373. *Pyrroles and Related Compounds. Part III.*[1] *Syntheses of Porphyrins from Pyrromethanes and Pyrromethenes.*

By J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner.

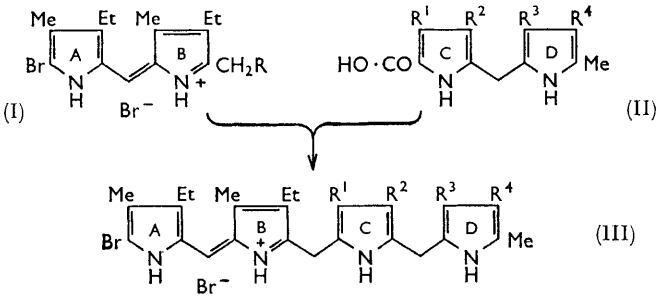
Pyrromethane-5-carboxylic acids (II) condense with 5-methoxymethylpyrromethene hydrobromides (I; R = OMe), giving mainly linear tetrapyrrolic " bilenes " (III). In a simultaneous reaction, up to 15% of porphyrin is formed; a mechanism through branched tetrapyrrolic intermediates (IV) is suggested on the basis of six syntheses of octa-alkylporphins (Table 1). Syntheses of new pyrroles and pyrromethanes are described, as well as syntheses of 5-bromomethylpyrromethenes (*e.g.*, Ib) from *t*-butyl pyrrole-5-carboxylates (*e.g.*, XVIa). Octa-alkylporphins have been purified by counter-current distribution between benzene and sulphuric acid.

Ideally synthesis of porphyrins would proceed through a characterised intermediate with four pyrrole rings arranged linearly, before closure of the macrocycle. The famous synthesis by Woodward and his co-workers [2] is unique in virtually achieving this ideal, although even here the intermediate is apparently too unstable for isolation. In Part I [3] we described methods for linking pyrrole rings stepwise by methylene groups, but they were only really effective for preparing pyrromethanes (*i.e.*, pyrrolylmethylpyrroles). Only two compounds containing three pyrrole rings (" tripyrranes ") were prepared, and there was no question of extending the route to tetrapyrrolic compounds. Accordingly our attention has been turned to condensation of pyrromethanes with other bipyrrolic compounds to form linear tetrapyrrolic compounds, potential precursors of macrocycles. This Paper describes experiments with pyrromethenes. These experiments led to porphyrins and initially they were very promising, but in fact the outcome was not synthetically useful. Nevertheless the results are recorded because they demonstrate aspects of the general chemistry of pyrroles. Experiments with dipyrroketones will be the subject of a subsequent Paper.

The 5-methoxymethylpyrromethene (I; R = OMe), readily available from

[1] Part II, *J.*, 1959, 185.
[2] Woodward *et al.*, *J. Amer. Chem. Soc.*, 1960, **82**, 3800.
[3] Hayes, Kenner, and Williams, *J.*, 1958, 3779.

" brominated cryptopyrromethene-I " (I; R = Br),[4a] condensed easily with a diethyltrimethylpyrromethane-2-carboxylic acid (II; $R^1 = R^3 = Me$, $R^2 = R^4 = Et$) [3] in boiling benzene. The crystalline product had the correct elemental analysis for the expected



" bilene hydrobromide " (III; $R^1 = R^3 = Me$, $R^2 = R^4 = Et$) and its visible absorption spectrum showed an intense maximum at 528 mμ (log ε 4·82). This may be compared with the maxima (490—495 mμ) of natural [5] and other synthetic [4b] bilene salts, and the maxima (about 580 mμ) of bilidiene pigments such as mesobiliviolin and mesobilirhodin; [6] the bathochromic displacement of 30 mμ could be caused by the 5′-bromo-substituent. The i.r. spectrum of this bilene hydrobromide showed intense absorption at 1613 cm.$^{-1}$, like that of other pyrromethenes [*e.g.*, 1619 cm.$^{-1}$ in the spectrum of (IV; R = OMe)].

When the foregoing condensation product, apparently the bilene hydrobromide (III; $R^1 = R^3 = Me$, $R^2 = R^4 = Et$), was heated with hydrobromic acid in acetic acid at 110—120° for one hour, it yielded ætioporphyrin (up to 20% estimated spectroscopically, 13% isolated by counter-currect distribution). Similar, although less-clean products were obtained from the 5-bromomethylpyrromethene (I; R = Br) and the same pyrromethane-2-carboxylic acid, and in this case ætioporphyrin could be obtained directly from the two components when they were heated at 110—120° in acetic acid (24 hr.; 6%) or hydrobromic–acetic acid (1 hr.; 9%). When the 5-bromomethylpyrromethene (I; R = Br) is treated alone under different conditions [4c] higher yields (up to 30%) of ætioporphyrin can be obtained but, under the milder conditions of the foregoing experiments, only 1—2% of ætioporphyrin is produced from this methene or the 5-methoxymethyl analogue (I; R = OMe). It was therefore concluded that the porphyrin had arisen from the entire bilene, rather than from self-condensation of the pyrromethene moiety with elimination of the pyrromethane moiety. However, the following experiments with other combinations of pyrromethenes and pyrromethanes showed that, while porphyrin was not produced by a trivial reaction of pyrromethenes, it was produced simultaneously with bilene not subsequently. The porphyrin is produced as its dihydrobromide, which is of comparable solubility and hence not easily separated from the bilene hydrobromide (III). When the bilene has been carefully purified by several recrystallisations, it no longer yields any porphyrin.

The foregoing syntheses should have led to ætioporphyrin I. Synthesis of the type III isomer from the same pyrromethene (I; R = OMe) and another pyrromethane (II; $R^1 = R^4 = Me$, $R^2 = R^3 = Et$) was investigated. The isomeric ætioporphyrins are indistinguishable by classical methods, but *X*-ray powder photographs [7] can be used and it seemed possible that the isomers might be separated by extensive counter-current distribution. Actually the product had the same partition coefficient, within experimental

[4] Fischer and Orth, " Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1937, Vol. II, Part I, (*a*) p. 106, (*b*) p. 610, (*c*) p. 193, (*d*) p. 582, (*e*) p. 197, (*f*) p. 436.
[5] Birch, *Chem. and Ind.*, 1955, 652; Gray and Nicholson, *Nature*, 1957, **179**, 264; **180**, 336.
[6] Gray, " The Bile Pigments," Methuen, London, 1953, p. 34.
[7] Siedel and Winkler, *Annalen*, 1943, **554**, 162.

