THE CHEMISTRY OF PYRROLIC COMPOUNDS

XVII.* FURAN AND THIOPHEN ANALOGUES OF OXYPORPHYRINS

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Abstract

The preparation of a thiophen and a furan analogue of the oxyporphyrins is described. The properties of these compounds and their derivatives are discussed and the general chemistry of these macrocycles compared with the tetrapyrrolic oxyporphyrins.

Introduction

Several reports[1–4] have appeared recently of the synthesis of porphyrin-like systems in which one or more pyrrolic units have been replaced by either furan or thiophen. It seemed that another approach to this type of macrocycle might be made by way of oxyporphyrin-like intermediates as this type of synthesis had been very successful in the preparation of porphyrins proper.[5,6] Moreover, it was of some interest to see how the inclusion of a furan or thiophen ring system in an oxyporphyrin type macrocycle affected the general properties of this species. This paper describes some aspects of the chemistry of these novel oxyporphyrin analogues.

Results and Discussion

Pyrrolyl Thienyl and Pyrrolyl Furyl Ketones

Since methods were available for the synthesis of α,α'-diformyldipyrrylketones[7] the preparation of the furan and thiophen analogues of oxyporphyrins was approached using this type of intermediate. Hence the furan and thiophen ring systems needed to be incorporated into a suitable methane derivative. Gilman and his co-workers[8] had reported the preparation of pyrrolyl furyl ketone by condensation of a Grignard

* Part XVI, *Aust. J. Chem.*, 1971, **24**, 1933.

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[1] Broadhurst, M. J., Grigg, R., and Johnson, A. W., *Chem. Commun.*, 1969, 23.

[2] Broadhurst, M. J., Grigg, R., and Johnson, A. W., *Chem. Commun.*, 1969, 1480.

[3] Broadhurst, M. J., Grigg, R., Shelton, G., and Johnson, A. W., *Chem. Commun.*, 1970, 231.

[4] Broadhurst, M. J., Grigg, R., and Johnson, A. W., *Chem. Commun.*, 1970, 807.

[5] Jackson, A. H., Kenner, G. W., McGillivray, G., and Smith, K. M., *J. chem. Soc.* (*C*), 1968, 294.

[6] Clezy, P. S., and Liepa, A. J., *Aust. J. Chem.*, 1970, **23**, 2461.

[7] Clezy, P. S., Liepa, A. J., Nichol, A. W., and Smythe, G. A., *Aust. J. Chem.*, 1970, **23**, 589.

[8] Gilman, H., Rowe, L. W., and Dickey, J. B., *Recl Trav. chim. Pays-Bas*, 1933, **52**, 395.

derivative of pyrrole with furoyl chloride. This ketone seemed a suitable starting material as it had been reduced to the corresponding methane using lithium aluminium hydride.[9]

Pyrrolyl furyl ketone was obtained essentially by Gilman's procedure although in reduced yield in spite of extensive experimentation to provide more efficient reaction conditions. The novel pyrrolyl thienyl ketone was synthesized in an analogous manner. In general, the properties of the pyrrolyl furyl and pyrrolyl thienyl ketones resembled those of the better investigated dipyrrylketones.[10–13] The three compounds had similar n.m.r. and u.v. spectra and the mixed ketones showed the abnormally low i.r. carbonyl frequencies characteristic of dipyrrylketones.

Jackson *et al.*[14] had studied the mass spectra of dipyrrylketones and in general the fragmentation pattern of the mixed ketones was similar. Loss of carbon monoxide had not been reported from dipyrrylketones although this type of fragmentation had been observed with some diaryl ketones.[15] The two mixed ketones demonstrated this type of breakdown in the mass spectrometer to form ions formulated as (1b, 1c); the appropriate metastable peaks were observed. Loss of a hydrogen atom followed to give the ions (2b, 2c).

(1a)	X = NH	*m/e* 132	0%		(2a)	*m/e* 131	6%
(1b)	X = O	*m/e* 133	7%	131* →	(2b)	*m/e* 132	4%
(1c)	X = S	*m/e* 149	7%	147* →	(2c)	*m/e* 148	5%

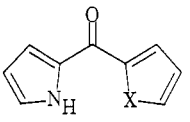
Re-examination of the mass spectrum of dipyrrylketone showed a peak corresponding to the ion (2a) of similar intensity to the analogous furyl and thienyl ions. An interesting feature of the mass spectrum of pyrrolyl thienyl ketone was the presence of an M—1 peak which was not observed in the fragmentation of the other two ketones.

Pyrrolylthienyl- and Furylpyrrolyl-methanes

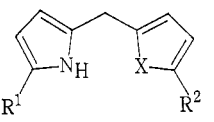
We had shown previously[16] that dipyrrylmethane (4a) could be conveniently obtained by reduction of the ketone (3a) with sodium borohydride in the presence of morpholine. However, attempts to extend this reduction to the mixed ketones (3b, 3c) yielded only small amounts of the corresponding methanes (4b, 4c); the two

[9] Gardner, T. S., Wenis, E., and Lee, J., *J. org. Chem.*, 1958, **23**, 823.
[10] Rapoport, H., and Willson, C. D., *J. Am. chem. Soc.*, 1962, **84**, 630.
[11] Clezy, P. S., and Nichol, A. W., *Aust. J. Chem.*, 1965, **18**, 1977.
[12] Osgerby, J. M., and Macdonald, S. F., *Can. J. Chem.*, 1962, **40**, 1585.
[13] Ballantine, J. A., Jackson, A. H., Kenner, G. W., and McGillivray, G., *Tetrahedron*, 1966, Suppl. No. 7, 241.
[14] Jackson, A. H., Kenner, G. W., Budzikiewicz, H., Djerassi, C., and Wilson, J. M., *Tetrahedron*, 1967, **23**, 603.
[15] Beynon, J. H., Lester, G. R., and Williams, A. E., *J. phys. Chem.*, 1959, **63**, 1861.
[16] Chong, R., Clezy, P. S., Liepa, A. J., and Nichol, A. W., *Aust. J. Chem.*, 1969, **22**, 229.

