331. *The Synthesis of Derivatives of Corrole (Pentadehydrocorrin).*

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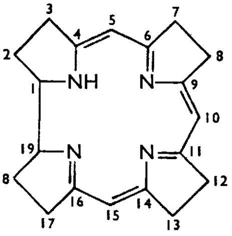
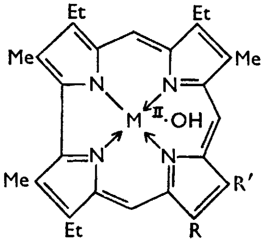
Palladium, copper, and cobalt derivatives of corrole, a new macrocyclic pyrrolic system, containing a direct link between two of the individual pyrrole rings, have been prepared from 5,5′-dibromodipyrromethenes.

THE name corrin has been given to the macrocyclic ring system (I) of vitamin B_{12}. In examining possible synthetic methods for the preparation of corrin, we have discovered a relatively simple synthesis of a series of metallic derivatives (II) of pentadehydrocorrin for which the name corrole * is now suggested.

5,5′-Dibromo-3,3′-diethyl-4,4′-dimethyldipyrromethene [2] (III), when treated with 3% palladium–strontium carbonate, gave the palladium derivative (IV; R = Et) of bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl).[3] Reaction of this compound in boiling ethanol with formaldehyde and concentrated hydrochloric acid [4] subsequently gave the palladium derivative, $C_{31}H_{36}N_4OPd$ (II; M = Pd, R = Et, R′ = Me), as glistening black rods. The light absorption of a solution in chloroform showed max. at 232, 319, 385, 515, 552, 620, and 670 mμ which covers a wider range than the corresponding spectrum of palladium ætioporphyrin (max. at 231, 272, 335, 393, 512, and 547 mμ), probably because of the lower degree of symmetry in the new macrocycle.



(I)



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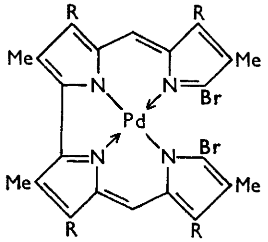
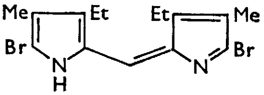


(IV)



(III)

In a previous paper,[2] the preparation of palladium ætioporphyrin I by reaction of 5-bromo-3,4′-diethyl-3′,4,5′-trimethyldipyrromethene and 5-bromo-5′-bromomethyl-3,4′-diethyl-3′,4-dimethyldipyrromethene in the presence of palladium–strontium carbonate was described. An adaptation of this method has been used in an alternative synthesis of the palladium derivative (II; M = Pd, R = Me, R′ = Et). 5,5′-Dibromo-3,3′-diethyl-4,4′-dimethyldipyrromethene and 5-bromo-3,4′-diethyl-3′,4,5′-trimethyldipyrromethene [2] were allowed to react in ethanolic solution in presence of palladium–strontium carbonate as before. In addition to palladium ætioporphyrin I and palladium bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (IV; R = Et), the palladium complex (II; M = Pd, R = Me, R′ = Et), formed by cyclisation of the intermediate (V) during the reaction, was isolated. These bivalent palladium compounds appear to contain a hydroxyl group, although the precise nature of the bond, shown as covalent in (II), between this group and the remainder of the molecule is not yet known with certainty. Dr. J. Chatt has kindly

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* We are indebted to the Editor for this suggestion. Numbering is as for corrin.

[1] I.U.P.A.C. " Nomenclature of Organic Chemistry, 1957," Butterworths, 1958, p. 85.

[2] Johnson, Kay, Markham, Price, and Shaw, *J.*, 1959, 3416.

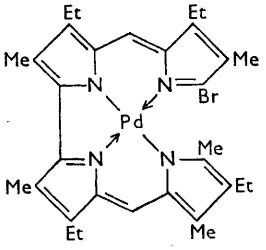
[3] Fischer and Stächel, *Z. physiol. Chem.*, 1939, **258**, 121.

[4] Cf. Treibs and Kolm, *Annalen*, 1958, **614**, 716.

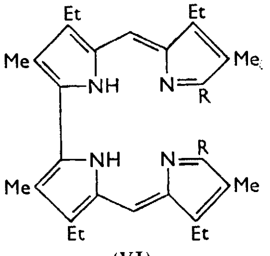
examined the conductivity of a solution of the palladium complex (II; M = Pd, R = Et, R′ = Me) in nitrobenzene and informs us that the value obtained indicates that the hydroxyl group cannot be ionic in character.

