

Additions to Porphins involving the Formation of New Carbon–Carbon Bonds

By **Henry J. Callott** and **Alan W. Johnson**,* School of Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ
Anthony Sweeney, Department of Chemistry, University of Nottingham, Nottingham

Protoporphyrin IX dimethyl ester acts as a diene in Diels–Alder additions with dimethyl acetylenedicarboxylate and with tetracyanoethylene. The copper(II) complex of octaethylporphin reacts with ethyl diazoacetate to yield mainly two isomeric chlorins formed by carbene addition to the cross-conjugated double bonds on the porphin. A small amount of the *meso*-substituted porphin is also observed.

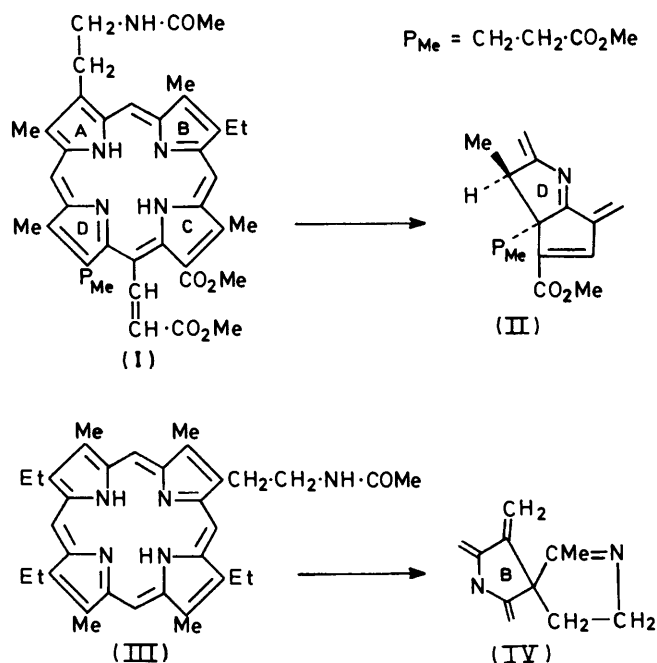
THE two peripheral cross-conjugated double bonds of the porphin nucleus permit a variety of addition reactions, such as hydrogenation to chlorins and dihydrochlorins, without affecting materially the aromatic character of the molecule. Such additions to porphin β - β -double bonds which involve the formation of new carbon–carbon bonds are of particular interest because of the relationship of the structures of vitamin B₁₂ and the porphins. Isolated examples of such reactions have been reported in the literature, an outstanding example being included in Woodward's synthesis of chlorophyll,¹ where the *meso*-substituted porphin (I) was converted into the purpurin (II), by the action of acetic acid.

Another example of intramolecular addition is the cyclisation of the β -acetylaminoethyl substituent² in (III) in the presence of phosphoryl chloride and pyridine to yield the spiro-derivative (IV). Also related to these intramolecular addition reactions is the pinacol rearrangement of the porphin hydroxylation products. Thus, oxidation of octaethylporphin using concentrated sulphuric acid and hydrogen peroxide gives, as the main product in yields of *ca.* 20%, a ketone (VI) formed by

¹ R. B. Woodward, A. W. Ayer, J. M. Beaton, J. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Itô, A. Langemann, E. le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, and H. Volz, *J. Amer. Chem. Soc.*, 1960, **82**, 3800.