reaction mixtures by thin-layer chromatography were shown to consist mainly of starting material and a product assumed to be the carbinol (5b, 5c). Support for the carbinol formulation came from the pyrrolyl furyl ketone reduction where a crystalline product was isolated. This material proved too unstable for thorough characterization but the i.r. spectrum of this compound did not contain a carbonyl absorption band although maxima were observed at 3300 and 3400 cm^{-1} corresponding to NH and OH frequencies respectively. Thin-layer chromatography failed to indicate the presence of the intermediate carbinol in the reduction of (3a) with sodium borohydride–morpholine.

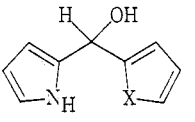


	X
(3a)	NH
(3b)	O
(3c)	S



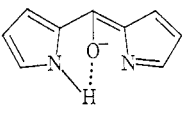
	X	R^1	R^2
(4a)	NH	H	H
(4b)	O	H	H
(4c)	S	H	H

	X	R^1	R^2
(4d)	O	CHO	CHO
(4e)	S	CHO	CHO
(4f)	O	CHO	H



	X
(5a)	NH
(5b)	O
(5c)	S

On the other hand, in the presence of potassium hydroxide, sodium borohydride reduced the ketones (3b, 3c) to the methanes (4b, 4c) and the yield of pyrrolylfuryl-methane obtained in this way was considerably higher than that claimed for an earlier procedure.[9] There was negligible conversion of dipyrrylketone (3a) into its methane (4a) in the presence of potassium hydroxide, due possibly to the formation of the anion (6) which would not be readily attacked by hydride ion at the carbonyl carbon. Intramolecular hydrogen bonding would be expected to stabilize this anion and thus aid its formation but this cannot occur in the thiophen or furan ketones. A similar stabilizing effect of hydrogen bonding has been suggested[17] as an explanation for the faster hydrolysis of pyrrole-2-carboxylic esters compared with the 3-isomers (cf. (7)).



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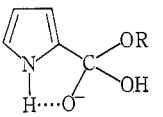


(7)

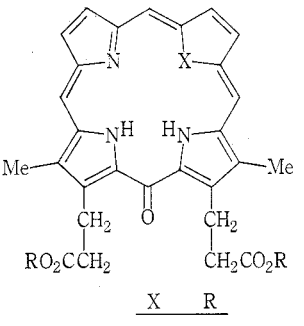
Pyrrolylfuryl- and pyrrolylthienyl-methanes were purified by vacuum distillation and obtained as colourless oils which solidified just below room temperature. Pyrrolylfurylmethane was particularly unstable and rapidly discoloured in contact with air. Consequently both methanes were stored under nitrogen at low temperature. The unstable nature of these compounds prevented a thorough investigation of their properties but the n.m.r. and i.r. spectra were in accord with their formulation as pyrrolylmethane derivatives. The n.m.r. spectra showed a resonance due to the

[17] Khan, M. K. A., and Morgan, K. J., *Tetrahedron*, 1965, **21**, 2197.

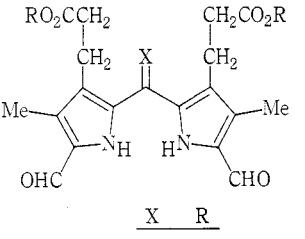
methylene protons of a pyrrolylmethane system but as with the ketones (3b, 3c) no attempt was made to analyse the complex splitting pattern of the aromatic protons. Infrared data indicated the absence of a carbonyl stretching vibration in (4b) and (4c) and in the latter compound an absorption maximum characteristic of the thiophen nucleus was observed.[18]

Preparation of Oxyporphyrin Analogues Containing Furan or Thiophen Ring Systems

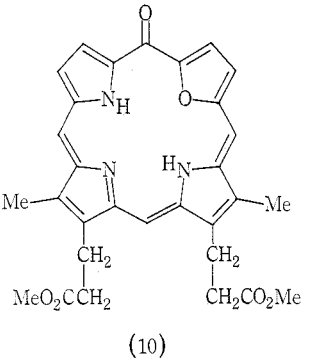
A furan analogue of an oxyporphyrin (8a) was obtained by allowing the methane (4b) to condense with the dipyrrylketone (9a) in trifluoroacetic acid following the general procedure employed to give oxyporphyrins proper.[6,19] However, longer reaction times were necessary for condensations involving the furan compound and reduced yields of macrocyclic product were obtained. Both these features probably arise from a lower reactivity of furan, compared with pyrrole, towards electrophilic substitution. Immediately the two reactants were added to the acid an intense red coloration was produced which showed no indication of porphyrin-like absorption. After an hour, however, the mixture developed a greenish tint which increased with time and was accompanied by sharp absorption maxima reminiscent of a tetrapyrrolic spectrum.



