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Studies on Tetrahydroisoquinolines. VI.[1] Synthesis of (±)-Thaliporphine and (±)-Glaucine *via* a *p*-Quinol Acetate[2]

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Acid-catalyzed (conc. sulfuric acid–acetic anhydride) reaction of *p*-quinol acetate (IIb) prepared by lead tetraacetate oxidation of (±)-codamine (Ic) was found to give (±)-4-acetoxy-O-acetylthaliporphine (VII) and (±)-O-acetylthaliporphine (IX), respectively. Both VII and IX were converted into (±)-thaliporphine (IV), whose methylation gave (±)-glaucine (X).

Previously, we reported that lead tetraacetate [$Pb(OAc)_4$] oxidation of corypalline (Ia) afforded the corresponding *p*-quinol acetate (IIa), whose acid treatment provided smoothly a rearrangement product, 4,7-diacetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[4] (IIIa), and its pronounced reactivity towards nucleophilic reagents such as alcohols,[5] amines[6] or active methylene compounds[1] and that similar sequence[4] of reactions of 1-benzylcorypalline (Ib) gave the corresponding 4,7-diacetate (IIIb).

Our interest was directed to intramolecular nucleophilic substitution in *p*-quinol acetate or 4,7-diacetate having activated 1-benzyl group, such as veratryl. Because, if an acid-catalized reaction in the former took place aporphine and/or morphinandienone type compound [(IV) or (V)] might well be formed, and the reaction in the latter would give rise to isopavine type compound (VI).

Although numerous synthesis of aporphine[7] or isopavine[8] alkaloids are already known, the present approach appears to be worthwhile in the sense that a *p*-quinol acetate constitutes essentially the key intermediate.

The starting material, (±)-codamine (Ic) was synthesized according to Shamma's method.[9] Namely, β-(4-benzyloxy-3-methoxyphenyl)ethylamine was condensed with methyl 3,4-dimethoxy-phenylacetate[10] at 175—180° (bath temp.) to give an amide, which was cyclised ($POCl_3$, anhydrous toluene) to 3,4-dihydroisoquinoline hydrochloride. Neutralization of the latter with conc. ammonium hydroxide (NH_4OH), and subsequent treatment with methyl iodide followed by sodium borohydride ($NaBH_4$) reduction provided oily (±)-benzyloxy codamine, which on hydrolysis (20% hydrochloric acid, acetic acid) gave (±)-codamine (Ic) as a yellow oil in quantitative yield.

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[1] Part V: O. Hoshino, Y. Yamanashi, T. Toshioka, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2166 (1971).

[2] The preliminary communication of this work appeared in O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Comm.*, **1971**, 1533.

[3] Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*

[4] B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue, and T. Toshioka, *Chem. Pharm. Bull.* (Tokyo), **19**, 2138 (1971).

[5] B. Umezawa, O. Hoshino, and Y. Yamanashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2154 (1971).

[6] O. Hoshino, Y. Yamanashi, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2161 (1971).

[7] See M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York and London, 1972, pp. 197—205, pp. 210—213.

[8] S.M. Kupchan and A. Yoshitake, *J. Org. Chem.*, **34**, 1062 (1969); D.W. Brown, S.F. Dyke, G. Hardy, and M. Sainsgurg, *Tetrahedron Letters*, **1969**, 1515; S.F. Dyke and A.C. Ellis, *Tetrahedron*, **27**, 3803 (1971); *idem.*, *ibid.*, **28**, 3999 (1972).

[9] M. Shamma and W.A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).

[10] H.R. Snyder, J.S. Quck, and W.S. Ide, "Organic Synthesis," Col. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 333.

