DEUTERATION OF VERAPAMIL BY ACID CATALYZED EXCHANGE

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SUMMARY

Deuteration of verapamil, 5-[(3,4-dimethoxyphenylethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile, an important calcium channel antagonist was accomplished by direct exchange in 25% $^{2}H_2SO_4$ in $^{2}H_2O$. Refluxing for 140 hr incorporated 4-6 atoms of deuterium, which were distributed into both aromatic rings, but primarily in the ring attached through position 5 of the valeronitrile moiety.

Key words: verapamil, deuterium exchange.

INTRODUCTION

Verapamil (1), 5-[(3,4-dimethoxyphenylethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile, is an orally effective antiarrhythmic and antianginal agent which selectively inhibits membrane transport of calcium ion.[1-4] Its effects on calcium ion influx into cells may account for its dilation of peripheral and coronary vessels, its effects on atrioventral conduction and its negative inotropic effect on the heart. The agent is widely used and/or being studied in a variety of cardiovascular diseases, including paroxysmal superventricular tachycardia, angina and hypertension.[2,3] In view of its present and potential therapeutic applications, its metabolic and pharmacokinetic properties have attracted a great deal of interest.[4-12]

Assays for the parent drug and some of its metabolites have depended upon GC,[13,14] HPLC[15,16] and GC-MS[17-20] methods. The latter method, using stable isotopically labeled

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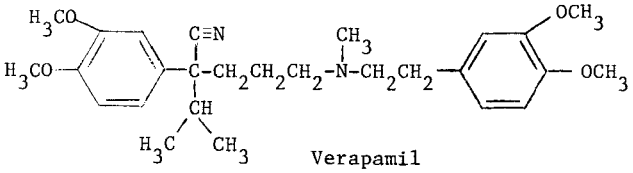

Verapamil

compounds, has been applied to kinetic studies on verapamil in man, based on use of synthesized derivatives containing one ^{13}C-atom (at C-5 of the valeronitrile moiety) and two deuterium atoms in the alkyl chain (at C-1 of the phenethyl side chain),[17] a deuterated methyl ether *para* to the quaternary carbon,[19] and the isopropyl-$^{2}H_{7}$ compound. These compounds were used as standards and/or in dosage forms to study oral absorption of the drug.[10,18,19] The application of GC-MS methodology for determining concentrations of verapamil would be made significantly easier by finding a suitable method for obtaining stable isotopically labeled drug.

RESULTS AND DISCUSSION

A facile method for incorporation of deuterium atoms into verapamil, by exchange in 25% $^{2}H_{2}SO_{4}$ in $^{2}H_{2}O$, was developed. The incorporation of 4-6 atoms of deuterium (mostly 5 and 6 atoms) was readily accomplished in 140 hours with about 50% recovery of verapamil. The reaction mixture was monitored by ^{1}H-NMR spectroscopy, following the disappearance of signals of the part of the aromatic protons, and by mass spectrometry. Under these conditions no hydrolysis of the nitrile (to the amide or imido ester) was noted, probably in part due to steric hindrance. The moderate recovery of verapamil may be related to cleavage of one or more methyl ethers, or other decomposition pathway.

The CI (methane) mass spectrum of deuterated verapamil showed ions at *m/e* 458, 459, 460, 461 and 462 (21:58:100:72:17) *vs.* verapamil *m/e* 455 and 456 [100:30 (^{13}C)] (Figure 1) indicating mostly incorporation of 4-6 atoms of deuterium. Some EI fragmentation also occurs in the CI mass spectrum as shown by ions at *m/e* 303, 304, 305, 306 and 307 (2:16:32:23:4) and at 236, 237 and 238 (3:37:6). The ion at *m/e* 303 is the dominant ion in the EI mass spectrum of verapamil.[12] It is accounted for by loss of the 3,4-dimethoxybenzyl group. The *m/e* 303-307 ions arise from incorporation of 0 to 3 atoms of deuterium [24% $^{2}H_{1}$, 46% $^{2}H_{2}$ and 26% $^{2}H_{3}$ (4% $^{2}H_{0}$)] into the aromatic ring of the

