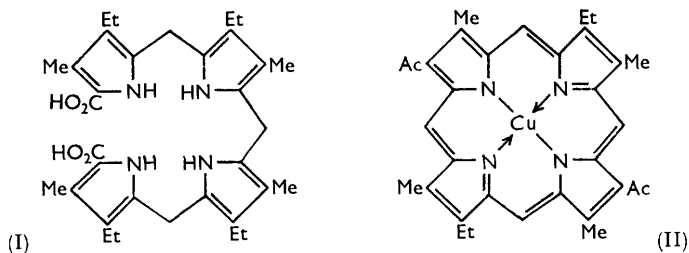


468. The Formation of Porphyrins by the Cyclisation of Bilenes.

By A. W. JOHNSON and I. T. KAY.

An oxidative cyclisation involving the terminal methyl groups of bilenes and biladienes can be brought about by the action of cupric acetate and yields porphyrins. Reaction of bilene-b derivatives with aluminium chloride causes fission at the terminal methylene bridges and also yields porphyrins by combination of two dipyrromethene fragments.

UNTIL recently there were few methods, which involved the cyclisation of a suitable tetrapyrrolic system, available for the synthesis of porphyrins. Such methods, which offer the possibility of preparing porphyrins with an unsymmetrical arrangement of β -substituents, frequently involved decarboxylations, *e.g.* the cyclisation of the acid (I) with hot formic acid to aetioporphyrin (claimed ¹ to be the II isomer).



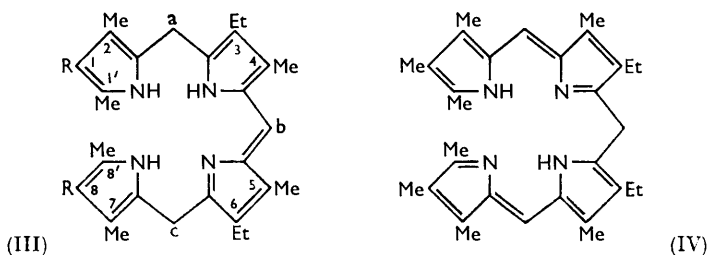
We have used the oxidation of terminal methyl groups with cupric acetate in methanol to effect cyclisations of linear tetrapyrrolic compounds, and a recent paper ² describing the use of this reagent at higher temperatures prompts us to record our findings. The American workers ² studied the oxidative self-condensation of certain 3-(and 4-)acetyl-5-methyldipyrromethanes with cupric acetate in molten naphthalene at 190° and showed

¹ Corwin and Coolidge, *J. Amer. Chem. Soc.*, 1952, **74**, 5196.

² Kleinspehn and Corwin, *J. Amer. Chem. Soc.*, 1960, **82**, 2750.

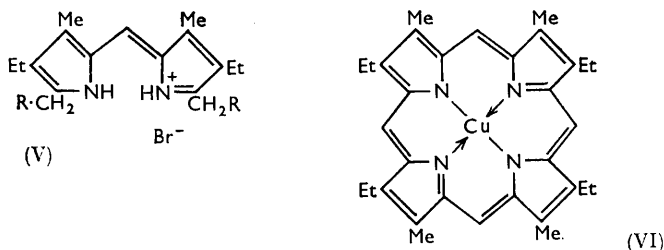
that the main product was the copper complex of diacetyldeuteroætioporphyrin (as II) although other porphyrins were undoubtedly present in the mixture.

The intermediate tetrapyrrolic compounds which we have employed have been of two types. The 1',8'-dideoxy-1',8'-dimethylbilene-b (III) derivatives were obtained, following Fischer and Kürzinger,³ by the condensation of 4,4'-diethyl-5,5'-bismethoxymethyl-3,3'-



dimethyldipyrromethene with two equivalents of a 2,3,4-trialkylpyrrole. The 1',8'-dideoxy-1',8'-dimethylbiladiene-ac (IV) derivatives,* which have not been previously described, were prepared by the reaction of two equivalents of 2-formyl-3,4,5-trimethylpyrrole with either 3,3'-diethyl-4,4'-dimethyldipyrromethane or the corresponding 5,5'-dicarboxylic acid.

