SYNTHESIS OF TRITIUM AND CARBON-14 LABELED 1,3-DIOXOLANES. II. D-2-ETHYL-2-PHENYL-4-(2-PIPERIDYL)-1,3-DIOXOLANE HYDROCHLORIDE.*

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SUMMARY

The synthesis of ^{3}H and ^{14}C labeled d-2-ethyl-2-phenyl-4-(2-piperidyl)-1, 3-dioxolane hydrochloride (Va and Vb respectively) is described. The optically pure α(-)-2-(2-piperidyl)ethane-1,2-diol hydrochloride (II), obtained by hydrolyzing α(+)-2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride[1] (I), is used as the starting material to minimize the need for separation of isomers in the products.

The dextrorotatory enantiomer of the α-racemate of 2-ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride[2] (V) is a dissociative anesthetic. Its pharmacologic and clinical properties have been studied by a number of investigators.[3-8] Radioactive V is needed for conducting absorption, distribution, excretion and metabolism studies with this compound in test animals and man. Because the compound is readily hydrolyzed under acid catalysis into two fragments, a diol and a ketone, V has been labeled with tritium in the piperidine ring and with carbon-14 in the dioxolane ring, so

* Generic Name: etoxadrol, jointly developed by Cutter Laboratories, Inc. and The Upjohn Company, also referred to as CL-1848C in the literature.

that biotransformations involving both the intact drug and each fragment may be investigated.

DISCUSSION AND RESULTS

The diol portions of the dioxolanes I and V possess identical absolute configurations at the two chiral centers. In order to minimize isomer separation problems in this work, compound I was hydrolyzed to provide optically pure II for conversion to V. It is of interest to note that the α(-) isomer of diol II is associated with the α(+) isomers of both dioxolanes I and V.* Because of the presence of a third chiral center in V at the 2-position of the dioxolane ring, reaction of the optically pure α(-) isomer of II with 1,1-diethoxy-1-phenylpropane gave rise to a mixture of two diastereoisomers of structure V. These were, however, readily separated by fractional crystallization to give the desired α(+) isomer of V.

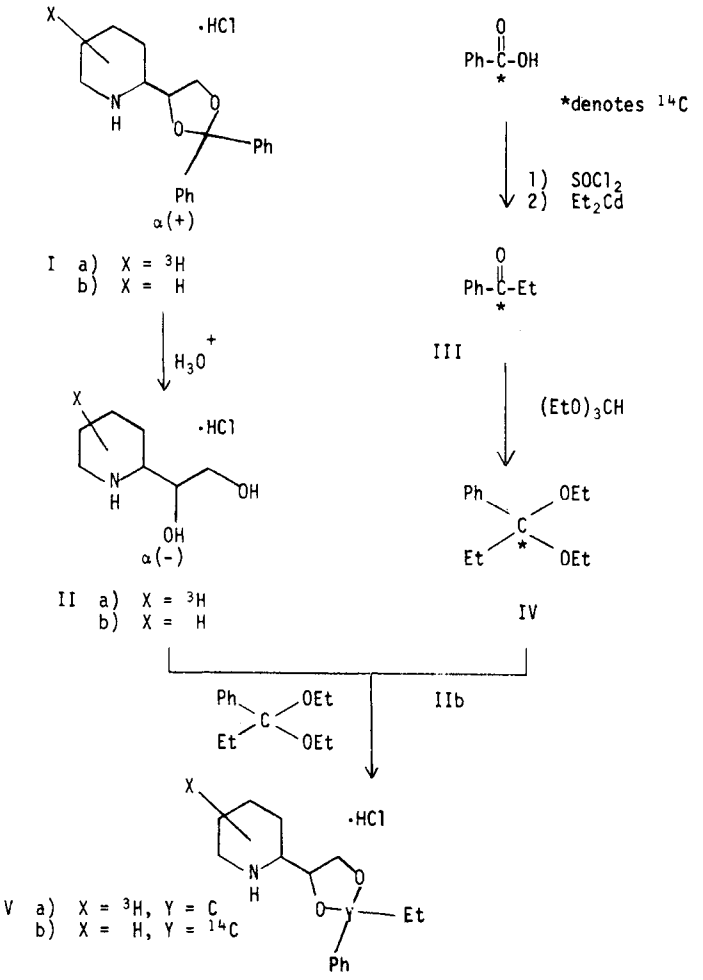
The synthetic pathways for preparing ^{3}H and ^{14}C labeled V are shown in Scheme 1. The α(+) isomer of Ia was hydrolyzed to give α(-) IIa which on treatment with 1,1-diethoxy-1-phenylpropane afforded Va. As with Ia (see Ref. 1), the tritium labels are at the 3,4- and/or 4,5- positions in the piperidine ring in Va. The starting material for the ^{14}C labeled product (Vb) was benzoic acid-α-^{14}C prepared by carbonation of phenylmagnesium bromide with $^{14}CO_2$. The acid was converted to its acid chloride which on reaction with diethylcadmium yielded propiophenone-^{14}C (III). Treatment of III with ethyl orthoformate led to 1,1-diethoxy-1-phenylpropane-1-^{14}C (IV), which was condensed with the non-radioactive α(-) diol IIb to produce Vb with the ^{14}C label at the 2- position in the dioxolane ring.

