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Synthesis of (*R*)-5-(Di[2,3-$^3H_2$]propylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one ([^{3}H]U-86170) and (*R*)-5-([2,3-$^3H_2$]Propylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one ([^{3}H]U-91356).

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SUMMARY

(*R*)-5-(diallylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (***12b***) was prepared in 9% overall yield from 3-aminoquinoline. Reaction of ***12b*** in ethyl acetate with tritium gas in presence of a 5% platinum on carbon catalyst afforded a mixture of (*R*)-5-(di[2,3-$^3H_2$]propylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]-quinolin-2(1*H*)-one ([^{3}H]U-86170, ***13***, 69 Ci/mmol) and (*R*)-5-([2,3-$^3H_2$]-propyl-amino)-5,6-dihydro-4*H*-imidazo-[4,5,1-*ij*]quinolin-2(1*H*)-one ([^{3}H]U-91356, ***14***, 34 Ci/mmol) which was separated by preparative reverse-phase chromatography. U-86170 and U-91356 are potent dopamine D2 agonists. The labelled compounds are useful for drug disposition studies. [^{3}H]U-86170 is also useful as a dopamine D2 agonist radioligand for receptor binding studies.

Key Words: synthesis, tritium, imidazoquinolinone, D2 dopamine agonist, radioligand.

INTRODUCTION

The title compounds are members of a series of imidazoquinolines which are potent dopamine D2 agonists and are being evaluated for the treatment of Parkinson's disease (1,2). Activity in these compounds has been shown to reside in the (*R*) enantiomer (1). In this manuscript, we describe the synthesis of [^{3}H]U-86170 (***13***), a compound which is useful for conducting drug metabolism and disposition studies in animals and which has found utility as a dopamine D2 agonist radioligand in receptor binding studies (3). In the synthesis, the related monopropylamine [^{3}H]U-91356 (***14***), a compound which is also of interest as a dopamine agonist, is obtained as a significant byproduct.

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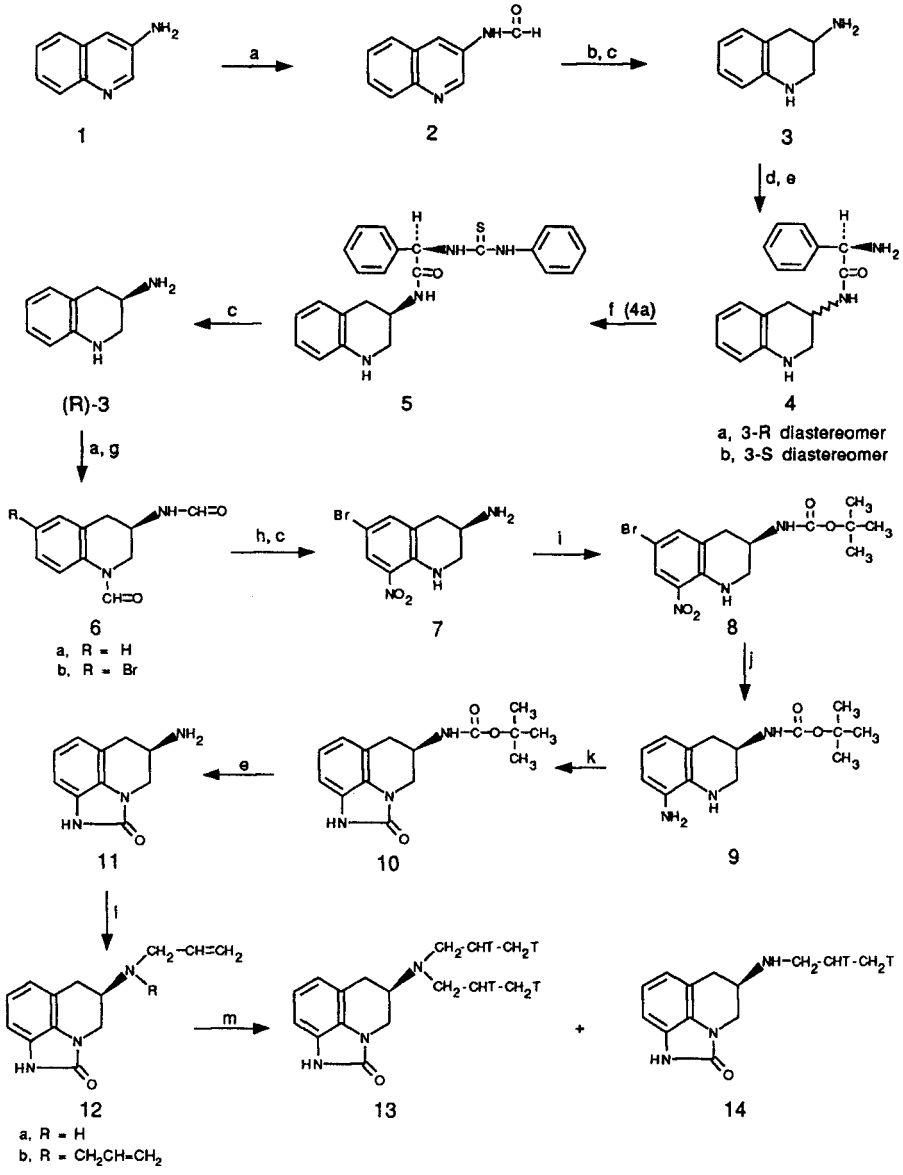
RESULTS AND DISCUSSION

