328. *Chlorophyll and Related Substances. Part III.* The Synthesis of Octamethylchlorin.*

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Octamethylchlorin (II; R = Me) and octamethylporphin (IV) have been synthesised from 2-dimethylaminomethyl-3 : 4-dimethylpyrrole (I; R = Me) in good yield. Metal derivatives of both pigments have been prepared and light-absorption data are given. The quantitative dehydrogenation of octamethylchlorin and of its magnesium derivative has been studied.

In Part I * the synthesis of chlorin (II; R = H) from 2-dimethylaminomethylpyrrole (I; R = H) was described. It was of interest to determine whether the new method, which is unique in providing the first direct synthesis of a dihydroporphyrin derivative, was general and could be applied to the synthesis of substituted chlorins. It was also desirable to study a substituted chlorin, closer in structure to those derived from chlorophyll, particularly from the viewpoint of its quantitative dehydrogenation.

It was decided to prepare a symmetrically substituted pigment in order to avoid the formation of a mixture of positional isomers. Our choice fell on the unknown octamethylchlorin (II; R = Me). The corresponding porphin (IV) has been prepared in up to 25%

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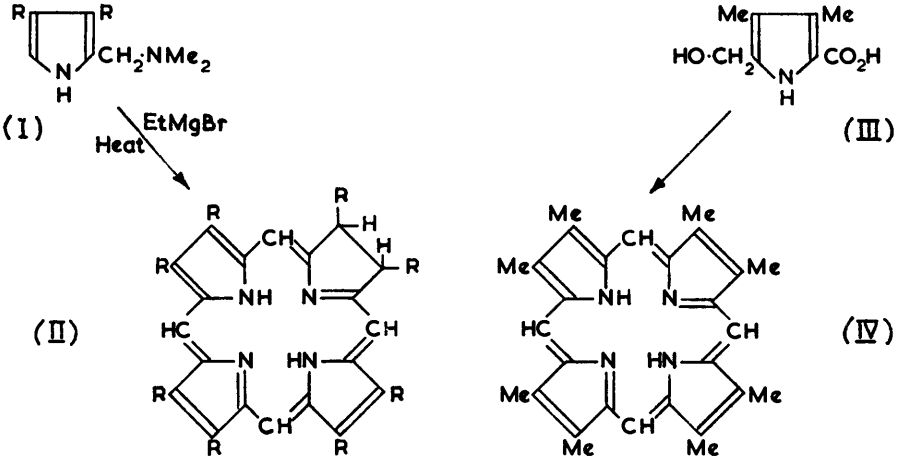
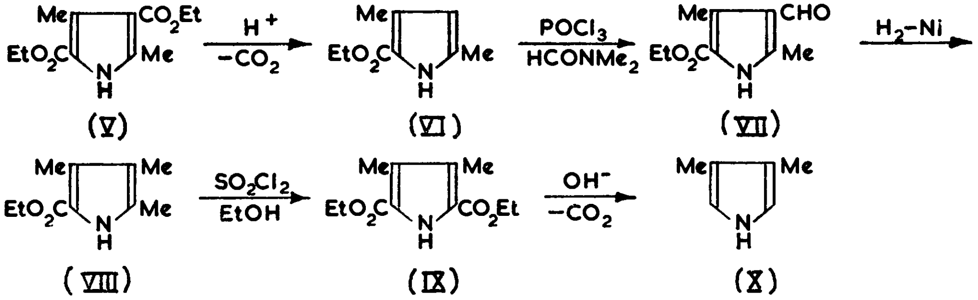
* Parts I and II, *J.*, 1955, 3742, 3749.

yield by Fischer and Walach,[1] and more recently by Siedel and Winkler [2] who employed 5-hydroxymethyl-3 : 4-dimethylpyrrole-2-carboxylic acid (III) as intermediate.



