THE INTERCONVERSION OF 5-CHLORO- AND 5-HYDROXY-DIPYRRYLMETHENES[1]

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ABSTRACT

Like the known II, the 5-halo-dipyrrylmethenes IV, X, and XI were obtained conventionally by halogenating the pyrroles I and IX. The 5-free dipyrrylmethene VIII, a new type of intermediate in such halogenations, was obtained from the pyrrole ester VII. The four 5-halo-dipyrrylmethenes were hydrolyzed to the 5-hydroxy derivatives VI and XIII, and these were reconverted into 5-chloro-dipyrrylmethenes.

INTRODUCTION

We have tried to obtain the dipyrrylmethene II (CH_2Br for CH_3) and its isomers as intermediates for the syntheses of polypyrranes related to porphobilinogen. They were attractive because, in their analogues, the bromomethyl group condensed with pyrroles (1, pp. 106 and 619; 2), and reduction converted the stable 5-bromo-dipyrrylmethenes into the labile 5-free dipyrrylmethanes (3, 4). Such bromomethyl-dipyrrylmethenes are often obtained by brominating either 5-methyl-dipyrrylmethenes or 2-methyl-pyrroles. However, these methods frequently fail, as in the case of XIV*b* (5), which has only recently been obtained as its ester by brominating 5-*t*-butoxycarbonyl-2,4-dimethyl-pyrrole-3-propionic acid methyl ester (6).

Having failed to halogenate the methyl groups in II or III, we prepared IV, X, and XI to study their halogenation. These were obtained, like II, from the pyrroles I and IX with bromine or sulfuryl chloride. For better characterization, they were esterified and then converted into the free bases III, V, and XII. The hydrochlorides IV and XI dissolved in water, but rapidly precipitated again as the rather unstable free bases, in which the halogen content tended to be low (lower still after recrystallization, the recovery being poor). The free base derived from XIV*a* is reportedly too unstable to be isolated (7).

The investigation of routes to the 5-halomethyl-dipyrrylmethenes was diverted when it was found that 2 moles of VII reacted with 1 mole of sulfuryl chloride to give the 5-free dipyrrylmethene VIII (43%). This was further identified as the free base and by conversion into the authentic 5-bromo-dipyrrylmethene III. It is thus clearly distinguished from another conceivable (cf. ref. 8) product, the ester of 5,5′-dimethyl-dipyrrylmethene-3,3′-diacetic acid 4,4′-dipropionic acid. The occurrence of this 5-free dipyrrylmethene cannot be reconciled with previous assumptions about the course of such halogenations: that the pyrrole is first halogenated in the 5-position and then in the 2-methyl group, and that the 2-halomethyl group (whether arising directly (1, p. 62) or indirectly (8)) then forms the bridge. However, the 5-free dipyrrylmethene would be a possible intermediate if anionotropy (cf. ref. 9, p. 588) made the 5-halo-2-methyl-pyrrole equivalent to the 5-free 2-halomethyl-pyrrole.

Another diversion occurred when the analysis of the hydrochloride XI showed that the ring halogen was unexpectedly labile, both chlorine atoms being determined as chloride

