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SITE-SPECIFIC ALKYLATION OF TETRA-ALKYLPYRROLES

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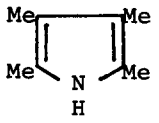
Summary Intramolecular cyclisation of the trifluoromethanesulphonate esters of the β-(4-hydroxy-n-butyl)-pyrroles (5a) and (5b) in each case yields a mixture of the α- and β-alkylated products whereas exclusive β-alkylation is observed for the β-(5-hydroxy-n-pentyl)-pyrrole (5c).

The problem of β-alkylation of pyrroles is of current interest because of the probable involvement of such a reaction in the biosynthesis of vitamin B_{12} from uroporphyrinogen-III,[1] but hitherto no good methods have been available for the in vitro β-alkylation of unsymmetrically tetra-substituted pyrroles at a particular site. Our earlier work in this area showed that little site specificity was to be expected for intermolecular alkylation, since methylation of 2,3,4,5-tetramethylpyrrole (1) by methylfluorosulphate yielded the pyrrole-nine salts (2) and (3) in approximately equal amounts[2]. In order to provide a solution to this problem we have investigated the intramolecular alkylation of the trifluoromethanesulphonate (triflate)esters of pyrroles containing β(4-hydroxy-n-butyl)- and β(5-hydroxy-n-pentyl)-substituents. The starting materials (4a, b, c) were prepared by conventional methods; reduction with diborane gave the pyrrole alcohols containing α-ester groups (5b, d) and reduction with lithium aluminium hydride gave alcohols containing α-methyl



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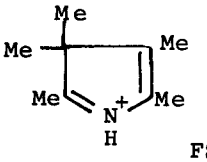

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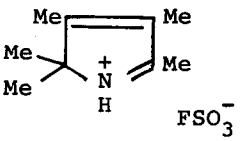

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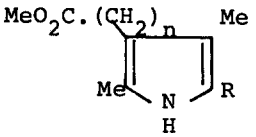

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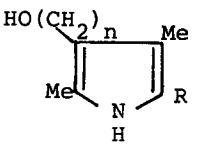
b n = 3 ; R = CO_2Bz

c n = 4 ; R = CO_2Me

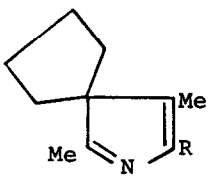


5 a n = 4 ; R = Me

b n = 4 ; R = CO_2Bz

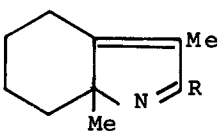
c n = 5 ; R = Me

d n = 5 ; R = CO_2Bz



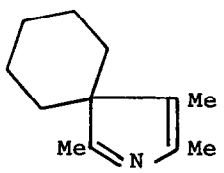
6 a R = Me

b R = CO_2Bz



7 a R = Me

b R = CO_2Bz



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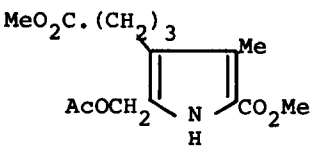

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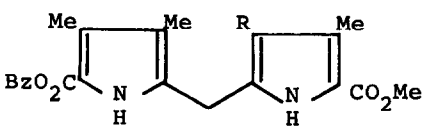

10 a R = $(CH_2)_3CO_2Me$

b R = $(CH_2)_4OH$

groups (5a, c). Cyclisation of the alcohols was achieved by treatment with trifluoromethanesulphonic anhydride in dichloromethane which presumably effected initial formation of the corresponding triflate ester. In the simplest case (5a), treatment with the reagent at -55°C for 10 min, followed by sodium hydrogen carbonate at -55° for 10 min, gave a mixture of the pyrrolenines (6a)[3] and (7a)[3], (3 : 1), which were separated by rapid t.l.c. It seems likely that at least some of the (7a) is derived by rearrangement of (6a) since the latter rearranged rapidly to (7a) in the presence of excess trifluoracetic acid ($t_{\frac{1}{2}}$ 3 min at 25°C in $CHCl_3$). Similarly (5b) was converted to a mixture of (6b)[3] and (7b)[3], (1 : 2). (6b) also rearranged to (7b) in the presence of acid, but more slowly ($t_{\frac{1}{2}}$ 22 min in $CHCl_3$).

Cyclisation of the alcohols (5c) and (5d) have also been investigated. Attempted cyclisation of (5d) gave only the corresponding triflate ester of the alcohol which was unaffected by further treatment with base. Under the conditions which had proved successful in the earlier series, (5c) gave only the spiro compound (8) albeit in lower yield (30%). Since this reaction also yielded much polymeric material which is presumably formed by intermolecular alkylation, attempts were made to minimise this by working at high dilution. In practice, treatment of a mixture of (5c) and diisopropylethylamine in dichloromethane at -70°C with trifluoromethanesulphonic anhydride, followed by dilution with cold (-70°C) dichloromethane and warming to 0°C afforded a 73% yield of (8) uncontaminated by any rearranged material. In contrast to the 5-membered spiro series, (8) did not show any tendency to rearrange in the presence of acid and could be recovered unchanged after treatment with trifluoroacetic acid for 42 h at 25°C. Cyclisation similar to the present examples have been reported in the indole series where related rearrangements of spiro derivatives were also described.[4]

In an attempt to extend these reactions into the dipyrromethane series, (4a) was treated with lead tetra-acetate to give (9) which was condensed with benzyl 3,4-dimethylpyrrole-2-carboxylate in the presence of p-toluenesulphonic acid at 1-2°C to give the dipyrromethane (10a) and this in turn was reduced with

diborane to (10b). However, application of the cyclisation reaction to (10b) gave only (11) and (12) which are presumably formed via breakdown of the initial cyclisation product (13).

Further experiments designed to effect multiple intramolecular β-alkylation in tetrapyrrolic species are in progress.

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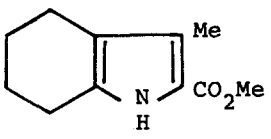

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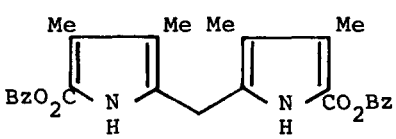

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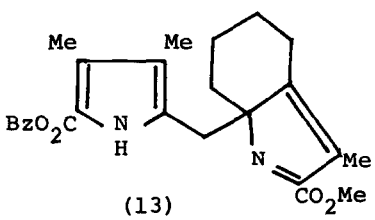

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2. A.P. Johnson and R.E. Winter, unpublished.

3. Structures were assigned on the basis of n.m.r. interpretations and particularly the observed shifts of individual methyl groups when the bases were converted to salts.

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