A NOVEL SYNTHESIS OF APORPHINE AND DEHYDROAPORPHINE C7 -C7' DIMERS[1]

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Dehydroglaucine (4) and dehydronuciferine (5) easily undergo C7-C7' coupling by reaction with mercuric salts to give the corresponding aporphine and dehydroaporphine dimers. The reaction appears to be solvent dependant.

The significant citotoxic activity of naturally occurring and synthetic dimers has stimulated the synthesis of analogs and derivatives[2].

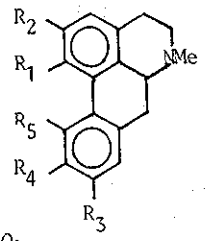
Recently Brossi et al.[3] reported the first example of a C7-C7' dimerization in aporphine and dehydroaporphine alkaloids, prepared by the oxidation of O-methylbulbocapnine (1) with iodine. The reaction appears not to be general since we have found that glaucine (2) afforded dehydroglaucine (4) under the same conditions, whereas this one remained unreacted.

Now we wish to report our finding on the oxidation of dehydroaporphines with mercuric salts (namely acetate and nitrate) leading to aporphine and dehydroaporphine dimers.

Thus, treatment of 4 with mercuric acetate (1:1 molar ratio) in aqueous solution at room temperature produced, after three hours,

a heavy precipitate, and the tlc observation showed that no starting material remained. Addition of sodium borohydride followed by extraction with methylene chloride afforded a single product (85% yield), mp 281-3°C (from MeOH or EtOAc) to which the dimeric C7-C7' glaucine structure (7)[4] was assigned on the basis of the following spectral data. The mass spectrum showed peaks at m/e 708 (41%, M+), 354 (80%, doubly charged ion) and 353 (100%); UV (EtOH) exhibited $\lambda_{max.}$ 302 and 286 (log ε 4.24 and 4.26) characteristic of a 1,2,9,10-tetrasubstituted aporphine and its pmr (80 MHz, $CDCl_3$) displayed unsplit signals at δ 2.57 (6H, NMe), 2.97, 3.58, 3.63 and 3.83 (6H each, OMe), 5.53, 6.57 and 7.59 (2H each, ArH). The off-resonance C-13 nmr spectra of 2 and 7 confirmed structure 7 by showing a doublet for C7 and C7' of 7 (39.36 ppm) and a triplet for C7 of 2 (34.73 ppm) which proves that the two glaucine units are linked by the C7-C7' bond in the dimer (7). The singlets at δ 2.97 and 6.57 were assigned to the methoxy groups at C1 and C1' and H3 and H3' of 7 by deuterio replacement as follows. When thalicmidine (3) was subjected to O-trideuteriomethylation[5] followed by dehydrogenation with 10% Pd/C[6] it was converted into O-trideuteriomethyldehydrothalicmidine (6) which on treatment with mercuric acetate as above afforded C7-C7' O-trideuteriomethylthalicmidine dimer (9). In its pmr and C-13 nmr the high field methoxy group at δ 2.97 and 59.09 ppm had vanished. Similarly, 3-deuterioglaucine[7] was converted into 3,3'-dideuterioglaucine dimer (10) which showed the disappearance of the singlet at δ 6.57 in its pmr spectrum.

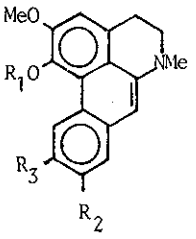
The simplicity of the pmr and cmr spectra of 7 (displaying only 20 signals for the 40 carbon atoms) strongly suggested a highly symmetrical structure. The observation that the resonance of the methoxy groups at δ 2.97 and the aromatic protons at δ 5.53 and 7.59 of the dimer are at a higher field than in the pmr spectrum of the monomer(2) together with inspection of the molecule by a Dreiding model showed that only the meso structure (7) having a C7ax-C7'ax bond can assume a conformation in which the methoxy groups at C1 and C1', and C11, C11' and C8, C8'-hydrogens can be shielded by the aromatic rings of the other aporphine half. The eq-eq or eq-ax possibilities can be ruled out because of the planarity or the lack of symmetry of the resulting molecule.



