SYNTHESIS OF 4-[2-(DI-n-PROPYLAMINO)ETHYL]-[2-^{14}C]-2(3H)-INDOLONE

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SUMMARY

4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone (1) labeled with ^{14}C at C2 was prepared by a simple and efficient procedure involving carbonation of a stabilized benzyllithium species, followed by ring closure under hydrolytic conditions.

Key words: [^{14}C]Oxindole, directed lithiation, carbonation, lactamization

INTRODUCTION

4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone (1) is a potent and selective nonphenolic prejunctional dopamine agonist which was discovered in a program aimed at development of novel antianginal and antihypertensive drugs(1,2). In animal studies, the compound was found to be a peripherally acting dopaminergic agent which decreases sympathetic neurotransmission and produces hypotension with concomitant bradycardia, but which lacks the CNS effects often seen with other dopamine agonists(1). A ^{14}C-labeled isolog was required for various studies, including metabolism, disposition and pharmacokinetics. Placement of ^{14}C in the 4-ethylindole substructure was preferred, in order to avoid possible metabolic loss of label through N-dealkylation.

Utilization of the original cold synthetic route(1) was considered unsatisfactory because it allowed for incorporation of label only by two possible methods:

- K^{14}CN incorporation in the construction of the 4-ethyl side chain, requiring 7 hot steps with an overall yield of less than 20%; or
- Incorporation of [^{14}C]oxaloyl chloride into the indole nucleus, with loss of half of the label.

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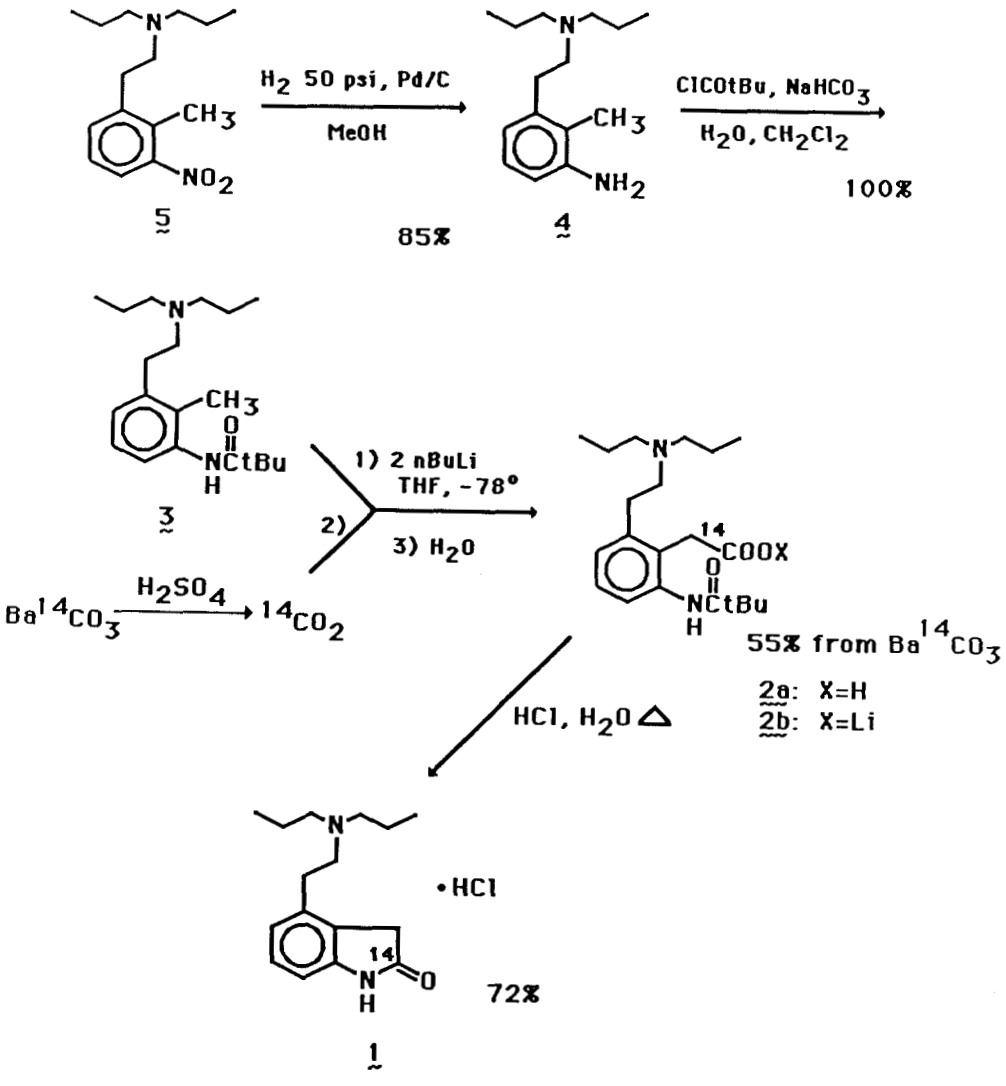
It was desirable to develop an alternative synthesis by which a readily available ^{14}C-labeled starting material could be efficiently incorporated into the nucleus of the target molecule.

