Chemistry of Pyrrocorphins: *C*-Methylations at the Periphery of Pyrrocorphins and Related Corphinoid Ligand Systems

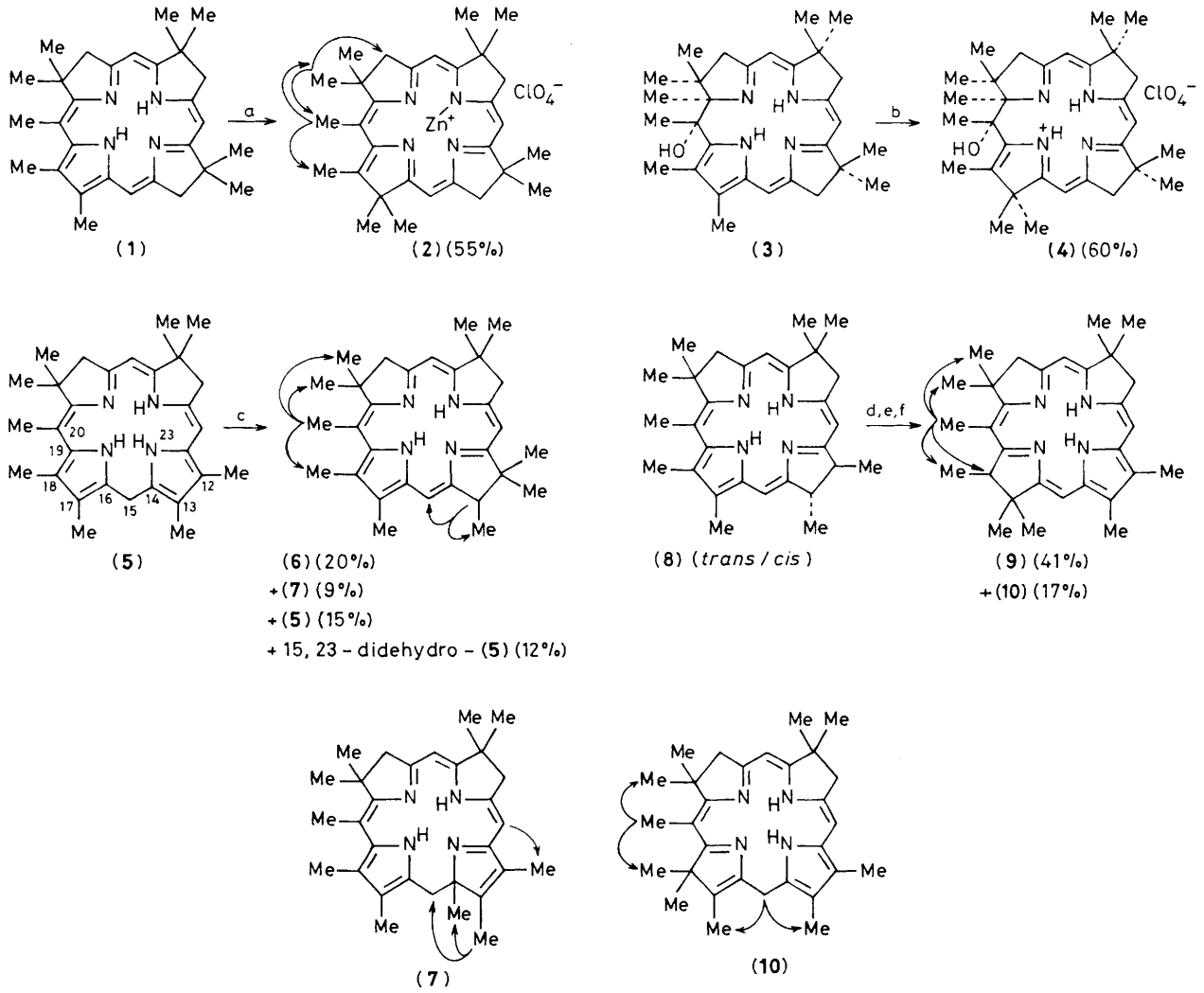
Christian Leumann, Kurt Hilpert, Jakob Schreiber, and Albert Eschenmoser*

Laboratory of Organic Chemistry, Swiss Federal Institute of Technology, Universitätstrasse 16, CH-8092 Zürich, Switzerland

Various corphinoid model systems bearing a methyl group at the *meso* position C-20 have been found to undergo regioselective chemical *C*-methylation at the ligand periphery, mimicking enzymic *C*-methylation occurring in vitamin-B_{12} biosynthesis.

