Novel Synthesis of Deuteriated Derivatives of Protoporphyrin-IX

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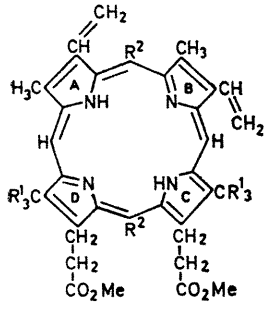
Summary A new efficient route to protoporphyrin-IX from pyrromethanes is described and employed in the synthesis of the 5,8-hexadeuterio and $\alpha\gamma$-dideuterio dimethyl esters.

IN order to settle the precise identity of certain resonances in the contact shift n.m.r. spectra of myoglobin and haemoglobin[1] we required the octadeuterio-derivative (**1b**) of protoporphyrin-IX. Taking into account the symmetry elements within this molecule[2] and economy of deuteriated materials, we adopted a strategy of synthesis based on MacDonald's procedure,[3] utilising the acid-catalysed condensation of the A–B and C–D pyrromethanes (**2**) and (**3**). Several different syntheses of protoporphyrin-IX (**1a**) have been reported,[4] but none of these has employed the MacDonald approach, which appears ideally suited to the construction of porphyrins with this substituent orientation. The vinyl groups in both of the protoporphyrin syntheses originating from this laboratory were fashioned from β-chloroethyl substituents, produced in two stages from the corresponding bis-(β-acetoxyethyl)porphyrins;[4b] this method was chosen again but, in order to reduce the number of synthetic operations on deuteriated materials we decided to introduce the β-chloroethyl functions at the dipyrrolic stage.



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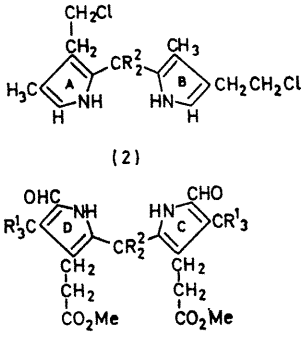
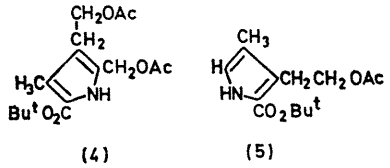


(2)

(3)

a; $R^1 = R^2 = H$
b; $R^1 = R^2 = D$
c; $R^1 = D$; $R^2 = H$
d; $R^1 = H$; $R^2 = D$

Brief treatment of t-butyl 3-(β-acetoxyethyl)-2-acetoxymethyl-4-methylpyrrole-5-carboxylate (**4**)[5] m.p. 82—84° (obtained in high yield from the corresponding 2-methylpyrrole, m.p. 89—90°, with lead tetra-acetate) with the 2-unsubstituted pyrrole (**5**)[6] m.p. 76—77°, and sodium acetate under reflux in acetic acid furnished the pyrromethane (**6a**; X = OAc). Like other t-butyloxycarbonylpyrromethanes that we have prepared,[4b] this material was low-melting and difficult to purify and therefore it was hydrolysed to the corresponding bis-(β-hydroxyethyl)pyrromethane (**6a**; X = OH) and thence converted into the bis-(β-chloroethyl)pyrromethane (**6a**; X = Cl)† m.p. 134—135°, with triphenylphosphine and carbon tetrachloride,[7]



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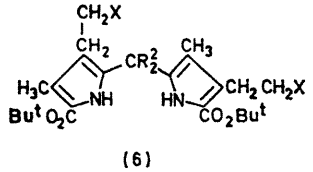

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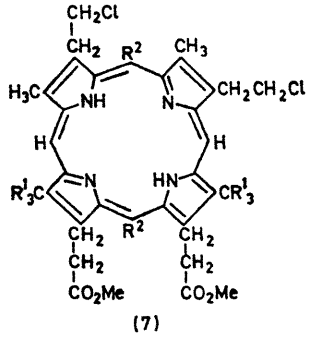


(7)