The synthesis of the unknown 2-dimethylaminomethyl-3 : 4-dimethylpyrrole (I; $R = Me$) was accordingly undertaken. This involved the large-scale preparation of 3 : 4-dimethylpyrrole (X) which had previously been prepared in small amounts.[3,4,5] We employed the following series of reactions, which are essentially those used by earlier workers :



This synthesis was carried out by Dr. E. A. Parkes, who showed that excellent yields could be obtained in all stages up to and including the preparation of the pyrrolic ester (VIII). The modifications by Chu and Chu [6] were used in the preparation of the pyrroles (VI) and (VII); the ester (VIII) was prepared by catalytic reduction of the ester (VII).[5] Difficulties, however, were encountered in the preparation of the diester (IX). Fischer and Höfelmann's method [5] was tried without success as was the modification by Corwin [7] *et al.* The desired product (IX) was finally obtained in 76% yield by strict control of the reaction conditions, in particular by working at a low temperature. The hydrolysis and decarboxylation of the diester (IX) were carried out by modifications of the methods of Fischer and Höfelmann [5] or of Chu and Chu,[6] whereby 3 : 4-dimethylpyrrole (X) was obtained in 50% yield.

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[1] Fischer and Walach, *Annalen*, 1926, **450**, 164.
[2] Siedel and Winkler, *ibid.*, 1943, **554**, 162.
[3] Fischer and Walach, *ibid.*, 1926, **450**, 109.
[4] Fischer and Hierneis, *ibid.*, 1932, **492**, 32.
[5] Fischer and Höfelmann, *ibid.*, 1938, **533**, 216.
[6] Chu and Chu, *J. Org. Chem.*, 1954, **19**, 266.
[7] Corwin, Bailey, and Viohl, *J. Amer. Chem. Soc.*, 1942, **64**, 1267; Corwin and Straughn, *ibid.*, 1948, **70**, 1416.

Treatment of the pyrrole (X) with dimethylamine and formaldehyde[8] afforded the crystalline Mannich base (I; R = Me) in 90% yield.

The reaction of the base (I; R = Me) with 1 mol. of ethylmagnesium bromide in boiling xylene or *o*-dichlorobenzene afforded a mixture of the magnesium complexes of octamethylporphin (IV) and -chlorin (II; R = Me). The yields of the chlorin were of the order of 5—12·5%, and those of the porphin 20—36%. It was subsequently found that octamethylchlorin (II; R = Me) is much more readily dehydrogenated than chlorin (II; R = H) itself and the preponderance of octamethylporphin (IV) in the reaction mixture is therefore not surprising. The total yields of macrocyclic pigment obtained are quite good for a method involving a monopyrrolic intermediate; they could probably be improved by suitable variations of the reaction conditions.

A rough preliminary separation was achieved by filtration of the crude insoluble magnesium octamethylporphin. The magnesium octamethylchlorin which remained in the filtrate was converted into the metal-free pigment by treatment with cold dilute hydrochloric acid. In contrast to unsubstituted chlorin (II; R = H)[9] octamethylchlorin was readily purified by adsorption chromatography on alumina. This treatment separated from it traces of the porphin (IV), as well as a green pigment with spectral characteristics very similar to those of octamethylchlorin. The green pigment has not yet been obtained pure, but it may well be analogous to the " oxychlorin " obtained in the earlier work.[9] In support of this idea it should be pointed out that its light absorption is similar to that of a pigment obtained by Fischer *et al.*[10] from the oxidation of octamethylporphin with hydrogen peroxide–sulphuric acid, a reaction which is known to produce "oxychlorins."

Octamethylchlorin is a deep blue crystalline solid. The solutions in benzene are green with an intense red fluorescence.

The light absorption of octamethylchlorin has been measured in benzene over the range 350—700 mμ. The results are given in detail in the Table and the Figure. The spectrum bears a close resemblance to both that of chlorin[9] and of ætiochlorin.[11]

When a benzene solution of octamethylchlorin was heated with methanolic cupric acetate, copper octamethylchlorin separated from the blue solution as purple crystals. It was purified by chromatography on heavy magnesium oxide to remove a trace of copper octamethylporphin, but was not obtained quite pure even after this treatment. Light-absorption data are given in the Table.

A solution of magnesium octamethylchlorin was prepared by treatment of a benzene solution of the chlorin (II; R = Me) with ethylmagnesium bromide. The solution was blue with an intense red fluorescence. Light-absorption data are given in the Table. The metal is extremely labile in this compound, being partially removed even by cold aqueous ammonium chloride or by traces of hydrogen chloride (see below). In this it differs markedly from unsubstituted magnesium chlorin.

