Synthesis of 20-Methyl and 20-Cyano Isobacteriochlorins: The Wittig–Photochemical Approach

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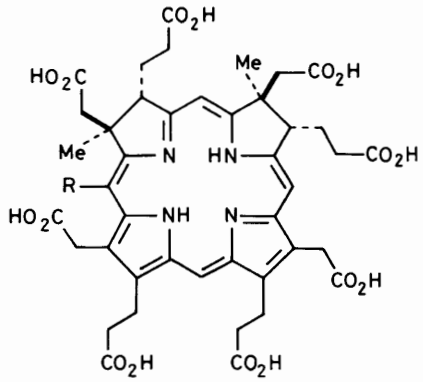
20-Methylisobacteriochlorins, important in relation to biosynthetic studies on vitamin B_{12}, and their 20-cyano analogues, have been synthesised by a mild route compatible with the side-chains of natural isobacteriochlorins; this involves assembly of the A—D ring system using a Wittig-type reaction and finally photochemical ring-closure to the macrocycle.

Research on the biosynthesis of vitamin B_{12} was given a new dimension by the isolation of the *C*-methylated isobacteriochlorins (**1**) and (**2**) from organisms which produce the vitamin.[1] Then it was found[2] that the true di-*C*-methylated intermediate on the biosynthetic pathway to vitamin B_{12} is a dihydro-derivative of the aromatic macrocycle (**1**) and the same is almost certainly true for the trimethylated system (**2**). The isolation of the latter[3] was of special importance in that it opened the way for a fuller understanding of the crucial ring-contraction process[4—6] required for formation of the final corrin macrocycle for vitamin B_{12}.

Future work on the biosynthesis of vitamin B_{12} would be greatly helped by having available much larger quantities of the naturally scarce 20-methylisobacteriochlorin (**2**). A practical synthesis would clear this bottle-neck and, further, would allow specifically and multiply labelled forms of the system (**2**) to be produced. In addition, a recent synthesis (quite different from ours) of a nonamethylisobacteriochlorin (one methyl group being at C-20) by Eschenmoser *et al.*[7] has led to fascinating biomimetic chemistry.[7,8]

A major step towards the natural pigments (**1**) and (**2**) was the development of a photochemical route[9] to isobacteriochlorins (unsubstituted at C-20) which was sufficiently mild to cope with the natural side-chains. In that synthesis, each of the two 'halves' of the final molecule [*cf. e.g.* (**8**) and (**15**)] was constructed using the Michael reaction. However, a different method will be needed to set up the substitution pattern on rings A and B of the natural pigments (**1**) and (**2**). As shown here, an approach based on Wittig-type chemistry, related to that used by Gossauer,[10] followed by the photochemical cyclisation,[9] is successful and also allows the 20-methyl group (and other groups) to be introduced into isobacteriochlorins.

The key reaction involves the stabilised ylide (**4**), the corresponding phosphonium salt being prepared from the 5-methylpyrrole by chlorination, treatment with cyanide, chlorination, and reaction with triphenylphosphine. This ylide (**4**) reacted with the readily prepared monothioimide (**3**) in the presence of an excess of potassium t-butoxide† to yield the *E*-product (**5**), >60% together with the separable *Z*-isomer, <10%. In these cases and those which follow, the geometry was assigned by n.m.r. spectroscopy, especially using the nuclear Overhauser effect (n.O.e.) difference method.[11] The t-butoxycarbonyl group was removed from the *E*-isomer (**5**) by acid catalysis and the product was formylated using trifluoroacetic acid (TFA) and trimethyl orthoformate (TMOF) to yield the aldehyde (**10**), 78% overall. This was converted into the corresponding imino ether (**12**), 33% (not optimised), using methyl iodide and silver carbonate; the product was taken through the steps (**12**) + (**15**)[9] → (**17**) as in the earlier synthesis[9] and then by photochemical cyclisation to the 20-cyanoisobacteriochlorin (**21**), 52% overall, m.p.



