A SIMPLE SYNTHESIS OF ISOPAVINE ALKALOID,, (±)-O-METHYLTHALISOPAVINE AND (±)-REFRAMINE

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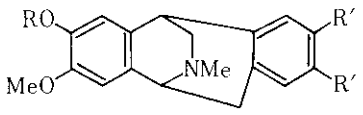
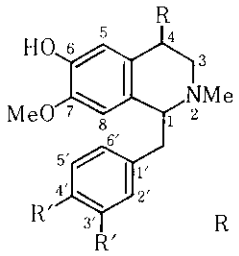
(±)-O-Methylthalisopavine (I) and (±)-reframine (II) were synthesized by acid treatment and subsequent methylation of (±)-4-acetoxytetrahydroisoquinoline [(V) and (VI)] directly derived from 6-hydroxytetrahydroisoquinoline [(III) and (IV)].

In the course of our investigation[1] on lead tetraacetate oxidation of phenolic tetrahydroisoquinolines, we found that similar reaction[2] of tetrahydroisoquinolines bearing a hydroxy group at 6-instead of 7-position gave directly 4-acetoxy





	R	R′	R′
I	Me	OMe	OMe
II	Me	O—CH_2—O	
VII	H	OMe	OMe
VIII	H	O—CH_2—O	

	R	R′	R′
III	H	OMe	OMe
IV	H	O—CH_2—O	
V	OAc	OMe	OMe
VI	OAc	O—CH_2—O	

products. Although Dyke and Ellis[3] have already achieved the Synthesis of (±)-O-methylthalisopavine (I)[4] or (±)-reframine (II) from the corresponding 4-hydroxytetrahydroisoquinoline or acetal amine, the yield of the key step, acid catalysed cyclization, amounts to only 35 or 33%. Hence similar treatment of 4-acetoxy counterparts appeared to give much better results and indeed (V) or (VI) was, in our hands, converted to (VII) or (VIII) in 92 or 90% yield as shown below. The present communication described a facile preparation of 4-acetoxytetrahydroisoquinoline (V) and (VI), and their application to a synthesis of I and II.

(±)-1-(3',4'-Dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (III)[5] was oxidized with lead tetraacetate in chloroform under ice-water cooling for a few minutes and silicic acid chromatography afforded a diastereoisomeric mixture of (±)-4-acetoxytetrahydroisoquinoline (V) as an oil [methiodide[6] of its 4,6-diacetoxy compound, mp 226-228.5° (decomp.)(isopropanol)](from eluate with chloroform) in 76% yield. N.m.r.[7] δ: 2.05, 2.10 [3H, each singlet, OAc(2:1)], 2.59, 2.68 [3H, each singlet, NMe(1:2)], 3.52, 3.55 [3H, each singlet, OMe(2:1)], 3.78, 3.86 (each 3H, singlet, OMe X 2); i.r.[8] ν_{max} (cm^{-1}): 3545 (OH), 1720 (OAc). (±)-4-Acetoxy compound (V), without further purification, was treated with conc. hydrochloric acid-ethanol[3] at room temperature for 12 hrs. to give a cyclised product (VII) as an oil [methiodide, mp 194-199°(ethanol-ether)] in 92% yield. N.m.r.δ: 2.51 (3H, singlet, NMe), 3.74, 3.80, 3.86 (each 3H, singlet, OMe X 3), 6.52, 6.65, 6.71, 6.77 (each 1H, singlet,

aromatic proton); i.r. $\nu_{max}(cm^{-1})$: 3545 (OH). VII was methylated with diazomethane in methanol to provide (±)-O-methylthalisopavine (I), mp 164-166.5°(methanol)(lit.[3] mp 165-166°), in 66% yield, n.m.r. spectrum of which was identical with that published[3,4] for an authentic sample.

Next, similar reaction of (±)-1-(3',4'-methylenedioxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV), mp 145-145.5°(benzene-ether), followed by silicic acid chromatography gave a diastereoisomeric mixture of (±)-4-acetoxy compound (VI) as an oil [methiodide of its 4,6-diacetoxy compound, mp 241-244°(decomp.)(ethanol)](from eluate with chloroform) in 60% yield. N.m.r.δ: 2.04, 2.08 [3H, each singlet, OAc(2:1)], 2.55, 2.60 [3H, each singlet, NMe(1:2)], 3.57, 3.61 [3H, each singlet, OMe(2:1)], 5.90, 5.93 [2H, each singlet, OCH_2O(1:2)], 5.70-6.00 (1H, multiplet, C_4-H); i.r. $\nu_{max}(cm^{-1})$: 3550 (OH), 1720 (OAc). Treatment of VI with conc. hydrochloric acid-ethanol at room temperature for 12 hrs. afforded (±)-isopavine (VIII)[9] as an oil [methiodide, mp 230-233°(decomp.)(ethanol-ether)] in 90% yield. N.m.r.δ: 2.48 (3H, singlet, NMe), 3.79 (3H, singlet, OMe), 5.80 (2H, multiplet, OCH_2O), 6.43, 6.57, 6.63, 6.71 (each 1H, singlet, aromatic proton); i.r. $\nu_{max}(cm^{-1})$: 3540 (OH). Methylation of VIII with diazomethane in methanol gave (±)-reframine (II) as an oil in 73% yield [methiodide, mp 272-274° (decomp.)(lit.[3] mp 272-274°(decomp.)], whose n.m.r. spectrum was consistent with that published[3] for an authentic sample.

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6. Analytical data for all new compounds described confirmed their structures.
7. N.m.r. spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in deutero-chloroform solution (5-10%) by using tetramethylsilane as internal standard.
8. I.r. spectra were run on a Hitachi 215 spectrometer in chloroform solution.
9. Having accomplished this work, we received Dr. Dyke's manuscript on synthesis of isopavine (VIII) and its isomer by the different manner from ours. We are grateful to him.

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