The second product, magnesium octamethylporphin (XI), was purified by repeated extraction with boiling benzene. It was, however, still contaminated with magnesium octamethylchlorin which was dehydrogenated to the porphin (XI) by extraction into benzene containing an excess of 1 : 4-benzoquinone. Two such treatments afforded magnesium octamethylporphin (XI) containing only traces of the chlorin derivative. The magnesium complex (XI) forms purple microcrystals. Its solutions are rose-red with a red fluorescence. Its spectrum (Table) shows a considerable solvent effect. By treatment with cold dilute hydrochloric acid, the porphin (XI) is converted into octamethylporphin (IV), spectroscopically identical with a specimen prepared by standard methods.[2]

When the magnesium porphin (XI) was treated with boiling acetic acid and cupric acetate, copper octamethylporphin was formed as purple microcrystals. Light-absorption data (Table) are in agreement with values recorded by Fischer and Walach[1] and are very similar to those of copper ætioporphyrin II.[12] It is remarkable that, in spite of its

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[8] Herz and Rogers, *J. Amer. Chem. Soc.*, 1951, **73**, 4921.
[9] Eisner and Linstead, *J.*, 1955, 3742.
[10] Fischer, Halbig, and Walach, *Annalen*, 1927, **452**, 268.
[11] Pruckner, *Z. phys. Chem.*, 1940, **187**, *A*, 257.
[12] Erdman and Corwin, *J. Amer. Chem. Soc.*, 1946, **68**, 1885.

preparation in acid medium, traces of the octamethylchlorin derivative, originally present in (XI), persist in copper octamethylporphin. The apparent stability of the copper complex of octamethylchlorin is not paralleled by the behaviour of the corresponding derivatives in the unsubstituted series.[9]

Light-absorption data.

Octamethylchlorin in benzene [a]

$\lambda_{max.}$, mμ	390 †	488	496	522	548	594	618	646
ε	175,000	12,900	13,100	4,300	1,800	4,500	4,600	58,500

Ætiochlorin in dioxan [b]

$\lambda_{max.}$, mμ	488	494	519	522	542	564	586	613	642
ε	13,200	13,400	4,200	4,100	1,800	1,200	4,000	4,100	59,400

Magnesium octamethylchlorin in benzene [a]

$\lambda_{max.}$, mμ	405·5 †	512·5	549	578	621
ε	231,000	7,600	5,000	10,500	70,400

Copper octamethylchlorin in benzenc [a]

$\lambda_{max.}$, mμ	399·5	494	532	573	615
ε	147,000	5,400	5,100	8,200	44,100

Octamethylporphin in o-*dichlorobenzene* [a]

$\lambda_{max.}$, mμ	402 †	499	533	570	594 *	624
ε	146,000	13,100	9,300	6,400	1,700	5,100

Ætioporphyrin II in dioxan [c]

$\lambda_{max.}$, mμ	496	528	566	595	621
ε	14,000	10,000	6,600	1,300	5,800

Magnesium octamethylporphin in benzene—8% *pyridine* [a]

$\lambda_{max.}$, mμ	411·5 †	422 †	499	547	582
ε	264,000	118,000	3,900	14,000	10,600

Magnesium octamethylporphin in pyridine [a]

$\lambda_{max.}$, mμ	412 †	423 †	507 *	555	582
ε	180,000	228,000	2,800	16,100	7,900

Copper octamethylporphin in chlorobenzene [a]

$\lambda_{max.}$, mμ	399 †	527	563
ε	318,000	13,400	27,700

Copper ætioporphyrin II in dioxan [d]

$\lambda_{max.}$, mμ	398 †	527	563
ε	225,000	14,000	24,200

* Inflection † Soret band.

References : *a*, This work. *b*, Pruckner, ref. 11. *c*, Stern and Wenderlein, *Z. phys. Chem.*, 1934, **170**, *A*, 337. *d*, Erdman and Corwin, ref. 12.

Octamethylchlorin is readily dehydrogenated to the porphin (IV) by quinones. Thus the reaction with excess of 2 : 3-dichloro-5 : 6-dicyano-1 : 4-benzoquinone is instantaneous in the cold, and with tetrachloro-1 : 2-benzoquinone it is complete after 5 min. at 80°. Quantitative dehydrogenations with dichlorodicyano-1 : 4-benzoquinone, carried out by Miss Stephen, show that octamethylchlorin is completely dehydrogenated by 1 mol. of quinone and that the relationship, % dehydrogenation : mols. of quinone, is linear. This is in agreement with the dihydro-structure assigned to octamethylchlorin.

