Synthesis of the Isobacteriochlorin Macrocycle: A Photochemical Approach

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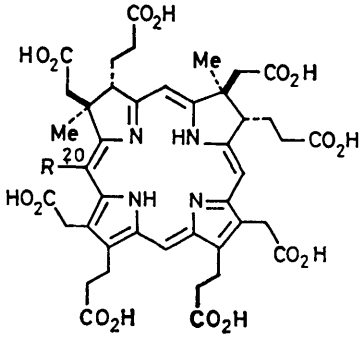
Summary The isobacteriochlorin macrocycle is synthesised by a mild route in which the key step is a photochemical cyclisation.

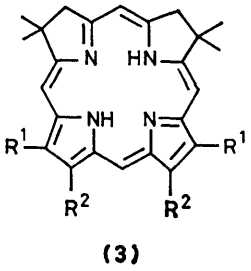
IT has been shown recently that the isobacteriochlorin[1-4] (**1**) and the corresponding 20-methyl derivative[5,6] (**2**), probably as their dihydro-derivatives, are important for

the biosynthesis of vitamin B_{12}; these studies[1,3–6] also led to the illustrated structures for the natural products (**1**) and (**2**). The substance (**1**), named sirohydrochlorin, had been isolated earlier[7] (its structure was not fully known at that time) as the metal-free form of the prosthetic group in the enzyme sulphite reductase.

Only small amounts of the natural materials (**1**) and (**2**) are available so their synthesis is of great interest. No rational route to the isobacteriochlorin macrocycle was known until 1979[8] and a simpler alternative method has been recently outlined.[9] The present strategy was based on the joining of eastern and western dipyrrolic components and we hoped this approach would be compatible with the acetate and propionate side-chains present in the longer-term targets, the natural materials (**1**) and (**2**). The successful route† to (**3a**) and (**3b**) is outlined here (Scheme).



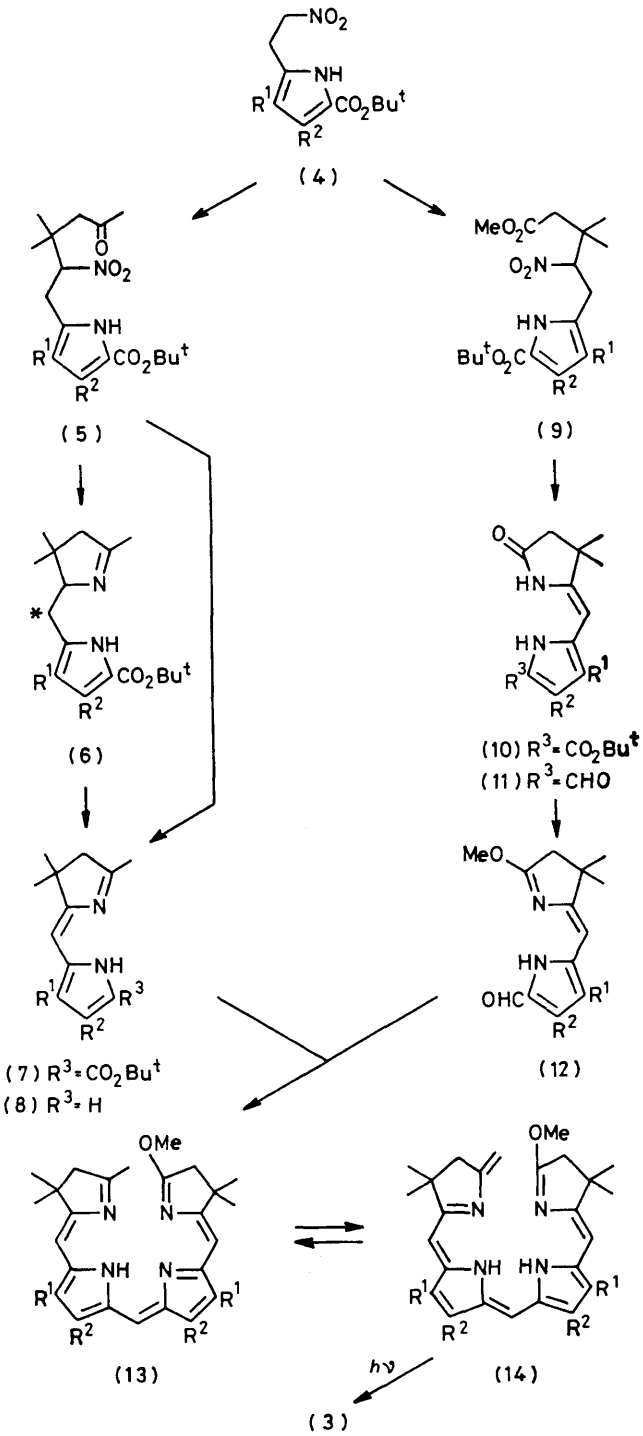
(**1**) R = H
(**2**) R = Me



(**3**)

The product (**5a**)‡, m.p. 122—123 °C, 73%, from Michael addition of the nitroethylpyrrole (**4a**)‡ to mesityl oxide in *NN*-dimethylformamide (DMF) using $Bu_4N^+F^-$ (2 h) was reduced with zinc–acetic acid and then with titanium(III) chloride[10] during 7 h to yield the imine (**6a**)‡, m.p. 68—73 °C, 93%. Lead tetra-acetate in acetic acid (30 min) introduced an acetoxy-group at the starred site of (**6a**) and elimination of acetic acid with HCO_2H–CH_2Cl_2 (18 h) then afforded the conjugated imine (**7a**)‡, m.p. 152—154 °C, 49%.

