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THE PREPARATION AND PROPERTIES OF THIOPHEN ANALOGUES OF PORPHYRINS AND RELATED SYSTEMS. PART II[1]

SYNTHESIS OF PORPHYRINOGEN ANALOGUES

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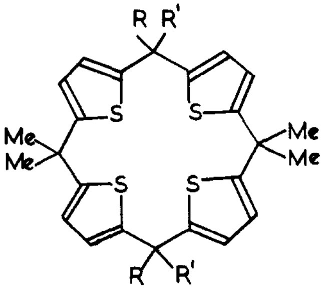
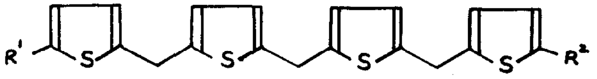
Although the chemistry and synthesis of the porphyrin ring system has been intensively investigated for more than fifty years, no reports have yet appeared regarding its thiophen isosteres. We report below the first syntheses of the thiophen isosteres of the porphyrinogen system (I). Three basic methods have been employed, commencing from a tetrathiophen (II), a dithienylmethane (III or IV) or a thiophen derivative.



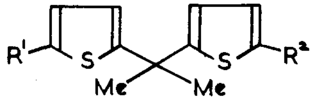
I

a; $R=H$, $R'=OH$.
b; $R=Me$, $R'=OH$.
c; $RR'=CH_2$



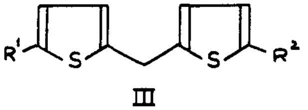
II

a; $R'=R^2=COOMe$.
b; $R'=H$, $R^2=COOH$.
c; $R'=R^2=H$.



IV

a; $R'=R^2=H$
b; $R'=R^2=CHO$
c; $R'=R^2=Li$
d; $R'=R^2=Ac$
e; $R'=H, R^2=Ac$



III

a; $R'=R^2=Li$
b; $R'=R^2=CHO$
c; R H R COOH

All attempts to bring about cyclisation of various derivatives of the tetrathiophen (II) were without success. For example, an attempted acylion condensation of the dimethyl ester (IIa) gave only the starting ester even at temperatures up to 130° for 9 hr., utilising either sodium or a Na/K alloy as recommended by Gol'dfarb[2]. The monocarboxylic acid (IIb) with P.P.A. gave only polymeric materials.

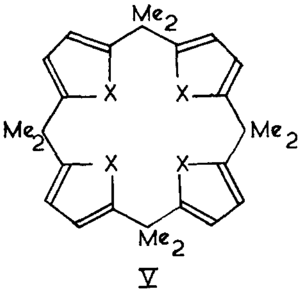
An attempted cyclisation by chloromethylation of the tetrathiophen (IIc) gave only the octathiophen, m.p. 102° and no cyclic product.

Reactions designed to couple dithienyl methane derivatives (III) were also unsuccessful. Thus the reaction of the dilithio compound (IIIa) with the dialdehyde (IIIb) resulted in dimetallation of the active methylene group of the aldehyde rather than interaction with the carbonyl groups. From the resulting deep turquuoise solution, the usual work-up procedure gave only dithienylmethane and the starting aldehyde. The metallated dialdehyde, however, may be utilised for substitution of the bridge position as indicated earlier[1] Again, the action of P.P.A. on the mono acid (IIIc) gave only polymeric material.

It thus appeared that steric constraints were necessary to fix the intermediates in configurations suitable for cyclisation. It is significant that porphyrin cyclisations always involve heavily substituted systems, both for reasons of stability and steric suitability. To this end we investigated the reactions of 2,2-dithienylpropane[3] derivatives (IV).