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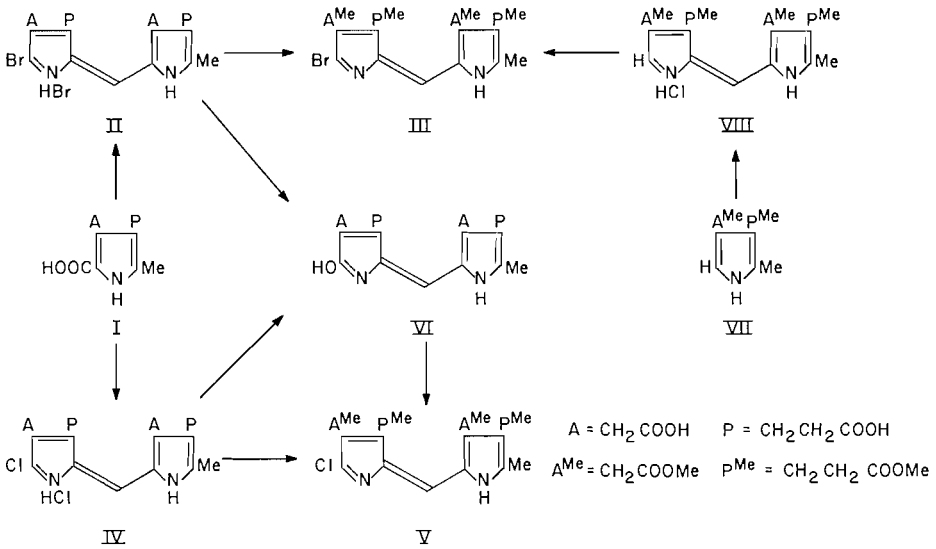
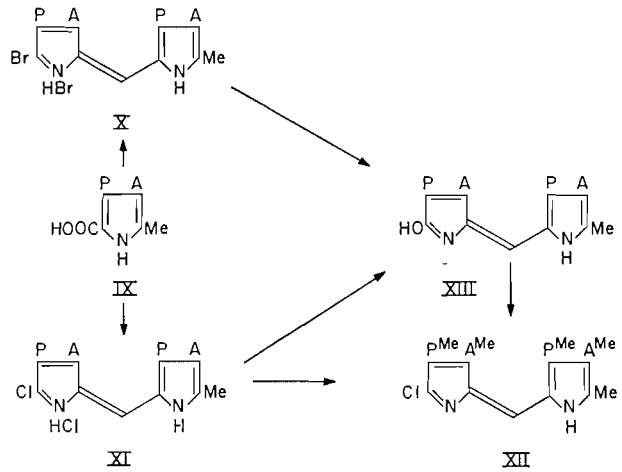


by adding mercuric nitrate and titrating the excess of mercury ion (10).[6] This observation was followed up, for we had had an interest in the likely product: the 5-hydroxy-dipyrrylmethene XIII. These 5-hydroxy-dipyrrylmethenes may have unexploited synthetic possibilities, because the nucleus is stable, the 5-position is blocked, and the reactivity at the 5′-position is similar to that of pyrroles (1, pp. 125, 136, 668, 670, 706, and 710). Other substituents may have the same effect as hydroxy (11). The 5-hydroxy-dipyrrylmethenes would then be attractive as intermediates if the hydroxy groups could be replaced by halogen and thus by hydrogen. However, there was no clear evidence that the replacement by halogen was possible (5, 12).

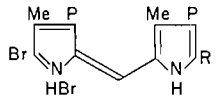
As well as being prepared directly from pyrroles, 5-methoxy- and 5-hydroxy-dipyrrylmethenes have been obtained from 5-bromo-dipyrrylmethenes by refluxing them with methanolic potash (5) or with potassium or silver acetate in acetic acid (13), or by heating them with alkali above 150° (1, p. 135). However, XV, the 5-hydroxy-dipyrrylmethene most closely related to VI, had been obtained from XIV*a* in only a 15% yield (5, 13).



[6]*We owe this observation to Mr. H. Séguin.*

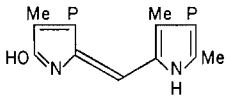
By using mercuric nitrate at room temperature, the 5-chloro-dipyrrylmethene XI was rapidly converted into the 5-hydroxy-dipyrrylmethene XIII, but this method failed with the 5-bromo-dipyrrylmethene X. However, the 5-halo-dipyrrylmethenes II, IV, X, and XI were converted into the corresponding 5-hydroxy-dipyrrylmethenes VI and XIII by Dowex 3 (a weakly basic resin) in boiling 50% ethanol, the chloro derivatives giving more consistent yields (50–60%). This method too is not general, for we did not obtain XV (5, 13) from XIV*a* by using either mercuric nitrate or Dowex 3.