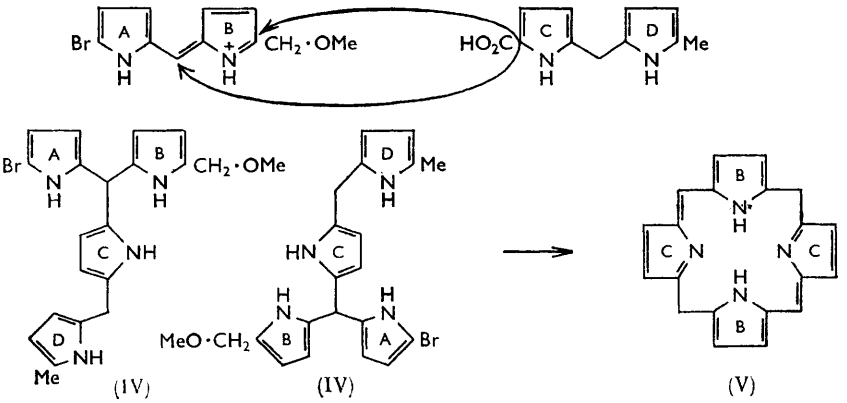
error, as that from the previous synthesis. Replacement of an ethyl group in the pyrromethane by an ethoxycarbonyl group should have led to a more characteristic porphyrin, but a bilene could not be obtained from the 5-methoxymethylpyrromethene (I; R = OMe) and the pyrromethane (II; $R^1 = R^3 = Me$, $R^2 = CO_2Et$, $R^4 = Et$). (At this juncture we still believed that the porphyrin arose from the bilene.) Deactivation of the ring containing the carboxyl group could have been responsible for this failure, and therefore an isomeric pyrromethane (II; $R^1 = R^3 = Me$, $R^2 = Et$, $R^4 = CO_2Et$) was used instead. In this instance a bilene was formed, but only ætioporphyrin could be detected after treatment with hydrobromic–acetic acid and that in small yield. (The expected ethoxycarbonylporphyrin would have possessed characteristic light absorption of the " rhodotype." [4d]) The hypothesis of bilene cyclisation was therefore re-examined in syntheses of octa-alkylporphins from six distinctive combinations of pyrromethenes and pyrromethanes. Only two pyrromethenes were used, namely compound (I; R = OMe) and the lower homologue with four methyl substituents instead of two methyl and two ethyl groups (XV; R = OMe). Our studies of p.m.r. spectra of porphyrins dissolved in trifluoroacetic acid [8] had provided a reliable method for gross analysis of octa-alkylporphins, whereas conventional analysis by combustion would have been inadequate. The porphyrins were purified by chromatography, and in some instances counter-current distribution (see later) was employed to check their purity. This technique separates porphyrins with different sizes of side-chains even though it will not distinguish the type isomers of octa-alkylporphins. We considered alternative mechanisms for formation of porphyrins from entire bilenes (rings ABCD) or merely the pyrromethene portions (2AB) but the results (Table 1) pointed clearly to porphyrin formation from half the pyrromethene and half the pyrromethane (2BC). This unexpected result is explicable in several ways, but to us the most plausible is the following. The nucleophilic 5-position in the pyrromethane-5-carboxylic acid (II) can attack (arrows) either the 5′-methoxymethyl substituent or the methine bridge in the pyrromethene. The former reaction leads to the bilene and the latter to a hypothetical branched tetrapyrrolic compound (IV). Two molecules of this compound (IV) could condense, eliminating four pyrrole rings, to a dihydroporphyrin (V) which would readily oxidise to the porphyrin. There are good analogies for the first step in the formation of tripyrrylmethanes [9] and for the cyclisation in (i) the classical syntheses of pyrromethanes from 2-bromomethyl- or 2-methoxymethyl-pyrroles,[10a] and (ii) a reaction between pyrromethanes and 2-bromomethylpyrroles [cf. formula (VII) in ref. 3]. Another piece of evidence in favour of this hypothesis is that reaction between the pyrromethene

TABLE 1.

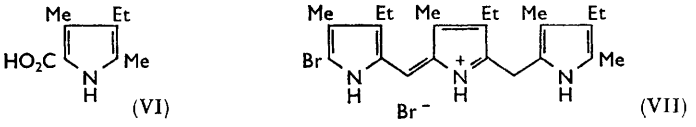
Octa-alkylporphins from pyrromethenes and pyrromethanes.

Reagents: Pyrromethene	Reagents: Pyrromethane (II)				Total substituents in porphyrin: From mechanism			Ratio of Me : Et in p.m.r. spectra	Yield (%) estimated, spectroscopically
	R^1	R^2	R^3	R^4	ABCD	2AB	2BC		
Compound I (R = OMe)	Me	Et	Me	Me	5Me 3Et	4Me 4Et	4Me 4Et	1·1 : 1	12·5
	Me	Me	Me	Et	5Me 3Et	4Me 4Et	6Me 2Et	2·6 : 1	23
	Me	Me	Me	Me	6Me 2Et	4Me 4Et	6Me 2Et	2·9 : 1	13
Tetramethyl analogue	Me	Et	Me	Me	7Me 1Et	8Me	6Me 2Et	3·1 : 1	15·5
	Me	Et	Me	Et	6Me 2Et	8Me	6Me 2Et	3·1 : 1	16·5
	Me	Me	Me	Et	7Me 1Et	8Me	8Me	only Me	10

[8] Abraham, Jackson, and Kenner, *J.*, 1961, 3468.
[9] Corwin and Andrews, *J. Amer. Chem. Soc.*, 1936, **58**, 1086.
[10] Fischer and Orth, " Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, Vol. I, (*a*) p. 333, (*b*) p. 257.

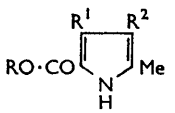


(I; R = OMe) and cryptopyrrolecarboxylic acid (VI) afforded a bilene-like tripyrrolic compound (VII) but no porphyrin.



In an attempt to confirm this interpretation and to define it more precisely by a synthesis of an identifiable mesoporphyrin dimethyl ester, the methoxymethylpyrromethene (I; R = OMe) was condensed with a pyrromethane containing a propionate side-chain (II; $R^1 = CH_2{\cdot}CH_2{\cdot}CO_2Me$, $R^2 = R^3 = Me$, $R^4 = Et$). A bilene was produced but only some 5% of porphyrin, and this was shown by thin-layer chromatography and p.m.r. to be a mixture of ætioporphyrin and porphyrins with one and two propionate side-chains. The condensation is evidently more complex than indicated in the foregoing diagram, although this accounts for the major products, and the method is really restricted to the synthesis of octa-alkylporphyrins, a relatively unimportant class of compounds.

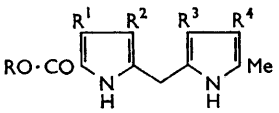
Syntheses of Pyrroles and Pyrromethanes.—Most of the pyrroles required for the synthesis of the pyrromethanes needed in these investigations were prepared by standard



(VIII); R = Et
(IX); R = CH_2Ph
(X); R = H

	R^1	R^2
(a)	Me	Me
(b)	Me	Et
(c)	Me	CO_2Et
(d)	Et	CO_2Et
(e)	Et	Me
(f)	Me	COMe

methods, but hæmopyrrole-carboxylic ester (IXe) was prepared by a new route. Knorr reaction of ethyl*iso*nitrosoacetoacetate with ethyl propionylacetate gave the pyrrole diester (VIIId).[10b] This was converted by a modification of Treibs and Zinsmeister's

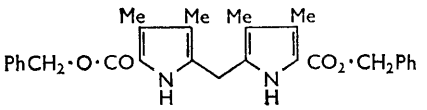


(XI); R = H
(XII); R = Et
(XIII); R = CH_2Ph

	R^1	R^2	R^3	R^4
(a)	Me	Et	Me	Et
(b)	Me	Et	Et	Me
(c)	Me	CO_2Et	Me	Et
(d)	Me	Et	Me	CO_2Et
(e)	Me	Et	Me	Me
(f)	Me	Me	Me	Et
(g)	Me	Me	Me	Me
(h)	$P^{(Me)}$	Me	Me	Et
(i)	Me	$P^{(Me)}$	Me	Et
(j)	Me	$P^{(Bz)}$	Me	Et

method [3,11] into the ethyl ester (VIIIe), which by transesterification gave the required benzyl ester (IXe). The trimethylpyrrole (IXa) was also prepared initially by an analogous route from " Knorr's pyrrole " (VIIIc), but later more conveniently by an alternative synthesis.[12]

The pyrromethanes (XII and XIII) were all synthesised by application of methods described in Part I.[3] The pyrroles (IXa, IXb, and IXe) were converted into the corresponding 5-bromomethyl derivatives by bromination in ether, and then condensed with the pyrrolecarboxylic acids (Xa and Xb) (prepared from the corresponding benzyl ester by hydrogenolysis). The reactions were usually carried out in refluxing chloroform solution in 10 min., except for the pyrromethane (XIIIg) when the reaction time was extended to 30 min.; with shorter times this product was contaminated with the symmetrical pyrromethane (XIV), which was difficult to separate off. The latter was

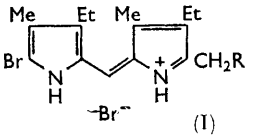


(XIV)

presumably formed by the self-condensation of unchanged 5-bromomethylpyrrole in the methanol used for recrystallisation of the product. A similar side-reaction occurred during the preparation of the pyrromethane (XIIIf) but only a trace of the symmetrical product (XIV) was formed, and in this case it was easily removed during recrystallisation.

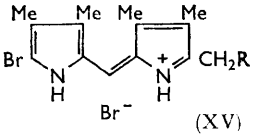
Two pyrroles (VIIIc and IXc) could not be brominated under the normal conditions in the 5-methyl group, but chlorination with sulphuryl chloride in acetic acid gave the corresponding 5-chloromethyl compounds. Reaction of the latter with cryptopyrrolecarboxylic acid (X) in boiling chloroform gave the pyrromethanes (XIIc and XIIIc). Alternatively the pyridinium salts of the chloromethylpyrroles were condensed with the lithium salt of the cryptopyrrolecarboxylic acid. In each case the yield was relatively poor (*ca.* 30%) presumably owing to the lower reactivity of a chloromethyl group, which is further deactivated by two nuclear ester groups.