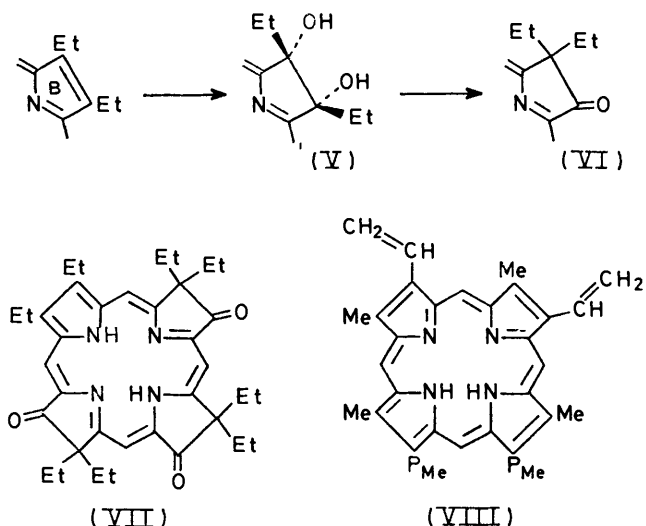
² G. L. Collier, A. H. Jackson, and G. W. Kenner, *Chem. Comm.*, 1966, 299.

acid-catalysed rearrangement of the intermediate diol (V).³ Using more forcing conditions, further oxidation

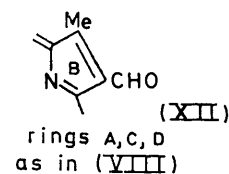
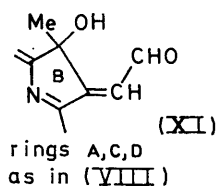
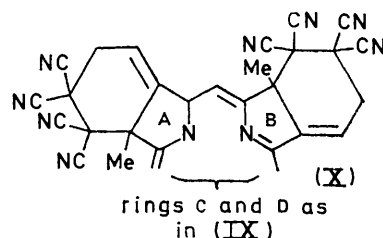
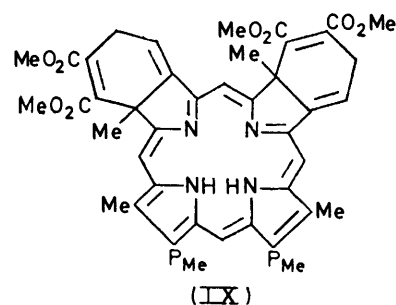


products, *e.g.* (VII) resulting from reaction at two or three of the pyrrole rings can be isolated.

In the present paper, we report two intermolecular addition reactions of porphins which result in *gem*- β -dialkyl substitution in one or two of the pyrrole rings. The first depends on the demonstration that the vinylic and cross-conjugated double bonds in each of rings A and B of protoporphyrin IX dimethyl ester (VIII) constitute a diene system capable of undergoing Diels-Alder reactions with activated dienophiles.⁴ Thus, reaction of (VIII) with dimethyl acetylenedicarboxylate or with tetracyanoethylene in refluxing chloroform solution gave the *a*-dihydrochlorin adducts (IX) and (X) (40 and 56% respectively). No reaction with dienophiles was observed with the iron(III) or nickel(II) complexes of (VIII) under similar conditions. The Diels-Alder additions of protoporphyrin dimethyl ester recall its reaction with oxygen to give the aldehyde (XI), an intermediate in a synthesis of spirographis porphyrin dimethyl ester [partial structure (XII)].⁵



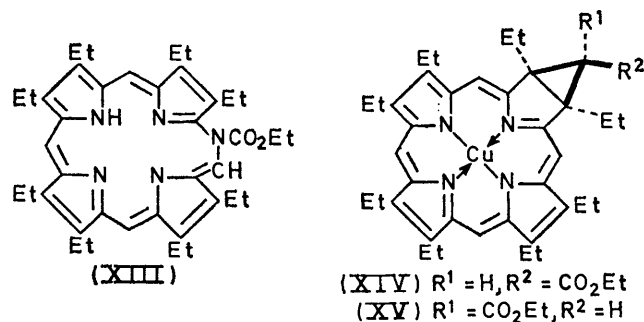
black crystals with a violet reflex and on the basis of their visible and mass spectra, they are regarded as the isomers



(XIV) and (XV). Their formation involves the copper-catalysed decomposition of ethyl diazoacetate (*cf.* ref. 9) to ethoxycarbonylcarbene, which then adds to one of the cross-conjugated double bonds of the porphyrin.

