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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DXXIII[1]

ENZYMIC OXIDATION OF HOMOORIENTALINE WITH HOMOGENISED POTATO PEELINGS

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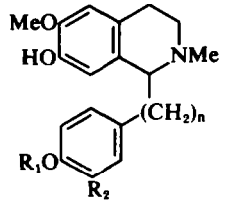
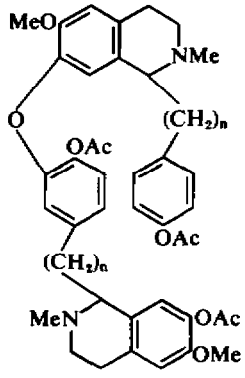
Abstract—Homoorientaline 4 was oxidised with homogenised potato peelings along, followed by acetylation, to give 1-hydroxyhomoorientaline triacetate 9, the structure of which was determined by spectroscopic data and an alternative synthesis.

Some natural products could be formed by an enzymic oxidation from the simple organic substances in the living system.[2] We have reproduced this mechanism in the isoquinoline alkaloid series by use of an enzymic system; thus, oxidation of N-methylcoclaurine 1 with homogenised potato peelings in the presence of hydrogen peroxide gave a liensinine type dimer 5,[3] and oxidation of N-methylhomococlaurine 2 with homogenised *Wasabia japonica* or homogenised potato peelings together with hydrogen peroxide gave the head to head 7[4] and head to tail coupling dimers 6,[3] respectively. Moreover, reticuline 3 on treatment with homogenised *Papaver rhoeas* and hydrogen peroxide afforded β-hydroxyreticuline 8.

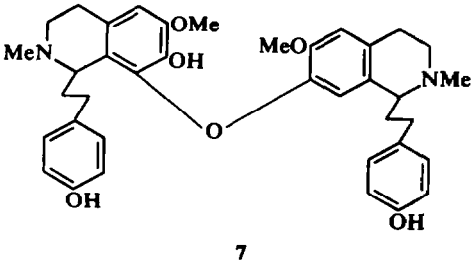
On the ground of these facts, we investigated whether the oxidation of homoorientaline 4[6] by homogenised potato peelings without hydrogen peroxide would give the dimer or not, and here report the result of this reaction.



1: $R_1 = R_2 = H$, n = 1
2: $R_1 = R_2 = H$, n = 2
3: $R_1 = Me$, $R_2 = OH$, n = 1
4: $R_1 = H$, $R_2 = OMe$, n = 2



5: n = 1
6: n = 2



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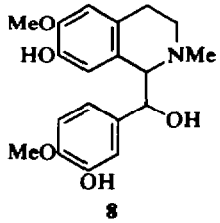

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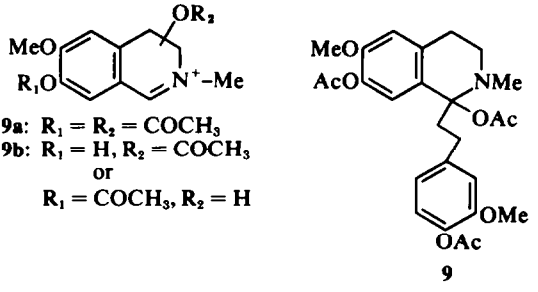
SCHEME 1

Homoorientaline 4[7] was oxidised with homogenised potato peelings at pH 4·8 at room temperature for 3 days and then acetylated in the usual way to give crystals, m.p. 93°, after chromatographic separation and purification. This product showed in its IR spectrum, and supported by the NMR spectrum, the absorption due to phenolic and alcoholic O-acetate. High resolution mass spectrum and microanalysis revealed the molecular formula $C_{26}H_{31}NO_8$, and this spectrum also showed the fragment ion at *m/e* 292 (**9a**) and 250 (**9b**) which indicated the presence of an alcoholic O-acetyl group located on the ring B. Recently, Umezawa reported the synthesis of the 4-acetoxy-2-methyltetrahydroisoquinoline,[8] the NMR spectrum of which showed a N-Me at 2·5 and an O-acetyl resonance at 2·2 ppm. In our specimen, these groups resonated at 3·0 and 1·9–2·1 ppm, respectively; thus the O-acetyl group should be located at the C_1 or C_3 position. Moreover, the structure having an O-acetyl group at C_3 or C_4 positions was ruled out by the lack of a methine proton on the C atom attached to the O-acetyl group, which would be observed at 6 ppm.[9] Therefore, the structure **9** was assigned to the product and this was also supported by an alternative synthesis.