It is difficult to rationalize these and analogous preparations of 5-hydroxy-dipyrrylmethenes. The rates of reaction (2) and the yields have been influenced strongly by the other substituents (13) and by the purity of the materials (14), and 5-hydroxy-dipyrrylmethenes may be oxidized further to tetrapyrroles (13). The variable stability of the 5-halo-dipyrrylmethenes may be important, for X lost nearly all of its halogen when treated with mercuric nitrate but, unlike XI, did not yield XIII. Earlier methods suggest that base catalysis is involved, but sodium hydroxide removed the halogen from IV and XI slowly and incompletely, and the recovery was poor. It was also possible that acid catalysis might be effective, as with the 4-chloroquinazolines (15), because the halogen in the free base of the methyl ester derived from XIV*a* was easily replaced by aniline though not by methylamine or ammonia (5). Apparently, the halogen in 5-bromo-5′-carbethoxy-4,4′-dimethyl-dipyrrylmethene-3,3′-dipropionic acid is more readily hydrolyzed in acidic than in alkaline media, but the report (16) is confused, and this behavior might be conditioned by the 5′-carbethoxy group. The above hydrolysis with mercuric nitrate suggests electrophilic catalysis (cf. ref. 9, p. 357), but there was no evidence of such when XVI*a* was hydrolyzed to XVI*b* with silver acetate rather than with potassium acetate (17).

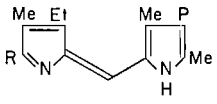


XIV

a, R = Me
b, R = CH_2Br

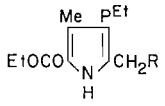


XV



XVI

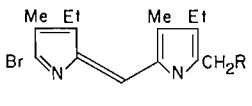
a, R = Br (Hydrobromide)
b, R = OH
c, R = OMe



XVII

a, R = Br
b, R = N_3

P^{Et} = CH_2CH_2COOEt



XVIII

a, R = Br (Hydrobromide)
b, R = N_3 (Hydrozoate)

The hydroxyl groups in VI and XIII were replaced with chlorine by methanolic hydrogen chloride at room temperature, the products being isolated as the methyl esters V and XII (30%). This was surprising because the hydroxy groups in the dipyrrylmethenes studied earlier (13, 17) were unchanged under these conditions; there the initial products were the hydrochlorides of 5-hydroxy-dipyrrylmethenes, which readily lost hydrogen chloride to give the 5-hydroxy-dipyrrylmethenes. It is unlikely that these hydrochlorides were actually very easily hydrolyzed 5-chloro-dipyrrylmethenes, for 5-chloro-4,3′,5′-trimethyl-3,4′-diethyl-dipyrrylmethene is not that easily hydrolyzed (18). A reaction

related to the above is the conversion of XVI*c* into XVI*b* by methanolic hydrogen chloride (17).

Attempts were made to improve the synthesis of uroporphyrin 1, which had been obtained in a 5.9% yield from II at 118° (19). At 135° the yield from II was 3%, and at 118° the yields from X and from IV were, respectively, 5.3% and <0.1%. In a preliminary experiment modelled on a synthesis of coproporphyrin 1 (20), no porphyrin was obtained from VIII with 6% potassium methoxide in methanol at 180°.[7]

Few meaningful comparisons have been made between 5-chloro- and 5-bromo-dipyrrylmethenes, although the differences are significant. We obtained better yields of 5-hydroxydipyrrylmethenes from the former, whereas the latter have given better yields of porphyrins (cf. ref. 18). Apparently, the labilities of the halogens are not very different, but the 5-bromo-dipyrrylmethenes are more prone to other changes (but less so as esters).

As one projected use of compounds such as II (CH_2Br for CH_3) involved replacing the side-chain halogen with an amino group, we treated XVII*a* and XVIII*a* with sodium azide to obtain XVII*b* and XVIII*b*.

EXPERIMENTAL

5'-Methyl-dipyrrylmethene-4,3'-diacetic Acid-3,4'-dipropionic Acid Tetramethyl Ester Hydrochloride (VIII)

Methyl cryptopyrrole dicarboxylate (VII, 238 mg, 2 moles (21)) in 10 ml of chloroform was treated with 0.04 ml (1 mole) of sulfuryl chloride in 2 ml of chloroform. After 20 h at 20°, the solvent was evaporated *in vacuo* and the crystalline residue recrystallized from chloroform–ether. For analysis, the product (110 mg, 43%, m.p. 156–158°) was recrystallized as red prisms, m.p. 164–165°.

Anal. Calcd. for $C_{24}H_{31}O_8N_2Cl$: C, 56.41; H, 6.12; N, 5.48; Cl, 6.94. Found: C, 56.59; H, 6.00; N, 5.60; Cl (total or ionic (10)), 7.00.

