602. *The Preparation of Some Cobaltic Porphyrin Complexes.*

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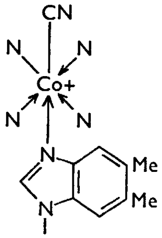
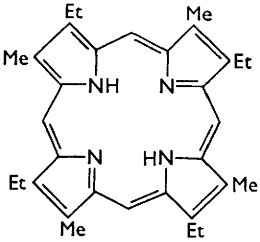
Crystalline cobaltic ætioporphyrin I complexes of three types have been prepared and their characteristic visible spectra and some chemical properties are recorded. The cobaltichromes are non-ionic and contain co-ordinated nitrogenous bases; the second type of complex contains the cobalt in the cation, and the third type contains the cobalt in the anion.

STUDIES of the physical and chemical properties of vitamin B_{12} (partial formula I; all metalloporphyrins will be represented in this abbreviated manner in this paper) have shown that it is an octahedral cobaltic complex of a modified porphyrin ring system.[1]

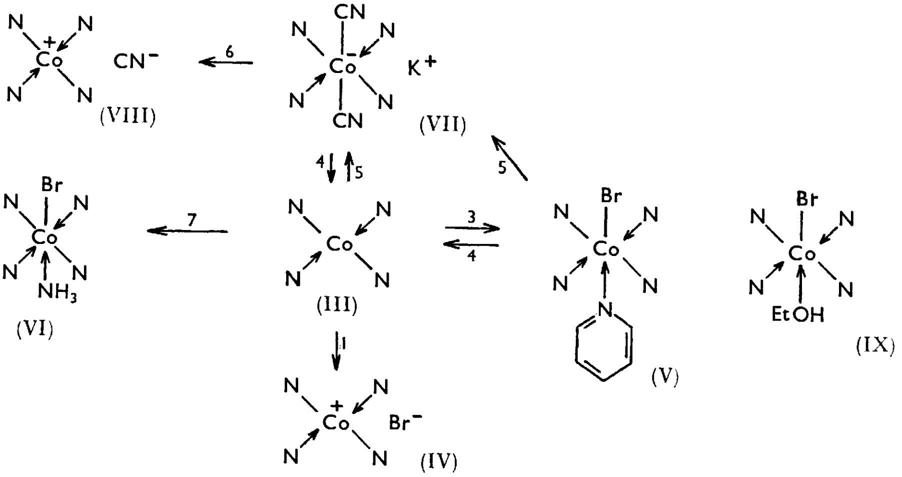


(I)



(II)

Before this, little was known [2] of the properties of cobaltic porphyrins but in 1953 Petrow and his co-workers [3] published an extensive study, largely spectroscopic, of the cobaltic derivatives of protoporphyrin and hæmatoporphyrin. As most of the products described in that paper were obtained in solution only, we have carried out a somewhat similar investigation of the cobalt derivatives of ætioporphyrin I (II) in view of its ready accessibility.[4] The planar cobaltous derivative (III) was readily obtained from the porphyrin by the action of cobaltous acetate in acetic acid, and with hydrogen bromide in chloroform–methanol it gave [ætioporphyrin I cobalt(III)] bromide (IV). On the other



Reagents: 1, HBr; 2, pyridine; 3, HBr, pyridine; 4, H_2–Pt; 5, KCN; 6, $CH_3{\cdot}CO_2H$; 7, HBr, NH_3.

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[1] Diehl, Vander Haar, and Sealock, *J. Amer. Chem. Soc.*, 1950, **72**, 5312; Folkers, Wolf, *et al.*, *ibid.*, 1951, **73**, 3569; *Vitamins and Hormones*, 1954, **12**, 32.

[2] Laidlaw, *J. Physiol.*, 1904, **31**, 464; Hill, *Biochem. J.*, 1925, **19**, 241; Holden, *Austral. J. Exp. Biol. Med. Sci.*, 1941, **19**, 89; Taylor, *J. Biol. Chem.*, 1940, **135**, 570.

[3] McConnel, Overell, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1953, **5**, 179.