Synthesis of Pyrromethenes.—The pyrromethene (Ib) was readily prepared by direct bromination of cryptopyrrole (3-ethyl-2,4-dimethylpyrrole) with 2·5 mol. of bromine in acetic acid, according to Fischer's method.[4a] The desired product was separated from the pyrromethene (Ia) perbromide, formed simultaneously, by extraction with warm chloroform, and then converted into the methoxymethylpyrromethene (Ic) by brief treatment with hot methanol. Similar bromination of 2,3,4-trimethylpyrrole also gave a mixture of two products, the pyrromethene (XVb) and the perbromide of the pyrromethene (XVa). Separation of these compounds was much more difficult and only a low yield of the pure methene (XVb) could be isolated and converted into the methoxymethyl compound (XVc).



(I)

(a) R = H, (b) R = Br, (c) R = OMe



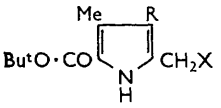
(XV)

(a) R = H, (b) R = Br, (c) R = OMe

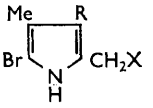
An alternative synthesis of these bromo- and methoxy-methylmethenes was sought, as even the bromination of cryptopyrrole was not entirely satisfactory owing to the formation of a large proportion of the unwanted methylmethene (Ia). At about this time, it was

[11] Treibs and Zinsmeister, *Chem. Ber.*, 1957, **90**, 87.
[12] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.

discovered that *t*-butyl cryptopyrrolecarboxylate (as XVIa) could be brominated directly, giving a mixture of the methenes (Ia and Ib), although in rather lower yield, and that ætioporphyrin was formed when the acetic acid solution of the products was heated.[13]



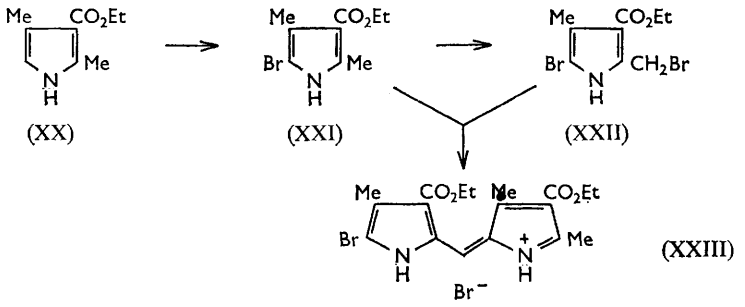
(XVI); R = Et (XVII); R = Me
(a) X = H (b) X = Br



(XVIII); R = Et (XIX); R = Me
(a) X = H (b) X = Br

Bromination of cryptopyrrole has been discussed by Fischer, Baumann, and Riedl,[14] and their reaction scheme has been revised by Corwin and Viohl [15] in the light of experiments on the bromination and further reactions of ethyl 2,4-dimethylpyrrole-3-carboxylate (XX).

The first step in the bromination of this (and other α′-methyl-α-free pyrroles) is formation of the α-bromopyrrole (*e.g.*, XXI). Presumably this undergoes further bromination



(XX) (XXI) (XXII) (XXIII)

forming the α′-bromomethyl-α-bromopyrrole (*e.g.*, XXII). Condensation of the latter with the foregoing α-bromopyrrole then leads directly to the 5-bromo-5′-methylpyrromethene (*e.g.*, XXIII). Supporting evidence [15] of the latter reaction was provided by the ready condensation of α-bromomethylpyrroles with α-bromo- or α-iodo-pyrroles to give pyrromethenes.

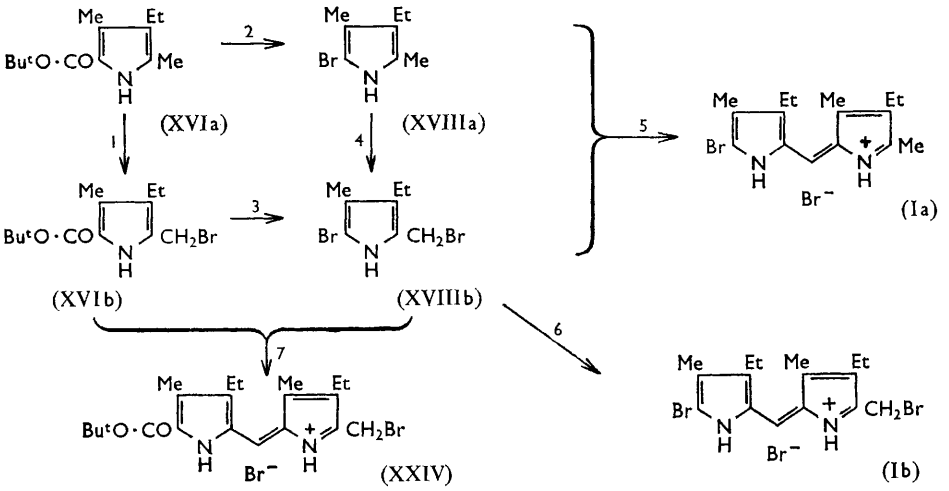
On the basis of this work and the results from bromination of cryptopyrrole, the following scheme can be envisaged for bromination of t-butyl cryptopyrrole-2-carboxylate (XVIa).

Initial attack of bromine could be either on the α-methyl group [reaction (1)] or electrophilic displacement of the *t*-butyloxycarbonyl group [(2)]. Further reaction of either product with more bromine [reactions (3) and (4)] could then lead to the α-bromo-α′-bromomethylpyrrole. (An alternative, though less likely, possibility is that hydrogen bromide, produced in the bromination of the α-methyl group, catalyses decomposition of the *t*-butyl ester to the acid, or to the α-free pyrrole, either of which would instantly react with bromine at the α-position. However, as will be evident from our work, this did not occur in brominations in ether solution.) Formation of methenes from these brominated pyrroles could then occur by reactions (5) and (6) and, since only the methene (Ia) was isolated in the direct one-stage bromination of *t*-butyl cryptopyrrole-2-carboxylate, it seemed likely that this involved mainly reactions (2), (4), and (5) [any α-bromo-α′-bromomethylpyrrole (XVIIIb) reacting immediately with the presursor (XVIIIa) rather than with itself].

We therefore investigated the stepwise bromination of the pyrrole *t*-butyl ester (XVIa)

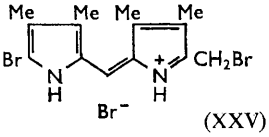
[13] Johnson, Kay, Markham, Price, and Shaw, *J.*, 1959, 3416.
[14] Fischer, Baumann, and Riedl, *Annalen*, 1929, **475**, 205; ref. 4, p. 63.
[15] Corwin and Viohl, *J. Amer. Chem. Soc.*, 1944, **66**, 1137.

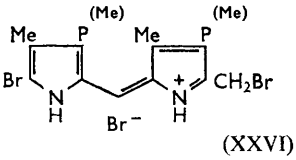
in ether. With one mol. of bromine, a good yield of the bromomethylpyrrole (XVIb) was obtained, and this, although relatively unstable in air, could be isolated by evaporation of the ether at low temperature and recrystallisation of the residue from petroleum. Addition



of one further mol. of bromine to the ether solution of the bromomethylpyrrole unexpectedly afforded a rather insoluble product, which was shown to be the methene *t*-butyl ester (XXIV) (analysis and i.r. spectrum); this was presumably formed by reaction (7). Larger amounts of bromine yielded a mixture of this methene (XXIV) and the desired α-bromomethylmethene (Ib). Evidently, formation of the latter compound was favoured by high concentrations of bromine, and this was confirmed by reversed mixture of the reactants; when an ethereal solution of bromomethylpyrrole (XVIa) was added slowly to bromine (2 mol.) in ether the pure bromomethylmethene (Ib) was obtained in 38% yield. This reverse addition was also tried with cryptopyrrole itself, but even with a large excess of bromine (4 mol.) a mixture of methenes resulted. However, this is not very surprising as initial bromination of cryptopyrrole at the free α-position should be much more rapid than bromination of the α′-methyl group.