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

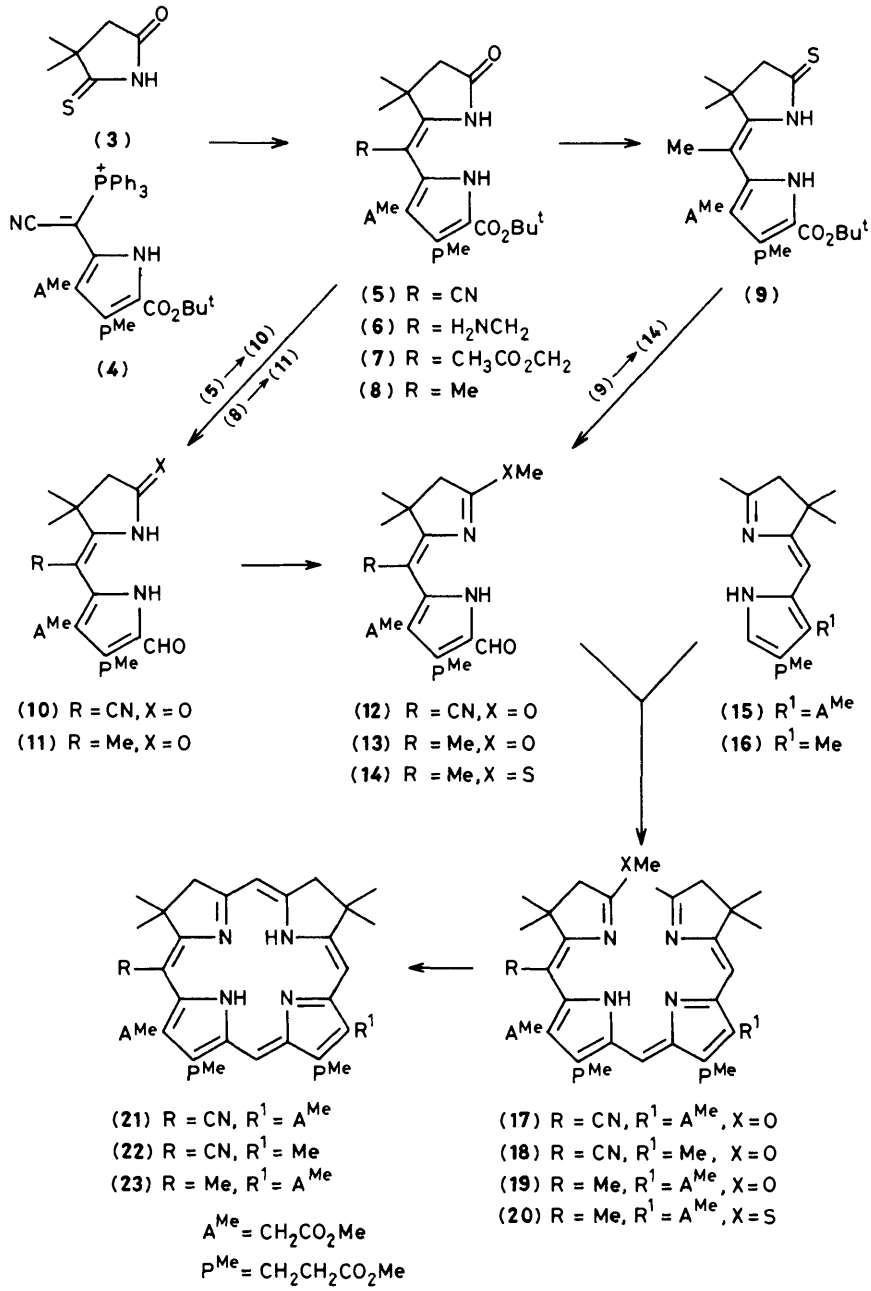
204.5—207 °C, *m/z* 711.3250; $C_{39}H_{45}N_5O_8$ requires 711.3268. The final steps were equally successful with the modified eastern 'half' (**16**) to yield *via* (**18**) the 20-cyano-12-methylisobacteriochlorin (**22**), 52% overall, m.p. 213—215 °C, *m/z* 653.3324; $C_{37}H_{43}N_5O_6$ requires 653.3313. The imine (**16**) was prepared in an analogous way to that used[9] for its relative (**15**).

Hydrogenation of the mixed *E*-nitrile (**5**) and its *Z*-isomer over Raney nickel gave the amines (**6**) and its *E*-isomer, 85%, which were treated with pentyl nitrite in acetic acid–tetrahydrofuran to yield the allylic acetates (**7**) and its *E*-isomer. These were characterised but normally were hydrogenolysed without separation over palladium black to afford the readily separable *C*-methyl derivatives (**8**) and its *E*-isomer, 55% overall from the amines. Either the pure *Z*-isomer (**8**), or the *E*-isomer, or the mixture gave, on removal of the t-butoxycarbonyl group followed by formylation, the same separable 2:1 mixture (80%) of the *Z*-aldehyde (**11**) and the *E*-isomer. The former gave (by MeI–Ag_2CO_3) the iminoether (**13**), 53%, which by condensation with the eastern 'half' (**15**) and irradiation of the resultant *seco*-product (**19**) gave the 20-methylisobacteriochlorin (**23**), 13% overall (not optimised); m.p. 152—155 °C, *m/z* 700.3476; $C_{39}H_{48}N_4O_8$ requires 700.3472.

The shortest route to the product (**23**) involved conversion of the lactam (**8**) or its *E*-isomer (or the mixture) by Lawesson's reagent into a 3:1 mixture of the thiolactam (**9**) and its *E*-isomer (combined yield 85%). The separated *Z*-form (**9**) on treatment with TFA–TMOF remarkably lost the t-butyl group, underwent decarboxylation and formylation, and also *S*-methylation, to yield directly the western portion (**14**), >95%. Condensation of this product with the imine (**15**) gave the *seco*-system (**20**) which cyclised on irradiation to afford the 20-methylisobacteriochlorin (**23**), 26% overall, identical to that produced above.

The methods outlined here, together with those from the earlier studies,[9] are well suited to the problems one faces in synthetic approaches to the natural pigments (**1**) and (**2**); experiments are in hand.

† Excess of base is essential which is not the case for the work in ref. 10; so the two processes differ. The mechanism of the base-catalysed reaction deserves study; a first step of attack by the anion of the imide *via* sulphur onto phosphorus is a possibility.



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