[4] McEwen, *J. Amer. Chem. Soc.*, 1946, **68**, 711.

hand, when pyridine was added to the reaction mixture, the cobalt assumed the octahedra form and there was obtained ætioporphyrin I pyridinobromocobalt(III) (V), a typical "cobaltichrome," a term used by Petrow's school as the generic name for co-ordination compounds derived from cobaltiporphyrins and nitrogenous ligands. The same compound was formed by reaction of the salt (IV) with pyridine. Substitution of ammonia for pyridine in the above reaction gave the ammino-derivative (VI). Octahedral complexes from benzimidazoles and purines analogous to (V) could be detected only in solution; attempts to isolate crystalline derivatives did not yield pure compounds, and it was evident that the base was easily detached during crystallisation. When cobaltous ætioporphyrin I was treated with an excess of potassium cyanide, a third type of cobaltic porphyrin complex (VII), in which the cobalt was present as part of the anion, was obtained. This compound was also prepared from the pyridino-compound (V) by the action of excess of cyanide and, like the pyridine complex, it reverted to the cobaltous porphyrin derivative on hydrogenation over platinum. Although the type of complex corresponding to vitamin B_{12}, *i.e.*, the cyanide corresponding to (V), has not been isolated, a cobaltic complex (VIII) containing ionic cyanide was obtained by the action of acetic acid on the dicyano-complex (VII). A dicyanide corresponding to (VII) from cobaltous ætiochlorin I was detected in solution (Fig. 3) but not isolated.

FIG. 1. *Absorption of* (*A*) *cobaltous ætioporphyrin and* (*B*) *ætioporphyrin I pyridinobromocobalt* (10 mg. per 100 c.c. of $CHCl_3$).

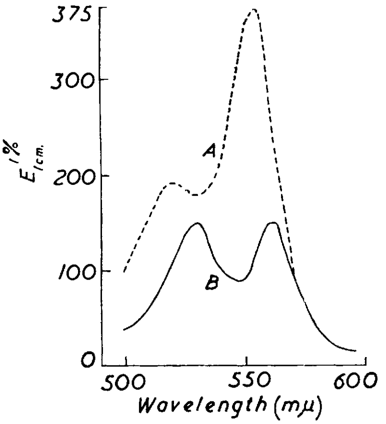
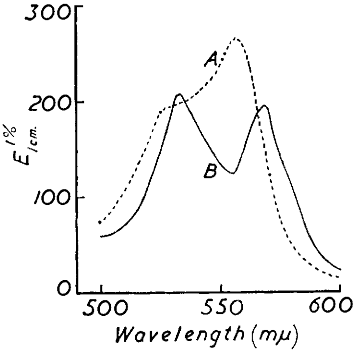


FIG. 2. *Absorption of* (*A*) [*ætioporphyrin I cobalt*] *bromide and* (*B*) *the same salt plus benzimidazole* (10 mg. per 100 c.c. of $CHCl_3$).



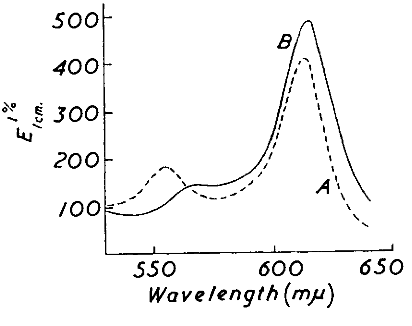


FIG. 3. *Absorption of* (*A*) *cobaltous ætiochlorin I in* $CHCl_3$ (10 mg./100 c.c.) *and* (*B*) *the same plus* KCN *in* 1 : 1 $CHCl_3$–EtOH.

As described by Petrow,[3] these cobalt porphyrin complexes can be differentiated by their visible spectra and the changes can be followed conveniently by the hand spectroscope. A chloroform solution of cobaltous ætioporphyrin shows the typical two-banded spectrum, in which the longer-wavelength band has the higher intensity (Fig. 1) whereas the octahedral cobaltic complexes of type (V) show two bands of approximately equal intensity.

The cobaltic dicyanide (VII) on the other hand shows only a single band, and the cobaltic bromide (IV) in chloroform shows a single band with an inflection (Fig. 2). In ethanolic solution the spectrum of the bromide (IV) comprises two bands of nearly equal intensity which is attributed to co-ordination with ethanol to give the complex (IX). A related compound containing co-ordinated water was obtained from cobaltous coproporphyrin I tetramethyl ester with hydrobromic acid.