[^{3}H]U-86170 (*13*) and [^{3}H]U-91356 (*14*) were prepared from 3-aminoquinoline as shown in Scheme 1. This sequence is similar to that already described for the synthesis of U-86170 (1),

SCHEME 1. Synthesis of [^{3}H]U-86170 (*13*) and [^{3}H]U-91356 (*14*).



Reagents: (a) H-CO-OAc; (b) H_2, Pt/C, AcOH; (c) HCl, EtOH; (d) BOC-*D*-Phe-OH, CDI; (e) HCl, MeOH; (f) $C_6H_5N{=}C{=}S$; (g) Br_2, AcOH; (h) $NaNO_3$, TFA; (i) BOC_2O; (j) H_2, Pd/C; (k) CDI; (l) $CH_2{=}CHCH_2Br$, Na_2CO_3, DMF; (m) T_2, Pt/C, EtOAc.

but resolution was carried out at an earlier stage in the reaction sequence (4) and the bis allyl derivative ***12b*** was prepared so as to permit incorporation of tritium. As we were unable to directly hydrogenate 3-aminoquinoline (***1***) to ***3***, compound ***1*** was first reacted with formic acetic anhydride to give ***2***. Hydrogenation of ***2*** in acetic acid with a platinum catalyst gave a mixture of 1- and 3-formamidotetrahydroquinolines (1) which was not purified, but was hydrolyzed to ***3*** (5) which was readily isolated as its dihydrochloride salt, a salt which is extremely insoluble in ethanol. Compound ***3*** was coupled to *tert*-butoxycarbonyl-*D*-phenylalanine to give a mixture of the (3***R***)- and (3*S*)-enantiomers of 3-{(***R***)-2-[(1,1-dimethylethoxy)carbonyl]amino-1-oxo-3-phenylpropyl}amino-1,2,3,4-tetrahydroquinoline. While this mixture could not be separated into its components, it was purified by silica gel chromatography to remove imidazole and other minor impurities. Hydrolysis of the purified product removed the *tert*-butoxycarbonyl protecting group and afforded a mixture of diastereomers ***4a*** and ***4b*** from which the bulk of ***4a*** was obtained in pure state by crystallization; the remainder of ***4a*** was readily separated from the second diastereomer (***4b***) by chromatography of the mother liquors on silica gel. Separation was conveniently followed by TLC in methanol/chloroform or by reverse-phase HPLC. Further synthesis was done using ***4a***, the diastereomer which affords ***7***, an intermediate of known stereochemistry from our previously reported synthesis of U-86170 (1). Compound ***4a*** was subjected to conditions of the Edman degradation (6) to remove the phenylalanine resolving agent. Thus, ***4a*** was reacted with phenyl isothiocyanate to give the thiourea ***5***. When treated with ethanolic hydrogen chloride, this afforded a precipitate of the dihydrochloride salt of (***R***)-***3***, the 2-anilino-4-benzyl-2-thiazolin-5-one byproduct formed in the reaction remaining in the ethanol solution.

