ON THE SYNTHESIS OF N-FORMYL-7-METHYLDEHYDRONORAPORPHINES

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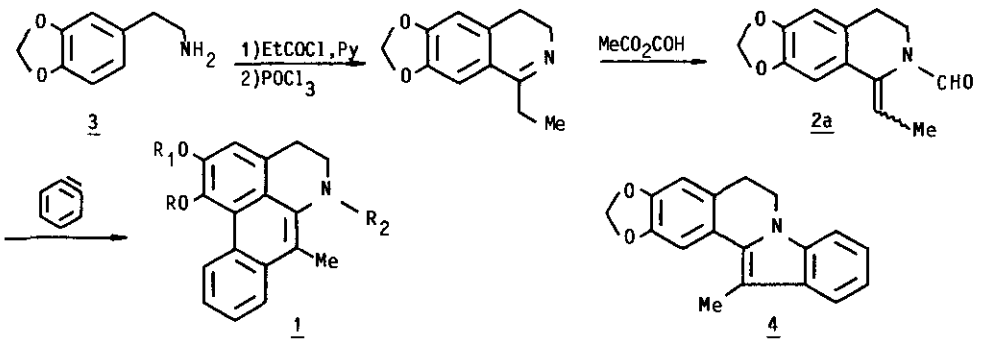
Abstract - Intermolecular benzyne cycloaddition (IBC) was used for the synthesis of the aporphinoid 1a, whose structure was corroborated by an independent photochemical route. Compound 1a is not trichoguattine.

Structure 1a and 1b have recently been ascribed to trichoguattine[1] (isolated from **Guatteria trichostemon**) and duguespixine[2] (isolated from **Duguetia spixiana**), respectively. However, on the basis of our long experience with dehydroaporphines we felt that these structure assignments had been made on very weak spectroscopic grounds: the UV spectra of both trichoguattine[3] and duguespixine[2] (λ_{max}: 430 nm) are quite different from those of N-ethoxycarbonylanonaine[4] (λ_{max}: 376 nm) and closely related compounds, and the assignment of a three-proton singlet at 3.3 ppm to a C-7 methyl group on an N-formylnordehydroaporphine[5] appeared highly speculative. We accordingly planned to check these structure assignments by synthesizing 1a by intermolecular benzyne cycloaddition (IBC), a powerful method for the synthesis of isoquinoline alkaloids[6-9].

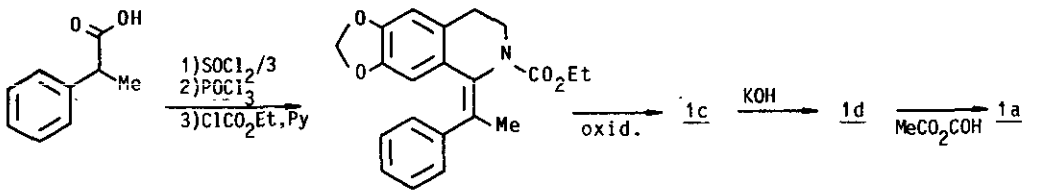
The dehydroaporphine 1a was synthesized by reacting 1-ethylidene-2-formyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline 2a with benzyne, as described in our previous reports[6-9]. The required precursor 2a was prepared uneventfully from 3,4-methylenedioxyphenethylamine 3 (Scheme 1). The key reaction of 2a with benzyne (generated by thermal decomposition of benzenediazonium-2-carboxylate[10]) yielded 1a in an unexpectedly low yield(11%), the major product being dibenzopyrrocoline 4[11]. The spectroscopic properties of synthetic 1a were those expected for this structure but differed considerably from those of trichoguattine. Particularly significant are the data: MS:m/z 305(M^+, 100%); IR(KBr) 1680 cm^{-1}; NMR($CDCl_3$): 9.09 (d,J=9 Hz,1H,H-11), 8.37(s,1H,CHO), 2.61(s,3H,Me); UV,λ_{max}: 253, 288, 325, 357, 376. Furthermore, the chromatographic behaviour of our synthetic 1a was found to be significantly different from that of an authentic sample of natural trichoguattine kindly provided by Prof. A. Cavé.

The structure of synthetic 1a was further confirmed by an independent synthesis along the lines of the classic photochemical approach (Scheme 2): N-carbethoxybenzylideneisoquinoline 5[12] prepared by conventional chemistry was irradiated (Hanovia lamp, 450 watts, vycor filter, I_2-copper acetate, 18 h) to yield 1c (50%), which was then hydrolysed under the conditions described by Lenz[4] (Scheme 2). The nordehydroaporphine 1d so obtained was finally converted into 1a (acetic-formic mixed anhydride), which was shown to be totally identical (MS,UV,PMR,tlc) with the product obtained by IBC.



a) R+R_1=CH_2: R_2=CHO. b) R=Me; R_1=H; R_2=CHO
c) R+R_1=CH_2: R_2=CO_2Et. d) R+R_1=CH_2; R_2=H

SCHEME 1



SCHEME 2

In conclusion, trichoguattine does not have the structure originally assigned to it. In our opinion, the structure proposed for the closely related duguespixine must also be wrong.

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12. All new compounds gave correct elemental analysis and/or spectroscopic data.

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