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Chemical behaviour of dicyanocob(III)yrinic acid heptamethyl ester and cob(I)yrinic acid heptamethyl ester in some preparative experiments

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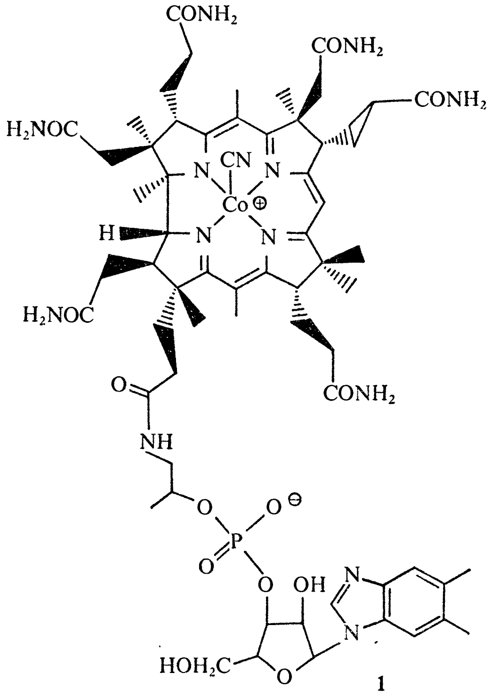
Preparations of C10 acetate, trifluoroacetate, and chloro derivatives of dicyanocobyrinic acid heptamethyl ester ('cobester') are described. The nature and properties of intermediates in the synthesis of the 10-chloro derivative are discussed, and the electronic absorption spectra of the products are presented.

Most publications dealing with the chemistry of vitamin B_{12} have employed the complete molecule, cyanocobalamin (**1**); in the work reported herein, we have chosen the less complex dicyanocobyrinic acid heptamethyl ester (**2**), called 'cobester'. We are grateful to Professor Eschenmoser for supplying details, in advance of publication, for the conversion of cyanocobalamin into cobester (**2**) (Werthemann 1968).



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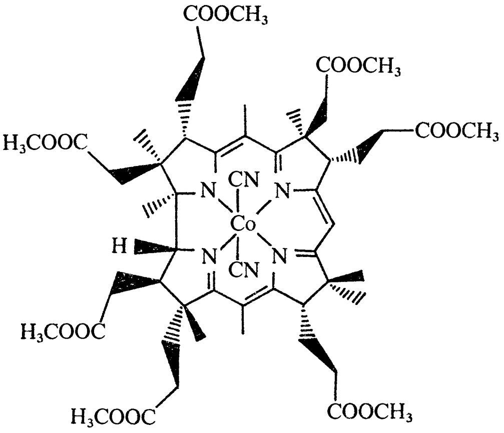

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Several advantages are inherent in the use of cobester in place of cyanocobalamin:

(i) The analytical situation is much easier and clearer.

(ii) Cobester is considerably more soluble than cyanocobalamin in several non-polar solvents.

(iii) Conversion of the amide groups, with their reactive hydrogen atoms, into methyl ester functions decreases the possibility of a number of unwanted side reactions. Consequently our present and future investigations will concentrate on what in our view is the most important part of the molecule, namely the chromophoric system.

Many reactions of cobester are associated with a change of valency at the complex-bound cobalt atom. This behaviour is easily explained by postulating that the lowest unoccupied molecular orbital is one of the d orbitals of the metal atom, with the consequence that outer influences on the molecule are absorbed through a change in oxidation state. Such valency alterations are dramatically demonstrated in the electronic absorption spectra, and can be monitored by observing the changes in colour of the solution.

Curve *a* (figure 1) corresponds to dicyanocob(III)ester. Substitution of one of the two axial cyanide ligands with another group causes a hypsochromic shift of the absorption maximum, giving curve *b*. Reduction of the central atom with Pt/H$_2$ under acidic conditions to the cobalt(II) complex (curve *c*) and finally with sodium borohydride under alkaline conditions to the cobalt(I) complex (curve *d*) provides an impressive change in the light absorption (Pratt 1972*a*, *b*, *c*).