The ability of cupric acetate to bring about this type of oxidative cyclisation was revealed by the conversion of 4,4'-diethyl-3,3',5,5'-tetramethyldipyrromethene hydrobromide⁵ (V; R = H) to the cupric derivative of ætioporphyrin II. In another sequence, the benzyl groups of 5,5'-dibenzoyloxy-4,4'-diethyl-3,3'-dimethyldipyrromethene (V; R = O-CH₂Ph) were removed by hydrogenolysis, and the resulting dihydroxymethyl derivative (V; R = OH) was treated with cupric acetate to give the copper derivative of ætioporphyrin II (VI) in 21% overall yield.



The tetrapyrrolic compounds (III; R = Me,Et) and (IV) were cyclised to a porphyrin by treatment with cupric acetate in methanol but when similar reactions were carried out with zinc or cobaltous acetate the products were complexes of type (VII) containing eight pyrrole rings to each metal atom. However, the action of aluminium chloride in pyridine on the bilene-b derivatives also yielded porphyrins and it was of interest to establish whether this cyclisation was operating by a mechanism similar to that brought about by cupric acetate. It was found from the results of X-ray powder photographs that the product of cyclisation with aluminium chloride of 1',8'-dideoxy-1,3,6,8-tetraethyl-1',2,4,5,7,8'-hexamethylbilene-b (III; R = Et) was ætioporphyrin II

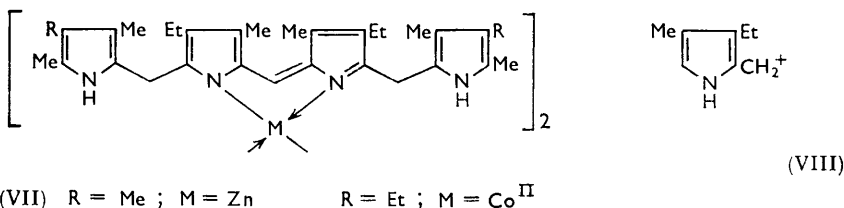
* The nomenclature used in this series is based on that of the bile pigments proposed by Lemberg and Legge,⁴ by removal of the two hydroxyl groups at positions 1' and 8' by use of the prefix deoxy. The numbering is that shown in Formula (III).

³ Fischer and Kürzinger, *Z. physiol. Chem.*, 1931, **196**, 213.

⁴ Lemberg and Legge, "Hematin Compounds and Bile Pigments," Interscience, New York and London, 1949, p. 105.

⁵ Johnson, Kay, Markham, Price, and Shaw, *J.*, 1959, **3416**.

and was identical with that obtained from a similar cyclisation of 1',8'-dideoxy-3,6-diethyl-1,1',2,4,5,7,8,8'-octamethylbilene-b (III; R = Me). A different product, a diethylhexamethylporphyrin was obtained from the latter bilene-b by cyclisation with cupric acetate, and the processes are therefore fundamentally different. It is concluded that cupric acetate causes cyclisation of the bilene-b by oxidation of the terminal methyl groups and subsequent cyclisation but that aluminium chloride causes fission of the bilene-b at the methylene groups with a subsequent union of two dipyrromethene fragments.



The unique properties of cupric salts were further revealed by an examination of the acid cyclisation of the various metallic complexes of 4,4'-diethyl-5,5'-bismethoxymethyl-3,3'-dimethyldipyrromethene.³ No porphyrin was obtained from the cobaltous or zinc complexes (or the free hydrobromide), only a trace (<1%) from the nickel complex, but 10% from the cupric complex. It is assumed that the cobalt, zinc, and nickel complexes, which are normally tetrahedral, must distort appreciably before cyclisation to the planar porphyrin can occur but the cupric complex, which is unstable in the tetrahedral form, is readily transformed to the planar state.

Reduction of the bilene-b derivatives gave the unstable bilanes which could not be isolated pure; treatment of solutions of the bilanes with acids gave porphyrins, presumably by fission of the methylene bridges to the carbonium ions (VIII) which are known to polymerise to porphyrins.⁶

EXPERIMENTAL

Ultraviolet and visible spectra were determined for chloroform solutions, except where otherwise stated. Light petroleum refers to the fraction, b. p. 60—80°.

