofuran.* Diethyl malonate (2·4 g, 2 mol) was added to a stirred suspension of sodium hydride (0·35 g, 2 mol) in cold tetrahydrofuran (40 ml). The mixture was left for 15 min and then a cold solution of the chlorocarbonylpyrrole (29) (1·7 g, 1 mol) in tetrahydrofuran (30 ml) was added. The mixture was stirred for 15 min at 0°, then for 30 min at 25°, and acidified with ice-cold dilute hydrochloric acid under ether (100 ml). The ethereal extract was washed with very dilute sodium hydroxide solution, then with water, and dried ($MgSO_4$). Evaporation gave a white semicrystalline residue (1·05 g), which crystallised from absolute ethanol; chromatography on alumina (neutral; grade IV) in benzene followed by recrystallisation from ethanol gave *diethyl bis-(5-ethoxycarbonyl-2,4-dimethylpyrrol-3-ylcarbonyl)malonate* (30) (650 mg), m.p. 207—208° (Found: C, 58·9; H, 5·9; N, 5·2; OEt, 32·8. $C_{27}H_{34}N_2O_{10}$ requires C, 59·3; H, 6·3; N, 5·1; OEt, 33·0%), $\nu_{max.}$ (Nujol) 1729, 1720, and 1666 cm^{-1}, τ ($CDCl_3$) 7·71 (2), 7·53, and 7·51 (4Me), 5·5—5·1 (m) and 7·5—8·1 (m) ($3CO_2Et$), and 0·7 and 0·9br (2NH). The complexity of the spectrum probably arises as a result of steric interference.

In an experiment in which the preformed diethyl sodiomalonate was added slowly to the pyrrole acid chloride, similar results were obtained.

(c) *Diethyl sodiomalonate* (5 *mol. equiv.*) *in tetrahydrofuran.* To a stirred suspension of sodium hydride (1·04 g, 5 equiv.) in dry tetrahydrofuran (40 ml), diethyl malonate (6·95 g, 5 equiv.) was added over 5 min. After the brisk effervescence had ceased the solution was left under anhydrous conditions for 30 min, and 5-ethoxycarbonyl-2,4-dimethylpyrrole-3-carbonyl chloride (29) (2·0 g, 1 equiv.) in dry tetrahydrofuran (50 ml) was then added during 30 min. After a further 30 min the solvent was removed *in vacuo* and the residue was partitioned between ether (100 ml) and 2N-hydrochloric acid (50 ml). The ethereal solution was washed with 0·5N-sodium hydroxide (50 ml) and water (2 × 100 ml), and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residual oil was purified by chromatography on alumina. Elution with benzene–ether (4 : 1) gave ethyl 4-(bisethoxycarbonylacetyl)-2,4-dimethylpyrrole-2-carboxylate (10) as an amorphous solid which crystallised from benzene–petroleum (b.p. 40—60°) as prisms (1·1 g, 37%), m.p. and mixed m.p. 121—123°, identical (i.r. spectrum) with the sample prepared by acylation of the acetylpyrrole with diethyl carbonate.

