Mercuration Reactions of Porphyrins: New Efficient Syntheses of Harderoporphyrin and Isoharderoporphyrin

By Kevin M. Smith* and Kevin C. Langry

(*Department of Chemistry, University of California at Davis, Davis, California* 95616)

Summary. Treatment with mercury(II) acetate of metal complexes of porphyrins bearing peripherally unsubstituted positions gives the corresponding mercurated derivatives, using the palladium–olefin reaction this observation is exploited in the synthesis of coproporphyrin III tetramethyl ester (**2**), harderoporphyrin trimethyl ester (**3**), and isoharderoporphyrin trimethyl ester (**4**).

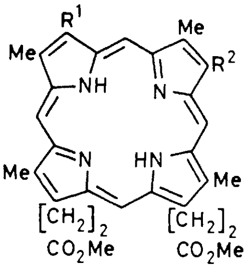
Substituent manipulations at the 2 and/or 4 positions of deuteroporphyrin IX dimethyl ester (**1**) have provided a host of porphyrins for physical, spectroscopic, and biological studies of porphyrin systems.[1] With only a few exceptions, these transformations have relied on classical chemistry, much of which was developed by Fischer.[2] In this communication we describe mercuration and palladium–olefin reactions on derivatives of (**1**) outlining as examples new and efficient routes to coproporphyrin III, harderoporphyrin, and isoharderoporphyrin esters (**2**—**4**), respectively.

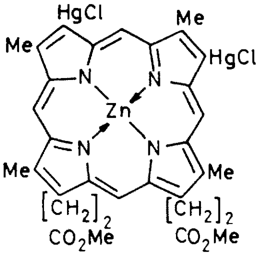
Zinc(II) deuteroporphyrin IX dimethyl ester in tetrahydrofuran was treated with an excess of mercury(II) acetate in methanol for 3 h at 70 °C, and gave a greater than quantitative yield† of the bis-mercurichloride porphyrin (**10**) after anion exchange using sodium chloride. With DCl this compound gave the fully 2,4-deuteriated deri-

---

† Yields for (**10**), (**14**) and (**15**) based on the structural formulae shown were uniformly between 120 and 125%. This indicates that more than two mercury atoms per porphyrin ligand [for (**10**)] and one [for (**14**) and (**15**)] may be present. It is possible that the excess of mercury(II) is simply co-crystallised with the highly insoluble chloromercuriporphyrins but it is also possible that 'double sandwich' species in which mercury(II) is associated with the central nitrogens of the porphyrin (see M. F. Hudson and K. M. Smith, *Tetrahedron*, 1975, **31**, 3077, 1976, **32**, 597) might be present.

vative (**5**)[‡] in which some *meso* deuteriation was also apparent[3] However, the DCl reaction confirmed that the mercurichloride units were substantially attached to the porphyrin at the 2 and 4 (rather than *meso*) positions



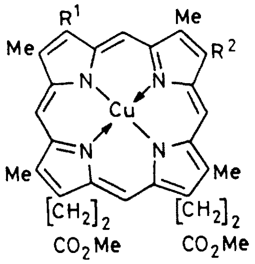


(**10**)

(**1**) $\mathrm{R^1 = R^2 = H}$
(**2**) $\mathrm{R^1 = R^2 = [CH_2]_2CO_2Me}$
(**3**) $\mathrm{R^1 = CH{=}CH_2,\ R^2 = [CH_2]_2CO_2Me}$
(**4**) $\mathrm{R^1 = [CH_2]_2CO_2Me,\ R^2 = CH{=}CH_2}$
(**5**) $\mathrm{R^1 = R^2 = D}$
(**6**) $\mathrm{R^1 = R^2 = CH{=}CHCO_2Me}$
(**7**) $\mathrm{R^1 = R^2 = CH{=}CH_2}$
(**8**) $\mathrm{R^1 = COMe,\ R^2 = [CH_2]_2CO_2Me}$
(**9**) $\mathrm{R^1 = [CH_2]_2CO_2Me,\ R^2 = COMe}$

With methyl acrylate and $\mathrm{LiPdCl_3}$ in acetonitrile,[4] compound (**10**) gave, after removal of zinc, a 31% yield of the bis-acrylate (**6**)[§] which was reduced by catalytic hydrogenation in formic acid to give a 90% yield of coproporphyrin III tetramethyl ester (**2**) Treatment of (**10**) with ethylene and $\mathrm{LiPdCl_3}$ in acetonitrile gave a low yield of protoporphyrin IX dimethyl ester (**7**) after removal of zinc with dilute acid

