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Coproporphyrin 3[1]

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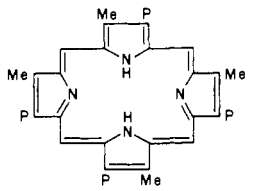
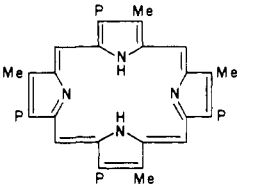
The syntheses of the coproporphyrins 3 and 4 have been repeated to provide reference material and to resolve differences between the natural and synthetic coproporphyrin 3. In four syntheses of the latter, ambiguous reactions were avoided and there was some control over those which might proceed in part irrationally. Data relevant to the identification of coproporphyrin 3 are corrected, extended and evaluated.

The type purity of synthetic uroporphyrin 3[3] could only be established by degrading to the coproporphyrin and comparing that with authentic coproporphyrin 3. The only acceptable reference specimens of this last had been those rationally synthesized by H. Fischer. Those in his collection were exhausted and had been characterized by melting points only. Natural coproporphyrin 3 has no status as reference material because its identification as such depends ultimately on comparison with synthetic specimens; no other methods will establish a presumption as to its structure or homogeneity. Unlike earlier ones,[4] recent specimens of natural coproporphyrin 3[5] (necessarily



COPROPORPHYRIN 3



COPROPORPHYRIN 4

P = $CH_2CH_2.COOH$

identified as such by m.p.'s alone although characterized more fully) have melted higher than did Fischer's synthetic specimens (Table I). This brought the purity of both into question particularly in view of the confusion surrounding the coproporphyrins 3 and 4.

TABLE I

REPORTED MELTING POINTS OF THE COPROPORPHYRINS

Type	Source	Methyl ester M.p., °C.	Methyl ester M.p. of copper complex, °C.
1	Synthetic[6]	252	
2	Synthetic[6]	288	
3	Synthetic[4,7]	142–148, (150...163), 165–172	206–207
4	Synthetic[4,7,8]	168–169, 177, 183–184	216–217
3	Natural *ex C. diphtheriae*[5]	155–157, 181–182	218

The natural coproporphyrins, frequently arising under pathological conditions, have been identified as or tacitly assumed to be coproporphyrin 1, coproporphyrin 3 or mixtures of these two. However, porphobilinogen is easily converted into a complex mixture of uroporphinogen isomers,[9,10] in which type 3 and 4 would be favored statistically, and all four uroporphinogens can be converted enzymically into coproporphyrins.[11] The purity of synthetic coproporphyrin 3 will reflect the uncertain purity of the unsymmetrical pyrromethene used in the synthesis (see below). The isomers suspected in hemin, chlorophyll and the bile pigments presented similar problems.[12] Coproporphyrin 4 in particular might thus be present in either natural or synthetic coproporphyrin 3 and remain undetected. These two isomers resemble each other closely and differ from the other isomers in their lower m.p.'s and higher solubilities. They have not been separated by paper chromatography[13] and their esters form mixed crystals (solid solutions).

The best data on the synthetic isomers (Table I) hardly sufficed for the identification of natural coproporphyrin 3 and were inadequately supplemented. The low m.p.'s usually quoted for the ethyl ester (124°) and for the copper complex of the methyl ester of coproporphyrin 3 (177°)[14] refer to irrationally synthesized material identified by an unsatisfactory mixed m.p.[7] The neglect[15] of the lower m.p.'s[4,7] of the obviously polymorphic coproporphyrin 4 methyl ester is not justified.[16] Also ignored have been the intermediate m.p.'s of coproporphyrin 3 methyl ester, both natural and synthetic, reported by Fischer. There was no infrared or X-ray data on coproporphyrin 4 and that on coproporphyrin 3 was confined to the low-melting form of the natural methyl ester.

We repeated the syntheses of the coproporphyrins 3 and 4 to provide authentic coproporphyrin 3 (having regard to the limitations of present methods), to resolve the discrepancies between its natural and synthetic forms, and to characterize the two isomers more satisfactorily. Coproporphyrin 3 was

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(2) National Research Council of Canada Postdoctorate Fellow, 1955–1956.

(3) E. J. Tarlton, S. F. MacDonald and E. Baltazzi, THIS JOURNAL, **82**, 4389 (1960).

(4) H. Fischer, K. Platz and K. Morgenroth, *Z. physiol. Chem.*, **182**, 265 (1929).

(5) C. H. Gray and L. B. Holt, *Biochem. J. (London)*, **43**, 191 (1948).

(6) H. Fischer, H. Friedrich, W. Lamatsch and K. Morgenroth, *Ann.*, **466**, 147 (1928).

(7) H. Fischer and J. Hiernis, *Z. physiol. Chem.*, **196**, 155 (1931).

(8) H. Fischer and A. Kurzinger, *ibid.*, **196**, 213 (1931).

(9) J. Waldenstrom and B. Vahlquist, *ibid.*, **260**, 189 (1939).

(10) G. H. Cookson and C. Rimington, *Biochem. J. (London)*, **57**, 476 (1954).

(11) D. Mauzerall, A.C.S. Meeting, Boston, Mass., 1959, Abstracts p. 54C.

(12) H. Fischer, *Z. physiol. Chem.*, **259**, 1 (1939); H. Fischer and G. Wecker, *ibid.*, **272**, 4 (1942).

(13) J. E. Falk, E. I. B. Dresel, A. Benson and B. Knight, *Biochem. J.*, **63**, 87 (1956).

(14) H. Fischer and H. Orth, "Chemie des Pyrrols," II/1, Leipzig, 1937, p. 491.

(15) Reference 14, p. 492.

(16) S. F. MacDonald and K. H. Michl, *Can. J. Chem.*, **34**, 1768 (1956).