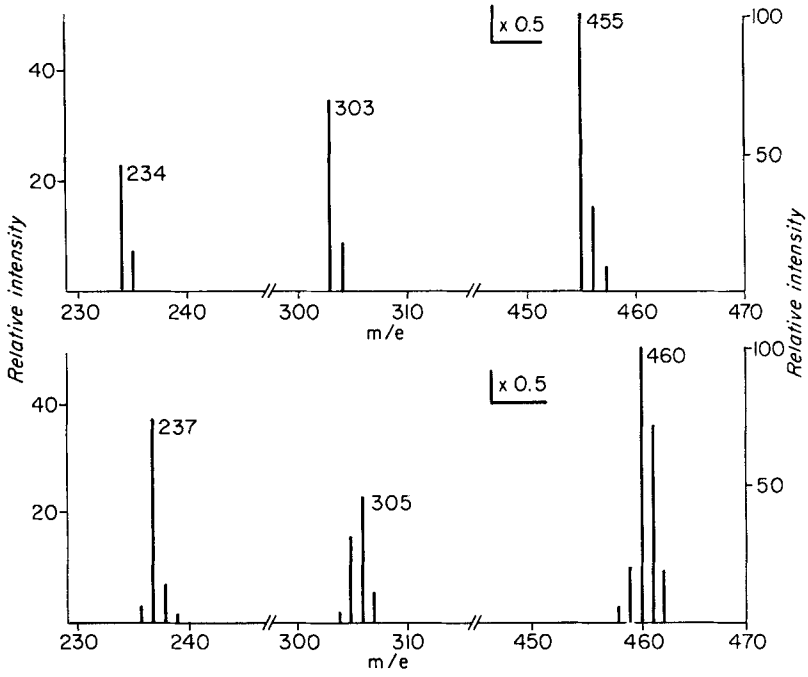

Figure 1. A. CI-mass spectrum of verapamil; B. CI-mass spectrum of deuterated verapamil.

3,4-dimethoxyphenylacetonitrile portion of the molecule. The ions at m/e 236-238, compared with ions at m/e 234 and 235 in verapamil, are thought to arise from a fragment which has lost the elements of 2-isopropyl-2-(3,4-dimethoxyphenyl)acetonitrile. These ions are also consistent with >90% incorporation of 3 atoms of deuterium (8% $^{2}H_{2}$) occurring in the aromatic ring of the 3,4-dimethoxybenzyl group.

Use of lower concentrations of $^{2}H_{2}SO_{4}$ (15-20%) in $^{2}H_{2}O$ or shorter reaction times produced decreased deuterium incorporation. The rate of exchange in 20% $^{2}H_{2}SO_{4}$ in $^{2}H_{2}O$ was approximately 25-35% slower. Deuterium incorporation was approximately linear over the 140 hour period.

The single step deuterium exchange has significant advantages over synthesis of the ^{13}C-$^{2}H_{2}$ compound, or the isopropyl-$^{2}H_{7}$ compound,[17-19] since each require a number of

synthetic steps. No data have been reported on the synthesis of the deuterated ether analog. In spite of the moderate recovery of verapamil from the exchange process, this method offers the significant advantage of ease of preparation. The facile exchange also may be applicable to the study of metabolites of verapamil which also maintain the activated aromatic rings, e.g., norverapamil,[20] a circulating metabolite in man. Related compounds like D-600 (methoxyverapamil) would also be expected to be amenable to similar procedures.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are uncorrected. NMR spectra were recorded on the Varian 360-A spectrometer using TMS as internal standard. Tlc plates used were silica gel-GF (Brinkman). Mass spectra were obtained on the VG-7070 mass spectrometer (direct insertion probe) in the chemical ionization (methane) and electron impact modes.

Deuteration of Verapamil. Verapamil hydrochloride (500 mg, 1.0 mmol) was added to a solution of 20 ml 25% $^2H_2SO_4$ in ^2H_2O (v/v) and 0.5 ml of CH_3O^2H. The solution was stirred for 140 hr at 90°C. The pH was adjusted to 12.0 and the mixture extracted with EtOAc (3 x 60 ml). The combined EtOAc extracts were washed with H_2O, dried ($MgSO_4$) and evaporated to yield a viscous oil. This oil was dissolved in ether and ethereal HCl was added to precipitate the HCl salt. The salt was collected by filtration and crystallized from EtOAc afforded 250 mg (50%) of deuterated verapamil as a white solid, mp 139.5-141.5°C (lit.[21,22] 138.5-140.5°C, 141-143°C, non-deuterated); ir of HCl salt (KBr) 2960, 2255, 1520, 1475, 1425, 1385, 1240, 1210, 1180, 1085, 1025 cm^{-1}; nmr of free base (acetone-d_6) δ 6.95-6.78 (m, ca. 1, ArH), 3.83-3.78 (4s, 12, OCH_3), 2.93-1.30 (m, 14, -CH, $-CH_2$ and NCH_3), 1.10 and 0.72 (2d, 6, J = 7 Hz, $-CH(CH_3)_2$). CIMS (methane) m/e 462, 461, 460, 459, 458, 457 (QM, 17, 72, 100, 58, 21, 7), 307, 306, 305, 304, 303 (4, 23, 32, 16, 2), 238, 237, 236 (6, 37, 3).

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