Ethyl 3-[*Benzyloxycarbonyl(ethoxycarbonyl)acetyl*]-2,4-*dimethylpyrrole-5-carboxylate* (31a).—Sodium hydride (1·57 g, 5 equiv.) was suspended in dry tetrahydrofuran (20 ml) and to the stirred suspension was added benzyl ethyl malonate (14·5 g, 5 equiv.) in dry tetrahydrofuran (10 ml) over 15 min. After the brisk effervescence had ceased the solution was left under anhydrous conditions for 30 min, and 5-ethoxycarbonyl-2,4-dimethylpyrrole-3-carbonyl chloride (29) (3·0 g, 1 equiv.) in dry tetrahydrofuran (75 ml) was then added during 30 min. After a further 20 min the solvent was removed *in vacuo* and the residual oil was partitioned between ether (300 ml) and 2N-hydrochloric acid (200 ml). The ethereal solution was washed with aqueous 10% sodium hydrogen carbonate solution (2 × 100 ml) and water (2 × 200 ml), dried ($MgSO_4$), and evaporated to leave an oil which was chromatographed on alumina. Elution with benzene–ether (4 : 1) gave an oil which crystallised slowly at 0° from ether–petroleum (b.p. 40—60°) as *prisms* (1·5 g, 26·5%), m.p. 90·5—91·5° (Found: C, 62·8; H, 6·0; N, 3·45. $C_{22}H_{25}NO_7$ requires C, 63·6; H, 6·1; N, 3·4%), τ ($CDCl_3$ 5·65 (m), 8·75 (t), and 8·61 (t) (2OEt), 7·51 (s) and 7·45 (s) (2Me), 2·65 (s, Ph), and 0·42br (NH), $\nu_{max.}$ (Nujol) 1745 and 1660 cm^{-1}, $\lambda_{max.}$ (MeOH) 242 (ε 24,200) and 289 nm (12,500), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 283 nm (ε 27,700), *m/e* 415 (M^+).

Ethyl 3-[*Benzyloxycarbonyl(methoxycarbonyl)acetyl*]-2,4-*dimethylpyrrole-5-carboxylate* (31b).—Sodium hydride (2·56 g, 5 equiv.) was suspended in dry tetrahydrofuran (30 ml) and stirred, and benzyl methyl malonate (22·2 g, 5 equiv.) in dry tetrahydrofuran (20 ml) was added over 15 min. After the brisk effervescence had ceased the solution was left at room temperature for 30 min, and 5-ethoxycarbonyl-2,4-dimethylpyrrole-3-carbonyl chloride (29) (4·0 g, 1 equiv.) in dry tetrahydrofuran (150 ml) was then added during 1·5 h. The mixture was stirred for a further 1 h, the solvent was removed *in vacuo*, and the residual oil was partitioned between ether (300 ml) and 2N-hydrochloric acid (200 ml). The ethereal solution was washed with aqueous 10% sodium hydrogen carbonate (2 × 200 ml) and water (2 × 500 ml), dried ($MgSO_4$), and evaporated to leave an oil, which was chromatographed on alumina. Elution with benzene–ether (4 : 1) gave an oil comprising the required product and a small amount of some other material (the products had similar R_F values). The crude product was divided into two equal parts and one half was used directly in subsequent experiments. The remainder was dissolved in ether–petroleum (b.p. 40—60°); after several days crystals were deposited. The *product* (31b) crystallised from benzene to give *prisms*, m.p. 112—113° (Found: C, 62·7; H, 6·0; N, 3·5. $C_{21}H_{23}NO_7$ requires C, 62·8; H, 5·8; N, 3·5%), τ ($CDCl_3$) 5·67 (q) and 8·64 (t) (OEt), 7·56 (s) and 7·50 (s) (2Me), 4·77 (s) and 2·72 (s) ($PhCH_2$), and 0·25br (NH), $\nu_{max.}$ (Nujol) 1760, 1740, and 1655 cm^{-1}, $\lambda_{max.}$ (MeOH) 242 (ε 27,100) and 288 nm (17,000), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 282 nm (ε 29,300), *m/e* 401 (M^+).