For conversion of (***R***)-***3*** to ***7***, the conditions already developed in the racemic series were used (1). Formylation of (***R***)-***3*** afforded ***6a*** which was brominated to give ***6b***. Compound ***6b*** was nitrated and the formyl protecting groups were removed to give ***7***. This product was protected as the *tert*-butoxycarbonyl derivative ***8***, reduced to ***9*** and heated with 1,1'-carbonyldiimidazole to give ***10***. Compound ***10*** was deprotected to give the primary amine ***11***, and this was alkylated with 3 equivalents of allyl bromide in DMF to give ***12b*** as the major product together with a small amount of ***12a*** (7). Reduction of ***12b*** with carrier-free tritium gas in the presence of a 5%

platinum on charcoal catalyst afforded the tritium labelled ***13*** and ***14*** in 73% and 22% yield, respectively. A platinum catalyst was chosen for the reduction as trial reductions with deuterium showed that more of the monopropyl byproduct was formed when a palladium catalyst was used (8). Compounds ***13*** and ***14*** were readily separated by reversed phase HPLC. Purification of both compounds was achieved with semi-preparative columns (22 mm ID x 250 mm) with packings identical to those used in analytical columns.

Of the two tritiated drugs, [^{3}H]U-86170 (***13***) has proven to be the more valuable. Using Chinese hamster ovarian cells stably transfected with the dopamine D2 receptor (9), this radioligand has been used routinely for more than a year to determine the activity of new compounds at the D2 dopamine receptor (3, 10). Used in conjunction with the D2 antagonist ligand [^{3}H]raclopride, active compounds can be classified as agonists, partial agonists or antagonists (3) and their intrinsic activities can be estimated (10). High specific activity [^{3}H]U-86170 has shown good stability. Radiochemical purity of samples stored in methanol (1 and 10 mCi/mL) at -70 °C for 18 months declined from 99% to 83%. Partially degraded samples of [^{3}H]U-86170 have been purified as needed by means of preparative HPLC as described in the Experimental Section.

EXPERIMENTAL

1,2,3,4-Tetrahydro-3-quinolinamine (*3*).

A mixture of *N*-(3-quinolyl)formamide (***2***, 45.0 g, 0.261 mol), prepared as described in reference 1, platinum oxide (2.5 g) and acetic acid (400 mL) was hydrogenated (50 psi initial H_2 pressure) for 18 h, after which time 2 equivalents of hydrogen had been consumed. The mixture was filtered through celite and the bulk of the acetic acid was removed under reduced pressure. The residual oil was dissolved in ethanol (200 mL), heated to 70 °C and stirred vigorously while 4.2 M ethanolic hydrogen chloride (200 mL) was added. A precipitate of the dihydrochloride of ***3*** separated after a few minutes and, after 30 min, the reaction was cooled to 0 °C and the solid was filtered off, washed with ethanol/ether (1:1), and air dried to give 46.4 g (80%) of product, mp 256-260 °C (11); lit mp 260-264 °C (3). The product was >90% pure (TLC R_f = 0.41 in 15% methanol/chloroform, with slower moving impurities having R_f's of 0.13 and 0.08).

(3*R*)-3-(*R*)-(2-Amino-1-oxo-3-phenylpropyl)amino-1,2,3,4-tetrahydroquinoline (*4a*).

