4. The Light-Induced Oxygenation of the B-Didehydrocorrinoid Vitamin-B_{12} Derivative 'Pyrocobester'

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Summary

The didehydrocorrinoid derivative of vitamin B_{12}, 'pyrocobester' **1** (hexamethyl *Coa, Coβ*-dicyano-7-de(carboxymethyl)-7,8-didehydrocobyrinate), is oxygenated in the presence of visible light and molecular oxygen to give the previously unknown '5,6-dioxosecopyrocobester' **3** (hexamethyl *Coa, Coβ*-dicyano-5,6-dioxo-7-de(carboxymethyl)-7,8-didehydro-5,6-secocobyrinate) under regioselective cleavage of the macrocycle at the 5,6-position. Efficiency and yield of this reaction involving 'singlet oxygen' depend on the solvent used: with CCl_4 a 96% yield of **3** is obtained.

A known chemical effect of the interaction of light with corrinoid Co(III)-complexes is the cleavage of the bond of an axial ligand to the metal center, an especially mild and specific way of homolytically dissociating the Co(III),C-bond (*e.g.*) of coenzyme B_{12} [1]. Other chemical properties of electronically excited corrinoid Co-complexes are not clearly documented, so far [2].

Therefore the observation[3]) of an efficient light-induced chemical reaction of the B-didehydrocorrinoid hexamethyl *Coa, Coβ*-dicyano-7-de(carboxymethyl)-7,8-didehydrocobyrinate [3] (**1**; 'pyrocobester'), and apparently not involving the axial ligands, was unusual and caught our attention. This reaction was observed during chromatographic purification of **1** [4] or during attempts to crystallize **1** without

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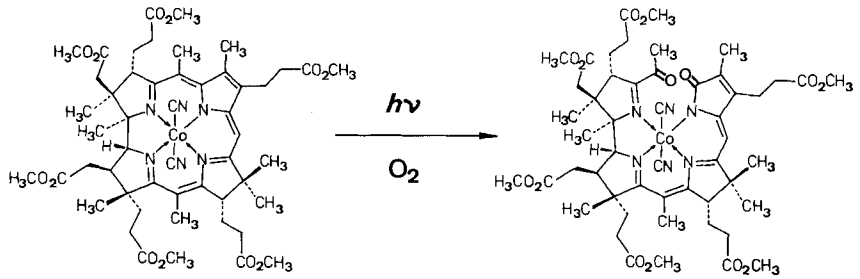
[3]) These observations were made by *B.K.* (Zürich) (results presented at the Herbstversammlung der Schweizerischen Chemischen Gesellschaft, Bern, Oct. 1981), and independently by *G.H.* (Berlin) (presented at the Seminar des Instituts für Organische Chemie, TU Berlin, Oct. 1981) as communicated to *B.K.* on Oct. 15, 1982.

Scheme



1 **3**

carefully excluding its exposure to dim daylight. Subsequently, this reaction of 'pyrocobester' **1** (itself a product of thermolysis of 'cobester' **2** [5] (heptamethyl *Coα, Coβ*-dicyanocobyrinate)) was analyzed to be the cleavage of **1** at the 5,6-position to the corresponding '5,6-dioxosecopyrocobester' **3** (hexamethyl *Coα, Coβ*-dicyano-5,6-dioxo-7-de(carboxymethyl)-7,8-didehydro-5,6-secocobyrinate), as shown in the *Scheme*.

The structure of **3** was deduced on the basis of the information from the ^{1}H- and ^{13}C-NMR. spectra as well as mass spectra, but already the pronounced hypsochromic shift of the absorption maxima in the UV./VIS. spectra on its own pointed to a considerable shortening of the main chromophore of **3** compared to that of **1** (see the *Figure*).