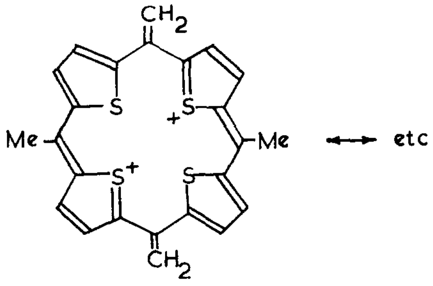
When the corresponding dialdehyde (IVb, m.p. 72°, prepared by the action of butyl lithium and dimethylformamide on the parent system (IVa) in 82% yield) was treated with the dilithio-compound (IVc) in high dilution in ether, the crude product yielded the dihydroxy tetramethyl porphyrinogen analogue (Ia, 4.2%) on elution through alumina with chloroform/benzene mixture (60:40). This compound, m.p. 280°d showed spectroscopic properties in accord with its structure [I.r. (nujol); 3180 (OH) and 795 cm^{-1} (2,5-disubst thiophen). N.m.r. (C_5D_5N), τ 2.96(4H, dd, J=3.3 and 0.2Hz aromatics), 3.24(4H, d, J=3.3 Hz aromatics), 3.52(2H, br, CH), ~5.0(2H, br, OH) and 8.27(12H, s, Me)] . The mass spectrum showed a strong molecular ion (m/e 472) and a fragmentation pattern compatible with the proposed structure. By a similar synthesis using the diketone (IVd), [m.p. 62°, obtained in 64% yield together with the liquid monoketone (IVe, 25%) by the action of refluxing acetic anhydride and phosphoric acid (2.5 hr.) on the parent system (IVa)] , the analogous dihydroxy hexamethyl porphyrinogen analogue (IIb) m.p. 280°d, was isolated (2.4%) by elution of the crude product through alumina with chloroform-benzene mixture (50:50). [I.r. (nujol); 3360, 3315 (OH) and 812, 797 cm^{-1} (2,5-disubst thiophen). N.m.r. ($CDCl_3$); τ 3.15(4H, d, J=4.0Hz, aromatics), 3.29(4H, d, J=4.0Hz aromatics), 7.96(6H, s, Me), 8.24(12H, s, CMe_2), 8.46(2H, s, OH). (C_5D_5N); τ 2.97, 3.27, 5.4 (OH), 7.79 and 8.27.] . A second product (0.8%) isolated from this chromatography with the same solvent, m.p. 250°d, proved to be the diolefin (Ic). The mass spectrum of the alcohol (Ib) also showed thermal dehydration to both the mono- and diolefin. Again the mass spectra were fully in accord with the cyclic structures.

The success of the above cyclisations led us to re-examine the reaction of thiophen and acetone in the presence of acid catalysts. Ackman, Brown and Wright[4] have shown that both pyrrole and furan react readily with acetone and hydrochloric acid to yield the corresponding porphyrinogen or its oxygen analogue (Va and Vb). We have examined the furan system (Vb) spectroscopically and confirm their proposed structure [N.m.r. ($CDCl_3$); τ 4.09(8H, s, aromatics) and 8.51(24H, s, Me). M.S.; M^+ 432]. However, they were unable to react thiophen in a similar manner.



V

a; X=N
b; X=O
c; X=S



VI

However, French workers[3] have recently shown that the dithienylalkanes (e.g. IVa) are readily obtained by use of thiophen, a ketone and 72% sulphuric acid. We have found that addition of chloroform to the residue after distillation of this reaction mixture precipitates a crystalline solid in low yield, m.p. 338°, which is clearly the octamethyl porphyrino-gen analogue (Vc), as shown by its spectral properties. [I.r. (nujol); 785, 805 cm^{-1} (2,5-disubst thiophen). N.m.r. ($CDCl_3$); τ 3.33(8H, s, aromatics) and 8.25 (24H, s, Me). M.S., M^+. 496]. This compound shows a very similar fragmentation pattern to the furan analogue (Vb) in the mass spectrum. We are examining this reaction further in order to increase the yield of this compound.

The mass spectra of these compounds are particularly interesting in that in all cases a successive cleavage of methyl groups is the predominant mode of breakdown, leading to systems which are in some cases fully conjugated ions of either aromatic (18 π - electrons) or anti-aromatic (20 π - electrons) character. Thus the base peak of the diolefin (Ic) is the doubly-charged ion (m/e 217) due to a loss of two methyl groups, which is probably the porphyrin analogue (VI), in that it has 18 peripheral π-electrons. The spectra will be discussed more fully elsewhere.

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