Peripheral *C*-methylation of hexahydroporphinoid intermediates is the typifying process in the biosynthesis of the porphinoid coenzymes that bear methionine-derived methyl groups at their ligand periphery, *e.g.* vitamin B_{12},[1] siroheme,[2] and factor F430.[3] The simulation of such enzymic *C*-methylations chemically has been a longstanding ambition in synthetic corrin and hydroporphyrin chemistry.[4] Recently, we have found that zinc and magnesium complexes of the pyrrocorphin[5] system, a new type of hexahydroporphinoid ligand that combines structural features of both corrins and porphyrins, can be selectively *C*-methylated at the periphery of the macrocycle.[6] We now describe further examples of such pyrrocorphin *C*-methylations, and we report that the pyrrocorphin ligand is but one of a group of corphinoid systems which are substrates for peripheral *C*-methylation by chemical means. These facts came to light as a result of a search for potentially biomimetic chemical properties of the 20-methyl corphinoids that were synthesised[7] as model systems for the structures of hypothetical[1b,8,9] intermediates of corrin biosynthesis.

Complexation of the nonamethyl-pyrrocorphin (**1**) with $ZnCl_2$ in degassed tetrahydrofuran (THF) in the presence of Et_3N, directly followed by methylation with excess of MeI, produced exclusively a material with the characteristic u.v.–visible spectrum of a zinc(II) corphinate[10] (one spot on t.l.c.). It crystallised as a mixture of perchlorates (67% yield), the main component of which (90% by ^1H n.m.r.) was the zinc corphinate (**2**) [see nuclear Overhauser effect (n.O.e.) correla-



Scheme 1. *Reaction conditions* (for details see refs. 11 and 12; c.c. = column chromatography on silica gel; arrows in formulae indicate observed n.O. enhancements): a, excess of $ZnCl_2$ + 5 equiv. of Et_3N in THF, room temp., 5 min; + excess (25 vol. %) of MeI, 85 °C, 15 min; work-up with benzene–1% aqueous $NaClO_4$; b, in MeI, 40 °C, 45 h; work-up with CH_2Cl_2–aqueous CF_3CO_2H–$NaClO_4$, prep. t.l.c. (SiO_2 + 1% $NaClO_4$); c, in MeCN–MeI (4:1), 60 °C, 20 h (ampoule degassed), work-up with benzene–H_2O; c.c. benzene–ether, 20:1; h.p.l.c. Partisil 5, pentane–ether, 2:1, 1.5% Et_3N; d, 10 equiv. of MeMgI (1.35 M in ether) in THF (*c* 9 × 10^{-3} M), room temp., 10 min; work-up with benzene–H_2O–NaCl (in glove-box, <5 p.p.m. O_2); e, in benzene–MeI (2:1) (*c* 9 × 10^{-3} M), room temp., 2 h; work-up as d; f, 10 equiv. of 1,5,7-triazabicyclo[4.4.0]dec-5-ene[5,6] in benzene (*c* 9 × 10^{-3} M), room temp., 35 min; $MeCO_2H$ added; work-up as d.