In the ^{1}H-NMR. spectrum of **3** four critical singlets due to CH_3-groups (at 1.73 ($H_3C(7^1)$); 1.98 ($H_3C(1^1)$); 2.17 ($H_3C(15^1)$) and 2.88 ($H_3C(5^1)$)) can be assigned with the help of specific nuclear *Overhauser* enhancements (NOE), obtained by difference NOE-measurements [6][4])[5])[6]). This spectrum is compatible with cleavage at the 5,6-position but excludes reaction at the 14,15-position (or at the methine bridge HC(10)). The ^{13}C-NMR. spectrum exhibits new signals at low field, one of which (at 196.7 ppm) is due to the new acetyl function ($CH_3C(5)=O$) at the cleavage site. The two signals for the quaternary C-atoms C(7) at 139.1 ppm[7]) and C(8) at 144.6 ppm[7]), and a new isolated high-field signal at 9.7 ppm for $H_3C(7^1)$ show ring B to be intact and support cleavage at the 5,6-position. The fragmentation pattern in the electron impact (EI.) mass spectrum is dominated by two signals at *m/z* 640 and 296 due to the characteristic break-down of A/B-secocorrinoid metal complexes [11] [12] into the tricyclic B, C, D and the ring A fragments, respectively. A positive-ion fast-atom-bombard-

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[4]) Significant nuclear *Overhauser* enhancements (enh.) for **3** upon irradiation (irr.) at the frequencies of the four critical singlets (300 MHz, C_6D_6)[6]): irr. at 1.73, enh. at 2.45 (*m*, $H_2C(8^1)$?); 2.88 (*s*, $H_3C(5^1)$), and 3.43 (*s*, $COOCH_3$); irr. at 1.98, enh. at 1.09 (*s*, $H_3C(2^1)$), and 3.08 (*d*×*t*, HC(18)); irr. at 2.17, enh. at 0.98 (*s*, $H_3C(17^1)$), and 2.70 (*m*, HC(13)?); irr. at 2.88, enh. at 1.73 (*s*, $H_3C(7^1)$), 3.43 (*s*, $COOCH_3$), and 3.57 (*t*-like, H–C(3)).

[5]) In a synthetic C/D-secocorrinoid Ni(II)-complex [7] X-ray structural analysis [8] shows ring D to be considerably out of the 'mean molecular plane', and in close contact with ring C (at the site of intended closure of the corrin ring). For **3** a gross structural similarity is indicated by the observation of NOE across the A/B-cleavage site (NOE between $H_3C(5^1)$ and $H_3C(7^1)$, and NOE on irradiation of $H_3C(5^1)$ or $H_3C(7^1)$ at a specific ester-CH_3-group (3.43 ppm), presumably of the propionic acid side chain of ring A).

[6]) The numbering follows that of vitamin-B_{12} derivatives [9a]; see *e.g.* also [9b], where recently the complete assignment of the ^{1}H-NMR. spectrum of 'cobester' **2** in C_6D_6-solution has been published.

[7]) Assigned by comparison with ^{13}C-NMR. studies on bile pigments [10].

