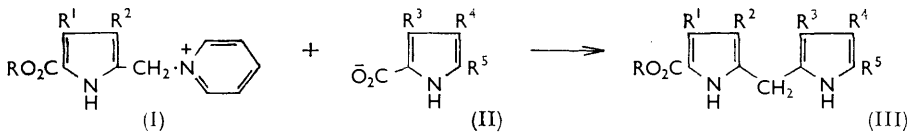
232. *Pyrroles and Related Compounds. Part V.*[1] *Syntheses of Some Pyrromethanes, Tripyrranes, and Porphyrins.*

By A. H. Jackson, G. W. Kenner, and D. Warburton.

Unsymmetrical pyrromethanes (III) with carboxylic ester substituents in both α-positions can be prepared from (2-pyrrolylmethyl)pyridinium salts (I) and pyrrole-2-carboxylates (II) by heating in formamide or aqueous methanol. Tripyrranes (XII) were obtained in moderate yield by condensation of pyrromethane-α-carboxylic acids (XI) (prepared by hydrogenolysis of the appropriate monobenzyl esters) with pyridinium compounds (I). Three porphyrins, including a rhodoporphyrin derivative, were synthesised by condensation of the 5,5′-diformylpyrromethane (XVII) with unsymmetrical α-unsubstituted pyrromethanes (XVI).

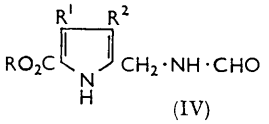
Methods for the synthesis of unsymmetrical pyrromethanes (pyrrolylmethylpyrroles) (III) by condensation of an α-bromomethylpyrrole, or the derived pyridinium salt (I), with, respectively, a pyrrole-α-carboxylic acid, or its alkali-metal salt (II), were described in Part I.[2] Such pyrromethanes are potentially useful intermediates in porphyrin syntheses, and indeed some applications of them have already been reported.[3] However, the examples in Part I were confined to 5-methylpyrrole-2-carboxylates (II and III; R^5 = Me), and the



(I) (II) (III)

purpose of the present work was to extend the range to pyrromethanes with alkoxycarbonyl groups in both α-positions, a series with much wider scope. Some porphyrin syntheses from these products are described below, and further examples will be given in later Papers.

Condensation of the pyridinium salts (I) with metal carboxylates (II) was previously accomplished in aqueous methanol at 40° ($R^3 = R^4 = R^5$ = alkyl) or in boiling 50% aqueous methanol ($R^3 = R^5$ = alkyl, $R^4 = CO_2Et$). A 5-alkoxycarbonyl substituent in the metal carboxylate (II) deactivates it considerably, but satisfactory yields are obtained (Table 1) after prolonged periods in formamide at 100° or in boiling 50% aqueous methanol. The use of anhydrous formamide is preferable because symmetrical pyrromethane is formed as a by-product in aqueous solvents or in ethylene glycol monoethyl ether, by self-condensation of the pyridinium salt (I). Symmetrical pyrromethanes were



(IV)

(a) R = R^2 = Et, R^1 = Me
(b) R = CH_2Ph, R^1 = Me, R^2 = Et
(c) R = CH_2Ph, R^1 = Me, R^2 = P^{Me} *

* " P^{Me} " is used in this and subsequent formulæ as a convenient abbreviation for the propionate ester side chain $CH_2CH_2CO_2Me$.

likewise formed when lithium benzoate was substituted for the pyrrole-2-carboxylate (II) in reactions in aqueous solvents. The formamide gave rise to small amounts of the formamidomethylpyrroles (IV), but fortunately these were readily separated from the pyrromethanes by crystallisation or chromatography.

Complete results of the present work are given in the Experimental section, but Table 1 summarises representative examples, including some from the earlier studies. The

[1] Part IV, Budzikiewicz, Djerassi, Jackson, Kenner, Newman, and Wilson, *J.*, 1964, 1949.
[2] Hayes, Kenner, and Williams, *J.*, 1958, 3779.
[3] Ellis, Jackson, Jain, and Kenner, *J.*, 1964, 1935.

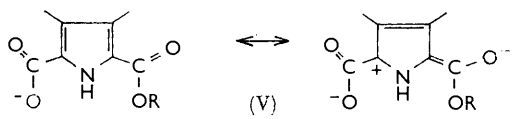
TABLE 1.

Comparison of the dissociation constants of pyrrole-2-carboxylic acids with reaction conditions and yields in syntheses of pyrromethanes (III).

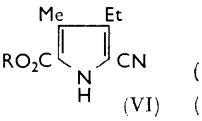
Pyridinium salt (I)			Pyrrole-2-carboxylic acid (II)			pK_{MCS} * (II)	Reaction conditions				
R	R^1	R^2	R^3	R^4	R^5	at 25°	Solvent	Temp.	Time (hr.)	Yield (%)	Ref.
CH_2Ph	Me	Et	Me	Et	Me		Aq. MeOH	40°	40	74	2
CH_2Ph	Me	P(Me)					,,	40	40	60	†
CH_2Ph	Me	Et	Et	Me	Me	8·24	,,	40	40	71	3
Et	Me	Et	Me	H	Me	7·93	,,	40	40	69	2
—	—	—	Me	P(Me)	Me	7·92	—	—	—	—	—
CH_2Ph	Me	Et	Me	CO_2Et	Me	7·11	,,	Reflux	8	78	2
Et	Me	CO_2Et					,,	Reflux	8	75	—
CH_2Ph	Me	Et	Me	Et	$CONMe_2$	7·03	,,	Reflux	9	25	—
							$H{\cdot}CONH_2$	100	20	53	—
CH_2Ph	Me	Et	Me	COMe	Me	6·98	Aq. MeOH	Reflux	20	50	—
CH_2Ph	Me	Et	Et	Me	CO_2Et	6·40	$H{\cdot}CONH_2$	100	48	46	—
Et	Me	Et	Et	Me	CO_2CH_2Ph	6·40	,,	100	48	39	—
CH_2Ph	Me	Et	P(Me)	Me	CO_2CH_2Ph	6·19	,,	100	72	43	—
CH_2Ph	Me	CO_2Et					,,	100	72	10	—
CH_2Ph	Me	Et	Me	Et	CN	6·12	,,	100	18	0	—
CH_2Ph	Me	P(Me)	CO_2Et	Me	CO_2CH_2Ph	5·66	,,	100	72	9	—

