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Chemistry

Ring contraction of hydroporphinoid to corrinoid complexes

(corrin synthesis/vitamin B_{12} biosynthesis/sulfide contractions/nucleophilic carbenes/photochemistry)

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ABSTRACT **Crystalline nickel(II) and dicyanocobalt(III) complexes of a racemic 1,2,2,7,7,12,12,17,17,20-decamethyl-20-hydroxy-1,2,3,7,8,12,13,20-octahydro-17*H*-porphyrin rearrange to the corresponding complexes of racemic 19-acetyl-1,2,2,7,7,12,12,17,17-nonamethyl-*trans*-corrin on melting (approximately 290°C and 260°C, respectively). The nickel(II) 19-acetylcorrinate formed in this way is shown to deacetylate to racemic nickel(II) 1,2,2,7,7,12,12,17,17-nonamethyl-*trans*-corrinate on treatment with 2 M KOH. These reactions are being studied as potentially biomimetic chemical models for the elusive ring contraction step in vitamin B_{12} biosynthesis.**

The crucial and still unknown step in the biosynthesis of vitamin B_{12} from uroporphyrinogen (1, 2) is the generation of the characteristic A/D-ring junction of the corrinoid ligand. A major stride towards a solution of this problem was made in 1979 when it was discovered (3–5) that the third methyl group in the consecutive methyl group transfers from adenosylmethionine to hydroporphinoid intermediates most surprisingly becomes attached at the *meso* position C-20 between rings A and D (cf. structure **1** in Fig. 1), only to leave the scene again, probably together with carbon atom C-20, at some unknown later stage of the uroporphyrinogen → corrin transformation. It was this important finding combined with the results of recent chemical studies on the mechanistic spectrum of A/D-secocorrin → corrin ring closures (6, 7) that led us to envisage and to test in a model system the chemical feasibility and characteristics of the hypothetical dihydrocorphinol‡ → corrin rearrangement depicted in Fig. 2.§

In a hexahydroporphinoid structure of type **2** protonation of the enaminoid double bond of ring D generates the structure **2a** containing an α-*tert*-hydroxyiminium function, which in principle should be prone to undergo two isomeric rearrangements, one of which constitutes a ring contraction to the 19-acetylcorrin structure **3**. Such a transformation is formally analogous to the known semibenzoin rearrangement of α-*tert*-hydroxyketones and is in fact—as is best recognized in its stepwise mechanistic variant (see structure **2b**)—very closely related to our previously described (7) A/D-secocorrin → corrin cycloisomerization of 1-methylidene-19-formyl-1,19-secocorrinates to 19-formylcorrinates.

A process of type **2** → **3** implies the isomerization of an allylic alcohol system to an unconjugated carbonyl function and may well, therefore, be thermodynamically feasible in the free ligand; on the other hand, in metal complexes the position of a corresponding equilibrium may reflect the preference of a given metal ion for either the hydroporphinoid or the (smaller) corrinoid coordination sphere. Kinetically, the rearrangement is expected to respond to acid/base catalysis and it may also offer a thermally inducible pathway via an intramolecular proton shift

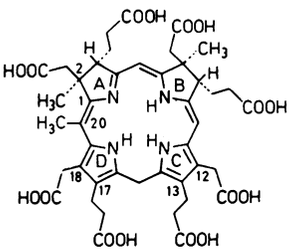

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FIG. 1. Hypothetical dihydro derivative of established vitamin B_{12} precursor 20-methylsirohydrochlorin (3–5).

from the tertiary hydroxyl group to the nucleophilic enamine carbon in ring D.

