PHOTOCHEMICAL SYNTHESIS AND REACTIVITY OF TETRADEHYDROAPORPHINES

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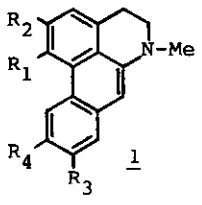
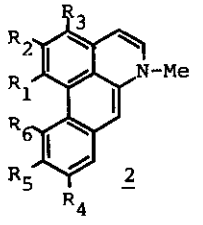
Abstract- An efficient method to prepare 4,5,6a,7-tetradehydroaporphines is described. It is based on the photoreduction of benzophenone by amines . Oxidation of 4,5,6a,7-tetradehydroaporphines under several conditions gave oxoaporphines.

While-6a,7-dehydroaporphines 1 are a rather stable class of alkaloids[1], the corresponding 4,5,6a,7-tetradehydroaporphines 2[2] have never been isolated from natural sources, although the presence of a mixture of didehydro- and tetradehydro-ocoteine 2a in Ocotea puberula has been reported[3].



1

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



2

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 tetradehydroglaucine 2b by dehydration-oxidation of 4-hydroxyglaucine (cataline) by sulphuric acid and Neumeyer and Gottlieb[5] reported the synthesis of tetradehydroapomorphine dimethyl ether 2c "via" cathodic cyclization of the corresponding iodobenzylisoquinolinium salt. In both cases tetradehydroaporphines have been described as rather unstable compounds.

We have recently reported[6] 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 tetradehydroaporphines 2 in good yields.

Thus irradiation[7] of a benzene solution of dehydroroemerine 1a and benzophenone under argon for 4 hr led to almost quantitative (tlc) conversion to tetradehydroroemerine 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=7.5Hz, H_5), 6.12 (s, 2H, OCH_2O), 5.99 (s, 1H, H_7), 5.68 (d, 1H, J=7.5Hz, H_4) and 3.17 ppm (s, 3H, $N-CH_3$).

Similar dehydrogenation of dehydronuciferine 1b gave the corresponding tetradehydronuciferine 2e[8,9]. Analogously dehydroglaucine 1c yielded a 60 % of tetradehydroglaucine 2b isolated as yellow prisms, mp 160- 161°C (from EtOH). Its spectroscopic data are the same as those previously reported[4].

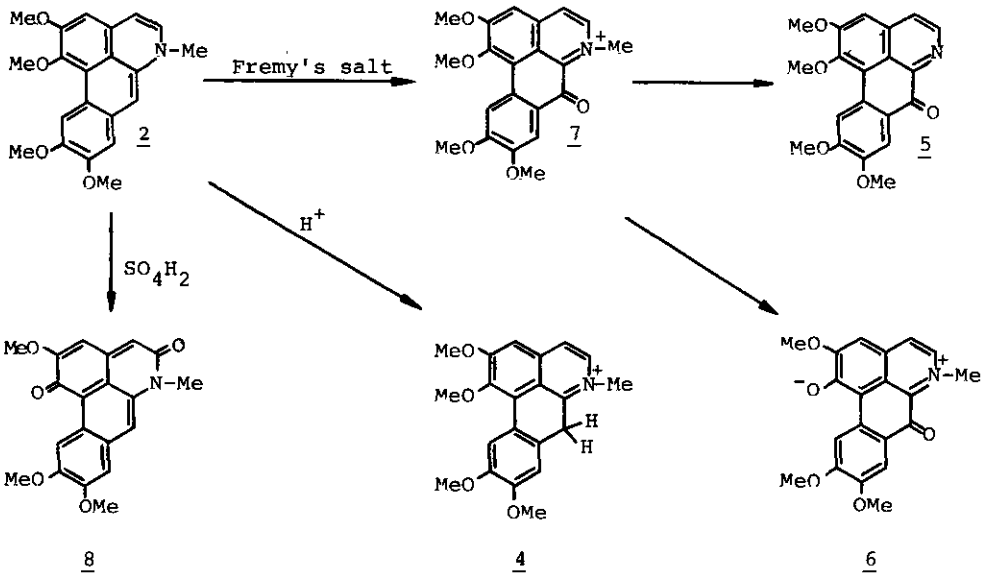
As expected[5] when glaucine and nuciferine were irradiated in benzene instead of stopping at the dehydroaporphine stage, they were converted into 2b and 2e, respectively, isolated in identical yields as before.

Since tetradehydroaporphines 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 tetradehydroaporphines 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 salt[12](dissolved in 4% aqueous sodium carbonate) for 3 days, gave oxoglaucine 5 and corunnine 6 in 40 and 20% yields,respectively. Probably the methosalt 7 will be initially formed followed by O- or N-demethylation[11]. 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 8[12] in 80% yield.

These results together with those of chemical oxidation of aporphines[1], dehydroaporphines [1] and 4-hydroxyaporphines [13] suggest that the latter are the most likely biogenetic precursors of 4,5-dioxoaporphines as well as 4-substituted oxoaporphines.

As a conclusion, tetradehydroaporphines 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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2. We have prefered to name compounds 2 as tetradehydroaporphines to avoid some confusion arising in the literature when dehydroaporphines 1 have been named in some instances as 6a,7-didehydroaporphines.
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4. I. Ribas, J. Sueiras and L. Castedo, Tet. Lett., 1972, 2033.
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6. L. Castedo, T. Iglesias, A. Puga, J. M. Saá and R. Suau, Heterocycles, 1981, 15, 915.
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, $CDCl_3$) δ 9.28 (dd, J =7.7 and J= 1.8 Hz, H_{11}), 7.54- 7.18 (m, 3H, H_8, H_9 and H_{10}), 6.62 (s, 1H, H_3), 6.45 (d, 1H, J= 7.4 Hz, H_5), 6.13 (s, 1H, H_7), 5.72 (d, 1H, J= 7.4 Hz, H_4), 3.96 and 3.82 (s, 6H, 2 OMe), and 3.21 ppm (s, 3H, N- CH_3). 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

kinetic protonation takes place at the N atom, and C_7 protonation under equilibration conditions. A. Venkateswarlu and M. P. Cava, Tetrahedron, 1976, 32, 2079.

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