The palladium atoms are very firmly bound within these complexes and no method has yet been found which will remove the metal without disrupting the organic part of the molecule. The same situation is found with vitamin B_{12}. It is well known[5] that palladium complexes are frequently more stable than the corresponding complexes of, say, copper, cobalt, and zinc, and in fact attempts to prepare the new macrocycle containing these metals by the above cyclisation were unsuccessful. Acid-treatment of the metallic bi-(5′-bromodipyrromethen-5-yls) removed the metal before cyclisation could occur and the product was identified as the metal-free bishydroxymethyl derivative (VI; R = CH_2·OH).

However, by syntheses involving a slight modification (comprising neutralisation of the acid with ammonia before the evaporation) of the original isolation procedure, copper and cobalt have been substituted for palladium in (II). It appears probable from these results that the metal complex of the hydroxymethyl derivatives (VI; R = CH_2·OH) is an intermediate in the cyclisation, the copper and cobalt derivatives of (VI; R = CH_2·OH) being decomposed by the acid present in the reaction mixture, whereas the more stable palladium complex is not. In the reactions with the copper and cobalt derivatives, addition of ammonia causes the metal complexes to be re-formed and cyclisation then occurs. The complexes (II; M = Cu^{II}, Co) so formed resembled the palladium derivative in physical and chemical properties; *e.g.*, the metal could not be removed by chemical means without extensive decomposition.



(V)



(VI)

Palladium derivatives (IV; R = Me or CH_2·CH_2·CO_2Et) have also been prepared in small amount and subjected to condensation with formaldehyde in the presence of hydrochloric acid. Although the corresponding palladium macrocyclic compounds were detected in solution by means of their characteristic spectra, they were obtained in quantities too small for isolation. Other methods for the cyclisation of compounds of type (IV) to macrocycles of type (II) were examined but the formaldehyde–hydrochloric acid method was the most efficient; for example, the palladium could easily be removed from compounds (IV) by treatment with acids, the free base (VI; R = Br) being obtained. Reaction of this with formic acid caused replacement of bromine by formate groups to yield an ester (VI; R = O·CHO).

These reactions can be followed conveniently by means of the hand spectroscope, for the open-chain compounds (*e.g.*, IV and VI) do not show the strong absorption lines of the macrocyclic pigments such as (II).

Experimental

Dibenzyl 3,3′,4,4′-*Tetramethyldipyrromethane*-5,5′-*dicarboxylate*.—Lead tetra-acetate (42·8 g.) was added to a solution of benzyl 3,4,5-trimethylpyrrole-2-carboxylate[6] (25·2 g.) in glacial acetic acid (1200 c.c.) at room temperature during 30 min. with stirring. Stirring was continued for a

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[5] Mellor and Maley, *Nature*, 1947, **159**, 370; 1948, **161**, 436.

[6] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.

further 2 hr., after which the volume was reduced to 200 c.c. under reduced pressure and the residue was poured into water (800 c.c.). The precipitated solid was separated, washed with water, and crystallised from acetone, benzyl 5-acetoxymethyl-3,4-dimethylpyrrole-2-carboxylate being obtained as colourless needles (19 g., 60%), m. p. 169—171°.

The ester (18·1 g.) produced was heated in ethanol (250 c.c.) containing concentrated hydrochloric acid (1·0 c.c.) for 1 hr. On cooling, the *product* crystallised. It was separated, washed with a little ethanol, and dried, then having m. p. 177—178° (14 g., 65%) unchanged after recrystallisation from ethanol (Found: C, 74·1; H, 6·15; N, 6·0. $C_{29}H_{30}N_2O_4$ requires C, 74·0; H, 6·45; N, 5·95%).

5,5'-*Dibromo*-3,3',4,4'-*tetramethyldipyrromethane*.—Dibenzyl 3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (8·6 g.) was dissolved in methanol (100 c.c.), and methanol-washed Raney nickel (5 g.) was added. The mixture was hydrogenated at 100—110°/140 atm. for 2 hr., after which the catalyst and solvent were removed. The residual oil was dissolved in glacial acetic acid (40 c.c.) and treated with bromine (3·0 c.c.) in glacial acetic acid (10 c.c.) for 2 hr. at room temperature. The precipitated hydrobromide (5·0 g., 60%) was separated, washed with light petroleum, and dried. The free base was prepared by treating a chloroform solution of the hydrobromide with ammonia. It crystallised from chloroform–methanol in orange needles, m. p. 197—198° (lit.,[7] 198°).