CHART 1

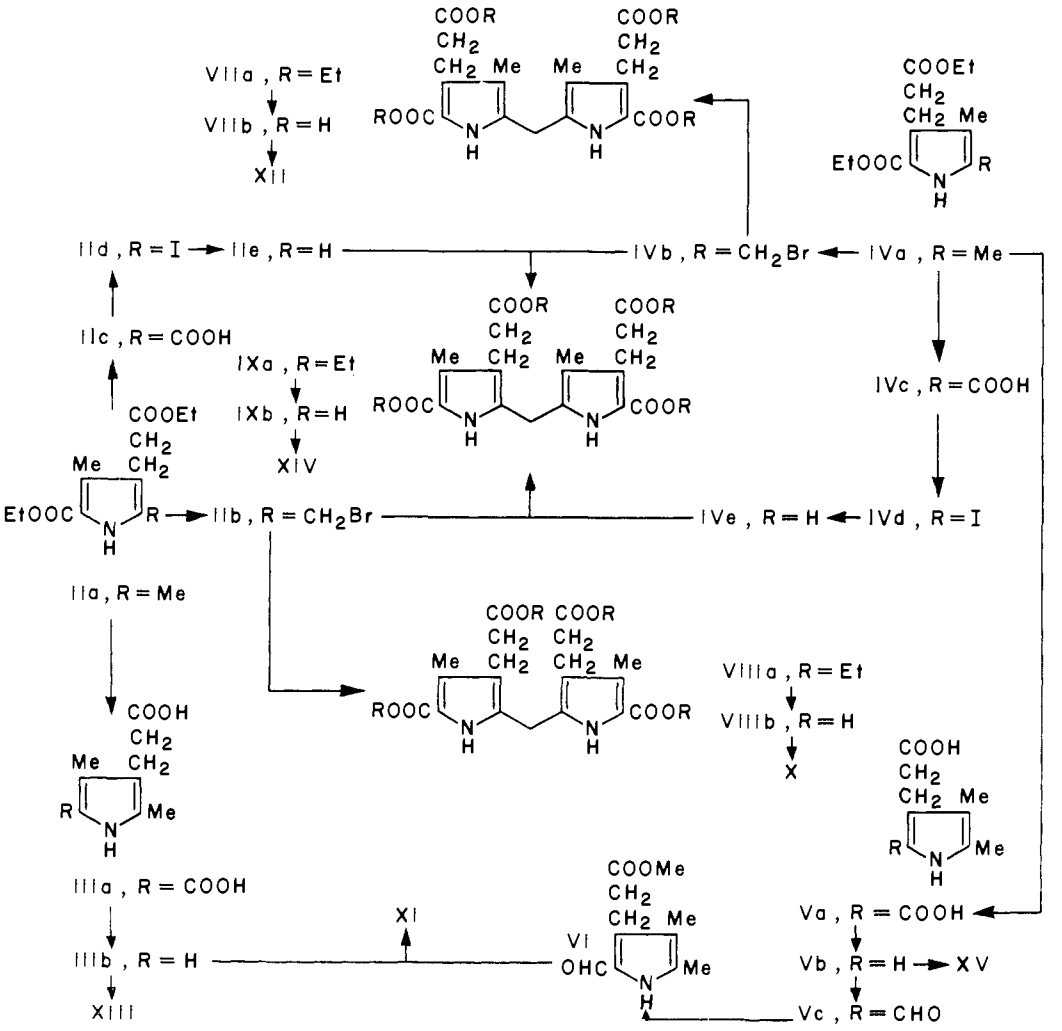
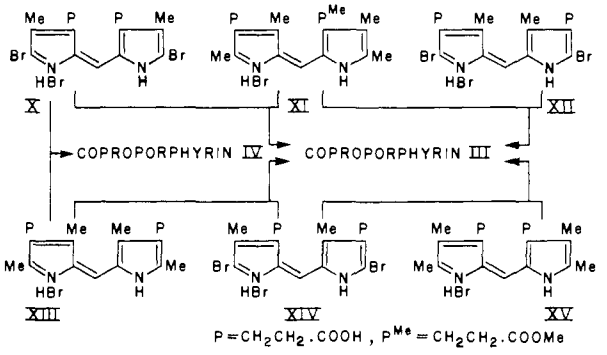


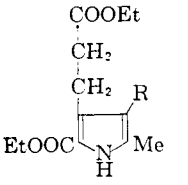
CHART 2



synthesized in four ways (Chart 2), in principle all those implied by Fischer's general and rational methods, fusing the pyrromethenes in succinic acid at 190°. The pair of syntheses using XI as the unsymmetrical pyrromethene had been used by Fischer, the pair using XIV are analogous to those of uroporphyrin 3.[3] Coproporphyrin 4, requiring only symmetrical pyrromethenes, was prepared by one of Fischer's methods only.

The required pyrromethenes (Chart 2), of which only XIV is new, were developed symmetrically from IIa and IVa (Chart 1) avoiding ambiguities except those inherent in the synthesis of unsymmetrical pyrromethenes. This development is essentially Fischer's treatment of the monoester (free propionic acid) corresponding to IIa except that the methyl groups of the diesters could be chlorinated directly. This required a convenient and unambiguous synthesis of IVa. Its derivatives had been obtained by the reduction of hemin (giving Vb) or by synthetic methods (giving Vb[17] and XII[18]) which likewise in themselves did not ensure the absence of the isomeric derivatives of IIa. A synthesis of Vb[19] was modified, improving the preparation of Ib from Ia and reducing the former to IVa; a more convenient variation has been reported.[20]

Ia, R = H
b, R = CHO



(17) H. Fischer and H. Orth, ref. 14, I, p. 282.
(18) H. Fischer and W. Lamatsch, *Ann.*, **462**, 240 (1928).
(19) S. F. MacDonald, *J. Chem. Soc.*, 4176 (1952).
(20) A. Hayes, G. W. Kenner and N. R. Williams, *ibid.*, 3779 (1958).

Bromination of IIa gave IIb which was converted into VIIIa in refluxing ethanol; VIIIa was hydrolyzed to VIIIb which was brominated to X. Similarly IVa was converted into XII through IVb, VIIa and VIIb. The hydrolysis of IIa or its monoester gave IIIa which was decarboxylated to IIIb in water at 100°; XIII was obtained as usual from IIIb with formic acid and hydrobromic acid at 100°. Likewise, XV was obtained from IVa through Va and Vb. Following the method of Fischer, Vb was converted into Vc which was esterified to VI, the latter being condensed with IIIb to obtain XI. This melted 50° higher than reported for Fischer's product but analyzed well, particularly for methoxy. The chlorination of IIa and IVa with 3 mols of sulfuryl chloride followed by hydrolysis gave IIc and IVc, respectively. These were decarboxylated to IIe and IVe by Corwin's method: conversion to IId and IVd by alkaline iodine followed by catalytic hydrogenation. The condensation of either IIe with IVb or IIb with IVe led to IXa. Unlike the corresponding uroporphyrin 3 intermediate,[3] this was purified by crystallization only, as chromatography was unsatisfactory. Like VIIa and VIIIa, IXa was hydrolyzed to IXb which was brominated to XIV.

The unambiguous synthesis of IVa eliminated one possible source of other isomers in the coproporphyrin 3. The consistent behavior of symmetrical pyrromethenes in porphyrin syntheses suggests that, in general, irrational processes in the melts, though not unknown,[21] should not contribute significantly to such impurities. However, contamination might result through the presence of symmetrical pyrromethenes in XI or XIV. The synthesis of pyrromethanes[3] or pyrromethenes under acid conditions may lead to such mixtures through redistribution reactions. It will be noted that IXa was not purified by a method known to be capable of separating it from VIIa and VIIIa. Also in an extreme case, a bromination analogous to that of IXb apparently led to a symmetrical product.[22] Similarly, condensations analogous to that leading to XI from IIIb and VI have sometimes given a symmetrical product[16] or a mixture.[6]

Our coproporphyrin 3 syntheses are summarized in Table II. Assuming then that any other isomers in the coproporphyrin 3 arose from symmetrical pyrromethenes in XI and XIV, only the coproporphyrins 2 and 4 would be possible impurities. If coproporphyrin 2 were present, the amounts were too small for certain identification by paper chromatography (sensitivity presumably 5%). Although the coproporphyrins 3 and 4 are not distinguished by paper chromatography, the proportion of coproporphyrin 4 in the coproporphyrin 3 from X and XI should then be that of XIII in XI or that of coproporphyrin 2 in the coproporphyrin 3 from XI and XII. *Mutatis mutandis* the proportion of coproporphyrin 4 resulting in each of the coproporphyrin 3 syntheses should be that of coproporphyrin 2 in the other member of its pair. Only by this rather precious argument can the ghost of coproporphyrin 4 be exercised from coproporphyrin 3.