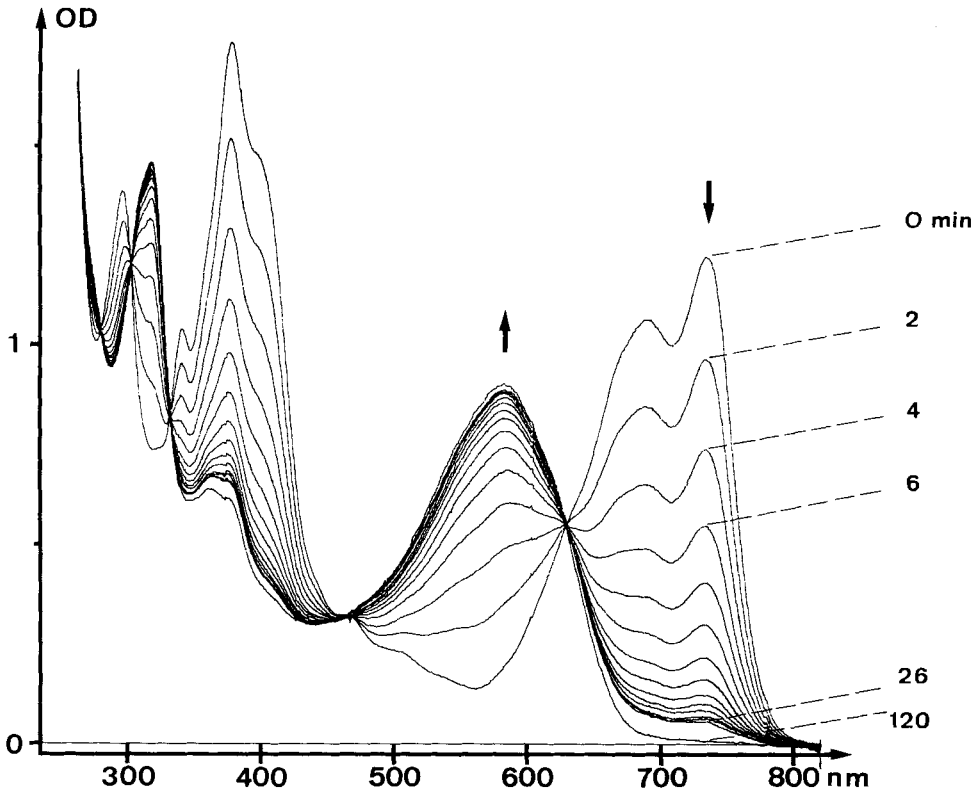

Figure. *Changes in the UV./VIS. spectrum as observed during the photo-oxygenation of 'pyrocobester'* **1** *in* CCl_4 [20] (exciting wavelength: 710 nm; initial concentration of **1**: $1.0 \cdot 10^{-3}$ mol/l; O_2 (1 atm), RT., 0.1 cm path length; spectra taken after irradiation for time intervals of 2 min (up to 26 min), final spectrum after 120 min irradiation)

ment(FAB.)-mass spectrum [13a] exhibits a base peak at *m/z* 994, due to loss of the axial ligands ($(M+1)^+ - CN - HCN$), while in a negative-ion-FAB./MS. [13b] the base peak appears at *m/z* 1046, corresponding to the molecular ion (M^-).

On further elaboration of this exceptional light-induced reaction of **1** (mainly for the purpose of accurate kinetic information [14], **3** could be isolated in 96% yield: Irradiation[8]) of an oxygen-saturated[9]), deep green solution of **1** in CCl_4[10]) at room temperature with the light of a tungsten lamp produced a rapid change of color of the reaction mixture to intense violet. Analysis by TLC. indicated a clean conversion to the secocorrinoid Co-complex **3**. The reaction can easily be monitored also with the help of UV./VIS. spectra (see *Fig.*).

[8]) Such an oxygen-saturated solution of **1** was found not to undergo any noticeable change during storage for 20 days at RT. in the absence of light.

[9]) Irradiation of a degassed solution of **1** in CCl_4 under comparable conditions (200 W W-lamp; 150 min, RT.) resulted in only a 5% decrease of the optical density at 722 nm (λ_{max} of **1** in CCl_4), and analysis by TLC. of this solution of **1** did not clearly indicate formation of **3**.

Aside from the preparative outcome reported here, parallel mechanistic investigations [14] of this photoreaction allow us to classify it as a reaction involving 'singlet oxygen' photogenerated *via* excitation of the didehydrocorrinoid Co(III)-complex **1** (findings, that already stimulated related studies on the parent heptamethyl cobyrinate **2** [15]. The regioselectivity of the oxygenation reaction[11]) at the 5,6-position of the B-didehydrocorrin **1** can be correlated with the minimal HMO '(atomic) localization energy' for the ligand π-system of **1** (decrease of π-electronic energy upon interruption at a specific C-center of the conjugated π-system of **1** [16], calculated (HMO calculation [17]) to be smallest for electrophilic attack at the 5-position. Apparently the reactions of corrinoid Co(III)-complexes with 'singlet oxygen' reflect the reactivity of their ligand π-systems towards electrophiles[12])[13]).

The results described here also underline the earlier proposal [15] to apply photo-oxygenation to vitamin-B_{12} derivatives as a selective and convenient method for the preparation of specific dioxosecocobyrinates, believed to be useful as precursors for the synthesis of metallocobyrinates not containing a Co-ion [12]. In this respect, further preparative work has allowed to remove the Co-ion from the secocobyrinate **3**[14]), to reinsert Co and to reconstitute **1** by reductive ring closure [19] (in analogy to the work reported in [12]).

