THE CHEMISTRY OF PYRROLIC COMPOUNDS

IV.* β-HYDROXY- AND β-METHOXY-PYRROLES

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Summary

Some aspects of the chemistry of β-hydroxypyrroles and their methyl ethers are described, with particular reference to the development of pyrrolic intermediates suitable for the synthesis of porphyrins carrying this type of substituent. Tautomerism in the β-hydroxypyrroles is discussed.

INTRODUCTION

A study of the visible spectra of porphyrins and the spectroscopic changes brought about by the use of specific reagents has played a major role in helping to elucidate the structure of new porphyrins.[1–5] However, the use of such a technique requires that a great deal of prior knowledge be available concerning the effect of a variety of substituents upon the spectrum of the tetrapyrrolic macrocycle. A considerable amount of such information is available for porphyrins substituted with electron-withdrawing groups (particularly carbonyls), but the corresponding effect of powerful electron-donating groups such as amino and hydroxy substituents has not been investigated. A programme, aimed at a general investigation of the preparations and properties of porphyrins of this type, has therefore been initiated.

The literature shows very few syntheses of porphyrins of this type. Fischer and Zeile[6] have reported the preparation of a porphyrin substituted with four acetylamino groups at β-positions, but this was so insoluble in neutral solvents that it was poorly characterized. Recently the preparation of *meso*-amino and *meso*-acetylamino-aetioporphyrin I[7] has been achieved, but our interest was directed mainly towards porphyrins which carried substituents, capable of electron release, at the β positions. Since a number of syntheses of β-hydroxypyrroles, and hence β-methoxypyrroles, were known, our interest centred initially in the preparation of porphyrins carrying substituents of these types.

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[1] Lemberg, R., and Falk, J. F., *Biochem. J.*, 1951, **49**, 674.

[2] Clezy, P. S., and Barrett, J., *Biochem. J.*, 1961, **78**, 798.

[3] Morell, D. B., and Clezy, P. S., *Biochim. biophys. Acta*, 1963, **71**, 157.

[4] Clezy, P. S., Parker, M. J., Barrett, J., and Lemberg, R., *Biochim. biophys. Acta*, 1964, **82**, 361.

[5] Newton, N., Morell, D. B., Clarke, L., and Clezy, P. S., *Biochim. biophys. Acta*, 1965, **96**, 476.

[6] Fischer, H., and Zeile, K., *Liebigs Ann.*, 1930, **483**, 251.

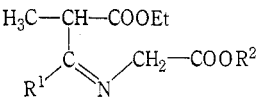
[7] Johnson, A. W., and Oldfield, D., *J. chem. Soc.*, 1965, 4303.

Most of the present knowledge of β-hydroxypyrroles and their methyl ethers has come from an examination of the tautomerism exhibited by the hydroxy compounds[8–14] and from the investigation of the chemistry of prodigiosin.[15,16] Little detailed chemistry of this group has been recorded. This paper therefore describes the synthesis of some new β-hydroxypyrroles and their derivatives, and discusses reactions likely to be of use in the development of porphyrin syntheses involving pyrroles of this type. Some comments are also offered upon the tautomeric nature of the β-hydroxypyrroles.

Results and Discussion

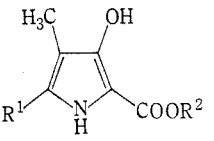
Preparation, Properties, and Reactions of β-Hydroxypyrroles

Treibs and Ohorodnik[12] have described the synthesis of β-hydroxypyrroles by a Dieckmann cyclization of Schiff bases of the type (I), and this method of synthesis appeared to lead to the type of pyrrolic product required in the present investigation.



	R^1	R^2
(Ia)	Me	Et
(Ib)	COOEt	CH_2Ph
(Ic)	COOEt	Et
(Id)	H	Et

In the first instance, ethyl 4-hydroxy-2,3-dimethylpyrrole-5-carboxylate (IIa), readily available via the Schiff base (Ia), seemed a pyrrole that might be further elaborated for our needs. It appeared possible that the aldehydic function necessary



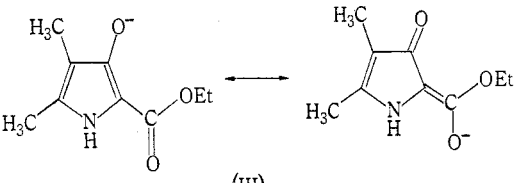
	R^1	R^2		R^1	R^2
(IIa)	Me	Et	(IId)	H	Et
(IIb)	COOEt	CH_2Ph	(IIe)	Me	CH_2Ph
(IIc)	COOEt	Et	(IIf)	H	CH_2Ph

for dipyrromethine formation might be readily introduced at either α-position—by MacFayden–Stevens reaction of the ester function or by the action of sulphuryl chloride at the methyl group. Alternatively, it seemed possible to provide a vacant α-position, where condensation to a dipyrrylmethine or dipyrrylmethane could be effected, by saponification of the ester group followed by decarboxylation.

However, attempts to hydrolyse the ester (IIa) under acidic conditions gave intractable tars, while an alkaline hydrolysis yielded starting material. Efforts to

[8] Benary, E., and Silbermann, B., *Chem. Ber.*, 1913, **46**, 1363.
[9] Kuster, W., *Hoppe-Seyler Z.*, 1922, **121**, 135.
[10] Davoll, J., *J. chem. Soc.*, 1953, 3802.
[11] Kuhn, R., and Osswald, G., *Chem. Ber.*, 1956, **89**, 1423.
[12] Treibs, A., and Ohorodnik, A., *Liebigs Ann.*, 1958, **611**, 139.
[13] Treibs, A., and Ohorodnik, A., *Liebigs Ann.*, 1958, **611**, 149.
[14] Atkinson, R. S., and Bullock, E., *Can. J. Chem.*, 1963, **41**, 625.
[15] Rapoport, H., and Holden, K. G., *J. Am. chem. Soc.*, 1960, **82**, 5510.
[16] Rapoport, H., and Willson, C. D., *J. Am. chem. Soc.*, 1962, **84**, 630.

produce the benzyl ester (IIe) by base-catalysed transesterification gave only trace amounts of the desired product and returned mainly the starting product (IIa). The failure of reactions of this type presumably stems from the fact that under alkaline conditions the anion (III) is produced in which the nucleophilic nature of the carbonyl carbon is greatly reduced.



(III)

The resistance of the hydroxy ester (IIa) to alkaline hydrolysis suggested that a Schiff base of type (Ib) might by cyclized to the pyrrole (IIb) in ethanol using ethoxide as the catalyst without transesterification taking place. This would have provided a useful hydroxypyrrolic intermediate capable of selective treatment at one of the ester groups. In the event, however, the only product isolated was the diethyl ester (IIc), identical in all respects with the pyrrole obtained by the cyclization of the Schiff base (Ic). It is concluded that transesterification took place prior to cyclization to the pyrrole.

This rapid transesterification suggested that the synthetically useful benzyl esters (IIe and IIf) could be prepared from the Schiff bases (Ia and Id) by carrying out the Dieckmann cyclization in benzyl alcohol. This has proved to be the case, and this procedure thus avoids the troublesome preparation of benzyl glycinate.

It did seem that an investigation of the chemistry of these pyrroles might be facilitated if the hydroxyl function were protected by some group which could be readily removed at a later stage. A crystalline product was obtained from the sodium salt of (IIa) and benzyl chloride (perhaps the benzyl ether) but this proved unstable and rapidly decomposed to a yellow gum. The hydroxypyrrole (IIa) gave a crystalline dihydropyranyl derivative but this proved not to be the expected ether. The structure of this material is discussed below.