Ethyl 3-[*Methoxycarbonyl(t-butoxycarbonyl)acetyl*]-2,4-*dimethylpyrrole-5-carboxylate* (31c).—Sodium hydride (0·6 g, 6 equiv.) was suspended in dry tetrahydrofuran (20 ml), and methyl t-butyl malonate (4·5 g, 6 equiv.) in dry tetrahydrofuran (40 ml) was added over 15 min to the stirred suspension. After the brisk effervescence had ceased the suspension was left at room temperature for 30 min. 5-Ethoxycarbonyl-2,4-dimethylpyrrole-3-carbonyl chloride (29) (1·0 g, 1 equiv.) in dry tetrahydrofuran (10 ml) was added with stirring over 1·5 h and the mixture was stirred for a further 60 min. The solvent was removed *in vacuo* and the residual semi-solid was partitioned between ether (250 ml) and water (250 ml). The aqueous layer was separated and acidified with 2N-hydrochloric acid in the presence of ether (100 ml). The ethereal solution was washed with N-sodium carbonate (2 × 50 ml) and water, dried ($MgSO_4$), and evaporated and the *product* crystallised from methylene chloride–petroleum (b.p. 40—60°) as prisms (0·56 g, 35%), m.p. 134—136·5° (Found: C, 59·1; H, 6·9; N, 3·6. $C_{18}H_{25}NO_7$ requires C, 58·8; H, 6·9; N, 3·8%), τ ($CDCl_3$) 5·67 (q) and 8·65 (t) (OEt), 7·49 (s) and 7·45 (s) (2Me), 8·55 (s, OBu^t), 6·23 (s, OMe), 4·98 (s, CH·CO), and 0·16br (NH), $\nu_{max.}$ (Nujol) 1750, 1730, and 1675 cm^{-1}, $\lambda_{max.}$ (MeOH) 241 (ε 23,900) and 288 nm (11,800), $\lambda_{max.}$ 0·1M-(NaOMe—MeOH) 283 nm (ε 28,400), *m/e* 367 (M^+).

Ethyl 3-(*Methoxycarbonylacetyl*)-2,4-*dimethylpyrrole-5-carboxylate* (32).—(*a*) To the crude malonate (31b) (2·18 g) dissolved in tetrahydrofuran (50 ml) were added 10% palladium–charcoal (0·21 g) and triethylamine (2 drops).

The solution was hydrogenated at room temperature and atmospheric pressure for 1 h. Filtration, evaporation, trituration of the residual oil with ether, and recrystallisation from benzene–petroleum (b.p. 60—80°) gave needles (0·65 g), m.p. 133·5—134·5° [overall yield 24% from the pyrrole acid chloride (29)] (Found: C, 58·4; H, 6·4; N, 5·2. $C_{13}H_{17}NO_5$ requires C, 58·7; H, 6·4; N, 5·1%), τ $CDCl_3$ 5·65 (q) and 8·62 (t) (OEt), 7·47 (s) and 7·43 (s) (2Me), 6·16 (s) and 6·23 (s) ($CO{\cdot}CH_2{\cdot}CO$), and 0·16br (NH), $\nu_{max.}$ ($CHCl_3$) 1735, 1675, and 1655 cm^{-1}, $\nu_{max.}$ (Nujol) 1735, 1660, and 1640 cm^{-1}, $\lambda_{max.}$ (MeOH) 238 (ε 21,100) and 285 nm (10,700), $\lambda_{max.}$ (0·1M-NaOMe–MeOH) 290 nm (ε 26,900), *m/e* 267 (M^+).

(*b*) Ethyl 3-[methoxycarbonyl(t-butoxycarbonyl)acetyl]-2,4-dimethylpyrrole-5-carboxylate (31c) (40 mg) was dissolved in trifluoroacetic acid (0·5 ml) and left at room temperature for 30 min. The solvent was removed *in vacuo* and the residual oil crystallised from ether to give needles (24 mg, 78%), m.p. 132—134°, identical (i.r. and t.l.c.) with the sample prepared by the previous method.

