PREPARATION OF CARBON-14 LABELED 2-PHENYL-3-[*p*-(2-DIETHYLAMINOETHOXY) PHENYL]-6-METHOXYINDENE HYDROCHLORIDE

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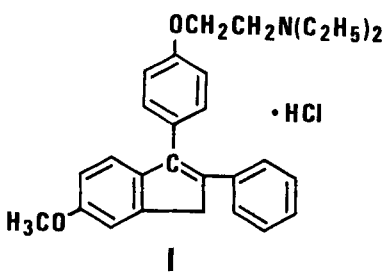
SUMMARY

2-Phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene-3-^{14}C hydrochloride was prepared from phenylacetic acid-1-^{14}C in a four step sequence of reactions. The final product was obtained in 12.5% yield at a specific activity of 0.79 mCi per mM.

Key Words: Carbon-14, Indene, Perkin Reaction

INTRODUCTION

Anticipated metabolism and mechanism of action studies with the antifertility agent (1), 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene hydrochloride (I), required preparation of a radioactive form of the drug. The



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established sequence of reactions* for preparing nonradioactive I permits convenient incorporation of both carbon-14 and tritium. Given this choice, carbon-14 was chosen as the radioactive label since it is somewhat more convenient than tritium to use in biological studies.

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*Developed by Dr. D. Lednicer.

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EXPERIMENTAL

Radioactivity Measurements

All counting was performed with a Packard Tricarb Model 314EX2A liquid scintillation spectrometer at -8° under conditions suitable for measuring carbon-14. Appropriate aliquots of samples were dissolved in 15 ml of scintillation solvent [toluene-dioxane-methanol (350:350:210 by volume) containing 73 g of naphthalene, 4.6 g of 2,5-diphenyloxazole, and 0.08 g of 1,4-bis [2-(5-phenyloxazolyl)] benzene per L.]. The absolute counting efficiency for each sample was determined by recounting following addition of an internal standard of toluene-^{14}C, and results were then converted to mCi.

Thin-Layer Chromatography

Thin-layer chromatography was carried out in the $CHCl_3$-cyclohexane (3:1 by volume) saturated with NH_4OH and the 1-butanol-acetic acid-H_2O (4:1:5 by volume) systems on 0.25-mm films of silica gel GF. The Rf value for I was 0.53 in the former system and 0.43 in the latter system. The UV absorption zones of standards and the product were detected by viewing the dried chromatograms under short-wavelength UV light. The zones of radioactivity were located by transferring sequential 0.5-cm segments of the developed chromatogram into individual vials and counting, using scintillation solvent containing 3% H_2O.

Synthesis

2-Phenyl-3-(m-methoxyphenyl)propenoic acid-1-^{14}C (III) - Sodium phenylacetate-1-^{14}C (II) was prepared by adding an equimolar quantity of sodium methoxide in methanol to 1.36 g (7.8 mCi) of the free acid** form of II in 10 ml of benzene. The solvent was removed *in vacuo*, and 1.28 g (10 mM) of *m*-methoxybenzaldehyde and 7.5 ml of acetic anhydride were added to the dry residue. The mixture was heated under reflux for 5 hrs, after which it was cooled to room temperature, washed into a larger flask with a solution of 6.4 g of NaOH in water and refluxed for 2 hrs. The reaction mixture was cooled to room temperature and then extracted twice with ether. The aqueous phase was adjusted to pH 2 with HCl, and, after cooling in the refrigerator, the product was filtered, washed with a little

**Purchased from New England Nuclear Corp.

cold H_2O and dried *in vacuo*. This crude product was recrystallized from acetic acid to give 1.34 g (53% yield based on II) of 2-phenyl-3-(*m*-methoxyphenyl) propenoic acid-1-^{14}C (III) having a specific activity of 0.79 mCi per mM; m.p. 192-193° (capillary, uncorrected).

2-Phenyl-3-(m-methoxyphenyl)propanoic acid-1-^{14}C (IV) - The 2-phenyl-3-(*m*-methoxyphenyl)propenoic acid-1-^{14}C (III) (1.33 g, 5.2 mM) was hydrogenated at atmospheric pressure in 50 ml of ethanol containing 1.5 ml of acetic acid and 0.1 g of a 5% Pd on charcoal catalyst. When hydrogen uptake (134 ml) had ceased, the catalyst was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The last trace of acetic acid was removed by taking the residue up in benzene and evaporating to dryness. The crude 2-phenyl-3-(*m*-methoxyphenyl) propanoic acid-1-^{14}C (IV) was transferred to a polyethylene bottle with ether, and the ether was removed by evaporation in a stream of nitrogen. This material was used without purification in the following step.

2-Phenyl-5-methoxy-1-indanone-1-^{14}C (V) - The 2-phenyl-3-(*m*-methoxyphenyl) propanoic acid-1-^{14}C (IV) in the polyethylene bottle was cyclized with 30 ml of liquid HF as described by Lednicer, *et al* (2). The crude product was recrystallized from methanol to give 0.96 g (77% yield based on III) of 2-phenyl-5-methoxy-1-indanone-1-^{14}C (V) having a specific activity of 0.82 mCi per mM; m.p. 110-112° (capillary, uncorrected).