A similar sequence of reactions starting from t-butyl 2,3,4-trimethylpyrrole-5-carb-


(XXV)


(XXVI)

oxylate (XVIIa) gave either the methene (XVb) or the methene (XXV), depending on the conditions. In this case, however, the 2-bromomethylpyrrole (XVIb) was much less stable and it decomposed on attempted recrystallisation; it was therefore brominated further without purification. Synthesis of the methene (XVb) by this route was thus effected more readily, and in much better yield, than by direct bromination of 2,3,4-trimethylpyrrole. More recently, the generality of this reaction for preparing α-bromo-α′-bromomethyl-methenes has been demonstrated by a similar synthesis of the methene (XXVI) required as an intermediate for the preparation of coproporphyrin I.[16]

Counter-current Distribution of Porphyrins.—Complex natural porphyrins, bearing carboxylic acids in their side-chains, have been separated by distribution between ether

[16] Abraham, Burbidge, Jackson, and Kenner, *Proc. Chem. Soc.*, 1963, 134.

and hydrochloric acid.[17] This system is not conveniently permanent because ether is volatile and tends to peroxidise during prolonged distributions. These disadvantages have been overcome, for simple alkylated porphyrins, by use of benzene–sulphuric acid systems—systems in which, moreover, these alkylporphyrins are rather more soluble than in ether–dilute hydrochloric acid. Most of the alkylporphyrins prepared during the course of this work were readily purified finally by counter-current distribution in a 25-tube hand-operated machine (with 25 ml. top and bottom phases).

The distribution coefficients of ætioporphyrin, diethylhexamethylporphin and octamethylporphyrins are shown in Table 2 [for 13 and 20% (w : v) sulphuric acid]. In determining these distribution coefficients, several hundred transfers were carried out in a 96-tube automatic counter-current machine (3 ml. each phase) fitted with a re-cycling device. The distribution curves were obtained by plotting the optical density of the

TABLE 2.

	H_2SO_4 (% w : v)	K
Ætioporphyrin	20	0·65
	13	2·70
Hexamethyldiethylporphin	13	0·91
Octamethylporphin	13	0·24

benzene phases at the strongest peak in the visible spectrum (*e.g.*, 498 mμ of ætioporphyrin). The distribution curve for ætioporphyrin I after 608 transfers between benzene and 20% sulphuric acid agreed very well with the theoretical curve. Attempts to separate authentic samples of ætioporphyrins I and II (prepared by Fischer's procedure [18]) were unsuccessful; even after 600 transfers, the distribution curve was still symmetrical and it agreed closely with the theoretical curve. Similar results were obtained with both the ætioporphyrins prepared from bilenes.

The other porphyrins obtained from the syntheses described in this Paper were also shown by counter-current distribution to be substantially single compounds or mixtures of isomers, *e.g.*, the diethyl hexamethylporphin from the third synthesis in Table 1 was found to contain *ca.* 20% ætioporphyrin; and in the fourth experiment the amount of octamethylporphin was approximately 10% of the total porphyrin. In both these cases the yield of by-product (2·5 and 1·5%, respectively) was within the limits expected from self-condensation of the corresponding methenes.

EXPERIMENTAL

Diethyl Propionylmalonate (cf. Lund and Voigt [19]).—Magnesium turnings (75 g.), ethanol (75 ml.), carbon tetrachloride (3 ml.), and 90 ml. of a solution of diethyl malonate (480 g.) in ethanol (240 ml.) were warmed gently. Evolution of hydrogen began after a short while and the remainder of the diethyl malonate solution was added at such a rate that reaction proceeded vigorously but not violently. When the addition was complete, the flask was cooled, dry ether (1500 ml.) was added, and the mixture was again heated under reflux until all the magnesium had dissolved. Propionyl chloride (294 g.) in dry ether (300 ml.) was then slowly added to the stirred solution, and, when addition was complete, the whole mixture was boiled under reflux for 1 hr. further. The cooled, syrupy magnesium complex was carefully decomposed by slow addition of excess of ice-cold dilute sulphuric acid. The usual ether extractions and distillation afforded diethyl propionylmalonate (500 g.; 77%), b. p. 129—130°/18 mm. (Found: C, 55·7; H, 7·7. Calc. for $C_{10}H_{16}O_5$: C, 55·5; H, 7·5%).

Ethyl Propionylacetate.—Diethyl propionylmalonate (500 g.) was hydrolysed by boiling with water (1500 ml.) according to MacDonald's procedure for the similar preparation of diethyl β-oxoadipate.[20] The mixture was stirred vigorously and heated so that slow distillation took place through a short fractionating column, and after 4½ hr. the distillate amounted to *ca.* 1000

[17] Granick, Bogorad, and Frankfort, *J. Biol. Chem.*, 1953, **202**, 781.
[18] Paul, *Scand. J. Clin. Lab. Invest.*, 1953, **5**, 212 (*Chem. Abs.*, 1954, **48**, 1459h).
[19] Lund and Voigt, *Org. Synth.*, Coll. Vol. **2**, 594.
[20] MacDonald and Stedman, *Canad. J. Chem.*, 1959, **37**, 1056.

ml. The organic material remaining in the flask was separated from the aqueous layer, and the latter was extracted with ether (2 × 500 ml.). A small amount of product which had steam-distilled was separated from the distillate, and combined with the original organic layer and ethereal extracts. The combined extracts were washed successively with saturated sodium bicarbonate solution (100 ml.), water (4 × 100 ml.), and saturated sodium carbonate solution (4 × 50 ml.). The sodium carbonate extracts were re-extracted with ether (100 ml.) and the combined ethereal extracts washed with water (3 × 50 ml.), dilute sulphuric acid (2 × 50 ml.), and finally with water (4 × 50 ml.). Evaporation of the dried ethereal extracts and distillation afforded ethyl propionylacetate (220 g.; 66%), b. p. 98—101°/26 mm., n_D^{16} 1·416.

Pyrroles

Diethyl 3-*Ethyl*-5-*methylpyrrole*-2,4-*dicarboxylate*.—Ethyl propionylacetate (210 g.) in acetic acid (525 ml.) was treated slowly with sodium nitrite (105 g.) in water (190 ml.) at 0—5°. After being kept overnight, this solution was run slowly with stirring into ethyl acetoacetate (189 g.) and acetic acid (525 ml.), a mixture of zinc dust (245 g.) and anhydrous sodium acetate (250 g.) being added portionwise simultaneously at 60—80°. The reaction mixture was stirred for a further hour at 100°, and then decanted into ice and water (10 l.). The product was filtered off, washed with water, dried in air, and crystallised from ethanol, forming needles (184 g.; 57%), m. p. 114—115° (lit.,[21] 115°).

Ethyl 4-*Diethylaminomethyl*-3-*ethyl*-5-*methylpyrrole*-2-*carboxylate*.—A mixture of 2-ethoxycarbonyl-3-ethyl-5-methylpyrrole-4-carboxylic acid (50 g.) (prepared [21] by partial hydrolysis of the corresponding diester), diethylamine (26 g.), 40% aqueous formaldehyde (42 ml.), and ethanol (190 ml.) was boiled under reflux for 5 hr. before being filtered and poured into ice-cold water (2 l.). Sufficient dilute hydrochloric acid was added to the solution to bring the pH down to 2, a small amount of unchanged acid was filtered off, and the filtrate was made alkaline with aqueous ammonia. The required Mannich base (48·5 g.; 82%) crystallised, and was sufficiently pure for hydrogenolysis. Recrystallisation from aqueous ethanol gave plates, m. p. 67—68° (Found: C, 67·5; H, 9·9; N, 10·3. $C_{15}H_{26}N_2O_2$ requires C, 67·6; H, 9·8; N, 10·5%).

Ethyl 3-*Ethyl*-4,5-*dimethylpyrrole*-2-*carboxylate*.—The foregoing Mannich base (48 g.) and Raney nickel (20 ml.) in ethanol (200 ml.) were stirred with hydrogen (100 atm.) at 150° during 12 hr. The filtered solution was concentrated under reduced pressure to about 100 ml., then heated to boiling and water added until the solution was slightly turbid. The ester (33 g.; 94%) crystallised in chunky needles, m. p. 96—97° (lit.,[21] 97°).