	X	R
(8a)	O	Me
(8b)	NH	Me
(8c)	S	Et



	X	R
(9a)	O	Me
(9b)	H_2	Me
(9c)	O	Et



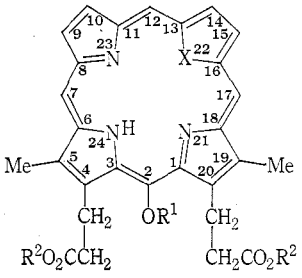
(10)

Efforts to synthesize the isomeric system (10) by allowing pyrrolyl furyl ketone (3b) to condense with the diformyldipyrrylmethane (9b) in the presence of acetic anhydride failed, although oxyporphyrins had been prepared in this manner.[19]

Attempts to prepare the thiophen analogue (8c) by the condensation of (9c) and (4c) in trifluoroacetic acid gave only trace amounts of the macrocycle. In an effort to increase the yield of this cyclization, acetic anhydride was incorporated into the reaction medium since this reagent had been shown in some cases to improve oxyporphyrin condensations.[19] In this manner the thiophen macrocycle was obtained as the enol acetate (11a) in increased but somewhat low yield (4%).

[18] Hartough, H. D., "Thiophen and its Derivatives." p. 106. (Interscience: New York 1952.)
[19] Clezy, P. S., Liepa, A. J., and Smythe, G. A., *Aust. J. Chem.*, 1970, **23**, 603.

Reactions employing hydrogen bromide as catalyst seemed too vigorous as only tarry products were formed; reactions carried out above room temperature also gave intractable material.



	X	R^1	R^2
(11a)	S	Ac	Et
(11b)	O	H	Me
(11c)	S	H	Et

The *meso*-acetoxy compound (11a) was purified by thick-layer chromatography and converted into the thiophen oxyporphyrin analogue (8c) by hydrolysis on alumina.

Properties of the Furan and Thiophen Oxyporphyrin Analogues

Several groups of workers had examined the chemistry of the tetrapyrrolic oxyporphyrins and it was clear that these compounds existed predominantly as the keto tautomer although derivatives of the enolic isomer could be readily prepared. The weight of available evidence pointed strongly to the oxophlorin-type structure (8b) being the best representation of the oxyporphyrin molecule although it was not possible to thoroughly substantiate this by n.m.r. spectroscopy due to the paramagnetic characteristic of these molecules.

In general the furan and thiophen analogues resembled the oxyporphyrins from a structural viewpoint although there were unexpected differences in some properties between the three macrocycles. The furan derivative (8a) and the thiophen compound (8c) showed strong absorption in the infrared between 1550 and 1600 cm^{-1}, which was the region where the carbonyl stretching frequency of oxyporphyrins had been found. This pointed to a ketone structure for (8a) and (8c) and as these molecules, unlike the oxyporphyrins, were diamagnetic (no e.s.r. signal was observed) additional structural information was available from n.m.r. spectroscopy. In chloroform solution both molecules showed resonances near τ 7·4 (ring methyls), 2·0–2·7 (methine protons), and 8·4 (NH) which indicated a greatly reduced ring current compared with a neutral porphyrin, a situation which was quite consistent with the formulation of these macrocycles as (8a) and (8c). It was also clear that these results parallelled closely the limited data available from poorly resolved n.m.r. spectra obtained with oxyporphyrins in $CDCl_3$ at $-30°$.[19,20]

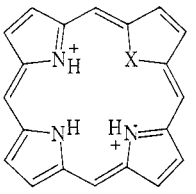
In trifluoroacetic acid the n.m.r. spectra of both (8a) and (8c) indicated a greatly increased ring current, suggesting that the macrocycles were present as the dication of the enolic tautomers (11b) and (11c). Oxyporphyrins behaved in the same way in acidic solutions.

The electronic spectra of (8a) and (8c) and their derivatives were characterized by an intense absorption near 400 nm which was typical of the porphyrin macrocycle.

[20] Jackson, A. H., Kenner, G. W., and Smith, K. M., *J. chem. Soc.* (*C*), 1968, 302.

Apart from this maximum the visible spectrum of (8a) in neutral solvent was five-banded; the intensities of these maxima decreased regularly from the long-wavelength band to the short-wavelength maximum (i.e. I > II > III > IV > V). Although five-banded spectra had previously been reported[19] for oxyporphyrins in neutral solvent none had similar relative intensities to those displayed by the furan-containing compound. There was however a certain similarity to the spectrum of the oxyporphyrin monocation reported by Kenner and his associates.[20] On the other hand, the thiophen derivative (8c) was very unstable to light in neutral solution, in fact too unstable to enable a quantitative electronic spectrum to be recorded. Oxyporphyrins proper had been observed to be degraded photolytically[21,22] and it seemed that the breakdown of (8c) was light induced since solutions stored in the dark were reasonably stable.

The electronic spectra of (8a) and (8c) in acidic solution showed three absorption maxima. The species present under these conditions was almost certainly the dication (12; X = S or O), although porphyrin monocations had been reported to give three-banded spectra.[23a] From a symmetry standpoint the chromophoric system of the dication (12) resembled that present in the monocation of a normal porphyrin (13) and it was this feature which was possibly responsible for the similarity in absorption pattern.



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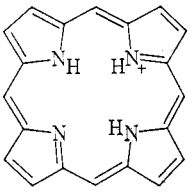


(13)

Copper and nickel complexes of (8a) were prepared in the usual way. The nickel chelate proved troublesome to purify but this difficulty was not encountered with the copper derivative. Lack of material prevented an investigation of metal chelates of (8c).

The electronic spectrum of the copper chelate of (8a) strongly resembled the absorption pattern of the neutral ligand. This was quite a different situation from the oxyporphyrin chelates but predictable in view of the replacement of an NH by O in the furan macrocycle. If an uncharged metal chelate was formed with Cu^{2+} ions the furan derivative must react in the keto form (8a) and hence the chromophoric system would be expected to be the same as that present in the metal free ligand. In agreement with this, the copper derivative of (8a) showed strong infrared absorption between 1550 and 1600 cm^{-1}.