The cobalt complex was prepared by treating the hydrobromide (1·0 g.) in ethanol (50 c.c.) and aqueous ammonia (0·5 c.c.; *d* 0·88) with a saturated solution (2·5 c.c.) of cobalt acetate in aqueous ammonia. After removal of the solvent the residue was dissolved in chloroform, washed with water, dried, and recovered. The cobalt complex (720 mg.) crystallised from chloroform–methanol as green needles (Found: C, 40·2; H, 3·25; N, 7·5. $C_{26}H_{26}Br_4CoN_4$ requires C, 40·4; H, 3·35; N, 7·25%), $\lambda_{max.}$ (in $CHCl_3$) 240, 319, 378, 515, 710, and 770 mμ (log ε 4·4, 3·82, 4·9, 3·55, 2·8, and 2·93 respectively).

Palladium Bi-(5'-*bromo*-3,3'-*diethyl*-4,4'-*dimethyldipyrromethen*-5-*yl*) (IV; R = Et).—5,5'-Dibromo-3,3'-diethyl-4,4'-dimethyldipyrromethene[2] (7·5 g.) and 3% palladium–strontium carbonate (50 g.) were mixed in ethanol (1200 c.c.) and heated under reflux for 20 hr. The catalyst was separated and washed with chloroform, and the solvent was removed from the combined filtrate and washings under reduced pressure. The residue was chromatographed in chloroform on a column of alumina (Spence type H; 50 × 3 cm.), the product being eluted as a deep red solution. After evaporation the product crystallised from chloroform–methanol in glistening black needles[3] (3·8 g., 53·5%), m. p. >300° (Found: C, 50·1; H, 4·65; N, 7·6. Calc. for $C_{30}H_{34}Br_2N_4Pd$: C, 50·2; H, 4·8; N, 7·8%), $\lambda_{max.}$ (in $CHCl_3$) 297, 437, 533, and 910 mμ (log ε 4·03, 4·58, 4·20, and 3·90 respectively).

Palladium Bi-(5'-*bromo*-3,3',4,4'-*tetramethyldipyrromethen*-5-*yl*) (IV; R = Me) (40·5%) was prepared by a similar method from 5,5'-dibromo-3,3',4,4'-tetramethyldipyrromethene[2] and crystallised from chloroform–methanol in glistening black needles, m. p. >300° (Found: C, 47·5; H, 4·05; N, 8·25; Br, 24·5. $C_{26}H_{26}Br_2N_4Pd$ requires C, 47·25; H, 3·95; N, 8·5; Br, 24·2%).

Palladium Bi-[5'-*bromo*-3,3'-*di*-(2-*ethoxycarbonylethyl*)-4,4'-*dimethyldipyrromethen*-5-*yl*] (IV; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) (with K. B. SHAW).—5,5'-Dibromo-3,3'-di-(2''-ethoxycarbonylethyl)-4,4'-dimethyldipyrromethene[2] (1·5 g.) was caused to react similarly with 3% palladium–strontium carbonate (8 g.). The *product* crystallised from chloroform–methanol in black needles, m. p. 113—115° (450 mg., 31%) (Found: C, 50·1; H, 4·85; N, 5·35. $C_{42}H_{48}Br_2N_4O_8Pd$ requires C, 50·2; H, 4·8; N, 5·6%), $\lambda_{max.}$ (in $CHCl_3$) 296, 435, 532, and 905 mμ (log ε 4·52, 4·61, 4·29, and 3·95 respectively).

Bi-(5'-*bromo*-3,3'-*diethyl*-4,4'-*dimethyldipyrromethen*-5-*yl*) (VI; R = Br).—A solution of palladium bi-(5'-bromo-3,3'-diethyl-4,4'-dimethyldipyrromethen-5-yl) (1·0 g.) in chloroform (150 c.c.) was shaken with 48% hydrobromic acid (8 c.c.). The resulting solution was washed with water, dilute ammonia solution, and finally water. After removal of solvent from the chloroform solution, the product crystallised from chloroform–methanol in green needles (0·6 g., 71%) (Found: C, 58·4; H, 5·7; Br, 26·1. $C_{30}H_{36}Br_2N_4$ requires C, 58·8; H, 5·9; Br, 26·1%).