Fig. 3 summarizes the synthesis of the model structure **12**, specifically prepared in order to put the above-mentioned expectations to an experimental test. In its first phase the synthesis makes use of previously described intermediates **4–10** (9, 10) and proceeds to the unusual and crucial photochemical cyclization step **10** → **11**. This process is assumed to imply an attack of a photochemically generated nucleophilic carbene function at position C-19 of ring D onto the nitrile group (which is held in close proximity to the carbenoid sp^2 lone pair by the complexing cadmium ion), followed by a proton transfer from C-18 to the negatively charged nitrogen of the newly formed ketiminate function (see **10a** → **10b** → **10c**, in Fig. 3). After chromatographic hydrolysis of the ketimine group of **10c** on silica gel and acidolytic decomplexation with trifluoroacetic acid, crystalline **11** is isolated in up to 60% yield. A Grignard reaction with CH_3MgI gives **12** as only one of the two possible diastereomers; the reaction is therefore assumed to proceed under steric control, and the configuration of **12** is tentatively assigned as indicated.

A variant of the synthesis of **12** (see Fig. 4) uses as rings A/B precursor the bicyclic acetylthiolactam **13** available from **4** by reaction with CH_3MgI, followed by (ketimine) hydrolysis and introduction of sulfur at the lactam function with the "Lawesson reagent" (11). A sequence of reactions analogous to the one described above converts **13** into a (noncrystallized) chloro-cadmium complex **14**. This is cyclized photochemically, either as such or, preferably, as the lithium complex **14a** to give

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Abbreviations: DBU, 1,5-diazabicyclo[5.4.0]undec-5-ene; RT, room temperature.

‡ For the hexahydroporphinoid ligand system named "corphin" see ref. 8.

§ Any extrapolation of structure **1** to a potential biosynthetic intermediate of structural type **2** has to obey only two *a priori* constraints: methylation at C-1 preceding methylation at C-17 and decarboxylation preceding methylation at C-12.

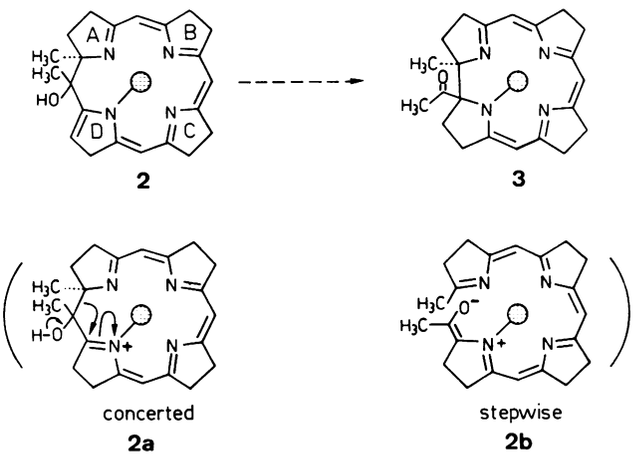

FIG. 2. Hypothetical dihydrocorphinol → corrin rearrangement.

two diastereomeric products, which can be separated and were isolated in the form of their crystalline nickel(II) (perchlorate) complexes **15**; the main diastereomer proved to be identical with the nickel(II) complex prepared from **12** derived from **11**.

The reaction sequence described in Fig. 4 had been carried out in the hope that the zwitterionic intermediate **15a** in the photochemical cyclization of **14** or **14a** would undergo directly ring contraction to the 19-acetylcorrinate (see discussion of Fig. 2). This, however, was not the case, the proton transfer leading from **15a** to **15** apparently being faster than the rearrangement under the conditions of the photochemical ring closure.

Ring contraction to 19-acetylcorrinate does occur, however, when crystalline samples of both the nickel(II) (chloride) complex **15** and the dicyanocobalt(III) complex **16** are heated for a few minutes above their melting points (approximately 290°C and 260°C, respectively) under exclusion of oxygen (yields up to 40%) (see Fig. 5). Mass, ultraviolet/visible, infrared, and ^{1}H NMR spectra of the (crystalline) products (see *Experimental Data*) fully support their structural assignments as racemic nickel(II) and dicyanocobalt(III) 19-acetyl-1,2,2,7,7,12,12,-17,17-nonamethyl-*trans*-corrinates **17** and **18**, respectively. For the nickel corrinate **17** this assignment is corroborated by x-ray analysis (see Fig. 6). Worthy of mention are the quite unusual chemical shifts of the CH_3CO- methyl singlets in the ^{1}H NMR spectra of **17** and **18** (2.79 and 2.58 ppm relative to tetramethylsilane); model considerations suggest, and the results of the x-ray analysis (see Fig. 6) support the contention, that the sterically least-crowded position of this methyl group is the one pointing towards the metal ion.