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Experimental Part[15]) [20]

A solution of 30.0 mg (29.5 µmol) of crystalline 'pyrocobester' **1** in 50 ml of CCl_4 *(Merck, p.a.)* was introduced into a photo-oxygenation vessel (*Pyrex*, internal cooling with water)[16]) and the solution purged with a stream of O_2 for *ca.* 5 min. Then the deep-green solution was irradiated with the unfiltered light of two 200 W W-lamps (placed externally, diametrically and at a distance of 5 cm from the reaction vessel), while continuously agitating the solution by a weak O_2-flow. After about 2 min of irradiation, the solution changed its color to intense violet, and the reaction was stopped after 5 min, when analysis of the mixture by TLC. indicated total conversion of **1** to **3**. The solution was transferred into a round bottom flask, and the solvent was evaporated under reduced pressure at RT. The residue was purified by chromatography on three thin layer plates (*Merck*, Kieselgel *60*, 20×20 cm; CH_2Cl_2/CH_3OH (1% HCN) 96:4)[17]). The violet fraction was scraped off and eluted with CH_2Cl_2/

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[10]) Preparative experiments with CH_2Cl_2 as solvent resulted in a strongly reduced rate of oxygenation and a somewhat lower yield of **3** (80%) [4].

[11]) The remaining side-products (*ca.* 3%), distributed over several fractions (separable by TLC.), were not identified.

[12]) The photo-oxygenation of **2** at the 5,6- and 14,15-positions [15] also correlates with minimal HMO 'localization energies' [18] for the corrin π-system.

[13]) Strain (as presumably) caused by the interaction of the methyl groups $H_3C(5^1)$ and $H_3C(7^1)$ should also enhance the reactivity of **1** towards photo-oxygenation at the 5,6-position.

[14]) A luminescing yellow compound, apparently the free 5,6-dioxo-didehydro-5,6-secocorrinoid ligand **4** is obtained [19] upon treatment of **3** with hydrogen sulfide in pyridine.

[15]) Abbreviations and specifications as in [15], unless otherwise stated.

[16]) A photoreactor, see *e.g.* [21], p. 131.

[17]) All these manipulations were performed at 0–5°.

CH_3OH (1% HCN) 10:1[17]). The filtrate was shaken with 20 ml of satd. aq. $NaHCO_3$ solution (to which 100 mg of KCN had been added)[17]), the org. layer was filtered through a plug of cotton-wool and the solvents were removed under reduced pressure[17]) giving **3** as a violet residue (30.0 mg; 28.6 μmol), pure by TLC. It was precipitated from a benzene solution (*ca.* 2 ml) by its addition to 50 ml of hexane. The violet, amorphous precipitate was separated from the (nearly colorless) supernatant liquid and was dried (V., then HV./RT., 1 h) to give 29.6 mg of **3** (28.2 μmol, 96% yield). This material was used for the subsequent analysis. *Hexamethyl* Co*α*,Co*β*-*dicyano-5,6-dioxo-7-de(carboxymethyl)-7,8-didehydro-5,6-secocobyrinate* (**3**). TLC. (CH_2Cl_2/CH_3OH (1% HCN) 96:4) Rf 0.18, m.p. 120–125° (darkens at 110°). – UV./VIS. ($c = 8.29 \cdot 10^{-5}$ mol/l, CH_3OH; 0.05% HCN): 300 *S* (4.06), 309 (4.09), 366 *S* (3.62), 397 *S* (3.40), 561 (3.83), 615 *S* (3.57); min. 277, 420. – CD. ($c = 8.29 \cdot 10^{-5}$ mol/l, CH_3OH; 0.05% HCN): 248 (13.3), 309 (71.8), 373 (−16.3), 426 (−24.1), 507 *S* (−8.8), 580 *S* (−4.5); λ_0 at 345. – IR. (4%)[15]): 2995*m*, 2130*w*, 1735*s*, 1605*w*, 1560*s*, 1480*m*, 1440*s*, 1410*m*, 1395*m*, 1375*m*, 1370*m*, 1355*w*, *etc.* – ^{1}H-NMR. (300 MHz, C_6D_6, C_6D_5H at 7.15 ppm)[6])[18]); 0.94, 0.98, 1.06 and 1.09 (4 *s*, 12 H, 4 CH_3); 1.5–3.0 (*m*, 34 H) overlapped by 1.73, 1.98, 2.17 and 2.88 (4 *s*, 4 CH_3)[4]); 3.08 ('*d*×*t*', *X* of *ABXY*, $J_{AX} = 10.5$, $J_{BX} = 3$, $J_{XY} = 10.6$, 1 H, H–C(18)); 3.24, 3.29, 3.31, 3.35, 3.37 and 3.43 (6 *s*, 18 H, 6 $COOCH_3$); 3.57 (*t*-like, 1 H, H–C(3)); 3.92 (*d*, *Y* of *XY*, 1 H, H–C(19)); 5.60 (*s*, 1 H, H–C(10)); 1.2–1.4 (br., *ca.* 4 H, H_2O). – ^{13}C-NMR.[6])[15]): 9.70 (*qa*, $H_3C(7^1)$); 15.70, 17.01, 18.36 and 19.44 (4 *qa*); 19.98 (*t*, $H_2C(8^1)$?); 20.07 (*qa*); 24.17 and 25.46 (2 *t*); 27.86 (*qa*, $H_3C_\beta(12^1)$?); 29.05 (*qa*, $H_3C(5^1)$); 29.89, 30.61, 31.75, 32.89, 33.07 and 33.58 (6 *t*); 40.23 (*d*, HC(18)?); 42.11 (*t*, $H_2C(2^1)$?); 46.91 and 49.21 (2 *s*, C(2), C(12)); 51.64 (double int.), 51.88, 51.97, 52.12 and 52.51 (5 *qa*, 6 $COOCH_3$); 53.88 (*d*, HC(13)?); 58.59 (*s*, C(17)); 59.43 (*d*, HC(3)?); 74.82 (*d*, HC(19)); 86.92 (*s*, C(1)); 92.67 (*d*, HC(10)); 109.33 (*s*, C(15)); 128.98 and 134.25 (2 *s*, 2 CN); 139.13 (*s*, C(7)?); 144.61 (*s*, C(8)?); 161.14, 164.98, 171.03, 171.39, 172.53, 172.80, 173.01, 173.69, 176.03, 177.92 and 183.34 (11 *s*, 6 $COOCH_3$, C(6), C(9), C(11), C(14), C(16)); 186.93 (*s*, C(4)); 196.73 (*s*, C(5)). – EI./MS. *(Hitachi RMU-6M):* 964 (14), 963 (39), 962 (77), 961 (39), 960 (65), 904 (14), 903 (33), 642 (21), 641 (66), 640 (80, $M^+ - 406$)[19]), 639 (29), 297 (23), 296 (100)[19]), etc. – Positive-ion-FAB./MS.[20]): 1029 (16), 1028 (27, $(M+1)^+ - 17$), 998 (19), 997 (32), 996 (69, $(M+1)^+ - 51$)[20]), 995 (31), 994 (100, $(M+1)^+ - 53$)[19]), 982 (26), 981 (29), 980 (47, $(M+1)^+ - 67$), 964 (18), 962 (19), etc. – Negative-ion-FAB./MS.[21]): 1048 (34), 1047 (67), 1046 (100, M^-), 1045 (48, $(M-1)^-$), 996 (19), 995 (34), 994 (62, $M^- - 52$), 993 (31), 963 (24), 962 (40), 961 (57), 960 (21), etc.