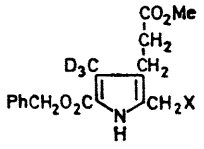
in an overall yield of 30% from pyrroles (**4**) and (**5**). With cold trifluoroacetic acid this compound gave the required A–B intermediate (**2a**) which, in the presence of 5,5′-diformyl-3,3′-bis-(β-methoxycarbonylethyl)-4,4′-dimethylpyrromethane (**3a**),[8] toluene-*p*-sulphonic acid hydrate, and zinc acetate gave the bis-(β-chloroethyl)porphyrin (**7a**) in 35—40% yield after treatment with 5% sulphuric acid in methanol. This compound was identical in all respects with an authentic sample[4b] and was transformed into protoporphyrin-IX dimethyl ester (**1a**) by treatment of its zinc chelate with potassium t-butoxide in t-butyl alcohol, as reported previously.[4b] The overall yield of 28—32% from dipyrrolic intermediates represents a more than two-fold improvement on the best claims of earlier workers.[4d]

Having established a new, easy route to protoporphyrin-IX and realising that specific deuteriation could only be achieved by a total synthesis, we prepared the deuteriated pyrrole (**8**; X = D),‡ m.p. 107°. Treatment

† New compound which gave a satisfactory elemental analysis.

‡ This was accomplished by ring synthesis from $CH(COCD_3)_2CH_2CH_2CO_2Me$; deuteriation (>90% in the acetyl functions) was carried out on the corresponding carboxylic acid precursor. During ring formation approximately 60% of the deuterium was lost from the acetyl function which formed the 2-methyl group in (**8**; X = D) but all of the deuterium from the other acetyl was retained in the 4-methyl group (>90% deuteriation). All deuteriated materials described showed n.m.r., i.r., and mass spectra compatible with the structures shown, and were compared with their undeuteriated counterparts, which have been fully characterised elsewhere. M.p.s were virtually identical with those of undeuteriated compounds, except for (**8**; X = D).

with lead tetra-acetate furnished the acetoxymethyl derivative m.p. 110° in 95% yield, and this was self-condensed in methanol and hydrochloric acid[9] to (**9a**; X = CH_2Ph) m.p. 100°; the residual deuterium in the acetoxymethyl function of the precursor was not retained at the interpyrrolic position of the pyrromethane, but (**9b**; X = CH_2Ph) m.p. 100°, could be efficiently prepared by carrying out the reaction in deuteriomethanol as solvent, the product showing >80% deuteriation at the inter-



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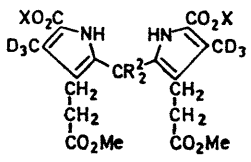

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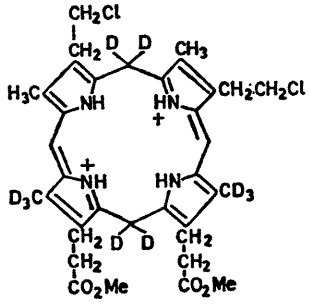

(10)

pyrrolic carbon atom. Catalytic hydrogenation of (**9b**; X = CH_2Ph) gave (**9b**; X = H) m.p. 190—191°, which was diformylated[8] to (**3b**) m.p. 180—181°. Condensation with (**2b**)§ in the presence of toluene-*p*-sulphonic acid and zinc acetate and subsequent methanolysis gave (**7c**) m.p. 216—217°; the zinc chelate of this compound was then converted[4b] into the hexadeuterioprotoporphyrin-IX dimethyl ester (**1c**) m.p. 228—229°. Loss of the deuterium at the *meso*-positions during macrocycle formation can be convincingly explained by the intermediacy of the phlorin dication[10] species (**10**) which, through equilibrium with the monocation, could lose the deuterium atoms from the interpyrrolic positions before oxidation to porphyrin. This theory was confirmed by condensation of (**2a**) with (**3a**) catalysed with deuteriotoluene-*p*-sulphonic acid in deuteriomethanol to give the $\alpha\gamma$-dideuterioporphyrin (**7d**) m.p. 216—217°; this porphyrin was transformed by our established procedure[4a] into $\alpha\gamma$-dideuterioprotoporphyrin IX dimethyl ester (**1d**) m.p. 228—229°.

The *meso*-exchange process, mediated by the phlorin dication (**10**) has thus enabled us to prepare the two proto-porphyrin-IX derivatives (**1c**) and (**1d**). Together, these serve the same purpose as (**1b**), and the results of n.m.r. studies will be reported elsewhere.

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§ Obtained as described earlier from (**4**) and (**5**), except that the pyrromethane condensation was performed in deuterioacetic acid. The product showed >80% deuteriation at the interpyrrolic carbon atom.

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