Enol Acetate Derivatives of the Furan and Thiophen Oxyporphyrin Analogues

An important difference between the oxyporphyrins and the furan analogue (8a) was the difficulty encountered in preparing an enol acetate derivative in the latter

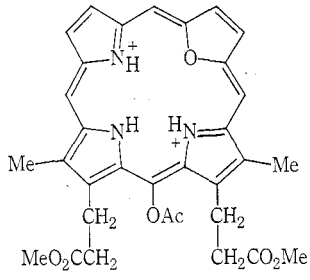
[21] Bonnett, R., Dimsdale, M. J., and Stephenson, G. F., *J. chem. Soc.* (*C*), 1969, 564.

[22] Nichol, A. W., Ph.D. Thesis, University of New South Wales, 1965.

[23] Falk, J. E., "Porphyrins and Metalloporphyrins." (*a*) p. 238; (*b*) p. 74. (Elsevier: Amsterdam 1964.)

system. Such derivatives had been readily formed from oxyporphyrins by base-catalysed acetylation (pyridine–acetic anhydride) and also from acid-catalysed reactions where acetic anhydride had been added to the acidic oxyporphyrin reaction mixture.[19]

Acetylation of (8a) with acetic anhydride–pyridine failed under several reaction conditions, including heating the mixture on the steam-bath for 2 hr. With isopropenyl acetate and catalytic amounts of perchloric acid, (8a) gave a red solid. This product upon neutralization yielded a green-yellow solution (490, 520, 580 nm, hand spectroscope) which rapidly reverted to the spectrum of the original furan derivative (8a). This result suggested that the *meso*-acetoxy compound was readily hydrolysed under basic conditions and hence it was decided to attempt the isolation of this derivative as a salt. This was achieved by allowing (8a) to react with acetic anhydride in the presence of perchloric acid. The red salt (14) was washed with acetone and chloroform to remove excess acetic anhydride and perchloric acid but was almost insoluble in the usual range of organic solvents and could not be further purified by recrystallization. Basification rapidly yielded the oxyporphyrin-like macrocycle (8a).



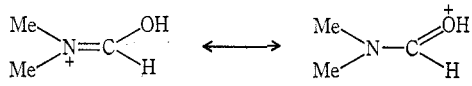
(14)

Although poor solubility prevented thorough purification of this salt, spectroscopic data were in accord with its formulation as (14) and combustion data on the crude product were in better agreement for a diperchlorate than a monoperchlorate. The carbonyl frequencies between 1550 and 1600 cm^{-1} which were prominent features of the infrared spectra of (8a) and its copper complex were missing from acetate salt (14) although maxima were to be found in this derivative at 1760 and 1100 cm^{-1} corresponding to the enol ester and the perchlorate[24] respectively. The poor solubility of (14) made determination of an accurate n.m.r. spectrum difficult but in dimethyl sulphoxide (DMSO) a weak spectrum was obtained which showed signals between τ −0·2 and τ 0·5 (methine protons and aromatic protons). A resonance at τ 6·82 due to the enol acetate group was also apparent.

Difficulty was also experienced in determining the visible spectrum of (14) since it was not soluble in the common neutral solvents and was hydrolysed in either strongly basic or acidic solutions. One of the two satisfactory solvents was *N*,*N*-dimethylformamide (DMF) but in this medium the initially pink salt became yellow-green when the concentration was adjusted to a level suitable for spectrophotometric measurement. Acidification of the yellow-green solution with perchloric acid gave the initial pink colour. It might have been that the DMF contained small amounts of dimethylamine

[24] Cross, A. D., "Introduction to Practical Infra-red Spectroscopy." 2nd Edn, p. 81. (Butterworths: London 1964.)

which neutralized the salt (14) to form the neutral enol acetate molecule. The spectrum of this solution could be recorded since it was stable for several hours. In DMSO the enol acetate salt (14) displayed the same colour change. Since no basic impurity was likely to be present in DMSO it was concluded that the two acidic NH protons were abstracted by the basic oxygen of the solvent. It was possible that a similar occurrence might explain the colour change in DMF since protonation of the carbonyl oxygen would give a resonance-stabilized ion. If the DMF and DMSO



solutions in fact contained the neutral acetoxyporphyrin analogue this species displayed a three-banded spectrum which differed significantly from the four-banded phyllo-type spectrum[23b] of similarly substituted *meso*-acetoxyporphyrins.

The acid spectrum of (14) in DMF was not well defined. The Soret peak was unusually broad as were the three absorption maxima in the visible part of the spectrum.

As indicated previously the enol acetate of the thiophen macrocycle (11a) was comparatively stable and could be completely characterized. Apart from the preparation given earlier the acetate (11a) was obtained directly from (8c) by reaction with acetic anhydride–pyridine although more vigorous conditions were necessary to achieve this transformation than was required for the conversion of an oxyporphyrin into a *meso*-acetoxyporphyrin. In this respect the thiophen analogue had properties intermediate between the furan derivative and the tetrapyrrolic oxyporphyrins.

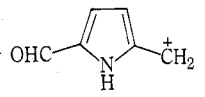
Spectroscopic data derived from (11a) were in agreement with its formulation as the enol acetate. A four-banded visible spectrum was observed in chloroform solution although this was aetio-type[23b] rather than the phyllo-type spectrum of similarly substituted acetoxyporphyrins. In acid (11a) exhibited two maxima; one of the bands was very broad and in the hand spectroscope appeared as two distinct absorptions. A stretching vibration due to the carbonyl was observed at 1775 cm^{-1} in the infrared spectrum.