To obtain the *free base*, 100 mg was dissolved in 3 ml of methanol and neutralized with ammonia, and the solution cooled. The product which separated was recrystallized from methanol as yellow needles (55 mg), m.p. 125–127°.

Anal. Found: Cl, 0.00.

5-Bromo-5'-methyl-dipyrrylmethene-4,3'-diacetic Acid-3,4'-dipropionic Acid Tetramethyl Ester (III)

(*a*) 5-Bromo-5'-methyl-dipyrrylmethene-4,3'-diacetic acid-3,4'-dipropionic acid hydrobromide (II, 350 mg (19)) was dissolved in methanol (5 ml) containing acetyl bromide (0.25 ml), and the solution was kept for 24 h at 20°. The solvent was removed *in vacuo* and the residue dissolved in chloroform. The solution was washed with aqueous sodium bicarbonate, and dried (sodium sulfate), and the solvent was evaporated. The residue was recrystallized from methanol as yellow needles (310 mg, 92%), m.p. 127–128°, with solid-phase changes at about 122°.

Anal. Calcd. for $C_{24}H_{29}O_8N_2Br$: C, 52.08; H, 5.28; Br, 14.44. Found: C, 52.35; H, 5.25; Br, 14.97.

A solution of this ester in methanol – acetyl bromide quickly set as a mass of brown prismatic needles of the *hydrobromide*, m.p. 158–163°.

Anal. Calcd. for $C_{24}H_{30}O_8N_2Br_2$: C, 45.44; H, 4.77; Br, 25.20. Found: C, 45.20; H, 4.72; Br, 24.95.

(*b*) 5'-Methyl-dipyrrylmethene-4,3'-diacetic acid-3,4'-dipropionic acid tetramethyl ester hydrochloride (VIII, 100 mg) was suspended in 2 ml of acetic acid, treated with 0.03 ml of bromine in 0.1 ml of acetic acid, and allowed to stand for 3 h at 20°. The solvent was removed *in vacuo*, the residue left overnight in 5 ml of methanol containing 0.25 ml of acetyl bromide, and the product (free base) isolated as in method *a* above to give orange-yellow needles (80 mg, 74%), m.p. 126–127°.

Anal. Found: Br, 14.47.

The products from methods *a* and *b* gave identical X-ray powder photographs and their mixed melting point was undepressed.

5-Bromo-5'-methyl-dipyrrylmethene-3,4'-diacetic Acid-4,3'-dipropionic Acid Hydrobromide (X)

5-Carboxy-hemopyrrole-dicarboxylic acid (IX, 500 mg (22)) was suspended in 3 ml of acetic acid at 50–60°, and 0.16 ml of bromine in 1 ml of acetic acid was added. After 20 min at this temperature, scratching induced crystallization, and the mixture was then left for 16 h in a partially evacuated vacuum desiccator over NaOH. The orange-brown rods (285 mg, 50%, m.p. 190–191° (decomp.)) were washed with acetic acid and then with ether. For analysis, it was recrystallized three times from acetic acid containing some formic acid, m.p. 197–198°.

Anal. Calcd. for $C_{20}H_{22}N_2O_8Br_2$: C, 41.54; H, 3.84; N, 4.85; Br, 27.64. Found: C, 41.26; H, 3.95; N, 4.91; Br, 27.65.

[7]*This was carried out by Dr. B. Gregorovich.*

5-Chloro-5'-methyl-dipyrrylmethene-3,4'-diacetic Acid-4,3'-dipropionic Acid Hydrochloride (XI)

Sulfuryl chloride (0.09 ml) was added to a suspension of 5-carboxy-hemopyrrole-dicarboxylic acid (IX, 245 mg) in 5 ml of acetic acid at 50–60°. After the evolution of gas ceased (about 10 min) the solution was left overnight in a partially evacuated vacuum desiccator over NaOH. The crystalline product (140 mg, 58%, m.p. 175° (decomp.)) was separated and washed with acetic acid and then with ether. For analysis, it was recrystallized from methanol–ether as red-brown prisms, m.p. 179–180° (decomp.), λ_{max} 481 mμ (in methanol).