* The "α" designation for these isomers is used here in accordance with the assignment of Hardie *et al.*[2]

Scheme 1

Synthesis of ^{3}H and ^{14}C Labeled

d-2-Ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride



EXPERIMENTAL

Radioactivity determinations were carried out with a Packard Tri-Carb Model 314 liquid scintillation spectrometer using diotol scintillation solvent[11] and toluene-α-^{3}H and ^{14}C as internal standards. Thin layer chromatography (tlc) plates were analyzed with a Vanguard Model 880 Autoscanner equipped with a Model 885 Glass Plate Scanner. Optical rotation determinations were carried out in MeOH solutions. Melting points are uncorrected. Microanalyses were obtained for the indicated elements, and all results were within ±0.4% of theory.

Propiophenone-^{14}C (III)

Benzoic acid-α-^{14}C, sp. act. 1.50 mCi/mM, was prepared by the carbonation of a 0.24 M solution of PhMgBr in Et_2O with $^{14}CO_2$ generated from $Ba^{14}CO_3$, according to the procedure of Eberson.[9] The acid (1.832 g, 15.0 mmoles) was converted to III by a modification of the procedure of Dauben, *et al.*[10] *via* benzoyl-α-^{14}C chloride. The crude reaction product mixture was treated with hot (85-90°C, 1 hr) 2N NaOH to remove benzoic acid-α-^{14}C and unreacted benzoyl-α-^{14}C chloride. The mixture of neutral reaction products was then chromatographed on a 3 x 50 cm column of 150 g of silica gel eluted with 5% v/v EtOAc in cyclohexane. The eluate was collected in 15 ml fractions at 4.5 ml/min after a forerun of 200 ml. The pooled residues from fractions 19 through 36, 1.131 g (56.2% yield), were found to be identical to an authentic sample of 1-phenyl-1-propanone by tlc (silica gel, 5% v/v EtOAC in cylclohexane) and were used without further purification in the next step.

1,1-Diethoxy-1-phenylpropane-1-^{14}C (IV)

To a mixture of 1.131 g (8.4 mmoles) of III and 2 ml (~11.5 mmoles) of ethyl orthoformate and 3.5 ml of absolute EtOH was added 0.5 ml of 20% w/w anhydrous HCl in EtOH. The initially mildly exothermic reaction mixture was kept at room temperature overnight and concentrated, first at 50°C and 70 mm Hg,

then at room temperature and 0.6 mm Hg, to give 1.570 g (90% yield) of IV. Similarly, from 2.684 mg (20 mmoles) of propiophenone and 3.112 mg (21 mmoles) of ethyl orthoformate, there was obtained 3.895 g (93.5% yield) of non-radioactive 1,1-diethoxy-1-phenylpropane.

Tritium Labeled α(-)-2-(2-Piperidyl)ethane-1,2-diol Hydrochloride (IIa)

A mixture of 900 mg (2.6 mmoles) of Ia, α(+), and 3.5 ml of MeOH containing 3.3% v/v 2N HCl was refluxed with stirring for 2 hrs and concentrated at 50°C and 70 mm Hg. The residual oil was repeatedly triturated with Et_2O, allowed to crystallize, and recrystallized from i-PrOH and dried under vacuum at 80°C to give 365 mg of IIa, α(-), 77.2% yield, sp. act. 73.6 μCi/mg or 13.4 mCi/mM. Similarly, Ib, α(+), was hydrolyzed to give IIb, α(-).

Tritium Labeled α(+)-2-Ethyl-2-phenyl-4-(2-piperidyl)-1,3-Dioxolane Hydrochloride (Va)

A mixture of 364 mg (2.0 mmoles) of IIa, α(-), 500 mg (2.4 mmoles) of 1,1-diethoxy-1-phenylpropane, 1.5 ml of i-PrOH and 0.1 ml of 20% w/w anhydrous HCl in i-PrOH was refluxed with stirring under N_2 for 2 hrs and kept at room temperature overnight. The resulting solids were dispersed with 1 ml of i-PrOH, filtered, washed with cold i-PrOH followed by Et_2O and dried. The crude product, 355 mg, 59.5% yield, mp 219-220°C, was recrystallized from 8:1 v/v i-PrOH-MeOH to give 251 mg of crop A, mp 220.5-222°C. The mother liquors were combined and concentrated under reduced pressure. The residue was recycled by refluxing with 230 mg of 1,1-diethoxy-1-phenylpropane in HCl-i-PrOH for 2 hrs and recrystallizing the crude from i-PrOH-MeOH to give 76 mg of crop B, mp 221-222°C. Combined crops A and B were again recrystallized from i-PrOH-MeOH to give 248 mg (41.5% yield) of Va, mp 222-224°C; $[\alpha]_D^{MeOH}$ + 15°; sp. act. 45.4 μCi/mg or 13.5 mCi/mM; radiochemically pure by tlc (silica gel, 10% v/v MeOH in CH_2Cl_2); *anal* ($C_{16}H_{24}ClNO_2$): C, H, N.

Carbon-14 Labeled α(+)-2-Ethyl-2-phenyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride (Vb)

Similarly as above, from 1.570 g (7.5 mmoles) of IV and 1.238 g (6.8 mmoles) IIb, α(-), there was obtained 1.303 g of crude product, mp 219-220°C, which was recrystallized from 8:1 v/v i-PrOH-MeOH to afford 1.007 g (49.6% yield) of Vb, mp 223-225°C; $[\alpha]_D^{MeOH}$ + 16°; sp. act. 5.03 μCi/mg or 1.50 mCi/mM; radiochemically pure by tlc (silica gel, 10% v/v MeOH in CH_2Cl_2; *anal* ($C_{16}H_{24}ClNO_2$): C, H, N.

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