Although (11a) was much more stable than the corresponding furan macrocycle it did hydrolyse slowly in trifluoroacetic acid which prevented a satisfactory n.m.r. spectrum being obtained in that solvent. However, it was evident from the spectrum observed in neutral solvent ($CDCl_3$) that the molecule sustained a ring current comparable with the tetrapyrrolic system. The NH protons were strongly shielded (τ *c.* 14·0) and the methine protons were found at characteristically low field (τ −0·4).

A wide range of *meso*-acetoxyporphyrins[5,6] had been converted into porphyrins proper by hydrogenation followed by oxidation but this useful reaction was not applicable to the furan analogue. Hydrogenation of (14) in DMF as solvent gave a colourless solution which upon oxidation yielded neither the starting material nor the *meso*-unsubstituted macrocycle. It was concluded that the furan compound was degraded by this procedure. Other reagents (Na/Hg; B_2H_6) which had been used to reduce the carbonyl group of oxyporphyrins[5] did not yield any detectable quantity of porphyrin-like compounds when they were allowed to react with the furan macrocycle (8a).

Other Approaches to Porphyrin-like Systems

A useful method of preparing certain types of porphyrin involves the condensation of a 5,5′-diformyldipyrrylmethane with a 5,5′-unsubstituted dipyrrylmethane. It seemed therefore if the compounds (4d) and (4e) were available that these might be useful intermediates for the preparation of porphyrin-like systems incorporating furan or thiophen ring systems. Formylation of (4b) using a modified Vilsmeier–Haack[16] procedure gave a crystalline monoformyl compound. This product was formulated as (4f) with the formyl group attached to the pyrrolic ring system since the ion (15) at *m/e* 108 occurred in the mass spectrum of this formyl derivative. N.m.r. data supported this structure as the NH proton was shifted downfield due to deshielding by the carbonyl group. There is evidence that in many electrophilic substitutions pyrrole is more reactive than furan[25–27] but statements to the contrary have appeared.[28,29]



(15)

The more usual Vilsmeier–Haack method employing DMF and phosphorus oxychloride was tried in an attempt to obtain the diformyl derivative (4d) but this procedure also failed to yield the desired product. This was surprising since furan had been formylated in this way.[30] Small quantities of the monoformyl compound were obtained by this procedure but the major product was a highly insoluble material, the general properties of which suggested that it was polymeric in nature.

Since the 5,5′-diformyl compound (4d) could not be synthesized attention was focused on the possible preparation of porphyrin-like compounds by condensation of pyrrolylfurylmethane with the diformyldipyrrylmethane (9b). Reactions were attempted under a variety of conditions but the only product recognized was a small amount of porphyrin derived from the self-condensation of (9b).

Attempts to self-condense the monoformyl derivative (4f) were also unsuccessful. This failure possibly correlates with the lack of success experienced in this Laboratory and noted by other workers when the synthesis of completely unsubstituted macrocycles of the porphyrin class was attempted. For example, we had no success in preparing porphin by the acid-catalysed condensation of dipyrrylmethane and 5,5′-diformyldipyrrylmethane[31] and Ahmed and Meth-Cohn[32] were unable to synthesize an unsubstituted tetrathiophen macrocycle by similar methods. It was suggested by these latter workers[32] that the lack of substituents on the molecule resulted in the absence of steric constraints which in substituted derivatives forced the molecule into a suitable conformation for cyclization.

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Experimental

(a) General

All melting points were uncorrected. Analyses were carried out by the Australian Microanalytical Service, Melbourne, and by Dr E. Challen of the School of Chemistry, University of New South Wales. Electronic spectra were recorded using a Beckman DB-G spectrophotometer. Infrared spectra were determined with the aid of a Perkin–Elmer 137 instrument or an Hitachi EPI-62 machine. N.m.r. spectra were determined on a Varian A60 or a Jeolco 100-MHz instrument; resonances are quoted on the τ scale relative to tetramethylsilane as an internal standard. Mass spectra were recorded on an A.E.I. MS12 spectrophotometer; the relative abundances of fragment ions are given as percentage of the base peak and ions of less than 5% are not recorded unless they are of special interest. All solutions in water-immiscible solvents were dried over anhydrous sodium sulphate before evaporation which was normally carried out using a Buchi rotary evaporator. Alumina refers to Peter Spence grade H and silica gel to Merck Kieselgel H. The petroleum fraction of b.p. 60–80° is referred to as light petroleum.

(b) Pyrrolylmethanes and Ketones

(i) *2-Furyl 2-Pyrrolyl Ketone*

This ketone was obtained in 25% yield by the method of Gilman *et al.*[8] λ_{max} in 95% EtOH (log ϵ): 272 (3·90), 329 (4·29) nm. ν_{max} (Nujol): 3250 (NH), 1600 (CO) cm^{-1}. τ ($CDCl_3$): −0·3 (1H, NH), 2·2–3·8 (6H, m, aromatic protons). *m/e* (%): 161 (100), 133 (7), 132 (4), 105 (6), 104 (14), 94 (81), 93 (40), 78 (5), 77 (4), 68 (51), 67 (4), 66·5 (7), 66 (29). *m**: 131 (133 → 132), 110 (161 → 133), 103 (105 → 104), 83·5 (133 → 105), 46·3 (94 → 66).

(ii) *2-Furyl-2-pyrrolylmethanol*

A solution of 2-furyl 2-pyrrolyl ketone (1 g) in ethanol (95%; 50 ml) containing morpholine (2 ml) was refluxed under nitrogen while sodium borohydride (6 × 0·5 g) was added portionwise over 3 hr. The mixture was refluxed for a further 2 hr, poured into water (100 ml), and extracted with ether (4 × 20 ml). The combined extracts were washed with water, concentrated (10 ml), and left to stand at 0°. Next day the *carbinol* (0·2 g) was collected as colourless prisms, m.p. 90° (sublimation) which rapidly decomposed when allowed to stand at room temperature. ν_{max} (Nujol): 3300 (NH), 3400 (OH) cm^{-1}.

