Porphobilinogen Synthesis

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Summary Porphobilinogen and [6-^{14}C]-porphobilinogen are synthesised by modification of an earlier route, the key step being the high-yield transformation of a readily available β-acetylpyrrole (**4**) into the corresponding methoxycarbonylmethylpyrrole (**2b**) with thallium(III) nitrate in methanol.

PORPHOBILINOGEN (PBG; **1**) is the only monopyrrole known to be of any biological significance, and has been shown to be a precursor of the porphyrins, chlorophylls, and vitamin B_{12}.[1] The greatest contributions to PBG synthesis have undoubtedly been made by MacDonald and his group in Ottawa, and over a period of years, these workers have systematically improved their approach to PBG (**1**) from the pyrrole (**2a**).[2] We now report simple and efficient routes[3,4] to the pyrrole (**2b**) and its [6-^{13}C]- and [6-^{14}C]-compounds, and ultimately (using MacDonald's route [2a]) to PBG and [6-^{14}C]-PBG.

Diethyl β-oxoadipate[5] (**3**) was oximinated with pentyl nitrite and then condensed with acetylacetone (in AcOH in the presence of Zn and NH_4OAc) to give a 50% yield of the β-acetylpyrrole (**4**).† With thallium(III) nitrate in methanol, compound (**4**) gave the methoxycarbonylmethylpyrrole (**2b**)† in 79% yield.[6] The Table shows the ^{13}C n.m.r. spectra of both (**4**) and (**2b**); though there is firm evidence[7] that the thallium(III)-promoted transformation of acetophenone into methyl phenylacetate proceeds with migration of the aryl group, we felt that it was necessary to establish this fact in the pyrrole series, using ^{13}C labelling, since we proposed to use this route for the synthesis of [6-^{14}C]-PBG required for our biosynthetic studies. Thus, copper–quinoline decarboxylation[8] of pyrrole (**5a**)[2b] gave the β-unsubstituted pyrrole (**5b**) which afforded [7-^{13}C]-labelled (**4**) when treated with [2-^{13}C]-enriched acetyl chloride and aluminium trichloride. The ^{13}C n.m.r. spectrum showed strong enhancement of the peak at δ 31·1, in accord with our assignments of the resonances (Table). After treatment with thallium(III) nitrate in methanol, the ^{13}C n.m.r. spectrum of the product showed strong enhancement of the resonance at δ 29·8, confirming that the aryl ring had undergone migration; none of the other resonances (Table) showed ^{13}C levels above natural abundance. Repetition of the reaction sequence, but using [2-^{14}C]-acetyl chloride, gave [6-^{14}C]-labelled (**2b**) in high overall yield.

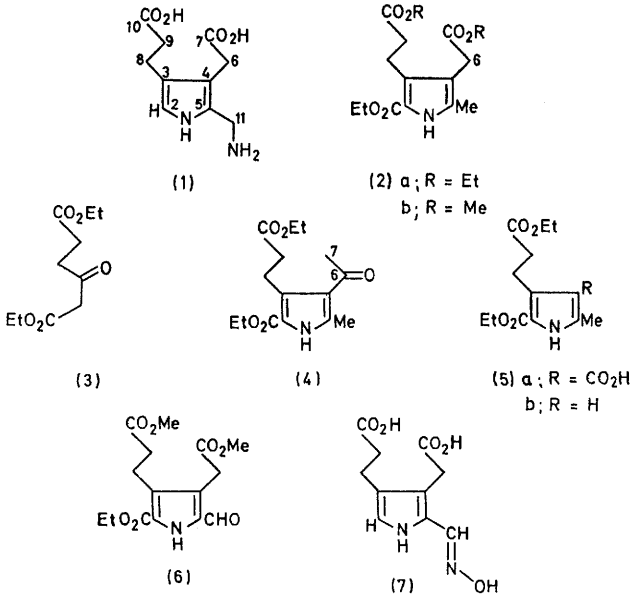
Compound (**2b**) and its [6-^{14}C]-labelled derivative were transformed into PBG, following the highly efficient route developed by MacDonald,[2a] *i.e.* dichlorination and hydrolysis, to give the formylpyrrole (**6**);† hydrolysis and oximation, to give the α-unsubstituted oxime (**7**), and finally, catalytic hydrogenation to PBG (**1**)[9] (see Table for ^{13}C n.m.r. shifts) [^{1}H n.m.r. spectrum in 1M-NaOH–D_2O, δ values in p.p.m.

