BIOTRANSFORMATION OF SOME 2-METHYLPAPAVERINIUM DERIVATIVES WITH RAT LIVER ENZYMES IN VITRO

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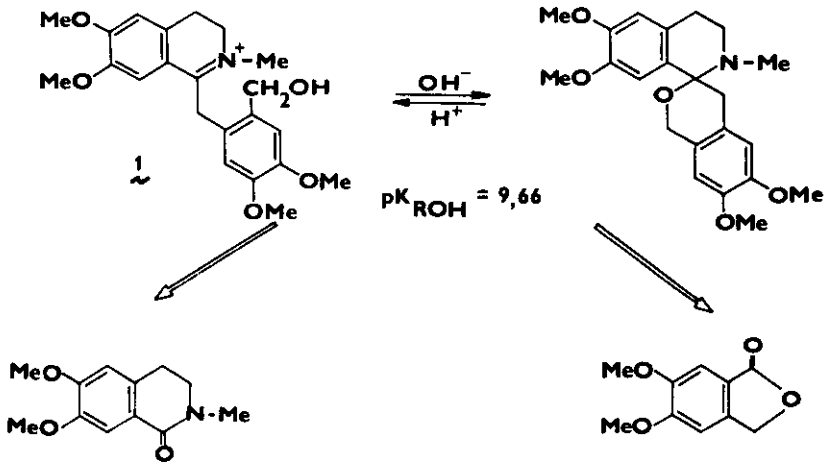
Abstract - 2-Methyl-3,4-dihydropapaverinium derivatives (1-3) and 2-methylpapaverinium chloride (4) have been converted into the corresponding isoquinolones and carbonyl compounds by incubation with rat liver preparations. The role of pseudobase formation in this biotransformation is discussed.

Recently, the two analogs 1 and 2 of the alkaloid hypecorine obtained from 3,4-dihydropapaverine have been synthesized.[1] In aqueous solution (in dependence of hydroxide ion concentrations), these compounds are in equilibrium with their immonium forms.[2]

In our work, the metabolism of the quaternary salts 1, 2, 2-methyl-3,4-dihydropapaverinium (3) and 2-methylpapaverinium (4) has been studied with rat liver enzymes in vitro and compared with that of papaverine (5). In mammals, 4'- and 6-demethylpapaverines are the major urinary metabolites of papaverine (5). The minor metabolites are 3'-, 7- and 4',6-didemethylpapaverines.[3-5] Papaverine (5) has been converted into its 4'-, 6- and 7-demethyl metabolites by incubation with hepatic microsomal preparations.[6]

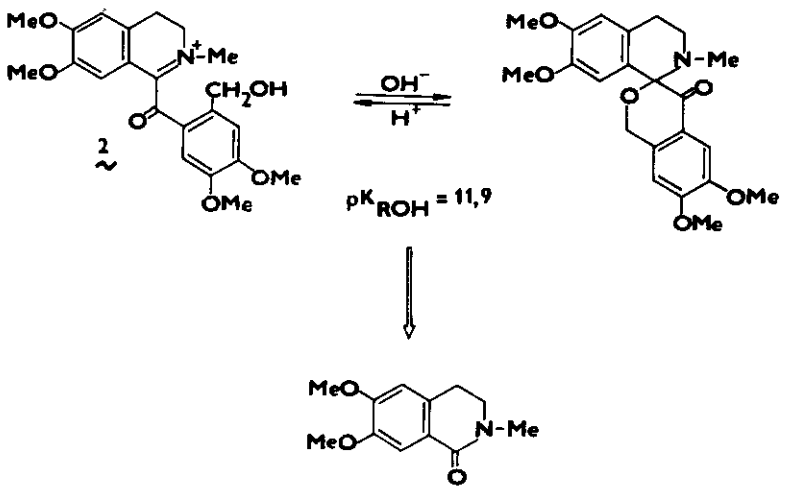
The chlorides of the compounds 1-5 (100 mg) were incubated at 37° for 2 h with a 9,000 g supernatant (50 ml) of 20% liver homogenate from phenobarbital induced rats, in phosphate buffer at pH 7.5. After incubation, the mixture was made alkaline with sodium carbonate to pH 8.5 and extracted with ether. The products were isolated by preparative t.l.c. on silica gel in the solvent system cyclohexane-chloroform-diethyl amine (7:2:1). The structures of the compounds were determined by mp, UV, IR, ^{1}H NMR and mass spectra.

The mixture of metabolites from 2'-hydroxymethyl-2-methyl-3,4-dihydropapaverinium chloride (1) showed the presence of one Dragendorff positive compound. The major metabolites were 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolone (35%) and 4,5-dimethoxyphthalide (9%) (Scheme 1). The initial compound 1 was recovered in 30% yield.