Magnesium octamethylchlorin was slowly dehydrogenated to (XI) in the cold by tetrachloro-1 : 2-benzoquinone. Quantitative results could, however, not be obtained because partial demetallation occurred, presumably by traces of hydrogen chloride produced in the reaction or by the action of the acidic tetrachloroquinol. The reaction with dichlorodicyano-1 : 4-benzoquinone was instantaneous. As in the case of metal-free octamethylchlorin, the results confirm the dihydro-level of the magnesium derivative.

The structure of octamethylchlorin (II; R = Me) is therefore established and the synthesis of chlorins from a Mannich base such as (I) thus appears to be applicable to β-substituted chlorins.

EXPERIMENTAL

(Microanalyses by Mr. Oliver of this Department.)

3 : 4-*Dimethylpyrrole*. (With Dr. E. A. PARKES.)—The pyrrole derivatives (V)—(VIII) were prepared by standard methods.

Diethyl 3 : 4-*dimethylpyrrole*-2 : 5-*dicarboxylate* (IX). Freshly distilled sulphuryl chloride (47 g., 3 mols.) was added dropwise with vigorous stirring during 2·5—3 hr. to ethyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate (VIII) suspended in anhydrous ether (150 c.c.) at −15° to −20°. The precipitate redissolved when the addition of sulphuryl chloride was almost complete. After being kept at 0° overnight the unchanged reagent was decomposed by the dropwise addition of water (10 c.c.) at <20°. The ethereal solution was dried (Na_2SO_4), the solvent removed under reduced pressure, and the oily residue treated dropwise with ethanol (80 c.c.) at room temperature with external cooling. The solution was heated to boiling for 5 min., the excess of ethanol removed under reduced pressure, and the residue dissolved in ether (200 c.c.). The ethereal solution was washed successively with aqueous sodium hydroxide, sodium hydrogen sulphite solution, and water, and dried (Na_2SO_4), and the volume reduced to 80 c.c. under reduced pressure. On rapid cooling the solution deposited crystals of the diester (IX) (16·2 g.), m. p. 67—68° (lit., m. p. 73°). A second crop (5·3 g.) was obtained by distillation of the mother liquors at 100°/10^{-5} mm. This distillate after one crystallisation from 80% ethanol, had m. p. 69—70° (3·8 g.). The total yield was 20 g. (76%) of material sufficiently pure for the next stage.

3 : 4-*Dimethylpyrrole* (X). (*a*) The diester (IX) (13·1 g.) was boiled under reflux with a solution of sodium hydroxide (15 g.) in water (30 c.c.) in an atmosphere of nitrogen. Excess of water was distilled off and the residue was heated to 250—350° under reduced pressure for 4 hr. The aqueous distillate was saturated with sodium chloride, and extracted with ether (5 times) in an atmosphere of nitrogen. The solid residue was dissolved in the minimum quantity of water and extracted with ether. The combined ethereal extracts were dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue distilled, affording 3 : 4-dimethylpyrrole (2·6 g., 50%) as low-melting crystals, b. p. 88—90°/22—24 mm. (lit., b. p. 65—66°/14 mm., m. p. 33°).

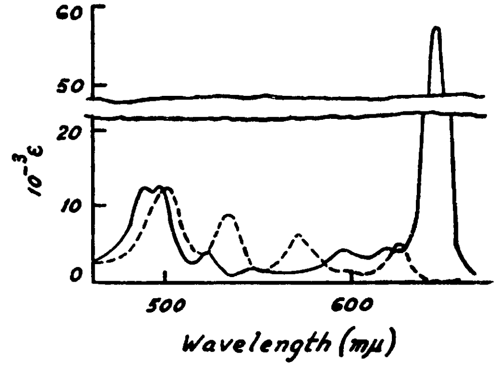
(*b*) The diester (14·9 g.) in 10% sodium hydroxide solution (60 c.c.) was boiled under reflux for 1 hr. The solution was cooled to 0° and acidified, and the precipitate was filtered off, dried, and boiled under reflux with 2-aminoethanol (10 c.c.) for 1 hr. The solution was cooled, neutralised with acetic acid, and repeatedly extracted with ether. The ethereal extracts were washed with aqueous copper sulphate followed by sodium hydrogen carbonate solution and dried (K_2CO_3). Removal of the solvent and distillation under reduced pressure afforded 3 : 4-dimethylpyrrole (2·65 g., 45%).