RESULTS AND DISCUSSION

2(3H)-Indolones and dihydroquinolones are easily prepared from 2-pivaloylaminophenylacetic esters(3) and 3-(2-pivaloylaminophenyl)propionic esters(4), respectively, via hydrolysis-lactamization. These precedents suggested that an intermediate such as 2a or a derived ester could be easily converted to the desired final product. Compound 2 could in turn be seen to result from carbonation of the appropriate benzylic anion of 3. Directed lithiation of 3 at the methyl site is expected to be favored due to the stabilizing potential(5) of the flanking pivaloylamide and dipropylaminoethyl groups, thus circumventing deprotonation at C1 of the ethyl function and accompanying amine β-elimination. Application of such a method beginning with $^{14}CO_2$ would result in 1 labeled at the C2 position.

These ideas were borne out in practice. A supply of the aniline 4 was prepared by Pd/C catalyzed hydrogenation of 5(1). Pivaloylation provided a quantitative yield of amide 3 as a clear oil. Lithiation using two equivalents of n-butyllithium in THF by the method of Fuhrer and Gschwend(6), and reaction with 0.9 equivalent of $^{14}CO_2$ was followed by aqueous/organic partition to remove unreacted starting material. The aqueous solution of salt 2b was adjusted to ca. 0.3N in HCl by addition of the concentrated acid, and then was heated to gentle reflux. Hydrolysis-lactamization was complete within 41h, as determined by HPLC analysis; basification followed by organic extraction provided 1 as the free base. This air-sensitive product was purified by flash chromatography, converted immediately to the HCl salt, diluted with unlabeled carrier, and recrystallized twice from iPrOH/MeOH to provide 1.07 g (79 mCi, 22.1 mCi/mmole) of 1.HCl as yellow prisms. The overall yield from $Ba^{14}CO_3$ was 39.5%. The chemical purity as determined by HPLC was found to be 98.6%. The radiochemical purity was 98.6% (TLC) to 98.8% (HPLC).



EXPERIMENTAL

General: High pressure liquid chromatography was carried out using either a Varian model 5020B with VISTA 402 data system or an Altex 110A pump with Rheodyne 7125 injector and Kratos SF 769Z UV-Vis detector. HPLC radiodetection was accomplished using a Radiomatic Flow-One instrument with a 0.5 ml liquid cell and Biofluor (New England Nuclear) cocktail. TLC plates were scanned using either a Berthold LB2722 scanner or Berthold LB2832 Linear Analyser. Liquid scintillation counting made use of a Tracor Mark III counter

and Biofluor cocktail. NMR spectra were recorded on a JEOL 270, and mass spectra on a Finnigan model 1020 with direct insertion probe. [^{14}C]Barium carbonate was purchased from ICN Radiochemicals.

2-Amino-6-[2-(di-n-propylamino)ethyl]-toluene (4): A 5.5 g (18.6 mmole) portion of 5(1) was dissolved in 50 ml absolute methanol. A 250 mg portion of 5% Pd/C was added and the compound was hydrogenated under 45 psi H_2 for 5.5 h on a Parr shaker. The catalyst was filtered off through a bed of Celite and the filtrate was evaporated under reduced pressure. The residual oil was distilled (bp 104-7^{o} at 0.02 mm) to provide 3.69 g (85%) of 4 as a clear liquid. Analytical data were found to correspond to those previously measured for the compound(7).