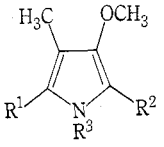
Preparation and Properties of β-Methoxypyrroles

The failure to prepare benzyl or dihydropyranyl ethers as protecting groups for the β-hydroxypyrrole (IIa) led to an investigation of the properties of its methyl ether (IVa).

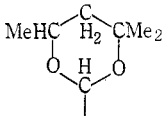
This compound was readily prepared from the hydroxypyrrole by using dimethyl sulphate in acetone in the presence of potassium carbonate. This procedure was superior to methods employing dimethyl sulphate in aqueous sodium hydroxide or methyl iodide in acetone/potassium carbonate while diazomethane produced no methylation at all. Other β-methoxypyrroles were prepared in similar fashion, although 2-ethoxycarbonyl-3-methoxy-4-methylpyrrole (IVh) could be obtained most readily by dimethyl sulphate methylation of the parent hydroxypyrrole dissolved in aqueous sodium hydroxide solution. Methylation of ethyl 3-hydroxy-

4-methylpyrrole-2,5-dicarboxylate (IIc) by the dimethyl sulphate/acetone procedure gave the *NO*-dimethyl derivative (IVi), due presumably to the increased acidity of the N–H group of this pyrrole caused by the two α-electronegative substituents.

The β-methoxypyrrole (IVa) was successfully converted into the formyl derivative (IVb) by the MacFayden–Stevens procedure, while reaction of (IVa) with lead tetraacetate produced the formyl ester (IVc). Surprisingly the hydroxyacetate (IVd) could be isolated from this latter reaction, provided water was excluded. It is not



	R^1	R^2	R^3
(IVa)	Me	COOEt	H
(IVb)	Me	CHO	H
(IVc)	CHO	COOEt	H
(IVd)	CH(OH)OAc	COOEt	H
(IVe)	CHO	COOH	H
(IVf)	$CH{=}C(CN)_2$	COOEt	H

	R^i	R^2	R^3
(IVg)	COOH	COOEt	H
(IVh)	H	COOEt	H
(IVi)	COOEt	COOEt	Me
(IVj)		COOEt	H

clear whether (IVd) is an actual intermediate of the reaction or is formed by the subsequent addition of acetic acid to the formyl group of (IVc). However, the latter suggestion does seem unlikely as most carbonyl compounds which form adducts of this type are substituted with electronegative groups (e.g. ninhydrin, chloral). In the presence of aqueous alcohol (IVd) readily formed acetic acid and the formyl derivative (IVc).

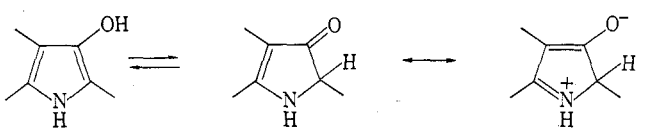
The hydroxy acetate (IVd) could be hydrolysed by base to the formyl acid (IVe), but attempts to decarboxylate this acid or its salts by direct heating, or with quinoline and copper, were unsuccessful. Also attempts to replace the carboxyl group by iodine or bromine produced no crystalline products. The formyl ester (IVc) gave a dicyanovinyl derivative (IVf) in the usual fashion, but the ester in this compound could not be hydrolysed under conditions which did not affect the dicyanovinyl group. With 2-methylpentane-2,4-diol the formyl ester (IVc) gave an acetal (IVj) in which the ester group could be successfully hydrolysed but attempts to decarboxylate the resultant acid failed.

Treatment of the β-methoxypyrrole (IVa) with sulphuryl chloride, followed by hydrolysis of the intermediate trichloro compound, yielded the acid (IVg). To obtain the maximum yield of the acid it proved necessary to define carefully the conditions of reaction with sulphuryl chloride. In acetic acid as solvent the acid was heavily contaminated by the aldehyde (IVc), but in ethereal solution sulphuryl chloride gave the acid in 19% yield. Best yields (56%) of the acid were obtained when ether/acetic acid (1 : 1) was used as solvent. Attempts to decarboxylate the acid (IVg) using ethanolamine gave poor yields of product, but reaction with iodine followed by reductive dehalogenation gave the β-methoxypyrrole (IVh). This pyrrole could also be prepared by methylation of the hydroxypyrrole (IId) obtained by cyclization of the Schiff base (Id). In practice, however, in spite of the additional steps involved, it proved more efficient to prepare this pyrrole by way of ethyl 4-methoxy-2,3-dimethylpyrrole-5-carboxylate (IVa), since the alternative

synthesis required the preparation of α-formylpropionate which could be made only in small yield, thus making the accumulation of large amounts of the Schiff base (Id) difficult.

Structure of β-Hydroxypyrroles

The problem of tautomerism in the α- and β-hydroxypyrroles has been the subject of many contributions to the literature. While it seems clear that the α-hydroxypyrroles are best represented as the keto tautomer, the position with respect to the isomeric β-hydroxy compounds is more obscure. Early workers,[8,9] on chemical evidence, concluded that the hydroxy tautomer contributed significantly to the tautomeric equilibrium of many β-hydroxypyrroles, and it has been shown[11] that ethyl 3-hydroxypyrrole-5-carboxylate has a similar ultraviolet spectrum to its ethyl ether, suggesting that this compound exists predominantly as the hydroxy isomer. On the other hand, Davoll[10] has examined the ultraviolet spectra of a number of β-hydroxypyrroles and their derivatives and found in most cases marked differences between the ultraviolet spectrum of the parent compound and its ether and ester derivatives. Davoll has concluded therefore that these pyrroles were best represented as the 4-oxo-Δ^2-pyrrolines (Vb).



(Va) (Vb) (Vc)

More recently Atkinson and Bullock[14] have examined the structure of some 4-alkoxycarbonyl-3-hydroxypyrroles making use of n.m.r. spectroscopy as well as u.v. and i.r. methods and have concluded that these pyrroles exist in the oxopyrroline (Vb) form. Treibs and Ohorodnik[12,13] have also proposed the keto isomer as the major tautomeric form of a number of β-hydroxypyrroles, although they suggest that the zwitterion (Vc) contributes significantly to the structure of these molecules.

From these considerations it became clear that it was not possible to predict with any certainty the tautomeric structure of a β-hydroxypyrrole, and therefore it seemed worthwhile to investigate the fine structure of the three new β-hydroxypyrroles prepared during this work. Davoll[10] has shown that compounds with the 4-oxo-Δ^2-pyrroline structure (Vb) show maxima in their ultraviolet spectra between 291·5 and 324·5 mμ and possess another band between 240 and 248 mμ if a 3-carboxy or ester group is present. Rapoport and Willson[16] have reported that a methoxyl group at a β-position in a pyrrolic ring has very much the same effect on the spectrum as a methyl group does at this position. Hence one would predict from the work of Cookson[17] that the three methoxypyrroles synthesized above (IVa, IVh, IVi) would have absorption maxima about 270–280 mμ. In practice the three methoxypyrroles, the corresponding acetoxypyrroles, and the parent hydroxypyrroles all had absorption maxima in this region (see Table 1). From this we conclude that these pyrroles are

[17] Cookson, G. H., *J. chem. Soc.*, 1953, 2789.

best represented as the hydroxy isomer (IIa, IIc, IId). In only one case (IIc) is there any evidence of the keto form being present to any significant degree. In the ultraviolet spectrum of this pyrrole the maximum at 278 mμ is somewhat asymmetric and tends to tail towards 340 mμ. In view of Davoll's work this would indicate a contribution from the 4-oxo-Δ^2-pyrroline form.