1,1'-Carbonyldiimidazole (19.0 g, 116 mmol) was added at 0 °C to a stirred solution of *tert*-butoxycarbonyl-*D*-phenylalanine (29.2 g, 110 mmol) in THF (400 mL). After 30 min, a solution of 1,2,3,4-tetrahydro-3-quinolinamine [18.7 g, prepared by partitioning the dihydrochloride salt (26.7 g, 120 mmol) between ethyl acetate and sodium hydroxide] in THF (100 mL) was added. The solution was stirred for 1 h, evaporated, and partitioned between ethyl acetate and water. The ethyl acetate was removed and the residual oil was chromatographed on silica gel using ethyl acetate/hexane (1:4) as the initial eluant. Fractions containing the (3*R*)- and (3*S*)-enantiomers of 3-{(*R*)-2-[(1,1-dimethylethoxy)carbonyl]amino-1-oxo-3-phenylpropyl}amino-1,2,3,4-tetrahydroquinoline were pooled and crystallized from ethyl acetate/hexane to give 32.5 g of product, mp 124-142 °C; evaporation of the mother liquors afforded an additional 3.0 g of product. The mixture of isomers (32.3 g) was dissolved in methanolic hydrogen chloride (400 mL of 4 N). After 18 h, the solution was evaporated under reduced pressure and the residual oil was partitioned between ethyl acetate and 4 N sodium hydroxide solution. The ethyl acetate was washed with water, evaporated, and the residue was crystallized from ethyl acetate/hexane (200 mL of 1:2) to give 10.1 g of ***4a*** (97% optical purity as determined by reverse-phase HPLC), mp 148-152 °C. This was recrystallized from ethyl acetate/hexane (150 mL of 2:1) to give 8.75 g of product, mp 150-152 °C. Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.11; H, 7.39; N, 14.02. $[\alpha]_D$ = -62.4° (c = 1.00, MeOH); TLC (5% methanol/chloroform) R_f = 0.59. Chromatography of the combined mother liquors on silica gel using 1.0-1.5% methanol in chloroform as eluant gave, as the first product eluted from the column, an additional 3.30 g of ***4a***; crystallization from ethyl acetate/hexane gave 2.95 g of product, mp 150-152 °C. Continued elution of the column gave 11.02 g of (3*S*)-3-(*R*)-(2-amino-1-oxo-3-phenylpropyl)amino-1,2,3,4-tetrahydroquinoline (***4b***). This was crystallized from ethyl acetate/hexane (1:1) to give 10.11 g of product, mp 99-101 °C. Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.24; H, 7.48; N, 14.16. $[\alpha]_D$ = -1.3° (c = 0.98, MeOH); TLC R_f = 0.52 (10% methanol/chloroform).

(*R*)-1,2,3,4-Tetrahydro-3-quinolinamine (*R*)-*3*.

Phenyl isothiocyanate (6.5 g, 48.1 mmol) was added at 0 °C to a stirred solution of (3*R*)-3-(*R*)-(2-amino-1-oxo-3-phenylpropyl)amino-1,2,3,4-tetrahydroquinoline (***4a***, 11.3 g, 38.2 mmol) in

THF. The solution was allowed to warm to room temperature and after 1 h was evaporated; the crude ***5*** thus obtained was reconstituted in ethanol (25 mL), and ethanolic hydrogen chloride (50 mL of 4 N) was added. After 15 min, the precipitated solid was filtered and washed with ethanol/ether and dried to give 9.05 g (104%) of (***R***)-***3*** dihydrochloride which was used without further purification (11); mp 275-282 °C. Anal. Calcd. for $C_9H_{12}N_2 \cdot 2HCl$: C, 48.88; H, 6.37; Cl, 32.07; N, 12.67. Found: C, 49.56; H, 6.28; Cl, 30.69; N, 12.36. $[\alpha]_D$ = -7.1° (c = 0.48, MeOH).

(*R*)-*N*-(1-Formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (*6a*).

(***R***)-1,2,3,4-tetrahydro-3-quinolinamine dihydrochloride [(***R***)-**3**, 8.8 g, 39.8 mmol] was converted to the free base by partitioning between ethyl acetate (200 mL) and 4 N sodium hydroxide solution (30 mL). The oil obtained after evaporation of the ethyl acetate (6.0 g) was dissolved in THF (20 mL) and added to a stirred solution of acetic formic anhydride [0.2 mol, prepared from 97% formic acid (10.4 g) and acetic anhydride (20.4 g)] in THF (100 mL). After 45 min, the solution was evaporated, the oil was dissolved in THF (15 mL) and ether (100 mL) was added. The resulting white solid was filtered to give 7.25 g (89%) of ***6a***, mp 138-144 °C, $[\alpha]_D$ = +57.4° (c = 1.02, MeOH). A sample (1.0 g) was recrystallized from methanol/ether (20 mL of 1:2) to give 0.81 g, mp 145-147 °C. Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.81; H, 6.16; N, 13.60. $[\alpha]_D$ = +59.4° (c = 0.98, MeOH).

(*R*)-*N*-(1-Formyl-6-bromo-1,2,3,4-tetrahydro-3-quinolyl)formamide (*6b*).

