SYNTHESIS OF THE C-11 OXYGENATED ERYTHRINA ALKALOIDS

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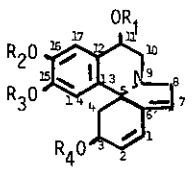
Abstract — Introduction of an oxygenated function at C-11 of the Erythrina alkaloid skeleton was obtained by treating erysovine with lead tetraacetate. Unfortunately simultaneous substitution of the C-3 OMe by -OAc has occurred and modifications as changing the reaction conditions and/or the phenolic compound to erysodine did not lead to successful results.

While developing our phytochemical study on Erythrina mulungu[1] we became aware that although much work has been devoted to the synthesis of Erythrina alkaloids, nothing has been mentioned on the C-11 oxygenated compounds of this type, 1. Our own efforts have been directed toward the introduction of an oxygenated function at the benzylic site of 2, which requires a highly regioselective reaction. This led us to lead tetraacetate oxidations (LTA) which have successfully been applied to phenolic tetrahydroisoquinoline derivatives by Umezawa et al[2].

Thus erysovine 2a (0.200 g)[3] in acetic acid (5 ml) was treated with LTA (0.250 g) at 0°C for 0.5 h producing the p-quinol acetate 3 [IR (cm^{-1}): 1740 (OAc), 1680 (C=O); UV. λ_{max}^{EtOH} 232 nm; ^1H NMR (δ $CDCl_3$): 2.13 (OCOMe), 3.37 (C-3 OMe), 3.72 (C-16 OMe), 6.62 and 6.80 (each 1H, H-14 and H-17)]. Crude p-quinol acetate 3 (0.100 g) in acetic anhydride (0.5 ml) was further treated with conc. H_2SO_4 (0.06 ml) and Ac_2O (1 ml) at -30°C for 15 min. Usual treatment of the reaction followed by



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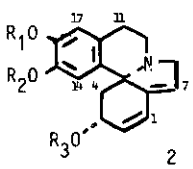

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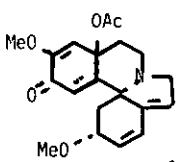

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1a - R_1=R_3=R_4=Ac; R_2=Me (3R, 11R)
1b - R_1=R_3=R_4=Ac; R_2=Me (3S, 11R)
1c - R_1=R_3=R_4=Ac; R_2=Me (3R, 11S)
1d - R_1=R_3=R_4=Ac; R_2=Me (3S, 11S)
1e - R_2=R_3=R_4=Me; R_1=Ac (3R, 11R)

2a - R_1=R_3=Me; R_2=H
2b - R_1=R_2=R_3=Me
2c - R_1=R_2=Me; R_3=Ac
2d - R_1=R_2=Me; R_3=H
2e - R_1=R_3=Me; R_2=Ac
2f - R_1=H; R_2=R_3=Me

layer chromatography afforded 1a, 1b, 1c and 1d in 17, 13, 6 and 0.5% yield respectively, which showed analogous UV (λ_{max}^{EtOH} ca. 275 and 223 nm) and mass [m/z M^+ 427, 266 (100%)] spectra, indicating a close relationship between these compounds. Formation of four diastereoisomers could be visualized taking into consideration that the introduction of the acetoxy group at C-11 would lead either to (R) C-11-OAc or (S) C-11-OAc and that the acidic treatment (Ac_2O-conc H_2SO_4) of the p-quinol acetate 3, could attack the allylic methyl ether at C-3 affording either (R) C-3-OAc or (S) C-3-OAc. Therefore in order to obtain further evidence on the acetoxy substitution of the C-3-OMe, erysotrine 2b, was treated with Ac_2O- conc. H_2SO_4 at -30°C to yield acetylerythravine 2c as a major compound [$\delta_H(CDCl_3)$ 2.02 (OAc), 3.37 (OMe), 3.83 (OMe), 5.46-5.76 (m, w1/2 18 Hz, H-3) 5.83 (H-7), 6.03 (lower field arm of a doublet, H-1) 6.68 (dd, J=10 and 2 Hz H-2), 6.67 (s, H-17), 6.90 (s, H-14)] which on hydrolysis ($HCl/H_2O/80^oC$) afforded erythravine 2d, with identical spectral data to those of the natural product[4].