9a: $R_1 = R_2 = COCH_3$
9b: $R_1 = H$, $R_2 = COCH_3$
or
$R_1 = COCH_3$, $R_2 = H$

9

SCHEME 2

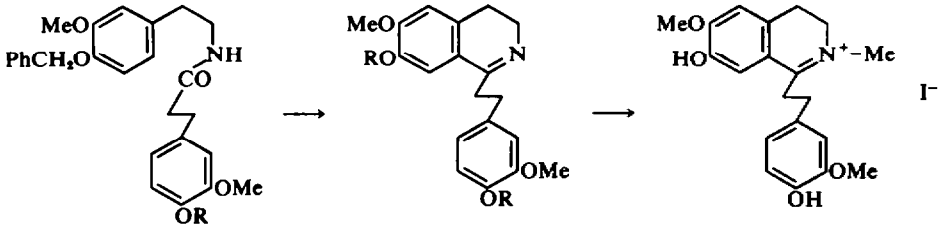
The amide **11**, prepared from N-(4-benzyloxy-3-methoxyphenethyl)-3-(4-hydroxy-3-methoxyphenyl)propionamide **10** by benzylation, was cyclised by the Bischler–Napieralski reaction to give the 3,4-dihydroisoquinoline **12**, which was debenzylated with hot hydrochloric acid. The resulting diphenolic base **13** was methylated with methyl iodide to afford the corresponding methiodide **14**, which was treated with acetic anhydride and potassium carbonate to give the triacetate **9**, identical with the oxidation product in all respects in spectral comparison.

It is interesting that the enzymic oxidation in the absence of hydrogen peroxide proceeded to give the hydroxylation product.

EXPERIMENTAL

Enzymic oxidation of homoorientaline (**4**). A soln of **4** (2 g) in AcOH was adjusted to pH 4·8 by NaOAc and to this soln was added the homogenised potato peelings prepared from 80 g of potato. After standing at room temp for 24 hr, homogenised potato peelings (prepared from 60 g of potato) were added to the above mixture and kept for 24 hr. In addition, the homogenised potato peelings (prepared from 70 g of potato) were then added and set aside for 24 hr, and the mixture made basic with 10% NH_4OH and extracted with n-BuOH. The extract was dried over K_2CO_3 and evaporated to leave an oil, which was acetylated with 10 ml of Ac_2O and 12 g of K_2CO_3 in 50 ml of THF by shaking for 4 hr. The excess of K_2CO_3 was filtered off and the filtrate was evaporated *in vacuo* to leave an oil, which was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a residue, which was chromatographed on silica gel. The $CHCl_3$–MeOH (99:1) eluant gave 10 mg of the triacetoxy derivative (**9**) as colorless needles, m.p. 93° (from benzene-hexane) (Found: C, 62·99; H, 6·32; N, 3·08; M$^+$, *m/e* 485·2031. $C_{26}H_{31}NO_8.0{\cdot}5H_2O$ requires: C, 63·02; H, 6·51; N, 2·81%: M$^+$, *m/e* 485·2049), ν_{max} (KBr) 1760, 1670 and 1620 cm^{-1}, δ (ppm) ($CDCl_3$) 1·90 and 2·05 (two s, 2:3, 3H, C_1–OCOC$\underline{H}_3$), 2·29 (s, 6H, OCOC$\underline{H}_3$), 3·0 (s, 3H, NC$\underline{H}_3$), 3·79 (s, 3H, OC$\underline{H}_3$), 3·87 (s, 3H, OC$\underline{H}_3$), 6·67 (s, 1H, ArH), 6·80 (broad s, 2H, Ar$\underline{H}$), 6·90 (s, 1H, Ar$\underline{H}$), and 7·44 (s, 1H, Ar$\underline{H}$), λ_{max} (MeOH) 270 nm, *m/e* 443·1955 (M$^+$-42, $C_{24}H_{29}NO_7$), 412·1561 (M$^+$-73, $C_{23}H_{24}O_7$), 371·1450 (M$^+$-114, $C_{21}H_{23}O_6$), 370·1448 (M$^+$-115, $C_{21}H_{22}O_6$), 328·1322 (M$^+$-157, $C_{19}H_{20}O_5$), 292·1158 (M$^+$-193, $C_{15}H_{18}NO_5$, **9a**), and 250·1096 (M$^+$-235, $C_{13}H_{16}NO_4$, **9b**).