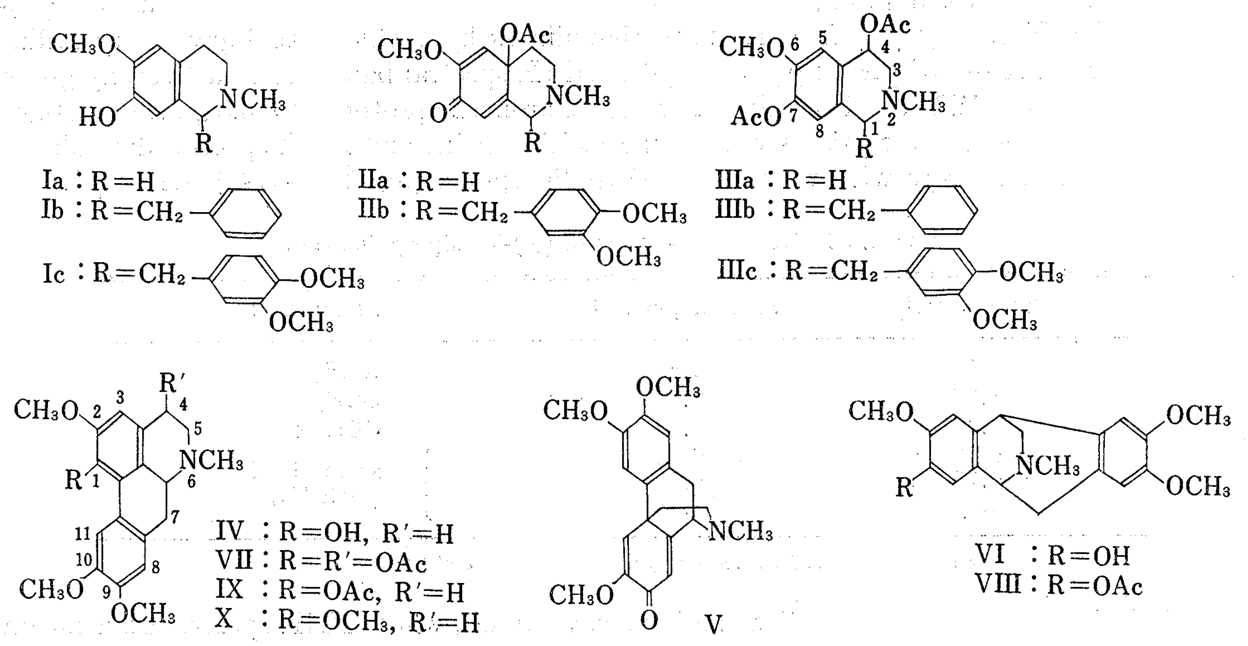

Chart 1

A solution of (±)-Ic in acetic acid was stirred with Pb $(OAc)_4$ under water cooling and usual work-up gave a dark brown amorphous *p*-quinol acetate (IIb) which was characterized by infrared (IR) absorption bands at 1740, 1680, 1650 and 1630 cm^{-1}. The crude *p*-quinol acetate (IIb) was used for the next step without further purification, since its instability was experienced in an attempted purification on silicic acid column chromatography. Acid treatment (conc. sulfuric acid, acetic anhydride) of the *p*-quinol acetate (IIb) and chromatography over silicic acid provided a crystalline product, mp 236—238° (decomp.), from the eluate with chloroform ($CHCl_3$) and another crystalline product, mp 156—158°, from the eluate with $CHCl_3$–methanol (CH_3OH) (200:1—100:1).

IR spectrum of the former showed characteristic bands at 1763 (aromatic OAc), 1727 (aliphatic OAc) and 1602 (C=C) cm^{-1} suggesting its structure as 4,7-diacetate. If so, five aromaic protons should be present in the molecule. But this was not the case since only three aromatic protons [δ: 6.87 (2H, s), and 7.60 (1H, s)] were revealed in its nuclear magnetic resonance (NMR) spectrum. Furthermore the molecular weight was counted as 441, 2 mass units less than that of 4,7-diacetate (IIIc). Provided that a new ring was formed, the above discrepancy would surely be solved. Hence the structure appeared to be (±)-4-acetoxy-O-acetylthaliporphine (VII) by evidences described above together with elemental analysis and the presence of one proton quartet ($J=10$ Hz and $J=7.5$ Hz) at δ 6.20 attributable to the proton at C-4 bearing acetoxy group.

The latter had molecular formula of $C_{22}H_{25}O_5N$ indicated by both mass spectrum [*m/e*: 383 (M^+)] and elemental analysis and should have one aromatic acetoxy group as revealed by IR band at 1762 cm^{-1}. At this stage it was possible to assume that by acid treatment 4,7-diacetate underwent direct ring closure to isopavine skeleton, (±)-O-acetyl-O-methylthalisopavine (VIII). But the presence of three aromatic protons at δ 6.12, 6.77 and 7.51 (each 1H) ruled out the possibility since the isopavine (VIII) must possess four aromatic protons.

Thus the structure would be altered to an aporphine. The correct structure was assumingly (±)-O-acetylthaliporphine (IX) excluding another aporphine obtainable by C-8 to C-2′ bond formation because of the fact that each aromatic proton was observed as distinct singlet and one proton among them suffered apparently down-field shift due to near by situated benzene ring.