(21) H. Fischer and H. Orth, ref. 14, II/1, p. 171.

(22) A. H. Corwin and K. J. Brunings, THIS JOURNAL, **64**, 2106 (1942).

The coproporphyrins 3 and 4 were compared using m.p.'s and X-ray powder photographs of the methyl esters, of the ethyl esters, of the copper complexes of the methyl esters, and infrared mull spectra of the methyl esters. The infrared spectra in carbon disulfide solution did not distinguish the coproporphyrin 3 and 4 methyl esters clearly if at all. The other criteria distinguish polymorphic forms as well as isomers and consequently only specimens in the same form, free of other polymorphs, are strictly comparable.

The m.p. data on various specimens of coproporphyrin 3 (Table II) show that the anomalies of Table I were real and have been resolved. The m.p.'s of Fischer's specimens (no. 5 and 6) like those reported for such, are lower than the corresponding m.p.'s of any of ours. The highest set of m.p.'s among those of our specimens (no. 1a) agrees well with that of natural material (no. 7), and the methyl esters of both specimens exhibit the intermediate forms. Further clarification came from the redetermined m.p. of coproporphyrin 4 methyl ester copper complex (230–233°). The reported m.p.'s of the coproporphyrin 3 and 4 ethyl esters were also shown to be incorrect (see Experimental). The specimen 1a (Table II) of coproporphyrin 3 thus provides a tentative standard of type and purity.

Coproporphyrin 3 (methyl ester m.p. or transition at 153–155°, about 165°, about 170°, 178–182°; copper complex of methyl ester m.p. 216–219°; ethyl ester m.p. 161–166°) as its methyl ester may crystallize from solution in the low- (1a, Table II) or in the high-melting form (3a), the first of which may be mixed with intermediate forms (1b). Recrystallization is more liable to change the lability of the low-melting form (m.p. and mull spectrum) than the form itself (X-ray powder photograph) as in 1b, 3b and 4. Some specimens have not been obtained in the low-melting form and we have not obtained an unmixed intermediate form. It was frequently difficult to obtain the high-melting form free of intermediate forms which depress the m.p. or of melt which obscures sintering. Depending on the specimen and on the rate of heating, the transitions involved anything from invisible changes in the solid phase to complete melting and any of the higher-melting solid phases might result. The generally higher-melting specimens (1a and 7) showed the expected changes most clearly and consistently. Coproporphyrin 4 (methyl ester m.p. or transition 168–170°, 175°, 182–186°; copper complex of methyl ester m.p. 230–233°, ethyl ester 156–168°) as its methyl ester crystallized from solution rather consistently in the one form. This is probably the only unmixed form of it we have obtained and all the expected transition or melting points were frequently visible. Of the revised melting points of coproporphyrin 3 and 4, the only characteristic ones are the lower m.p. of coproporphyrin 3 methyl ester and those of the copper complexes. The latter are consistently observable and are comparable to the ester m.p.'s as criteria of purity.

Only X-ray powder photographs[23] could be relied on to reveal the unperturbed form present and

(23) The X-ray powder photographs and their interpretation are by Dr. Maria Przybylska. Those of coproporphyrin 3 methyl ester

TABLE II: COPROPORPHYRIN 3 METHYL ESTERS

No.	Source Synthesis:	Low melting form M.p.,[d] °C.	Low melting form X-Ray photograph	Low melting form Infra-red mull	Intermediate forms Appearance and m.p., °C.	High melting form M.p.,[d] °C.	High melting form X-Ray photograph	High melting form Infra-red mull	Copper complex m.p.,[d] °C.	Types in chromatogram
1a	X and XI	152–154[a,b]	A	M[1], M[3]	Sparkling,[h] 165–168	176–179[h]	D[h]		(213) 216–219	3 or 4
		150–151[e]			Fibrous, <173[h]	178–179[e,h]				
		153–155[e,g]				178–182[e,h]				
1b	X and XI	150–151[f]	A and a few lines of B		Sparkling,[h] 165–168	175–179[h]			(209) 213–218	3 or 4 trace(?) 1
			A and B and C[j]	MN						
		(148) 152–154[e]				(175) 178–181[e,h]				
2	XII and XI	152–154[h]	A	M[1]	Sparkling,[h] 160–168	176–179[h]		N	(208) 213–215	3 or 4 trace(?) 1
		150–153[e]				175–180[e,h]				
3a	XIII and XIV	Form absent[b]				172–176[h]	D	N	(206) 210–216	
						(168) 172–178[e]				
3b	XIII and XIV	Not seen[b]	A and one line of C[b]	MN	162–168[e,k,u]	172–176[h]			(210) 212–215	3 or 4 trace(?) 2
		(147) 149–153[e]				(170) 172–178[e,h]				
4	XV and XIV	Not seen[h]	A[b]	M[3]	Fibrous,[h] 170	172–176[h]			(213) 217–219	3 or 4
		(151) 152–155[e]				178–181[e,h]				
5	H. Fischer (rational?)	Form absent				(146) 159–168[l]	D		(188) 193–206	
6	H. Fischer (not rational?)	Form absent			135–190[e,n]	Form absent			185–199	
7	Natural: *C. diphtheriae*	153–156	A	M[2]	Sparkling,[h] 163–168	178–182[h]	D and extra lines		(210) 216–219	
					Fibrous,[h] 168–173; Plates,[i,p] 167–170					

[a] From chloroform–methanol. [b] From acetone–methanol. [c] Recrystallized after two years from chloroform–methanol. Only these m.p.'s were taken on the same apparatus as were those of no. 5, 6 and 7. [d] Temperature in parens indicates onset of sintering. [e] Capillary. [f] Solid phase change without sintering. [g] Sometimes sintering from 150°. [h] By heating low-melting form. [i] Melt cooled quickly from 180° and washed with methanol. [j] Recovered from Nujol mull using petrol. [k] After countercurrent distribution (see Experimental). [l] Unchanged after recrystallization or heating. [m] X-Ray: very similar to D, slight differences in interplanar spacings and intensities. [n] X-Ray: similar to B but spacings different. [p] X-Ray: B plus extra lines.

mixtures of forms. Assuming any small amounts of other isomers present would be in solid solution, the extra lines noted suggest further polymorphs. One specimen (no. 4, Table II, m.p. 172–176°) was thus shown to be the low-melting form. Another (no. 1b) was shown to be a mixture of forms which was further altered by mulling for the infrared spectrum. Sometimes the m.p. was only indicative of the purity after the form had been defined by an X-ray powder photograph. Two specimens (no. 7, m.p. 167–170°, and no. 5, m.p. 159–168°) were thus shown to be an intermediate form and a low-melting specimen of the high-melting form, respectively. In general, X-ray photographs should distinguish the relatively low-melting coproporphyrin 3 derivatives from possibly unrelated mixtures of isomers. The behavior of a mixture of the coproporphyrins 3 and 4 (see Experimental), and of no. 5 suggests that X-ray photographs of the methyl esters are more sensitive criteria of purity than those of their copper complexes but less sensitive than m.p.'s. In proving two specimens identical, as the high-melting forms of no. 1a and 7, it was sometimes difficult to obtain identical photographs because of their sensitivity to the homogeneity of the crystal form.

