Chemistry of Pyrrocorphins: Methylative Opening of the Macrocycle between Rings A and D, a Side Reaction in the Peripheral *C*-Methylation of a 20-Methyl-pyrrocorphinate

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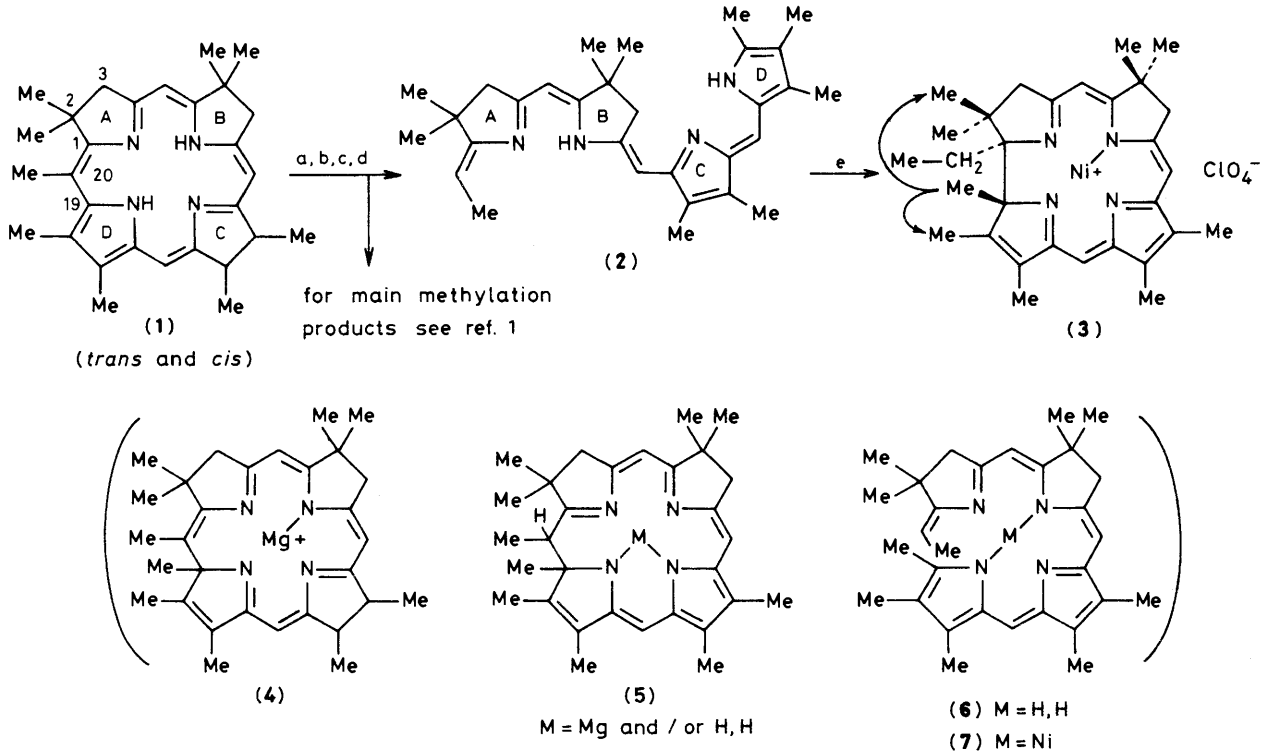
One of the minor products from the previously described peripheral *C*-methylation of a magnesium(II)-20-methyl-D-pyrrocorphinate is a C-19-methylated 19,20-seco-corphinoid derivative which, on complexation with nickel(II) acetate, recyclizes to a nickel(II)-tetradehydro-corrinate.