2-*Dimethylaminomethyl*-3 : 4-*dimethylpyrrole* (I; R = Me).—3 : 4-Dimethylpyrrole (X) (2·65 g., 1 mol.) in methanol (10 c.c.) was treated with a solution of dry dimethylammonium chloride (2·36 g., 1·05 mol.), potassium acetate (2·9 g., 1 mol.), and 40% aqueous formaldehyde solution (2·3 g.) in water (10 c.c.) at −5° to 5° in an inert atmosphere. The solution was kept at 0° for 2 hr., acidified, and extracted with ether. The aqueous layer was basified (NaOH) and extracted with ether. The ethereal extracts were washed with water, and dried ($MgSO_4$) for 1 hr., and the solvent removed under reduced pressure. Distillation of the residue in a high vacuum afforded the pure *Mannich base* (3·78 g., 89%) as a crystalline solid, m. p. 46—47°, b. p. 55°/0·2 mm. (Found: C, 70·8; H, 10·6; N, 18·4. $C_9H_{16}N_2$ requires C, 71·0; H, 10·6; N, 18·4%). The *picrate*, prepared from the base (56 mg.) and picric acid (85·5 mg.) in methanol, was obtained as bright yellow crystals, m. p. 110—112° (Found: C, 47·1; H, 5·1; N, 18·6. $C_9H_{16}N_2,C_6H_3O_7N_3$ requires C, 47·2; H, 5·0; N, 18·4%). It darkened on attempted crystallisation.

Preparation of Octamethylchlorin (II; R = Me).—The Mannich base (I; R = Me) (696 mg.) in xylene (50 c.c.) was treated with ethylmagnesium bromide (1 mol.) in ether (1·3 c.c.). The solution was boiled under reflux in an atmosphere of oxygen-free nitrogen for 10 hr., cooled, and filtered, and the residue washed with cold benzene. The combined filtrate and washings were shaken with 2N-hydrochloric acid and basified with ammonia solution. The benzene solution was concentrated to 250 c.c. under reduced pressure and the intensity of the main band at 646 mμ was determined spectroscopically after an appropriate dilution. From spectral data subsequently determined for pure octamethylchlorin, the concentration of the crude product was calculated to be 12·5% (60·7 mg.). The residual solid (see above) was continuously extracted with boiling benzene in an atmosphere of nitrogen, affording magnesium octamethylporphin (XI) (see below). The mother liquors contained more magnesium octamethylchlorin which was converted into the metal-free pigment.

With a reaction period of 20 hr., the yield of octamethylchlorin was 6·6% and that of magnesium octamethylporphin was 36·5%. In boiling *o*-dichlorobenzene (6 hr.) the yields were 5·2% and 22%, respectively.

Purification of Octamethylchlorin.—The crude benzene extracts from the above preparations were evaporated under reduced pressure and chromatographed on alumina (grade I), benzene–ether (9 : 1) being used as eluant. Octamethylchlorin was eluted first as a green diffuse band. Gradual increase of the ether concentration eluted octamethylporphin as a pink band, followed by a narrow dark green band of " octamethyloxychlorin " which was eluted with ether. The latter pigment, which was not obtained pure, had light-absorption maxima at 389·5, 495, 530, 586, and 641 mμ; $E^{1\%}_{1\,\text{cm.}}$ = 2375, 211·5, 11·0, 8·65, 438·4.



Absorption spectra :
——— *Octamethylchlorin (in benzene).*
- - - - *Octamethylporphin (in o-dichlorobenzene).*

The octamethylchlorin was rechromatographed on alumina with benzene–ether (19 : 1) as eluant. Concentration of the solution under reduced pressure in an atmosphere of nitrogen afforded deep blue crystals of *octamethylchlorin* which after one crystallisation from benzene were analytically pure (Found : C, 79·5, 79·45; H, 7·9, 7·8; N, 13·4%; C/H, 10·1, 10·2. $C_{28}H_{32}N_4$ requires C, 79·2; H, 7·6; N, 13·2%; C/H, 10·4).

Copper Octamethylchlorin.—Octamethylchlorin (14 mg.) in boiling benzene was treated with a slight excess of cupric acetate in methanol in an atmosphere of nitrogen. The solution was cooled, diluted with benzene, and washed with aqueous ammonia and water. The solution was concentrated and chromatographed on heavy magnesium oxide. Elution was carried out with benzene containing 20—30% ether until a separation was achieved between the faster-moving blue band of copper octamethylchlorin and the pink band of the corresponding porphin derivative. The column was then extruded and the two zones separated mechanically. Elution with chloroform, evaporation of the solution under reduced pressure, and addition of methanol afforded *copper octamethylchlorin* as deep blue crystals (Found : Cu, 13·7. $C_{28}H_{30}N_4Cu$ requires Cu, 13·1%).