Benzyl 3-*Ethyl*-4,5-*dimethylpyrrole*-2-*carboxylate*.—A solution of the above ethyl ester (20 g.) and sodium (0·4 g.) in benzyl alcohol (50 ml.) was heated at 100° under reduced pressure (10 mm.) for 4 hr. Excess of benzyl alcohol was removed by distillation at 100°/1—2 mm., and the cooled residue was taken up in ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated until crystallisation began. The *benzyl ester* crystallised at 0°. A second crop was obtained by evaporation of the mother-liquors, and the combined products were recrystallised from light petroleum (b. p. 60—80°) in prisms (22 g.; 83%), m. p. 89—90° (Found: C, 74·7; H, 7·6; N, 5·5. $C_{16}H_{19}NO_2$ requires C, 74·7; H, 7·4; N, 5·4%).

Benzyl 3,4,5-*Trimethylpyrrole*-2-*carboxylate*.—Ethyl 4-diethylaminomethyl-3,5-dimethylpyrrole-2-carboxylate, m. p. 110° (48 g.) (prepared from ethyl 3-carboxy-3,5-dimethylpyrrole-2-carboxylate in 67% yield by a method analogous to that described for the 3-ethyl-5-methyl homologue above) was hydrogenated in ethanol over Raney nickel at 150°/100 atm. for 12 hr. to ethyl 3,4,5-trimethylpyrrole-2-carboxylate (33 g.; 94%), chunky crystals (from aqueous ethanol), m. p. 96—97° (lit.,[10b] 97°). Transesterification with benzyl alcohol, as above, gave the required benzyl trimethylpyrrole-2-carboxylate (82%) as needles, m. p. 118° (lit.,[22] 119—120°) from light petroleum (b. p. 60—80°).

Benzyl 5-*Bromomethyl*-3,4-*dimethylpyrrole*-2-*carboxylate*.—A solution of bromine (2·0 ml.) in dry ether (400 ml.) was added rapidly to a vigorously stirred solution of benzyl 3,4,5-trimethylpyrrole-2-carboxylate (10 g.) in dry ether (400 ml.). After 1 hr. the colour had faded to pale yellow, and the solution was then concentrated under reduced pressure to about 150 ml. and stored overnight at 0°. The *bromomethylpyrrole* (10 g.; 81%) crystallised as needles, m. p. 131—132°, raised to 133—134° by recrystallisation from light petroleum (80—100°) (Found: C, 56·0; H, 5·1; N, 4·2. $C_{15}H_{16}BrNO_2$ requires C, 56·3; H, 5·0; N, 4·3%).

[21] Fischer and Stangler, *Annalen*, 1927, **459**, 81.
[22] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.

The following bromomethylpyrroles were also prepared by the same method: (i) *Ethyl 5-bromomethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate* (77%), m. p. 126—128° (Found: C, 48·5; H, 5·6; N, 4·2. $C_{14}H_{20}BrNO_4$ requires C, 48·6; H, 5·5; N, 4·1%). (ii) *Benzyl 5-bromomethyl-3-2′-methoxycarbonylethyl-4-methylpyrrole-2-carboxylate* (84%), m. p. 137—139° (Found: C, 55·3; H, 5·4; N, 3·7. $C_{18}H_{20}BrNO_4$ requires C, 54·8; H, 5·1; N, 3·6%). (iii) *Benzyl 5-bromomethyl-4-2′-benzyloxycarbonylethyl-3-methylpyrrole-2-carboxylate* (75%), m. p. 140—141° (Found: C, 61·5; H, 5·2; N, 3·0. $C_{24}H_{24}BrNO_4$ requires C, 61·3; H, 5·1; N, 3·0%).

Benzyl 5-Chloromethyl-4-ethoxycarbonyl-3-methylpyrrole-2-carboxylate.—Benzyl 3,5-dimethyl-4-ethoxycarbonylpyrrole-2-carboxylate[3] (10·5 g.) in glacial acetic acid (20 ml.) was heated to *ca.* 50—60° and stirred during the addition of sulphuryl chloride (2·8 ml.) in glacial acetic acid (6 ml.). The reaction mixture was heated at 70° for a further ½ hr. and then allowed to cool to room temperature. The *chloromethylpyrrole* (6·5 g.; 54%) which separated was washed with light petroleum, dried, and recrystallised from benzene, forming needles, m. p. 137—138° (Found: C, 60·7; H, 5·7; N, 4·3. $C_{17}H_{18}ClNO_4$ requires C, 60·8; H, 5·4; N, 4·2%).

t-Butyl 5-Bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate.—A solution of the corresponding 5-methylpyrrole [13] (5·0 g.) in dry ether (200 ml.) was stirred rapidly during the addition of bromine (1·2 ml.) in dry ether (200 ml.). After a further hour, the ether was removed *in vacuo* at 25° and a little light petroleum (b. p. 40—60°) added to the residue, which then solidified. The pale brown crystals were recrystallised from light petroleum (b. p. 60—80°), giving the desired *bromomethylpyrrole* as needles (4·96 g.; 73%), m. p. 130° (decomp.), which were unstable in air and slowly decomposed to a red oil (Found: C, 51·6; H, 6·8; N, 4·3. $C_{13}H_{20}BrNO_2$ requires C, 51·6; H, 6·6; N, 4·6%).

t-Butyl 5-Bromomethyl-3,4-dimethylpyrrole-2-carboxylate.—This was prepared as was the foregoing compound, but it proved to be more unstable. It could not be recrystallised for analysis, and the crude product was therefore used directly in subsequent experiments.

Pyrromethanes (Pyrrolylmethylpyrroles)

The pyrromethanes required in this work were all prepared by reaction between 2-bromomethylpyrroles and pyrrole-2-carboxylic acids. (The latter were obtained from the corresponding benzyl esters by catalytic hydrogenolysis.) The two components were heated in boiling dry chloroform (usually for 10 min.), according to method A of Part I of this series.[3] The following new pyrromethanes were prepared in this way and recrystallised from light petroleum (b. p. 60—80°).

(XIII)	R^1	R^2	R^3	R^4	Yield (%)	M. p.	Formula †
(b)	Me	Et	Et	Me	71	103—104°	$C_{24}H_{30}N_2O_2$
(e)	Me	Et	Me	Me	74	133—135	$C_{23}H_{28}N_2O_2$
(f)	Me	Me	Me	Et	31 *	107—108	$C_{23}H_{28}N_2O_2$
(g)	Me	Me	Me	Me	73	108—109	$C_{22}H_{26}N_2O_2$
(j)	Me	$P^{(Bz)}$	Me	Et	53	97—98	$C_{32}H_{36}N_2O_4$

* Reaction mixture heated for 30 min. Shorter reaction times gave a product contaminated with symmetrical pyrromethane, m. p. 178—179° (dibenzyl 3,3′,4,4′-tetramethylpyrromethane-5,5′-dicarboxylate) derived from the bromomethylpyrrole. Mixed m. p. with authentic material, 178—179° (see later).

† Analysis of the products for carbon, hydrogen, and nitrogen gave the following results (figures required by the formulæ being in parentheses): (b) 76·1 (76·2), 8·0 (8·0), 7·4 (7·4); (e) 75·7 (75·8), 7·6 (7·7), 7·7 (7·7); (f) 75·4 (75·8), 7·8 (7·7), 7·5 (7·7); (g) 75·1 (75·0), 7·4 (7·2), 8·0 (8·3); (j) 75·1 (75·0), 7·3 (7·1), 5·4 (5·5)%.

Dibenzyl 3,3′,4,4′-Tetramethylpyrromethane-5,5′-dicarboxylate.—A solution of benzyl 5-bromomethyl-3,4-dimethylpyrrole-2-dicarboxylate (1·0 g.) in methanol (5 ml.) was heated under reflux for 4 hr. The crude product separated from the cooled mixture and when recrystallised from light petroleum (b. p. 100—120°) gave pure *pyrromethane* (0·5 g.; 68·5%) as fluffy needles, m. p. 179° (Found: C, 74·2; H, 6·5; N, 5·9. $C_{29}H_{30}N_2O_4$ requires C, 74·0; H, 6·4; N, 5·9%).