The infrared mull spectra[24] were less useful than X-ray powder photographs. In those of the coproporphyrin 3 and 4 methyl esters only the following were strikingly characteristic: unique maxima at 763 and 778 cm.$^{-1}$ in the low-melting form of the coproporphyrin 3 ester and the relatively low maximum at 1200 cm.$^{-1}$ in its high-melting form (below that at about 1240 cm.$^{-1}$). The spectra of coproporphyrin 3 methyl ester reflected the polymorphs present although, unlike X-ray powder photographs, not in ways which could be rationalized. Thus one spectrum (no. 1b, Table II) appeared to be merely a composite of those of the low- and high-melting forms. The X-ray photographs of this specimen showed that its form was altered by mulling so, in general, the mull spectra depend on both the form and its lability. The two spectra of the high-melting form N were identical but the more complex spectra of the low-melting form M showed differences which were, however, not greater than generally anticipated between mulls. Similar differences are apparent between three spectra of one specimen in its low-

are described in terms of four patterns: A and D, the simplest typical of the low- and high-melting forms, respectively; B and C representing intermediate forms; that of one high melting form had extra lines.

(24) The infrared spectra and their interpretation are by Dr. R. N. Jones and Mr. Lauzon. In Table II they are described in terms of the two spectra M and N of the low- and high-melting forms, respectively; M[1], M[2] and M[3] refer to increasing degrees of resolution.

melting form (M of No. 7 and those reported for it).[25,26]

The solubility in methanol, as determined in the mother liquors, did not distinguish the coproporphyrin 3 and 4 methyl esters (0.03–0.07 mg./ml.) but did distinguish these from a mixture of the two (0.3 mg./ml.) and from one of Fischer's specimens (no. 6, Table II, 0.7 mg./ml.). The selective enzymic conversion of coproporphinogen 3 to protoporphyrin[11] would appear to be the most promising method for distinguishing these two isomers in mixtures.

The criteria of identity and purity were more satisfactory among the coproporphyrins than among the uroporphyrins. A mixture of the four coproporphyrin methyl esters crystallized well, but unlike the corresponding uroporphyrin mixture[3] the crystals did not appear homogeneous and melted over a wide range (see Experimental). However, the identification of one specimen (no. 6, Table II) as coproporphyrin 3 seemed hardly justified and that of another (no. 3b, m.p. 162–168°) was only possible in other crystal forms.

Experimental[27,28]

2,4-Dimethyl-5-carbethoxy-pyrrole-3-propionic Acid.—The corresponding acrylic acid[29] was hydrogenated in a 20% excess of 10% sodium hydroxide over Raney nickel (20°, 8 hr., 60 p.s.i.). The product (92%, m.p. 156–158°) was precipitated by sulfur dioxide from the filtered solution and washed with water. This compound is dimorphic. It melted at 152° after recrystallization from ether and we have repeatedly from the two reported melting points (152°[30,31] and 159°[32]).

2,4-Dimethyl-5-carboxy-pyrrole-3-propionic Acid Diethyl Ester (IIa).—The monoester (100 g.) was warmed to solution in 300 ml. of 5% ethanolic hydrogen chloride. After standing overnight the solution was seeded and left at 0°. The crude product was filtered off and recrystallized by extracting from a thimble with pentane, the extract passing through a second lower thimble filled with charcoal. A nearly colorless product (86 g., 77%), m.p. 76–77°, was separated by filtration. For analysis it was thrice recrystallized from 50% ethanol giving colorless rods, m.p. 77–78° (lit.[33] 73°).

Anal. Calcd. for $C_{14}H_{21}O_4N$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.05; H, 7.74; N, 5.12.

2-Methyl-3-formyl-5-carboxy-pyrrole-4-propionic Acid Diethyl Ester (Ib).—The following is a considerable improvement on the original method. A mixture of 62 g. of Ia,[34] 62 ml. of hydrogen cyanide, 360 ml. of dry ether and 90 ml. of chloroform (dry and ethanol-free, stabilized with dry ether[35]) was cooled in ice and salt, stirred mechanically, and protected from moisture. Dry hydrogen chloride was passed into saturation, then for 2 hr. longer while an oily precipitate formed. After standing overnight at 0°, the solvent was removed by a stream of dry air while the container was in a bath at 20°. Dry ether (60 ml.) was then added and evaporated in the same way. The solid residue was dissolved in 500 ml. of ice-water and left at 0° overnight while the crude product crystallized. After drying and extracting some Ia (3 g.) with pentane (thimble), recrystallization from aqueous ethanol gave colorless irregular plates (59 g., 86%), m.p. 121–122° (lit.[19] 122–123°).

2,3-Dimethyl-5-carboxy-pyrrole-4-propionic Acid Diethyl Ester (IVa).—The aldehyde Ib (59 g.) in 120 ml. of ethanol was hydrogenated over Raney nickel (175–180°, 2 hr., initially 1700 p.s.i.). The product crystallized from aqueous ethanol in colorless prisms (45 g., 80%), m.p. 88–89° (lit.[20] 91°).

Anal. Calcd. for $C_{14}H_{21}O_4N$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.03; H, 8.05; N, 5.43.

The half-ester with a free propionic group has also been reported.[36]

2-Bromomethyl-4-methyl-5-carboxy-pyrrole-3-propionic Acid Diethyl Ester (IIb).—Bromine (10 g.) in 40 ml. of carbon tetrachloride was added dropwise to a stirred solution of IIa (15 g.) in 90 ml. of carbon tetrachloride, later warming to 50° to maintain solution. After irradiating for 30 min. with an ultraviolet lamp, the solvent was removed *in vacuo* at 20° and the residue slurried with 100 ml. of dry ether. The latter was taken off *in vacuo* and the nearly colorless product (18.5 g., 95%), m.p. 128–129°, washed into the filter with a little ether. The analytical sample formed colorless needles, m.p. 130–131° (lit.[20] 126–128°) after four recrystallizations from heptane. It was dried *in vacuo* for 4 hr. at 56°.

Anal. Calcd. for $C_{14}H_{20}O_4NBr$: C, 48.56; H, 5.82; N, 4.05. Found: C, 48.80; H, 5.95; N, 4.22.

The half-ester (free propionic acid[31]) was also prepared.