Deformylation of nickel(II) 19-formylcorrinates by hydroxide ions has been demonstrated previously (7); deacetylation of the nickel(II) 19-acetyl-corrinate **17** also proceeds under similar conditions, though, understandably, much more sluggishly (days instead of hours at 70°C with 2 M KOH). The crystalline product of deacetylation was shown to be racemic nickel(II) 1,2,2,7,7,12,12,17,17-nonamethylcorrinate perchlorate **19** by direct comparison (ultraviolet/visible, infrared, ^{1}H NMR, mass spectroscopy, thin-layer chromatography) with a previously synthesized (9) authentic sample.

It remains to be learned whether the ring contraction/deace-

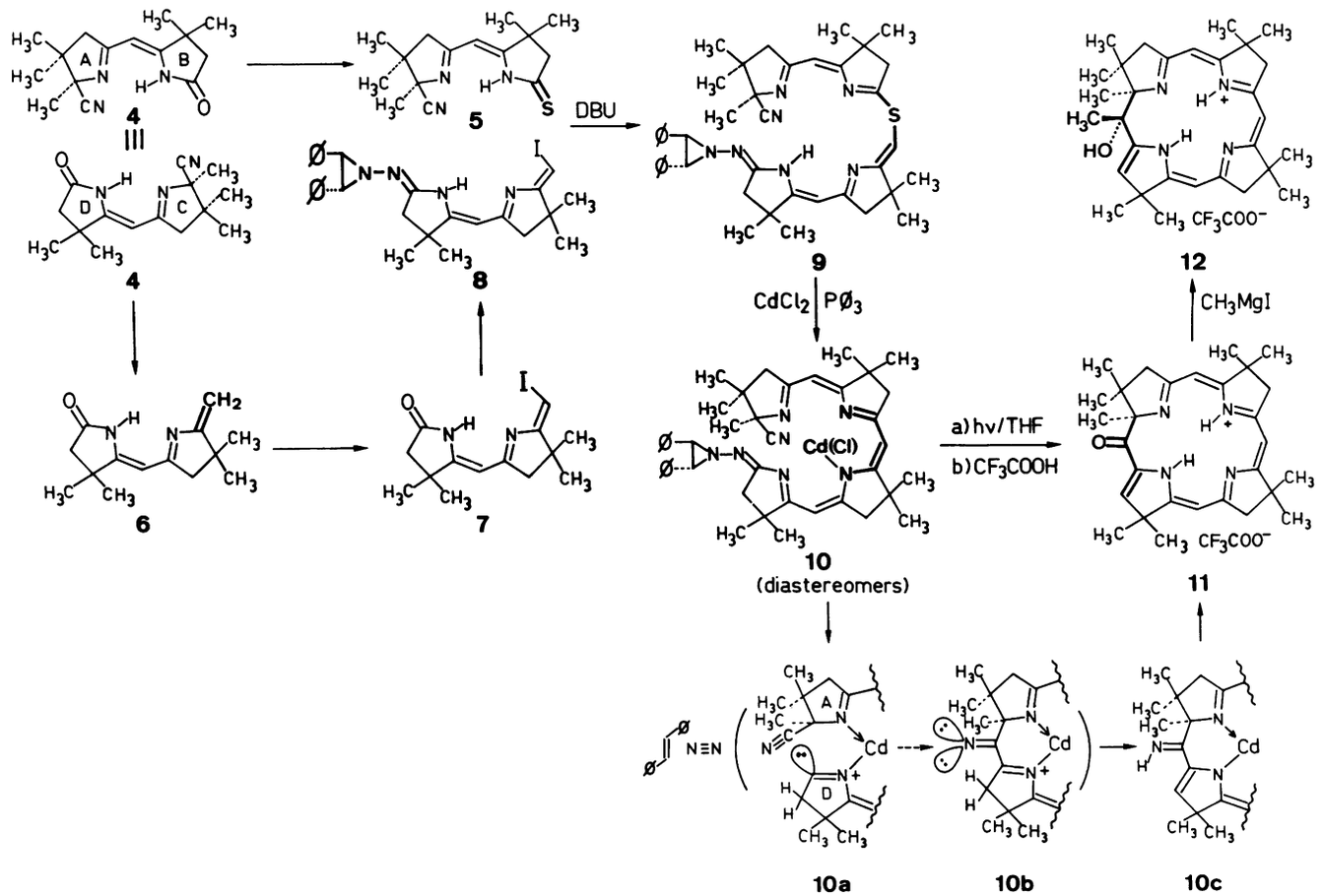

FIG. 3. Synthesis of **12**. THF, tetrahydrofuran; DBU, 1,5-diazabicyclo[5.4.0]undec-5-ene.

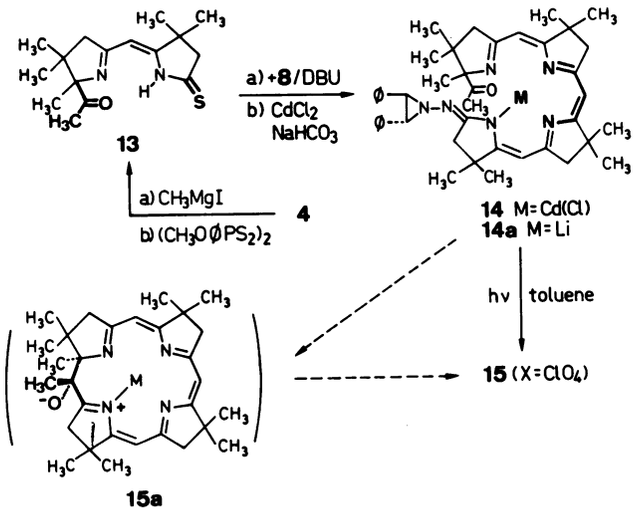

FIG. 4. Variant of the synthesis of **12**.