EXPERIMENTAL

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

Ætioporphyrin I Pyridinobromocobalt(III) (V).—(i) Cobaltous ætioporphyrin I [5] (800 mg.) was dissolved in pyridine (160 c.c.), 48% hydrobromic acid (40 c.c.) was added, and the mixture aerated on the steam-bath for 45 min.; the solution was then poured into water (*ca.* 1 l.) and extracted with chloroform (5 × 100 c.c.) until the chloroform layer showed no metal porphyrin bands. The combined chloroform extract was washed with water, dried ($MgSO_4$), and evaporated to dryness, traces of pyridine being removed under reduced pressure. The residual *complex* crystallised from chloroform–light petroleum as purple plates (850 mg., 82%), decomp. >200° (Found: C, 64·0; H, 6·25; N, 9·9. $C_{37}H_{41}BrCoN_5$ requires C, 63·95; H, 5·95; N, 10·1%), $\lambda_{max.}$ at 232, 348, 417, 530, and 561 mμ (log ε 4·66, 4·35, 5·06, 3·98, and 3·99 respectively).

(ii) [Ætioporphyrin I cobalt(III)] bromide (100 mg.) was dissolved in pyridine (10 c.c.) and heated on the steam-bath for 30 min. The pyridine was removed under reduced pressure and the residue crystallised from chloroform–light petroleum, forming purple plates (110 mg., 97%) (Found: N, 9·95%). The light absorption was similar to that of the product of the previous experiment.

Catalytic Reduction of Ætioporphyrin I Pyridinobromocobalt(III).—The complex (200 mg.) was dissolved in methanol (75 c.c.) and hydrogenated at atmospheric pressure by using Adams catalyst. When the liquid had become nearly colourless the product separated; it crystallised from chloroform–methanol as purple needles (130 mg., 84%) (Found: C, 71·6; H, 6·35; N, 10·25. Calc. for $C_{32}H_{36}CoN_4$: C, 71·75; H, 6·25; N, 10·45%), $\lambda_{max.}$ at 266, 326, 392, 519, and 553 mμ (log ε 4·17, 4·21, 5·23, 4·00, and 4·30 respectively).

Potassium [*Ætioporphyrin I Dicyanocobaltate*(III)].—(i) To a solution of potassium cyanide (200 mg.) in hot methanol (60 c.c.), was added a solution of cobaltous ætioporphyrin I (300 mg.) in hot chloroform (60 c.c.). The mixture was kept for 30 min. with occasional shaking, then the excess of potassium cyanide was removed by filtration and the filtrate evaporated to dryness. The residual *salt* crystallised from ethanol–light petroleum as purple needles (300 mg., 86%) (Found: N, 13·6. $C_{34}H_{36}CoKN_6$ requires N, 13·4%), $\lambda_{max.}$ 214, 233, 279, 344, 412, 436, and 550 mμ (log ε 4·67, 4·64, 3·92, 4·51, 4·85, 5·02, and 4·12 respectively).

(ii) To the pyridino-complex (V) (400 mg.) in methanol (25 c.c.) was added potassium cyanide (1 g.), and the solution kept overnight at room temperature. Water (50 c.c.) was then added and the precipitated complex separated, washed with water, and dried. It crystallised from ethanol–light petroleum as purple needles (200 mg., 56%) (Found: N, 13·3%). The light absorption was identical with that of the product from the foregoing experiment.

Reduction of Potassium [*Ætioporphyrin I Dicyanocobaltate*(III)].—The salt (30 mg.) in methanol (25 c.c.) was hydrogenated by using Adams catalyst. The solution rapidly became colourless as the cobaltous ætioporphyrin I was precipitated. This was separated, washed with methanol, and crystallised from chloroform–methanol; it formed red needles (23 mg., 90%) (Found: N, 10·2. Calc. for $C_{32}H_{36}CoN_4$: N, 10·45%). The light absorption was similar to that of the product formed by hydrogenation of ætioporphyrin I pyridinobromocobalt(III) (above).

