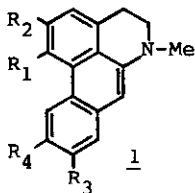


PHOTOCHEMICAL SYNTHESIS AND REACTIVITY OF TETRADEHYDROAPORPHINES

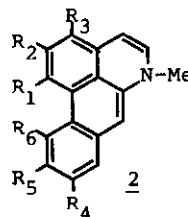
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Abstract- An efficient method to prepare 4,5,6a,7-tetrahydroaporphines is described. It is based on the photoreduction of benzophenone by amines. Oxidation of 4,5,6a,7-tetrahydroaporphines under several conditions gave oxoaporphines.

While 6a,7-dehydroaporphines 1 are a rather stable class of alkaloids¹, the corresponding 4,5,6a,7-tetrahydroaporphines 2² have never been isolated from natural sources, although the presence of a mixture of dihydro- and tetrahydrocoteine 2a in *Ocotea puberula* has been reported³.



- a) $R_1 + R_2 = OCH_2O$, $R_3 = R_4 = H$
 b) $R_1 = R_2 = OMe$, $R_3 = R_4 = H$
 c) $R_1 = R_2 = R_3 = R_4 = OMe$



- a) $R_1 + R_2 = OCH_2O$, $R_3 = R_4 = R_5 = OMe$, $R_6 = H$
 b) $R_1 = R_2 = R_4 = R_5 = OMe$, $R_3 = R_6 = H$
 c) $R_5 = R_6 = OMe$, $R_1 = R_2 = R_3 = R_4 = H$
 d) $R_1 + R_2 = OCH_2O$, $R_3 = R_4 = R_5 = R_6 = H$
 e) $R_1 = R_2 = OMe$, $R_3 = R_4 = R_5 = R_6 = H$

On the other hand, Castedo et al.⁴ have described the formation of tetrahydroglauanine 2b by dehydration-oxidation of 4-hydroxyglauanine (cataline) by sulphuric acid and Neumeyer and Gottlieb⁵ reported the synthesis of tetrahydroapomorphine dimethyl ether 2c "via" cathodic cyclization of the corresponding iodobenzylisoquinolinium salt. In both cases tetrahydroaporphines have been described as rather unstable compounds.

We have recently reported⁶ that aporphines are efficiently oxidized by triplet benzophenone to dehydroaporphines 1 in pyridine/water as solvent, these dehydro derivatives being stable under the irradiation conditions. In the present paper we wish to describe that when benzene is used as solvent, dehydroaporphines 1 are further oxidized by triplet benzophenone, giving tetrahydroaporphines 2 in good yields.

Thus irradiation⁷ of a benzene solution of dehydroroemerine 1a and benzophenone under argon for 4 hr led to almost quantitative (tlc) conversion to tetrahydrooroemerine 2d. During work-up some decomposition could not be avoided and a 60% yield of crystalline 2d was obtained, mp 161-163°C (from hexane-ethyl

ether)⁸. Its structure was assigned on the basis of the following spectroscopic data. The mass spectrum gave relevant peaks at m/e 275 (M^+ , 100%), 260 (35%) and 137.5 (M^{++} , 21%). The UV exhibited λ_{\max} (EtOH) (log ϵ) 234 (4.84), 265 (sh, 4.62), 274 (sh, 4.46), 310 (3.50), 366 (4.19), 418 (3.85) and 444 (3.68) nm; λ_{\max} (EtOH-HCl aq.) (log ϵ) 258 (4.81), 274 (4.69), 315 (3.78), 329 (3.87), 370 (sh, 3.87) and 388 (3.90) nm. The pmr (80MHz, $CDCl_3$, TMS) revealed δ at 8.69 (d, 1H, $J=7.8$ Hz, H_{11}), 7.30 (m, 3H, H_8, H_9, H_{10}), 6.55 (s, 1H, H_3), 6.37 (d, 1H, $J=7.5$ Hz, H_5), 6.12 (s, 2H, OCH_2O), 5.99 (s, 1H, H_7), 5.68 (d, 1H, $J=7.5$ Hz, H_4) and 3.17 ppm (s, 3H, $N-CH_3$).

Similar dehydrogenation of dehydronuciferine 1b gave the corresponding tetrahydro-nuciferine 2e^{8,9}. Analogously dehydroglaucone 1c yielded a 60% of tetrahydroglaucone 2b isolated as yellow prisms, mp 160-161°C (from EtOH). Its spectroscopic data are the same as those previously reported⁴.