Benzyl 3-Ethoxycarbonyl-4′-ethyl-3′,4,5′-trimethylpyrromethane-5-carboxylate.—(i) Benzyl 5-*chloromethyl*-4-*ethoxycarbonyl*-3-*methylpyrrole*-2-*carboxylate* (1·0 g.) and 4-ethyl-3,5-dimethylpyrrole-2-carboxylic acid (0·5 g.) were heated in boiling dry benzene (10 ml.) for ¾ hr. After removal of the benzene *in vacuo*, the residual solid was crystallised from ether–n-hexane, giving pale yellow needles of the desired *pyrromethane* (0·52 g.; 42%), m. p. 85—87° (Found: C, 71·0; H, 7·5; N, 6·4. $C_{25}H_{30}N_2O_4$ requires C, 71·0; H, 7·2; N, 6·6%).

(ii) The same chloromethylpyrrole (5 g.) was dissolved in dry pyridine (5 ml.) and treated

with lithium 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (2·6 g.) in aqueous methanol (50 ml.; 50%). The mixture was heated for 48 hr. at 40° in a flask fitted with a Bunsen valve, and during this period a crystalline solid (contaminated with oily material) separated. The mixture was cooled overnight in the refrigerator, then the clear supernatant liquid was decanted and the residue taken up in ether. The ethereal solution was washed with water, dried (Na_2SO_4), filtered through a short column of charcoal, and evaporated to small bulk at room temperature. Addition of n-hexane gave the required pyrromethane (2·5 g.; 40%) as pale yellow clusters of small needles, m. p. 85—86°.

Diethyl 4′-Ethyl-3′,4,5′-trimethylpyrromethane-3,5-dicarboxylate.—Diethyl 5-chloromethyl-3-methylpyrrole-2,4-dicarboxylate (5·47 g.) was condensed with lithium 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (3·46 g.) in pyridine (10 ml.) and 50% aqueous methanol (100 ml.) at 40° for 40 hr. The reaction was worked up in the same manner as the foregoing example; the required *pyrromethane* (2·35 g.; 34%) crystallised from ether–n-hexane as micro-prisms, m. p. 91—92° (Found: C, 66·5; H, 7·7; N, 8·1. $C_{20}H_{28}N_2O_4$ requires C, 66·7; H, 7·8; N, 7·8%).

Pyrromethenes

5-Bromo-5′-bromomethyl-3,4′-diethyl-3′,4-dimethylpyrromethene Hydrobromide.[2a]—(i) Bromination of cryptopyrrole in glacial acetic acid yielded a mixture of the desired hydrobromide and the perbromide of 5-bromo-3,4′-diethyl-3′,4,5′-trimethylpyrromethene hydrobromide, separated by extraction with chloroform. The desired hydrobromide (11%) was recrystallised from benzene to give red prisms which did not melt below 350°. Higher yields were not obtained by addition of the cryptopyrrole to a solution of excess of bromine in glacial acetic acid.

(ii) 3,4′-Diethyl-3′,4,5′-trimethylpyrromethane-5-carboxylic acid (2·3 g.; 0·006 mole) (prepared from the corresponding benzyl ester by hydrogenolysis in methanol over palladium charcoal) was dissolved in the minimum amount of glacial acetic acid at 50° and then cooled and treated with bromine (1 ml.; 0·02 mole) in glacial acetic acid (5 ml.) at room temperature. After 24 hr. the mixture of methene hydrobromides (1·6 g.) was filtered off, washed with a little dry ether, and extracted with warm chloroform. The insoluble red material (300 mg.) had m. p. 148—149° and gave no depression when mixed with the perbromide above. The chloroform extracts were evaporated to dryness and the residual solid recrystallised from benzene, giving 5-bromo-3,4′-diethyl-3′,4,5′-trimethylpyrromethene hydrobromide (1·1 g.) as red prisms, m. p. 224° (decomp.) (lit.,[4a] 215°) (Found: C, 47·6; H, 5·9; N, 7·1. Calc. for $C_{16}H_{22}Br_2N_2$: C, 47·8; H, 5·5; N, 7·0%). A solution of this pyrromethene hydrobromide (1·0 g.) in glacial acetic acid was boiled under reflux with bromine (0·4 g.) until hydrogen bromide was no longer evolved. The desired 5-bromo-5′-bromomethylpyrromethene hydrobromide separated from the cooled solution and was recrystallised from chloroform–light petroleum (b. p. 60—80°), forming red prisms, which did not melt below 350°.

(iii) A solution of t-butyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate in ether (500 ml.), prepared from the corresponding 5-methylpyrrole (10·0 g.) by treatment with bromine (2·4 ml.; 1 mol.) as described previously, was added during 1 hr. to a stirred solution of bromine (4·8 ml.; 2 mols.) in dry ether (400 ml.). The mixture was stirred for a further ½ hr. and then kept overnight to complete crystallisation. The product (4·73 g.; 46%) was filtered off, washed with a little dry ether, and dried (NaOH) *in vacuo*.

The light absorptions of the products obtained by the three methods were all identical, and they all gave the same methoxymethylmethene hydrobromide (see below) on treatment with methanol.

5-Bromo-5′-bromomethyl-3,3′,4,4′-tetramethylpyrromethene Hydrobromide.[23]—(i) Bromine (13·5 ml.; 2·5 mol.) in glacial acetic acid (70 ml.) was added rapidly to a stirred solution of 2,3,4-trimethylpyrrole (15 g.) in glacial acetic acid (130 ml.), and the mixture left overnight. The mixture of red methene salts (15·5 g.) was filtered off, washed with light petroleum, and dried (NaOH) *in vacuo*. Extraction with boiling chloroform left a brick-red solid (5·6 g.) undissolved. This was assumed to be the perbromide of 5-bromo-3,3′,4,4′,5-pentamethylpyrromethene, since treatment with acetone gave immediately the characteristic pungent odour of bromoacetone. Attempts to purify this product by recrystallisation from benzene or chloroform were abandoned owing to its low solubility.

On concentrating the chloroform extracts, crude 5-bromo-5′-bromomethylpyrromethene

[23] Fischer and Walach, *Annalen*, 1926, **450**, 125.

hydrobromide (3·25 g.) crystallised. On recrystallisation from chloroform several times (until the " bromoacetone test " was negative) the methene hydrobromide was obtained as crimson prisms (1·35 g.; 5%), which did not melt below 250°. (Fischer and Walach [23] described this compound as yellow plates and gave no melting point.) (Found: C, 37·6; H, 4·0; N, 6·0. Calc. for $C_{14}H_{17}N_2Br_3$: C, 37·1; H, 3·8; N, 6·2%).

(ii) Preparation from t-butyl 3,4,5-trimethylpyrrole-2-carboxylate by a similar method to that described for the analogue gave deep red prisms (37%) (Found: C, 36·6; H, 3·6; N, 5·8%).

t-Butyl 5'-Bromomethyl-3,4'-diethyl-3',4-dimethylpyrromethene-5-carboxylate Hydrobromide.—Bromine (0·6 ml.; 1 mol.) in dry ether (100 ml.) was added to a stirred solution of t-butyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (2·4 g.) in dry ether (100 ml.). After 1 hr. more bromine (0·6 ml.) in ether (100 ml.) was added rapidly and the solution was stirred for a further hr. before being left overnight at 0°. The *pyrromethene hydrobromide* (1·3 g.; 48%) was filtered off, washed with a little ether, and dried (NaOH) *in vacuo*, giving orange needles, m. p. 136° (decomp.) (Found: C, 50·1; H, 6·2; N, 5·5. $C_{21}H_{30}Br_2N_2O_2$ requires C, 50·2; H, 6·0; N, 5·6%); $\nu_{max.}$ (Nujol) 1710 (carbonyl) and 1632 (methene) cm.$^{-1}$. Attempted recrystallisation of the product from benzene or chloroform gave a black gum.

t-Butyl 5'-Bromomethyl-3,3',4,4'-tetramethylpyrromethene-5-carboxylate.—A preparation similar to that just described gave this compound (45% yield) as orange needles, m. p. 135—136° (decomp.), which decomposed on attempted recrystallisation and could not be obtained analytically pure. It had $\nu_{max.}$ (Nujol) 1708 (carbonyl) and 1615 cm.$^{-1}$ (methene).