tylation sequence can also be effected in the experimentally more demanding metal-free model series. Encouragement for the pursuit of such studies comes from recent results that Arigoni and Battersby and their colleagues describe in the accompanying papers (12–14), which show that one acetic acid equivalent is extruded during the biosynthetic ring contraction process. The special appeal of the dihydrocorphinol → corrin rearrangement as a model for this process resides in that it assigns to the methyl group at C-20 a chemically transparent function in the ring contraction and, furthermore, that it would allow corrin biosynthesis to proceed from the beginning to the end at a single oxidation level (7).

EXPERIMENTAL DATA

Reaction conditions

Percentages in parentheses indicate product yields. Numbers indicate molar ratios of reagents or solvents. RT, room temperature. **4** → **10**: see refs. 7 and 9. **10** → **11**: (*i*) $h\nu$ (Hg) in dry

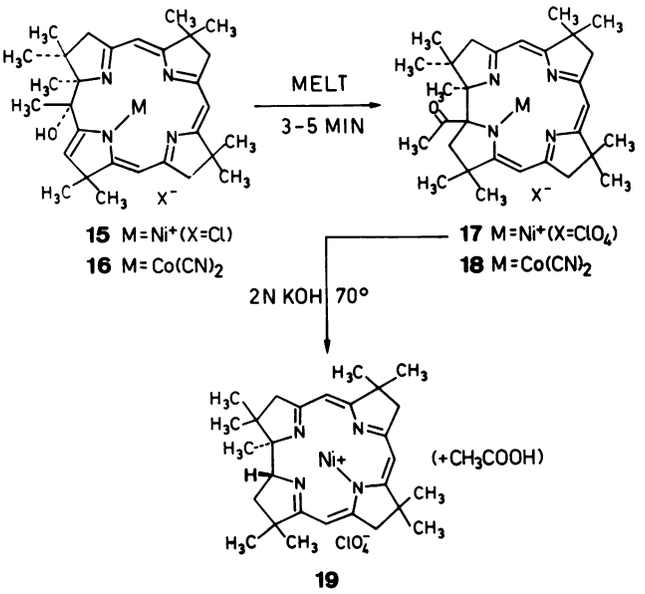

FIG. 5. Ring contraction and deacetylation.