(iii) *2-Furyl-2-pyrrolylmethane*

A solution of 2-furyl 2-pyrrolyl ketone (2·5 g) in ethanol (95%; 50 ml) containing potassium hydroxide (0·1 g) was refluxed under nitrogen while being treated portionwise over 2 hr with sodium borohydride (4 × 0·5 g). The solution was refluxed for a further 2 hr and then diluted with water (150 ml). The aqueous solution was extracted with ether (4 × 30 ml) and the combined ethereal extracts washed with water. Removal of solvent left a dark oil which was distilled to give the product (1·8 g) as a colourless oil, b.p. 78–80°/2 mm (lit.[9] 80–96°/3 mm) (Found: C, 73·8; H, 6·4; N, 9·7. Calc. for C_9H_9NO: C, 73·4; H, 6·2; N, 9·5%). ν_{max} (liquid film): 3500 (NH) cm^{-1}. τ ($CDCl_3$): 1·8 (1H, NH), 2·6–4·1 (6H, m, aromatic protons), 6·08 (2H, methane CH_2).

(iv) *5-Formylpyrrol-2-yl-2-furylmethane*

A stirred solution of 2-furyl-2-pyrrolylmethane (1 g) in *N*,*N*-dimethylformamide (8 ml) was maintained at 10° while benzoyl chloride (2 ml) was added dropwise. The mixture was stirred at room temperature for a further hour, benzene (50 ml) was added, and the supernatant liquid was decanted from the tarry residue 2 hr later. A solution of this gum in aqueous sodium carbonate solution (5%; 20 ml) was warmed at 60° for 20 min and next day the product was collected and recrystallized from aqueous ethanol to give the *formyl derivative* (0·4 g) as colourless plates, m.p. 74–75° (Found: C, 68·7; H, 5·4; N, 7·8. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2; N, 8·0%). ν_{max} (Nujol): 3250 (NH), 1640 (CHO) cm^{-1}. λ_{max} in 95% EtOH (log ϵ): 245 (3·64), 300 (4·35) nm. τ ($CDCl_3$): −0·5 (1H, NH), 0·60 (1H, CHO), 2·6–3·9 (5H, m, aromatic protons), 5·92 (2H,

methane CH_2). *m/e* (%): 175 (100), 174 (20), 146 (80), 118 (37), 117 (20), 108 (4), 106 (4), 91 (18), 89 (6), 81 (6), 78 (6), 65 (8). *m**: 122 (175 → 146), 95·5 (146 → 118), 70·2 (118 → 91), 46·5 (91 → 65).

(v) *2-Pyrrolyl 2-Thienyl Ketone*

A suspension of pyrrolylmagnesium bromide was prepared by the addition of pyrrole (6·7 g) in ether (25 ml) to a stirred ethereal (50 ml) suspension of ethylmagnesium bromide [derived from ethyl bromide (11·1 g) and magnesium (2·4 g)]. 2-Thienylcarbonyl chloride (14·3 g)[33] in ether (70 ml) was added dropwise to this suspension over 3 hr at a temperature which was not allowed to exceed −5°. The mixture was stirred overnight at room temperature, hydrolysed with aqueous ammonium chloride solution (5%; 100 ml), and extracted with ether (2 × 100 ml). The combined ethereal extracts were evaporated to dryness and the residue chromatographed on alumina in benzene solution. The same solvent eluted a pale yellow fraction from which the *ketone* (5·3 g) was obtained as yellow needles, m.p. 76–77°, from light petroleum (Found: C, 61·1; H, 3·9; N, 8·0. C_9H_7NOS requires C, 61·0; H, 4·0; N, 7·9%). ν_{max} (Nujol): 3300 (NH), 1580 (CO), 1410 (thiophen) cm^{-1}. λ_{max} in EtOH (log ϵ): 262 (3·91), 328 (4·23) nm. τ ($CDCl_3$): −0·5 (1H, NH), 2·0–3·8 (6H, m, aromatic protons). *m/e* (%): 177 (100), 176 (6), 160 (5), 149 (7), 148 (5), 111 (51), 94 (60), 93 (24), 84 (54), 83 (5), 74·5 (6), 66 (12). *m**: 175 (177 → 176), 147 (149 → 148), 144·7 (177 → 160), 125·3 (177 → 149), 62 (111 → 83), 46·5 (95 → 66).

(vi) *2-Pyrrolyl-2-thienylmethane*

A refluxing solution of 2-pyrrolyl 2-thienyl ketone (2·5 g) in ethanol (95%; 50 ml) containing potassium hydroxide (0·1 g) was treated under nitrogen with sodium borohydride (4 × 0·5 g) added over 2 hr. The solution was refluxed for a further 2 hr, diluted with water (150 ml), and the aqueous mixture extracted with ether (4 × 30 ml). The combined ethereal extracts were washed with water and the solvent removed. The residual oil was distilled to give the *methane* (1·9 g) as a colourless oil, b.p. 112–114°/2·5 mm (Found: C, 65·8; H, 5·6; N, 8·4. C_9H_9NS requires C, 66·2; H, 5·6; N, 8·6%). ν_{max} (liquid film): 3400 (NH), 1420 (thiophen) cm^{-1}. τ ($CDCl_3$): 2·2 (1H, NH), 2·8–4·1 (6H, m, aromatic proton), 5·90 (2H, methane CH_2).