Demetallation of each of the copper chlorins with sulphuric acid gave an equilibrium mixture of the isomeric chlorins C and D, which was separated by chromato-

Our second method involves the addition of carbenes to the porphyrin cross-conjugated double bonds. It is known⁶ that reaction of ethyl *N*-*p*-nitrophenylsulphonyloxycarbamate with octaethylporphyrin yields, as the main product, an adduct (XIII) formed by insertion of ethoxycarbonylnitrene into the macrocycle. However, we have found that octaethylporphyrin fails to react with ethyl diazoacetate even in the presence of copper(I) iodide, but when the copper complex⁷ of octaethylporphyrin was heated with ethyl diazoacetate in refluxing benzene in the presence of copper(I) iodide for 30 min, two major products, isomeric copper chlorins (each *ca.* 30% based on converted porphyrin) were isolated as well as a new copper porphyrin and a third copper chlorin in lower yields.⁸ The main copper chlorins, A and B, formed



graphy. Isomer C, m.p. 198–200°, when heated above its m.p., was converted into isomer D, m.p. 220–223°.

³ A. W. Johnson and D. Oldfield, *J. Chem. Soc.*, 1965, 4303; H. H. Inhoffen and W. Nolte, *Annalen*, 1969, **725**, 167; R. Bonnett, M. J. Dimsdale, and G. F. Stephenson, *J. Chem. Soc. (C)*, 1969, 564.

⁴ Preliminary communication, R. Grigg, A. W. Johnson, and A. Sweeney, *Chem. Comm.*, 1968, 697.

⁵ H. H. Inhoffen, H. Brockman, jun., and K.-M. Bliesener, *Annalen*, 1969, **730**, 173.

⁶ R. Grigg, *J. Chem. Soc. (C)*, 1971, 3664.

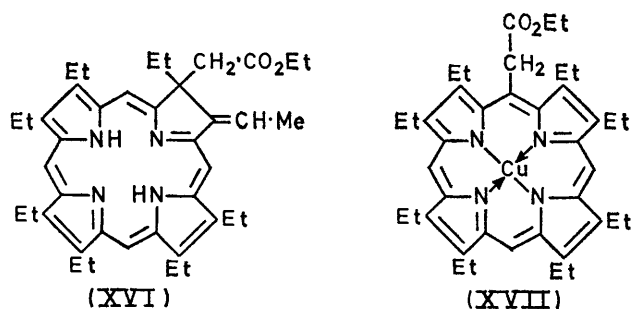
⁷ H. H. Inhoffen, J. H. Fuhrhop, H. Voigt, and H. Brockman, jun., *Annalen*, 1966, **695**, 133.

⁸ H. J. Callot and A. W. Johnson, *Chem. Comm.*, 1969, 749.

⁹ W. R. Moser, *J. Amer. Chem. Soc.*, 1969, **91**, 1135, 1141.

The overall structure of the chlorins is deduced from the n.m.r. spectrum (isomer C only; identical signals at τ 0.27 and 0.85 for each of two pairs of *meso*-protons indicating a plane of symmetry in the molecule), the typical chlorin visible spectra, and the mass spectra. Each of the free chlorins could be reconverted into the corresponding copper complex without isomerisation, isomer C giving the copper chlorin B and isomer D giving the copper chlorin A. Unfortunately the amount of the chlorin, isomer D, was insufficient for a determination of its n.m.r. spectrum and consequently it has not been possible to assign precise structures to these isomers as has been done more recently by one of us (H. C.),¹⁰ with the corresponding isomers derived from the interaction of ethyl diazoacetate and zinc *meso*-tetraphenylporphyrin. When a cyclohexane solution of the chlorin, isomer C, was irradiated with visible light for 4.5 h, another crystalline chlorin was obtained which resulted from fission of the cyclopropane ring (*cf.* ref. 11). The structure of this product (XVI), obtained in *ca.* 50% yield, was deduced from the visible (typical chlorin type) and mass spectra, the latter showing that an isomerisation had occurred (M^{++} 620) and that an acetic ester side-chain was present (M^{++} — Et, M^{++} — CO₂Et, and M^{++} — CH₂CO₂Et).