4,4'-Diethyl-5,5'-bismethoxymethyl-3,3'-dimethyldipyrromethene Hydrobromide.—Prepared by heating the corresponding 5,5'-dibromomethyldipyrromethene under reflux with methanol, this had m. p. 177° [lit.³ 178°].

Metal Complexes.—(i) The methene hydrobromide (1 g.) in methanol (10 c.c.) was treated with a saturated solution of cupric acetate in ammonia (2.5 c.c.; *d* 0.88), and the solution boiled for 5 min. After cooling, the copper complex was separated, washed with water and methanol, and crystallised from chloroform-methanol (to which several drops of concentrated ammonia solution had been added). It then formed green plates (730 mg.), m. p. 169° (lit.³ 168°) (Found: N, 8.15. Calc. for C₃₈H₅₄CuN₄O₄: N, 8.0%); λ_{max.} 475 and 516 mμ (log ε 4.81 and 4.85, respectively).

(ii) Prepared in an analogous manner, by using ammoniacal nickel chloride, the *nickel complex* formed green prisms, m. p. 143° (Found: C, 66.2; H, 8.05; N, 8.2. C₃₈H₅₄N₄NiO₄ requires C, 66.2; H, 7.95; N, 8.1%); λ_{max.} 235, 392, and 509 mμ (log ε 4.38, 4.13, and 5.03, respectively).

(iii) Prepared similarly by using ammoniacal cobaltous acetate, the *cobalt complex* formed green prisms, m. p. 150° (Found: C, 66.4; H, 8.15; N, 8.5. C₃₈H₅₄CoN₄O₄ requires C, 66.15; H, 7.9; N, 8.1%); λ_{max.} 234, 379, and 510 mμ (log ε 4.39, 4.22, and 4.07, respectively).

(iv) Prepared similarly by using ethanolic zinc acetate, the *zinc complex* formed yellow plates with a green lustre, m. p. 151° (Found: C, 65.8; H, 7.75; N, 7.9. C₃₈H₅₄N₄O₄Zn requires C, 65.55; H, 7.85; N, 8.05%); λ_{max.} 289, 311, and 508 mμ (log ε 3.58, 3.38, and 5.32, respectively).

1',8'-Dideoxy-3,6-diethyl-1,1',2,4,5,7,8,8'-octamethylbilene-b Hydrobromide.—4,4'-Diethyl-5,5'-bismethoxymethyl-3,3'-dimethyldipyrromethene hydrobromide (3 g.) in benzene (30 c.c.) and

⁶ Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.

2,3,4-trimethylpyrrole (1.9 g.; 2 mols.) were heated under reflux for 30 min. Hot light petroleum (10 c.c.) was then added and the solution was cooled. The *salt* was washed with light petroleum; it crystallised from chloroform–light petroleum as orange plates with a metallic sheen, m. p. 187° (decomp.) (3.5 g.; 84%) (Found: C, 67.3; H, 7.8; N, 9.95. $C_{31}H_{43}BrN_4$ requires C, 67.5; H, 7.85; N, 10.15%); λ_{max} . 235, 368, 512 $m\mu$ (log ϵ 4.29, 3.83, and 4.53, respectively).

The *zinc complex* (290 mg.) from this hydrobromide (500 mg.) formed green plates, decomp. $>200^\circ$ (Found: C, 73.8; H, 8.15; N, 11.0. $C_{62}H_{82}N_8Zn$ requires C, 74.15; H, 8.25; N, 11.15%); λ_{max} . 233, 356, 373, 513 $m\mu$ (log ϵ 4.53, 4.15, 4.13, and 4.94, respectively).

1',8'-Dideoxy-1,3,6,8-tetraethyl-1',2,4,5,7,8'-hexamethylbilene-b Hydrobromide.—Prepared (37%) in an analogous manner from the condensation of cryptopyrrole (2 mol.) with 4,4'-diethyl-5,5'-bismethoxymethyl-3,3'-dimethyldipyrromethene hydrobromide (1 mol.) in benzene, this *salt* formed red-brown hexagonal plates, m. p. 180° (from chloroform–light petroleum) (Found: C, 68.1; H, 7.85; N, 9.55. $C_{33}H_{47}BrN_4$ requires C, 68.35; H, 8.15; N, 9.65%); λ_{max} . 235, 368, 512 $m\mu$ (log ϵ 4.26, 3.82, and 4.48, respectively).