Bromine (11.5 g, 72 mmol, 2.0 equiv.) was added over a 20 min period to a stirred solution of (*R*)-*N*-(1-formyl-1,2,3,4-tetrahydro-3-quinolyl)formamide (***6a***, 7.25 g, 35.5 mmol) and anhydrous sodium acetate (8.2 g, 100 mmol) in acetic acid (50 mL) . The solution was stirred for 30 min and water (400 mL) was added. The precipitate was filtered off and air dried to give 8.65 g (86%) of ***6b***, mp 191-195 °C; $[\alpha]_D$ = +63.2° (c = 1.02, MeOH). The analytical sample (1.35 g) was obtained by recrystallizing 1.60 g from methanol (50 mL); mp 198-200 °C. Anal. Calcd. for $C_{11}H_{11}BrN_2O_2$: C, 46.66; H, 3.92; Br, 28.23; N, 9.90. Found: C, 46.58; H, 3.82; Br, 28.15; N, 9.90. $[\alpha]_D$ = +63.6° (c = 0.99, MeOH).

(*R*)-6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (7).

A mixture of (***R***)-*N*-(1-formyl-6-bromo-1,2,3,4-tetrahydro-3-quinolyl)formamide (***6b***, 8.11 g,

28.6 mmol) and sodium nitrate (4.87 g, 57.3 mmol) in trifluoroacetic acid (50 mL) was stirred at room temperature for 12 h. The bulk of the solvent was removed under reduced pressure and the product was partitioned between ethyl acetate (200 mL) and water (20 mL). The precipitate of (*R*)-*N*-(1-formyl-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolyl)formamide was filtered off and the ethyl acetate was evaporated to afford more of the same product. The two fractions were combined, dissolved in ethanolic hydrogen chloride (200 mL of 4 N) and the solution was refluxed for 1 h, during which time the bulk of **7** separated as the dihydrochloride salt. The solution was cooled, ether (200 mL) was added and the solution was filtered to give 8.12 g (88%) of the dihydrochloride salt of **7**, mp >325 °C. The product was partitioned between ethyl acetate and sodium hydroxide solution to obtain 6.88 g (89%) of the free base of **7**, mp 155-163 °C. The analytical sample was crystallized from ethyl acetate; mp 165-168 °C. Anal. Calcd. for $C_9H_{10}BrN_3O_2$: C, 39.72; H, 3.70; Br, 29.37; N, 15.44. Found: C, 39.66; H, 3.80; Br, 28.82; N, 15.11. $[\alpha]_D$ = -133° (c = 1.00, MeOH).

***tert*-Butyl (*R*)-(6-Bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl)carbamate (*8*).**

A mixture of (*R*)-6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (**7**, 5.50 g, 20.2 mmol), and di *tert*-butyl dicarbonate (5.40 g, 25.5 mol) in THF (50 mL) was heated under reflux for 30 min. The bulk of the solvent was removed, hexane (40 mL) was added and the precipitate was filtered to afford 7.10 g (94%) of **8**, mp 199-201 °C. A sample (1.0 g) was recrystallized from acetonitrile (30 mL) to provide the analytical sample (0.97 g), mp 192-201 °C. Anal. Calcd. for $C_{14}H_{18}BrN_3O_4$ C, 45.18; H, 4.88; Br, 21.47; N, 11.29. Found: C, 45.13; H, 4.91; Br, 21.46; N, 11.11. $[\alpha]_D$ = -142.7° (c = 1.05, DMF).

***tert*-Butyl (*R*)-(1,2,5,6-Tetrahydro-2-oxo-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)carbamate (*10*).**

A mixture of *tert*-butyl (*R*)-(6-bromo-1,2,3,4-tetrahydro-8-nitro-3-quinolinyl)carbamate (**8**, 6.70 g, 18.0 mmol), absolute ethanol (150 mL) and 10% palladium on carbon (1.50 g) was hydrogenated (50 psi hydrogen pressure) for 18 h. The mixture was neutralized with 4.0 N sodium hydroxide solution (4.50 mL, 18 mmol), filtered through celite, and the solvent removed. The residue was partitioned between ethyl acetate and water, and the ethyl acetate was