The other component (**12a**) was also prepared from (**4a**) by analogous Michael addition in DMF at 50 °C to methyl 3-methylbut-2-enoate yielding (**9a**)‡, m.p. 104—106 °C, 66%. This was reduced with zinc–acetic acid for 1 h at 70 °C and then with titanium(III) chloride for 1·5 h to yield the lactam‡, m.p. 199—200 °C, 88%. Introduction of additional unsaturation by the above lead tetra-acetate procedure at 40 °C and elimination of acetic acid using toluene-*p*-sulphonic acid in boiling CH_2Cl_2 (2 h) gave (**10a**)‡, m.p. 187—189 °C, 74%. This was formylated by treatment with trifluoroacetic acid (TFA) and trimethyl-orthoformate[11] (total 30 min) and the resulting aldehyde (**11a**)‡, m.p. 221—222 °C, 86%, was converted by $Me_3O^+BF_4^-$ and Hunig's base in CH_2Cl_2 (2 h) into the imino-ether (**12a**)‡, m.p. 132—134 °C, 76% based on unrecovered starting material. This in methanol condensed with the pyrrole (**8a**), formed from (**7a**) by treatment with TFA, to yield the seco-system (**13a**) after 10 min. Irradiation of (**13a**) in tetrahydrofuran (THF)–MeOH containing TFA



SCHEME. **a**; $R^1 = R^2 = Me$
b; $R^1 = CH_2CO_2Me$, $R^2 = [CH_2]_2CO_2Me$.

† This route stemmed from earlier work in this laboratory by Dr. L. A. Reiter using nitrones as intermediates (to be published separately).

‡ Fully characterised new compound; prepared at room temperature unless otherwise stated.

and Hunig's base (*ca.* 0·3% of each) for 2 h with a tungsten lamp gave the crystalline isobacteriochlorin (**3a**)‡§ in 27% overall yield from the precursors (**7a**) and (**12a**); this decomposed rather than melted. Photochemical cyclisation of the 18π-tautomer (**14a**), followed by loss of methanol, is a plausible mechanism for this transformation.

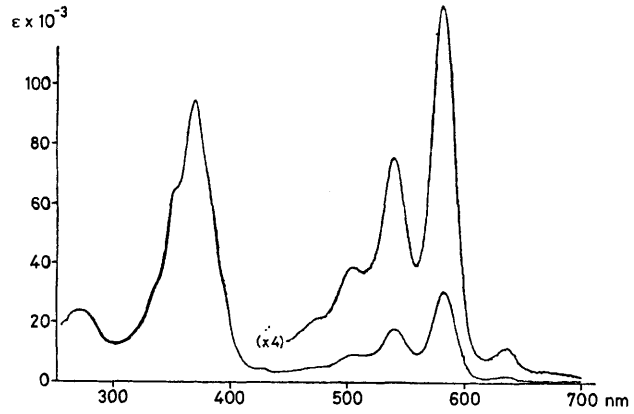


FIGURE. U.v.–vis. absorption spectrum of isobacteriochlorin (**3b**) in methyl acetate.

This approach was also successful for the isobacteriochlorin (**3b**) carrying acetic and propionic residues. The eastern component (**12b**) was synthesised analogously to (**12a**), the yields being (**9b**)‡, 60%, the intermediate lactam‡, 91%, (**10b**)‡, 86%, (**11b**)‡, 88%, and (**12b**)‡, 76%. A change was necessary for the other component (**7b**). The adduct (**5b**)‡, 73%, was converted into its nitronate anion and reduced with titanium(III) chloride[12] to yield the unsaturated imine (**7b**)‡ directly, 31% overall. Condensation of the corresponding α-free pyrrole (**8b**), prepared as for (**8a**), with the aldehyde (**12b**) gave the seco-system (**13b**) ⇌ (**14b**). Irradiation then yielded the isobacteriochlorin (**3b**)‡ in 33% overall yield from the pyrrolic precursors (**7b**) and (**12b**); its absorption spectrum is shown in the Figure.

The mild conditions for this route, particularly in the final cyclisation step, and its success for the construction of the isobacteriochlorin (**3b**) make it attractive for the synthesis of sirohydrochlorin (**1**).

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§ An *X*-ray structure analysis of (**3a**) will be published elsewhere.

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