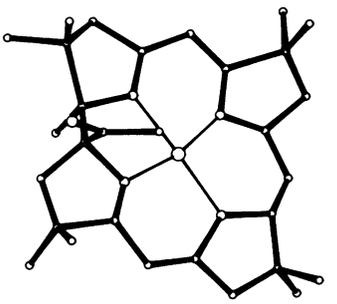

FIG. 6. Crystal structure of **17**. The molecule is projected into the plane of atoms N-21–N-22–N-23 and tilted by 21° to minimize overlap. The radii of circles around atom positions are arbitrary and increase in the order C < N < O < Ni.

H_4furan, 15°C; (*ii*) CF_3COOH/CH_2Cl_2, RT (ca. 60%). **11** → **12**: (*i*) DBU, H_4furan; (*ii*) CH_3MgI, ether, 33°C (ca. 50%). **12** → **16**: (*i*) 15 $Co(OAc)_2 \cdot 4H_2O$, CH_3CN, 60°C; (*ii*) KCN, air (ca. 80%). **16** → **18**: ca. 265°C under argon, 3 min (ca. 30%). **4** → **13**: (*i*) 4.5 CH_3MgI, diethyl ether, RT, work up with aqueous 0.1 M HCl, 2 hr, RT (60% yield of acetyllactam, mp 128°C); (*ii*) 0.55 *p*-anisylthionophosphine sulfide (**11**) in H_4furan, 20°C, 1 hr (90%). **13** + **8** → **14**: (*i*) 6 DBU, CH_3CN, RT; (*ii*) 2.5 $CdCl_2 \cdot 2H_2O$, 2.0 $(C_6H_5)_3P$, $NaHCO_3$, CH_3OH, RT (40–55%). **14** → **14a** → **15** (X = ClO_4^-): (*i*) 10 KCN, CH_3OH, RT; (*ii*) excess $LiClO_4$, solid NaOH, H_4furan, RT; (*iii*) $h\nu$ (Hg/Pyrex), toluene, 5–10°C; (*iv*) 10 $NiCl_2 \cdot 6H_2O$, acetate buffer, CH_3OH, 60°C, work up with 0.1 M $HClO_4$, chromatographic separation (silica gel, $NaClO_4$) of two diastereomers (5:1) (40%). **15** (X = Cl) → **17**: melt (295°C) 5 min, under argon, work up with 0.1 M $HClO_4$ (40%). **17** → **19**: 2 M KOH in C_2H_5OH/H_2O (9:1), 70°C, 20 days in evacuated tube (ca. 20%).

Spectral data

Data are given in the following order: ultraviolet/visible (λ_{max} in nm, log ε (M^{-1} cm^{-1}); spectra taken in C_2H_5OH), infrared ($\tilde{\nu}$ in cm^{-1}; $CHCl_3$), ^1H NMR (δ in ppm, δ tetramethylsilane = 0 ppm, C^2HCl_3), molecular weight as determined by mass spectroscopy. Only selected infrared and NMR data are given. sh, shoulder; s, singlet; M^+, parent ion.

11. (mp 183°C): λ_{max} = 230 (3.98), 261 (4.31), 292 (4.29), 322 (sh/4.23), 339 (sh/4.36), 353 (4.41), 504 (4.11); $\tilde{\nu}$ = 3270, 1775/1730, 1665, 1620, 1565; δ = 7.18/5.62 (2s/2H), 5.68 (s/2H) (4 =CH—); M^+ (− CF_3COOH) = 458.