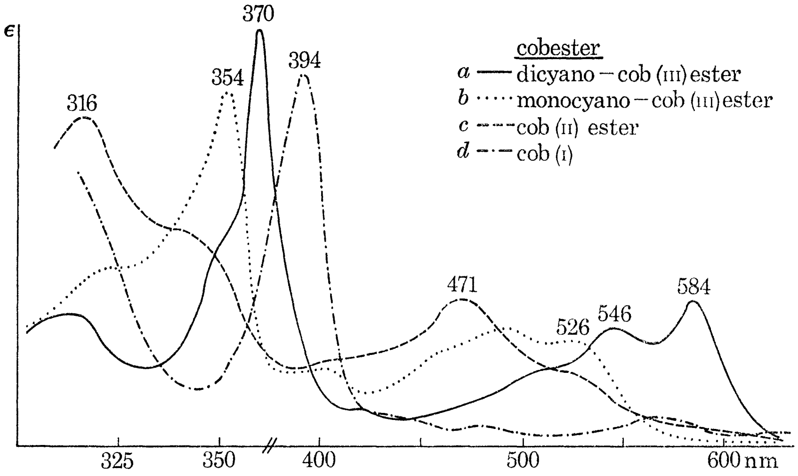
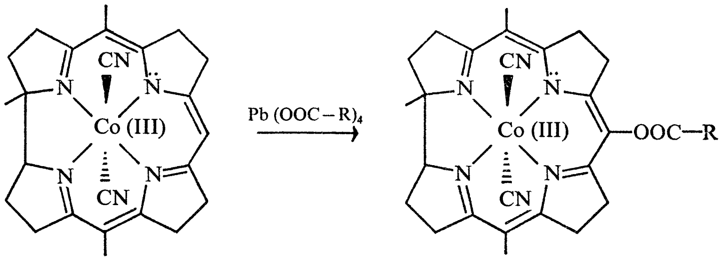


FIGURE 1

Like cyanocob(I)alamin, the reactivity of cob(I)ester is distinguished by its extreme reactivity towards oxygen. Reoxidation in the absence of cyanide affords the cobalt(II) species; after addition of cyanide ions the cobalt(III) complex is rapidly and quantitatively produced. However, as will be seen later, the presence of electron-withdrawing substituents at C10 stabilizes the lower oxidation states of the cobalt atom.

The reactivity of the macrocyclic ligand of the cobyric acid ester complex is mainly limited to two positions, namely C8 and C10. Electrophilic substitution (e.g. halogenation, nitration, nitrosation) has been shown by many authors to take place at C10 (Bonnett *et al.* 1957). We have confirmed these observations in the case of cobester; reaction of cobester (**2**) with lead tetra-acetate or lead tetrakis(trifluoracetate) affords, as expected, the C10 acetoxy or C10 trifluoroacetoxy derivative. The C10 acetate was prepared as a potential source of the C10-hydroxy compound which, in alkaline solution, should exist as a mesomeric anion. One of the resonance structures has the constitution of a C10-oxo-cob(I)complex, which has the generic structure corresponding to the (unisolated) intermediate of electrophilic substitution at C10. Moreover, reduction of the C10-hydroxy-cob(III)ester should be facilitated by its electronegative C10 substituent; this is in agreement with the stabilization of the lower cobalt oxidation states mentioned earlier.



2 $R=CH_3$ or CF_3 **3**

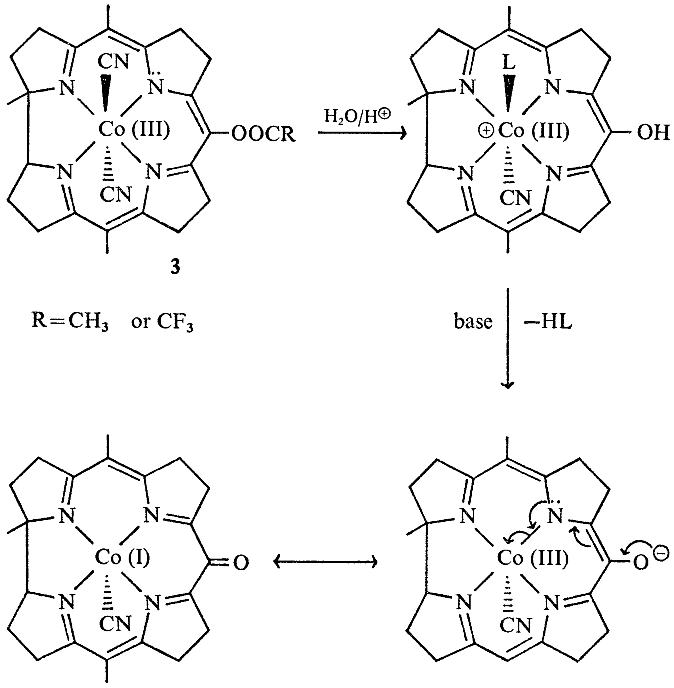
Figure 2

After cleavage of the acetate group it is our aim to establish the constitution of the 10-hydroxy-cob(III)ester by spectroscopic methods, and to correlate the chemical properties of this new C10 substituted derivative with its electronic configuration.