The conclusion, based on ultraviolet spectroscopy, that the three new hydroxypyrroles reported here exist mainly as the hydroxy isomer, is supported by their infrared spectra. The pyrroles show no evidence of a carbonyl frequency apart from the maxima due to the esters, but do exhibit a strong OH absorption near 3500 cm^{-1} in addition to the NH frequency at about 3200 cm^{-1}.

TABLE 1

SPECTRAL DATA

Pyrrole Substituents					U.V. Spectrum		I.R. Spectrum
N	C2	C3	C4	C5	λ_{max}* (mμ)	ϵ	ν_{max}† (cm^{-1})
	CO_2Et	OH	Me		266	18100	3370, 3330, 1660, 1620
	CO_2Et	OMe	Me		268	15400	3300, 1655
	CO_2Et	OAc	Me		268	11000	
	CO_2Et	OH	Me	Me	278	20300	3530, 3280, 1660
	CO_2Et	OMe	Me	Me	279	20700	3280, 1650
	CO_2Et	OAc	Me	Me	278	15000	
	CO_2Et	OH	Me	CO_2Et	278	16500	3445, 3425, 3210, 1725, 1685
Me	CO_2Et	OMe	Me	CO_2Et	284	17600	
	CO_2Et	OAc	Me	CO_2Et	278	17000	3255, 1755, 1720, 1700

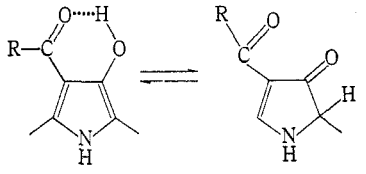
* In ethanol. † In Nujol.

It is interesting to note that 3-hydroxypyrroles substituted in the 2-position with carbonyl groups usually exist as the hydroxy tautomer while the 3-hydroxy-4-carbonylpyrroles are usually found as the keto isomer. In addition to the three examples arising from the present investigation, 5-ethoxycarbonyl-3-hydroxypyrrole[11] and the recently described 2-acetyl-4-ethoxycarbonyl-3-hydroxy-5-methylpyrrole[18] have been reported to exist as the hydroxy tautomer. The reasons for this difference in equilibria, depending on the substitution pattern of the pyrrole, remain to be determined, although two factors influencing the tautomeric equilibrium may be the effect of intramolecular hydrogen bonding and stabilization of the various tautomeric forms by conjugation with the carbonyl group.

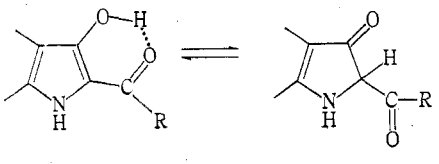
Intramolecular hydrogen bonding has often been suggested as contributing to the stabilization of enols. Hydrogen bonding is possible in 3-hydroxypyrroles carrying carbonyl substituents either in the 2 or 4 positions, but it is possible that stronger hydrogen bonds could be formed when the carbonyl function occupies the α-position. This is due to the greater double bond character of the 2–3 bond

[18] Atkinson, R. S., and Bullock, E., *Can. J. Chem.*, 1964, **42**, 1524.

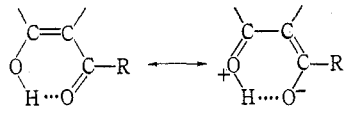
relative to the 3–4 bond[19] which increases the contribution from the canonical form (VIb), thus strengthening the hydrogen bond. Such mesomeric effects have been used to explain the differences in hydrogen bond strengths in β-naphthols substituted



(A)



(B)



(VIa) (VIb)

by carbonyl groups in position 1 or 3[20] and also probably play a role in the 3-hydroxythiophene series which have been shown[21] to form stronger intramolecular hydrogen bonds when carrying a carbonyl substituent at position 2 than at position 4.

In addition, it does seem possible that the carbonyl group may stabilize one tautomeric form more than another by extending the conjugation of the system. The presence of a carbonyl group at position 2 in the 3-hydroxypyrroles might tend to favour the enolic form rather than the ketonic isomer, since in the latter structure the ester group is no longer conjugated with the ring system (see equilibrium (B), above). This situation does not arise when the carbonyl group is in position 4. In this case the ester group remains in conjugation with the ring system in both the ketonic and enolic forms (see equilibrium (A)). However, neither of these considerations seems to apply to 5-ethoxycarbonyl-3-hydroxypyrrole which is considered[11] to exist predominantly as the hydroxy tautomer. Presumably other factors, which remain to be defined, influence the tautomeric equilibrium of β-hydroxypyrroles.

Tetrahydropyranyl Derivatives of β-Hydroxypyrroles

In the course of this study an attempt was made to prepare the tetrahydropyranyl ethers (VIIa–c) and examine the potential of this substituent as a protecting

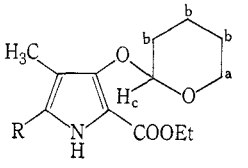
[19] Bak, B., Christensen, D., Hansen, L., and Rastrup-Anderson, J., *J. chem. Phys.*, 1956, **24**, 720.

[20] Poste, A. L., Gutowsky, H. S., and Hunsberger, I. M., *J. Am. chem. Soc.*, 1960, **82**, 5057.

[21] Jakobsen, H. J., and Lawesson, S-O., *Tetrahedron*, 1965, **21**, 3331.

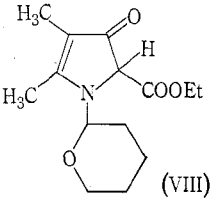
group for the hydroxyl function of the β-hydroxypyrroles. Although these derivatives proved unsatisfactory for this purpose, one of them posed a structural problem because it was clearly not the tetrahydropyranyl ether.

The tetrahydropyranyl ether (VIIc) could not be obtained in a crystalline state, but crystalline derivatives were obtained from the hydroxypyrroles (IIa) and (IId) by treatment with 2,3-dihydropyran in the presence of an acidic catalyst.



(VIIa) R = H
(VIIb) R = Me
(VIIc) R = COOEt

Analytical results for these derivatives were in agreement with the calculated figures for the expected ethers, and the ultraviolet spectrum of (VIIa) was essentially similar to the spectra of (IId) and its *O*-acetyl and *O*-methyl derivatives. Moreover, the n.m.r. spectrum of the tetrahydropyranyl derivative of (IId) could be rationalized on the basis of the structure (VIIa). However, examination of the ultraviolet spectrum of the tetrahydropyranyl derivative obtained from (IIa) revealed a single maximum at 328 mμ (ε 11900) which clearly indicated that the pyrrolic structure (VIIb) was not correct. In the light of Davoll's[10] investigation of the ultraviolet spectra of the 4-oxo-Δ^2-pyrroline system, it seemed that this chromophore was present in the tetrahydropyranyl derivative of (IIa). Moreover, this compound proved resistant to hydrolysis in ethanolic hydrochloric acid. In this reagent the tetrahydropyranyl ether (VIIa) produced a ferric chloride colour in 1 min at room temperature, indicating the regeneration of the free phenolic hydroxyl group, but after 30 min there was no indication of a positive ferric chloride reaction from the tetrahydropyranyl derivative obtained from (IIa). This confirmed the absence of the ether structure (VIIb) and also indicated that the isomeric *N*-tetrahydropyranyl derivative (VIII) was an unlikely alternative since this compound too would have been expected to hydrolyse under these conditions. Moreover an infrared frequency at 3380 cm^{-1} in this derivative was best assigned to an NH group, which indicated that structure (VIII) was not correct.