Ethyl 2-Chloromethyl-3-(2-ethoxycarbonylacetyl)-4-methylpyrrole-5-carboxylate (33).—Ethyl 3-(2-ethoxycarbonylacetyl)-2,4-dimethylpyrrole-5-carboxylate (9a) (0·3 g) was dissolved in dry ether and cooled to *ca.* 2°. t-Butyl hypochlorite (0·184 g, 0·202 ml, 1·4 equiv.*) in ether (10 ml) was added with stirring during 5 min, and the mixture was stirred for a further 30 min under anhydrous conditions. The solvent was removed *in vacuo*; the residual orange gum crystallised from benzene–petroleum (b.p. 60—80°) as feathery needles (56 mg, 17%), m.p. 148—152° (raised to 154·5—156° by recrystallisation), τ ($CDCl_3$) 5·67 (q), 5·65 (q), 8·62 (t), and 8·58 (t) (2OEt), 7·37 (s, Me), 6·11 (s, $CO{\cdot}CH_2{\cdot}CO$), 5·02 (s, CH_2Cl), and 0·27br (NH), $\nu_{max.}$ (Nujol) 1720 and 1665 cm^{-1}.

Diethyl 5-(2-Carboxyethyl)-3-methylpyrrole-2,4-dicarboxylate (39).—Diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate was chlorinated with sulphuryl chloride by Fischer's method,[18] but with dry chloroform as solvent at 10° rather than ether, and the 5-dichloromethyl derivative was hydrolysed directly to the 5-formylpyrrole (35a) (80%), m.p. 124°. The latter was condensed with malonic acid in presence of aniline, and the resulting pyrrole-5-acrylic acid (36a) was obtained as yellow needles (25%), m.p. 240—244° (decomp.) (lit.,[16] 244°) after Soxhlet extraction of the crude product with acetone. The acrylic acid was hydrogenated in methanol over 10% palladium–charcoal to give the pyrrolylpropionic acid (39) (65%) as needles, m.p. 216° (from methanol) (lit.,[19] 209°). Attempts to convert this material into a cyclic ketone by heating for 1 h in polyphosphoric acid at 100° gave an intractable brown solid after pouring the mixture into water, even though, as expected, considerable evolution of carbon dioxide was observed during the heating period.

Dibenzyl 5-Formyl-3-methylpyrrole-2,4-dicarboxylate.—Sulphuryl chloride (6 g, 2·2 equiv.) was added dropwise to a solution of dibenzyl 3,5-dimethylpyrrole-2,4-dicarboxylate (9 g, 1 equiv.) in dry chloroform (80 ml) cooled to 10°. The mixture was left overnight at 20°, then evaporated, and the oily orange residue was dissolved in warm ethanol. Water was added to the hot solution until it was just turbid, and on cooling a pale yellow solid separated. This was recrystallised from aqueous ethanol to give the *formylpyrrole* (5·6 g, 60%) as plates, m.p. 136—137° (Found: C, 69·7; H, 5·0; N, 3·6. $C_{22}H_{19}NO_5$ requires C, 70·0; H, 5·1; N, 3·7%).

Diethyl 5-(2-Cyano-2-ethoxycarbonylvinyl)-3-methylpyrrole-2,4-dicarboxylate (38a).—(*a*) The foregoing 5-formylpyrrole was condensed with ethyl cyanoacetate in ethanol in the presence of diethylamine according to Fischer and Neber's procedure,[20] and gave the acrylic ester as lemon yellow needles, m.p. 129° [from light petroleum (b.p. 60—80°)] (25—40%) (Found: C, 58·7; H, 5·7; N, 7·85. Calc. for $C_{17}H_{20}N_2O_6$: C, 58·6; H, 5·8; N, 8·0%).

(*b*) Cope's method [21] for this type of condensation gave higher and more reliable yields. The pyrrole aldehyde (5 g) was heated under reflux in benzene (50 ml) with ethyl cyanoacetate (2·5 g), ammonium acetate (0·4 g), and glacial acetic acid (0·2 ml) (Dean–Stark head). After 4 h the benzene was evaporated off *in vacuo* and the orange-red residue was chromatographed on alumina in benzene–light petroleum (b.p. 60—80°). The yellow eluates afforded the pyrrole cyanoacrylate (68%) as yellow needles, m.p. 129° [from light petroleum (b.p. 60—80°)].

