ON THE STRUCTURE OF GLAUVINE: SYNTHESIS OF OXOLIRIOFERINE, NORLIRIOFERINE AND N,O-DIACETYLNORLIRIOFERINE[1].

Luis Castedo*, José M. Saá, Rafael Suau, and Carmen Villaverde

Departamento de Química Orgánica de la Facultad de Química e
Instituto de Productos Naturales Orgánicos (Sección Alcaloides)
del C.S.I.C.
Santiago de Compostela (Spain)

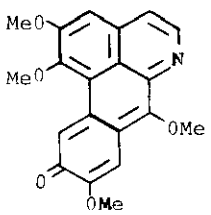
Abstract- Further support for structure (2) of glauvine by proving that its reduction product and norlirioferine (3c) were distinct compounds is described. Norlirioferine (3c) and its N,O-diacetyl-derivative (3d) were obtained via oxolirioferine (4a), which was synthetized by two independent routes.

We have seriously questioned the structure of glauvine {assumed to be (1)[2] } by proving its identity with corunnine [3]. The structure of corunnine (2) has been unambiguously confirmed by two different syntheses [4]. However, Zn-AcOH reduction of corunnine (2) [4b] gave thalicmidine (3a) while similar reduction of glauvine followed by acetylation has been reported by Yakhontova et al.[2] to afford a product (A) (mp 148-150ºC), which claimed from its spectroscopic data to be the new compound N,O-diacetylnorlirioferine (3d). The latter result has been used by Yakhontova et al.[2] to establish the previous structure (1) of glauvine. However, our new structure (2) of glauvine seems to be contradictory to his result. This together with the lack of a direct comparison of glauvine and corunnine as mentioned by Shamma [5] led us to study the synthesis of N,O-diacetylnorlirioferine (3d). This was achieved via oxolirioferine (4a), which was obtained by two independent routes involving the regioselective demethylation of isoquinoline alkaloids by mineral acids [6].

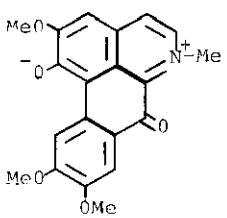
Thus, treatment of 6'-bromopapaverinol (5a) [7] with 80% orthophosphoric acid and a small amount of P_2O_5 gave in 35% yield the phenolic compound (5b), mp 189-91ºC [8]. Photocyclization of (5b) in a solution of methanol at or near neutrality [4b] afforded in 25% yield oxolirioferine (4a) as orange needles {mp 270ºC (dec.); UV (EtOH) λ_{max} (log ε) 244(4.35),274(4.32), 294(sh, 4.12), 359(3.82),394(sh, 3.73) nm; IR (KBr) ν_{max} 1650 cm^{-1}; pmr δ ($CDCl_3$) 8.86(1H, d, J=5.5, H-5), 8.68(1H, s, H-11), 8.03(1H, s, H-8), 7.74(1H, d, J=5.5, H-4), 7.16(1H, s, H-3), 4.06(6H, s, C-2 and C-9 OMe) and 4.01 ppm (3H, s, C-1 OMe); m/e (%) 337(100 M^+), 312(34), 294(25)}. Oxolirioferine (4a), upon acetylation with acetic anhydride in pyridine, afforded the acetate (4b) as yellow needles {mp 227-9ºC(dec.); UV(EtOH)λ_{max}(log ε) 242(4.59), 272(4.54),286 (sh,4.26), 333(3.85), 376(3.79), 430(3.77) nm; IR(KBr)ν_{max} 1760 (ester C=O), 1665 (ketone C=O) cm^{-1}; pmr δ($CDCl_3$) 8.86(1H, d, J=5.2, H-5), 8.83(1H, s, H-11), 8.08(1H, s, H-8), 7.75(1H, d, J=5.2, H-4), 7.14(1H, s, H-3), 4.06, 4.00 and 3.98(3H each, s, 3xOMe) and 2.39 (3H, s, $\underline{CH_3}$-CO-); m/e(%) 379 (22, M^+), 337 (100)}.

The other approach to the synthesis of O-acetyloxolirioferine (4b), started with the selective demethylation of dehydroglaucine (6a) with sulfuric acid which afforded in 48% yield the unstable dehydrolirioferine (6b) [9]. This, upon acetylation, gave O-acetyl-

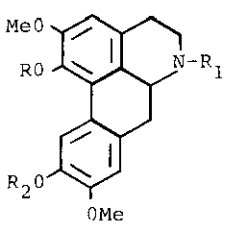
dehydrolirioferine(6c) [9], which when submitted to eosine-sensitized photooxidation [10] was converted into O-acetyloxolirioferine (4b) (82% yield).
Reduction of (4b) with Zn-AcOH gave in 90% yield norlirioferine (3c){ mp 112-4ºC ($CHCl_3$); UV(EtOH) λ_{max} (log ε) 220(4.45), 273(sh, 3.95), 280(4.02), 305(3.98), 316(sh, 3.91) nm; pmr δ($CDCl_3$) 7.99(1H, s, H-11), 6.69(1H, s, H-8), 6.55(1H, s, H-3), 3.89 and 3.85(3H each, s, C-2 and C-9 OMe), and 3.66 ppm (3H, s, C-1 OMe); m/e(%) 327(76, M^+), 326(100)}. Norlirioferine (3c), upon acetylation, afforded N,O-diacetylnorlirioferine (3d) {mp 202-4ºC ($CHCl_3$-ether); UV(EtOH) λ_{max} (log ε) 216(4.71), 282(4.29), 294(sh, 4.22), 302(sh, 4.11) nm; pmr δ($CDCl_3$) 8.13(1H, s, H-11), 6.82(1H, s, H-8), 6.59(1H, s, H-3), 3.84(6H, s, C-2 and C-9 OMe), 3.63(3H, s, C-1 OMe), 2.32, and 2.19 ppm (3H each, s, N-CO-CH_3, O-CO-CH_3)}.