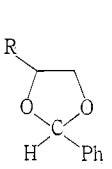


(VIII)

The n.m.r. spectrum of the tetrahydropyranyl ether (VIIa) shows an ill-defined triplet at τ 4·63 due to one proton which did not exchange with deuterium. This is assigned to the H_c proton of (VIIa), since this proton would be expected as a triplet due to the adjacent methylene and should be found at low field due to the deshielding effect of two neighbouring oxygens and the pyrrolic ring system. The literature[22] shows that the benzylic proton of the 2-phenyl-1,3-dioxalans (IX)

[22] Baggett, N., Buck, K. W., Foster, A. B., Randall, M. H., and Webber, J. M., *J. chem. Soc.*, 1965, 3394.

has been reported at τ 4·2–4·7 while in the 2-phenyl-1,3-dioxans (X) it appears in the region τ 4·70–4·95.



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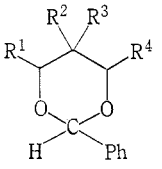
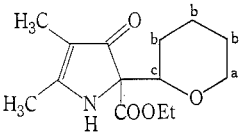


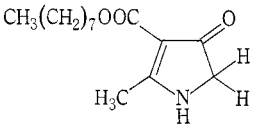
(X)

The n.m.r. spectrum of the tetrahydropyranyl derivative of (IIa) has a signal in this region at τ 4·46. However, unlike the resonance present in the tetrahydropyranyl ether (VIIa) at τ 4·63, this peak was a broad singlet and readily exchanged with D_2O. This indicated the absence of the O–CH(–O)–CH_2 structure and we ascribe this peak at 4·46 to the NH of the 4-oxo-Δ^2-pyrroline system.

Absorption in the τ 5·0–6·7 region of n.m.r. spectra is characteristic of protons on carbon atoms α to one oxygen function.[23] The n.m.r. spectrum of the tetrahydropyranyl derivative from (IIa) shows three such protons in addition to the methylene group of the ethyl ester. This would suggest that the tetrahydropyranyl moiety is attached directly to carbon, a fact which, taken with the u.v. data indicating an oxopyrroline chromophoric system, strongly suggests that the tetrahydropyranyl derivative obtained from (IIa) should be formulated as (XI).



(XI)



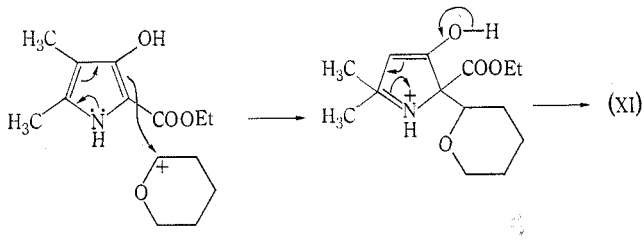
(XII)

The remaining spectroscopic data can be interpreted on the basis of the structure (XI). N.m.r. peaks at τ 7·77 and 8·38 are assigned to the C2 and C3 methyl groups respectively while an envelope at 8·1–9·1 accounts for the shielded protons in the system including the six C_b protons of the tetrahydropyranyl residue. Atkinson and Bullock[14] have reported the ring methyl of n-octyl 2-methyl-4-oxo-Δ^2-pyrroline-3-carboxylate (XII) at τ 7·36, but in their compound additional deshielding of the methyl due to the ester carbonyl would be expected. Infrared maxima at 3380, 1725, 1687, and 1603 cm^{-1} are assigned to the NH, ester carbonyl, ring carbonyl, and carbon–carbon double bond respectively. Atkinson and Bullock[14] report carbonyl maxima at 1710 and 1675 cm^{-1} for (XII).

The formation of a *C*-alkylated product from 2,3-dihydropyran and a hydroxy compound appears to be a novel reaction but analogous reactions involving other

[23] Jackman, L. M., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry." p. 55. (Pergamon Press: London 1962.)

systems are to be found in the literature.[24] The present reactions can be rationalized according to the following scheme:



Presumably the additional methyl group at C2 is necessary to increase the electron density of the pyrrolic ring system to bring about *C*-alkylation since the α-free hydroxypyrrole (IId) forms a normal tetrahydropyranyl ether.

Experimental

Melting points are uncorrected. U.v. data were obtained with the aid of a Perkin–Elmer 137 u.v. spectrophotometer. N.m.r. spectra were obtained by Mr V. Pickles of this University employing a Varian A60 instrument, while i.r. measurements were determined by Mr M. Withers using a Perkin–Elmer 421 machine. Solutions in water-immiscible solvents were dried over anhydrous sodium sulphate or magnesium sulphate before removal of solvent. Light petroleum refers to the fraction of b.p. 60–80°. Analyses are by Dr E. Challen of the University of New South Wales and by the Australian Microanalytical Service, Melbourne. Alkoxyl analyses on compounds containing both ethoxyl and methoxyl groups are reported in terms of a methoxyl equivalent. Alumina for chromatography was grade H of Peter Spence.

(*a*) *5-Ethoxycarbonyl-4-hydroxy-2,3-dimethylpyrrole*

A mixture of ethyl 2-methyl-3-oxobutanoate (50·3 g; prepared by methylation of acetoacetic ester after the general procedure of ref.[25]) and ethyl glycinate (36·0 g) was warmed on the steam-bath until it became turbid and then allowed to stand overnight at room temperature. Water was removed under vacuum and the residue dissolved in ether (50 ml). This solution was filtered and the solvent removed to leave ethyl 3-(*N*-carbethoxymethyl)imino-2-methylbutanoate as a viscous oil. This material, without further purification, was dissolved in absolute alcohol (250 ml, "superdry") to which sodium (2·45 g) was added, and this solution refluxed for 3 hr. Glacial acetic acid (22 ml) was added to the cold reaction mixture and the solvent removed under vacuum to leave a dark red solid which was purified by recrystallization from ethanol and toluene/light petroleum to give *5-ethoxycarbonyl-4-hydroxy-2,3-dimethylpyrrole* (29 g) as colourless silky needles, m.p. 115° (Found: C, 58·8; H, 7·1; N, 7·8. $C_9H_{13}NO_3$ requires C, 59·0; H, 7·15; N, 7·6%). λ_{max} (ε) in C_2H_5OH: 278 mμ (20300). ν_{max} (Nujol): 3530, 3280, 1660 cm^{-1}. τ ($CDCl_3$): 8·66 (3H, triplet, *J* 7·0 c/s, OCH_2CH_3), 5·69 (2H, quartet, *J* 7·0 c/s, OCH_2CH_3), 8·10 (3H, aromatic methyl), 7·85 (3H, aromatic methyl), 1·3–3·3 broad peak (2H, OH, NH).

(i) *Acetate.*—A mixture of the hydroxypyrrole (0·61 g), acetic anhydride (5 ml), and fused sodium acetate (0·1 g) was refluxed for 15 min and water (5 ml) added to the warm reaction mixture. The product, which crystallized on cooling, was purified by recrystallization from aqueous alcohol to give *4-acetoxy-5-ethoxycarbonyl-2,3-dimethylpyrrole* (0·36 g), m.p. 140–141° (Found: C, 58·4; H, 6·4; N, 6·35. $C_{11}H_{15}NO_4$ requires C, 58·65; H, 6·7; N, 6·2%). λ_{max} (ε) in C_2H_5OH: 277 mμ (15000).

[24] Patinkin, S. H., and Friedman, B. S., in "Friedel–Crafts and Related Reactions." Vol. II, Part 1. Chap. XIV. (Ed. G. A. Olah.) (Interscience: New York 1964.)