Anal. Calcd. for $C_{20}H_{22}O_8N_2Cl_2$: C, 49.09; H, 4.53; N, 5.73; Cl, 14.49. Found: C, 49.17; H. 4.69; N, 5.63; Cl, 14.29.

To obtain the *free base*, 100 mg of the hydrochloride was dissolved in 2 ml of water to give a clear solution. After a few seconds the base separated as yellow-brown needles (60 mg), m.p. 191–193° (decomp.) (block preheated to 180°), λ_{max} 462 mμ (in methanol).

Anal. Calcd. for $C_{20}H_{21}O_8N_2Cl$: Cl, 7.83. Found: Cl, 7.31.

The Methyl Ester of the Free Base (XII)

(A) This was prepared from 100 mg of XI and 5 ml of 5% HCl in methanol by the same method as III, except that it was crystallized from ether–*n*-hexane instead of from methanol. It formed yellow prismatic rods (85 mg, 82%), m.p. 101°. For analysis it was recrystallized in the same way, m.p. 103–104°.

Anal. Calcd. for $C_{24}H_{29}N_2O_8Cl$: C, 56.63; H, 5.74; N, 5.50; Cl, 6.97. Found: C, 56.83; H, 5.59; N, 5.66; Cl, 6.80.

(B) 5-Hydroxy-5'-methyl-dipyrrylmethene-3,4'-diacetic acid-4,3'-dipropionic acid (XIII), prepared by methods *a*, *b*, and *c* below, was used. In each case 100 mg of the hydroxy-dipyrrylmethene was dissolved in 10 ml of 10% methanolic hydrogen chloride, and the solution was allowed to stand for 48 h at 20°. The solvent was removed *in vacuo* at 20°. The solution of the residue in chloroform was washed with aqueous sodium bicarbonate, dried, and evaporated. The resulting residue was extracted with 20 ml of ether. The ether was evaporated, leaving the product, which was crystallized from ether–*n*-hexane as yellow prisms (35 mg, 30%), m.p. 100–101°, mixed melting point with the product from method A above 100–101°. The X-ray powder photographs of the products from methods A and B (using XIII prepared by method *b* below from XI and Dowex 3) were identical.

The material insoluble in ether was recrystallized from chloroform–*n*-hexane to give a yellow product (15 mg) which was halogen free, m.p. 220° ("urobilirubin"? (cf. ref. 13)).

5-Chloro-5'-methyl-dipyrrylmethene-4,3'-diacetic Acid-3,4'-dipropionic Acid Hydrochloride (IV)

This was prepared in the same way as its isomer (above), except that 5-carboxy-cryptopyrrole-dicarboxylic acid (I (23)) was used. The crystalline product (200 mg, 81%), m.p. 179–180° (decomp.), was recrystallized for analysis from methanol–ether as orange-brown prisms, m.p. 180–181° (decomp.).

Anal. Calcd. for $C_{20}H_{22}O_8N_2Cl_2$: C, 49.09; H, 4.53; N, 5.73; Cl, 14.49. Found: C, 49.29; H, 4.52; N, 5.66; Cl, 14.45.

The *free base*, like its isomer above, was formed by dissolving the hydrochloride in water, from which the base separated as brown needles (68 mg), m.p. 195–200° (decomp.) (block preheated to 180°).

Anal. Calcd. for $C_{20}H_{21}O_8N_2Cl$: Cl, 7.83. Found: Cl, 7.29.

The Methyl Ester of the Free Base (V)

(A) This was prepared from 100 mg of IV and 5 ml of 5% HCl in methanol by the same method as III, except that it was crystallized from ether–*n*-hexane instead of from methanol. It formed orange-yellow prismatic needles (87 mg, 84%), m.p. 117–118°. Recrystallized for analysis, it formed yellow needles, m.p. 119–120°.

Anal. Calcd. for $C_{24}H_{29}O_8N_2Cl$: C, 56.63; H, 5.74; N, 5.50; Cl, 6.97. Found: C, 56.51; H, 5.69; N, 5.59; Cl, 6.82.