To confirm the assumption, both VII and IX were led to the same known alkaloid, (±)-thaliporphine (IV). Hydrolysis of IX in methanolic 4N hydrochloric acid gave a crystalline substance, mp 193—195° (decomp.), which showed IR spectral band due to a hydroxy group at 3480 cm^{-1} and NMR chemical shift due to three aromatic protons at δ 6.52, 6.78 and 8.08. Moreover its elemental analysis as well as the melting point and NMR spectral data shown in Table I agreed nicely with those[9] of (±)-thaliporphine (mp 192—194°) (decomp.).

Table I. NMR Data (δ-Value) of (±)-Thaliporphine (IV)

Present work	Shamma, *et al.*[a]	Assignment
2.59	2.53	NCH_3
3.87	3.85	OCH_3
3.89	3.88	$OCH_3 \times 2$
6.52	6.52	aromatic H (each 1H)
6.75	6.78	
8.04	8.08	

[a] M. Shamma and W.A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967)

Methylation of (±)-IV with diazomethane gave an oil, whose NMR spectral data shown in Table II together with its picrate [mp 191—193° (decomp.)] were well accordant with those of (+)-glaucine (X) [lit.[11] mp 193—194°].

Table II. NMR Data (δ-Value) of (±)-Glaucine (X)

Present work	Jackson, *et al.*[a]	Assignment
2.68	2.57	NCH_3
3.62	3.68	OCH_3 (C-1)
3.87	3.90	OCH_3 (C-10)
3.89	3.94	$OCH_3 \times 2$ (C-2, C-9)
6.58	6.53	aromatic H (C-3)
6.76	6.83	aromatic H (C-8)
8.07	8.14	aromatic H (C-11)

[a] A.H. Jackson and J.A. Martin, *J. Chem. Soc.*, (*C*), **1966**, 2061

Conversion of the above (±)-4-acetoxy-O-acetylthaliporphine (VII) to (±) -thaliporphine (IV) was examined for firm establishment of its structure. Removal of acetoxy group at 4-position by hydride ($LiAlH_4$ in boiling tetrahydrofuran) was undertaken to give rise to a crystalline substance, mp 186—189° (decomp.), which was identified as (±)-IV by comparison with their thin-layer chromatography (TLC) and IR (KBr) spectrum, while attempted hydrogenolysis with palladium on carbon in acetic acid containing conc. sulfuric acid failed.

As to the mechanistic pathway, the following explanation would reasonably be acceptable. Namely, initially formed unstable *p*-quinol acetate (IIb) would suffer intramolecular Michael reaction by electron movement as depicted in Chart 2 and concerted elimination of 10-acetoxy group with 1,2-shift (C-9-C-6′ bond to C-8-C-6′) followed by deprotonation would provide aporphine skeleton. Formation of (±)-4-acetoxy-O-acetylthaliporphine (VII), however, was mechanistically uncertain.

In any event, (±)-thaliporphine (IV) was synthesized from (±)-codamine (Ic) *via p*-quinol acetate (IIc). As compared to typical aporphine synthesis, where Pschorr, benzyne or photolytic reaction was applied, the present method[12] was undoubtedly not tedious because

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[11] A.H. Jackson and J.A. Martin, *J. Chem. Soc.*, (*C*), **1966**, 2061.

[12] One biosynthetic example akin to our approach was reported by Battersby and his co-workers (A.R. Battersby, J.L. McHugh, J. Staunton, and M. Todd, *Chem. Commun.*, **1971**, 985).