The *cobalt complex* (380 mg.) from this hydrobromide (500 mg.) formed green plates, m. p. 230–231° (Found: C, 75.3; H, 8.55; N, 10.45. $C_{66}H_{90}CoN_8$ requires C, 75.2; H, 8.6; N, 10.65%); λ_{max} . 233, 382, 521 $m\mu$ (log ϵ , 4.57, 4.29, and 5.07, respectively).

1',8'-Dideoxy-4,5-diethyl-1,1',2,3,6,7,8,8'-octamethylbiladiene-ac Dihydrochloride.—Dibenzyl 3,3'-diethyl-4,4'-dimethyldipyrromethane-5,5'-dicarboxylate (5 g.) in methanol (75 c.c.) was hydrogenated at 100°/100 atmos. for 2 hr., Raney nickel being used. After separation of the catalytic, the solution was concentrated to ca. 40 c.c. and then cooled. Concentrated hydrochloric acid (3 c.c.) and 3,4,5-trimethylpyrrole-2-aldehyde (2.7 g.; 2 mol.) were then added and the solution kept at room temperature for 2 hr. Water (500 c.c.) was added to the solution which was then extracted with chloroform (ca. 250 c.c.), and the chloroform layer dried ($MgSO_4$). After removal of the solvent, the residual *salt* formed red needles with a green lustre (2.2 g.; 41%), m. p. $>350^\circ$, from chloroform–light petroleum (Found: C, 68.4; H, 7.6; N, 10.2. $C_{31}H_{42}Cl_2N_4$ requires C, 68.75; H, 7.8; N, 10.35%); λ_{max} . 291, 371, 457, 527 $m\mu$ (log ϵ 4.41, 4.19, 4.36, and 5.31, respectively).

1',8'-Dideoxy-1,1',2,3,4,5,6,7,8,8'-decamethylbiladiene-ac Dihydrochloride.—3,3',4,4'-Tetramethyldipyrromethane-5,5'-dicarboxylic acid (1.1 g.) was suspended in methanol (15 c.c.) containing concentrated hydrochloric acid (5 c.c.). 3,4,5-Trimethylpyrrole-2-aldehyde (1 g.; 2 mol.) was then added, and the solution was heated (steam-bath) for 20 min. On cooling, the *product* which separated was washed with a little methanol; it crystallised from chloroform–light petroleum as brown rods with a green lustre (1.4 g.; 72%), m. p. $>350^\circ$ (Found: C, 67.4; H, 6.9; N, 10.7. $C_{29}H_{38}Cl_2N_4$ requires C, 67.8; H, 7.45; N, 10.9%); λ_{max} . 290, 370, 456, and 526 $m\mu$ (log ϵ 3.35, 4.12, 4.32, and 5.23, respectively).

5,8-Diethyl-1,2,3,4,6,7-hexamethylporphyrin.—1',8'-Dideoxy-3,6-diethyl-1,1',2,4,5,7,8,8'-octamethylbilene-b hydrobromide (500 mg.) and cupric acetate (1 g.) in methanol (100 c.c.) were heated under reflux for 48 hr. The solvent was then removed by distillation, the residue dissolved in chloroform (ca. 40 c.c.), and this solution set aside over anhydrous potassium carbonate for 2 hr. The solid was separated, and the filtrate concentrated to ca. 20 c.c. and chromatographed on alumina (Spence type H). The elution of the metal porphyrin was followed by means of a hand spectroscope. After removal of the solvent from the porphyrin fraction, the residue crystallised from chloroform–methanol as blue needles (140 mg.; 30%), m. p. $>350^\circ$ [Found: C, 70.1; H, 6.05; N, 10.8; residue (CuO), 15.5. $C_{30}H_{32}CuN_4$ requires C, 70.35; H, 6.3; N, 10.95; CuO, 15.5%]; λ_{max} . 237, 328, 397, 525, and 562 $m\mu$ (log ϵ 4.45, 4.24, 5.56, 4.11, and 4.40, respectively). The *porphyrin-copper complex* (100 mg.), suspended in concentrated sulphuric acid (6 c.c.), was heated (steam-bath) for 5 min. The solution was cooled, diluted with water, basified ($NH_4\cdot OH$), and extracted with chloroform, and the dried ($MgSO_4$) chloroform layer chromatographed on alumina. The porphyrin fraction yielded steel-blue prismatic needles (65 mg.) from chloroform–methanol (Found: C, 79.8; H, 7.45; N, 12.1. Calc. for $C_{30}H_{34}N_4$: C, 79.95; H, 7.6; N, 12.45%); λ_{max} . 269, 398, 497, 532, 566, and 620 $m\mu$ (log ϵ 3.91, 5.21, 4.13, 3.99, 3.82, and 3.67 respectively).