The following pyrrole acrylic esters were also prepared by method (*b*) from the appropriate 5-formylpyrrole and diethyl malonate, dibenzyl malonate, ethyl cyanoacetate, or benzyl cyanoacetate. Yields were consistently 60—70%, and the products were crystallised from light petroleum (b.p. 60—80°), chromatography not usually being necessary. *Diethyl 5-(2,2-bisethoxycarbonylvinyl)-3-methylpyrrole-2,4-dicarboxylate* (37a) formed pale orange needles, m.p. 48° (Found: C, 57·6; H, 6·3; N, 3·6. $C_{19}H_{25}NO_8$ requires C, 57·7; H, 6·4; N, 3·5%). *Ethyl 4-benzyloxycarbonyl-5-(2,2-bisethoxycarbonylvinyl)-3-methylpyrrole-2-carboxylate* formed pale yellow needles, m.p. 76—77° (Found: C, 62·9; H, 6·15; N, 3·3. $C_{24}H_{27}NO_8$ requires C, 63·0; H, 5·95; N, 3·1%). *Ethyl 4-benzyloxycarbonyl-5-(2,2-bisbenzyloxycarbonylvinyl)-3-methylpyrrole-2-carboxylate* formed pale yellow needles, m.p. 64—65° (Found: C, 70·4; H, 5·5; N, 2·1. $C_{34}H_{31}NO_8$ requires C, 70·2; H, 5·4; N, 2·4%), τ ($CDCl_3$) 7·45 (Me), 5·68 (q) and 8·63 (t) (OEt), 4·82, 4·74, 4·74, and 2·75br (OCH_2Ph), 1·37 (CH), and *ca.* −2·0 (NH). *Dibenzyl 5-(2,2-bisbenzyloxycarbonylvinyl)-3-methylpyrrole-2,4-dicarboxylate* formed pale yellow needles, m.p. 82° (Found: C, 72·7; H, 5·2; N, 2·1. $C_{39}H_{33}NO_8$ requires C, 72·8; H, 5·2; N, 2·2%). *Ethyl 4-benzyloxycarbonyl-5-(2-cyano-2-ethoxycarbonylvinyl)-3-methylpyrrole-2-carboxylate* (38b) formed pale yellow needles, m.p. 117° (Found: C, 64·1; H, 5·4; N, 6·8. $C_{22}H_{22}N_2O_6$ requires C, 64·4; H, 5·4; N, 6·8%), τ ($CDCl_3$) 7·44 (Me), 5·65 (q), 5·69 (q), 8·61 (t), and 8·65 (t) (2OEt), 4·68 and 2·63 (m) (OCH_2Ph), 1·06 (CH), and *ca.* −0·7 (NH).

Attempted Preparation of Ethyl 4-Benzyloxycarbonyl-5-(2-carboxyvinyl)-3-methylpyrrole-2-carboxylate (36b).—The 5-formylpyrrole was refluxed in absolute ethanol with malonic acid and redistilled aniline. However, owing to the occurrence of transesterification under these conditions, the benzyloxycarbonyl group was replaced by an ethoxycarbonyl group, and the product was entirely the 2-(2-carboxyvinyl)-3,5-bisethoxycarbonyl-4-methylpyrrole (36a).

Ethyl 4-Benzyloxycarbonyl-5-(2,2-dicarboxyvinyl)-3-methylpyrrole-2-carboxylate (43).—The 5-formylpyrrole (2·5 g) was treated with malonic acid (2·3 g, 2 mol. equiv.) and piperid-

* When 1 equiv. was used, the product was contaminated by the starting pyrrole; separation, by fractional crystallisation, was difficult and resulted in a lower yield of the required product.