Treatment of a solution of cobester in carbon tetrachloride or methanol with a 15- to 20-fold excess of chlorine accomplishes the instantaneous decoloration of the solution. With carbon tetrachloride as solvent, white needles appear after a few seconds. In solution, the chlorination product is quite stable, and especially so at low temperatures or in presence of excess chlorine.

Mild catalytic hydrogenation of the colourless chlorination solution rapidly produces a coloured substance which after treatment with potassium cyanide was shown to be identical with C10-chlorodicyanocob(III)ester (**4**) earlier obtained by treatment of **2** with chloramin T.

Following the normal mechanism for electrophilic substitution at C10 of cobester it is possible to formulate an intermediate product (A) which possesses interrupted conjugation at this position. Elimination of a proton regenerates the chromophoric system, leading to the C10-chloro derivative (**4**a). Whether or not exchange of an axial ligand also takes place remains an



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$R=CH_3$ or CF_3

Figure 3

open question, but this is not in our view an important factor in this reaction sequence. Immediate further treatment of the monochloro intermediate with chlorine can, following the mechanism outlined above, afford a 10,10-dichloro derivative (**5**). This intermediate di-chloro derivative exhibits an absorption maximum at surprisingly short wavelength ($\lambda_{\max}^{\mathrm{MeOH}} = 240$ nm) and contains, according to formula **5**, two diazahexamethine chromophores which are conjugated only through the metal atom. This could lead to a twist of the molecular skeleton which could be responsible for the absorption at 240 nm. The analytical figures for this very labile chlorination product (**5**) are not yet settled. The assigned structure (**5**) relates only to the situation at C10, and there may well be more chlorine in the molecule, which is expelled very

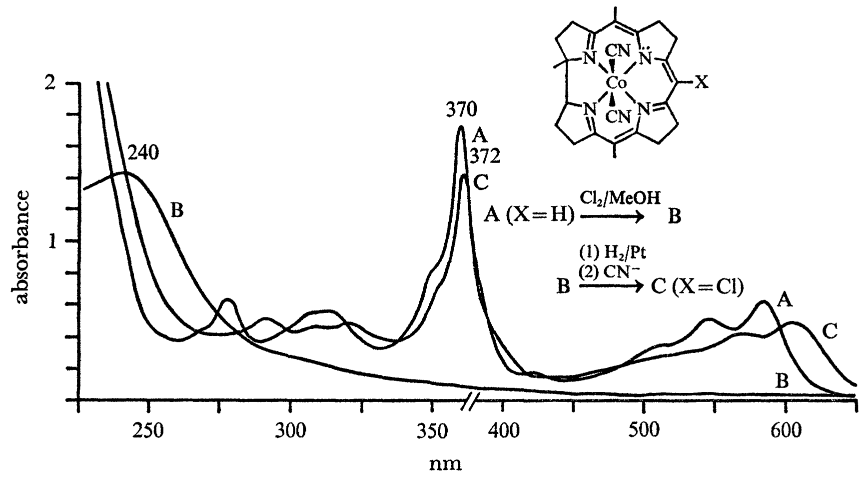
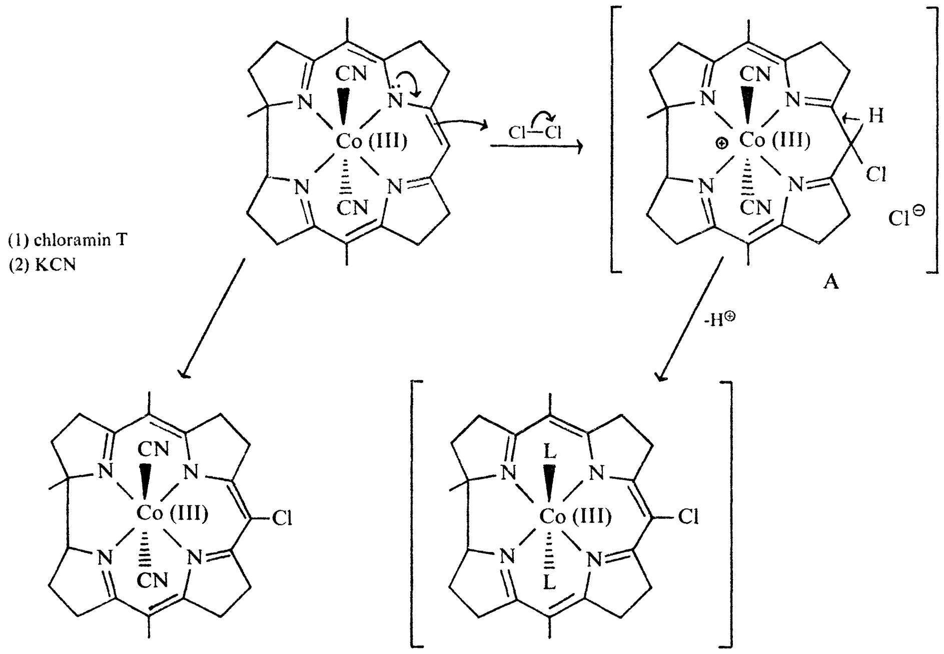