Ætioporphyrin IV Copper Complex.—1',8'-Dideoxy-1,3,6,8-tetraethyl-1',2,4,5,7,8'-hexamethylbilene-b hydrobromide (1 g.) in methanol (160 c.c.) was treated with cupric acetate (2 g.), and the solution heated under reflux for 48 hr. The metal porphyrin after chromatography and isolation in the usual manner formed red felted needles (204 mg.; 22%), m. p. 292–293°, from

chloroform-methanol [Found: C, 70.8; H, 6.75; N, 10.2; Ash (CuO), 14.8. Calc. for $C_{32}H_{36}CuN_4$: C, 71.15; H, 6.7; N, 10.35; CuO, 14.7%]; λ_{max} 238, 327, 397, 524, and 561 $m\mu$ ($\log \epsilon$ 4.45, 4.24, 5.56, 4.10, and 4.38, respectively).

1,2-Diethyl-3,4,5,6,7,8-hexamethylporphyrin Copper Complex.—1',8'-Dideoxy-4,5-diethyl-1,1',2,3,6,7,8,8'-octamethylbiladiene-ac dihydrochloride (500 mg.) in methanol (100 c.c.) was treated with cupric acetate (1 g.), and the solution heated under reflux for 48 hr. The *metal porphyrin* was isolated by chromatography in the usual manner and formed blue needles (82 mg.; 17%) from chloroform-methanol [Found: C, 70.2; H, 6.3; N, 11.1; Ash (CuO), 15.5. $C_{30}H_{32}CuN_4$ requires C, 70.35; H, 6.3; N, 10.95; CuO, 15.1%]. Its light absorption was identical with that of the copper complex of 5,8-diethyl-1,2,3,4,6,7-hexamethylporphyrin (above).

Ætioporphyrin.—1',8'-Dideoxy-1,3,6,8-tetraethyl-1',2,4,5,7,8'-hexamethylbilene-b hydrobromide (500 mg.) in ethanol (40 c.c.) was reduced over Adams's catalyst. After 2 hr. the solution was colourless, and the catalyst was removed by filtration. Concentrated hydrochloric acid (5 c.c.) was then added and the solution refluxed for 3 hr. Water (200 c.c.) was added, the solution basified with ammonia and extracted with chloroform, and the dried ($MgSO_4$) chloroform layer chromatographed on alumina. The porphyrin fraction yielded purple needles (15 mg.) from chloroform-methanol (Found: N, 11.8. Calc. for $C_{32}H_{38}N_4$: N, 11.7%); λ_{max} 270, 399, 498, 533, and 620 $m\mu$ ($\log \epsilon$ 3.38, 5.21, 4.09, 3.98, 3.79, and 3.66, respectively).

