

FISCHER'S SYNTHESIS OF AETIOPORPHYRIN-I. A RE-INVESTIGATION

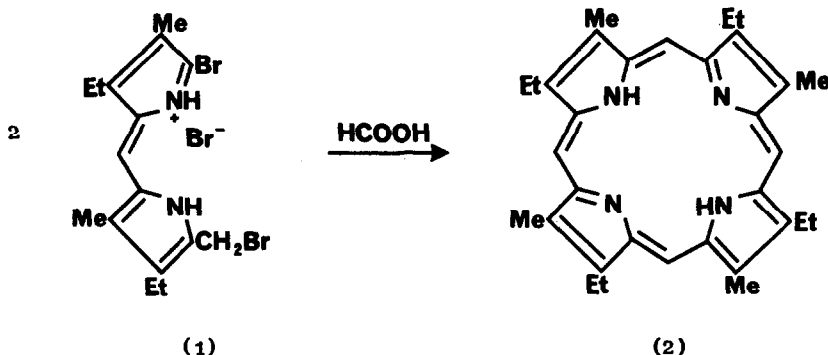
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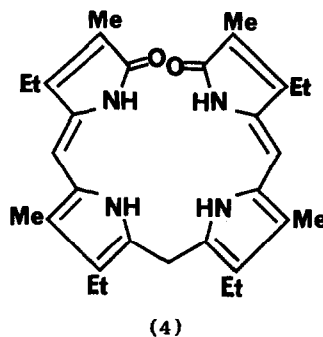
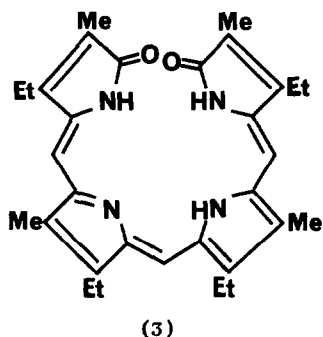
Despite modern developments in porphyrin synthesis¹ a most convenient route to aetioporphyrin-I (2) is still the heating of 5-bromo-5'-bromomethyl-3,4'-diethyl-3',4'-dimethylpyrromethene hydrobromide (1) under reflux in formic acid². The



porphyrin is separated from the dark reaction products by liquid-liquid partition, making use of the basicity ("acid number"³) of the macrocycle, and the dark residues usually discarded.

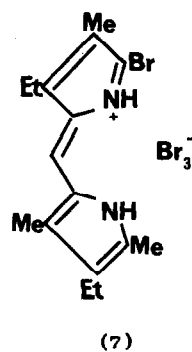
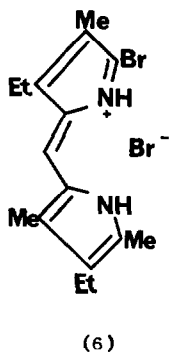
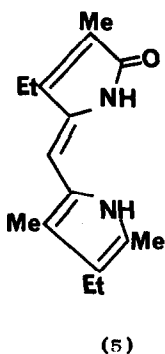
However, if the reaction is worked up by chromatography on alumina, along with the expected aetioporphyrin-I (2) (15% yield; Lit. yield² 16%), quantities of a deep blue compound were also easily isolated, and shown to be aetiobiliverdin-IV Ψ (3) (7% yield), (mp 263-264° (Lit.⁴ 263-265°); λ_{\max} nm (ϵ_{\max}) in CH₂Cl₂ 366(52,000), 638(16,000): n.m.r. spectrum in CDCl₃ τ 1.3, 3NH(broad); 3.37, 1 methine-H; 4.12, 2 methine-H; 7.42, 4H(q), 7.52, 4H(q), -CH₂-; 7.95, 6H(s), 2 CH₃-; 8.22, 6H(s), 2 CH₃-; 8.80, 6H(t), 8.84, 6H(t), -CH₂CH₃ : m/e(%) 498(100) P⁺, 374(5). Elemental analysis, Found C,74.71; H,7.64; N,11.02%. Calculated for C₃₁H₃₈N₄O₂ C,74.66; H,7.68; N,11.24%.)