The red copper porphyrin obtained from the initial reaction has been identified as the copper(II) complex of *meso*-ethoxycarbonyl ethyloctaethylporphyrin (XVII), and, with sulphuric acid, it was converted into the metal-free derivative which in turn was converted into the nickel(II) complex. The visible spectrum of this last complex



was nearly superimposable on that of another nickel(II) *meso*-ethoxycarbonylmethylocta-alkylporphyrin.¹² In this reaction of copper(II) octaethylporphyrin, the carbene behaves similarly to ethoxycarbonylnitrene which yields the copper *meso*-ethoxycarbonylaminoporphyrin.⁶

EXPERIMENTAL

N.m.r. spectra were determined at 60 MHz (Varian T 60 instrument) for solutions in deuteriochloroform using tetramethylsilane as internal reference. Mass spectra were determined by direct insertion into the ion source of an A.E.I. MS 902 instrument. U.v. and visible spectra were

determined for solutions in chloroform except where otherwise stated.

Diels-Alder Additions of Protoporphyrin IX Dimethyl Ester.—(i) *With dimethyl acetylenedicarboxylate.* The acetylenic ester (2 ml) was added to a solution of protoporphyrin IX dimethyl ester (100 mg) in dry, freshly distilled chloroform (5 ml), and the solution heated under reflux for 48 h. The solution was then evaporated, the residue triturated with methanol (3 ml), and the resulting solid separated. It was washed with ether (100 ml) and then crystallised from chloroform–light petroleum to give the adduct as black microcrystals (59 mg, 40%) (Found: C, 65.7; H, 5.85; N, 6.75. C₄₈H₅₀N₄O₁₂ requires C, 65.9; H, 5.7; N, 6.4%), λ_{\max} 412 (ϵ 92,100), 507 (9710), 542 (7360), 550 (7430), 579 (4980), and 666 nm (9100), λ_{inf} 609 (ϵ 3500) and 649 nm (4100), ν_{\max} 1738 (ester carbonyl), 2955, and 3345 cm⁻¹.

(ii) *With tetracyanoethylene.* The analogous adduct was obtained from tetracyanoethylene (100 mg) and protoporphyrin IX dimethyl ester (100 mg) in chloroform (5 ml) as above in the form of purple-black microprisms (80 mg, 56%) from chloroform–light petroleum (Found: C, 68.05; H, 4.65; N, 19.65. C₄₈H₃₈N₁₂O₄ requires C, 68.1; H, 4.5; N, 19.8%), λ_{\max} 409 (ϵ 132,000), 502 (13,400), 537 (9360), 543 (9340), 576 (8250), 640 (6660), and 663 nm (13,900), λ_{inf} 604 (6090) and 724 nm (3710), ν_{\max} 1738 (ester carbonyl), 2208(CN), 2953, and 3342 cm⁻¹.

Reaction of Copper Octaethylporphyrin with Ethyl Diazoacetate.—A solution of copper octaethylporphyrin (300 mg) in benzene (5 ml) was warmed to 60–70°. Copper(I) iodide (100 mg) was added followed dropwise by ethyl diazoacetate (3 ml over 0.5 h) to the vigorously stirred suspension. The resulting brown reaction mixture was cooled and the solid was separated and washed with benzene. Extraction of this solid with hot chloroform gave unchanged copper octaethylporphyrin (280 mg). The mixed product and washings were chromatographed on silica gel (40 × 2 cm) and eluted with benzene when a violet fraction was obtained which was shown (t.l.c.) to contain four products one of which (trace) was starting material. Further elution of the column gave a mixture of diethyl maleate, diethyl fumarate, and a green chlorin.