This chemistry was further illustrated in a new synthesis of harderoporphyrin and isoharderoporphyrin trimethyl esters (**3**) and (**4**), respectively Harderoporphyrin has been identified[5,6] as the tricarboxylic acid porphyrin present, along with protoporphyrin IX and coproporphyrin III, in the Harderian glands of certain rodents The porphyrinogen derived from harderoporphyrin has also been shown[5,7] to be a fleeting intermediate in the biosynthesis of protoporphyrin IX from coproporphyrinogen III We have already described syntheses of harderoporphyrin and isoharderoporphyrin esters[8] from protoporphyrin IX dimethyl ester (**7**), but the following syntheses from deuteroporphyrin IX dimethyl ester are more efficient Mono-acetylation of copper(II) deuteroporphyrin IX dimethyl ester (**11**) with acetic anhydride and tin(IV) chloride in benzene[9] gave a mixture of the two isomers (**12**) and (**13**) which were mercurated using mercury(II) acetate to give a >100% yield[†] of (**14**) and (**15**) after treatment with sodium chloride With methyl acrylate and $\mathrm{LiPdCl_3}$ in acetonitrile, these compounds gave a 76% yield[¶] of (**16**) and (**17**) which were easily separated using preparative thick layer chromatography on Kieselgel G The most mobile band from the plates correlated with harderoporphyrin trimethyl ester (**3**) [*i e* it had the structure (**16**) bearing a 2-acetyl group] The individual copper(II) complexes were hydrogenated over 10% palladised charcoal in tetrahydrofuran–ethyl acetate and gave the acetyl–propionate isomers (**18**) and (**19**) Demetallation using sulphuric acid in trifluoroacetic acid gave (**8**) and (**9**) which were reduced with sodium borohydride and then dehydrated with toluene *p*-sulphonic acid in hot *o*-dichlorobenzene to give, after re-esterification in 5% sulphuric acid–methanol, harderoporphyrin trimethyl ester (**3**) and its isomer (**4**) The identity of the final products was established by m p and mixed m p with an authentic sample,[5] as well as ^{1}H n m r spectroscopy and h p l c comparisons



(**11**) $\mathrm{R^1 = R^2 = H}$
(**12**) $\mathrm{R^1 = COMe,\ R^2 = H}$
(**13**) $\mathrm{R^1 = H,\ R^2 = COMe}$
(**14**) $\mathrm{R^1 = COMe,\ R^2 = HgCl}$
(**15**) $\mathrm{R^1 = HgCl,\ R^2 = COMe}$
(**16**) $\mathrm{R^1 = COMe,\ R^2 = CH{=}CHCO_2Me}$
(**17**) $\mathrm{R^1 = CH{=}CHCO_2Me,\ R^2 = COMe}$
(**18**) $\mathrm{R^1 = COMe,\ R^2 = [CH_2]_2CO_2Me}$
(**19**) $\mathrm{R^1 = [CH_2]_2CO_2Me,\ R_2 = COMe}$

Harderoporphyrin and isoharderoporphyrin esters could also be obtained by a slightly different route in which the mono-acetyldeuteroporphyrin IX esters were separated prior to the mercuration by preparative t l c[10] It is, however, our impression that the t l c separation of (**16**) and (**17**) is more readily achieved

A study of the precise nature of the mercurated porphyrins (**10**), (**14**) and (**15**), and of their further use for functionalisation of porphyrin systems is in progress

We thank the National Institutes of Health for generous support of this research

(*Received*, 31*st October* 1979, *Com* 1162)

[‡] This same compound, but with a slightly different pattern for *meso* deuteriation, can be obtained by fusion of protohemin in $[^2\mathrm{H}_5]$-resorcinol followed by demetallation and esterification

[§] Yield not optimised An almost equal yield of the separable (preparative t l c) 2- or 4-monoacrylates was also obtained

[¶] This yield is raised to 90% when based on consumed starting material, isomer yields are 44% of (**16**) and 46% of (**17**)

[1] 'Porphyrins and Metalloporphyrins,' ed K M Smith, Elsevier, Amsterdam, 1975
[2] H Fischer and H Orth, 'Die Chemie des Pyrrols,' Akademische Verlag Leipzig 1937, vol II, pt 1
[3] K M Smith, K C Langry, and J S de Ropp, *J C S Chem Comm* , 1979, 1001
[4] R F Heck, *J Amer Chem Soc* , 1968, **90**, 5518
[5] J A S Cavaleiro, G W Kenner, and K M Smith, *J C S Perkin I*, 1974, 1188
[6] A H Jackson, G W Kenner, K M Smith and C J Suckling, *Tetrahedron*, 1976, **32**, 2753
[7] D E Games, A H Jackson, J R Jackson, R V Belcher, and S G Smith, *J C S Chem Comm* , 1976, 187
[8] G W Kenner, J M E Quirke, and K M Smith, *Tetrahedron*, 1976, **32**, 2753
[9] H Brockmann, Jr , K -M Bliesener, and H H Inhoffen, *Annalen*, 1968, **718**, 148
[10] K M Smith, K C Langry, and R Nayyir-Mazhir, unpublished results