In particular, the symmetry of the n.m.r. spectrum was compatible with the proposed structure (3) for the verdin, which is no doubt obtained as a result of "tail to tail"



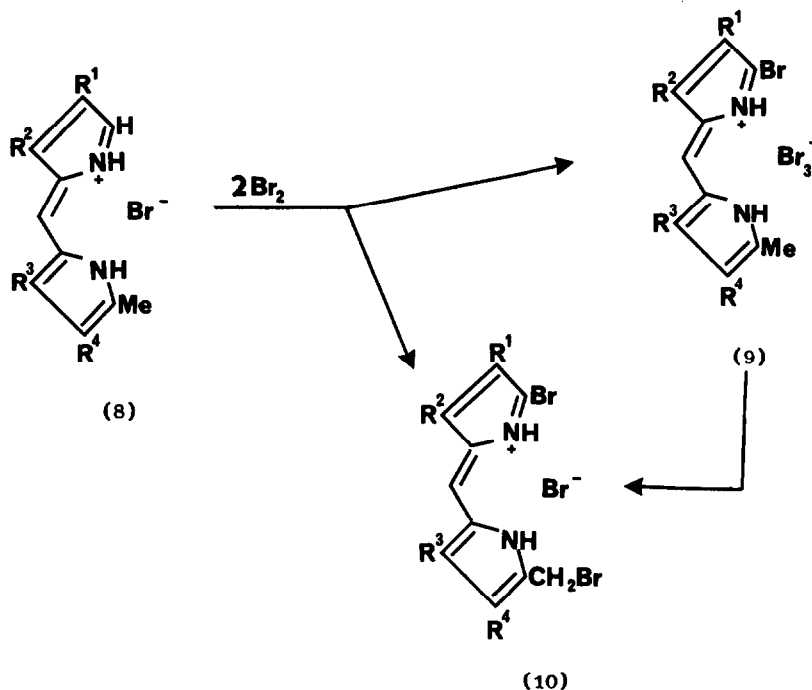
self-condensation of the pyrromethene (1) compared with the "head to tail" mode which results in aetiopyrphyrin-I (2). Production of the verdin can be visualised as involving elimination of the elements of methylene bromide in a self-condensation⁵ combined with hydrolysis of the terminal bromine functions⁶ at some point, to give the rubinoid compound (4), from which (3) is obtained *in situ* by oxidation; heating in formic acid is a standard method⁷ for the conversion of rubins to verdins.

Aetiobiliverdin-IV Ψ (3) has been prepared earlier⁴ by treatment of (5) (obtained by hydrolysis of the corresponding 5-bromo-5'-methylpyrromethene (6)) with two moles of bromine in acetic acid, presumably by a mechanism akin to that reported above.



The best yield⁸ of aetiopyrphyrin-I from the dibrominated pyrromethene (1) is in the region of 40%, but the direct preparation⁹ of (1) by bromination of kryptopyrrole (3-ethyl-2,4-dimethylpyrrole) is complicated by production of large

quantities of the perbromide (7)¹⁰, which is more easily isolable than (1). Indeed, in the preparation of more unsymmetrical dibrominated pyrromethenes (10), bromination



of 5-methylpyrromethenes (8) also leads to a mixture of the required materials (10) and the corresponding perbromides (9) which can only be converted to (10) in low yield^{2,11}.

Apart from a brief statement by Fischer¹² that the perbromide (9; R¹=R³=Et, R²=R⁴=Me) and the corresponding 5-bromo-5'-methylpyrromethene (cf. (6)) give porphyrin with formic acid but not with concentrated sulphuric acid, perbromides do not appear to have been exploited in porphyrin synthesis. Instead, workers have preferred to use the less accessible dibrominated pyrromethenes (10) and discard the former. However, if the perbromide (7) is heated in formic acid, aetioporphyrin-I is isolated in yields between 50 and 60%. In a typical experiment, the perbromide (7) (5.62g.) was suspended in formic acid (40 ml.) and heated under reflux during two hours. The solvent was removed by distillation (oil bath at 140°) over a period of 45 minutes and the residue chromatographed on alumina (Brockmann Grade III) in methylene chloride. Crystallisation from methylene chloride/ methanol gave aetioporphyrin-I (1.25g.; 52%). Further elution with the same solvent furnished aetiobiliverdin-IV † (69 mg.; 3%), identical with the material described earlier.

The higher yield of porphyrin from the perbromide may be a consequence of the presence of an internal dehydrogenation agent which converts the macrocycle initially formed (by expulsion of two moles of hydrogen bromide) to porphyrin before it can be decomposed. The small quantity of verdin is probably obtained from dibrominated pyrromethene (1) produced by bromination of the 5-methyl group with bromine liberated from the perbromide.

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5. The preparation of symmetrical pyrromethanes by self-condensation of bromo-methylpyrroles is well documented: H. Fischer and H. Orth, "Die Chemie des Pyrrols", Akademische Verlag., Leipzig, Vol. I, p. 333 (1934).
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9. H. Fischer, E. Baumann, and H.J. Riedl, Annalen, 475, 205 (1929); H. Fischer and J. Klarer, Annalen, 450, 189 (1926); Ref. 7, p. 106.
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11. Ref. 7, p. 73; W. Siedel and F. Winkler, Annalen, 554, 162 (1943).
12. Ref. 2, p. 91.