The solvent was removed from the violet benzene solution and the products were separated by t.l.c. on silica gel using benzene for elution when two copper chlorins and a copper porphyrin were separated. The first copper chlorin (6 mg; isomer A) formed black crystals with a violet reflex and had R_F 0.8, m.p. 213–215°, λ_{\max} 397 (ϵ 129,000), 495 (3200), 533 (4680), 560 (3800), and 606 nm (26,000), ν_{\max} 1710 and 1640 cm⁻¹, m/e 681 (44%, M^+), 608 (100, $M - \text{CO}_2\text{Et}$), m^* 543 (calc. 542.5) (Found: M^+ , 681.324. Calc. for C₄₀H₅₀CuN₄O₂: M , 681.323). The second isomeric copper chlorin (6 mg; isomer B) also formed black crystals with a violet reflex and had R_F 0.6, m.p. 237–239°, λ_{\max} 395 (ϵ 132,000), 492 (2200), 530 (3050), 558 (3400), and 602 nm (24,800), ν_{\max} 1720 and 1645 cm⁻¹, m/e 681 (32%; M^+), 608 (10; $M - \text{CO}_2\text{Et}$), m^* 543 (calc. 542.5) (Found: M^+ , 681.324). The third product from the violet benzene eluate was a copper porphyrin and was obtained as red crystals (2 mg), m.p. 170–180°, R_F 0.7, λ_{\max} 404 (ϵ 115,000), 530 (17,400), and 565 nm (21,000), m/e 681 (100; M^+), 608 (10; $M - \text{CO}_2\text{Et}$), m^* 543 (calc. 542.5) (Found: M^+ , 681.324. Calc. for C₄₀H₅₀CuN₄O₂: M , 681.323).

The copper chlorin from the later fraction of the chroma-

¹² R. Grigg, A. W. Johnson, K. Richardson, and K. W. Shelton, *J. Chem. Soc. (C)*, 1968, 655.

¹⁰ H. J. Callot, *Tetrahedron Letters*, 1972, 1011.

¹¹ R. M. Roberts and R. G. Landolt, *J. Amer. Chem. Soc.*, 1965, **87**, 2281.

togram was obtained only as a green gum, R_F 0.2, λ_{\max} 407 (relative ϵ 100), 480 (3.2), 507 (4.4), 543 (4.2), 593 (8.1), and 625 nm (22), ν_{\max} 1715, 1630, and 1595 cm^{-1} , m/e 767 (99%; M), 738 (10; $M - \text{Et}$), m^* 711 (calc. 710.5), 694 (100, $M - \text{CO}_2\text{Et}$), m^* 629 (calc. 629), 680 (28, $M - \text{CH}_2\text{CO}_2\text{Et}$), m^* 603.5 (calc. 603).

Attempted reactions of octaethylporphin with ethyl diazoacetate in the presence of copper using either dimethoxyethane or *o*-dichlorobenzene as solvents were unsatisfactory as was an attempted reaction in benzene in the presence of copper(I) iodide.

meso-Ethoxycarbonylmethyl-octaethylporphin.—The copper complex (above; 2 mg) was dissolved in concentrated sulphuric acid (1 ml) and heated on the water-bath (15 min at 40°). The resulting solution was cooled, poured into an ice-cold concentrated solution of ammonium carbonate, and extracted with chloroform (3 \times). The mixed extracts were dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue was purified by t.l.c. on alumina with benzene as solvent in order to remove unchanged starting material. The *product* crystallised from dichloromethane-methanol to give dark brown crystals (1.3 mg), m.p. 144–147°, λ_{\max} 402 (ϵ 174,000), 502 (10,100), 535 (5300), 571 (4500), and 623 nm (1910), ν_{\max} 1720 cm^{-1} , m/e 620 (100%; M^+), 547 (30; $M - \text{CO}_2\text{Et}$) (Found: M^+ , 620.408. Calc. for $\text{C}_{40}\text{H}_{52}\text{N}_4\text{O}_2$: M , 620.409).

Treatment of a chloroform solution of the porphin with a drop of a concentrated methanolic solution of nickel(II) acetate, followed by aqueous washing and then drying caused λ_{\max} to change to 394, 524, and 556 nm with the formation of the porphin nickel complex.

