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Structure of the metabolite of carisoprodol, hydroxycarisoprodol

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EARLIER investigations of the metabolic fate of carisoprodol (N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate) in the dog showed that four products are excreted after drug administration. These are (1) unchanged carisoprodol excreted in trace quantities; (2) the dealkylated derivative, meprobamate, found in minor amounts; (3) hydroxymeprobamate [2-methyl-2-(β-hydroxypropyl)1-3-propanediol dicarbamate], present in moderate amounts; and (4) the major metabolite tentatively characterized as hydroxycarisoprodol.[1] This manuscript describes the results of further studies directed to the identification of the latter compound which now confirm the structure of the major metabolite as N-isopropyl-2-methyl-2-(β-hydroxypropyl)-1,3-propanediol dicarbamate.

EXPERIMENTAL

A male mongrel dog, weighing 10 kg, was given 9·3 g of carisoprodol by capsule in two doses and his urine collected under toluene for a period of 24 hr. After removal of the toluene, the urine was adjusted to pH 9·2 with concentrated ammonium hydroxide and extracted continuously with ether for 24 hr. The ether extract was concentrated by evaporation and the residual oil dissolved in butanol previously saturated with water. The crude mixture was fractionated by adsorption on a cellulose column, 1·8 × 40 cm, followed by water-saturated butanol as eluting solvent. The first 70-ml volume of eluate was collected and passed through another cellulose column, 1 × 23 cm, and eluted with the organic phase of carbon tetrachloride : acetic acid : water (1 : 2 : 1). Fractions 8 to 20, 5 ml each, which contained hydroxycarisoprodol and hydroxymeprobamate as identified by paper chromatography, were combined and subjected to paper chromatographic separation, with carbon tetrachloride : acetic acid : water (1 : 2 : 1).[2] In this solvent system hydroxymeprobamate has an R_f value of 0·02 and hydroxycarisoprodol, 0·30. The faster moving component was obtained by extracting that portion of the chromatogram, R_f 0·25–0·35, with acetone. This component, which could not be crystallized, was chromatographically pure in two solvent systems (butanol : acetic acid : water, 4 : 1 : 5, R_f 0·90; carbon tetrachloride : acetic acid : water, 1 : 2 : 1, R_f 0·30), and its infrared spectrum was identical with that reported earlier for this metabolite.[1]

The purified metabolite (25 mg) was hydrolyzed by heating in 5 ml of 3% KOH for 3 hr at 100°. The gaseous amine liberated was collected in 1 N HCl and extracted into ether after alkalization of the solution with 50% KOH. The ether solution was then subjected to gas-liquid chromatography in an F and M model 609 unit equipped with a flame ionization detector. The column employed was 3·0% triethanolamine on base washed and silanized Gas-Chrom S support. The conditions used were: column temperature, 62°; flow rate of nitrogen, 3·0 ml/min; oxygen, 6·0 ml/min; and hydrogen, 9·0 ml/min, The amine gave a gas chromatographic pattern identical with that of isopropylamine.

The remaining hydrolysis reaction mixture was extracted with butanol and the extraction solvent removed under reduced pressure. The residue was dissolved in acetone, the solution concentrated under reduced pressure, and the α-napthyl urethane derivative of the triol prepared by warming with an excess of α-napthyl isocyanate. The resulting di-α-napthyl urethane after recrystallization melted at 97°. No melting point depression occurred when the compound was mixed with an authentic specimen of N,N′-di-α-napthyl-2-methyl-2-(β-hydroxypropyl)-1,3-propanediol dicarbamate prepared in the same manner from 2-methyl-2-(β-hydroxypropyl)-1,3-propanediol dicarbamate,[3] and the infrared spectra of both derivatives were identical.

RESULTS AND DISCUSSION

Earlier studies had indicated that the major metabolite of carisoprodol in the dog was a hydroxylated derivative. This compound, which has resisted all attempts at crystallization, has been further investigated principally through a study of its hydrolytic products. Alkaline cleavage of the metabolite has yielded two compounds which have been identified as isopropylamine and 2-methyl-2-(β-hydroxypropyl)-1,3-propanediol.

The identity of the metabolite on the basis of its degradation products is consistent with a hydroxycarisoprodol structure of N-isopropyl-2-methyl-2-(β-hydroxypropyl)-1,3-propanediol dicarbamate.

It is interesting to note that the related compounds, meprobamate[3] and mebutamate,[4] are oxidized at the penultimate carbon atom of the propyl side chain during passage through the animal body, in a manner analagous to carisoprodol.

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