A Short, Versatile Synthesis of Porphobilinogen

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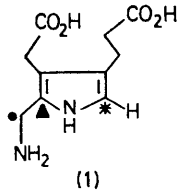
Summary A short synthesis of the tetrapyrrole pigment precursor porphobilinogen (**1**) has been developed which requires only readily available and inexpensive starting materials, and which is amenable to introduction of isotopic labels at key positions required for biosynthetic studies.

BIOSYNTHETIC studies on porphyrin and corrin biosynthesis require preparation of isotopically labelled monopyrroles, notably porphobilinogen (**1**). Although a number of syntheses of (**1**) and related derivatives have been reported,[1] most routes are either exceedingly lengthy, or lack



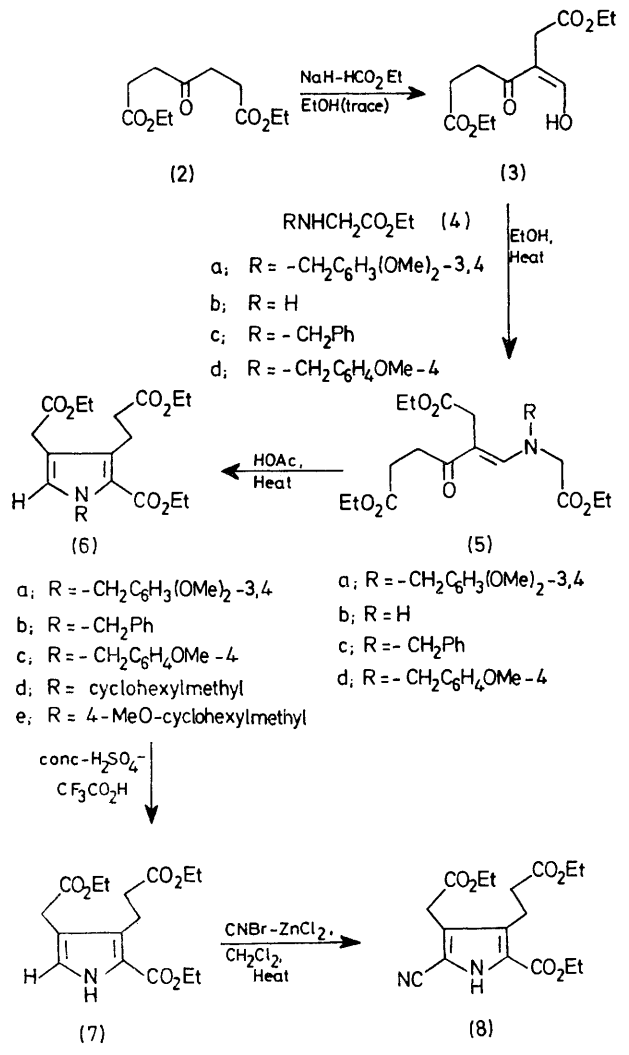
(1)

the versatility required for easy introduction of isotopic carbon labels. We report here a general synthesis of *N*-substituted pyrrole-2-carboxylates which additionally leads to the synthesis of (**1**).

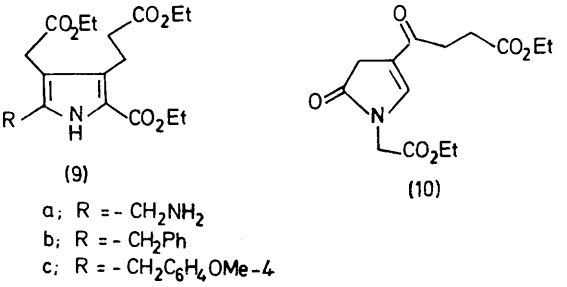
The oxopimelate (**2**), which is cheaply and conveniently prepared in two steps from furfural[2,3] was formylated using ethyl formate–sodium hydride to give the β-keto-enol (**3**) in 85% yield, characterised as the copper chelate complex.† Condensation of (**3**) with the ester (**4a**) in refluxing ethanol for 30 min afforded the vinylogous amide (**5a**) which was readily cyclised to the α-free pyrrole (**6a**) by heating under reflux for 5 h in glacial acetic acid–sodium acetate. Although (**5a**) can be purified by preparative t.l.c. [Merck Silica Gel GF_{254} with 3:1 EtOAc–light petroleum (b.p. 60—80 °C) as eluant] the crude product was normally subjected to cyclisation followed by purification at the pyrrole stage by column chromatography on alumina followed by recrystallisation. Yields of the combined stages were typically 20—30% of pure (**6a**), although material of sufficient purity for subsequent reactions could be obtained in higher yields. The *N*-3,4-dimethoxybenzyl protecting group was removed to afford (**7**) in 84% yield after preparative t.l.c. [as above, with 2:3 EtOAc–light petroleum] by 5% conc. H_2SO_4 in anhydrous CF_3CO_2H in the presence of an excess of anisole which traps the dimethoxybenzyl carbonium ion produced. Reaction of (**7**) with excess of cyanogen bromide and anhydrous zinc chloride in refluxing methylene chloride afforded the cyanopyrrole (**8**) in 70% yield after preparative t.l.c. [as above, with 3:7 EtOAc–light petroleum]. Con-

† All unknown compounds were fully characterised by combination of spectroscopic and analytical data.

version of (**8**) into porphobilinogen by hydrogenation to the aminomethyl derivative (**9a**), followed by saponification and decarboxylation, has already been described.[3]



The use of the *N*-3,4-dimethoxybenzyl unit as a 'blocking group' for the glycine derivative was dictated by the observation that the unsubstituted glycine derivative (**5b**) [prepared as a *ca.* 1:1 *Z*:*E* mixture of geometric isomers from (**3**) and (**4b**)] cyclised to (**10**) in 65% yield in glacial acetic acid–sodium acetate. Furthermore, whereas substitution with benzyl (**4c**) and *p*-methoxybenzyl (**4d**) groups led respectively to the vinylogous amides (**5c**) and (**5d**) which were successfully cyclised to the pyrroles (**6b**) and (**6c**), the subsequent removal of these groups proved troublesome. Catalytic hydrogenation methods led to reduction of the benzyl units to afford (**6d**) and (**6e**), whereas acid-catalysed removal with conc. H_2SO_4 in CF_3CO_2H led to migration of the *N*-substituent largely to the free α-position to give (**9b**) and (**9c**).



The novel introduction of a potential aminomethyl group as a nitrile function into the free α-position of a pyrrole-2-carboxylate using a Lewis acid-catalysed acylation with cyanogen bromide has resulted from our work on cyanopyrrole preparations.[4] It is notable that omission of the Lewis acid leads in general to the bromopyrrole. Since cyanogen bromide can be prepared in *ca.* 80% yield from sodium cyanide, the method used here suggests a convenient introduction of a ^{13}C-label from $Na^{13}CN$ into the aminomethyl carbon atom (●) of (**1**), which becomes one of the *meso*-carbon atoms of a biosynthesised porphyrin nucleus.[5] In addition, C-5 (▲) and C-2 (*) of the pyrrole nucleus originate respectively from ethyl formate and glycine in the synthetic scheme, again suggesting a potentially simple method of introduction of labels at these positions.

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