1 R_1=R_2=-O-O-, R_3=H, R_4=R_5=OMe

2 R_1=R_2=R_3=R_4=OMe, R_5=H

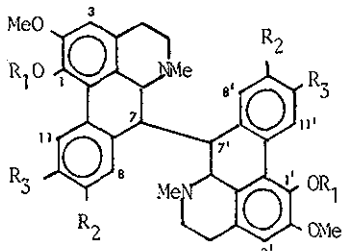
3 R_1=OH, R_2=R_3=R_4=OMe, R_5=H



4 R_1=Me, R_2=R_3=OMe

5 R_1=Me, R_2=R_3=H

6 R_1=CD_3, R_2=R_3=OMe

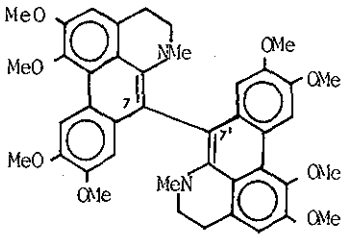


7 R_1=Me, R_2=R_3=OMe

8 R_1=Me, R_2=R_3=H

9 R_1=CD_3, R_2=R_3=OMe

10 R_1=Me, R_2=R_3=OMe, 3,3'-d_2



11

Compound 7 was also obtained in 85-90% when 2 was reacted with mercuric nitrate in acetonitrile, followed by reduction with sodium borohydride.

Reaction of dehydronuciferine (5) with mercuric acetate in aqueous solution as above afforded the corresponding dimer (8) as evidenced by the following spectroscopic data [mp 262-4°C; m/e 588 (15%, M^+), 294 (40%, doubly charged ion), 293 (100%); δ($CDCl_3$) 2.55 (6H, NMe), 2.78 and 3.87 (6H each, OMe), 5.91 (2H,d, J=9, H8 and H8'), 6.5-6.9 (4H, m, H9, H9', H10, H10'), 6.62 (2H,s, H3, H3'), 7.81 (2H,d, J=9, H11, H11'); UV (EtOH) $\lambda_{max.}$ 312,274 and 239 (log ε 3.77,4.29 and 4.31), (practically the same as that of nuciferine)].

Surprisingly, similar oxidation of dehydroglaucine (4) with mercuric acetate in methanol (1:1 molar ratio) gave the C7-C7' dehydroglaucine dimer (11), mp 272-4°C in almost quantitative yield. It exhibited

practically the same UV absorption (EtOH) [$\lambda_{max.}$ 337 and 266 nm (log ε 4.27 and 4.91)] as the monomer (4), the mass spectrum displayed a molecular ion at m/e 704 (58%) and its pmr ($CDCl_3$) showed unsplit signals at δ 2.23 (6H, NMe), 3.41 and 3.98 (6H each, OMe), 4.03 (12H, OMe), 6.72, 7.06 and 8.78 (2H each, ArH). The off-resonance C-13 nmr spectra of 11 and 4 supported structure 11 by showing a singlet for C7 and C7' of 11 in the region 124.9-126.1 ppm and a doublet for C7 of 4 at 101.36 ppm which proves the presence of a C7-C7' bond in the dimer 11. Further confirmation of this assumption was obtained from conversion of 7 into 11 by mercuric acetate oxidation in aqueous solution at room temperature.

Although mercuric salts have been used in the oxidation of aporphine to dehydroaporphine[8], the yields reported are low and the work-up often tedious. However, when glaucine (2) was treated with mercuric acetate in aqueous solution as above for two hours, two major compounds were formed: dehydroglaucine (4) and C7-C7' dehydroglaucine dimer (11). These results can be explained if we assume that dehydroglaucine as it is being formed reacts futher to dehydroglaucine dimer (11).

Further investigations on the scope and mechanistic aspects of this dimerization are under study.

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