6-[2-(Di-n-propylamino)ethyl]-2-(2,2-dimethylpropionylamino)-toluene (3): The product of the previous step was dissolved in 20 ml CH_2Cl_2 and to this was added 20 ml of a saturated aqueous $NaHCO_3$ solution. Twenty millimoles (2.46 ml) 2,2-dimethylpropionyl chloride was added dropwise to the rapidly stirred mixture over a period of 30 min. After 3.5 more hours of stirring, an additional 0.3 ml (2.4 mmole) portion of the acyl chloride was added, and stirring was continued for 64 h, at which time HPLC analysis (Partisil 10 ODS-3, 1 ml/min 30:70 0.05M NH_4OOCH:MeOH) indicated completion of reaction. The organic layer was separated, washed with saturated $NaHCO_3$ then saturated NaCl, and dried by passage through a ClinElut tube. Solvent was removed first on a rotary evaporator then under high vacuum to constant weight of product, yielding 5.40 g of clear syrup (106% yield). NMR (CDCl3): 7.54 (1H, d, J=7.8), 7.13 (1H, t, J=7.8), 6.99 (1H, d, J=7), 2.78 (2H, m), 2.60 (2H, m), 2.47 (4H, m), 2.20 (3H, s), 1.49 (4H, m), 1.34 (9H, s), 0.90 (6H, t, J=7.3); EIMS (70 ev, M/z, %): 318 (25%, M+), 289 (27%), 218 (10%), 134 (21%), 132 (21%), 114 (100%); anal calcd for $C_{20}H_{34}N_2O$: C, 75.42; H, 10.76; N, 8.80; found: C, 74.99; H 10.55; N 8.40.

4-[2-(Di-n-propylamino)ethyl]-[2-14C]-indolone (1): [^{14}C]Carbon dioxide was prepared by H_2SO_4 treatment of 200 mCi of $Ba^{14}CO_3$ (3.55 mmoles, 56.3 mCi/mmole) and dried over P_2O_5, providing by manometric measurement a

quantitative yield of the gas. A 1.61 g (5.06 mmole) portion of pivaloylamide 3 was lithiated in 30 ml THF at -78° by addition of 1.96 equivalents (3.97 ml, 2.50M in hexane) of n-butyllithium and brief warming to 0°. The $^{14}CO_2$ was condensed into the frozen and evacuated reaction mixture, and the reaction vessel was isolated from the manifold. Upon warming to 0°, the orange solution became clear white, and subsequent vacuum transfer of ca. 1 ml of the solvent failed to carry over significant radioactivity, indicating consumption of $^{14}CO_2$. The solution was refrozen and excess unlabeled CO_2 was condensed in. The reaction was stirred at 0° for one hour, then quenched by addition to 120 ml water.

The mixture was extracted with ether (3 x 50 ml) to remove unreacted starting material. The aqueous solution was analyzed by HPLC (Partisil 10 ODS-3, 1 ml/min 46:54 0.05M NH_4OOCH:MeOH, 250 nm) and found to contain principally the carbonation product 2 (93% by UV peak area; 99% by radioactivity). The pH of the aqueous solution of 2 was adjusted to ca. 1 with concentrated HCl, then an additional 3 ml was added. The solution was heated to gentle reflux, and the course of the reaction was followed by HPLC (Partisil 10 ODS-3, 1 ml/min 30:70 0.05M NH_4OOCH:MeOH; Rt of 2, 7.25 min; Rt of 1, 5.05 min). Reaction was complete after 41 h, and assay of the cooled solution revealed 110 mCi of activity, 99% of which eluted in a peak corresponding to a standard of 1. The solution was basified with aqueous $NaHCO_3$ to pH 8 and extracted with ether (4 x 50 ml). The combined extracts were dried (ClinElut tube) and evaporated in vacuo to constant weight to give 690 mg brown oil. This was purified by flash chromatography on a 1.8 x 30 cm column of silica gel eluted with 1:9 EtOH:CH_2Cl_2. Fractions were collected in tubes containing 2 ml 3N HCl/EtOH, yielding 650 mg [2-^{14}C]1.HCl as a beige solid. This was combined with 808 mg of pure unlabeled 1.HCl and recrystallized twice from iPrOH/MeOH to provide 1.07 g yellow prisms (39.5% radiochemical yield from $Ba^{14}CO_3$). Analysis by HPLC (μBondapak C18, 1 ml/min 2:8 CH_3CN:(0.06M $NaClO_4$ adjusted to pH 2.4 with $HClO_4$) indicated a chemical purity of 98.6% when compared with an unlabeled analytical

reference standard of 1.HCl. Radiochemical purity was determined to be 98.6% by TLC (Analtech SiO_2 GF, 90:10:1 $CHCl_3$:MeOH:NH_4OH) or 98.8% by HPLC (μBondapak C18 and same mobile phase as above). The ^1H NMR spectrum was identical to an unlabeled standard of 1.HCl. The specific activity was determined to be 22.1 mCi/mmole by use of the internal standard method.

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