evaporated to give 4.72 g of *tert*-butyl (*R*)-(8-amino-1,2,3,4-tetrahydro-3-quinolyl)carbamate (***9***) as an oil. This was dissolved in DMF (40 mL) and 1,1'-carbonyldiimidazole (3.50 g, 21.6 mmol) was added. The solution spontaneously warmed to 40 °C and was then heated at 100 °C for 1 h. The solvent was removed and the crude material was purified by chromatography on silica gel in 1% methanol/chloroform to give 4.25 g of product. Crystallization from ethyl acetate/hexane (1:1) gave 3.85 g (74%) of ***10***, mp 182-185 °C. A sample was recrystallized for analysis: mp 191-193 °C. Anal. Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.26; H, 6.62; N, 14.52. Found: C, 62.37; H, 6.70; N, 14.22. $[\alpha]_D$ = +10.6° (c = 1.01, MeOH).

(*R*)-5-Amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (*11*).

Compound ***10*** (3.71 g, 12.8 mmol) was stirred in methanolic hydrogen chloride (50 mL of 4 N) until deprotection was complete (2 h). The precipitate was filtered off and washed with methanol/ether (1:1) to give 2.76 g (94%) of ***11***, mp >300 °C. Anal. Calcd. for $C_{10}H_{11}N_3O{\cdot}HCl{\cdot}0.25H_2O$: C, 52.18; H, 5.47; Cl, 15.40; N, 18.26. Found: C, 52.11; H, 6.11; Cl, 15.27; N, 18.06. $[\alpha]_D$ = -27.6° (c = 0.97, MeOH). Evaporation of the mother liquors afforded an additional 0.32 g of product.

(*R*)-5-Diallylamino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (*12b*).

(*R*)-5-amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (***10***, 1.17 g, 5.0 mmol) was dissolved in methanol (5 mL) and neutralized by addition of 1.25 mL of 4 N sodium hydroxide. The solution was evaporated to dryness, reconstituted in DMF (20 mL), evaporated to remove water, and redissolved in DMF (20 mL). Allyl bromide (1.80 g, 15 mmol) and sodium carbonate (2.0 g, 19.0 mmol) were added and the solution was stirred at 70 °C for 3 h. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The oil obtained after evaporation of the ethyl acetate was chromatographed on silica gel to give 1.02 g of ***12b*** which was crystallized from cyclohexane/hexane to give 825 mg (62%), mp 68-72 °C. Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.40; H, 7.24; N, 15.60. $[\alpha]_D$ = +7.7° (c = 1.0, MeOH). Continued elution of the column gave 115 mg of ***12a*** (10%) which was converted to the hydrochloride salt, mp 295 °C (dec) from methanol (7). Anal. Calcd. for $C_{13}H_{15}N_3O{\cdot}HCl$: C, 58.75; H, 6.07; Cl, 13.34; N, 15.81. Found: C, 58.67; H, 6.13; Cl, 13.33; N, 15.80. $[\alpha]_D$ = -33.5° (c = 1.03, MeOH).

(*R*)-5-(Di[2,3-$^3H_2$]propylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one [^{3}H]U-86170, (*13*).