2-Phenyl-3-[p-(2-diethylaminoethoxy)phenyl]-6-methoxyindene-3-^{14}C hydrochloride (I) - A Grignard reagent was prepared from 0.104 g (4.3 mM) of Mg and 1.12 g (4.1 mM) of freshly distilled (b.p. 110-112°, 0.4-0.45 mm) *p*-(2-diethylaminoethoxy) bromobenzene† in 17 ml of tetrahydrofuran. A reflux period of approximately 2 hrs. was required to consume the Mg. The flask containing Grignard reagent was placed in an ice bath, and a solution of 0.95 g (4.0 mM) of 2-phenyl-5-methoxy-1-indanone-1-^{14}C (V) in 15 ml of tetrahydrofuran was added. The reaction mixture was heated under reflux overnight. After cooling to room

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†Prepared by Dr. D. Lednicer.

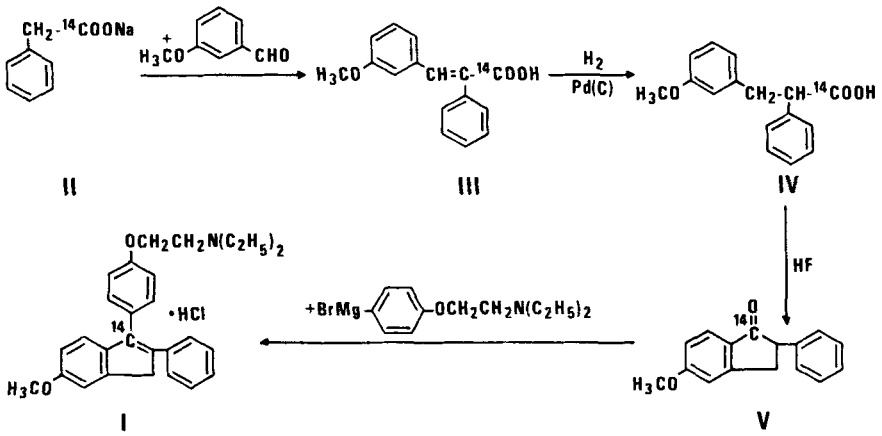
temperature, 0.5 ml of H_2O was added to the reaction mixture, and the resulting gel was removed by filtration through Super-cel® and washed well with tetrahydrofuran and ether. The filtrate was washed twice with water, and the organic layer was evaporated to dryness. The residual oil was dissolved in ether, and the resulting solution was extracted five times with 0.5 N HCl. The aqueous phase was extracted with four portions of $CHCl_3$. The residue obtained from evaporation of the $CHCl_3$ phase was dissolved in benzene to which was added 0.04 g of *p*-toluenesulfonic acid. The solution was refluxed for 2.5 hrs. under a Dean-Stark trap. After cooling to room temperature and extracting with saturated $NaHCO_3$ solution and water, the benzene phase was dried over Na_2SO_4. Hydrogen chloride gas was bubbled through the solution for 15 minutes after which the benzene was removed *in vacuo*. The residue was crystallized twice from ethyl acetate-methylene chloride to yield 0.55 g (30.5% yield based on V) of 2-phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene-3-^{14}C hydrochloride (I) having a specific activity of 0.79 mCi per mM; m.p. 175.5-176.5° (capillary, uncorrected). The IR [(Nujol mull) 2560, 2470 (N-H); 1610, 1600, 1590, 1580, 1565, 1508 (C=C); 1285, 1270, 1225, 1105, 1030 (C-O/C-N); 860, 840, 825, 765, 690 (Aromatic C-H) cm^{-1}] and UV [(EtOH) 314 mμ (ε 18,600), 250 mμ (ε 16,400), shoulder 235 mμ (ε 18,000)] spectra of the product corresponded to those of authentic standard I. Thin-layer chromatography of the product in the two systems previously described revealed a single UV-absorbing and radioactive zone corresponding to that of authentic standard.

RESULTS AND DISCUSSION

2-Phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-methoxyindene-3-^{14}C hydrochloride (I) was prepared from phenylacetic-acid-1-^{14}C by the sequence of reactions shown in Scheme I. The first two steps of the sequence were carried out by modifications of the methods reported by Morris (1). The Perkin condensation of II, as a mixed anhydride with acetic acid, and *m*-methoxybenzaldehyde gave a 53% yield of the unsaturated acid, III. Catalytic reduction of III, followed by cyclization of the reduction product (IV) with liquid HF, resulted in a 77% yield of the indanone, V. The last two steps were carried out by the

methods reported by Lednicer (2,3). The final step, condensation of V with the Grignard reagent to give the desired product (I), the most difficult reaction

Scheme 1



in the sequence, resulted in a yield of only 30.5%. The product was both chemically and radiochemically pure. An overall yield of 12.5% was attained by the sequence of reactions shown in Scheme 1.

An alternate synthesis of the intermediate IV was investigated. This involved condensation of phenylacetic acid and *m*-methoxybenzylchloride with KNH_2 in liquid ammonia as described by Lednicer, *et al* (2,3). Cyclization with liquid HF of IV thus prepared gave a 43% yield of the indanone V (based on phenylacetic acid), essentially the same as that obtained by the method shown in Scheme 1. The alternate method, however, proved to be less reproducible than that shown in Scheme 1 when carried out on a millimolar scale.

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