$C_{51}H_{67}CoN_6O_{14}$ Calc. C 58.50 H 6.45 N 8.03% Found C 58.45 H 6.43 N 8.10%

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[18]) ^{1}H-NMR. ($CDCl_3$)[15]): 1.22, 1.25, 1.27 and 1.31 (4 *s*, 12 H, 4 CH_3); 1.4–2.9 (*m*, *ca.* 35 H) overlapped by 1.95 (double int.), 2.26, 2.59 (3 *s*, $H_3C(1^1)$, $H_3C(7^1)$, $H_3C(15^1)$, $H_3C(5^1)$); 2.96 (*t*-like, HC(13)) overlapped by 3.02 (*m*, HC(18)); 3.47 (*d*×*d*, 1 H, HC(3)); 3.61, 3.65, 3.67, 3.70, 3.72 and 3.77 (6 *s*, 18 H, 6 $COOCH_3$); 3.82 (*d*, *J* = 10.6, 1 H, HC(19)); 5.62 (*s*, 1 H, HC(10)).

[19]) Interpretation of fragments: 53 = HCN + CN; 296 = ring A; 406 = 296 + (52(2 CN) + ^{59}Co) − H.

[20]) This spectrum, taken at *M-Scan*, Iver (England), of a sample of **3** from another experiment [4] showed a less pronounced fragment at *m/z* 996 than the corresponding spectrum of **3** from this preparation and recorded at the ETH (*m/z* 996 (100%), 994 (69%)).

[21]) This spectrum, kindly provided by Prof. Dr. *H. Schwarz* (Berlin), was collected for a sample of **3** prepared in Berlin and identified by UV./VIS., ^{1}H- and ^{13}C-NMR. spectra.

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