[*Ætioporphyrin I Cobalt*(III)] *Bromide*.—To cobaltous ætioporphyrin I (150 mg.) in chloroform (25 c.c.) and methanol (25 c.c.) was added 48% hydrobromic acid (0·5 c.c.), and the solution was kept for 2 hr. with frequent shaking. Chloroform (25 c.c.) was then added, the solution washed with water (100 c.c.), and the chloroform layer dried ($MgSO_4$) and evaporated to dryness. The dark blue residual *complex* crystallised from ethanol–light petroleum as purple plates (125 mg., 72%) (Found: C, 62·5; H, 6·0; N, 9·05. $C_{32}H_{36}BrCoN_4$ requires C, 62·45; H, 5·9;

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[5] Fischer and Newmann, *Annalen*, 1932, **494**, 225.

N, 9·1%), $\lambda_{\text{max.}}$ at 264, 412, and 557 mμ (log ε 4·39, 4·92, and 4·22 respectively), with inflections at 370 and 530 mμ (log ε 4·57 and 4·09 respectively), (in EtOH) 231, 337, 410, 525, 558 mμ (log ε 4·68, 4·34, 5·22, 4·06, and 4·26 respectively).

Ætioporphyrin I Benzimidazolobromocobalt(III).—(i) Benzimidazole (10·6 mg.) was added to a solution of [ætioporphyrin I cobalt] bromide (10·5 mg.) in chloroform (100 c.c.), and the mixture kept for 30 min. with occasional shaking. The light absorption max. at 234, 273, 353, 424, 535, and 569 mμ ($E_{1\,\text{cm.}}^{1\%}$, 927, 577, 514, 2145, 189, and 180 respectively) indicated that the base was incorporated in the co-ordination complex.

(ii) Cobaltous ætioporphyrin I (200 mg.) was dissolved in chloroform (30 c.c.) and methanol (30 c.c.). Benzimidazole (200 mg.) and 48% hydrobromic acid (0·5 c.c.) were then added and the mixture kept for 30 min. with occasional shaking. The solution was filtered and chloroform (30 c.c.) added to the filtrate which was washed with water (3 × 100 c.c.) and dried. On addition of warm light petroleum, a dark blue amorphous solid (200 mg.) separated (Found: C, 63·5; H, 6·35; N, 12·0; Br, 10·85. $C_{39}H_{42}BrCoN_6$ requires C, 63·85; H, 5·75; N, 11·45; Br, 10·9%). A solution of this *product* had the same visible spectrum as the previous preparation. The solid decomposed on attempted crystallisation.

Ætioporphyrin I Amminobromocobalt(III).—48% Hydrobromic acid (1 c.c.) was added to cobaltous ætioporphyrin I (300 mg.) in chloroform (60 c.c.)–methanol (50 c.c.), and the solution kept for 2 hr. with occasional shaking. Aqueous ammonia (10 c.c.; *d* 0·88) was then added and the mixture set aside for a further 1 hr., then washed with water (3 × 100 c.c.), and the chloroform layer was dried ($MgSO_4$) and evaporated to dryness. The residual *complex* crystallised from chloroform–light petroleum and formed purple needles (300 mg., 85%) (Found: C, 60·7; H, 6·25; N, 10·9. $C_{32}H_{39}BrCoN_5$ requires C, 60·75; H, 6·2; N, 11·1%), $\lambda_{\text{max.}}$ 233, 345, 415, 529, and 561 mμ (log ε 4·67, 4·42, 5·23, 4·10, and 4·11 respectively), inflection at 275 mμ (log ε 4·23).

[*Ætioporphyrin I Cobalt*(III)] *Cyanide.*—Potassium [ætioporphyrin I dicyanocobaltate(III)] (200 mg.) in glacial acetic acid (8 c.c.) was warmed on the steam-bath for 90 min. On cooling, the *product* was precipitated by addition of light petroleum, separated, washed with light petroleum and crystallised from ethanol–light petroleum as red needles (160 mg., 89%) (Found: C, 70·2; H, 6·25; N, 12·4. $C_{33}H_{36}CoN_5$ requires C, 70·55; H, 6·45; N, 12·45%), $\lambda_{\text{max.}}$ 235, 279, 342, 412, 528, and 559 mμ (log ε 4·63, 4·03, 4·44, 5·11, 4·05, and 4·21 respectively).