* Apparent dissociation constant in 2-methoxyethanol–water (78·5 : 21·5, v/v) (cf. Simon and Heilbronner, *Helv. Chim. Acta*, 1955, **38**, 508). † Unpublished work by (the late) W. G. Terry.

difficulty of reaction is clearly related to the number and position of electron-withdrawing groups in the pyrrole-2-carboxylate. The pK_a values of the corresponding acids provide a very useful criterion of their reactivity, and they presumably reflect the relative electron densities at the 2-position in the various pyrroles, *i.e.*, a high pK_a value corresponds to a high electron density (and hence high reactivity), whilst a low pK_a value points to a low electron density (or low reactivity) and thus accounts for the more forcing conditions required in the latter cases. It is interesting to note the relatively large range of pK_a values in this series compared with the range in benzoic acids, and it highlights the great sensitivity of the pyrrole ring to substituent effects. The difference between the effects of electron-withdrawing substituents at position 4 and 5 in the pyrrole-2-carboxylates (II) is pre-



(V)



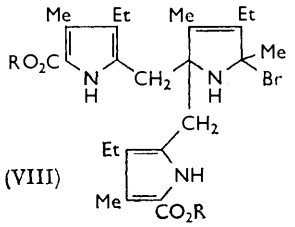
(VI) (a) R = H (b) R = CH_2Ph

sumably due to the more effective conjugation [as in (V)] possible between a 5-substituent and the 2-position (see ref. 1). The cyanopyrrole-2-carboxylic acid (VIa) was recovered unchanged from attempts to condense its lithium salt with the pyridinium salt (I; R = CH_2Ph, R^1 = Me, R^2 = Et), in formamide or aqueous methanol, and the only other product isolated was the formamidomethylpyrrole (IVb).

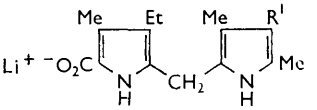
The nature of the substituents in the pyridinium salts (I) appears to have a relatively much smaller effect on the ease of pyrromethane formation, although a second electron-withdrawing substituent, (*e.g.*, R^2 = CO_2Et) may reduce the yield (see Table 1).

Preliminary attempts [2] to extend the scope of our pyrromethane synthesis to "tripyrranes" (pyrrolylmethylpyrrolylmethylpyrroles) by coupling pyrromethane-α-carboxylic acids with α-bromomethylpyrroles led to the formation of non-linear adducts, *e.g.*, (VIII). The pyridinium salt method was slightly more successful,[2] *e.g.*, a minute yield of the tripyrrane (Xa) was obtained by condensation of the pyridinium compound (I; R = CH_2Ph, R^1 = Me, R^2 = Et) with the lithium salt (IXa), whilst a second tripyrrane (Xb) was obtained in 23% yield from the pyridinium salt (I; R = Et, R^1 = Me, R^2 = CO_2Et) and the lithium salt (IXb). The higher yield in the latter case was presumably due to the electron-withdrawing effect of the 4′-ethoxycarbonyl substituent in the pyrromethane,

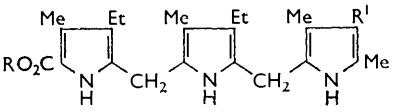
which hindered the formation of adducts of type (VIII). An electron-withdrawing substituent in the 5′-position of the pyrromethane was expected to have a similar (if not greater) effect in favouring the formation of tripyrranes, and we tested this hypothesis with the new pyrromethanes (III; $R^5 = CO_2Et$), prepared as described above. The lithium salt of the pyrromethane-5-carboxylic acid (XIa) (prepared by hydrogenolysis of the corresponding benzyl ester) condensed with the pyridinium salt (I; $R = CH_2Ph$, $R^1 = Me$,



(VIII)

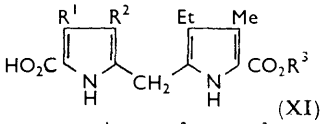


(IX) (a) $R^1 = Et$ (b) $R^1 = CO_2Et$



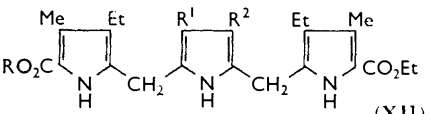
(X) (a) $R = CH_2Ph, R^1 = Et$ (b) $R = Et, R^1 = CO_2Et$

$R^2 = Et$) giving the tripyrrane (XIIa) in 29% yield. The latter was also obtained from the lithium salt of the pyrromethane (XIb) and the pyridinium salt (I; $R = R^2 = Et$, $R^1 = Me$), and a similar preparation gave the tripyrrane (XIIb). Attempts to synthesise these tripyrranes by direct condensation of α-bromomethylpyrroles with pyrromethane-α-carboxylic acids, *i.e.*, the alternative technique for pyrromethane synthesis,[2] gave no recognisable products. Condensation of the lithium salt (XIII) with the pyridinium salt



(XI)

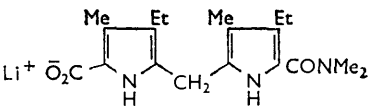
(a) $R^1 = Et, R^2 = Me, R^3 = Et$
(b) $R^1 = Me, R^2 = Et, R^3 = CH_2Ph$



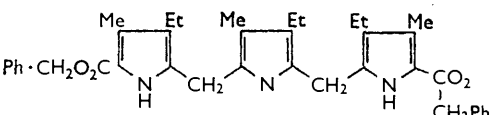
(XII)

(a) $R = CH_2Ph, R^1 = Et, R^2 = Me$
(b) $R = CH_2Ph, R^1 = Me, R^2 = Et$

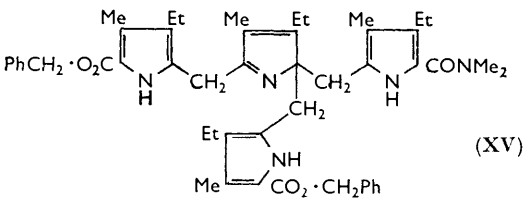
(I; $R = CH_2Ph$, $R^1 = Me$, $R^2 = Et$) unexpectedly gave the tripyrrane (XIV), identified by elemental analysis, molecular weight, and proton magnetic resonance (p.m.r.) spectroscopy. In this instance, two moles of the pyridinium salt (I) must have condensed with the pyrromethane carboxylate (XIII), one in the usual manner, and the second in such a way as to give a non-linear adduct (XV), (structurally analogous to the adducts (VIII) encountered in our earlier work); loss of the ring bearing the dimethylamido-substituent would then give the observed product.



