Synthesis of (±)-Thaliporphine; Acid-catalysed Rearrangement of a *p*-Quinol Acetate

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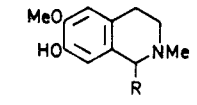
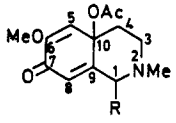
Summary $Pb(OAc)_4$ oxidation followed by acid treatment of (±)-codamine gives (±)-*O*-acetylthaliporphine.

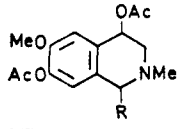
IN a previous communication,[1] we have reported that $Pb(OAc)_4$ oxidation of 7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (I) in AcOH gives *p*-quinol acetate (10-acetoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,8}$-hexahydroisoquinoline) (II), treatment of which with Ac_2O-conc. H_2SO_4 at room temperature affords 4,7-diacetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (III). This finding appeared to imply that acid treatment of the *p*-quinol acetate (IV) of (±)-codamine [(±)-1-(3,4-dimethoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline] would give isopavine type[2] and/or aporphine type[3] products [(V) and/or (VI)]. The application of this reaction to (±)-codamine (VII) was therefore investigated, and shown to give rise principally to an aporphine type product, (±)-thaliporphine, (±)-1-hydroxy-2,9,10-trimethoxyaporphine (VIII).[3,4]



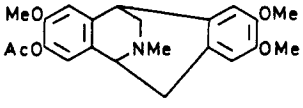
(I) R = H
(VII) R = $CH_2C_6H_3(OMe)_2$(3,4



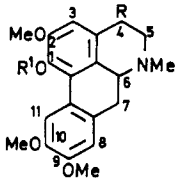
(II) R = H
(IV) R = $CH_2C_6H_3(OMe)_2$(3,4)



(III) R = H
(XI) R = $CH_2C_6H_3(OMe)_2$(3,4)



(V)



(VI) R^1 = Ac, R^2 = H
(VIII) R^1 = R^2 = H
(IX) R^1 = Ac, R^2 = OAc
(X) R^1 = Me, R^2 = H

Reaction of (VII)[3,5] with $Pb(OAc)_4$ in AcOH at room temperature for 0·5 h gave an amorphous product, which, without purification, was treated with Ac_2O–conc. H_2SO_4 at room temperature for 1 h, and chromatography over silicic acid (Mallinckrodt) furnished (±)-4-acetoxy-*O*-acetylthaliporphine† (IX) (from eluate with $CHCl_3$) [6%, m.p. 236—238° (decomp.) (benzene–n-hexane), and (±)-*O*-acetylthaliporphine (VI) [from eluate with $CHCl_3$–CH_3OH (200:1)–(200:2)] [14%, m.p. 156—158° (benzene–petroleum)], respectively.

Hydrolysis of (VI) in 4N-HCl–CH_3OH (1:1) at 80° for 1·5 h gave (±)-thaliporphine (VIII) [68%, m.p. 193—195° (decomp.) (benzene–petroleum) (lit.[3] m.p. 192—194° (decomp.)], which was methylated with CH_2N_2–CH_3OH to afford (±)-glaucine (X) (oil); picrate, m.p. 191—193° (EtOH) (lit.[6] m.p. 193—194°)].

Additional evidence on the structure of (IX) was obtained by reduction ($LiAlH_4$) of (IX) in refluxing anhydrous tetrahydrofuran for 3·5 h, to give (±)-thaliporphine in 20% yield.

Thus acid treatment of (IV) gives neither the isopavine type product (V) nor (±)-4,7-diacetoxycodamine (XI), but rather the di- and mono-acetates of (±)-thaliporphine [(IX) and (VI)].

Formation of (VI) is inferred to proceed as follows: Michael-type addition of the 6-position in the veratryl group to the 9-position in (IV), and concerted elimination of the 10-acetoxy-group followed by 1,2-shift of the C-6–C-9 bond to the 8-position, and aromatisation. The mechanism of formation of (IX), however, remains obscure.

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† Satisfactory analytical data and spectra (i.r., n.m.r., mass) were obtained for all new compounds described.

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