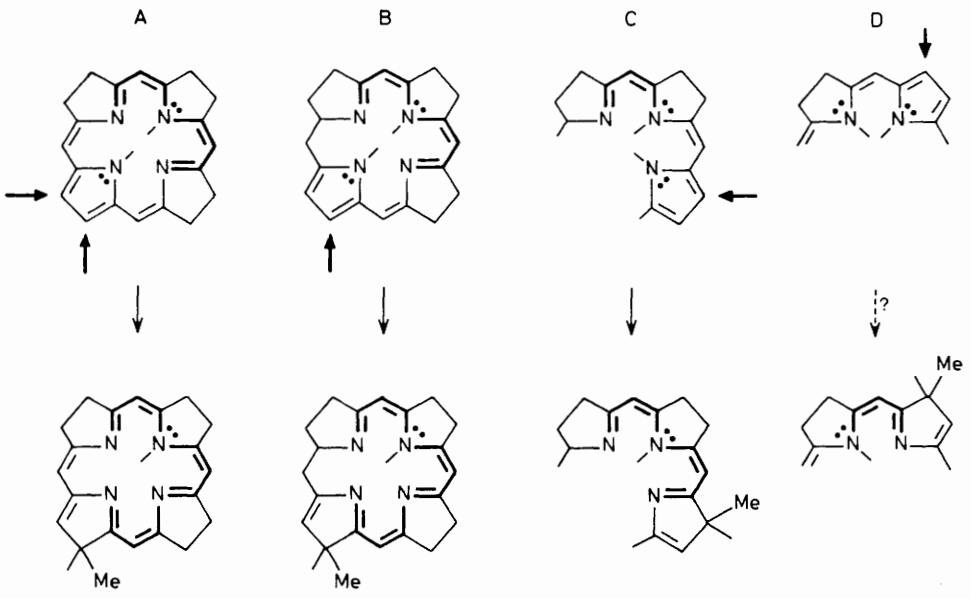
tions indicated in the structural formula]. The minor component has not been identified; ^1H n.m.r. signals assigned to it point to the C-18 monomethylated isomer.

Peripheral *C*-methylation with virtually complete regioselection for position C-17 was observed when a solution of the (metal free) 1,20-dihydro-pyrrocorphinol (**3**) in MeI was allowed to stand for two days at 40 °C. Besides unchanged as well as dehydrated starting material, a single monomethylation product was isolated as the crystalline perchlorate (pure by ^1H n.m.r.). Its structure (**4**) is an exact analogue of the previously described[9] model substrate for the dehydrocorphinol → corrin rearrangement [see formula (**2**) in preceding communication]. The very close u.v.–visible and ^1H n.m.r. spectral correspondence between the two compounds excludes the alternative structure of a C-18 methylated isomer for the methylation product of (**3**).

Whereas the direction of the observed regioselectivity in the methylation of (**1**) had not been foreseen, the regioselectivity (but not the overall occurrence) of the *C*-methylation of (**3**) was predictable; only electrophilic attack at position C-17 (but not at C-18) extends the corrinoid donor–acceptor conjugation from three rings (in the reactant) to four (in the product). This sort of rationale led us to investigate the methylation of the 'dipyrrocorphin' (**5**) in which *C*-methylation would be expected at C-12 and C-18 (if at all); analogy with the behaviour of (**1**) further suggested that, of these, C-12 should be more favoured.

Treatment of (metal free) (**5**) with degassed MeCN–MeI (4:1) at 60 °C for 20 h gave, after chromatography, a non-polar main fraction showing the characteristic u.v.–visible spectrum of 20-methyl-D-pyrrocorphins,† starting material

† D- and C-Pyrrocorphins containing a methyl group at C-20 can be distinguished by their u.v.–visible spectra, see ‡ and ref. 7; for ^1H n.m.r. spectra of pyrrocorphins see refs. 5, 6, and 7.



Scheme 2

(15%), the corresponding isobacteriochlorin[7] (12%), and a small amount of a polar (protonated) material. H.p.l.c. of the crystalline pyrrocorphin fraction showed it to consist mainly of (**6**) (>90% of the crystallisate, 20% overall) besides a small amount of the C-13 methylated isomer‡ (<2% overall) and a trace of bismethylated material (mass spectrum). On deprotonation ($NaHCO_3$), the non-moving polar fraction referred to above became accessible to chromatography; h.p.l.c. and ^1H n.m.r. spectroscopy showed it to contain mainly the angularly monomethylated compound (**7**) (9% overall). The structural assignments for (**6**) and (**7**) are based on ^1H n.m.r. spectra and n.O.e. correlations (see structural formulae).