(XIII)



(XIV)

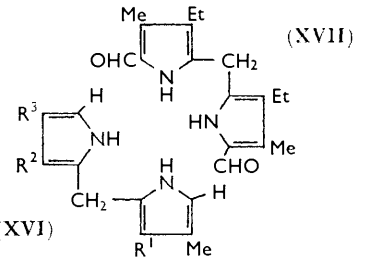


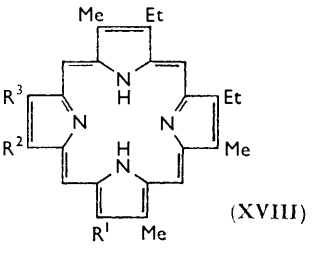
(XV)

No attempts were made to prepare tetrapyrranes from the tripyrranes, since the central pyrrole ring of these tripyrranes was not "protected" by an electron-withdrawing substituent, and therefore it should be more susceptible to electrophilic attack than the two end rings; consequently, non-linear adducts, analogous to (XV), or their cleavage products

might well be obtained. The relative inaccessibility of α-halogenomethylpyrromethanes precluded the synthesis of tetrapyrranes by coupling of two pyrromethanes. Pyridinium salts of α-halogenomethyldipyrroketones can, however, be coupled with pyrromethane-2-carboxylic acids successfully, as will be described in a later Paper.

Syntheses of porphyrins required for p.m.r. studies [4] have been accomplished using certain of the new pyrromethanes. The method was a variant of MacDonald's,[5] in which the di-α-unsubstituted pyrromethanes (XVI) (prepared by thermal decarboxylation of the corresponding dicarboxylic acids) were condensed with the symmetrical 5,5′-diformylpyrromethane (XVII) in acetic acid containing a catalytic amount of hydriodic acid. The dihydroporphyrins presumably produced as intermediates were oxidised directly by atmospheric oxygen to the desired porphyrins (XVIII). The yields were 20, 22, and





(a) $R^1 = R^2 = P^{Me}$, $R^3 = Me$. (b) $R^1 = P^{Me}$, $R^2 = Et$, $R^3 = Me$. (c) $R^1 = CO_2Me$, $R^2 = P^{Me}$, $R^3 = Me$.

5%, respectively, in series (a), (b), and (c); the lower yield in the last case was presumably due to the deactivating influence of the ethoxycarbonyl substituent in the starting pyrromethane (XVIc). In the cases of the porphyrins (XVIIIa or b) the pyrromethane dicarboxylic acids could be used instead of the decarboxylated methanes (XVIa or b). The structures of the products were confirmed by means of their visible and p.m.r. spectra and by comparison on paper and thin-layer chromatograms with similar porphyrins of known structure (see ref. 4).

Most of the required pyrroles were prepared by established methods.[2,3,6] The 5-cyanopyrrole (VIb) was synthesised from the corresponding 5-methylpyrrole by the sequence shown below. Hydrolysis of the dichloromethylpyrrole intermediates in such

$$-CH_3 \xrightarrow{SO_2Cl_2} -CHCl_2 \longrightarrow -CHO \xrightarrow{H_2NOH} -CH{=}NOH \xrightarrow{Ac_2O} -CN$$

preparations of pyrrole aldehydes is usually carried out by boiling with water or aqueous alkali (*e.g.*, sodium acetate). A better and more convenient method, discovered by Dr. J. A. Ballantine, is to treat the chloro-compound with gaseous dimethylamine before hydrolysis with boiling water; the immonium salt ($-CH{=}\overset{+}{N}Me_2Cl^-$) is presumably formed at first, and this undergoes hydrolysis more readily than the original dichloromethylpyrrole. A useful extension of this dimethylamine method is conversion of the analogous α-trichloromethylpyrroles into α-dimethylamidopyrroles (cf. Experimental section).

$$-CH_3 \longrightarrow -CCl_3 \longrightarrow -CONMe_2$$

Experimental

Benzyl 5-Bromomethyl-3-ethyl-4-methylpyrrole-2-carboxylate.—Bromine (0·63 ml.; 1 mol.) in dry ether (250 ml.) was added rapidly to a well-stirred solution of benzyl 3-ethyl-4,5-dimethylpyrrole-2-carboxylate (3 g.; 1 mol.) in dry ether (250 ml.). After 1 hr. the colour had faded to pale yellow, and the solution was concentrated under reduced pressure to about 80 ml. and stored overnight at 0°. The *bromomethylpyrrole* (3·2 g.; 82%) crystallised out as colourless

[4] Burbidge, Jackson, and Kenner, unpublished results.
[5] Arsenault, Bullock, and MacDonald, *J. Amer. Chem. Soc.*, 1960, **82**, 4384.
[6] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 287; Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254; Johnson, Kay, Markham, Price, and Shaw, *J.*, 1959, 3416.

needles, and after recrystallisation from light petroleum (b. p. 60—80°) had m. p. 137—138° (Found: C, 57·1; H, 5·4. $C_{16}H_{18}BrNO_2$ requires C, 57·0; H, 5·5%).

5-Benzyloxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylic acid (with DR. J. A. BALLANTINE).—Sulphuryl chloride (9·5 ml.; 3 mol.) was added slowly during 90 min. to a well-stirred solution of benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (10 g.; 1 mol.) in dry ether (200 ml.) and kept overnight. The mixture was treated with ice–water (100 ml.) and the ether layer separated and extracted with 2N-sodium carbonate solution (5 × 100 ml.). The combined aqueous extracts were saturated with sulphur dioxide, the precipitated *pyrrole-2-carboxylic acid* was filtered off, washed with water, dried in air, and recrystallised from chloroform–light petroleum (b. p. 60—80°) to give colourless needles (5·0 g.; 45%) m. p. 165—166° (Found: C, 66·9; H, 6·3; N, 4·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0; N, 4·9%).