(c) *Macrocyclic Derivatives of Furan and Thiophen*

(i) *Dimethyl 2-Hydroxy-5,19-dimethyl-22-oxa-21,23,24-triazapentacyclo[16,2,1,1^{3,6},1^{8,11},1^{13,16}]tetracosa-1(21),2,4,6,8(23),9,11,13,15,17,19-undecaene-4,20-dipropionate** (*11b* ⇌ *8a*)

A chloroform solution (20 ml) of bis(5-formyl-3-2′-methoxycarbonylethyl-4-methyl-2-pyrryl) ketone (0·4 g)[7] and 2-furyl-2-pyrrolylmethane (0·18 g) was added dropwise over 1 hr, with stirring, to trifluoroacetic acid (8 ml). The solution was allowed to stand for 3 hr after which chloroform (40 ml) was added and the mixture neutralized with aqueous ammonia (5N). The organic layer was filtered, washed with water, and evaporated to dryness. The residue from the filtration was suspended in methanol–sulphuric acid (20 : 1; 100 ml) and left overnight. This acidic solution was filtered, the filtrate concentrated (20 ml) and worked up as for the main batch of material. The combined organic residues were dissolved in a minimum volume of chloroform and applied to an alumina column. Elution with chloroform–benzene (2 : 3) yielded a green fraction from which the product (75 mg) was obtained as green *needles*, m.p. 218–220°, from chloroform–methanol (Found: C, 68·5; H, 5·6; N, 8·1. $C_{30}H_{29}N_3O_6$ requires C, 68·3; H, 5·6; N, 8·0%). ν_{max} (KBr): 1730 (ester), 1610, 1580, 1550 (CO) cm^{-1}. λ_{max} in $CHCl_3$ (log ϵ): 698 (3·99), 641 (3·72), 570 (3·57), 526 (3·53), 490 (3·42), 430 (4·69), 406 (4·71) nm. λ_{max} in 7·5N HCl (log ϵ): 614 (4·03), 564 (3·86), 535 (3·84), 399 (5·30) nm. τ ($CDCl_3$): 1·99 (1H) 2·87 (1H) 2·96 (1H) (methine protons), 2·38 (1H, d, *J* 4·0 Hz) 2·50 (1H, d, *J* 4·0 Hz) (pyrrole aromatic protons), 2·39 (1H, d, *J* 5·5 Hz) 2·73 (1H, d, *J* 5·5 Hz) (furan aromatic protons), 6·26 (3H) 6·30 (3H) (OCH_3), 6·4 (4H, t, *J* 7·0 Hz, CH_2CH_2CO), 7·0 (4H, t, *J* 7·0 Hz, CH_2CH_2CO), 7·34 (3H) 7·40 (3H) (aromatic CH_3), 8·3 (2H,

* For simplicity the molecules are named as their hydroxy tautomer with the macrocycle numbered as indicated in formula (11).

[33] Blicke, F. E., and Zienty, M. F., *J. Am. chem. Soc.*, 1941, **63**, 2945.

broad s, NH). τ (CF_3CO_2D): −0·73 (1H) −0·58 (1H) −0·33 (1H, methine protons), −0·23 (1H, d, J 5·0 Hz) 0·00 (1H, d, J 5·0 Hz) (pyrrole aromatic protons), 0·22 (1H, d, J 5·0 Hz) 0·48 (1H, d, J 5·0 Hz) (furan aromatic protons), 5·7 (4H, m, CH_2CH_2CO), 6·02 (3H) 6·10 (3H) (OCH_3), 6·3 (4H, m, CH_2CH_2CO), 6·48 (3H) 6·55 (3H) (aromatic CH_3).

(ii) *Copper Complex of Furan Macrocycle (8a)*

A mixture of the furan macrocycle (8a) (0·1 g), chloroform (10 ml), methanol (10 ml), and copper acetate (0·1 g) was refluxed for 20 min, and the solvents removed. The residue was dissolved in chloroform (20 ml) and the solution filtered to remove excess copper acetate; the *copper complex* (90 mg) was obtained from the filtrate and recrystallized from chloroform–methanol to yield blue-green needles, m.p. 230–232° (Found: C, 60·8; H, 4·6; N, 7·0. $C_{30}H_{27}CuN_3O_6$ requires C, 61·2; H, 4·6; N, 7·1%). ν_{max} (KBr): 1735 (ester), 1620, 1600, 1560sh, 1530 (CO) cm^{-1}. λ_{max} in $CHCl_3$ (log ϵ): 702 (4·27), 574 (3·58), 534 (3·93), 500 (3·52), 445 (4·97), 420 (4·85), 384 (4·66) nm.

(iii) *Dimethyl 2-Acetoxy-5,19-dimethyl-22-oxa-21,23,24-triazapentacyclo[16,2,1,$I^{3,6}$,$I^{8,11}$,$I^{13,16}$]tetracosa-1(21),2,4,6,8(23),9,11,13,15,17,19-undecaene-4,20-dipropionate Diperchlorate (14)*

A mixture of the furan macrocycle (8a) (100 mg), acetic anhydride (2·5 ml), and perchloric acid (0·5 ml) was allowed to stand at room temperature for 30 min. The precipitate was collected and washed with chloroform and acetone to give the *perchlorate* (91 mg) as a red powder, m.p. 190° (dec.), which was not sufficiently soluble in the usual range of organic solvents to allow further purification (Found: C, 47·3; H, 4·2; N, 5·0. $C_{32}H_{31}N_3O_7,2HClO_4$ requires C, 49·9; H, 4·3; N, 5·5%). λ_{max} in DMF (log ϵ): 590 (3·40), 520 (3·70), 490 (4·06), 398 (4·94) nm. λ_{max} in DMF containing 0·3% $HClO_4$ (log ϵ): infl. 595 (3·30), 552 (4·00), 536 (3·88), 383 (5·14) nm. ν_{max} (KBr): 1760 (acetate), 1721 (ester), 1100 (perchlorate) cm^{-1}. τ [$(CD_3)_2SO$]:* −0·2 to 0·52 (aromatic protons), 6·12, 6·22, 6·42 (aromatic CH_3), 6·82 (CH_3COO).