The angular methylation site C-14 is a position vinylogous to the main methylation site C-12 and, therefore, (**7**) may be considered an 'allowed' *C*-methylation product according to the rationale above. The main methylation site C-12 happens to correspond to the methyl-bearing site of ring C in vitamin B_{12}. The position corresponding to the other methyl-bearing site in the C, D-part of the B_{12}-structure, position C-17 in ring D, could be shown in the present model study to be accessible to chemical *C*-methylation with comparable ease and selectivity simply by choosing, instead of the dipyrrocorphin (**5**), its major tautomer,[7] the D-pyrrocorphin (**8**), as methylation substrate.

Treatment of the magnesium complex of (**8**) with benzene–MeI (2:1) at 20 °C, followed by tautomerisation of the primary methylation products (Mg corphinates) with a guanidine base[6] and demetallation with $MeCO_2H$, gave (after chromatography) the two crystalline isomeric monomethylation products (**9**) and (**10**) in yields of 41 and 17% respectively§ (see n.O.e. correlations). The minor product (**10**) is a new *C*-pyrrocorphin tautomer and as such (luckily¶) produced by an incomplete (kinetically controlled) tautomerisation of the primary C-18 methylation product. On melting, it is converted into the corresponding *C*-pyrrocorphin.

All three chromophores that have been found to undergo smooth peripheral *C*-methylation have a common structural feature, namely, conjugation between a pyrrole ring and an enamine system such that a vinylogously hydrazinoid arrangement of two nitrogen electron pair centres is involved. *C*-Methylation at the pyrrole ring periphery converts this relationship into an amidinoid donor–acceptor conjugation (Scheme 2). The increase in conjugative stabilisation that (supposedly) accompanies this may be an important part of the thermodynamic driving force for peripheral and regioselective *C*-methylation. Experimentally investigated so far have been cases A, B, and C; the extrapolation to case D (methylation of porphyrinogen mono- or bis-tautomers) remains hypothetical, but is of considerable interest with regard to open questions in synthesis and biosynthesis.

For complete spectral data for the compounds reported see refs. 11 and 12.**

‡ *m/z* 456 (M^+, 100%); λ_{max} 333 (relative absorbance 0.98), 344 (1.0), 360 (0.88), 377 (0.70), 492 (0.16), 535 (0.15), and 576 (0.14) nm (hexane). We suspect that this minor product is not formed by methylation of (**5**) but rather of its *C*-pyrrocorphin tautomer [see formula (**18**) in ref. 7] which may be formed during the reaction. Treatment of that *C*-pyrrocorphin tautomer[7] with MeCN–MeI (4:1) under the same conditions gave (**6**) and its C-13-methylated isomer in a 1:1 ratio (h.p.l.c.).

§ Traces of a monomethylated dipyrrocorphin and small amounts of a seco-corphinoid material (u.v.–visible) were also observed.

¶ The corresponding *C*-pyrrocorphin tautomer was not distinguishable from *C*-pyrrocorphin (**9**) in h.p.l.c., although clearly different in its ^1H n.m.r. spectrum.

** Selected spectral data: (**2**): m.p. 172 °C; λ_{max} (EtOH) 305 nm (log ϵ 4.48), 354 (4.51), and 516 (3.88); δ ($CDCl_3$) 2.11 (s, 18-CH_3), 2.31 (s, 20-CH_3), 1.45 (s, 2-CH_3), and 2.84 (s, 3-CH_2); (**4**): m.p. 179 °C; λ_{max} (EtOH) 323 (4.51), 387 (3.99), and 506 (4.08); (**6**): m.p. 249 °C; u.v.–visible similar to spectrum of (**8**); δ (C_6D_6) 2.81 (s, 20-CH_3), 2.69 (s, 18-CH_3), 7.01 (d, *J* 1.5 Hz, 15-H), and 3.06 (dq, J_1 1.5, J_2 7 Hz, 13-H); (**9**): m.p. 291 °C; u.v.–visible similar to spectrum of (**18b**) in ref. 7; δ (C_6D_6) 2.37 (s, 20-CH_3), 3.08 (q, *J* 7 Hz, 18-H), and 7.17 (s, 15-H); (**10**): m.p. 232 °C (decomp.); λ_{max} 284 (4.31), 364/377 (4.40), and 493 (3.77) (hexane); δ (C_6D_6) 3.70 (s, 15-CH_2).