Recently, in the context of a chemical study related to problems of vitamin-B_{12} biosynthesis, we reported on the peripheral *C*-methylation of the magnesium complex of pyrrocorphin (**1**)[1] with methyl iodide. The main product of the methylation reaction was found to contain the new methyl group at carbon C-17 in ring D; three minor products were also



Scheme 1. Reaction conditions (for details see ref. 9, c.c. = column chromatography): a (complexation), 10 equiv. of MeMgI (1.35 M in diethyl ether) in tetrahydrofuran (c 10^{-2} M), room temp., 10 min, work-up with benzene–H_2O–NaCl in glove-box ($c < 5$ p.p.m. O_2); b (methylation), in benzene–MeI (2:1) (c 7×10^{-3} M), 40 °C, 1 h, work-up as a; c (tautomerization), 10 equiv. of 1,5,7-triazabicyclo[4.4.0]dec-5-ene in benzene (10^{-2} M), room temp., 45 min; d (decomplexation), excess of $MeCO_2H$ added, room temp., 5 min, work-up as a; c.c. (SiO_2, benzene + 2% Et_3N) followed by h.p.l.c. [Partisil 5μ, pentane-diethyl ether (2:1) + 1.5% Et_3N); e (complexation and cyclization), 20 equiv. of $Ni(OAc)_2.4H_2O$ in MeCN–CH_2Cl_2 (2:1) (c 2×10^{-3} M), room temp., 20 min; excess of $MeCO_2H$ added, 90 min, work-up with CH_2Cl_2–2% aqueous $NaClO_4$; c.c. [SiO_2 + 5% $NaClO_4$, CH_2Cl_2–diethyl ether (1:1)], cryst. from CH_2Cl_2–diethyl ether–hexane.

observed, one of which was identified as the *C*-methylation isomer with the methyl group at position C-18. Since then, a complementary study has shown that, of the two further minor products, one results from *N*-methylation† and the other from a remarkable methylative ring opening which prompted this additional report.

In the previous study, the side product in question was observed as an h.p.l.c. fraction and was assumed to be a seco-corphinoid derivative on the basis of its u.v.–visible spectrum (see footnote § in ref. 1). In contrast to the spectra of corrinoid and corphinoid derivatives, this spectrum showed a visible band distinctly more intense than the absorption band in the u.v. region. Such an absorbance ratio is characteristic[2] for metal-free‡ seco-corrinoid, and (so we extrapolate) for seco-corphinoid chromophore systems with an extended (non-quasicyclic) configuration and conformation. In the present study, the compound was isolated as a crystalline solid in 10% overall yield after column chromatography on silica gel (benzene + 2% Et_3N), followed by h.p.l.c. [Partisil 5μ; pentane–diethyl ether (2 : 1) containing 1.5 vol.% Et_3N].§ It is a monomethylation product (*m/z* 456) and has structure (**2**) according to the results of ^1H n.m.r. nuclear Overhauser enhancement (n.O.e.) difference spectroscopy symmarized in Figure 1. The configurational assignments (*Z*) to the double bonds C-1/C-20, C-5/C-6, and C-14/C-15 follow from the observation of relevant pairs of n.O.e. involving the corresponding *meso* protons, whereas the *E*-configuration of the C-9/C-10 double bond follows from the absence of an n.O.e. between the C-10 *meso* protons and the methylene protons at C-8. Both these latter protons and those of the two methyl groups at C-7 are found, however, to interact with the methyl group at position C-19; this n.O.e. over a large constitutional distance not only corroborates the configurational assignment of the double bond C-9/C-10, but also shows that the preferred conformation of the molecule is as indicated in formula (**2**). The extended form of the chromophore reflects itself in the large intensity ratio $\varepsilon_{visible}/\varepsilon_{u.v.}$ 2.8 in the electronic spectrum (see Figure 2). Both the configuration and the conformation of the molecule seem plausible in so far as they allow the chromophore system to be planar and to retain the two conjugationally favoured structural units of a *cis*-vinamidine[3] and a *cis*-pyrromethene.