12. (mp 194°C): λ_{max} = 264 (4.15), 324 (4.48), 335 (4.48), 349 (sh/4.37), 382 (sh/3.92), 406 (sh/3.75), 504 (4.09); $\tilde{\nu}$ = 3595/3455/3270, 1660, 1617, 1565; δ = 6.18/5.57/5.51/5.49 (4s/4 =CH—), 1.75/1.50/1.42/1.39/1.37/1.34/1.31/1.27/1.22/1.18 (10s/10 CH_3); M^+ (− CF_3COOH) = 474.

13. (mp 128°C): λ_{max} = 245 (4.15), 332 (4.33), 410 (3.49); $\tilde{\nu}$ = 1700, 1655, 1570; δ (CH_3CO) = 2.32; M^+ = 292.

14. λ_{max} = 276 (4.40), 346 (4.49), 550 (4.08); $\tilde{\nu}$ = 1700, 1628, 1600, 1572; δ = 5.20/5.03/5.00 (3s/3 =CH—), 2.17 (s/CH_3CO).

15. (X = ClO_4^- main diastereomer, mp 240°C): λ_{max} = 284 (4.02), 338 (4.34), 348 (sh/4.28), 396 (sh/3.75), 420 (sh/3.80), 467 (4.00); $\tilde{\nu}$ = 3595/3460, 1637, 1568, 1515; δ = 6.23/6.12/6.04/5.77 (4s/4 =CH—), 1.97/1.44/1.39/1.30/1.20/1.05 (6s/6 CH_3), 1.34/1.29 (2s/4 CH_3); M^+ (− $HClO_4$) = 530 (^{58}Ni).

16. (mp 248°C): λ_{max} = 304 (3.91), 346 (sh/3.95), 362 (sh/4.27), 380 (4.41), 422 (sh/3.43), 553 (3.85); $\tilde{\nu}$ = 3590, 2120, 1637, 1573, 1520; δ = 6.11/5.47/5.41/5.40 (4s/4=CH—), 1.89/

1.50/1.35/1.30/1.28/1.26/1.25/1.19/1.16/1.02 (10s/10 CH_3); M^+ (− 2CN) = 532.

17. Racemic nickel(II) 19-acetyl-1,2,2,7,7,12,12,17,17-nonamethylcorrinate perchlorate (mp 172°C): λ_{max} = 245 (4.17), 254 (sh/4.07), 270 (sh/3.94), 308 (sh/4.30), 323 (4.38), 433 (4.02), 454 (sh/3.95); $\tilde{\nu}$ = 1707, 1628, 1582, 1554, 1510; δ = 6.30/6.04/5.94 (3s/3=CH—), 2.79 (s/CH_3CO); M^+ (− $HClO_4$) = 530 (^{58}Ni).

X-ray analysis of **17** (see Fig. 6) (crystal from methyl acetate/hexane): orthorombic, $Pna2_1$, a = 20.58 Å, b = 11.44 Å, c = 14.68 Å, Z = 4. There were 4508 reflections ($\sin\vartheta/\lambda \leq 0.54$) measured at −168°C, of which 2268 were observed [$|F| > 2.5\sigma(|F|)$], R = 0.15 (208 parameters refined). The asymmetric unit contains one disordered ClO_4^- ion and a disordered solvent molecule.

18. Racemic dicyanocobalt(III) 19-acetyl-1,2,2,7,7,12,12,17,17-nonamethylcorrinate (mp 215°C): λ_{max} = 274 (4.00), 290 (3.91), 304 (3.93), 318 (3.90), 345 (sh/4.14), 363 (4.38), 415 (3.56), 495 (sh/3.61), 526 (3.73), 567 (3.81); $\tilde{\nu}$ = 2120 (CN), 1695 (C=O), 1624, 1583, 1560, 1510; δ = 5.57 (s/1H), 5.52 (s/2H) (=CH—), 2.58 (s/CH_3CO); M^+ (− HCN, − CN) = 531.

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