N-(4-*Benzyloxy*-3-*methoxyphenethyl*)-3-(4-*benzyloxy*-3-*methoxyphenyl*)*propionamide* (**11**). A soln of **10** (15 g), benzyl chloride (3 g), K_2CO_3 (3 g) and 200 ml EtOH was refluxed for 5 hr, and the resulting ppt was removed by filtration. The filtrate was evaporated to leave



10: R = H
11: R = CH_2Ph

12: R = CH_2Ph
13: R = H

14

SCHEME 3

a residue, which was dissolved in $CHCl_3$, and the extract was washed with water, dried over Na_2SO_4, and evaporated to give 15 g of the amide **11** as colorless needles, m.p. 135–136° (from benzene-hexane) (Found: C, 75·00; H, 6·62; N, 3·12. $C_{33}H_{35}NO_5$ requires: C, 75·40; H, 6·71; N, 2·67%).

7-Benzyloxy-1-(4-benzyloxy-3-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (**12**). A mixture of **11** (14 g), $POCl_3$ (14 g), and 200 ml dry benzene was refluxed for 2 hr, and the excess of reagent and solvent was distilled off *in vacuo* to leave a residue, which was extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to afford 12 g of **12** as a yellow brown syrup, which was characterised as the methiodide, m.p. 126–127° from MeOH. (Found: C, 62·74; H, 5·62; N, 2·10. $C_{34}H_{36}INO_4$ requires: C, 62·87; H, 5·59; N, 2·16%).

3,4-Dihydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenethyl)-6-methoxyisoquinoline (**13**). A soln of **12** (11 g) in 150 ml conc HCl and 150 ml EtOH was refluxed for 5 hr, and evaporated *in vacuo* to give 4 g of **13** hydrochloride as a yellow powder, m.p. 215–217° (dec) from isopropanol. (Found: C, 61·76; H, 6·29; N, 3·55. $C_{19}H_{21}NO_4$, HCl requires: C, 61·70; H, 6·00; N, 3·79%). The free base, obtained by the usual method, was converted into the methiodide **14** as a hygroscopic syrup (Found: C, 49·48; H, 5·64; N, 2·43. $C_{20}H_{24}INO_4 \cdot H_2O$ requires: C, 49·29; H, 5·38; N, 2·87%).

1,7-Diacetoxy-1-(4-acetoxy-3-methoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (**9**). To a suspension of **14** (300 mg) in 50 ml THF was added slowly 10 ml Ac_2O during 20 min at 5°, and then K_2CO_3 (12 g) was added in portions within 2 hr. The mixture was stirred for 1 hr at room temp and filtered. The filtrate was decomposed with water, and after the mixture had been set aside overnight, the solvent was removed by evaporation. The residue was extracted with $CHCl_3$, and the extract was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to leave a syrup, which was chromatographed on silica gel. The $CHCl_3$–MeOH (99 : 1 v/v) eluant gave 100 mg of the triacetoxy derivative **9**, which was identified with the oxidation product by IR and NMR spectra and chromatographical comparisons.

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