Structures 1a, 1b and 1c were confirmed to be (3R, 11R) - 3,15-diacetyl-11-acetoxyerysoline, (3S, 11R) - 3,15-diacetyl-11-acetoxyerysoline and (3R, 11S) - 3,15-diacetyl-11-acetoxyerysoline respectively by inspection of their ^1H NMR spectra (Table 1). The assignments of H-2, H-3 and H-10 were confirmed by selective irradiation experiments and those of the acetoxy groups by comparison with acetylerythravine 2c, erythrascine 1e[5] and acetylerysovine 2e [$\delta_H(CDCl_3)$ 2.35 (OAc)].

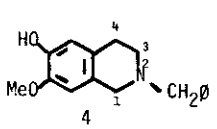
The absorption patterns of H-2, H-3 and H-10 (compound 1a, 1b and 1c) in the ^1H NMR spectra were of diagnostic importance in our configurational analysis, when compared to the corresponding ones of 2c, 1e and 2e.

The minor compound 1d was regarded as the fourth diastereoisomer (3S, 11S) 3,15-diacetyl-11-acetoxyerysoline.

Facing these facts we came to the conclusion that although LTA oxidation of 2a afforded the C-11 oxygenated Erythrina alkaloid, the isomerization at C-3 had to be overcome either by changing the reaction conditions or the phenolic compound.

Thus p-quinol acetate 3 was treated with CF_3COOH and $CF_3COOH(CF_3CO)_2O$[6] instead of H_2SO_4/Ac_2O and in both cases we did not recuperate an 11-oxygenated Erythrina alkaloid.

We were then left with the possibility of changing the phenolic compound. Based on the fact that LTA oxidation of 2-benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline 4, gives the



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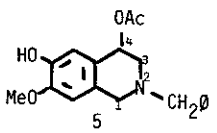

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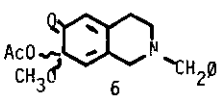

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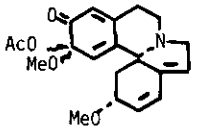
Table 1

Assignment of ^{1}H NMR signals of the oxidation products of 2a in $CDCl_3$.

1a	H-14	H-17	H-2	H-1	H-7 - H-11
	7.06 (s)	6.89 (s)	6.60 (dd,J = 10, 2.5)	5.92 (s) lower field arm of a doublet	5.84 - 5.74 (m)
1b	7.26 (s)	6.82 (s)	6.05 (dd,J = 10, 5)	6.74 (s) higher field arm of doublet	H-7 - H-11 - H-1 5.88 - 5.82 (m)
1c	7.02 (s)	6.82 (s)	6.55 (dd,J = 10, 2)	-	5.72 - 6.18 (m)

1a	H-3	H-10a	H-10e	OMe	OAc
	5.70 - 5.40 (m, wl/2 = 18)	3.23 (dd, J = 15, 2)	3.58 (dd, J = 15, 4)	3.80 (s)	2.28 (C-15) 2.10 (C-11) 2.02 (C-3)
1b	5.62 - 5.40 (m, wl/2 = 10)	3.26 (dd, J = 15, 2)	3.62 (dd, J = 15, 4)	3.78	2.26 (C-15) 2.11 (C-11) 1.90 (C-3)
1c	5.64 - 5.40 (m, wl/2 = 17)	3.20 - 3.60 (m)	3.20 - 3.60 (m)	3.77 (s)	2.24 (C-15) 2.12 (C-11) 2.01 (C-3)

corresponding 4-acetoxy derivatives 5, on a spontaneous rearrangement of the o-quinol acetate 6[2], we have submitted erysodine 2f[3] (0.162 g) an Erythrina alkaloid possessing an isoquinoline moiety similar to 4, to LTA oxidation (0.202 g) in CH_2Cl_2 (5 ml) at 5°C. Usual work up[2] led to the expected C-15 epimeric mixture of o-quinol acetates 7 [^{1}H NMR δ($CDCl_3$) 2.08 (6H, OAc), 3.30 (OMe), 3.33 (OMe), 3.40 (OMe), 3.43 (OMe), 5.80-6.90 (H-1, H-2, H-7, H-14 and H-17)] which unfortunately decomposed prior to its rearrangement to the corresponding 11-acetoxy derivative 8.



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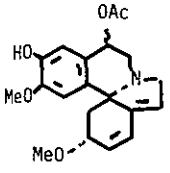

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We are now looking for other reagents which could introduce an oxygenated function at C-11 of the Erythrina alkaloid (dienoid type), without isomerizing carbon-3.

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