Copper Bi-(5'-*bromo*-3,3'-*diethyl*-4,4'-*dimethyldipyrromethen*-5-*yl*).—A solution of cupric acetate (1·0 g.) in aqueous ammonia (3·0 c.c.; *d* 0·88) was added to a solution of bi-(5'-bromo-3,3'-diethyl-4,4'-dimethyldipyrromethen-5-yl) (1·0 g.) in dioxan (100 c.c.). The resulting

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[7] Fischer and Walach, *Annalen*, 1926, **450**, 109.

solution was heated on the water-bath for 30 min. and water (100 c.c.) was added. The precipitated solid was separated and washed with water and then methanol and finally dried. The *product* crystallised from chloroform–methanol in green rods (0·77 g., 70%) (Found: C, 53·4; H, 5·1; N, 8·35. $C_{30}H_{34}Br_2CuN_4$ requires C, 53·45; H, 5·1; N, 8·3%).

Cobalt bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (65%) was prepared by a similar method, using a solution of cobalt acetate in ammonia, and crystallised from chloroform–methanol in green prisms (Found: C, 54·0; H, 4·7; N, 8·2. $C_{30}H_{34}Br_2CoN_4$ requires C, 53·85; H, 5·1; N, 8·35%).

Bi-[5′-bromo-3,3′-di-(2-ethoxycarbonylethyl)-4,4′-dimethyldipyrromethen-5-yl] (with K. B. Shaw).—The corresponding palladium complex (400 mg.; above) was dissolved in acetone (40 c.c.), and 48% hydrobromic acid (4 c.c.) was added. The resulting green solution was poured into water (150 c.c.), rendered alkaline with aqueous ammonia, and extracted with chloroform (6 × 50 c.c.) until the aqueous layer was colourless. The combined chloroform extracts were dried and the solvent was removed. The residual *product* crystallised from chloroform–methanol in green needles (300 mg., 83%), m. p. 195—197° (Found: C, 55·7; H, 5·3; N, 6·35. $C_{42}H_{50}Br_2N_4O_8$ requires C, 56·1; H, 5·6; N, 6·25%), $\lambda_{\max}$ (in $CHCl_3$) 272, 333, and 650 mμ (log ε 4·52, 4·18, and 4·92 respectively) with an inflection at 595 mμ (log ε 4·75).

Palladium 3,7,13,17-Tetraethyl-2,8,12,18-tetramethylcorrole Hydroxide.—Palladium bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (2·0 g.) in ethanol (800 c.c.) was heated under reflux for 20 min., then 34% aqueous formaldehyde (80 c.c.) was added. After a further 20 minutes' heating, concentrated hydrochloric acid (16·0 c.c.) was added dropwise in 5 min. and heating was continued for a further 8 hr. The crystals which were formed on cooling were separated, dissolved in chloroform, washed with dilute ammonia, and chromatographed in chloroform on alumina (Spence type H; 50 × 3 cm.). Elution of the product was followed by means of a hand spectroscope. After removal of the solvent, the *product* (300 mg., 19%) crystallised from chloroform–methanol in black rods, m. p. $\nless$300° (Found: C, 63·0, 63·1; H, 6·1, 6·2; N, 9·45, 9·25. $C_{31}H_{36}N_4OPd$ requires C, 63·3; H, 6·0; N, 9·55%), $\lambda_{\max}$ (in $CHCl_3$) 232, 319, 385, 515, 552, 620, and 670 mμ (log ε 4·39, 3·78, 4·81, 3·93, 4·15, 3·78, and 3·99 respectively).

Palladium 3,7,12,17-Tetraethyl-2,8,13,18-tetramethylcorrole Hydroxide.—5,5′-Dibromo-3,3′-diethyl-4,4′-dimethyldipyrromethene[2] (1·5 g.), 5-bromo-3,4′-diethyl-3′4,5′-trimethyldipyrromethene[2] (3·0 g.) and 3% palladium–strontium carbonate (25 g.) were mixed in ethanol (900 c.c.) and heated under reflux for 20 hr. The solid was separated and washed repeatedly with hot chloroform (see below for treatment of the filtrate). The combined chloroform washings were washed with dilute aqueous ammonia and chromatographed on alumina (Spence type H; 50 × 3 cm.). Elution of the product was followed by means of a hand spectroscope. After removal of the solvent the *product* (90 mg., 4%) crystallised from chloroform–methanol in black rods, m. p. $\nless$300° (Found: C, 63·5; H, 6·3; N, 9·85. $C_{31}H_{36}N_4OPd$ requires C, 63·3; H, 6·0; N, 9·55%), $\lambda_{\max}$ (in $CHCl_3$) 232, 320, 383, 515, 551, 620, and 665 mμ (log ε 4·41, 3·75, 4·80, 3·95, 4·16, 3·76, and 3·96 respectively). After removal of solvent from the filtrate (above), the residue was dissolved in chloroform, washed with dilute aqueous ammonia, and chromatographed on alumina (Spence type H; 30 × 1 cm.). Palladium bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl), identical with that described above, was eluted first followed by palladium ætioporphyrin I.