5-Bromo-3,4'-diethyl-3',4-dimethyl-5'-methoxymethylpyrromethene Hydrobromide.—A solution of the foregoing 5'-bromomethylpyrromethene hydrobromide (2 g.) in dry methanol (30 ml.) was boiled under reflux for 15 min. and then rapidly cooled in acetone–solid carbon dioxide. The *methoxymethylpyrromethene hydrobromide* (1·4 g.; 78%) was collected, washed with a little ether, and crystallised from benzene, forming orange-red prisms, m. p. 148° (decomp.) (Found: C, 47·2; H, 5·9; N, 6·6. $C_{17}H_{24}Br_2N_2O$ requires C, 47·2; H, 5·6; N, 6·5%); $\lambda_{max.}$ (in $CHCl_3$) 230, 275, and 494 (log ε 4·17, 3·47, and 4·89, respectively); $\nu_{max.}$ (Nujol) 1619 cm.$^{-1}$ (methene).

5-Bromo-5'-methoxymethyl-3,3',4,4'-tetramethylpyrromethene Hydrobromide.—A preparation similar to the foregoing gave this *methene* (87%) as red needles [from chloroform–light petroleum (b. p. 60—80°)], m. p. 172° (Found: C, 44·3; H, 5·1; N, 6·8. $C_{15}H_{20}Br_2N_2O$ requires C, 44·5; H, 4·9; N, 6·9%).

5-Bromo-3-2'-carboxyethyl-4'-ethyl-3',4,5'-trimethylpyrromethene Hydrobromide.—Benzyl 3,2'-benzyloxycarbonylethyl-4'-ethyl-3',4,5'-trimethylpyrromethane-5-carboxylate (2·0 g.) in dry methanol (40 ml.) was hydrogenated at 1 atm. over 10% palladium charcoal (0·4 g.) until uptake ceased. Filtration and removal of the solvent under reduced pressure (nitrogen leak) gave the corresponding pyrromethane di-acid as pale pink crystals. These were dissolved in glacial acetic acid (15 ml.) and treated rapidly with bromine (0·6 ml.; 3 mols. assuming a 95% yield of the di-acid) in glacial acetic acid (2·5 ml.). The mixture was kept for 5 min. at room temperature, then heated on the steam-bath for 15 min., and finally concentrated *in vacuo* to *ca.* 10 ml. The pyrromethene hydrobromide (0·81 g.; 47%) crystallised from the cooled solution in red prisms with a blue-green sheen, m. p. 158°, not raised by recrystallisation from acetic acid (lit.,[24] 160°) (Found: C, 45·6; H, 5·1; N, 6·1. Calc. for $C_{17}H_{22}Br_2N_2O_2$: C, 45·7; H, 5·0; N, 6·3%).

5-Bromo-3-ethoxycarbonyl-4'-ethyl-3',4,5'-trimethylpyrromethene Hydrobromide.—Benzyl 3-ethoxycarbonyl-4'-ethyl-3',4,5'-trimethylpyrromethane-5-carboxylate (1·8 g.) was converted into the corresponding 5-carboxylic acid, m. p. 171—172°, by hydrogenation in methanol over palladium–charcoal as described for the analogue above. This acid was dissolved in glacial acetic acid (10 ml.) and treated with bromine (1·5 ml.) in acetic acid (1·5 ml.). Hydrogen bromide was evolved briskly and a red solid (1·3 g.; 95%) separated during 40 hr. at room temperature. Recrystallisation from chloroform–ether furnished the *bromo-pyrromethene* as shining red, elongated prisms, decomp. above 200° (Found: C, 45·8; H, 5·1; N, 6·6. $C_{17}H_{22}Br_2N_2O_2$ requires C, 45·7; H, 4·9; N, 6·3%).

Porphyrins

The pyrromethanecarboxylic acids, which were condensed with pyrromethenes in the following experiments, were prepared from their benzyl esters by hydrogenolysis in methanol

[24] Fischer and Adler, *Z. physiol. Chem.*, 1931, **200**, 228.

over 10% palladised charcoal. They were used directly after removal of the catalyst and solvent.

Ætioporphyrin.—(1) Solutions of 5-bromo-3,4′-diethyl-5′-methoxymethyl-3′,4-dimethylpyrromethene hydrobromide (I; R = OMe) (432 mg.) in dry benzene (100 ml.) and of 3,4′-diethyl-3′,4,5′-trimethylpyrromethane-5-carboxylic acid (XIa) (288 mg.) in dry benzene (100 ml.) were heated under reflux during 1 hr. The deep red solution was concentrated to *ca.* 20 ml. and then diluted with dry ether. Crude bilene hydrobromide (512 mg., 79%) crystallised in dark red needles with a characteristic green sheen. Three recrystallisations from benzene–ether furnished pure *1′-bromo-1,3,5,7,8′-pentamethyl-2,4,6,8-tetraethylbilene-a-hydrobromide* (III; $R^1 = R^3 = Me$, $R^2 = R^4 = Et$), m. p. 256° (decomp.) (Found: C, 59·9; H, 7·1; N, 9·1. $C_{32}H_{44}Br_2N_4$ requires C, 59·6; H, 6·9; N, 8·6%); $\lambda_{max.}$ (in alcohol-free chloroform) 283, 378, 462, and 528 mμ (log $\varepsilon_{max.}$ 3·74, 4·17, 4·35, and 4·83, respectively); $\nu_{max.}$ (Nujol) at 1613 cm.$^{-1}$ (methene). Dilute solutions in benzene or chloroform exhibited a pink colour with greenish fluorescence.

The crude bilene hydrobromide (13 mg.), in acetic acid (1·2 ml.), was heated at 110—120° during 1 hr. with 48% hydrobromic acid in acetic acid (1·2 ml.). The acid was neutralised with 1% sodium hydroxide solution, and the solid product was dried and dissolved in chloroform. The solution was chromatographed on alumina (neutral " Woelm," Grade I). The pink band was eluted in chloroform, which was diluted to a definite volume before measurement of optical density at 498, 531, 565, 592, and 618 mμ. By using extinction coefficients, log ε 4·14, 4·00, 3·79, 3·07, and 3·66, respectively, which were determined for isolated porphyrin in agreement with the literature,[25] the yield could be estimated as 1·95 mg. (20%). In experiments on eight times the scale, the product was purified by counter-current distribution (25 transfers) between benzene and sulphuric acid (20% w : v) (25 ml. each phase). Tubes 8—16 yielded 13% of ætioporphyrin, estimated spectrophotometrically, when they were neutralised with ammonia solution and the benzene layer was evaporated. Recrystallisation of the residue from chloroform–methanol afforded violet needles of authentic ætioporphyrin.

When the bilene hydrobromide had been purified by repeated recrystallisation from chloroform–light petroleum (b. p. 60—80°) or by chromatography, it no longer yielded any porphyrin.

(2) *N*-Methylmorpholine (0·1 ml., 1 mole) was mixed with a suspension of 5-bromo-5′-bromomethyl-3,4′-diethyl-3′,4-dimethylpyrromethene hydrobromide (I; R = Br) (481 mg.) in freshly distilled anisole (50 ml.). A solution of the same pyrromethanecarboxylic acid (XIa) (288 mg.) in anisole (10 ml.) containing *N*-methylmorpholine (0·1 ml.) was then added and the mixture was boiled under reflux during 1 hr. The deep red solution was evaporated and a solution of the residue in acetic acid (15 ml.) was heated under reflux at 110—120° during 1 hr. with 48% hydrobromic acid in acetic acid (15 ml.). Chromatography, etc., as in the foregoing experiment, yielded violet needles of ætioporphyrin (70 mg., 11%). When the pyrromethanecarboxylic acid was omitted, ætioporphyrin was still obtained but only in 0·9% yield.

Alternatively, the two components were heated directly at 110—120° in acetic acid (24 hr.) or 48% hydrobromic acid in acetic acid (1 hr.); the yields of ætioporphyrin were 6 and 9%, respectively.