Demetallation of the Copper Chlorins.—The copper chlorin (isomer A above; 10 mg) in concentrated sulphuric acid (3 ml) was heated on a water-bath at 50° for 30 min. The resulting solution was treated with aqueous ammonium carbonate as in the previous experiment and then extracted with chloroform as before to yield a crystalline mixture of two chlorins which were separated by t.l.c. on alumina with benzene as eluant. The first chlorin (4.5 mg), R_F 0.5, isomer C, formed black needles, m.p. 198–200° (from methylene chloride-methanol). It showed λ_{\max} 390 (ϵ 136,000), 484 (8700), 492 (9500), 520 (3600), 584 (1850), 613 (1940), and 638 nm (26,400), λ_{\max} [$\text{CHCl}_3\text{-CF}_3\text{CO}_2\text{H}$ (25 : 1)] 393 (175,000), 405 (160,000), 518 (4000), 538 (3750),

580 (3250), and 627 nm (25,000), ν_{\max} 1725 and 1615 cm^{-1} , τ 0.85sh and 0.27sh (2H, each s, meso-H), 8.12br (18H, t), and 6.05 (12H, m), (EtC=), 8.48 (6H, t) and 7.32 (4H, q) (EtC-), m/e 620 (29%; M^+), 547 (100; $M - \text{CO}_2\text{Et}$), m^* 483 (calc. 483) (Found: M^+ , 620.408. $\text{C}_{40}\text{H}_{52}\text{N}_4\text{O}_2$ requires M , 620.409).

The second chlorin (1 mg), R_F 0.8, isomer D, formed black needles, m.p. 220–223° (from methylene chloride-methanol), λ_{\max} 390 (ϵ 135,000), 484 (7900), 493 (8200), 519 (2750), 588 (1500), 607 (2600), and 641 nm (29,000), ν_{\max} 1715 and 1610 cm^{-1} , m/e 620 (30%; M^+), 547 (100; $M - \text{CO}_2\text{Et}$), m^* 483 (calc. 483) (Found: M^+ , 620.408).

The second copper chlorin fraction (above) was demetallated in the same manner and gave an identical mixture of the two foregoing chlorins (R_F , m.p., λ_{\max}).

When the chlorin, isomer C, was heated above its m.p. and then cooled, it was converted into isomer D, m.p. 217–220° (t.l.c., λ_{\max}). Furthermore, the chlorin, isomer C (0.5 mg), when dissolved in chloroform (2 ml) and treated with a concentrated methanolic solution (2 drops) of copper(II) acetate was converted into the copper chlorin, isomer B (t.l.c., λ_{\max}), and the chlorin, isomer D, when treated similarly gave the copper chlorin, isomer A (t.l.c., λ_{\max}).

Irradiation of the Chlorin, Isomer C.—The recrystallised chlorin (3 mg) was dissolved in pure cyclohexane (20 ml) and irradiated with two 100 W tungsten bulbs at 5 cm. The reaction was monitored by repeated measurements of the visible spectrum. After 4.5 h no more starting material remained and a new absorption band at 657 nm had appeared. The solvent was removed under reduced pressure and the product was purified by t.l.c. on alumina using benzene for elution. The major *product*, R_F 0.4, was extracted into chloroform and crystallised from chloroform-methanol when it formed black crystals (1.5 mg), m.p. 125–128°, λ_{\max} 398 (ϵ 130,000), 496 (10,000), 532 (10,000), 604 (6000), and 657 nm (25,000), ν_{\max} 1725 (ester carbonyl) and 1605 (C=C) cm^{-1} , m/e 620 (100%; M^+), 591 (18, $M - \text{Et}$), 547 (47, $M - \text{CO}_2\text{Et}$), 533 (32, $M - \text{CH}_2\text{CO}_2\text{Et}$).

We thank Dr. R. Grigg for discussions and Imperial Chemical Industries Limited, Pharmaceuticals Division, for the gift of intermediates.

[2/2876 Received, 22nd December, 1972]