2-Bromomethyl-3-methyl-5-carboxy-pyrrole-4-propionic Acid Diethyl Ester (IVb).—Prepared as was its isomer IIb, 1 g. of IVa and 0.64 g. of bromine using 14 ml. of carbon tetrachloride gave 0.9 g. (70%), m.p. 147–149°, crystallized from ether–heptane. For analysis it was recrystallized thrice from ether–heptane (charcoal) giving colorless needles, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{20}O_4NBr$: C, 48.55; H, 5.77; N, 4.00. Found: C, 48.40; H, 5.75; N, 4.13;

Other esters have been reported.[20,37]

4,4′-Dimethyl-5,5′-dicarboxypyrromethane-3,3′-dipropionic Acid Tetraethyl Ester (VIIIa). (a).—The pyrrole IIb (0.5 g.) in 15 ml. of ethanol was refluxed for 2 hr. then cooled, diluted with 10 ml. of water, and scratched. The crude product, m.p. 113–115°, was recrystallized thrice from aqueous ethanol from which it separated as colorless prisms (0.16 g.), m.p. 115–116°, Ehrlich reaction negative.

Anal. Calcd. for $C_{27}H_{38}O_8N_2$: C, 62.53; H, 7.39; N, 5.40. Found: C, 62.76; H, 7.48; N, 5.52.

(b).—The pyrrole IIb (2.5 g.) was refluxed for 4.5 hr. in 15 ml. of ethanol and 7.5 ml. of water. The crude product (1.3 g., 70%) was separated and recrystallized thrice from ethanol. It formed colorless prisms, m.p. 102–104°; mixed with the product of (a) above softened at 102–103° and melted at 113–114°; evidently it is dimorphic.

Anal. Found: C, 62.41; H, 7.27; N, 5.49.

The diester (free propionic acid groups),[31] m.p. 201–202°, was also prepared.

3,3′-Dimethyl-5,5′-dicarboxypyrromethane-4,4′-dipropionic Acid Tetraethyl Ester (VIIa).—Prepared as was its isomer VIIIa by method a, it forms prismatic rods (38%) after three crystallizations from aqueous ethanol, m.p. 116–117° depressed to 98–100° when mixed with VIIIa, Ehrlich reaction negative.

Anal. Calcd. for $C_{27}H_{38}O_8N_2$: C, 62.53; H, 7.39; N, 5.40. Found: C, 62.70; H, 7.43; N, 5.48.

The diester (free propionic acid groups) has been described.[37]

(25) C. H. Gray, A. Neuberger and P. H. A. Sneath, *Biochem. J.*, **47**, 87 (1950).

(26) J. E. Falk and J. B. Willis, *Austral. J. Sci. Research, Ser. A*, **4**, 579 (1951).

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(28) Paper chromatography was done, using two runs by the lutidine and two by the dioxane method, through the kindness of Professor C. Rimington whose assessments are quoted.

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(35) S. F. MacDonald, *J. Chem. Soc.*, 2378 (1954).

(36) H. Fischer and M. Hussong, *Ann.*, **492**, 128 (1932).

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2-Carboxy-3-(2-carbethoxyethyl)-4-methyl-5-carbethoxypyrrole (IIc). (a).—Sulfuryl chloride (1.3 ml.) was added at 20° to a stirred suspension of IIa (1.3 g.) in 20 ml. of ether. The next day the clear solution was refluxed for 40 min. after which the solvent was removed *in vacuo*. Two further additions of ether (10 ml.) were similarly removed. The oily residue was stirred on the steam-bath for 10 min. with a hot solution of 5 g. of sodium acetate in 40 ml. of water. On cooling, crystals separated and the mixture was extracted with ether. The ether was extracted with sodium carbonate (5 g. in 30 ml.) and the aqueous layer acidified with sulfur dioxide. The precipitate (1 g. 70%) was recrystallized from aqueous ethanol giving slender colorless needles, m.p. 151–152° dec. undepressed by the product of method b.

On a larger scale 20 g. of IIa and 30.4 g. of sulfuryl chloride gave 14.3 g. (64%) of the same product, m.p. 150–151°.

(b).—Similarly 1.7 g. of IIb and 0.9 ml. of sulfuryl chloride gave 1. g. (75%) of the recrystallized product. For analysis it was recrystallized four times from ethanol, m.p. 153–153.5° dec., Ehrlich reaction negative.

Anal. Calcd. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.75; H, 6.50; N, 4.63.

The monoester (free propionic acid) has been prepared by method b.[18]

2-Carboxy-3-methyl-4-(2-carbethoxyethyl)-5-carbethoxypyrrole (IVc) was prepared like the isomer IIc using 15 g. of IVa, 22.7 g. of sulfuryl chloride and 250 ml. of ether, immediately refluxing 1 hr. and heating with hot sodium acetate (30 g. in 200 ml. of water) for 15 min. After recrystallizing from ethanol, the product (10 g., 60%) formed colorless plates, m.p. 202–203°. The analytical sample, m.p. 204–205° dec., had been recrystallized four times from ethanol, Ehrlich reaction negative.

Anal. Calcd. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.40; H, 6.34; N, 4.73.

2-Carboxy-3-methylpyrrole-4-propionic Acid Diethyl Ester (IIe).—The acid IIc (1.1 g.) was heated to solution in 13 ml. of water containing 0.74 g. of potassium bicarbonate. Iodine (0.94 g.) in 15 ml. of ethanol was then added dropwise over a few minutes. After heating to boiling to discharge the color, the solution was poured into 70 ml. of water and the colorless IId filtered off. This product was hydrogenated at 18 p.s.i. in 20 ml. of ethanol with 1 g. of magnesium oxide and 1.1 g. of 5% palladium-on-charcoal for 24 hr. After the addition of sodium sulfite the catalyst was separated and the solvent evaporated *in vacuo*. The residue was shaken with ether and water. The ether layer was washed, dried, and the ether removed. The oily residue was crystallized from ether–hexane giving colorless prismatic needles (0.6 g., 64%), m.p. 40–41°. For analysis it was recrystallized thrice, m.p. unchanged, Ehrlich reaction positive cold.

Anal. Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.40; H, 7.41; N, 5.52.

On a larger scale, 9.9 g. of IIc, 6.66 g. of potassium bicarbonate and 8.46 g. of iodine gave 5.6 g. (66%) of IIe.

The half-ester (free propionic acid) has been prepared by this and other methods.[6,36,38]

2-Carboxy-4-methylpyrrole-3-propionic Acid Diethyl Ester (IVe). (a)—The acid IVc (0.25 g.) was decarboxylated by heating under nitrogen to 240° then sublimed at 60–70° *in vacuo*. The colorless product (0.12 g., 56%), m.p. 65–68°, was recrystallized thrice from hexane giving fine rods, m.p. 66–68°, Ehrlich reaction slowly positive cold.

Anal. Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.50; H, 7.37; N, 5.62.

(b).—Following the method given for the isomer IIe but on 6 times the scale, IVc was iodinated then reduced. After crystallization from hexane the product IVe (70–85%) melted at 65–67°.