The reaction sequence assumed to connect the secocorphinoid product (**2**) with the pyrrocorphinoid starting material (**1**) is delineated in formulae (**4**), (**5**), and (**6**). The steps are: (i) *C*-methylation of the magnesium pyrrocorphinate at the angular carbon C-19¶ (a position vinylogous to C-17 where the main methylation occurs), (ii) tautomerization such that ring c becomes pyrrolic (reaction condition c), (iii) protonation at the *meso* position C-20 to form an intermediate containing the chromophore structure of type (**5**) (reaction conditions d), (iv)

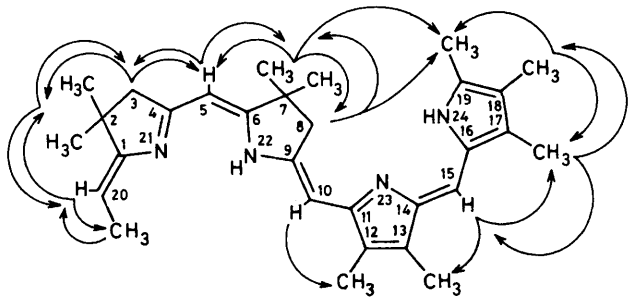


Figure 1. ^1H N.m.r. (300 MHz) n.O.e. correlations for (**2**) (enhancement intensities not less than *ca.* 1%).††

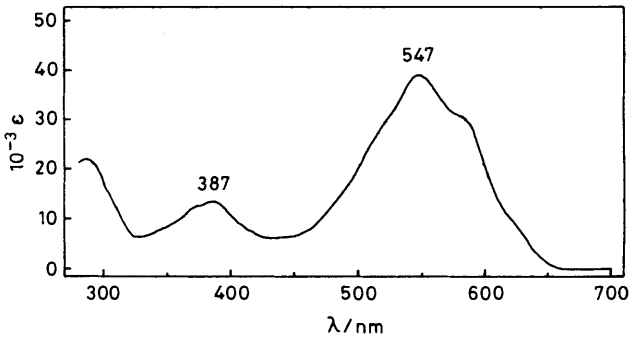


Figure 2. U.v.–visible spectrum of (**2**) (*c* 3.1 × 10^{-5} M) in benzene.††

electrocyclic fragmentation of (**5**) (presumably with M = H, H) between carbons C-19 and C-20 to form the pyrromethenoid seco-chromophore (**6**) and, finally, (v) epimerization of the Δ^9-double bond to give (**2**).

Complexation of (**2**) with nickel(II) acetate in MeCN–CH_2Cl_2 (2 : 1) followed by addition of acetic acid at room temperature (reaction conditions e) led to a practically quantitative (u.v.–visible) cyclization *via* (**3**) to the nickel(II)-12,13,17,18-tetradehydro-corrinate (**3**), which was isolated as the crystalline perchlorate in 85% yield. The structural assignment rests on the ^1H n.m.r. data (see n.O.e. correlation) and on the u.v.–visible spectrum; the latter is similar to the spectrum of a previously obtained nickel(II) complex**

† This is the 'monomethylated dipyrrocorphin' mentioned in footnote § in ref. 1; *m/z* 456 (100%; M^+); $\lambda_{max.}$ (hexane) 284 (log ε 4.37), 322 (sh., 3.91), 342 (sh., 3.83), 424 (sh., 3.96), 445 (4.02), 469 (3.97), and 509 nm (sh., 3.60); δ (C_6D_6) 5.94 (s, 10-CH), 4.71 (s, 5-CH), 4.14 and 3.65 (2 × d, *J* 17 Hz, 15-CH_2), and 2.98 (s, N-CH_3). The position of the *N*-methyl group remains undetermined.

‡ The relationship does not hold for metal complexes of seco-corrinoid (corphinoid) ligand systems since their ligand conformation is quasi-macrocyclic.

§ Product distribution in this experiment: 41% C-17 methylation, 14% C-18 methylation, 12% *N*-methylation.

¶ An angular *C*-methylation at C-19 has previously been observed with nickel(II)-1-methyl-2,3,7,8,12,13,18,19-octadehydro-(24H,Δ^{17})-corrinates by Johnson *et al.*[4]

†† Selected spectral data (for complete data and experimental details see ref. 9).