TABLE[a]

^{13}C *Chemical shifts for pyrroles at* 25·2 MHz; δ *values in p.p.m. downfield from* Me_4Si

Pyrrole	Solvent	Ring carbon atoms[b] [C(2)—C(5)]	Ar-CH_3	Ar-CH_2·NH_2	Ar-CH_2·CH_2·CO_2CH_2·CH_3	Ar-CO·CH_3	Ar-CH_2·CO·OCH_3	Ar-CO·OCH_2·CH_3
(**1**)	1M D_2O–NaOH	114·1, 114·6[C(2)]	—	36·6	22·9, 39·3, (182·3), —, —	—	33·7, (183·8), —	—
PBG	pD 12·5	123·0, 130·8						
(**2b**)	$CHCl_3$	113·8, 116·8	11·6	—	20·8, 35·0, 173·2, —, (51·3)	—	29·8, 171·7, (51·8)	160·9, 59·9, 14·5
	76·9	129·8, 131·0						
(**4**)	$CHCl_3$	118·0, 122·6	15·2	—	21·6, 35·2, 172·6, (60·1), 14·3		—	161·3, (60·5), 14·3
	77·2	132·3, 137·7				194·3, 31·1		

[a] Assignments are made from complete coupled ^{13}C spectra and from comparisons within the group of compounds (**1**), (**2**), (**4**), (**5**), (**6**), and (**7**). Chemical shifts shown in parentheses are not specifically assigned, owing to the presence of similar carbon atoms in the same molecule. [b] Pyrrole α-carbon atoms normally appear at lower field than β-carbon atoms: T. F. Page, jun., T. Alger, and D. M. Grant, *J. Amer. Chem. Soc.*, 1965, **87**, 5333. We have confirmed this observation with compound (**5b**) in $CHCl_3$, but compound (**1**), in alkaline solution, appears anomalous.



† New compound which gave a satisfactory elemental analysis, and mass and n.m.r. spectra compatible with the structure shown. M.p.s (**2b**) 90—91°; (**4**) 107—108°; (**6**) 83—85°.

from DSS, 2·1—2·6 (4H, m, $CH_2 \cdot CH_2 \cdot CO$), 3·18 (2H, s, $Ar–CH_2 \cdot CO$), 3·49 (2H, s, $CH_2 \cdot NH_2$), and 6·44 (1H, s, α-*H*).] The purity of the synthetic PBG was also clearly established by ascending paper chromatography.[2a]

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[1] For a review, see B. F. Burnham, 'Metabolic Pathways,' ed. D. M. Greenberg, Academic Press, New York, 3rd edn., vol. III, 1969.

[2] (a) G. P. Arsenault and S. F. MacDonald, *Canad. J. Chem.*, 1961, **39**, 2043; (b) S. F. MacDonald and R. J. Stedman, *ibid.*, 1955, **33**, 458; (c) A. H. Jackson, D. M. MacDonald, and S. F. MacDonald, *J. Amer. Chem. Soc.*, 1956, **78**, 505; A. H. Jackson and S. F. MacDonald, *Canad. J. Chem.*, 1957, **35**, 715.

[3] An attractive simplification to the arduous synthesis of (**2a**) has recently been described: H. Plieninger, P. Hess, and J. Ruppert, *Chem. Ber.*, 1968, **101**, 240. This modification requires the difficult molecular distillation of a complex dione, and we have been unable to obtain more than mediocre yields from this process.

[4] A significant breakthrough in PBG synthesis, using azaindoles and PBG lactam as intermediates, has recently been reported: B. Frydman, S. Reil, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, 1969, **91**, 2338.

[5] Obtained by treatment of the magnesium complex of ethyl hydrogen malonate with β-ethoxycarbonylpropionyl chloride; the product (**3**) from this reaction was pure on the basis of the established n.m.r. criterion: E. C. Taylor and A. McKillop, *Tetrahedron*, 1967, **23**, 897.

[6] A 72% yield of benzyl 4-(methoxycarbonylmethyl)-3,5-dimethylpyrrole-2-carboxylate was obtained in a similar way, from the corresponding β-acetylpyrrole. The former compound has been a key pyrrole in all of our syntheses of vinyl substituted porphyrins: *cf.* R. P. Carr, A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1971, 487.

[7] A. McKillop, B. P. Swann, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1971, **93**, 4919.

[8] T. Cohen and R. A. Schambach, *J. Amer. Chem. Soc.*, 1970, **92**, 3189.

[9] For an alternative route from (**2a**) to PBG, see A. R. Battersby, J. Moron, E. McDonald, and J. Feeney, *J.C.S. Chem. Comm.*, 1972, 920.