Ætioporphyrin II and Metal Complexes.—(i) 1',8'-Dideoxy-3,6-diethyl-1,2,4,5,7,8,8'-octamethylbilene-b hydrobromide (1 g.) in dry pyridine (20 c.c.) was treated with anhydrous aluminium chloride (1 g.), and the mixture heated (steam-bath) for 30 min. The resultant dark brown solution was kept overnight at room temperature, poured into water, and thoroughly extracted with chloroform (3 \times 100 c.c.); the combined chloroform extracts were dried ($MgSO_4$) and evaporated to dryness, traces of pyridine being removed under reduced pressure. The residue was dissolved in chloroform (20 c.c.) and, after chromatography, the porphyrin fraction yielded purple needles (120 mg.; 27%) from chloroform-methanol (Found: C, 80.4; H, 8.15; N, 11.8. Calc. for $C_{32}H_{38}N_4$: C, 80.3; H, 8.0; N, 11.7%); λ_{max} 269, 398, 497, 533, 566, and 620 $m\mu$ ($\log \epsilon$ 3.88, 5.2, 4.11, 3.98, 3.81, and 3.66, respectively).

(ii) The previous experiment was repeated with 1',8'-dideoxy-1,3,6,8-tetraethyl-1',2,4,5,7,8'-hexamethylbilene-b hydrobromide (1 g.), and the porphyrin isolated in an identical manner (87 mg.; 21%) (Found: C, 80.0; H, 7.9; N, 11.6%). The light absorption was identical with that of the previous preparation.

(iii) 4,4'-Diethyl-3,3',5,5'-tetramethyldipyrromethene hydrobromide (1 g.) in methanol (160 c.c.) was treated with cupric acetate (3 g.) and the solution heated under reflux for 48 hr. The solvent was then removed by distillation, chloroform (50 c.c.) added to the residue, and the solution dried (anhydrous K_2CO_3). The solution was then concentrated to ca. 30 c.c. and, after chromatography, the porphyrin fraction yielded red-brown felted needles (72 mg.; 9%) from chloroform-glacial acetic acid (Found: C, 71.2; H, 6.95; N, 9.95. Calc. for $C_{32}H_{36}CuN_4$: C, 71.15; H, 6.7; N, 10.35%); λ_{max} 328, 398, 525, and 562 $m\mu$ ($\log \epsilon$ 4.22, 5.57, 4.07, and 4.36, respectively).

(iv) Glacial acetic acid (2.5 c.c.) was added dropwise to refluxing solutions of various metal complexes (500 mg.) of 4,4'-diethyl-5,5'-bismethoxymethyl-3,3'-dimethyldipyrromethene in methanol (100 c.c.) during 10 min. The mixture was heated under reflux for a further 1 hr., then evaporated to dryness, and the residue dissolved in chloroform (20 c.c.) and chromatographed on alumina. The following yields were obtained: Cu^{II} (35 mg.; 10%); Co^{II}, nil; Zn, nil; Ni^{II}, trace (<1%); free hydrobromide, nil. The light absorption of the copper ætioporphyrin II complex was identical with that of the previous preparation.

(v) 5,5'-Bisbenzyloxymethyl-4,4'-diethyl-3,3'-dimethyldipyrromethene hydrobromide (500 mg.; see below), in ethanol (20 c.c.) containing fused sodium acetate (100 mg.), was hydrogenated over Adams's catalyst. Hydrogen (2 mol.) was rapidly absorbed and, after removal of the catalyst, cupric acetate (300 mg.) was added to the solution which was then heated under reflux for 1 hr. The metal porphyrin (52 mg.; 21%) was isolated as in the previous preparations.

5,5'-Bisbenzyloxymethyl-4,4'-diethyl-3,3'-dimethyldipyrromethene Hydrobromide.—The corresponding 5,5'-bisbromomethyldipyrromethene hydrobromide (13 g.) was suspended in benzyl alcohol (80 c.c.) and heated (steam-bath) until it had all dissolved. Ethyl acetate (80 c.c.) was then added to the hot solution, and on cooling, the *benzyloxy-compound* crystallised. It was separated and washed with ethyl acetate; it crystallised from ethyl acetate as golden-orange

needles (9.6 g.; 72%), m. p. 169—170° (decomp.) (Found: C, 68.1; H, 7.1; N, 4.85. $C_{31}H_{37}BrN_2O_2$ requires C, 67.75; H, 6.8; N, 5.0%); λ_{max} 380 and 493 $m\mu$ ($\log \epsilon$ 3.88 and 5.52, respectively).

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