5-Benzyloxycarbonyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole-2-carboxylic Acid.—Sulphuryl chloride (7·7 ml.; 3 mol.) was added during 75 min. to a well-stirred solution of benzyl 4-(2-methoxycarbonylethyl)3,5-dimethylpyrrole-2-carboxylate (10 g.) in ether (250 ml.). After being stored overnight at room temperature, the solution was boiled for 45 min. under reflux, and the solvent removed *in vacuo* (nitrogen leak). Residual sulphuryl chloride was removed by addition and evaporation of two further portions of ether (50 ml. each). The remaining oil was stirred vigorously with sodium acetate (20 g.) in water (150 ml.) for 30 min. at 80—90°, and the mixture was cooled and extracted with ether. The ethereal solution was extracted with 2N-sodium carbonate solution (5 × 100 ml.), and the combined aqueous extracts saturated with sulphur dioxide. The precipitated pyrrole carboxylic acid was filtered off, washed with water, dried in air, and recrystallised from chloroform–light petroleum (b. p. 40—60°) to give prisms (8·7 g.; 79%), m. p. 149—150° (lit.,[7] 156—157°) (Found: C, 62·6; H, 5·6; N, 4·4. Calc. for $C_{18}H_{19}NO_6$: C, 62·6; H, 5·5; N, 4·1%).

5-Benzyloxycarbonyl-3-ethoxycarbonyl-4-methylpyrrole-2-carboxylic Acid.[8]—Bromine (3·5 ml.; 1 mol.) was added dropwise to a vigorously stirred solution of benzyl 2,4-dimethyl-3-ethoxycarbonylpyrrole-2-carboxylate (20 g.) in glacial acetic acid (170 ml.). Sulphuryl chloride (10·8 ml.; 2 mol.) was added during 90 min., and the mixture kept overnight before being stirred with water (800 ml.) at 60—70° for 30 min. The hot mixture was poured into ice–water (2 l.), and the resulting precipitate filtered off, dissolved in warm methanol, and treated with powdered sodium hydrogen carbonate until effervescence ceased. The solution was poured into water, set aside for several hours, filtered, and the filtrate saturated with sulphur dioxide. The precipitated *acid* was filtered, washed with water, dried in air, and crystallised from methanol as colourless needles (10·4 g.; 47%), m. p. 154—156° (Found: C, 61·5; H, 5·2; N, 4·4. $C_{17}H_{17}NO_6$ requires C, 61·6; H, 5·2; N, 4·2%).

Benzyl 5-Dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylate (with DR. J. A. BALLANTINE).—Sulphuryl chloride (14·2 ml.) was added dropwise during 90 min. to a stirred solution of 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (15 g.) in dry ether (200 ml.) at 0°. The solution was stored overnight at 0° before removal of the solvent *in vacuo* (nitrogen leak). The residue was taken up in benzene (200 ml.) and stirred and cooled during the addition of aqueous dimethylamine (150 ml.; 40%). The mixture was boiled and stirred under reflux for 30 min., cooled, and the benzene layer separated and washed with dilute hydrochloric acid and water. The benzene was removed under reduced pressure, leaving an oil which solidified on cooling, and was crystallised from benzene–light petroleum (b. p. 60—80°) to give the *dimethylamidopyrrole* (14·2 g.; 78%) as needles, m. p. 138—139° (Found: C, 69·1; H, 7·1; N, 8·9. $C_{18}H_{22}N_2O_3$ requires C, 68·8; H, 7·1; N, 8·9%).

5-Dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylic Acid (with DR. J. A. BALLANTINE).—Benzyl 5-dimethylamido-4-ethyl-3-methylpyrrole-2-carboxylate (10 g.) in acetone (200 ml.). was shaken in hydrogen at 1 atm. and 20° for 20 hr. with palladium–charcoal (0·4 g.; 10%) After removal of the catalyst, the solution was evaporated to dryness under reduced pressure of nitrogen. The residual solid crystallised from ethyl acetate to give the *pyrrole-2-carboxylic acid* (5·5 g.; 77%) as needles, m. p. 205° (decomp.) (Found: C, 59·1; H, 7·3; N, 12·2. $C_{11}H_{16}N_2O_3$ requires C, 58·9; H, 7·2; N, 12·5%).

Benzyl 4-Ethyl-5-formyl-3-methylpyrrole-2-carboxylate.—(*a*) Sulphuryl chloride (7·0 ml.) was added during 1 hr. to a vigorously stirred solution of benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (11·0 g.) in ether (100 ml.) at 0°, and the mixture stored overnight at 0°. The

[7] Grigg, Johnson, and Wasley, *J.*, 1963, 359.
[8] Corwin, Bailey, and Viohl, *J. Amer. Chem. Soc.*, 1942, **64**, 1267.

solvent was removed under reduced pressure of nitrogen and the residual oily solid was boiled with water (500 ml.) and sodium acetate (40 g.) for 5 min. On cooling the mixture to 0° a dark brown solid precipitated out and was recrystallised from aqueous alcohol (charcoal) to give the desired *formylpyrrole* (5·1 g.; 44%) as needles, m. p. 86—87° (Found: C, 70·7; H, 6·4; N, 5·2. $C_{16}H_{17}NO_3$ requires C, 70·8; H, 6·3; N, 5·2%).

(*b*) (With DR. J. A. BALLANTINE). Sulphuryl chloride (28·4 ml.) was added during 90 min. to a vigorously stirred solution of benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (45 g.) in ether (600 ml.) at 0°, and the mixture stored overnight at 0°. After removal of the solvent under reduced pressure of nitrogen, the residual oil was dissolved in benzene (300 ml.), and the solution saturated with a stream of dimethylamine. Water (500 ml.) was added and the mixture stirred vigorously under reflux on a steam-bath for 2 hr. The cooled and separated benzene layer was washed with 2N-hydrochloric acid, then with water until neutral, and the solvent removed *in vacuo*. The residual oil was taken up in benzene, and chromatographed on alumina (250 g.) with benzene as eluent. The appropriate fractions were collected, evaporated to dryness and the residual formylpyrrole (36·4 g.; 77%) crystallised from light petroleum (b. p. 60—80°) as needles, m. p. and mixed m. p. with the sample prepared in (*a*) above, 86—87°.