FIGURE 4



4 **4 a**

FIGURE 5

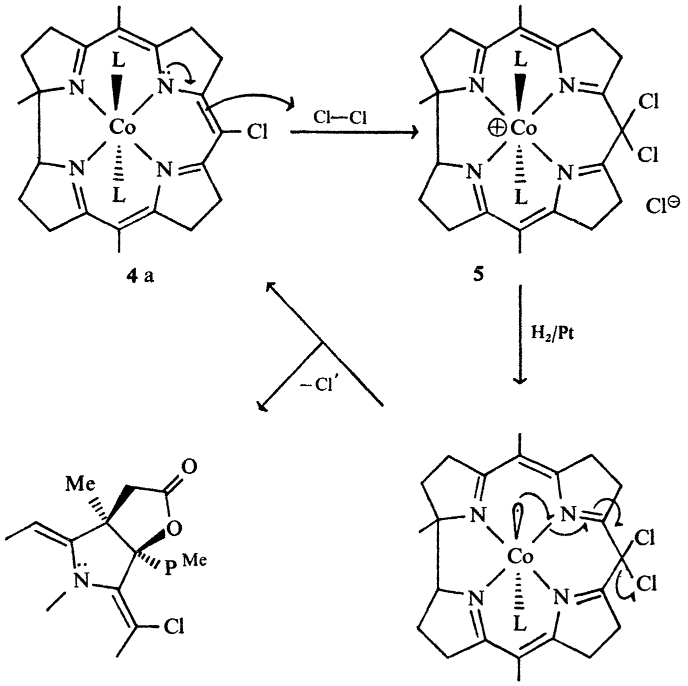


Figure 6

easily under numerous conditions with formation of the 10-chloro-cobester (**4**a or **4**, whose structure is established in every respect).

Stabilization of the 10,10-dichloro product by expulsion of a positively charged fragment is no longer possible, and this probably explains the stability of the 10,10-dichloro compound under the conditions of the reaction. Mild catalytic hydrogenation (platinum catalyst) of a methanol solution of this compound as shown in figure 4, followed by treatment with cyanide ions gives dicyano-10-chlorocob(III)ester (**4**) in more than 80 % yield. This compound (**4**) can also be prepared direct by chlorination of cyanocobalamin, followed by catalytic hydrogenation of the intermediate chlorination product and then boiling with concentrated sulphuric acid in methanol (the conditions of Eschenmoser's preparation of cob(III)ester from cyanocobalamin).

We interpret this result as reduction of the central cobalt atom to yield intially the Co(II) state; this could revert to the Co(III) level through elimination of a chlorine radical. This proposal is in agreement with the concept that the lowest unoccupied orbital of the molecule is a metal orbital.

Along with the 10-chlorocob(III)ester approximately 10 % of the corresponding ring B lactone is formed, the formation of which has been interpreted in the literature as an intramolecular redox reaction with participation of the cobalt atom. It is possible that in our case the lactone formation is associated with a prior chlorination at C8.

Figure 7 shows the electronic absorption spectra of the three valency stages of 10-chlorocobester. Finally, figure 8 presents the reoxidation of 10-chlorocob(I)ester in two stages to **4**, firstly with air, and then with addition of potassium cyanide, and this clearly shows the retarding influence of the 10-chloro substituent. Meanwhile we also have chlorinated dichlorocob(III)-ester, obtained via reduction of dicyanocob(III)ester to descyanocob(I)ester and subsequent reoxidation by treatment with chlorine.