2,3-Dimethylpyrrole-4-propionic Acid (Hemopyrrolecarboxylic Acid) (Vb).—The ester IVa (20 g.) was refluxed on the steam-bath for 3 hr. with 100 ml. of water, 30 ml. of ethanol and 20 g. of sodium hydroxide. After boiling off ethanol, the cooled solution was acidified with sulfur dioxide and extracted with ether. The washed and dried ether layer was evaporated. The residual yellowish red solid Va was decarboxylated by stirring with 15 ml. of boiling water on the steam-bath as long as gas was evolved (10 min.). The mixture was quickly cooled and dried *in vacuo* giving 11.1 g. (89%), m.p. 127–129° (lit.[17] 130–131°). It darkens readily in the presence of air and light and was always crystallized from chloroform–petroleum ether (b.p. 65–90°) with charcoal just prior to use.

This compound has been synthesized directly from Ib[19] but has usually been obtained by the reduction of hemin or by ambiguous synthetic methods.[17]

2,4-Dimethyl-pyrrole-3-propionic Acid (Cryptopyrrolecarboxylic Acid) (IIIb).—The ester IIa was hydrolyzed and decarboxylated to IIIb exactly as in the preparation of the isomeric Vb. The crude product (92%), m.p. 139–140° (lit.[39] 140–140.5°), was always crystallized as prisms from chloroform–petroleum ether (charcoal) just prior to use.

This compound is usually obtained from the half-ester (free propionic acid) corresponding to IIa.[39]

2,3-Dimethyl-5-formylpyrrole-4-propionic Acid (Vc).—The dry aldimine hydrochloride[4] was prepared from 7 g. of the pyrrole Vb, 175 ml. of dry chloroform and 17.5 g. of hydrogen cyanide. It was boiled with aqueous sodium hydroxide until the evolution of ammonia ceased (about 4 hr.). After cooling, the clear red solution was acidified with sulfur dioxide and the dark solid taken up in ether. The ether layer was washed with a little water, dried, filtered with charcoal, concentrated, and cooled. The product separated as almost colorless irregular prisms (2.5 g. 31%), m.p. 155–156° (lit.[4] 155°).

2,3-Dimethyl-5-formylpyrrole-4-propionic Acid Methyl Ester (VI).—The acid Vc (1 g.) was dissolved in ethereal diazomethane from 5 g. of nitrosomethylurea. Next day most of the ether was removed in a stream of nitrogen and the colorless crystalline product separated (0.7 g., 65%), m.p. 92° after softening at 89–90° (lit.[4] 89°).

4,5,3′,5′-Tetramethylpyrromethene-3-propionic Acid Methyl Ester 4′-propionic Acid Hydrobromide (XI).—Hydrobromic acid (48%, 1.2 ml.) was added to a solution of the aldehyde VI (0.6 g.) and the pyrrole IIIb (0.5 g.) in ethanol at room temperature. On cooling and scratching, crystals separated. After 15 min. the solid was filtered off and washed with a little ethanol then with ether. Recrystallization from ethanol afforded yellowish-orange short stout needles (0.7 g. 55%), m.p. 188–189°. For analysis it was dried at 78° for 3 hr. *in vacuo*.

Anal. Calcd. for $C_{20}H_{27}O_4N_2Br$: C, 54.67; H, 6.20; OCH_3, 7.06. Found: C, 54.55; H, 6.06; OCH_3, 7.02.

Similarly 0.84 g. of VI and 0.7 g. of IIIb in 6 ml. of ethanol gave 1.5 g. (85%) of recrystallized XI, m.p. 188–189°. Prepared in the same way, this product was reported to melt at 138°.[4] Other derivatives have been reported.[40]

4,4′-Dimethyl-5,5′-dicarboxypyrromethane-3,3′-dipropionic Acid (VIIIb). (a).—The diester corresponding to VIIIa (free propionic acid groups) was hydrolyzed[31] and the crude product, insoluble in ethanol, dissolved in aqueous acetone. Removal of the acetone under nitrogen left the product as an almost colorless powder (35%), m.p. 175–176° dec. (lit.[31] 176°).

(b).—The tetraester VIIIa was hydrolyzed in the same way and the crude product (100%) purified by extraction with acetone (thimble) giving a pinkish solid, m.p. 151–152°. Evidently it is dimorphic. For analysis it was dried *in vacuo* at 56° for 2 hr.

Anal. Calcd. for $C_{19}H_{22}O_8N_2$: C, 56.15; H, 5.46. Found: C, 56.30; H, 5.59.

4,4′-Dimethyl-5,5′-dibromopyrromethene-3,3′-dipropionic Acid Hydrobromide (X).—The acid VIIIb was brominated according to Fischer and Kurzinger[8] giving the product (73%) as purplish glittering prisms, m.p. >250° (lit.[4] > 250°).

3,3′-Dimethyl-5,5′-dicarboxypyrromethane-4,4′-dipropionic Acid (VIIb).—The pyrrole IVb (2.5 g.) was refluxed for 4 hr. in 25 ml. of ethanol and 15 ml. of water. The next day the crystalline solid VIIa was heated for 2 hr. in 15 ml. of water, 5 ml. of ethanol and 1.5 g. of sodium hydroxide. The cooled solution was acidified with hydrochloric acid. The precipitated product was purified until colorless by dissolving in warm 70% acetone and removing the acetone with nitrogen giving 1.1 g. (75%), m.p. 155–157° dec. The analysis was unsatisfactory. As it readily turns red, it was converted quickly into XII.

(38) G. G. Kleinspehn and A. H. Corwin, THIS JOURNAL, **76**, 564 (1954).

(39) H. Fischer and H. Orth, ref. 14, I, 286.

(40) H. Fischer and A. Rothhaas, *Ann.*, **484**, 85 (1930).

The same product, m.p. 153–155° dec., was obtained using the recrystallized intermediate VIIa.

3,3′-Dimethyl-5,5′-dibromopyrromethene-4,4′-dipropionic Acid Hydrobromide (XII).—The acid VIIb (1 g.) was suspended in 5 ml. of 98% formic acid and 0.4 ml. of bromine in 5 ml. of formic acid added dropwise at 40–50°. After standing in a vacuum desiccator for a few hours acetic acid was added and the solid washed with acetic acid then dry ether. The brick-red product formed tiny rods (1 g., 73%), m.p. >250°.

Anal. Calcd. for $C_{17}H_{19}O_4N_2Br_3$: C, 36.78; H, 3.45; N, 5.05; Br, 43.19. Found: C, 36.64; H, 3.62; N, 4.87; Br, 43.36.

Heretofore, this has been prepared from the 5,5′-free pyrromethene. Despite the ambiguous synthesis of the latter, its conversion to coproporphyrin 2 had established its purity.[18]

3,4′-Dimethyl-5,5′-dicarboxypyrromethane-4,3′-dipropionic Acid Tetraethyl Ester (IXa). (a).—The pyrroles IIe (506 mg.) and IVb (692 mg.) were refluxed in 20 ml. of benzene for 1 hr. while protected from moisture. Benzene was removed *in vacuo* and the residue dissolved in ether. The ether was washed with 1% sodium hydroxide then with water, dried and the ether evaporated. The residue was crystallized thrice from aqueous ethanol giving 480 mg. (46%), m.p. 100–102°. The analytical sample was recrystallized thrice more to give colorless prismatic needles, m.p. 101–102° not depressed by the product obtained under (b).