Magnesium Octamethylchlorin.—A solution of octamethylchlorin in benzene was treated with excess of ethereal ethylmagnesium bromide, water was added at 10—20°, and the solution was filtered from magnesium hydroxide. All operations were carried out in an atmosphere of nitrogen in diffuse light. The blue benzene solution was made up to 50 c.c. and the light absorption determined immediately (see Table). Aliquot portions were treated with 2N-hydrochloric acid to convert it into the metal-free pigment, the concentration of which was determined spectroscopically.

Octamethylporphin (IV).—The crude pigment was prepared in 28% yield by Siedel's method.[2] After three continuous extractions from a thimble by boiling *o*-dichlorobenzene, it was obtained analytically pure as purple microcrystals (Found: C, 79·6; H, 7·3; N, 13·3%; C/H, 10·9. Calc. for $C_{28}H_{30}N_4$: C, 79·6; H, 7·2; N, 13·3%; C/H, 11·1). For light-absorption data, see the Table and the Figure. It could not be converted into the magnesium derivative on account of its insolubility.

Magnesium Octamethylporphin (XI).—The crude pigment (629 mg.) (see above) was placed in a thimble and continuously extracted into a solution of benzene containing 1 : 4 benzoquinone (160 mg.). Treatment was repeated and the pigment was finally extracted into pure benzene. *Magnesium octamethylporphin* separated as purple microcrystals (Found: C, 75·3; H, 6·5; N, 12·8; Mg, 5·75. $C_{28}H_{28}N_4Mg$ requires C, 75·6; H, 6·3; N, 12·6; Mg, 5·5%). It was converted into octamethylporphin by treatment of a benzene solution with cold 2N-hydrochloric acid. The precipitated hydrochloride was suspended in ammonia solution and filtered. The spectrum of the pigment (in *o*-dichlorobenzene) was identical with that of the material prepared by Siedel's method.

Copper Octamethylporphin.—Magnesium octamethylporphin (40 mg.) was placed in a thimble and continuously extracted into a solution of cupric acetate in acetic acid. The precipitated *copper octamethylporphin* was crystallised twice from pyridine (Found: C, 69·8, 69·9; H, 6·2; 6·1; N, 12·1. $C_{28}H_{28}N_4Cu$ requires C, 69·5; H, 5·8; N, 11·6%).

Dehydrogenation Experiments (With EDITH STEPHEN).—(a) *Octamethylchlorin.* The techniques used were essentially those described in Part II.[13] A solution of octamethylchlorin (0·0236 g./l.; $5·5 \times 10^{-5}$M) in purified *o*-dichlorobenzene was treated with dichlorodicyano-1 : 4-benzoquinone. The mixed solutions were either sealed into ampoules (in the case of a long reaction period) or mixed in volumetric flasks. All experiments were carried out in the dark at room temperature. The concentration of pigments was determined spectroscopically from the absorption band at 645 mμ for octamethylchlorin and at 535 and 570 mμ for octamethylporphin. The intensities of the last two bands being relatively low, results calculated from them do not have the same accuracy as those calculated from the 645 mμ band. For 1 mol. of octamethylchlorin, the following results were obtained:

Mols. quinone	Time, hr.	Unchanged chlorin, %	Porphin formed, % (535 mμ)	(570 mμ)
1	18	2	100	102
1	18	4	98	106
0·84	0·5	15	88	90
0·6	0·5	33	65	67
0·5	0·5	47	49	53
0·42	0·5	58	40	45
0·33	0·5	69	29	30
0·25	0·5	76	18	17

(b) *Magnesium octamethylchlorin.* The dehydrogenations were carried out at room temperature in benzene solution with dichlorodicyanoquinone. Spectrophotometric measurements (of bands at 620, 545, and 580 mμ) were made immediately after mixing the solutions:

Mols. quinone	Unchanged chlorin, %	Porphin formed, % (545 mμ)	(580 mμ
1	13	86	89
1	7	87	92
1	5	93	100
1	0	95	99
0·5	49	42	42
0·5	50	47	46
0·5	50	43	42

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[13] Eisner and Linstead, *J.*, 1955, 3749.