Benzyl 5-Cyano-4-ethyl-3-methylpyrrole-2-carboxylate.—The foregoing formylpyrrole (50 g.), hydroxylamine hydrochloride (16 g.), and pyridine (30 ml.) were boiled with methanol (100 ml.) under reflux for 75 min. The solvents were removed *in vacuo* and the residual oil cooled and stirred with water until it solidified. The water was removed by decantation and the solid washed with water (50 ml.) by decantation. Crystallisation of the residue from aqueous ethanol gave the *oxime* (48 g.; 91%), as needles, m. p. 126—127°. (Found: C, 67·0; H, 6·0; N, 9·7. $C_{16}H_{18}N_2O_3$ requires C, 67·1; H, 6·3; N, 9·8%). Mr. G. S. Sach has since found m. p.s in the range 125—135° for samples, which all gave satisfactory elemental analyses and yielded the cyanopyrrole. The probable explanation is varying proportions of the two possible geometrical isomers.

The oxime (48 g.) was boiled with acetic anhydride (150 ml.) for 90 min., the solution evaporated to dryness *in vacuo*, and the residue taken up in ether, washed with 2N-sodium carbonate, and then with water. The dried ($MgSO_4$) ether solution was evaporated to dryness, and the *cyanide* remaining crystallised from benzene–light petroleum (b. p. 60—80°) as needles (34 g.; 75%), m. p. 100—101° (Found: C, 71·6; H, 6·3; N, 10·1. $C_{16}H_{16}N_2O_2$ requires C, 71·6; H, 6·0; N, 10·4%).

2-Cyano-3-ethyl-4-methylpyrrole.—The foregoing cyanopyrrole (2·7 g.) in methanol (50 ml.) was hydrogenated over palladium–charcoal (0·1 g.; 10%) at 1 atm. and 25° until one mol. of hydrogen had been taken up. On removal of the catalyst and solvent, *5-cyano-4-ethyl-3-methylpyrrole-2-carboxylic acid* was obtained in quantitative yield as a pale pink crystalline solid. An analytical sample had m. p. 203—205° (decomp.) (from water) (Found: C, 60·5; H, 5·8; N, 15·5. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·7; N, 15·7%). It sublimed unchanged at 160°/0·1 mm.

The cyano-acid (1·7 g.) was boiled under reflux with ethanolamine (3 ml.) for 1 hr., and the mixture poured into water (50 ml.) and extracted with ether (2 × 50 ml.). Evaporation of the dried ($MgSO_4$) extracts gave an oily solid, which sublimed (cold finger) at 100—110°/0·5 mm. to give the *2-cyano-3-ethyl-4-methylpyrrole* (0·91 g.; 70%) as stout needles, m. p. 80° (Found: C, 71·7; H, 7·4; N, 20·7. $C_8H_{10}N_2$ requires C, 71·6; H, 7·5; N, 20·9%).

Pyrromethanes (Pyrrolylmethylpyrroles)

Most of the pyrromethanes were prepared by the pyridinium salt method.[2] Typical reaction conditions were as follows. A solution of the pyrrole-2-carboxylic acid (0·01 mole) and lithium methoxide (0·38 g.; 0·01 mole) in warm aqueous methanol (100 ml.; 50%) was added to the 2-bromomethylpyrrole (0·01 mole) in pyridine (3·2 ml.; 0·04 mole). The mixture was heated under reflux on a steam-bath for several hours in an atmosphere of nitrogen. On cooling the mixture to room temperature overnight the pyrromethane usually crystallised out, and was filtered off, washed with water, and dried before crystallisation. In some cases more pyrromethane could be recovered from the mother-liquors by dilution with water and extraction with ether, although second crops obtained in this manner often required chromatographic purification. When ethylene glycol or formamide was used as solvent, the mixture was worked up by dilution with water (*ca.* 1 l.) and extraction with ether (4 × 150 ml.); the ethereal

TABLE 2.

Pyrromethanes (III).

No.	R	R^1	R^2	R^3	R^4	R^5	Reaction time (hr.)	Solvent [a]	Yield (%)	By-product	Yield (%)
1	CH_2Ph	Me	Et	Et	Me	CO_2Et	24	A	23	—	—
							48	A	46	(IVb)	10
							24	B	21	—	—
							48 [b]	A	39	(IVa) [c]	14
2	CH_2Ph	Et	Me	Et	Me	CO_2Et	48	A	45	—	—
3	CH_2Ph	Me	Et	Me	Et	$CONMe_2$	20	A	53	(IVb)	7
							9 [d]	C	25	—	—
4	CH_2Ph	Me	Et	P[Me]	Me	CO_2CH_2Ph	72	A	43	(IVb)	16
							72 [b]	A	48	(IVc)	9
5	CH_2Ph	Me	P[Me]	CO_2Et	Me	CO_2CH_2Ph	72	A	9	(IVc)	23
							72 [b,c]	A	10	—	—
6	Et	Me	CO_2Et	Me	COMe	Me	10	C	70	—	—
7	CH_2Ph	Me	Et	Me	COMe	Me	18	C	50	—	—
8	Et	Me	COMe	Me	CO_2Et	Me	8 [e]	C	65	—	—
9	Et	Me	CO_2Et	Me	CO_2Et	Me	8 [e]	C	75	—	—
10	CH_2Ph	Me	CO_2Et	Me	CO_2Et	Me	8 [e]	C	75	—	—
11	CH_2Ph	Me	Et	Me	Et	CN	18 [f]	A	0	(IVb)	30