Anal. Calcd. for $C_{27}H_{38}O_8N_2$: C, 62.53; H, 7.39; N, 5.40. Found: C, 62.76; H, 7.49; N, 5.25.

(b).—By the same method, the isomeric pyrroles IIb (2.768 g.) and IVe (2.024 g.) in 40 ml. of benzene gave the thrice recrystallized product (2 g., 48%) as colorless prismatic needles, m.p. 102–104°.

3,4′-Dimethyl-5,5′-dicarboxypyrromethane-4,3′-dipropionic Acid (IXb).—The ester IXa (2 g.) was heated on the steam-bath for 2.5 hr. with 20 ml. of water, 5 ml. of ethanol and 2 g. of sodium hydroxide. The cooled solution was poured into ice and hydrochloric acid (3 ml.). The gelatinous precipitate was filtered off and washed twice with 10% ethanol by decantation. The product (1 g., 64%) a reddish amorphous powder, m.p. 130–133° dec., turned deep red even *in vacuo* and away from light.

Anal. Calcd. for $C_{19}H_{22}O_8N_2$: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.24; H, 5.73; N, 6.68.

3,4′-Dimethyl-5,5′-dibromopyrromethene-4,3′-dipropionic Acid Hydrobromide (XIV).—Bromine (0.75 ml.) was added in one lot to 1 g. of IXb suspended in 7.5 ml. of formic acid. Most of the formic acid was removed from the resulting clear solution in a vacuum desiccator over sodium hydroxide during 2 hr. The addition of 5 ml. of acetic acid caused the product to crystallize. It was washed with acetic acid and dry ether. The red needles (400 mg., 29%) decomposed above 200°.

Anal. Calcd. for $C_{17}H_{19}O_4N_2Br_3$: Br, 43.19. Found: Br, 43.42.

3,5,3′,5′-Tetramethylpyrromethene-4,4′-dipropionic acid hydrobromide (XIII) was prepared from IIIb by th usual method,[6] m.p. 212–214° (lit. 214–215°) (71%).

4,5,4′,5′-Tetramethylpyrromethene-3,3′-dipropionic acid hydrobromide (XV) was prepared by the method given for its isomer XIII.[6] From 1.1 g. of Vb, 1.5 ml. of 98% formic acid and 20 drops of 48% hydrobromic acid, 1.2 g. (86%) was obtained as greenish glittering crystals, m.p. 199–200° dec.

Anal. Calcd. for $C_{19}H_{25}N_2O_4Br$: C, 53.65; H, 5.92; N, 6.59. Found: C, 51.33, 52.63; H, 6.24, 6.42; N, 6.15, 6.68.

This compound has been used[8] but not otherwise mentioned except as the hydrochloride.[41]

1,3,5,8-Tetramethylporphin-2,4,6,7-tetrapropionic Acid (Coproporphyrin 3) Tetramethyl Ester. Method 1, from X and XI. (a).—A well-ground mixture of 720 mg. of XI, 570 mg. of X and 5.2 g. of succinic acid was dried at 20° under high vacuum for 4 hr. It was then heated at 190° (bath 195–200°) for 20 min. in a tube protected from moisture. The cooled melt was dissolved in 250 ml. of hot water, heated in the steam-bath, and the *p*H adjusted to 5 with disodium phosphate (5 g.). The crude porphyrin was centrifuged off, washed thrice with 100 ml. of water, dried, and left overnight in 80 ml. of saturated methanolic hydrogen chloride. The solution was poured into 300 ml. of ice-water which was then extracted with chloroform. The chloroform was filtered through alumina (Grade V, 40 g., diameter 2 cm.) and the porphyrin washed through with more chloroform. The concentrated solution (200 ml.) was washed with 45% aqueous resorcinol (6 × 30 ml.) which was in turn washed with a little chloroform. The chloroform solution was washed six times with water, dried over sodium sulfate, and again filtered through alumina. The solution was then concentrated, finally boiling off all the chloroform while maintaining the volume with hot methanol. On cooling, the ester separated as needles (specimen 1a, Table II, 203 mg., 22%). This method was reported[4] to give an 11% yield, m.p. between either 144–148° or 167–172°. The positive Beilstein test for halogen and the analysis were unchanged after catalytic dehalogenation.[42]

Anal. Calcd. for $C_{40}H_{46}N_4O_8$: C, 67.59; H, 6.52; N, 7.88; Br, 0.00. Found: C, 67.49; H, 6.40; N, 7.95; Br, 0.00.

The copper complex separated as needles when a chloroform solution of the ester was treated hot with methanolic copper acetate containing a little acetic acid, and the chloroform partially displaced by methanol. This was also characterized by an X-ray powder photograph.

(b).—Repetition of the above synthesis again gave the methyl ester (22%, specimen 1b, Table II).

The ethyl ester, prepared from this specimen by hydrolysis and esterification, may have been dimorphic. Crystallization from ethanol gave clumps of radiating needles, m.p. 161–163°, also bent needles and hairs, m.p. 164–166°, remelt 161–166° (lit. for material not rationally synthesized 124°,[32] 147–149°[43]). This was also characterized by an X-ray powder photograph.

Method 2, from XII and XI.—The same procedure gave the methyl ester (16%, specimen 2, Table II). This method was reported[7] to give 11%, m.p. 142–143° and 166–169°, copper complex m.p. 206–207°. This specimen was also characterized by its infrared spectrum in carbon disulfide solution.

Anal. Found: C, 67.38; H, 7.63; Br, 0.00.

Method 3, from XIII and XIV. (a).—The same procedure gave the methyl ester (15%, specimen 3a, Table II).

Anal. Found: C, 67.55; H, 6.69; N, 8.00.

(b).—Repetition of this synthesis gave the methyl ester (18%, specimen 3b, Table II). After hydrolysis to the free acid, countercurrent distribution between hydrochloric acid and ether (one symmetrical maximum), and re-esterification with methanolic hydrogen chloride, it had m.p. 162–168° (Table II) remelt 170–179° (whether or not previously heated for 4 hr. *in vacuo* at 150°).

Method 4, from XV and XIV.—The same procedure gave the methyl ester (19%, specimen 4, Table II).

Anal. Found: C, 67.65; H, 6.70.

1,4,6,7 - Tetramethylporphin - 2,3,5,8 - tetrapropionic acid (coproporphyrin 4) tetramethyl ester was prepared like coproporphyrin 3 from 300 mg. of X, 230 mg. of XII and 3 g. of succinic acid. The ester (67 mg., 17%; a "very poor" yield was reported by this method[4]) melted at 182–186° after a solid phase change at 165–167°. After two recrystallizations from acetone–methanol there was a solid phase change at 168–170°; at 175° a further solid phase change accompanied by some melting resulted in red rods (Nicolls crossed), m.p. 182–184°, and yellow needles, m.p. 184–186° (lit.[16] 168–169°,[4] 177°,[7] 183–184°[8]). Paper chromatography showed the coproporphyrin 3 or 4 spot only. This ester, one of Fischer's coproporphyrin 4 preparations (Hiernis) and that from uroporphyrin 4[16] gave identical X-ray powder photographs. After heating to 170° this ester gave a clear but different photograph. Its infrared spectrum in carbon disulfide solution was not distinguishable from that of coproporphyrin 3 methyl ester. Its infrared spectrum in Nujol mull showed less general absorption but otherwise differed from Fischer's coproporphyrin 4 ester.