Cobaltous Ætiochlorin I.—Ætiochlorin I was prepared by reduction of ætioporphyrin I as described by Eisner [6] for ætiochlorin II. The chlorin (300 mg.) was continuously extracted from a thimble with acetic acid (25 c.c.) in the presence of cobaltous acetate (1 g.). After cooling, the *product* was filtered off, washed with water, methanol, and ether, and crystallised from chloroform–methanol as black needles (250 mg., 75%) (Found: C, 71·2; H, 7·1; N, 10·6. $C_{32}H_{38}CoN_4$ requires C, 71·45; H, 7·1; N, 10·4%), $\lambda_{\text{max.}}$ 270, 392, 485, 518, 554, and 615 mμ (log ε 3·23, 5·01, 3·66, 3·80, 3·99, and 4·33 respectively).

Potassium [*Ætiochlorin I Dicyanocobaltate*(III)].—Cobaltous ætiochlorin I (11·0 mg.) was dissolved in 1 : 1 chloroform–ethanol (100 c.c.). Excess of potassium cyanide was added to the solution which was kept for 2 hr. with occasional shaking and then examined spectroscopically. Maxima were found at 231, 413, 500, 528, 569, and 615 mμ ($E_{1\,\text{cm.}}^{1\%}$ 799, 1189, 808, 84·9, 128, and 446 respectively) with an inflection at 320 mμ ($E_{1\,\text{cm.}}^{1\%}$ 264).

Coproporphyrin I Tetramethyl Ester Aquobromocobalt(III).—This was prepared (82%) from cobaltous coproporphyrin I tetramethyl ester and hydrobromic acid in an analogous manner to that used for the ætioporphyrin I bromide (above). The *aquo-complex* crystallised from chloroform–ethanol as mauve needles (Found: C, 55·6; H, 5·3; N, 6·15. $C_{40}H_{46}BrCoN_4O_9$ requires C, 55·5; H, 5·35; N, 6·45%), $\lambda_{\text{max.}}$ 262, 414, 532, and 561 mμ (log ε 4·38, 5·03, 4·11, and 4·18 respectively).

5-*Bromo*-3,4′-*di*-(2′-*methoxycarbonylethyl*)-3′,4,5′-*trimethyldipyrromethene Hydrobromide.*—t-Butyl 3,2′-methoxycarbonylethyl-2,4-dimethylpyrrole-2-carboxylate (5·6 g.) in glacial acetic acid (25 c.c.) was treated with bromine (2·4 c.c.). After the vigorous reaction had subsided, the mixture was kept for 15 min., then ethyl acetate (50 c.c.) was added. The product separated gradually and crystallised from chloroform–methanol as orange plates (2 g., 35%).

The above methene hydrobromide (500 mg.) was dissolved in boiling ethanol (20 c.c.) containing aqueous ammonia (0·5 c.c.; *d* 0·88) and a saturated solution of cobaltous acetate in aqueous ammonia (2·5 c.c.) was added followed by water (20 c.c.). On cooling, the *cobalt complex* crystallised; it recrystallised as green prisms (300 mg., 66%), m. p. 154—155°, from

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[6] Eisner, *J.*, 1957, 3461.

chloroform–methanol (Found: C, 51·7; H, 5·5; N, 6·2. $C_{40}H_{48}Br_2CoN_4O_8$ requires C, 51·5; H, 5·2; N, 6·0%), $\lambda_{max.}$ at 373 and 507 mμ (log ε 4·21 and 5·09 respectively).

Coproporphyrin I Tetramethyl Ester (with E. BULLOCK).—The above methene hydrobromide (10 g.) was thoroughly ground with succinic acid (50 g.) and dried over sodium hydroxide *in vacuo* for 24 hr. The mixture was fused at 195—205° for 1 hr., and after cooling, the succinic acid was washed out of the melt with hot water (1·5 l.). The washings were extracted once with chloroform (200 c.c.), and the material so extracted was combined with the solid residue from the fusion. The combined solids were dried and esterified with methanolic hydrogen chloride (5% w/w) overnight. The porphyrin ester was isolated in the usual way and recrystallised from chloroform–methanol, then having m. p. 245—247° (lit.[7] 248—252°) (1·90 g., 27%).

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[7] Fischer and Berg, *Annalen*, 1930, **482**, 213.