	Found (%)				Required (%)			
No.	C	H	N	Formula	C	H	N	M. p.
1	71·4	7·4		$C_{26}H_{32}N_2O_4$	71·5	7·5		93—95°
2	71·2	7·5	6·4	$C_{22}H_{32}N_2O_4$	71·5	7·4	6·4	115—116
3	71·7	7·9	9·6	$C_{26}H_{33}N_3O_3$	71·7	7·6	9·6	179—180
4	71·3	6·4	5·2	$C_{33}H_{36}N_2O_6$	71·2	6·5	5·0	86—88
5	67·8	6·2	4·6	$C_{34}H_{36}N_2O_8$	68·0	6·0	4·7	152—153
6	63·9	7·0	7·5	$C_{20}H_{26}N_2O_5$	64·1	7·0	7·4	174—175
7	73·5	7·3	7·2	$C_{23}H_{28}N_2O_3$	73·4	7·2	7·1	161—162
8	64·3	7·0	7·5	$C_{20}H_{26}N_2O_5$	64·2	7·0	7·5	172—173
9	62·3	7·2	7·2	$C_{21}H_{28}N_2O_6$	62·4	7·0	6·9	159—160 [g]
10	66·8	6·4	6·0	$C_{26}H_{30}N_2O_6$	66·9	6·5	6·0	160—162
By-products								
(IVb)	68·1	6·7	9·2	$C_{17}H_{20}N_2O_3$ [h]	68·0	6·7	9·3	185 [i]
(IVc)	63·5	6·2	8·0	$C_{19}H_{22}N_2O_5$	63·7	6·1	7·8	122 [i]

[a] A, formamide; B, ethylene glycol monomethyl ether; C, 50% aqueous methanol. [b] Reaction carried out in the reverse manner, *i.e.*, R, R^1, and R^2 derived from a pyrrole-2-carboxylate and R^3, R^4, and R^5 from a pyridinium salt. [c] See text. [d] With Mr. G. McGillivray up to 40% of benzyl 4-ethyl-5-methoxymethyl-3-methylpyrrole-2-carboxylate was also isolated. [e] Pyridinium salt derived from the appropriate chloromethylpyrrole (not the bromomethylpyrrole). [f] In a similar reaction in aqueous methanol benzyl 4-ethyl-5-methoxymethyl-3-methylpyrrole-2-carboxylate (25%), m. p. and mixed [2] m. p. 86—87° (see above), was the only compound isolated apart from the unchanged acid (VIa); in *N*-methylformamide at 100° for 48 hr. dibenzyl 3,3′-diethyl-4,4′-dimethylpyrromethane-5,5′-dicarboxylate (60%), m. p. 127° (lit.,[6] 126—127°) was formed and the cyano-compound (VIa) (75%) recovered. [g] Lit.,[9b] m. p. 157—158°. [h] Found: O, 16·1. Required O, 16·0%. [i] From chloroform–light petroleum (b. p. 60—80°).

extracts were dried ($MgSO_4$), evaporated to dryness and chromatographed on alumina using light petroleum (b. p. 60—80°)–benzene mixtures as eluents.

In preliminary experiments it was found that the required unsymmetrical pyrromethanes were contaminated with symmetrical pyrromethanes (derived from the pyridinium-methylpyrrole) when reactions were carried out in aqueous methanol, ethylene glycol monomethyl ether, or aqueous formamide, and with the formamidomethylpyrroles when reactions were carried out in formamide. The effect of different solvents on the coupling reaction between ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate and 5-ethoxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylic acid was investigated first, since the same symmetrical methane would be produced either by self-condensation of the pyridinium salt or by the desired coupling reaction, and this would avoid the difficulties involved in the chromatographic separation of similar pyrromethanes. The yields of diethyl 3,3′-diethyl-4,4′-dimethylpyrromethane-5,5′-dicarboxylate, m. p. 127° (lit.,[9a] 126°), produced by heating the mixture at 100° under reflux for

[9] Fischer and Orth, "Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, (*a*) Vol. I, p. 343; (*b*) Vol. I, p. 342; (*c*) Vol. II, Part I, p. 619; (*d*) Vol. II, Part I, p. 437.

17 hr. in various solvents, are shown below. For comparison, lithium benzoate (1·28 g.; 0·01 mole) was substituted for the pyrrole-2-carboxylate and the second figure after each solvent shows the yield of the pyrromethane isolated in a similar series of experiments: 50% aqueous methanol (34, 12·5%), 70% aqueous methanol (24, 10%), ethylene glycol monomethyl ether (29, 4%), formamide (32, 0%), 80% aqueous formamide (27, 5%). When the product from reaction in formamide was worked up, the pyrromethane was eluted from a column of alumina by benzene–light petroleum (b. p. 60—80°) (1 : 1), and, on changing the eluent to benzene or benzene–ether, *ethyl 4-ethyl-5-formamido-3-methylpyrrole-2-carboxylate* (IVa) (5%) was also obtained. This compound crystallised from chloroform–light petroleum (b. p. 60—80°) as needles, m. p. 151—152° (Found: C, 60·7; H, 7·6; N, 11·5. $C_{12}H_{18}N_2O_3$ requires C, 60·5; H, 7·6; N, 11·8%). In view of these results, all further coupling reactions were carried out in formamide solution, and the pyrromethanes (Table 2) were prepared in this way and crystallised from light petroleum (b. p. 60—80°).

The *pyrromethane carboxylic acids* (Table 3) were obtained in quantitative yield by hydrogenolysis of the corresponding benzyl esters in ethyl acetate over palladium–charcoal (10%) at 1 atm. and 20°. After filtration and removal of solvent the acids were usually used directly without purification, but for analysis they were crystallised from ethanol.

TABLE 3.

Pyrromethane carboxylic acids (III; R = H).

Compound						Found (%)				Required (%)		
R^1	R^2	R^3	R^4	R^5	M. p.*	C	H	N	Formula	C	H	N
Me	Et	Et	Me	CO_2Et	168—169° †	65·6	7·5	7·8	$C_{19}H_{26}N_2O_4$	65·9	7·6	8·1
Me	Et	Et	Me	CO_2CH_2Ph	94—106 ‡							
Et	Me	Et	Me	CO_2Et	199—200	65·9	7·7	7·7	$C_{19}H_{26}N_2O_4$	65·9	7·6	8·1
Me	Et	Me	Et	$CONMe_2$	223—225	66·3	8·2	12·3	$C_{19}H_{27}N_3O_3$	66·1	7·9	12·2
Me	P^{Me}	Me	Me	CO_2H	194—197	58·0	6·2	6·4	$C_{21}H_{26}N_2O_8$	58·1	6·0	6·4
Me	Et	P^{Me}	Me	CO_2H	147—149	60·5	6·4	7·3	$C_{19}H_{24}N_2O_6$	60·6	6·4	7·4
Me	CO_2Et	P^{Me}	Me	CO_2H	225—227	57·1	5·7	6·4	$C_{20}H_{24}N_2O_8$	57·1	5·7	6·7

* With decarboxylation. † Corwin and Coolidge (*J. Amer. Chem. Soc.*, 1952, **74**, 5196) give m. p. 148—150° for the acid obtained by partial hydrolysis of the corresponding diethyl ester. ‡ Crude product prepared from the corresponding dibenzyl ester by stopping the hydrogenation after the uptake of 1 mol.