(41) H. Fischer and H. Orth, ref. **14**, II/1, p. 52.

(42) A. H. Corwin and R. H. Krieble, THIS JOURNAL, **63**, 1829 (1941).

(43) E. Bullock, A. W. Johnson, E. Markham and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).

phyrin 4 only in having a shallow minimum instead of a flat maximum at 920 cm.$^{-1}$; after heating to 170° its spectrum was similar but more diffuse.

Anal. Calcd. for $C_{40}H_{46}N_4O_8$: C, 67.59; H, 6.52. Found: C, 67.49; H, 6.39.

The copper complex of the methyl ester formed needles from chloroform–methanol, m.p. 230–233° (lit.[4] 216–217°), characterized by an X-ray powder photograph.

The ethyl ester of coproporphyrin 4, from the methyl ester by hydrolysis and esterification, separated from ethanol as sheaved prismatic needles, characterized by an X-ray powder photograph. It showed a solid phase change at 90°, traces melted at 145°, a phase change and melting at 156–160°, final melting at 165–168° (lit.[4] m.p. 152°).

Natural Coproporphyrin 3.—The methyl ester (no. 7, Table II) from *C. diphtheriae*[5,44] (lit. m.p. Table I; X-ray powder photograph[45] and infrared mull spectrum[25,26] also reported) was recrystallized from methanol. Its mixed m.p. with a synthetic specimen (1a, Table II) 153–155° and 178–182° also revealed the fibrous intermediate form.

Fischer's Synthetic Coproporphyrin 3. (a) Specimen No. 5[46] Table II (lit. m.p. 150–153°[47]).—Its m.p. as received was essentially unchanged after filtering a chloroform solution through alumina and crystallizing from chloroform–methanol. The m.p. is too high for irrationally synthesized material.[7]

(b) Specimen 6,[48] Table II.—Labeled "Coproporphyrin 3 methyl ester, m.p. 133°, Hiernis, presumably not quite pure" was presumably irrationally synthesized.[7] Recrystallization either once or twice from chloroform–methanol left 0.7 mg./ml. in the methanol.

The behavior of mixtures. (a).—The mixed m.p. of coproporphyrin 4 methyl ester and coproporphyrin 3 methyl ester (specimen 3a) was 145–160°. Equal weights of the two crystallized together from acetone–methanol gave homogeneous glistening prismatic needles (85% recovery, 0.3 mg./ml. remained in the methanol), m.p. 138–141° after sintering from 133°, remelt 134–147°. Except for some lines in common with coproporphyrin 4 methyl ester, the X-ray powder photograph was distinctive.

(b).—The methyl esters of the coproporphyrins 1,2,3 and 4 were crystallized together in the ratio 1:1:4:2 from chloroform–methanol giving various types of needles (90% recovery, 0.3 mg./ml. remained in the methanol), m.p. 152–240°.

(c).—Equal weights of the coproporphyrin 3 and 4 methyl ester copper complexes (mixed m.p. 190–215°) were crystallized together from chloroform–methanol giving homogeneous bent hair-like crystals sintering at 188° and melting at 191–204° (mostly 193–194°). The X-ray powder photograph was very similar to that of the pure coproporphyrin 3 derivative, the differences being chiefly in the intensities.

(44) We are grateful to Professor C. H. Gray for this specimen.
(45) O. Kennard and C. Rimington, *Biochem. J.*, **55**, 105 (1953).
(46) We are grateful to Professor C. Rimington for this specimen.
(47) C. Rimington, *Proc. Roy. Soc. (London)*, **B127**, 106 (1939).
(48) We are grateful to Professor A. Treibs for this specimen.

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Pyrromethanes and Porphyrins Therefrom[1]

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The three 5,5′-free pyrromethanes Ic, IIc and IIIc related to porphobilinogen were synthesized. Their behavior did not support the assumption that pyrromethanes without stabilizing groups are two unstable to work with. At room temperature they condensed with the 5,5′-diformyl derivative Ie to the pure uroporphyrins 2, 4 and 3 (55–65%) the choice of the acid catalyst being critical. Formally this porphyrin synthesis is comparable to those from pyrromethenes; while less sensitive to the nature of the substituents, it is more limited by symmetry. Some related porphyrin syntheses were also investigated.

Among the intermediates in the biosynthesis of heme, those between porphobilinogen and uroporphinogen 3 appear least amenable to accumulation, isolation and characterization by current biochemical and analytical methods. It is natural to assume that these intermediates are pyrromethanes and polypyrranes, which are in the right state of oxidation. Their structures, like those of the porphyrins, could only be determined by synthesis. Comparable substances were unknown and thought to be very unstable. We synthesized some related pyrromethanes to clarify the analytical problem and to provide possible intermediates for testing in appropriate enzyme systems. Further study of these has been concerned with the development of porphyrin syntheses.

Dipyrrylmethane itself and derivatives with negative or hydroxyl groups on the nuclei are well known and stable; both N-[5] and *meso*-substituted derivatives[6,7] have also been described. However, the only known derivative without such groups, 3,3′-diethyl-4,4′-dimethylpyrromethane,[8] has been ignored in the belief that instability made work with such compounds impracticable.[6,9] Apparently the uncertain behavior of the stabilized pyrromethanes in porphyrin synthesis[10,11,12] discouraged interest in the unstabilized ones whose preparation had usually been attempted in acid media which minimized their stability.

Many simple pyrroles lose their ring carboxyl groups on heating with aqueous sodium hydroxide, and 3,3′-diethyl-4,4′-dimethylpyrromethane (but not its symmetrical isomer[13]) had also been obtained thus from its 5,5′-dicarboxylic acid in low and uncertain yield.[8] We found that Ia was too insoluble to react with 10% sodium hydroxide at

(1) Issued as N.R.C. 5724. Brief accounts of this work have appeared.[3,4]
(2) National Research Council of Canada Postdoctorate Fellow.
(3) S. F. MacDonald, THIS JOURNAL, **79**, 2659 (1957).
(4) S. F. MacDonald and K. H. Michl, *Angew. Chem.*, **70**, 54 (1958).
(5) A. H. Corwin and W. M. Quattlebaum, THIS JOURNAL, **58**, 1081 (1936).
(6) A. Treibs and A. Scherer, *Ann.*, **577**, 139 (1952).
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(8) H. Fischei, P. Halbig and B. Wallach, *ibid.*, **452**, 268 (1927).
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(11) H. Fischer and C. E. Staff, *ibid.*, **234**, 97 (1935).
(12) H. Fischer and P. Halbig, *Ann.*, **447**, 123 (1926).
(13) H. Fischer and G. Stangler, *ibid.*, **459**, 53 (1927).