[25] Marvel, C. S., and Heyer, F. D., *Org. Synth.*, 1951, Coll. Vol. I, 248.

(ii) *Methyl ether.*—A mixture of the hydroxypyrrole (5·05 g), dimethyl sulphate (4·0 ml), anhydrous potassium carbonate (9·5 g), and dry acetone (25 ml) was refluxed for 8 hr. The inorganic salts were removed by filtration and the filtrate, after concentration under vacuum, was treated with aqueous ammonia (sp. gr. 0·88) to destroy excess dimethyl sulphate, poured into water (50 ml), and the aqueous mixture extracted with ether (3 × 20 ml). The combined ethereal solutions were washed with aqueous sodium hydroxide solution and water. Removal of the ether under vacuum yielded *5-ethoxycarbonyl-4-methoxy-2,3-dimethylpyrrole* (3·8 g), further purified by recrystallization from aqueous acetone, m.p. 98–99° (Found: C, 60·7; H, 7·5; N, 7·1. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%. λ_{max} (ϵ) in C_2H_5OH: 279 mμ (20700). ν_{max} (Nujol): 3280, 1650 cm^{-1}. τ ($CDCl_3$): 8·63 (3H, triplet, J 7·0 c/s, OCH_2CH_3), 5·69 (2H, quartet, J 7·0 c/s, OCH_2CH_3), 8·10 (3H, aromatic methyl), 7·84 (3H, aromatic methyl), 6·16 (3H, OCH_3), 0·9 (1H, NH). Unchanged hydroxypyrrole (0·65 g) was recovered from the sodium hydroxide washings.

(iii) *Tetrahydropyranyl derivative.*—To a solution of the hydroxypyrrole (0·5 g) in anhydrous methylene chloride (5 ml) was added 2,3-dihydropyran (0·5 ml), followed by dioxan (0·5 ml), which had previously been saturated with dry hydrogen chloride. The mixture was kept at room temperature for 24 hr after which triethylamine (1 ml) and ether (20 ml) were added. The ethereal solution was washed with water and the solvent removed under vacuum to leave an oil which slowly crystallized from ether/light petroleum. Sublimation at 150°/1 mm and subsequent recrystallization from chloroform/light petroleum gave colourless needles of *5-ethoxycarbonyl-2,3-dimethyl-4-oxo-5-(2′-tetrahydropyranyl)-Δ^2-pyrroline* (0·19 g), m.p. 163–166° (Found: C, 62·7; H, 7·9; N, 5·35. $C_{14}H_{21}NO_4$ requires C, 62·9; H, 7·9; N, 5·2%). ν_{max} (CCl_4): 3380, 1725, 1687, 1603 cm^{-1}. λ_{max} (ϵ) in C_2H_5OH: 328 mμ (11900). τ ($CDCl_3$): 4·46 (1H, NH, exchanged with D_2O), 5·5–7·0 (5H, complex multiplet including an ill-defined quartet due to $-OCH_2CH_3$; other protons due to those present at C 2 and C 6 of tetrahydropyranyl ring system), 7·77 (3H, methyl at C 2 of pyrrolic ring), 8·38 (methyl at C 3 of pyrrolic ring) 8·70 (triplet, $COOCH_2CH_3$), 8·1–8·9 (multiplet, C 3, C 4, C 5 protons of tetrahydropyranyl ring; combined proton count including peaks at 8·38 and 8·70 is 12H).

(iv) *Attempted preparation of benzyl ether.*—A solution of the hydroxypyrrole (2·66 g) in alcohol (5 ml) was treated with aqueous sodium hydroxide solution (2·9 ml; 20%). The solvent was removed in vacuum and the residual sodium salt refluxed with benzyl chloride (3 ml) for 1 hr. The cold reaction mixture was washed once with water and the excess benzyl chloride removed under vacuum to leave a product (0·65 g) purified by recrystallization from aqueous acetone, m.p. 123–124°, which rapidly decomposed to a semi-resinous yellow material.

(v) *Attempted hydrolysis.*—The hydroxypyrrole was refluxed in alcoholic sodium hydroxide solution (1N; 25 ml) for 5 hr after which the reaction mixture was diluted with water (50 ml) and acidified (HCl) to Congo red. The precipitate which formed was collected and purified by recrystallization from aqueous alcohol to give a product, m.p. 111–115° undepressed by 5-ethoxycarbonyl-4-hydroxy-2,3-dimethylpyrrole.

(vi) *Benzyl 4-hydroxy-2,3-dimethylpyrrole-5-carboxylate.*—A solution of 5-ethoxycarbonyl-4-hydroxy-2,3-dimethylpyrrole (1·5 g) in benzyl alcohol (15 ml) containing sodium (0·03 g) was heated for 4 hr at 80–90° at 0·5 mm. Glacial acetic acid (0·2 ml) was added and the solvent removed under vacuum. An ethereal solution of the residue was washed well with water and the solvent removed. Sublimation (100°/0·5 mm) of the residue gave a solid (0·72 g), m.p. 114–116°, alone or on admixture with the starting material.

The residue remaining after sublimation (70 mg) was purified by recrystallization from alcohol to give silky needles of *benzyl 4-hydroxy-2,3-dimethylpyrrole-5-carboxylate* (8 mg), m.p. 151–152° (Found: N, 5·9. $C_{14}H_{15}NO_3$ requires N, 5·7%).

(*b*) *Ethyl 3-Hydroxy-4-methylpyrrole-2-carboxylate*

Ethyl glycinate (5·52 g) and ethyl 2-formylpropionate[26] (6·87 g) were cautiously mixed at 0° and allowed to stand at room temperature for 1 hr. The Schiff base (10·10 g) obtained

[26] Harkins, H. H., and Johnson, T. B., *J. Am. chem. Soc.*, 1929, **51**, 1237.

as above was dissolved in ethanol (60 ml, "superdry") containing sodium (1·30 g) and the mixture refluxed for 2·5 hr. Removal of the solvent under vacuum left a slurry which was dissolved in water (50 ml); the pH of this solution was adjusted to 2 by the addition, at 0°, of dilute hydrochloric acid. The precipitate was collected and recrystallized from methanol to yield *ethyl 3-hydroxy-4-methylpyrrole-2-carboxylate* (4·75 g), m.p. 85–86° (Found: C, 57·15; H, 6·4; N, 8·4. $C_8H_{11}NO_3$ requires C, 56·8; H, 6·55; N, 8·3%). λ_{max} (ϵ) in C_2H_5OH: 266 mμ (18100). ν_{max} (Nujol) 3370, 3330, 1660, 1620 cm^{-1}. τ ($CDCl_3$): 8·66 (3H, triplet, J 7·0 c/s, OCH_2CH_3), 5·66 (2H, quartet, J 7·0 c/s, OCH_2CH_3), 8·00 (3H, aromatic methyl), 3·46 (1H, aromatic proton), 2·55 (1H, OH), 1·7 (1H, NH).