(iv) *Diethyl 2-Acetoxy-5,19-dimethyl-22-thia-21,23,24-triazapentacyclo[16,2,1,$I^{3,6}$,$I^{8,11}$,$I^{13,16}$]tetracosa-1(21),2,4,6,8(23),9,11,13,15,17,19-undecaene-4,20-dipropionate (11a)*

A solution of bis[3-(2-ethoxycarbonylethyl)-5-formyl-4-methyl-2-pyrryl] ketone (0·5 g)[7] and 2-pyrrolyl-2-thienylmethane (0·19 g) in chloroform (20 ml) was added dropwise at room temperature over 2 hr to a vigorously stirred mixture of trifluoroacetic acid (9 ml) and acetic anhydride (5 ml). The reaction mixture was allowed to stand for 48 hr, then chloroform (40 ml) was added, followed by water (100 ml). The solution was neutralized with aqueous ammonia (5N); the chloroform layer was separated and washed with water (100 ml), and the product was purified by thick-layer chromatography using chloroform as the developing solvent. A fast-running yellow band was collected from which the product (27 mg) was obtained as brown *plates*, m.p. 238–241°, from chloroform–ethanol (Found: C, 66·3; H, 5·8; N, 6·6. $C_{34}H_{35}N_3O_6S$ requires C, 66·5; H, 5·7; N, 6·8%). ν_{max} (KBr): 1770 (acetate), 1730 (ester) cm^{-1}. λ_{max} in $CHCl_3$ (log ϵ): 658 (2·77), 598 (3·64), 529 (3·94), 500 (4·36), 410 (5·24) nm. λ_{max} in CH_3OH–10N HCl (1 : 1) (log ϵ): 652 (3·56), 590 (3·53), 429 (4·90) nm. τ ($CDCl_3$): −0·56 (1H) −0·46 (1H) −0·12 (1H) (methine protons), 0·12 (2H, pyrrole aromatic protons), 0·91 (1H, d, J 4·0 Hz) 1·02 (1H, d, J 4·0 Hz) (aromatic thiophen protons), 5·75 (2H, q) 5·78 (2H, q) (OCH_2CH_3), 6·0 (4H, m, CH_2CH_2CO), 6·32 (3H) 6·60 (3H) (aromatic CH_3), 6·92 (3H, $OCOCH_3$), 7·00 (4H, m, CH_2CH_2CO), 8·76 (3H, t), 8·78 (3H, t) (OCH_2CH_3), 14·0 (1H, NH).

(v) *Diethyl 2-Hydroxy-5,19-dimethyl-22-thia-21,23,24-triazapentacyclo[16,2,1,$I^{3,6}$,$I^{8,11}$,$I^{13,16}$]tetracosa-1(21),2,4,6,8(23),9,11,13,15,17,19-undecaene-4,20-dipropionate (8c)*

A solution of the foregoing enol acetate (11a) (30 mg) in the minimum volume of chloroform was applied to an alumina column which was washed with chloroform–benzene (5 : 95) for 30 min. Chloroform–benzene (2 : 3) eluted a blue-green band which was immediately evaporated. The

* The solubility was too low to allow a very satisfactory n.m.r. spectrum to be obtained; in particular, it was not possible to derive an accurate integral.

residue was recrystallized from chloroform–ethanol to give the *product* (25 mg), m.p. 170–172°* (Found: C, 67·2; H, 6·1; N, 7·0. $C_{32}H_{33}N_3O_5S$ requires C, 67·2; H, 5·8; N, 7·4). ν_{max} (KBr): 1730 (ester), 1600, 1560 (CO) cm^{-1}. λ_{max} in CH_3OH–10N HCl (1 : 1) (log ϵ): 666 (3·83), 600 (3·67), 558 (3·58), 429 (5·05) nm. τ ($CDCl_3$): 2·10 (1H) 2·24 (1H) 2·42 (1H) (methine protons), 2·47 (2H, pyrrole aromatic protons), 2·75 (2H, m, thiophen aromatic protons), 5·8 (4H, overlapping q, OCH_2CH_3), 6·4 (4H, m, CH_2CH_2CO), 7·1 (4H, m, CH_2CH_2CO), 7·31 (3H) 7·43 (3H) (aromatic CH_3), 8·30 (2H, exchanges with D_2O, NH), 8·74 (3H, t) 8·77 (3H, t) (OCH_2CH_3). τ (CF_3CO_2D): −1·20 (1H) −0·90 (1H) −0·82 (1H) (methine protons), −0·30 (1H, d, J 4·0 Hz) −0·18 (1H, d, J 4·0 Hz) (pyrrole aromatic protons), 0·30 (1H, d, J 4·0 Hz) 0·44 (1H, d, J 4·0 Hz) (thiophen aromatic protons), 5·71 (8H, m, CH_2CH_2CO and OCH_2CH_3), 6·3 (4H, m, CH_2CH_2CO), 6·42 (3H), 6·44 (3H) (aromatic CH_3), 8·52 (3H, t) 8·54 (3H, t) (OCH_2CH_3).

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* On one occasion a sample of this material of m.p. 210–212° was obtained. In other respects (t.l.c.; i.r. and visible spectrum) the two forms were identical.