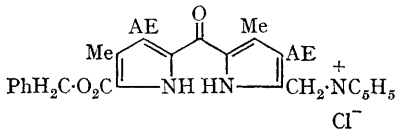
New Syntheses of Protoporphyrin-IX

By R. P. CARR, P. J. CROOK, A. H. JACKSON, and G. W. KENNER*

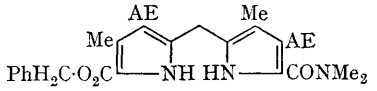
(*The Robert Robinson Laboratories, University of Liverpool, Liverpool* 7)

PROTOPORPHYRIN-IX is biologically the most important porphyrin, not only on account of the roles its iron complexes play in oxygen and electron transport but also because it is the precursor of chlorophyll. For biosynthetical experiments it seemed desirable to have much more versatile syntheses than H. Fischer's classical route[1] through deuteroporphyrin and its 2,4-diacetyl derivative. We now describe two syntheses, utilizing respectively each of our oxobilane methods[2] and a new way of introducing vinyl substituents into the porphin nucleus.

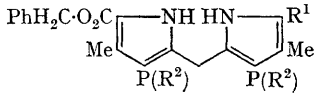
The pyridinium salt (I) was prepared by methods developed for simpler analogues[3] and coupled with the lithium salt of the pyrromethane carboxylic acid (III; $R^1=CO_2H$, $R^2=Me$) to afford the *a*-oxobilane (IV) (41%), from which the 2,4-diacetoxyethylporphyrin (V) (30%) was obtained as indicated. Alternatively the pyrromethane amide (II) was condensed (phosphoryl chloride) with the α-unsubstituted pyrromethane (III; $R^1=H$, $R^2=Me$) and the resultant *b*-oxobilane (VI) (48%) was cyclized to the oxophlorin (VII)[4] (25%), which was transformed into the porphyrin (V) (68%) by acetylation and elimination of the *meso*-acetoxy group.[5]



(I)



(II)



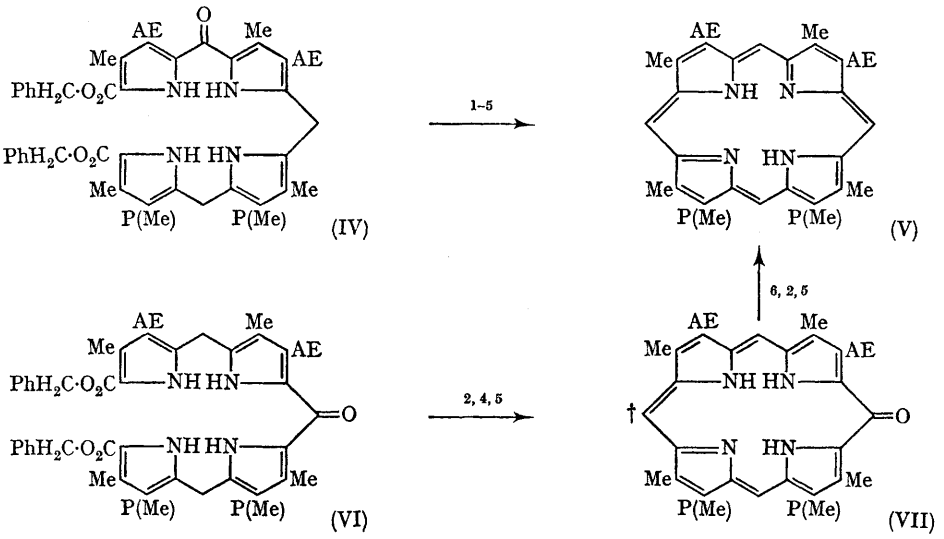
(III)

[AE=$CH_2{\cdot}CH_2{\cdot}O{\cdot}COMe$; $P(R^2)=CH_2{\cdot}CH_2{\cdot}CO_2R^2$]

carried out at room temperature on the zinc complex of the 2,4-dichloroethylporphyrin. The resultant 2,4-divinylporphyrin [15% overall yield from (V)] was identical in all respects with protoporphyrin-IX dimethyl ester derived from natural sources.

Tritiated protoporphyrin-IX, specifically labelled at the δ-position, was prepared from the oxophlorin (VII), which undergoes exchange with tritiated acetic acid at the *meso*-position († in formula) opposite the oxo-group (as shown by n.m.r. studies of deuterium exchange); in more strongly acidic media the di-cation is formed and consequently exchange no longer occurs.

These two new syntheses also offer the possibility of preparing protoporphyrin-IX specifically ^{14}C-labelled at various positions, especially as the requisite pyrromethanes (III) have now been made



(IV) (V) (VI) (VII)

Reagents: 1, B_2H_6; 2, H_2/Pd–C; 3, Bu^tOCl; 4, $CH(OMe)_3$–$CCl_3{\cdot}CO_2H$; 5, air; 6, Ac_2O.

The two acetoxyethyl side-chains of the porphyrin (V) were converted into vinyl groups as shown schematically below, the final elimination being

$$-CH_2{\cdot}CH_2{\cdot}OAc \xrightarrow{1,2} -CH_2{\cdot}CH_2{\cdot}Cl \xrightarrow{3,4,1} -CH=CH_2$$

Reagents: 1, $MeO\overset{+}{H}_2$; 2, MesCl–pyridine; 3, $Zn(OAc)_2$; 4, Bu^tO^-

rationally instead of merely by semi-hydrogenation of the symmetrical dibenzyl ester (III; $R^1=CO_2{\cdot}CH_2Ph$, $R^2=Me$). Mild alkaline hydrolysis of the pyrromethane pentachlorophenyl ester (III; $R^1=CO_2{\cdot}C_6Cl_5$, $R^2=Me$) gave the salt of the tri-acid (III; $R^1=CO_2H$, $R^2=H$), which was coupled with the pyridinium salt (I); treatment of the resultant *a*-oxobilane di-acid with diazomethane gave the intermediate (IV). The α-unsubstituted pyrromethane (III; $R^1=H$, $R^2=Me$),

required for the alternative *b*-oxobilane synthesis, was generated by treatment of the t-butyl ester (III; $R^1=CO_2Bu^t$, $R^2=Me$) with trifluoroacetic acid at room temperature.

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[1] H. Fischer and K. Zeile, *Annalen*, 1929, **468**, 114.
[2] A. H. Jackson, G. W. Kenner, G. McGillivray, and G. S. Sach, *J. Amer. Chem. Soc.*, 1965, **87**, 676.
[3] A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), in the press.
[4] A. H. Jackson, G. W. Kenner, and K. M. Smith, *J. Chem. Soc.* (*C*), in the press.
[5] A. H. Jackson, G. W. Kenner, G. McGillivray, and K. M. Smith, *J. Chem. Soc.* (*C*), in the press.