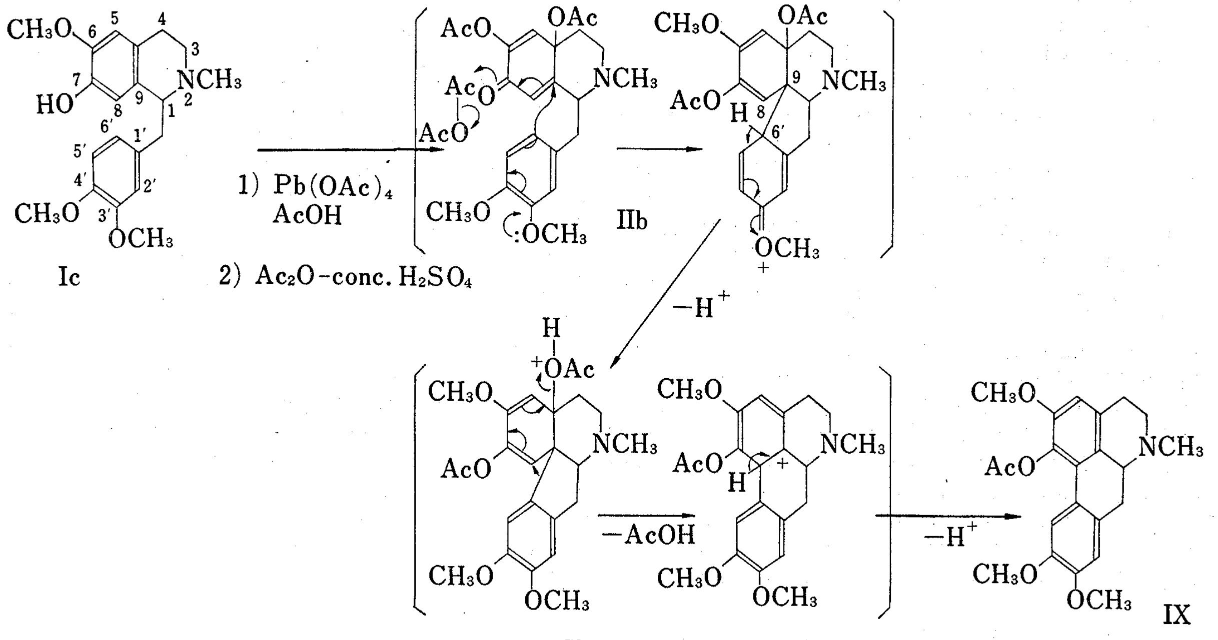

Chart 2

pre-introduction of substituent such as amino or bromo was by no means neccessary in the starting benzylisoquinoline.

Experimental[13]

(±)-Codamine (Ic)——A solution of (±)-O-benzylcodamine[9] (3.6 g) in AcOH (70 ml) and 20% HCl (70 ml) was refluxed at 110—115° (bath temp.) for 1.5 hr. On evaporation of the solvent under reduced pressure, water was added to the residue and the mixture was washed with ether. The aqueous layer was basified with conc. NH_4OH and the product was taken up in $CHCl_3$. The $CHCl_3$ layer was washed well with brine, dried over $MgSO_4$, and distilled under reduced pressure to provide (±)-codamine (Ic) (2.85 g) as an oil. NMR δ: 2.74 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 3.82 (6H, s, $OCH_3 \times 2$). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3550 (OH), 1590 (C=C). Picrate: mp 187—190° (95% C_2H_5OH) (lit.[9] mp 187°).

(±)-O-Acetylthaliporphine (IX) and (±)-4-Acetoxy-O-acetylthaliporphine (VII)——To a stirred solution of (±)-codamine (Ic) (2.85 g) in AcOH (60 ml) was added $Pb(OAc)_4$ (7.4 g) in one portion and stirring was continued for 0.5 hr. On addition of water to the mixture to decompose excess of the oxidant, the whole was made alkaline with $NaHCO_3$ (powder) and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave *p*-quinol acetate (2.45 g) as a dark brown mass. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1740 (OAc), 1680, 1650, and 1630 (dienone).

The crude *p*-quinol acetate (IIb) was dissolved in Ac_2O (30 ml). To the ice-cooled, stirred solution was added dropwise a mixture of conc. H_2SO_4 (1 g) and Ac_2O (2 ml) over a period of 10 min and the whole was stirred at room temperature for 1 hr. The reaction mixture was poured into ice-water and washed with ether. After basification of the aqueous layer with $NaHCO_3$ (powder), the product was extracted with $CHCl_3$. Usual work-up of the $CHCl_3$ extract left an amorphous substance (1.84 g), which was chromatographed over silicic acid (Mallinckrodt) (55 g). Elution with $CHCl_3$ gave (±)-4-acetoxy-O-acetylthaliporphine (VII) (286 mg, 8%), mp 184—196° (decomp.), which was treated with benzene–*n*-hexane to afford yellow needles (217 mg, 6%), mp 228—232° (decomp.). Recrystallization from the same solvent furnished an analytical sample, mp 236—238° (decomp.). *Anal.* Calcd. for $C_{24}H_{27}O_7N$ (mol. wt.=441.46): C, 65.29; H, 6.16; N, 3.17. Found: C, 65.59; H, 6.15; N, 3.58. NMR δ: 2.17, 2.32 (each 3H, s, $OAc \times 2$), 2.55 (3H, s, NCH_3), 3.85, 3.90, 3.92 (each 3H, s, $OCH_3 \times 3$), 6.20 (1H, q, $J=10$ Hz, $J=7.5$ Hz, C-4 H), 6.87 (2H, s, aromatic H),

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[13] All melting points were uncorrected and measured on a Büchi melting point measuring apparatus. NMR spectral were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard. Following abbreviations were used: s: singlet; q: quartet. IR spectra were run on a Hitachi Model 215 infrared spectrometer, unless otherwise noted. Mass spectra were measured with a Hitachi mass spectrometer Model RMU-6E. Preparative TLC was run over Silica gel GF_{254} (Merck).