(B) 5-Hydroxy-5'-methyl-dipyrrylmethene-4,3'-diacetic acid-3,4'-dipropionic acid (VI), prepared by methods *a* and *b* below, was used. In each case 100 mg of the hydroxy-dipyrrylmethene was converted into the crude 5-chloro-dipyrrylmethene in the same manner as the isomeric XIII was converted into XII (see above). After the chloroform was evaporated the black crude product was extracted several times with ether. When the extract was evaporated a brown crystalline product remained which was recrystallized three times from ether–*n*-hexane as yellow needles (35 mg, 30%), m.p. 118–119°, undepressed on admixture with the product from method A above. Of the two products here, that of the sequence IV → VI → V was analyzed.

Anal. Found: C, 56.91; H, 6.17; N, 5.33; Cl, 6.82.

The nuclear magnetic resonance spectra of the product from method A and the two products from method B above showed the same chemical shifts.

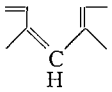
The Behavior of the 5-Chloro-dipyrrylmethenes IV and XI with Sodium Hydroxide

The dipyrrylmethene XI (100 mg) was allowed to stand at 20° for 1 h in 2 ml of 10% sodium hydroxide, and the product (60 mg containing 6.33% Cl) was then precipitated with acetic acid. This product (60 mg) was twice recycled in the same way, allowing the solution to stand for 3 h (45 mg recovered, 3.42% Cl) and then overnight (20 mg recovered, 0.1% Cl).

When IV was given the same three treatments, the final product contained 0.3% Cl.

TABLE I

Chemical shifts of dipyrrylmethenes (p.p.m., τ scale)

				OCH_3	CH_2CH_2COO		Solvent
V	3.12	—	6.38, 6.51	6.30, 6.33	7.25	7.67	$CDCl_3$ + tetramethysilane
XII	3.18	—	6.40, 6.52	6.31, 6.33	7.29	7.69	$CDCl_3$ + tetramethylsilane
VI	3.92	—	6.62, 6.78	—	7.52	7.85	$D_2O/Na + CH_3CN$
XIII	3.85	—	6.53, 6.72	—	7.55	7.80	$D_2O/Na + CH_3CN$
VIII (HCl)	2.55		6.28, 6.22, 6.18		7.30, 7.75		$CDCl_3$
VIII (base)	3.10	2.72	6.27, 6.35		7.33	7.63	$CDCl_3$

5-Hydroxy-5'-methyl-dipyrrylmethene-3,4'-diacetic Acid-4,3'-dipropionic Acid (XIII)

(a) With mercuric nitrate.—The corresponding 5-chloro-dipyrrylmethene hydrochloride (XI, 100 mg) was dissolved in 10 ml of 80% ethanol and the pH adjusted to 9–10 with 5% sodium hydroxide, giving a clear solution. The pH was then brought to 3.6 with 0.1% nitric acid, and 20 ml of mercuric nitrate solution (10) was added. The dark solution was concentrated and the crystalline product (40 mg, 45%) separated. It was extracted into methanol (thimble) and the solution was concentrated, filtered while hot, and cooled. The product (30 mg) formed yellow prisms, m.p. 230° (decomp.) (block preheated to 210°).

Anal. Calcd. for $C_{20}H_{22}O_9N_2$: C, 55.30; H, 5.11; N, 6.45; Cl, 0.00. Found: C, 55.18; H, 5.29; N, 6.60; Cl, 0.00.

(b) With Dowex 3 and aqueous ethanol.—The 5-chloro-dipyrrylmethene hydrochloride (XI, 500 mg) was dissolved in 50 ml of 50% ethanol, and 2.5 g (dry weight) of Dowex 3 was added. The mixture was refluxed on the steam bath for 30 min with occasional shaking. The resin was filtered off and washed well with water, and the combined filtrate and washings were evaporated in a rotary evaporator to give the yellow crystalline product (266 mg, 60%). It was recrystallized from methanol (thimble) or from hot water as yellow prisms, m.p. 231–232° (decomp.) (block preheated to 210°) alone or admixed with the product from method *a* above.

Anal. Found: C, 55.57; H, 5.28; N, 6.23; Cl, 0.00.