A solution of ***12*** (27 mg, 0.10 mmol) in ethyl acetate (2.5 mL) was placed in a micro-hydrogenation cell attached to a stainless steel tritiation line, was frozen in a liquid nitrogen bath, and the line was degassed at 25 μm and filled with nitrogen to 1 atm. This was repeated twice more and, after final evacuation of nitrogen, the line was filled to ca 650 torr with carrier-free tritium gas. The cell was allowed to warm to room temperature, whereupon a 10 mg charge of 5% Pt/C catalyst which had been suspended over the reaction mixture in a glass spoon, was dropped into the solution. The mixture was stirred at room temperature as the pressure in the tritiation line decreased to a constant level in 3.5 h. After 4 h, the stirring was stopped and the line was evacuated to remove unused tritium gas. After methanol (2-3 mL) was added to the thawed reaction mixture, the mixture was again frozen and lyophilized to remove labile tritium. This was repeated twice and the mixture was passed under pressure from a syringe, through a filtering device consisting of a Supelclean Si SEP PAK cartridge in series with a Gelman Acrodisc, both of which had been wetted with methanol. Without allowing them to go dry, the filters were rinsed with 3x5 mL of methanol. The combined filtrate and rinses were lyophilized overnight. Analysis of the residue by radio-HPLC showed that the crude product was a mixture of 73% ***13***, 22% ***14*** and 5% of an unknown polar product. Pure ***13*** and ***14*** were obtained by means of preparative HPLC done with a 5μm Supelcosil LC-18 semi-preparative stainless steel column (22 mm ID x 250 mm) using as mobile phase 1:4 V/V acetonitrile:buffer (0.1 M triethylamine, 0.1 M trifluoroacetic acid, pH 2.3) pumped isocratically at 16 mL/min. The estimated 25 mg of crude product was dissolved in a mixture of 250 μL of acetonitrile and 50 μL of methanol and was divided into three shots for the preparative chromatography. The eluate was monitored with a UV detector at 254 nm, and the fraction from each shot containing ***14*** (first fraction) and ***13*** (later fraction) were collected and pooled. Each pool was concentrated at reduced pressure and 35 °C to remove acetonitrile. The aqueous residues were each basified with 6 N NaOH and extracted with methylene chloride. The extracts were washed with brine and dried over anhydrous sodium sulfate. The residue from the compound ***13*** pool was found to contain 3.4 Ci of total activity. HPLC analysis of this material showed its radiochemical

purity was in excess of 99%. Using UV response to determine the mass of known radioactive dose of ***13***, the specific activity of ***13*** was calculated to be 252 mCi/mg (69 Ci/mmol).

(*R*)-5-([2,3-$^3H_2$]Propylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one [^{3}H]U-91356, (*14*).

The residue from the compound ***14*** pool above (0.92 Ci) was dissolved in 200 µL of 1:1 V/V acetonitrile:1 N HCl, and subjected to further preparative HPLC purification, as a single shot, on a 5 µm Phenomenex ODS semi-preparative stainless steel column (22 mm ID x 250 mm). The mobile phase used was 1:4 V/V acetonitrile:buffer (0.1 M triethylamine, 0.1 M trifluoroacetic acid, pH 2.3) pumped isocratically at 16 mL/min with UV monitoring at 254 nm. The eluate containing ***14*** was collected, concentrated to remove acetonitrile, and the aqueous residue was basified and extracted with methylene chloride. The extract was washed with brine, dried over sodium sulfate, and concentrated to give pure ***14***, 0.425 Ci, >98% radiochemical purity by HPLC, specific activity 34 Ci/mmol.

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(4) This simplifies the synthesis, as intermediates in the resolution (***4a***, ***4b***, the

corresponding BOC-protected compounds, and **5**) have good solubility in organic solvents, and crystallization rather than chromatography can be used to isolate ***4a***. Resolution of racemic **7** as described in reference 1 proceeds through extremely insoluble intermediates and products, which makes the chromatographic separation and scale-up difficult.

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(7) When ***11*** was alkylated in DMF at room temperature with 2 equivalents of allyl bromide, the monoallylamine ***12a*** was obtained as the major product (47%). Tritiation of ***12a*** would afford a better route to [^{3}H]U-91356 (***14***).

(8) In catalytic reductions of ***12b***, the monopropylamine ***14***, resulting from loss of an allyl group during reduction, was a ubiquitous byproduct. The extent of its formation was dependent on the catalyst employed. In trial runs using deuterium gas, a 5% Pt/C catalyst was found to minimize the formation of the deuterated analogue of ***14*** (22% of the product). When 5% Pd/C was used as catalyst, up to 55% of the deuterated analogue of ***14*** was produced.

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(10) Lahti, R.L.; Figur, L. M.; Piercey, M. F.; Ruppel, P. L.; Evans, D. L. - *Molecular Pharmacol,* in press.

(11) Impurities in racemic ***3*** or its ***R***-enantiomer may be removed by converting the product to the free base, purifying the free base by silica gel chromatography, and reforming the dihydrochloride salt. A sample of the racemic salt prepared in this manner had a mp of 260-264 °C. As compound ***3*** is somewhat unstable, purification is of questionable value unless purity of the crude product is low. While analytical data for (***R***)-***3*** were outside usually accepted limits, no problems were encountered continuing the synthesis with this product; the minor impurities present in the product were readily removed at the next reaction step.