[18] H. Fischer and P. Halbig, *Annalen*, 1926, **447**, 137.
[19] H. Fischer and A. Schörmuller, *Annalen*, 1930, **472**, 249.
[20] H. Fischer and M. Neber, *Annalen*, 1932, **496**, 10.
[21] A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.

ine (0·2 ml) in dry pyridine at 100° for 90 min. The solution turned deep red, and carbon dioxide was evolved. The solution was boiled for 10 min, and then poured into a large volume of dilute hydrochloric acid. The yellow solid was filtered off and dissolved in 2N-sodium hydroxide; the solution was filtered and treated with dilute hydrochloric acid. After washing with water, the deposited pyrrole (2·0 g, 65%) was recrystallised from acetone, giving deep yellow *needles*, m.p. 218—219° (Found: C, 60·0; H, 4·95; N, 3·6. $C_{20}H_{19}NO$ requires C, 59·85; H, 4·8; N, 3·5%).

Diethyl 5-(2,2-*Bisethoxycarbonylethyl*)-3-*methylpyrrole*-2,4-*dicarboxylate* (40).—The 5-acrylic ester (37a) (10 g) was hydrogenated at 1 atm and 20° in methanol (25 ml) over 10% palladium–charcoal (100 mg). Catalyst and solvent were removed and the residue was recrystallised from light petroleum to give the *pyrrole* (0·60 g, 60%) as needles, m.p. 87—89° (Found: C, 57·35; H, 6·9; N, 3·4. $C_{19}H_{27}NO_8$ requires C, 57·4; H, 6·85; N, 3·5%), τ ($CDCl_3$) 7·46 (Me), 6·55 (d) and 6·21 (q) (CH_2·CH), 5·6—6·0 (m), 8·65 (t), and 8·77 (t) (4OEt), and *ca.* 0·4 (NH).

An attempt to hydrolyse the 4-ester group selectively with concentrated sulphuric acid led only to recovery of starting material.

Diethyl 5-(2-*Cyano*-2-*ethoxycarbonylethyl*)-3-*methylpyrrole*-2,4-*dicarboxylate* (41).—This was prepared (62%) from the corresponding cyanoacrylic ester (38a) by hydrogenation in ethyl acetate over palladium–charcoal, and crystallised from light petroleum (b.p. 60—80°) as fluffy *needles*, m.p. 96° (Found: C, 58·3; H, 6·4; N, 8·15. $C_{17}H_{22}N_2O_6$ requires C, 58·3; H, 6·3; N, 8·0%).

Ethyl 4-*Carboxy*-5-(2,2-*dicarboxyethyl*)-3-*methylpyrrole*-2-*carboxylate* (45a).—(*a*) The unsaturated tribenzyl ester (44b) (3·0 g) was hydrogenated in methanol–ethyl acetate (60 ml) over 10% palladium–charcoal at 20° and 1 atm. Catalyst and solvent were removed and the residual solid was crystallised from aqueous methanol to give the *tricarboxylic acid* (1·0 g, 57%) as tiny needles, m.p. 220° (Found: C, 49·7; H, 4·9; N, 4·5. $C_{13}H_{15}NO_8$ requires C, 49·8; H, 4·8; N, 4·5%).

(*b*) The 4-benzyloxycarbonyl-5-(2,2-dicarboxyvinyl)pyrrole (43) gave the same product (77%) on catalytic hydrogenation in ethyl acetate; m.p. and mixed m.p. 220°.

Ethyl 4-*Carboxy*-5-(2-*carboxy*-2-*cyanoethyl*)-3-*methylpyrrole*-2-*carboxylate* (45b).—This was prepared (70%) from the 4-benzyloxycarbonyl-5-(2-benzyloxycarbonyl-2-cyanovinyl)pyrrole (44b) by catalytic hydrogenation over palladium–charcoal; m.p. 250° (from aqueous methanol) (Found: C, 53·35; H, 4·6; N, 9·8. $C_{13}H_{14}N_2O_6$ requires C, 53·1; H, 4·8; N, 9·5%).