(*c*) The 5-bromo-dipyrrylmethene hydrobromide (X, 500 mg) was heated with Dowex 3 and 50% ethanol as under method *b* above. When the very-dark filtered solutions and washings were evaporated a brown residue (250 mg) remained. This was extracted with methanol (from a thimble, above a second thimble containing Darco), and the methanol concentrated. The product (100 mg, 27%) separated as yellow prisms, m.p. 230° (decomp.) (block preheated to 210°) alone or admixed with the product from method *a* above.

Anal. Found: Br, 0.00.

The Dowex 3 had been washed well with water. Some lots of the resin adsorb the products, and the apparent yields are low. In this case, the products were extracted from the resin by leaving it overnight in dilute ammonia. The resin was then washed with water as long as the washings were yellow. The extracts (500 ml) were evaporated in a rotary evaporator, the residue was dissolved in a little water, and the product was precipitated with acetic acid.

The products obtained by methods *a*, *b*, and *c* above, λ_{max} 421 mμ (in water), showed the same chemical shifts in their nuclear magnetic resonance spectra and were converted into the same 5-chloro-dipyrrylmethene methyl ester (XII, see above).

5-Hydroxy-5'-methyl-dipyrrylmethene-4,3'-diacetic Acid-3,4'-dipropionic Acid (VI)

(*a*) The 5-chloro-dipyrrylmethene hydrochloride (IV, 500 mg) was refluxed in 50% ethanol with Dowex 3 in the same manner as its isomer (above), and a crude brown product (270 mg) was isolated. It was recrystallized from methanol as yellow-brown prisms (250 mg, 56%), m.p. 238° (decomp.) (block preheated to 220°). For analysis it was again recrystallized as yellow prisms, m.p. 238–240° (decomp.).

Anal. Calcd. for $C_{20}H_{22}O_9N_2$: C, 55.30; H, 5.11; N, 6.45; Cl, 0.00. Found: C, 55.25; H, 5.38; N, 6.60; Cl, 0.00.

(*b*) The 5-bromo-dipyrrylmethene hydrobromide (II, 500 mg) was treated as in method *a*. The crude brown product (220 mg) was extracted with methanol (thimble, above a second thimble containing Darco), and the extract concentrated. The product (200 mg, 53%) separated as brownish-yellow prisms, m.p. 236–238° (decomp.) (block preheated to 220°) alone or admixed with the product from method *a* above.

Anal. Found: Br, 0.00.

The products obtained by methods *a* and *b* above, λ_{max} 419 mμ (in water), showed the same chemical shifts in their nuclear magnetic resonance spectra, and were converted into the same 5-chloro-dipyrrylmethene methyl ester (V, see above).

Uroporphyrin 1 Octamethyl Ester

(*a*) 5-Bromo-5'-methyl-dipyrrylmethene-3,4'-diacetic acid-4,3'-dipropionic acid hydrobromide (X) was heated with methylsuccinic acid at 118°, and the product was isolated in the same way as was that from the isomeric dipyrrylmethene II (19), 5.3%, m.p. 282–285°, raised to 284–285° (lit. (19) m.p. 285–286°) after several recrystallizations.

Anal. Calcd. for $C_{48}H_{54}O_{16}N_4$: C, 61.14; H, 5.77; N, 5.94; OMe, 26.33. Found: C, 61.06; H, 5.68; N, 5.90; OMe, 26.18.

This uroporphyrin methyl ester was degraded to coproporphyrin 1 methyl ester, m.p. 251–254° (lit. (19) m.p. 251–252°).

(*b*) 5-Chloro-5'-methyl-dipyrrylmethene-4,3'-diacetic acid-3,4'-dipropionic acid hydrochloride (IV, 250 mg) was heated with 1 g of methylsuccinic acid at 118° and the melt worked up as above. The product (0.13 mg, 0.06% (estimated spectroscopically)) did not crystallize.