3,3′-Diethyl-5,5′-diformyl-4,4′-dimethylpyrromethane. A slow stream of dry hydrogen chloride was passed through a suspension of 3,3′-diethyl-4,4′-dimethylpyrromethane-5,5′-dicarboxylic acid [10] (2·4 g.) in dry ethanol-free chloroform (50 ml.) at 0°. The diacid slowly dissolved to give a yellow solution and, after 1 hr., dry hydrogen cyanide (6 ml.) was added, and hydrogen chloride was passed through the mixture for a further 1½ hr. After storage of the mixture overnight at 0°, the solvent was removed *in vacuo* at room temperature and the residue treated with hydrated disodium hydrogen phosphate (12 g.) in water (150 ml.). The mixture was heated for 5 min. under reflux, allowed to cool, and the precipitate filtered and washed with water. On crystallisation from aqueous ethanol the diformylpyrromethane (1·2 g.; 55%) gave needles, m. p. 219—222° (lit.,[11] >300°) (Found: C, 71·2; H, 7·7; N, 9·7. Calc. for $C_{19}H_{22}N_2O_2$: C, 71·3; H, 7·7; N, 9·8%).

Tripyrranes * (*Pyrrolylmethylpyrrolylmethylpyrroles*)

1′-Benzyloxycarbonyl-6′-ethoxycarbonyl-2,4,5-triethyl-1,3,6-trimethyltripyrrane (XIIa).—(*a*) 5′-Ethoxycarbonyl-3′,4-diethyl-3,4′-dimethylpyrromethane-5-carboxylic acid (1·13 g.) and lithium methoxide (0·13 g.) in dry formamide (100 ml.) were added to benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·1 g.) in dry pyridine (1·2 ml.) and the mixture heated at 100° for 6 hr. under nitrogen. Water (1 l.) was added and the product extracted with ethyl acetate

* β-Positions in the tripyrranes are numbered consecutively 1—6, and the corresponding α-positions 1′—6′, by analogy with Fischer and Orth's system [9c] for the bile pigments.

[10] Abraham, Jackson, Kenner, and Warburton, *J.*, 1963, 853.
[11] Bullock, Grigg, Johnson, and Wasley, *J.*, 1963, 2326.

(4 × 150 ml.). The combined extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure of nitrogen at room temperature. The residual oil solidified on trituration with light petroleum (b. p. 40—60°) at 0° and was recrystallised from light petroleum (b. p. 40—60°) to give the *tripyrrane* (0·53 g.; 29%) as light yellow needles, m. p. 182° [Found: C, 73·1; H, 7·9; N, 7·5%; *M* (Rast), 549. $C_{34}H_{43}N_3O_4$ requires C, 73·2; H, 7·8; N, 7·5%; *M*, 557].

(*b*) Dibenzyl 3,3′-diethyl-4,4′-dimethylpyrromethane-5,5′-dicarboxylate (2·0 g.) in ethyl acetate (50 ml.) was hydrogenated over palladium–charcoal (0·3 g.; 10%) at 25° and 1 atm. until one mol. of hydrogen had been taken up. After removal of the catalyst, the solvent was evaporated to dryness *in vacuo* (nitrogen leak) at room temperature to leave a pink crystalline residue (1·56 g.), m. p. 94—106° (decomp.). This crude product and lithium methoxide (0·15 g.) in dry formamide (100 ml.) were added to ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·05 g.) in dry pyridine (1·2 ml.), and the mixture treated as in (*a*) above. The tripyrrane was isolated as before and crystallised from light petroleum (b. p. 40—60°) as pale yellow needles (0·34 g.; 16%), m. p. and mixed m. p. with the product above 182°.

In a similar manner, 5′-ethoxycarbonyl-3,3′-diethyl-4,4′-dimethylpyrromethane-5-carboxylic acid (1·13 g.) and benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·1 g.) gave 1′-*benzyloxycarbonyl*-6′-*ethoxycarbonyl*-2,4,5-*triethyl*-1,3,6-*trimethyltripyrrane* (0·41 g.; 23%) which crystallised from light petroleum (b. p. 60—80°) as pale yellow needles, m. p. 171—172° (Found: C, 73·1; H, 7·7; N, 7·7. $C_{34}H_{43}N_3O_4$ requires C, 73·2; H, 7·8; N, 7·5%).

Attempted Synthesis of 1′-*Benzyloxycarbonyl*-6′-*dimethylamido*-2,4,6-*triethyl*-1,3,5-*trimethyltripyrrane*.—5′-Dimethylamido-3,4′-diethyl-3′,4-dimethylpyrromethane-5-carboxylic acid (1·0 g.) and lithium methoxide (0·11 g.) in formamide (125 ml.) were heated at 100° for 6 hr. in an atmosphere of nitrogen with benzyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (1·0 g.) in pyridine (0·8 ml.). The product was worked up as in the previous experiments and gave *dibenzyl* 2,4,5-*triethyl*-1,3,6-*trimethyltripyrrane*-1,6′-*dicarboxylate* as needles (0·29 g.), m. p. 198—199° [Found: C, 75·4, 75·9; H, 7·6, 7·4; N, 6·7, 7·1. $C_{39}H_{49}N_3O_4$ requires C, 75·6; H, 7·3; N, 6·8% ($C_{33}H_{44}N_4O_3$ requires C, 73·4; H, 8·0; N, 10·1%)]. The structure was confirmed by the proton magnetic resonance spectrum [12] in deuterochloroform, and by mass-spectrometric determination [13] of molecular weight.