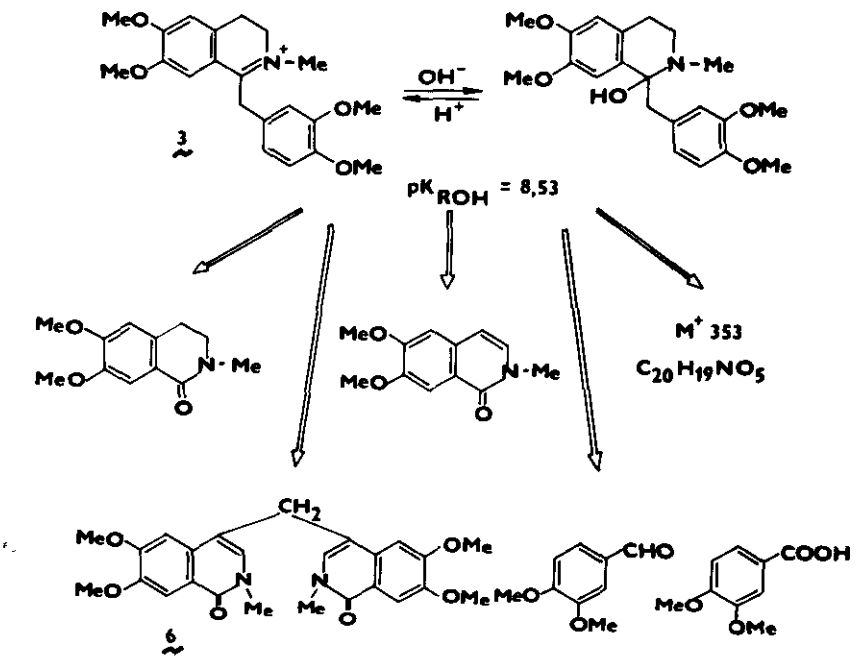
Scheme 1

9-Oxo-2'-hydroxymethyl-2-methyl-3,4-dihydropapaverinium chloride (2) gave the metabolite 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolone (35%) and the initial compound (25%) (Scheme 2).



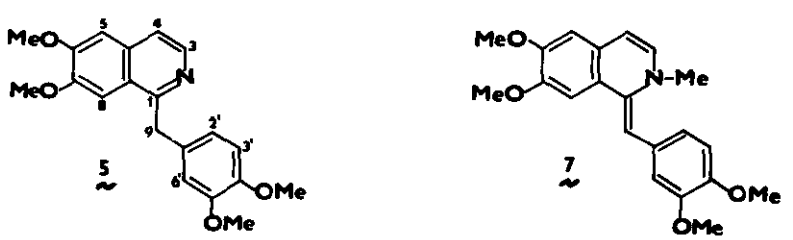
Scheme 2

2-Methyl-3,4-dihydropapaverinium chloride (3) was converted into a mixture of four Dragendorff positive metabolites. The major metabolite was 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolone (21%). The mixture also contained 6,7-dimethoxy-2-methylisoquinolone (6%), an unidentified compound M^+ 353 ($C_{20}H_{19}NO_5$), and a small quantity of a substance (1%) which on the basis of MS was assigned the tentative structure 6, MS: 450 (M^+, $C_{25}H_{26}N_2O_6$), 232 ($C_{13}H_{14}NO_3$) and 220 ($C_{12}H_{14}NO_3$). 3,4-Dimethoxybenzaldehyde and the 3,4-dimethoxybenzoic acid were also isolated (Scheme 3). The initial compound was recovered in 26% yield.



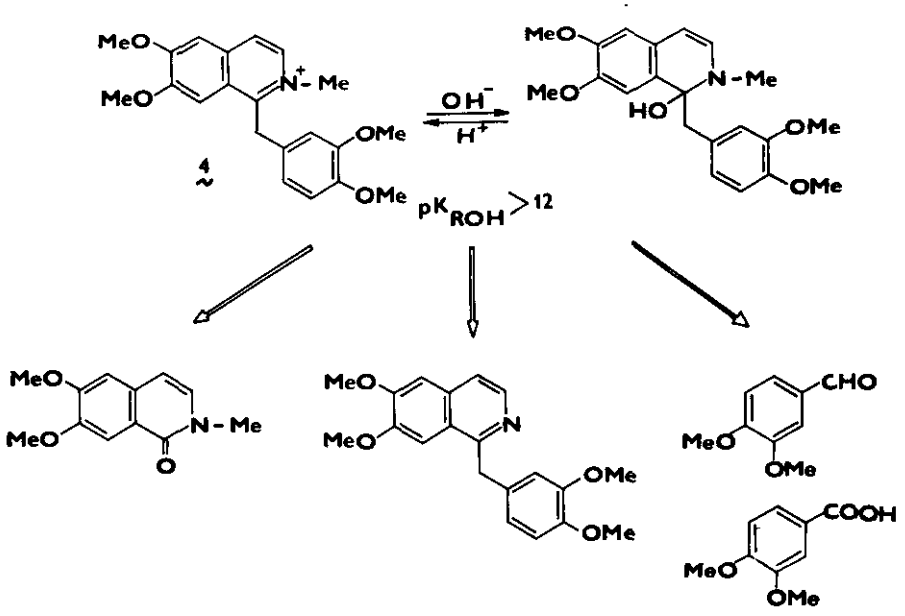
Scheme 3

2-Methylpapaverinium chloride (4) gave 6,7-dimethoxy-2-methylisoquinolone (32%) and papaverine (5) (5%). The other isolated compounds were 3,4-dimethoxybenzaldehyde and the 3,4-dimethoxybenzoic acid (Scheme 4).



Papaverinium chloride (5) gave papaverine N-oxide (8%) as the major metabolite, unchanged papaverine (80%), and O-demethylated products in traces.

The results showed that the main metabolic activity of biotransformation of 2-methylpapaverinium derivatives is oxidative cleavage of the bond between C-1 and C-9. Reaction of 1-benzyl-2-methylisoquinolinium derivatives with cuprous chloride/oxygen or singlet oxygen in alkaline medium gave isoquinolone derivatives and the corresponding carbonyl compounds.[7] This is interpreted as a reaction of the enamine intermediate 7 with singlet oxygen. It is assumed that this oxidation is brought about by a similar mechanism *in vivo*.[8] However, in aqueous solution of sodium hydroxide, 2-methylpapaverinium iodide (4) forms the corresponding pseudobase (Scheme 4) and not the enamine 7.[1] The values of the



Scheme 4

equilibrium constants of pseudobase formation in the compounds 1-4 also indicate that in biological systems the quaternary form is oxidized.[9]

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9. The pK_{ROH} values were taken from ref.[1] They were measured spectrophotometrically in 50% w/w aqueous ethanol.

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