This diacid was also prepared by partial hydrolysis of ethyl 4-carboxy-5-(2-cyano-2-ethoxycarbonylethyl)-3-methylpyrrole-2-carboxylate with sodium hydroxide (2 equiv.) in 50% aqueous ethanol by heating under reflux for 1 h. After removal of most of the solvent the solution was made just acid with dilute hydrochloric acid. The precipitate was filtered off and crystallised from aqueous methanol to give tiny needles, m.p. 250°, identical with the former product.

Ethyl 4-*Carboxy*-5-(2-*cyano*-2-*ethoxycarbonylethyl*)-3-*methylpyrrole*-2-*carboxylate*.—This was prepared from the 4-benzyl ester by hydrogenation in ethyl acetate–methanol. Crystallisation from aqueous methanol gave the 4-*carboxypyrrole* (92%) as tiny needles, m.p. 217° (Found: C, 55·75; H, 5·5; N, 8·5. $C_{15}H_{18}N_2O_6$ requires C, 55·9; H, 5·6; N, 8·7%).

Ethyl 5-(2,2-*Bisethoxycarbonylethyl*)-4-*carboxy*-3-*methylpyrrole*-2-*carboxylate*.—This was prepared (74%) like the foregoing pyrrole and crystallised from aqueous methanol as *needles*, m.p. 153° (Found: C, 56·0; H, 6·2; N, 3·8. $C_{17}H_{23}NO_8$ requires C, 55·3; H, 6·3; N, 3·8%).

Diethyl 5-(2-*Carboxy*-2-*cyanoethyl*)-3-*methylpyrrole*-2,4-*dicarboxylate*.—The 5-(2-ethoxycarbonyl-2-cyanoethyl)pyrrole (41) (0·5 g) was boiled under reflux with sodium hydroxide (0·06 g, 1 equiv.) in methanol (8 ml) and water (8 ml) for 6 h. Dilute hydrochloric acid was then added and the flocculent white precipitate was filtered off and crystallised from aqueous methanol to give tiny *needles* (0·45 g, 90%), m.p. 200° (decomp.) (Found: C, 55·8; H, 5·5; N, 8·5. $C_{15}H_{18}N_2O_6$ requires C, 55·9; H, 5·6; N, 8·7%).

Diethyl 5-(2-*Cyanoethyl*)-3-*methylpyrrole*-2,4-*dicarboxylate* (42).—The foregoing carboxylic acid was heated to its m.p. and maintained at 200—205° until effervescence ceased. The residual oil was cooled, and crystallised from aqueous ethanol to afford the *cyanoethylpyrrole* (40%) as needles, m.p. 163° (Found: C, 60·1; H, 6·5. $C_{14}H_{18}N_2O_4$ requires C, 60·4; H, 6·5%).

Cyclisation of Ethyl 4-*Carboxy*-5-(2,2-*dicarboxyethyl*)-3-*methylpyrrole*-2-*carboxylate* (45a).—The tricarboxylic acid (200 mg) was heated at 100° in polyphosphoric acid (3 g) for 45 min until carbon dioxide evolution ceased. The brown syrupy solution was diluted with water, and extracted with ether (3 × 10 ml). The extracts were washed with sodium hydrogen carbonate solution, then water, dried (Na_2SO_4), and evaporated. The residual gum crystallised from dilute aqueous ethanol to give *ethyl* 3-*methyl*-4-*oxocyclopenta*[b]*pyrrole*-2-*carboxylate* (46a) (20 mg) as needles, m.p. 172—174° (Found: C, 63·6; H, 6·3; N, 7·0. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%), τ ($CDCl_3$) 7·51 (Me), 7·06 (s, CH_2·CH_2), 5·63 (q) and 8·60 (t) (OEt), and *ca.* 0·0br (NH).

Attempts to cyclise the corresponding 4-carboxy-5-(2-carboxy-2-cyanoethyl)pyrrole (45b) to (46b) by the same procedure were unsuccessful.

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