We thank Dr. Deirdre Hickey and Dr. E. Zass for their help in preparing the final manuscript. The work was supported by Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung.

Received, 8th September 1983; Com. 1209

References

1 (a) R. C. Bray and D. Shemin, *J. Biol. Chem.*, 1963, **238**, 1501; (b) A. R. Battersby and E. McDonald, in 'Vitamin B_{12},' ed. D. Dolphin, Wiley, New York, 1982, p. 108.

2 M. J. Murphy, L. M. Siegel, H. Kamin, and D. Rosenthal, *J. Biol. Chem.*, 1973, **248**,' 2801; A. R. Battersby, E. McDonald, H. R. Morris, D. C. Williams, V. Ya. Bykhovskii, N. I. Zaitseva, and V. N. Bukin, *Tetrahedron Lett.*, 1977, 2217; K. H. Bergmann, R. Deeg, K. D. Gneuss, H. P. Kriemler, and G. Müller, *Hoppe-Seyler's Z. physiol. Chem.*, 1977, **358**, 339; A. I. Scott, A. J. Irwin, L. M. Siegel, and J. N. Shoolery, *J. Am. Chem. Soc.*, 1978, **100**, 316, 7987.

3 R. P. Gunsalus and R. S. Wolfe, *FEMS Microbiol. Lett.*, 1978, **3**, 191; A. Pfaltz, B. Jaun, A. Fässler, A. Eschenmoser, R. Jaenchen, H. H. Gilles, G. Dieckert, and R. K. Thauer, *Helv. Chim. Acta*, 1982, **65**, 828.

4 A. W. Johnson, in 'Vitamin B_{12} and Intrinsic Factor,' ed. H. C. Heinrich, Enke, Stuttgart, 1962, p. 1; A. W. Johnson, *Chem. Soc. Rev.*, 1975, **4**, 1; K. Hosaka, A. P. Johnson, and A. W. Johnson, *Tetrahedron Lett.*, 1978, 2959.

5 J. E. Johansen, V. Piermattie, C. Angst, E. Diener, C. Kratky, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 261; R. Schwesinger, R. Waditschatka, J. Rigby, R. Nordmann, W. B. Schweizer, E. Zass, and A. Eschenmoser, *Helv. Chim. Acta*, 1982, **65**, 600.

6 R. Waditschatka, E. Diener, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 631.

7 K. Hilpert, C. Leumann, A. Davis, and A. Eschenmoser, *J. Chem. Soc., Chem. Commun.*, 1983, preceding communication.

8 A. R. Battersby, M. J. Bushell, C. Jones, N. G. Lewis, and A. Pfenninger, *Proc. Natl. Acad. Sci. USA*, 1981, **78**, 13; A. R. Battersby, K. Frobel, F. Hammerschmidt, and C. Jones, *J. Chem. Soc., Chem. Commun.*, 1982, 455; H. Uzar and A. R. Battersby, *ibid.*, 1982, 1204.

9 V. Rasetti, A. Pfaltz, C. Kratky, and A. Eschenmoser, *Proc. Natl. Acad. Sci. USA*, 1981, **78**, 16; V. Rasetti, K. Hilpert, A. Fässler, A. Pfaltz, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 1058.

10 P. M. Müller, S. Farooq, B. Hardegger, W. S. Salmond, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 914; exp. details in P. M. Müller, Dissertation, ETH Zürich, Nr. 5135, 1973.

11 K. Hilpert, Dissertation, ETH Zürich, 1983, No. 7390.

12 C. Leumann, Dissertation, ETH Zürich, in preparation.