(i) *Methyl ether.*—The hydroxypyrrole (3·00 g) dissolved in aqueous sodium hydroxide solution (75 ml; 2N) was treated with dimethyl sulphate (3·0 ml), and the mixture shaken vigorously at room temperature for 30 min. The precipitate which formed was collected and the filtrate again shaken with fresh dimethyl sulphate (3·0 ml) for a further 30 min. This process was repeated on two further occasions, the aqueous solution being kept strongly alkaline with additional sodium hydroxide solution as required. The combined solids were purified by sublimation (70–75°/1 mm) and recrystallized from chloroform/light petroleum to yield *ethyl 3-methoxy-4-methylpyrrole-2-carboxylate* (2·15 g) as white prisms, m.p. 78–79° (Found: C, 59·2; H, 7·1; N, 7·9; OCH_3, 31·9. $C_9H_{13}NO_3$ requires C, 59·0; H, 7·15; N, 7·6; alkoxyl calculated as OCH_3, 33·8%). λ_{max} (ϵ) in C_2H_5OH: 268 mμ (15400). ν_{max} (Nujol): 3300, 1655 cm^{-1}. τ ($CDCl_3$): 8·66 (3H, triplet, J 7·0 c/s, OCH_2CH_3), 5·70 (2H, quartet, J 7·0 c/s, OCH_2CH_3) 8·01 (3H, aromatic methyl), 3·47 (1H, aromatic proton), 6·15 (3H, OCH_3), 1·1 (1H, NH).

(ii) *Acetate.*—The hydroxypyrrole (0·15 g) was refluxed with acetic anhydride in the presence of anhydrous sodium acetate (5 mg) for 15 min and excess anhydride hydrolysed with aqueous sodium hydrogen carbonate solution at room temperature. The hydrolysis mixture was extracted with ether and the solvent removed from the ethereal layer under vacuum to give *ethyl 3-acetoxy-4-methylpyrrole-2-carboxylate* (0·1 g), m.p. 88–89° after recrystallization from aqueous methanol (Found: C, 56·8; H, 6·25; N, 6·9. $C_{10}H_{13}NO_4$ requires C, 56·85; H, 6·2; N, 6·6%). ν_{max} (Nujol): 3250, 1760, 1670 cm^{-1}.

(iii) *Tetrahydropyranyl derivative.*—Dioxan (0·1 ml), previously saturated with dry hydrogen chloride, was added to a mixture of ethyl 3-hydroxy-4-methylpyrrole-2-carboxylate (0·25 g) and 2,3-dihydropyran (1 ml), and the solution allowed to stand at room temperature overnight. Ether (20 ml) containing triethylamine (0·5 ml) was added to the mixture and the ethereal solution was successively washed with water, aqueous sodium hydroxide solution, and water. Removal of the solvent in vacuum gave an oily residue which, when triturated with light petroleum at −70°, solidified. Recrystallization of this solid from chloroform/light petroleum gave *ethyl 4-methyl-3-(2′-tetrahydropyranyloxy)pyrrole-2-carboxylate* (0·18 g), m.p. 94–95° (Found: C, 61·3; H, 7·4; N, 5·8. $C_{13}H_{19}NO_4$ requires C, 61·6; H, 7·6; N, 5·5%). ν_{max} (CCl_4): 3475sh, 3455, 3300b, 1700sh, 1675 cm^{-1}. λ_{max} (ϵ) in C_2H_5OH: 268 mμ (16200). τ ($CDCl_3$): 1·2 (1H, NH, broad), 3·45 (1H, poorly resolved doublet, aromatic proton), 4·63 (1H, poorly resolved triplet, –O–CH(–O)–CH_2), 5·71 (quartet, J 7·0 c/s, OCH_2CH_3), 5·7–6·6 (multiplet, $-OCH_2CH_2-$, 4H including 5·17 quartet), 7·95 (aromatic methyl), 7·8–8·6 (multiplet, –O–CH_2–$CH_2CH_2CH_2$-CH(–O)–, 9H including 7·95 peak), 8·68 (3H, triplet, J, 7·0 c/s, OCH_2CH_3).

(c) *Ethyl 3-Hydroxy-4-methylpyrrole-2,5-dicarboxylate*

A benzene solution (100 ml) of ethyl glycinate (7·97 g) and ethyl 3-methyl-2-oxosuccinate[27] (15·40 g) was refluxed under a Dean and Stark head for 1 hr. Removal of the solvent left an oil (19·2 g) which was dissolved in ethanol (60 ml, "superdry"), sodium (1·5 g) was added, and the resultant solution refluxed for 2·5 hr. Removal of the solvent under vacuum gave a residue which was dissolved in water and the aqueous solution, after careful acidification with hydrochloric acid (10N), was extracted with ether. The ethereal solution was washed in turn with aqueous sodium hydrogen carbonate solution and with aqueous sodium hydroxide solution (2N). The latter solution produced a precipitate of the insoluble sodium salt of the hydroxypyrrole

[27] Cox, R. F. B., and McElvain, S. M., *Org. Synth.*, 1943, Coll. Vol. II, 272.

which was collected and suspended in ethanol (50 ml) at 50° under stirring. The pH was adjusted to 2 with hydrochloric acid (2N); the solid dissolved. Removal of the solvent under vacuum gave a crystalline residue which was purified by recrystallization from aqueous methanol to give *ethyl 3-hydroxy-4-methylpyrrole-2,5-dicarboxylate* (1·61 g), m.p. 74–75° (Found: C, 55·05; H, 6·2; N, 6·1. $C_{11}H_{15}NO_5$ requires C, 54·8; H, 6·3; N, 5·8%). ν_{max} (Nujol): 3445, 3425, 3210, 1725, 1685 cm^{-1}. λ_{max} (ϵ) in C_2H_5OH: 278 mμ (16500). τ ($CDCl_3$): 1·1 (1H, NH, exchanged with D_2O), 2·75 (1H, OH, exchanged with D_2O), 5·63 (4H, 2 overlapping quartets, $2\times OCH_2CH_3$), 7·78 (3H, aromatic methyl), 8·62 (6H, triplet, $2\times OCH_2CH_3$).

(i) *Methyl derivative.*—A mixture of the hydroxypyrrole (0·25 g), dimethyl sulphate (0·3 ml), anhydrous potassium carbonate (1 g), and dry acetone (25 ml) was heated under reflux for 24 hr. After removal of the inorganic salts the solvent was removed under vacuum to give an oil which was purified by chromatography on alumina in benzene solution. Distillation (95°/1 mm) onto a cold finger condenser gave *ethyl 4-methoxy-1,3-dimethylpyrrole-2,5-dicarboxylate* (0·25 g), m.p. 36–38° (Found: C, 58·1; H, 6·8; N, 5·5. $C_{13}H_{19}NO_5$ requires C, 58·0; H, 7·1; N, 5·2%). λ_{max} (ϵ) in C_2H_5OH: 284 mμ (17600). τ ($CDCl_3$): 5·66 (4H, quartet, $2\times OCH_2CH_3$), 5·90 (3H, NCH_3) 6·25 (3H, OCH_3), 7·81 (3H, aromatic methyl) 8·60 (6H, triplet, $2\times OCH_2CH_3$).

(ii) *Acetate.*—The hydroxypyrrole (0·1 g) was heated with acetic anhydride (2 ml) and anhydrous sodium acetate for 1 hr at 100°. Excess acetic anhydride was hydrolysed with aqueous sodium hydrogen carbonate solution at room temperature; the solid product was collected and recrystallized from aqueous methanol to give *ethyl 3-acetoxy-4-methylpyrrole-2,5-dicarboxylate* (0·1 g), m.p. 90–93° (Found: C, 55·0; H, 5·95; N, 5·15. $C_{13}H_{17}NO_6$ requires C, 55·1; H, 6·05; N, 4·95%). ν_{max} (Nujol): 3250, 1770, 1725 cm^{-1}. λ_{max} (ϵ) in C_2H_5OH: 278 mμ (17000).