(3) An experiment similar to (1) with 3,3′-diethyl-4,4′,5′-trimethylpyrromethane-5-carboxylic acid (XIb), instead of the isomer (XIa), gave *1′-bromo-2,4,6,7-tetraethyl-1,3,5,8,8′-pentamethylbilene-a-hydrobromide* (III; $R^1 = R^4 = Me$, $R^2 = R^3 = Et$) (79%), which was recrystallised from benzene–light petroleum (b. p. 60—80°) in dark red needles with a green sheen and lacking a definite m. p. (Found: C, 60·1; H, 7·0; N, 8·5%); $\lambda_{max.}$ (in $CHCl_3$) 283, 378, 462, and 528 mμ (log $\varepsilon_{max.}$ 3·68, 4·21, 4·38, and 4·80, respectively); $\nu_{max.}$ (Nujol) 1613 cm.$^{-1}$ (methene). Treatment of this bilene hydrobromide with hydrobromic and acetic acid, as above, gave only 3% of ætioporphyrin.

(4) The pyrromethene hydrobromide (I; R = OMe) was recovered unchanged from attempts to condense it with ethyl 5-carboxyl-4′-ethyl-3′,4,5′-trimethylpyrromethane-3-carboxylate (XIc) under the conditions described in (1) above, even if the heating in benzene was prolonged for several hours.

(5) (With Dr. J. A. Ballantine). Condensation of ethyl 5-carboxy-3-ethyl-3′,4,5′-trimethylpyrromethane-4′-carboxylate (XId) with the pyrromethene hydrobromide (I; R = OMe) [under the same conditions as in (1), except that heating was prolonged for 3 hr.] gave

[25] Stern and Wenderlein, *Z. phys. Chem.*, 1934, **170***A*, 337.

the 1′-bromo-8-ethoxycarbonyl-2,4,6-triethyl-1,3,5,7,8′-pentamethylbilene-a-hydrobromide (63%) as a dark red solid with a green sheen, and of indeterminate melting point. The light absorption and i.r. spectra were closely similar to those of the two bilenes obtained above, with the exception of an additional peak in Nujol at 1687 cm.$^{-1}$ (due to the ester carbonyl at position 8). Attempts to obtain a rhodoporphyrin derivative by cyclisation of this bilene under acidic conditions as described above, or more drastically by fusing it in molten succinic acid, yielded only ætioporphyrin (maximum yield 2%).

Alkylporphins (Table 1). In each experiment the methoxymethylpyrromethene hydrobromide (0·001 mole) and the pyrromethane-5-carboxylic acid (0·001 mole) were heated in boiling benzene (200 ml.) under reflux for 1 hr., and the resulting solution was kept for 2 days at room temperature. The solvent was decanted and filtered, and the porphyrin salt left in the flask and on the filter paper taken up in chloroform and neutralised with ammonia. The chloroform solution was then washed with water, dried ($MgSO_4$), and chromatographed on alumina. The porphyrin was eluted with chloroform, or benzene, and then recovered by evaporation of the solvent, followed by recrystallisation of the residue from chloroform–methanol. To overcome the low solubility of octamethylporphin, it was extracted (Soxhlet) with *o*-dichlorobenzene containing a little ammonia. The extracts were washed with water and dried by azeotropic distillation, and the solution then concentrated to small bulk and allowed to cool, the octamethylporphin then crystallised out as purple needles.

The mother-liquors, from all these experiments, on evaporation yielded dark red solids with a green sheen, and having typical " bilene-like " visible absorption spectra.

Attempted Syntheses of Mesoporphyrins.—(1) Condensation of 4′-ethyl-4-2″-methoxycarbonylethyl-3,3′,5′-trimethylpyrromethane-5-carboxylic acid (XIh) with the pyrromethene hydrobromide (I; R = OMe) under the conditions described above for syntheses of alkylporphins. The product was isolated in the usual manner and crystallised from chloroform as red-brown microprisms (5%), which melted over the range 240—280°. [The m. p. of authentic mesoporphyrin II dimethyl ester prepared by Fischer's method was 236—238°.] The i.r. spectrum of the product also differed from that of authentic mesoporphyrin II dimethyl ester, although it showed a peak at 1738 cm.$^{-1}$ in chloroform (which could be attributed to propionic ester carbonyl groups). The n.m.r. spectrum of the product in trifluoroacetic acid solution [8] indicated that it was probably a mixture of ætioporphyrin and porphyrins containing propionate methyl ester side-chains; this was confirmed later by thin-layer chromatography [26] in acetone–n-hexane (30 : 70 v/v) which showed the presence of ætioporphyrin, a mesoporphyrin dimethyl ester, and traces of a porphyrin bearing a single propionic ester side-chain.

(2) (With Dr. A. Hayes). On concentration, the mother-liquors from the above preparation gave *1′-bromo-5-2″-methoxycarbonylethyl-2,4,8-triethyl-1,3,6,7,8′-pentamethylbilene-a-hydrobromide* (III; R^1 = propionate, $R^2 = R^3$ = Me, R^4 = Et) as a dark solid with a green lustre, in 62% yield. After several recrystallisations from benzene–ether the bilene had m. p. 185—190° (decomp.) (Found: C, 59·5, 59·6; H, 7·3, 7·8; N, 7·7, 7·5. $C_{34}H_{46}Br_2N_4O_2,\frac{1}{2}C_6H_6$ requires C, 59·9; H, 6·6; N, 7·6%). The analysis was unchanged even after extensive chromatography on powdered cellulose, and the discrepancies were therefore attributed to benzene of crystallisation. A small amount of the bilene set aside in ethyl acetate for 2 months, slowly deposited purple crystals which gave a satisfactory analysis (Found: C, 58·4; H, 7·1; N, 8·3. $C_{34}H_{46}Br_2N_4O_2$ requires C, 58·2; H, 6·6; N, 8·0%). The bilene obtained in these experiments gave a pink solution in chloroform with a green fluorescence; $\lambda_{max.}$ 525 and 474 mμ; $\nu_{max.}$ (Nujol) 1607 cm.$^{-1}$ (pyrromethene) and 1725 cm.$^{-1}$ (broad low intensity, CO_2Me).

Treatment of this bilene with hydrobromic and acetic acid at 110—120° gave a crude product, which was esterified with diazomethane in ether–chloroform, and then purified by chromatography in chloroform on neutral alumina. The porphyrin-containing eluates were evaporated to dryness and the residue crystallised from chloroform–methanol giving purple needles of ætioporphyrin (*ca.* 3%), m. p. >350°. The i.r. spectrum showed no absorption in the carbonyl region (1630—1750 cm.$^{-1}$), and the u.v. and visible light absorption were indistinguishable from authentic ætioporphyrin.

(3) (With Dr. A. Hayes). In experiments involving condensation of the pyrromethene hydrobromide (I; R = OMe) with 4′-ethyl-3-2″-methoxycarbonylethyl-3′,4,5′-trimethylpyrromethane-5-carboxylic acid (XIi) a mixture of porphyrins was also obtained rather than

[26] Burbidge, Jackson, and Kenner, unpublished experiments.

a pure mesoporphyrin dimethyl ester. The mother-liquors from these experiments likewise gave bilene-like material (90%) which showed absorption maxima at 472 and 523 mμ and gave a pink solution in chloroform with a green fluorescence; attempts to convert this material into a porphyrin bearing propionate substituents gave only traces of ætioporphyrin (identified spectroscopically).

Porphyrins Prepared by Modifications of Standard Methods.—Ætioporphyrins I [4c] and II [4e] and mesoporphyrin II [4f] dimethyl ester were all prepared by Fischer's methods in 30, 30, and 24% yield, respectively, but the products were all purified chromatographically on alumina in benzene or chloroform before crystallisation; with mesoporphyrin II the crude acid prepared initially was esterified by treatment with methanolic hydrogen chloride before chromatography.

Octamethylporphin was prepared (18% yield) by formic acid treatment of 5-bromo-5′-bromomethyl-3,3′,4,4′-tetramethylpyrromethene hydrobromide (cf. the analogous preparation of ætioporphyrin I [4c]), and the crude product worked up by Soxhlet extraction with *o*-dichlorobenzene (after removal of the more-soluble impurities by extraction with methanol, and then with chloroform) and then crystallised from *o*-dichlorobenzene.

We thank the Nuffield Foundation for support, the Government of India for a scholarship (A. C. J.), Dr. J. Lee for certain spectra, and Courtaulds Ltd. for supplies of diketen, used in the preparation of t-butyl acetoacetate.

The Robert Robinson Laboratories,
University of Liverpool.

[*Received, May 29th,* 1963.]