Bi-(3,3′-diethyl-5′-hydroxymethyl-4,4′-dimethyldipyrromethen-5-yl) (VI; R = $CH_2{\cdot}OH$).—Cobalt bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (240 mg.) in ethanol (100 c.c.) was heated under reflux, aqueous formaldehyde (5·0 c.c.) was added, and heating continued for a further 20 min. Concentrated hydrochloric acid (2·0 c.c.) was then added dropwise in 5 min. and heating was continued for a further 6 hr. The crystalline solid which was formed on cooling was separated, washed with methanol, dissolved in chloroform, washed with dilute ammonia solution, and chromatographed on alumina (Spence type H; 30 × 1 cm.), the product being eluted as a red solution. After removal of solvent, the *product* (100 mg., 54%) crystallised from chloroform–methanol in red needles (Found: C, 74·4; H, 8·6; N, 11·0. $C_{32}H_{42}N_4O_2$ requires C, 74·7; H, 8·25; N, 11·0%).

Cupric 3,7,13,17-Tetraethyl-2,8,12,18-tetramethylcorrole Hydroxide (II; M = Cu, R = Et, R′ = Me).—(i) Cupric bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (500 mg.) in ethanol (200 c.c.) was heated under reflux, aqueous formaldehyde (20 c.c.) was added, and heating continued for a further 20 min. Concentrated hydrochloric acid (4 c.c.) was added and heating was continued for a further 6 hr. Aqueous ammonia (5·0 c.c.; *d* 0·88) was added and the volume of the solution was reduced to 20 c.c., then water (100 c.c.) was added. The precipitated solid was separated, washed with water and then with methanol, and dried. The product was chromatographed in chloroform on alumina (Spence type H; 50 × 3 cm.), elution of the product being followed by means of a hand spectroscope. After removal of the solvent the *product* (40 mg., 10%) crystallised from chloroform–methanol in black rods (Found: C, 68·0; H, 6·9; N, 10·45. $C_{31}H_{36}CuN_4O$ requires C, 68·25; H, 6·65; N, 10·3%), $\lambda_{max.}$ (in $CHCl_3$) 409, 436, 505, 540, 585, and 625 mμ (log ε 4·66, 4·69, 3·9, 4·03, 3·89, and 4·31 respectively).

(ii) The above experiment was repeated but before addition of ammonia, the solution was divided into two equal portions which were treated as follows: Part A was worked up as described above to give the cupric corrole derivative (23 mg., 11·5%). Part B was concentrated to *ca.* 20 c.c. and water (100 c.c.) was added. The precipitated solid was separated, washed with water and then methanol, and dried. The solid was dissolved in chloroform, washed with dilute aqueous ammonia, and chromatographed on alumina (30 × 1 cm.), the product being eluted as a red solution. After removal of solvent, bi-(5′-hydroxymethyl-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (VI; R = CH_2·OH) (92 mg., 50%) crystallised from chloroform–methanol in red needles (Found: C, 74·6; H, 8·1; N, 11·1%).

Cobaltous 3,7,13,17-*tetraethyl*-2,8,12,18-*tetramethylcorrole hydroxide* (II; M = Co, R = Et, R′ = Me) (5%) was prepared similarly from cobalt bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) and crystallised from chloroform–methanol as black rods (Found: C, 69·3; H, 7·1; N, 10·05. $C_{31}H_{36}CoN_4O$ requires C, 69·0; H, 6·75; N, 10·4%), $\lambda_{max.}$ (in $CHCl_3$) 400, 443, 500, 535, 570, and 620 mμ (log ε 4·61, 4·59, 3·83, 4·03, 3·90, and 4·08 respectively).

Bi-(3,3′-*diethyl*-5′-*formyloxy*-4,4′-*dimethyldipyrromethen*-5-*yl*) (VI; R = O·CHO).—A mixture of bi-(5′-bromo-3,3′-diethyl-4,4′-dimethyldipyrromethen-5-yl) (150 mg.), 90% formic acid (10 c.c.), and sodium formate (500 mg.) was heated under reflux for 1 hr. and the resulting solution was poured into water (100 c.c.). The mixture was neutralised with sodium hydroxide solution and extracted with chloroform. After removal of the solvent from the dried chloroform extracts the product (50 mg., 37%) crystallised from chloroform–methanol in red-brown needles (Found: C, 70·9; H, 7·35; N, 10·2. $C_{32}H_{38}N_4O_4$ requires C, 70·8; H, 7·05; N, 10·3%).

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