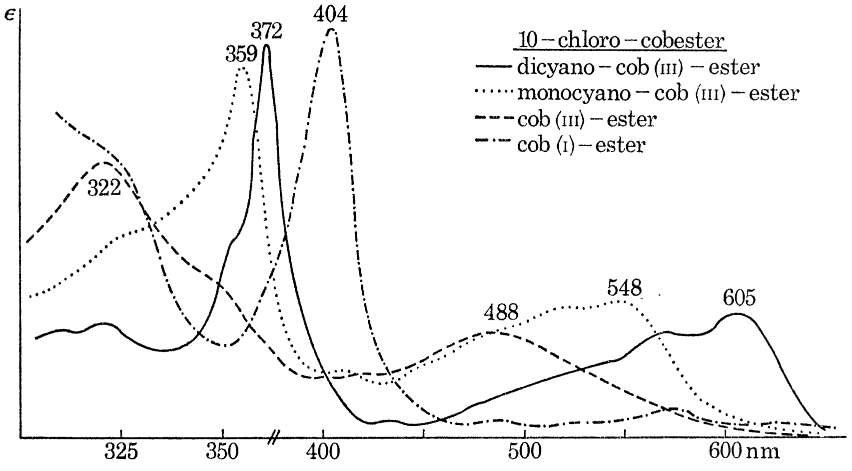


FIGURE 7

The corresponding colourless intermediate has the following elemental analytical data:

	C	H	N	Cl	OCH_3
found	48.03	5.63	4.14	19.06	17.40
	48.69	5.44	4.07	18.87	16.45
$C_{52}H_{70}N_4O_{14}CoCl_7$ would require ...	48.71	5.50	4.37	19.36	16.74

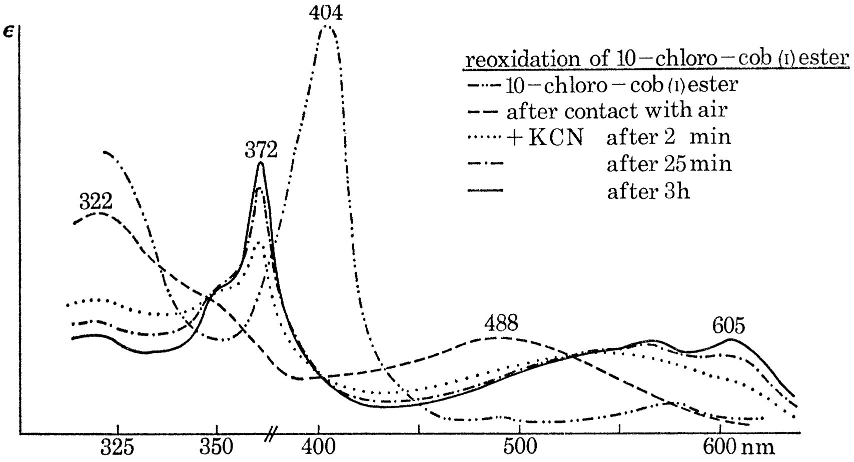


FIGURE 8

Note added in proof (*October* 1975)

In accordance with the analytical figures and chemical behaviour, the heptachloro compound (former partial structure **5**) has most probably five chlorine atoms at the positions: 5, 4 (or 6), 10, 15, 14 (or 16).

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Pratt, J. M. 1972 *Inorgnic chemistry of vitamin* B_{12}. (*a*) Electronic spectra, p. 44. (*b*) Cobalt(I) corrinoids, p. 107. (*c*) Chemical reduction, p. 196. London: Academic Press.

Werthemann, L. 1968 Dissertation, E.T.H. Zürich.

Discussion

G. W. Kenner, F.R.S. Would other electrophilic substitution reactions, such as nitration, be expected to occur at position 10 of cobester?

A. Gossauer. I do not believe that any are reported in the literature.

B. Franck (*Organisch-Chemisches Institut der Universität D-44 Münster, F.R.G.*). In answer to Professor Kenner's question, I would like to mention that Dr Montforts in our group at Münster has prepared, by direct nitration and in high yield, a crystalline dicyanocobalt(III)-10-nitrocobyrinic acid heptamethyl ester (m.p. 137–139 °C). This nitro derivative can be reduced to the amino compound.