(*d*) *Benzyl 3-Hydroxy-4-methylpyrrole-2-carboxylate*

Ethyl glycinate (8·3 g) and ethyl 2-formylpropionate[26] (10·2 g) were allowed to condense as above to give the Schiff base which was added to dry benzyl alcohol (150 ml) containing dissolved sodium (1·75 g). The mixture was heated at 30–40° for 1 hr, at 100° for 2 hr, and allowed to stand at room temperature overnight. Benzyl alcohol was removed under vacuum and the residue partitioned between aqueous acetic acid (50 ml; 10%) and ether (75 ml). The ethereal layer was washed successively with water, aqueous sodium hydrogen carbonate solution, and aqueous sodium hydroxide solution. The latter solution precipitated the gelatinous sodium salt of the hydroxypyrrole which was collected and dissolved in ethanol, and the pH of this solution adjusted to 2 with dilute hydrochloric acid. Removal of the solvent under vacuum left a semicrystalline mass which after recrystallization from ethanol gave *benzyl 3-hydroxy-4-methylpyrrole-2-carboxylate* (3·10 g) as shiny plates, m.p. 99–100°. A benzene solution of material recovered from the recrystallization mother liquors was chromatographed on alumina to afford an additional quantity (1·15 g) of the benzyl ester, m.p. 98–100° (Found: C, 67·95; H, 5·8; N, 6·3. $C_{13}H_{11}NO_3$ requires C, 67·5; H, 5·7; N, 6·1%).

Acetate.—The hydroxypyrrole (2·50 g), acetic anhydride (5 ml), and pyridine (0·2 ml) were warmed until solution occurred when the mixture was allowed to stand at room temperature for 24 hr. Excess acetic anhydride was hydrolysed with aqueous sodium carbonate solution; the solid product was collected and recrystallized from aqueous alcohol to yield *benzyl 3-acetoxy-4-methylpyrrole-2-carboxylate* (2·10 g), m.p. 81–82° (Found: C, 65·9; H, 5·5; N, 5·3. $C_{15}H_{15}NO_4$ requires C, 65·9; H, 5·5; N, 5·1%). τ ($CDCl_3$): 0·7 (1H, NH), 2·64 (5H, protons of benzene ring), 3·39 (1H, pyrrolic proton), 4·78 (2H, OCH_2Ph), 7·97 (3H, $COCH_3$?), 8·10 (3H, aromatic methyl?).

(*e*) *Benzyl 4-Hydroxy-2,3-dimethylpyrrole-5-carboxylate*

A mixture of ethyl glycinate (28·2 g) and ethyl 2-methylacetoacetate[25] (41·0 g) was warmed on the steam-bath until it became turbid and then allowed to stand at room temperature overnight. The reaction mixture was worked up as before to give the Schiff base (47·9 g) which was dissolved in dry benzyl alcohol (300 ml) containing sodium (5·05 g). The mixture was heated at 35–45° for 1·5 hr, at 100° for 2·5 hr, and allowed to stand overnight at room temperature. Benzyl alcohol was removed under vacuum, and ethanol/acetic acid (5 : 2; 70 ml) added at 0°

to the residue which was left to stand for 24 hr. The crystalline product was collected and recrystallized from ethanol to yield benzyl 4-hydroxy-2,3-dimethylpyrrole-5-carboxylate (9·40 g), m.p. 148–149°, undepressed by the material prepared as above (Found: C, 68·6; H, 6·2; N, 5·75. Calc. for $C_{14}H_{15}NO_3$: C, 68·55; H, 6·2; N, 5·7%). τ ($CDCl_3$): 1·7–2·3 (1H, NH), 2·68 (6H, benzene protons plus OH), 4·73 (2H, OCH_2Ph), 7·90 (3H, aromatic methyl), 8·12 (3H, aromatic methyl).

Methyl ether.—A mixture of the hydroxypyrrole (9·40 g), dimethyl sulphate (9 ml), anhydrous potassium carbonate (20 g), and acetone (100 ml) was refluxed for 16 hr and worked up as for the ethyl ester to give *benzyl 4-methoxy-2,3-dimethylpyrrole-5-carboxylate* (6·83 g), m.p. 85–86°, from ethanol (Found: C, 69·9; H, 6·55; N, 5·7. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%).

(*f*) *Derivatives of 5-Ethoxycarbonyl-4-methoxy-2,3-dimethylpyrrole*

(i) *Ethyl 2-(1′,1′-Acetoxyhydroxymethyl)-4-methoxy-3-methylpyrrole-5-carboxylate.*—At room temperature lead tetraacetate (15 g) was added over 15 min to a stirred solution of ethyl-4-methoxy-2,3-dimethylpyrrole-5-carboxylate (2·85 g) in glacial acetic acid (120 ml) and the mixture allowed to stand for 16 hr. Acetic acid was removed under vacuum and the residue partitioned between ether and water. The ethereal layer was washed successively with water, aqueous sodium hydrogen carbonate solution, and water. The solvent was removed under vacuum and the residue purified by recrystallization from chloroform/light petroleum to yield *ethyl 2-(1′,1′-acetoxyhydroxymethyl)-4-methoxy-3-methylpyrrole-5-carboxylate* (2·00 g), m.p. 127–128° (Found: C, 53·4; H, 6·1; N, 4·9. $C_{12}H_{17}NO_6$ requires C, 53·1; H, 6·3; N, 5·2%). ν_{max} (Nujol): 3465, 3455, 1770, 1717, 1692, 1672 cm^{-1}. τ ($CDCl_3$): −0·2 (1H, exchanged with D_2O, NH), 2·29 (1H, −CH(OAc)OH), 5·63 (2H, quartet, OCH_2CH_3), 6·12 (3H, OCH_3), 7·89, 7·92 (7H, one proton exchanged with D_2O; aromatic methyl, $COCH_3$, OH), 8·63 (3H, triplet, OCH_2CH_3).

(ii) *Ethyl 2-formyl-4-methoxy-3-methylpyrrole-5-carboxylate.*—The acetoxyhydroxymethylpyrrole (0·5 g) was heated under reflux in aqueous ethanol (5 ml; 30%) for 30 min, and allowed to stand at 5° for 24 hr. The crystalline precipitate was collected and sublimed (90°/1 mm) to give *ethyl 2-formyl-4-methoxy-3-methylpyrrole-5-carboxylate* (0·32 g), m.p. 96–98° (Found: C, 56·8; H, 6·2; N, 6·8. $C_{10}H_{13}NO_4$ requires C, 56·8; H, 6·2; N, 6·6%). ν_{max} (CCl_4): 3380, 3220, 2710, 1720sh, 1700, 1670 cm^{-1}. τ ($CDCl_3$): 0·20 (1H, aldehyde proton), 0·2–0·6 (1H, NH), 5·59 (2H, quartet, OCH_2CH_3), 6·11 (3H, OCH_3), 7·70 (3H, aromatic methyl), 8·60 (3H, triplet, OCH_2CH_3).

The filtrate remaining after the collection of the aldehyde was treated with *S*-benzylisothiouronium chloride (0·3 g) in water (2 ml) and the mixture allowed to stand for 30 min. The solid was collected and recrystallized from dioxan to give *S*-benzylisothiouronium acetate, m.p. 132–135° (lit.[28] 136°), alone or upon admixture with an authentic sample of this acetate.