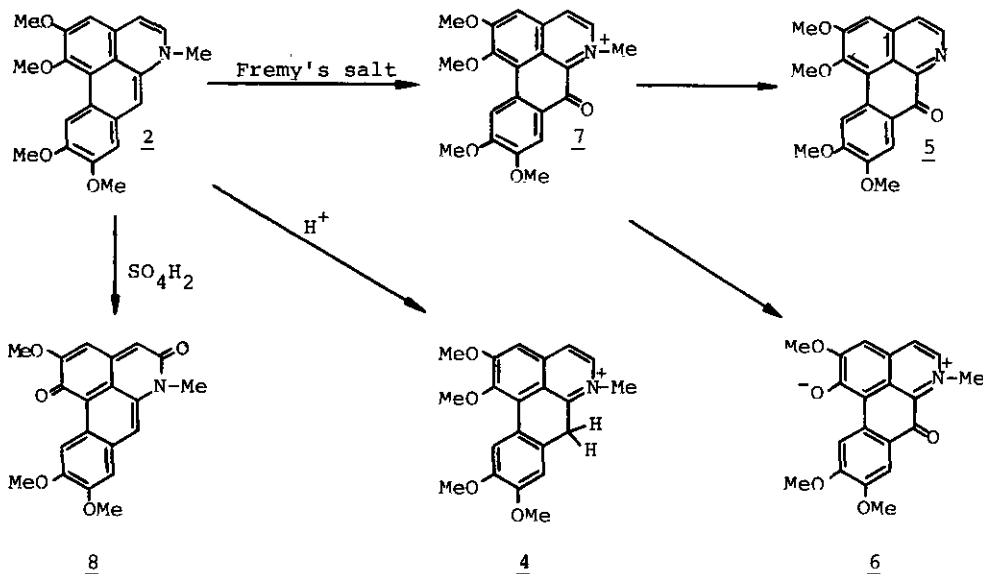
As expected⁵ when glaucine and nuciferine were irradiated in benzene instead of stopping at the dehydroaporphine stage, they were converted into 2b and 2e, respectively, isolated in identical yields as before.

Since tetrahydroaporphines 2 are a special type of cyclic dienamine, it was interesting to know the site of protonation of such a system. Three protonation sites were possible: C_4 , C_7 and N. Examination of the pmr spectrum of 2d taken in $CDCl_3$ /TFA showed the ^+N -Me group appearing at δ 4.27, an AB system (H_4 and H_5) at 8.15 and 7.8 ppm ($J=7.0$ Hz). Furthermore the disappearance (as compared to the unprotonated spectrum) of the proton signal corresponding to H_7 and the simultaneous arising of the benzylic CH_2 group as singlet at δ 4.77, ruled out the possibilities of protonation at C_4 or at N ¹⁰, therefore 4 being the protonated structure in solution. Analogous results have also been achieved with 2b and 2e.

Considering that tetrahydroaporphines could be regarded as chemical intermediates between aporphines and highly oxidized aporphines (7-oxo and 4,5-dioxoaporphines), it was of interest to study its oxidation under several conditions. Thus, reaction of an ethanolic solution of 2b with Fremy's salt¹² (dissolved in 4% aqueous sodium carbonate) for 3 days, gave oxoglaucone 5 and corunnine 6 in 40 and 20% yields, respectively. Probably the methosalt 7 will be initially formed followed by O- or N-demethylation¹¹. When oxidation of 2b was carried out with photochemically generated singlet oxygen (eosine as sensitizer) a 70% yield of 5 was obtained. However treatment of 2b with 90% sulphuric acid gave the 1,5-dioxoaporphine 8¹² in 80% yield.

These results together with those of chemical oxidation of aporphines¹, dehydroaporphines¹ and 4-hydroxyaporphines¹³ suggest that the latter are the most likely biogenetic precursors of 4,5-dioxoaporphines as well as 4-substituted oxoaporphines.

As a conclusion, tetrahydroaporphines are not expected to be found as natural products due to their high instability in solution, although they are rather stable in the crystalline form.



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7. A 13:1 molar ratio of benzophenone:amine was necessary to ensure part of light being absorbed by the ketone. A 450 watts Hanovia medium-pressure lamp with a Pyrex filter was used.
8. Satisfactory combustion analyses were obtained for all new compounds.
9. 55% yield of 2e hydrobromide, mp 170-172°C (from methanol). MS, m/e, 291 (M⁺, 6%), 276 (9%) and 182 (100%). Pmr (80MHz, CDCl₃) δ 9.28 (dd, J=7.7 and J=1.8 Hz, H₁₁), 7.54-7.18 (m, 3H, H₈, H₉ and H₁₀), 6.62 (s, 1H, H₃), 6.45 (d, 1H, J=7.4 Hz, H₅), 6.13 (s, 1H, H₇), 5.72 (d, 1H, J=7.4 Hz, H₄), 3.96 and 3.82 (s, 6H, 2 OMe), and 3.21 ppm (s, 3H, N-CH₃). UV, λ_{max} (EtOH) 238, 272, 278, 361, 415 and 440 nm. (Spectral data of 2e as free base).
10. A distinct behaviour has been observed in the case of dehydroaporphines, where

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