Porphyrins

2,3-*Diethyl*-6,7-*di*-(2-*methoxycarbonylethyl*)-1,4,5,8-*tetramethylporphin* (*Mesoporphyrin III dimethyl ester*).—(*a*) 3,3′-Di-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylic acid (1·0 g.) was heated at 150—170°/0·03 mm., and the corresponding di-α-unsubstituted pyrromethane (0·47 g.; 59%) distilled out as a colourless oil, which was used immediately in the following reactions.

The pyrromethane (104 mg.) in glacial acetic acid (30 ml.) was mixed with a solution of 3,3′-diethyl-5,5′-diformyl-4,4′-dimethylpyrromethane (86 mg.) in glacial acetic acid (35 ml.) and hydriodic acid (56%; 0·3 ml.) and stored for 1 hr. in the dark at 20°. A solution of anhydrous sodium acetate (1·0 g.) in glacial acetic acid (30 ml.) was added and the mixture aerated overnight in the dark, before being poured on to ice and neutralised with concentrated aqueous ammonia. Three identical reactions were carried out and the four aqueous solutions were combined and extracted with chloroform (5 × 150 ml.). The extracts were washed with water until neutral, dried ($MgSO_4$), and evaporated to dryness under reduced pressure of nitrogen. The residue was chromatographed twice on alumina (150 g.), first using chloroform as eluent, and secondly benzene. The purple porphyrin-containing fractions were evaporated to dryness, and the residue crystallised from chloroform–methanol to give mesoporphyrin III dimethyl ester (144 mg.; 20%) as purple plates m. p. 273—276° (lit.,[9d] 277—279°).

(*b*) 3,3′-Di-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylic acid (43·4 mg.) in glacial acetic acid (100 ml.) was combined with 3,3′-diethyl-5,5′-diformyl-4,4′-dimethylpyrromethane (28·6 mg.) in glacial acetic acid (60 ml.) containing hydriodic acid (0·6 ml.; 56%), and the mixture stored for 4 hr. at 25° in the dark. Anhydrous sodium acetate (2 g.) in glacial acetic acid (30 ml.) was added, the mixture aerated overnight in the dark, and worked up as in (*a*) above. Mesoporphyrin III dimethyl ester (6·7 mg.; 11%) was isolated as purple plates.

[12] Jackson and Kenner, unpublished results.
[13] Budzikiewicz, Djerassi, Jackson, Kenner, and Wilson, unpublished results.

The homogeneity of the products obtained in this way was checked by paper chromatography of the corresponding free acid (prepared by hydrochloric acid hydrolysis) in lutidine (10 vol.) and 0·7M-aqueous ammonia (7 vol.).[14] Each gave a single spot which ran at the same R_F (0·73) as natural mesoporphyrin IX. In the same solvent system coproporphyrin III had R_F 0·32. This was also confirmed by thin-layer chromatography [4] on silica gel in n-hexane–acetone (70 : 30; v/v), when both products gave single spots running at the same R_F as mesoporphyrin IX dimethyl ester.

2,3,7-*Triethyl*-6-(2-*methoxycarbonylethyl*)-1,4,5,8-*tetramethylporphin*.—3-Ethyl-3′-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylic acid (113 mg.) in glacial acetic acid (100 ml.) was combined with 3,3′-diethyl-5,5′-diformyl-4,4′-dimethylpyrromethane (86 mg.) in glacial acetic acid (60 ml.) and hydriodic acid (0·6 ml.; 56%), and the mixture treated as in the foregoing preparation (*b*) of mesoporphyrin III. The products from eight similar experiments were combined before chromatography and the total yield of the *porphin monopropionate methyl ester* was 318 mg. (22%); it formed purple plates, m. p. 263—265, $\lambda_{max.}$ (C_6H_6) 401, 498, 530, 568, 595, 620 mμ (log ε 5·28, 4·20, 4·06, 3·90, 3·18, 3·74). The gross structure was confirmed by p.m.r. spectroscopy [4] in trifluoroacetic acid, and the homogeneity of the product was shown when it ran as a single spot on thin-layer chromatograms at the position expected for a porphyrin monoester.[4]

6-*Ethoxycarbonyl*-2,3-*diethyl*-7-(2-*methoxycarbonylethyl*)-1,4,5,8-*tetramethylporphin*. —3-Ethoxycarbonyl-3′-(2-methoxycarbonylethyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylic acid (0·7 g.) was heated at 240—250° in nitrogen at 1 atm. until evolution of carbon dioxide ceased. The α-unsubstituted pyrromethane was then distilled at 0·03 mm. (bath temp. 180—200°) to give a pale yellow oil which was used immediately, without purification, in the following reactions.

The pyrromethane (100 mg.) in glacial acetic acid (100 ml.) was mixed with 3,3′-diethyl-5,5′-diformyl-4,4′-dimethylpyrromethane (86 mg.) in glacial acetic acid (60 ml.) and hydriodic acid (0·6 ml.; 56%), and the mixture treated in the same way as the previous porphyrin preparations. The crude product was finally chromatographed on alumina in benzene, and after isolation the *porphyrin diester* (8·5 mg.; 5·1%) crystallised from benzene–light petroleum (b. p. 60—80°) as purple prisms, m. p. 226—232° $\lambda_{max.}$ (C_6H_6) 408, 507, 547, 574, 633 mμ (log ε 5·27, 4·05, 4·14, 3·89, 3·35), $\lambda_{max.}$ (6N-HCl) 411, 556, 605 mμ (log ε 5·39, 4·10, 3·82) [lit.,[15] for rhodoporphyrin XV dimethyl ester $\lambda_{max.}$ (dioxan) 506, 545, 573, 632 mμ (log ε 4·07, 4·18, 3·92, 3·33) $\lambda_{max.}$ (3N-HCl), 554, 602·5 mμ (log ε 4·13, 3·92)]. The product ran as a single spot on thin-layer chromatograms, and at the same R_F as rhodoporphyrin XV dimethyl ester prepared by degradation of chlorophyll. The p.m.r. spectrum was also in agreement with the proposed structure, and it was very similar to that of rhodoporphyrin XV dimethyl ester (except that in our porphyrin there is an ethoxycarbonyl substituent, and in the rhodoporphyrin it is a methoxycarbonyl).[4]

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