1

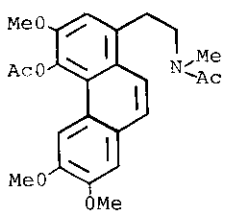


2

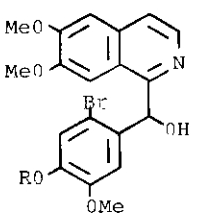


3

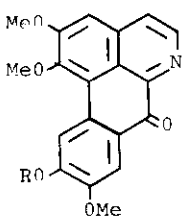
a) R=H; R_1=R_2= Me
b) R=Ac; R_1=R_2=Me
c) R=Me; R_1=R_2=H
d) R=Me; R_1=R_2=Ac
e) R=R_2=Me; R_1=Ac
f) R=R_1=Ac; R_2=Me



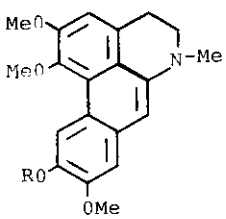
7



5
a) R=Me
b) R=H



4
a) R=H
b) R=Ac



6
a) R=Me
b) R=H
c) R=Ac

When the melting point and the spectroscopic data (pmr and IR) (Table I) of product (A) and N,O-diacetylnorlirioferine (3d) are compared it clearly shows that both are distinct compounds . Signals corresponding to the N- acetyl group of N,O-diacetylnorlirioferine (3d) appeared at 1635 cm^{-1} and at δ 2.75 ppm (Table I) and we have found the same chemical shift value (in TFA-d_1) in other N- acetyl aporphines such as N-acetylnorglaucine (3e) and N,O-diacetylwilsonirine (3f). However, for product (A) a further high field singlet (at δ 2.25 ppm) and an absorption band at 1698 cm^{-1} (too high for a tertiary amide carbonyl) have been reported [2] and both values on the other hand agree with acetic acid (Table I). Therefore, bearing in mind the identity of glauvine and corunnine and its reduction to thalicmidine (3a) we conclude that product (A) can only be O-acetylthalicmidine (3b) or phenanthrene (7). The compound (7) can be obtained when an aporphine is heated in acetic anhydride [11] . This last possibility was discarded by pmr comparison of product (A) and phenanthrene (7) obtained from thalicmidine (3a) [11]. Consequently , product (A) can only be the higher melting O-acetylthalicmidine (3b) (mp 184-5ºC) possibly impurified by acetic acid.

In this way, we found that O-acetylthalicmidine (3b) plus acetic acid gave the same pmr spectrum (in TFA-d_1) as reported for product (A) (Table I) [12] . Hence we further prove that glauvine should have the same structure (2) as corunnine.

TABLE I

	NMR data in TFA-d_1, δ, ppm					IR data (KBr) ν_{max} (cm^{-1})	
	H-3	H-8	H-11	N-Ac	O-Ac		
N,O-diacetylnorlirioferine (3d)	6.87	7.02	8.21	2.75	2.48	1770	1635
Product (A)	6.87	6.95	7.56	2.25	2.48	1770	1698
O-Acetylthalicmidine (3b)	6.85	6.97	7.67		2.49	1770	
Acetic acid					2.26		1700

ACKNOWLEDGMENT: To the Comisión Asesora de Investigación Científica y Técnica (Spain) for its financial support.

REFERENCES

1. Isoquinoline alkaloids XV. Part XIV: L.Castedo, J.M.Saá, R. Suau, C. Villaverde, and P. Potier, An. Quím., in press.
2. L. D. Yakhontova, V. I. Sheichenko, and O. N. Tolkachev, Khim. Prirod. Soedinenii, 1972, 214; Chem. Natural Compounds, 1974, 212 .

3. L.Castedo, R.Suau, and A.Mouriño, Heterocycles, 1975, 3, 449.

4. a) I.Ribas, J.Saá, and L.Castedo, Tetrahedron Letters, 1973, 3617;
b) S.M.Kupchan and P.F.O'Brien, J. C. S. Chem. Comm., 1973, 915.

5. M.Shamma in "The Alkaloids", ed. M.F.Grundon (Specialist Periodical Reports), The Chemical Society, London, 1976, Vol. 6, p. 182.

6. a) L.Castedo, J.M.Saá, R.Suau, and C.Villaverde, Heterocycles, 1978, 9, 659;
b) S.Ruchirawat, S.Suparlucknaree, and N.Prasitpan, Heterocycles, 1978, 9,859.

7. T.Vitali, and G.Azzolini, Boll. Soc. Ital. Biol. Sper., 1955, 31, 1025;
C.A., 1956, 50, 8139g.

8. Satisfactory analytical and/or spectral data were obtained for all new compounds.

9. L.Castedo, A.R. de Lera, J.M.Saá, R.Suau, and C.Villaverde, Heterocycles, accompanying paper.

10. L.Castedo, R.Suau, and A.Mouriño, An. Quím., 1977, 73, 290.

11. S.R.Johns, J.A.Lamberton, and A.A.Sioumis, Aust. J. Chem., 1966, 19, 2339.

12. We have been unable to isolate the acetate salt of 3b.

Received, 25th April, 1980