(iii) *2-Formyl-4-methoxy-3-methylpyrrole-5-carboxylic acid.*—A solution of ethyl 2 (1′,1′-acetoxyhydroxymethyl)-4-methoxy-3-methylpyrrole-5-carboxylate (1·50 g) in 80% aqueous methanolic potassium hydroxide solution (10 ml; 2N) was heated on the steam-bath for 2 hr and diluted with water (15 ml). Acidification of the cooled mixture with dilute hydrochloric acid gave *2-formyl-4-methoxy-3-methylpyrrole-5-carboxylic acid* (0·61 g), m.p. 181–184° with initial darkening at 150°, from carbon tetrachloride (Found: C, 52·3; H, 5·0; N, 7·6. $C_8H_9NO_4$ requires C, 52·5; H, 4·95; N, 7·65%).

(iv) *Ethyl 2-(2′,2′-dicyanovinyl)-4-methoxy-3-methylpyrrole-5-carboxylate.*—Triethylamine (0·05 ml) was added to a solution of malononitrile (0·07 g) and ethyl 2-formyl-4-methoxy-3-methylpyrrole-5-carboxylate (0·2 g) in absolute ethanol (5 ml) and the mixture allowed to stand at room temperature for 1 hr. The product was collected and recrystallized from ethanol to give yellow silky needles of *ethyl 2-(2′,2′-dicyanovinyl)-4-methoxy-3-methylpyrrole-5-carboxylate* (0·21 g), m.p. 169–170° (Found: C, 60·4; H, 5·1; N, 16·4. $C_{13}H_{13}N_3O_3$ requires C, 60·2; H, 5·05; N, 16·2%).

[28] Vogel, A. I., "A Textbook of Practical Organic Chemistry." p. 365. (Longmans: London 1956.)

(v) *Ethyl 4-methoxy-3-methyl-2-(4′,4′,6′-trimethyl-1′,3′-dioxan-2′-yl)pyrrole-5-carboxylate.*—A benzene solution (15 ml) of ethyl 2-formyl-4-methoxy-3-methylpyrrole-5-carboxylate (0·1 g), and 2-methylpentane-2,4-diol (0·3 ml) and a trace of *p*-toluenesulphonic acid was refluxed for 30 min under a Dean and Stark head. The oily residue remaining after evaporation of solvent was dissolved in ether and the ethereal solution washed with aqueous sodium hydrogen carbonate solution and water. The solvent was removed and the residue, dissolved in light petroleum, was cooled to −70° whereupon the crude acetal crystallized. Recrystallization from light petroleum gave *ethyl 4-methoxy-3-methyl-2-(4′,4′,6′-trimethyl-1′,3′-dioxan-2′-yl)pyrrole-5-carboxylate* (0·15 g), m.p. 75–76° (Found: C, 61·4; H, 8·0; N, 4·3. $C_{16}H_{25}NO_5$ requires C, 61·7; H, 8·1; N, 4·5%).

(vi) *5-Formyl-4-methoxy-2,3-dimethylpyrrole.*—Ethyl 4-methoxy-2,3-dimethylpyrrole-5-carboxylate (1·1 g) was refluxed with hydrazine (2·5 ml; 95%) for 2 hr after which water (5 ml) was added to the warm reaction mixture. From the cold mixture *5-hydrazinocarbonyl-4-methoxy-2,3-dimethylpyrrole* (0·97 g) was obtained as colourless prisms, m.p. 209–210°, from methanol (Found: C, 52·1; H, 7·2; N, 22·7. $C_8H_{13}N_3O_2$ requires C, 52·45; H, 7·15; N, 22·9%).

A stirred suspension of the hydrazide (0·9 g) in dry pyridine (10 ml) was treated at 0° with a solution of *p*-toluenesulphonyl chloride (1·16 g) in dry pyridine (5 ml), whereupon the hydrazide dissolved. After 15 min at room temperature the mixture was poured into ice-cold hydrochloric acid (2N, 100 ml), the precipitate collected and recrystallized from carbon tetrachloride to give the sulphonylhydrazide (1·44 g), m.p. 150–151°.

A mixture of sulphonylhydrazide (1·44 g), anhydrous sodium carbonate (1·44 g), and diethylene glycol (25 ml) was stirred under nitrogen at 170° for 5 min. The warm reaction mixture was then poured into ice-cold water (50 ml) and the precipitate collected. Chloroform extraction (2 × 20 ml) of the filtrate and removal of the solvent gave a residue which was combined with the original precipitate and the total solid purified by recrystallization from alcohol to give *5-formyl-4-methoxy-2,3-dimethylpyrrole* (0·45 g), m.p. 133–135° (Found: C, 62·55; H, 7·0; N, 9·2. $C_8H_{11}NO_2$ requires C, 62·7; H, 7·2; N, 9·1%).

The *2,4-dinitrophenylhydrazone* was obtained in the usual way as dark red needles from alcohol, m.p. 241–244° (Found: C, 50·5; H, 4·7; N, 21·0. $C_{14}H_{15}N_5O_5$ requires C, 50·4; H, 4·5; N, 21·0%).

(vii) *Ethyl 2-carboxy-4-methoxy-3-methylpyrrole-5-carboxylate.*—To a stirred solution of ethyl 4-methoxy-2,3-dimethylpyrrole-5-carboxylate (5·0 g) in acetic acid/dry ether (1 : 1; 100 ml), cooled to −5°, was added dropwise over 40 min freshly distilled sulphuryl chloride (7·8 ml). The reaction mixture was allowed to return to room temperature over a period of 2–3 hr and then allowed to stand overnight. Water (10 ml) was added, and after 30 min the solvent was removed under vacuum. The residue was partitioned between ether and water and the ethereal layer extracted with aqueous sodium hydrogen carbonate solution. This alkaline extract, after acidification with dilute hydrochloric acid, yielded *ethyl 2-carboxy-4-methoxy-3-methylpyrrole-5-carboxylate* (2·5 g), m.p. 210–211°, purified by recrystallization from aqueous alcohol (Found: C, 53·0; H, 6·0; N, 6·4. $C_{10}H_{13}NO_5$ requires C, 52·9; H, 5·8; N, 6·2%). Attempts to work on a larger scale reduced the yield of the reaction.

(viii) *Ethyl 2-iodo-4-methoxy-3-methylpyrrole-5-carboxylate.*—A solution of iodine (4·64 g) and potassium iodide (10 g) in water (25 ml) was added dropwise over 15 min to a well-stirred solution of ethyl 2-carboxy-4-methoxy-3-methylpyrrole-5-carboxylate (3·73 g) in aqueous sodium carbonate solution (1·5N; 240 ml) maintained at 0°. After allowing the mixture to stand at room temperature for 2 hr with occasional stirring the yellow precipitate of *ethyl 2-iodo-4-methoxy-3-methylpyrrole-5-carboxylate* was collected and washed well with water. This was sufficiently pure for the next step. For analysis a sample was recrystallized from ethanol to give white prisms, m.p. 129–130° (Found: C, 35·3; H, 4·1; N, 4·8. $C_9H_{12}INO_3$ requires C, 35·0; H, 3·9; N, 4·5%).

(ix) *Ethyl 3-methoxy-4-methylpyrrole-2-carboxylate.*—The wet filter cake of iodopyrrole from above was immediately dissolved in ethanol (100 ml) containing triethylamine (2 ml). This solution was hydrogenolysed over palladium–charcoal (10%; 0·50 g) at room temperature and pressure for 16 hr. The catalyst was removed by filtration and the filtrate evaporated to

dryness under vacuum to give a semicrystalline residue which was partitioned between ether and water. The ethereal layer was evaporated to dryness and the residue crystallized from light petroleum to give ethyl 3-methoxy-4-methylpyrrole-2-carboxylate (2·5 g), m.p. 76–78°, alone or on admixture with a sample of this compound prepared above. The i.r. spectra of both materials were identical.

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