2-Azidomethyl-4-methyl-5-carboxy-pyrrole-3-propionic Acid Diethyl Ester (XVIIb)

Powdered sodium azide (1 g) was warmed in 240 ml of dimethylformamide (distilled over P_2O_5) until it dissolved. A solution of 5 g of 2-bromomethyl-4-methyl-5-carboxy-pyrrole-3-propionic acid diethyl ester (XVII*a* (24)) in 10 ml of warm dimethylformamide was added. The solution was heated on the steam bath for 2 h and the solvent then removed at 50° in a rotary evaporator. The residue was washed with

water (2 × 10 ml), and then extracted with 60 ml of chloroform. The chloroform solution was washed with water (3 × 10 ml), and dried with sodium sulfate; then the solvent was evaporated. This residue was dissolved in 10 ml of warm chloroform, and 45 ml of pentane was added. The product (3.38 g) separated slowly as stable colorless needles, m.p. 110–110.5°.

Anal. Calcd. for $C_{14}H_{20}O_4N_4$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.64; H, 6.44; N, 18.20.

5-Bromo-5′-azidomethyl-4,3′-dimethyl-3,4′-diethyl-dipyrrylmethene Hydrazoate (XVIIIb)

The hydrobromide of 5-bromo-5′-bromomethyl-4,3′-dimethyl-3,4′-diethyl-dipyrrylmethene (XVIII*a*, 480 mg (4)) and 140 mg of sodium azide were refluxed in 20 ml of acetone and 5 ml of water for 1 h. The solvent was evaporated *in vacuo* and the residue, after being washed with water, crystallized from 85% acetone. This product (300 mg), m.p. 125–126°, was recrystallized three times to give brown rods, m.p. 129–130° (decomp.).

Anal. Calcd. for $C_{16}H_{21}N_8Br$: C, 47.41; H, 5.22; N, 27.65; Br, 19.72. Found: C, 47.52; H, 5.16; N, 27.42; Br, 19.60.

The *free base*, though crystalline, was quite unstable.

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REFERENCES

1. H. Fischer and H. Orth. Chemie des Pyrrols. Vol. II. Akademische Verlagsgesellschaft, Leipzig. 1937. Part I.
2. H. Fischer and H. Reinecke. Z. Physiol. Chem. **258**, 243 (1939).
3. G. P. Arsenault, E. Bullock, and S. F. MacDonald. J. Am. Chem. Soc. **82**, 4384 (1960).
4. A. Markovac and S. F. MacDonald. Can. J. Chem. **43**, 3364 (1965).
5. H. Fischer and W. Fröwis. Z. Physiol. Chem. **195**, 49 (1931).
6. J. Ellis, A. H. Jackson, A. C. Jain, and G. W. Kenner. J. Chem. Soc. 1935 (1964).
7. H. Fischer, H. Friedrich, W. Lamatsch, and K. Morgenroth. Ann. **466**, 147 (1928).
8. A. H. Corwin and P. Viohl. J. Am. Chem. Soc. **66**, 1137 (1944).
9. C. K. Ingold. Structure and mechanism in organic chemistry. Cornell University Press, Ithaca, New York. 1953.
10. D. C. White. Mikrochim. Acta, 449 (1960).
11. F. Endermann and H. Fischer. Ann. **538**, 172 (1939).
12. W. Siedel and H. Möller. Z. Physiol. Chem. **259**, 121 (1939).
13. H. Fischer and E. Adler. Z. Physiol. Chem. **210**, 139 (1932).
14. H. Fischer and G. Fries. Z. Physiol. Chem. **231**, 231 (1935).
15. R. C. Elderfield and I. Serlin. J. Org. Chem. **16**, 1669 (1951).
16. H. Fischer and J. Aschenbrenner. Z. Physiol. Chem. **229**, 71 (1934); **245**, 107 (1937).
17. H. Fischer and E. Adler. Z. Physiol. Chem. **197**, 237 (1931).
18. H. Fischer, E. Baumann, and H. J. Riedl. Ann. **475**, 205 (1929).
19. S. F. MacDonald and R. J. Stedman. Can. J. Chem. **32**, 896 (1954).
20. H. Fischer and H. Berg. Ann. **482**, 213 (1930).
21. S. F. MacDonald and K. H. Michl. Can. J. Chem. **34**, 1671 (1956).
22. S. F. MacDonald and R. J. Stedman. Can. J. Chem. **33**, 458 (1955).
23. S. F. MacDonald. J. Chem. Soc. 4184 (1952).
24. F. Morsingh and S. F. MacDonald. J. Am. Chem. Soc. **82**, 4377 (1960).