(**2**): m.p. 222 °C; $\lambda_{max.}$ (benzene) 287 (log ε 4.34), 370 (sh., 4.07), 387 (4.12), 412 (sh., 3.90), 523 (sh., 4.47), 547 (4.59), 578 (sh., 4.50), and 622 nm (sh., 3.99); *m/z* 457 (35%), 456 (M^+, 100), 442 (21), 441 (M^+-CH_3, 60); ^1H n.m.r. (300 MHz) δ (C_6D_6) 1.02 [s, 6H, 2-$(CH_3)_2$], 1.18 [s, 6H, 7-$(CH_3)_2$], 1.81 (d, *J* 7 Hz, 3H, 20-CH_3), 1.90 (s, 3H, 18-CH_3), 2.01 (s, 3H, 12-CH_3), 2.03 (s, 3H, 13-CH_3), 2.09 (s, 3H, 17-CH_3), 2.16 (s, 3H, 19-CH_3), 2.30 (s, 2H, 3-H_2), 3.23 (d, *J* 2 Hz, 2H, 8-H_2), 4.39 (q, *J* 7 Hz, 1H, 20-H), 4.88 (s, 1H, 5-H), 6.76 (t, *J* 2 Hz, 1H, 10-H), 6.82 (s, 1H, 15-H), and 12.30 (s, br., 2 × NH). (**3**): m.p. 251 °C; $\lambda_{max.}$ (CH_2Cl_2) 244 (sh., 4.11), 266 (4.27), 329 (4.53), 394 (sh., 3.40), 428 (sh., 3.51), 495 (sh., 3.99), and 520 (4.12); *m/z* (fast atom bombardment) 513 (M^+, 100%); δ ($CDCl_3$) 0.55 (m, 4H) and 1.66 (m, 1H) (ethyl group at C-1), 1.29 (s, 3H, 19-CH_3), 1.51 (s, 6H, 2 × CH_3, one of them 2-CH_3, see n.O.e.), 1.47 and 1.53 (2 × s, 6H, 2 × CH_3), 2.26 (s, 3H, 18-CH_3, see n.O.e.), 2.27, 2.36, and 2.40 [3 × d, *J* 1 Hz, 9H, 3 × C(sp^2)-CH_3], 3.08 and 3.39 (AB system, *J* 18 Hz, 2H), 3.38 and 3.43 (AB system, *J* 18.2 Hz, 2H), 6.25, 6.85, and 6.86 (3 × s, *meso* protons); no n.O.e. between 19-CH_3 and 1-CH_2CH_3 (*trans*!).

** Nickel(II)-complex of *rac.*-1,2,2,7,7,12,13,17,18-nonamethyl-12,13,18,19-tetradehydro-(24H,Δ^{17})-corrin (formula 29 in ref. 5b). Its u.v.–visible spectrum in CH_2Cl_2–CF_3CO_2H (500 : 1) is recorded in ref. 5a, p. 239.

which, in protonating medium, contains the same chromophore system.[5] The type of cyclization reaction occurring in the transformation (**7**) → (**3**) is analogous to earlier findings from this and other laboratories.[5,6]

The overall conversion of a pyrrocorphin into a (tetradehydro)corrin induced by angular methylation is reminiscent of the way in which the corrin ring is generated in the biosynthesis of vitamin B_{12}. In mechanistic detail, however, the conversion is not a biomimetic model of the natural process, the essence of the latter being the marvellous way in which Nature combines the ring contraction with an intramolecular transfer (and eventual extrusion) of redox equivalents such that a corrin rather than a tetradehydrocorrin is formed.[7] Nonetheless, the transformation (**1**) → (**2**) → (**3**) adds a remarkable variant to the already rich palette of modes of formation of corrinoid structures[6,8] and may well be a specific manifestation of the steric crowding that is expected to arise when methyl groups accumulate at and around the *meso* position C-20 of corphinoid ligands.

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