The Oxidation of (±)-Armepavine Methiodide

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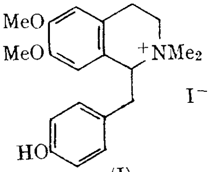
IN attempts to produce bisbenzylisoquinolines by oxidative coupling of phenolic benzylisoquinolines, armepavine methiodide (I) failed[1] to undergo oxidation. The failure of what is formally a substituted *p*-cresol to react with ferricyanide was surprising, and the reaction has been re-examined.

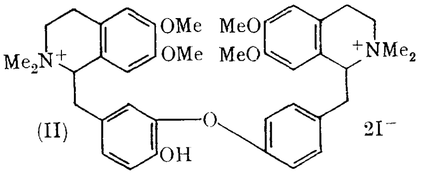


(I)

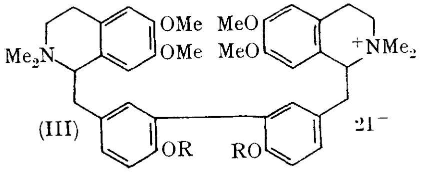
Oxidation of (±)-armepavine methiodide with alkaline ferricyanide under conditions markedly more severe than those used by the earlier workers generated at least two compounds with R_F values in t.l.c. lower than that of the starting material. Oxidation with silver cation gave the same result, but was in several ways advantageous, and our investigation was therefore confined to this reaction.

Methiodide fractions *A* and *B* were isolated by thick-layer chromatography. These have not been obtained analytically pure, but we believe the evidence summarised below is adequate to identify fraction *A*. A third fraction of what was probably polymeric material was not further examined. *A* and *B* each represented 10—15% of the crude reaction mixture, but the separation was not quantitative, and the relative intensities of t.l.c. spots of the oxidation product suggested that *A* and *B* were in fact each formed in considerably higher yield. The i.r. spectra of *A* and B were almost identical, and very similar to that of armepavine methiodide.

Two structures are possible for primary oxidative coupling products derived from armepavine methiodide, namely (II) and (III; R = H). The former would be racemic dauricine methiodide, and the latter a biaryl type which might be regarded as containing the skeleton of a precursor of such alkaloids as rodiasine.[2] Chromatographic comparison of *A* and *B*, and of the tertiary base from *A* (obtained by de-quaternising *A* with either ethanolamine[3] or sodium benzenethiolate in butan-2-one[4]) with dauricine methiodide and dauricine, respectively, showed that neither *A* nor *B* could have the structure (II).



(II)



(III)

Accordingly, the compounds (III; R = H), (III; R = Me), and the tertiary bases corresponding to these were synthesised by conventional methods starting from 2,2′-dibenzyloxybiphenyl-5,5′-diacetic acid (m.p. 188—189°) and dimethyl 2,2′-dimethoxybiphenyl-5,5′-diacetate (m.p. 91—93°). Synthetic (III; R = H), (III; R = Me), and the corresponding tertiary bases were compared chromatographically with *A*, *O*-methylated *A*, de-quaternised *A*, and *O*-methylated de-quaternised *A*, respectively. These comparisons made it extremely probable that the major oxidation product *A* is in fact the biaryl (III;

R = H). This identification is confirmed by the identical i.r. spectra shown by *A* and synthetic (III; R = H), and their identical ^{1}H n.m.r. spectra.

The synthetic compounds (III; R = H) and (III; R = Me) were both mixtures of two racemates, as shown by chromatography. Substance *A* corresponded to the racemate of synthetic (III; R = H) having the R_F value 0·33 [silica gel G, developed with methanol–2N-HCl–acetic acid–acetone 14 : 6 : 3 : 3)], no trace of the other racemate being found in the oxidation product. Its absence may be due to its being formed in smaller amount in the oxidation, but loss due to its greater solubility is most probably the important factor.

Satisfactory analyses have been obtained for the synthetic compounds.

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