7.60 (1H, s, aromatic H). IR[14] $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1763 (aromatic OAc), 1727 (aliphatic OAc), 1602 (C=C). Mass Spectrum *m/e*: 441 (M$^+$).

Elution with $CHCl_3$–CH_3OH (200: 1—200: 2) gave (±)-O-acetylthaliporphine (IX) (554 mg, 18%), mp 128—136°, which was treated with benzene–petr. benzine afforded yellow needles (439 mg, 14%), mp 153—156°. Recrystallization from the same solvent left an analytical sample, mp 156—158°. *Anal.* Calcd. for $C_{22}H_{25}O_5N$ (mol. wt.=383.43): C, 68.91; H, 6.57; N, 3.65. Found: C, 69.07; H, 6.73; N, 3.54. NMR δ: 2.29 (3H, s, OAc), 2.54 (3H, s, NCH_3), 3.81, 3.87, 3.89 (each 3H, s, $OCH_3 \times 3$), 6.62, 6.77, 7.51 (each 1H, s, aromatic H). IR[14] $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1762 (aromatic OAc), 1600 (C=C). Mass Spectrum *m/e*: 383 (M$^+$).

(±)-Thaliporphine (IV)——A solution of (±)-IX (100 mg) in 4N HCl (10 ml) and CH_3OH (10 ml) was warmed at 80° (bath temp.) for 1.5 hr. On removal of the solvent under reduced pressure, the residue was basified with $NaHCO_3$ (powder) and extracted with $CHCl_3$. Usual work-up of the extract gave (±)-thaliporphine (IV) (82 mg, 92%), mp 142—153° (decomp.), treatment with benzene–petr. benzine giving yellow prisms (61 mg, 68%), mp 177—182° (decomp.). Recrystallization from the same solvent afforded an analytical sample, mp 193—195° (decomp.) [lit.[9] mp 192—194° (decomp.)]. *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.97; N, 4.10 Found: C, 70.73; H, 6.84; N, 3.86. NMR δ: 2.59 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 3.89 (6H, s, $OCH_3 \times 2$), 6.52, 6.75, 8.04 (each 1H, s, aromatic H). IR[14] $\nu_{\max}^{KBr}$ cm^{-1}: 3480 (OH), 1600 (C=C).

(±)-Glaucine (X)——To a solution of (±)-IV in CH_3OH (1 ml) was added ethereal CH_2N_2 (10 ml) and the whole was allowed to stand at room temperature overnight. Evaporation of the solvent gave an oil (14 mg), which was purified using preparative TLC ($CHCl_3$: CH_3OH=7: 1) to afford (±)-glaucine (X) (11 mg, 91%). NMR δ: 2.68 (3H, s, NCH_3), 3.62, 3.87 (each 3H, s, $OCH_3 \times 2$), 3.89 (6H, s, $OCH_3 \times 2$), 6.58, 6.76, 8.07 (each 1H, s, aromatic H). Picrate: yellow needles from C_2H_5OH, mp 191—193° (decomp.) (lit.[11] mp 193—194°).

$LiAlH_4$ Reduction of (±)-4-Acetoxy-O-acetylthaliporphine (VII)——To an ice-cooled, stirred suspension of $LiAlH_4$ (20 mg) in THF (2 ml) was added a solution of (±)-4-acetoxy-O-acetylthaliporphine (VII) (40 mg) in anhyd. THF (6 ml) and the whole was refluxed for 3.5 hr. The reaction mixture was treated successively with moist ether, water and dil. HCl. The base was thoroughly extracted with 5% HCl. Basification of the extract with $NaHCO_3$ (powder) followed by extraction with $CHCl_3$ and usual work-up gave amorphous mass (36 mg). Preparative TLC ($CHCl_3$: CH_3OH=7: 1) afforded (±)-thaliporphine (IV) (14 mg, 45%), mp 175—179° (decomp.) and a crystalline product (9 mg), mp 103—112°. Recrystallization of the former from benzene–*n*-hexane furnished a sample of mp 186—189° (decomp.), which was identical in all respects with (±)-thaliporphine (IV) derived from (±)-O-acetylthaliporphine (IX) by comparison of each IR (KBr) spectrum and TLC. The latter was probably the corresponding diol. However, the exact structure was not studied further.

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[14] A Hitachi Model 225 infrared spectrometer was used.