SYNTHESIS OF [^{14}C]LABELLED PYRANO[3,4-b]-AND THIOPYRANO[3,4-b]INDOLES, AND INDENO[2,1-c]PYRAN DERIVATIVES

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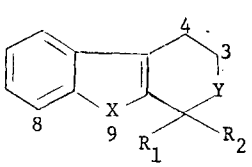
SUMMARY

The synthesis of four structurally similar [^{14}C]labelled compounds having a novel heterocylic ring system is described. Three compounds with a tetrahydropyrano (or thiopyrano) indole nucleus were prepared from suitably substituted [^{14}C]tryptophols and were labelled in the pyrano or thiopyrano ring. The preparation of the [^{14}C]tryptophol intermediates from the appropriate gramine is described. The synthesis of the fourth compound, a tetrahydroindenopyran derivative labelled in the indene nucleus, involved a novel preparation of [^{14}C]indene.

Key Words: [^{14}C]Pyranoindole, [^{14}C]Thiopyranoindole, [1-^{14}C]Indene, [^{14}C]Indenopyran

INTRODUCTION

A series of compounds having a novel tetrahydropyranoindole (I, X = NH, Y = O), (1, 2a, 2b), tetrahydrothiopyranoindole (I, X = NH, Y = S) (3a) and tetrahydroindenopyran (I, X = CH_2, Y = O) (4a) structure has been prepared in our laboratories. The compounds with an acetic acid substituent in the 1-position (I, R_1 = alkyl, R_2 = CH_2CO_2H) exhibit anti-inflammatory activity (1, 2a), while those



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with R_1 = alkyl and R_2 = N,N-dimethylaminoethyl have antidepressant properties (2b, 3a, 3b, 3c, 4a, 4b). We describe herein the synthesis of [^{14}C]labelled,

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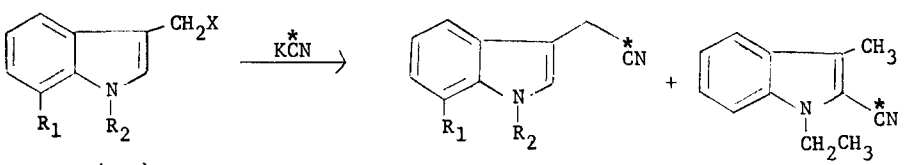
structurally related, prodolic acid 8a, etodolic acid 8b, tandamine hydrochloride 10, and pirandamine hydrochloride 15*.

DISCUSSION

The synthesis of prodolic acid 8a (1), etodolic acid 8b (2a) and tandamine hydrochloride 10 (3a) requires tryptophol intermediates 6 with appropriate substituents on the indole nucleus. Since the tryptophols 6 could be readily prepared from the appropriately substituted quaternary gramines 2, this route was also chosen for the labelled synthesis (Scheme 1). The [^{14}C] label was thus

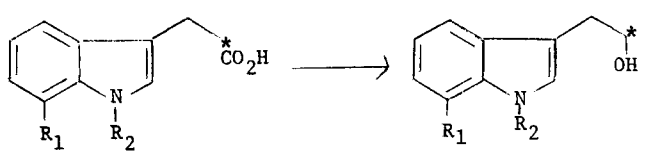
Scheme 1



1 X = $N(CH_3)_2$

2 X = $N(CH_3)_3$ $CH_3SO_4^-$

3 4



5 6

a R_1 = H, R_2 = H

b R_1 = CH_2CH_3, R_2 = H

c R_1 = H, R_2 = CH_2CH_3

*[^{14}C]label

*Non-proprietory names adopted by the USAN Council. Prodolic acid (AY-23,289) 8a: 1-n-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid; etodolic acid (AY-24,236) 8b: 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid; tandamine hydrochloride (AY-23,946) 10: 9-ethyl-1,3,4,9-tetrahydro-N,N,1-trimethyl-thiopyrano[3,4-b]indole-1-ethanamine hydrochloride; pirandamine hydrochloride (AY-23,713) 15: 1,3,4,9-tetrahydro-N,N-1-trimethylindeno[2,1-a]pyran-1-ethanamine hydrochloride.

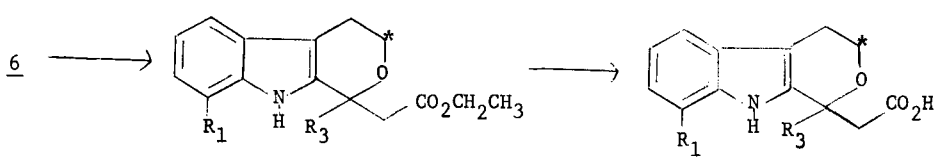
introduced in each case by displacement of the quaternary amine with potassium [^{14}C]cyanide to give the nitrile 3. While the reaction of 2b with KCN gave only the nitrile 3b, the N-substituted indole 2c gave a mixture of the nitriles 3c (65%) and 4 (35%). N-Substituted quaternary gramines are known to react with nitriles to give the 2-cyanoindoles as minor products (5).

The nitriles 2b and 2c were converted readily to the indole-3-acetic acids 5b and 5c by hydrolysis with 20% aqueous potassium hydroxide. The stability of the 2-cyanoindole 4 under the hydrolytic conditions eliminated the need to separate the two isomeric nitriles 3c and 4; the indole-3-acetic acid 5c being the only product isolated from the acidic fraction after hydrolysis of the nitrile mixture.

Reduction of the indole-3-acetic acid derivatives 5 with lithium aluminum hydride in tetrahydrofuran gave the tryptophols 6 in overall yields of 80% for 6a*, 95% for 6b and 59% for 6c.

The tryptophols 6a and 6b were condensed with ethyl butyrylacetate or methyl propionylacetate using boron trifluoride etherate as the catalyst to afford the tetrahydropyranoindoles 7a and 7b (1, 2) (Scheme 2). Basic hydrolysis of the esters 7a and 7b gave the [3-^{14}C]prodolic acid 8a and [3-^{14}C]etodolic acid 8b in overall yields of 26% from the [^{14}C] labelled starting material (Table 1). In both cases the compounds are unstable under neutral or slightly acidic conditions

Scheme 2



7 8

a R_1 = H, R_3 = $CH_2CH_2CH_3$

b R_1 = CH_2CH_3, R_3 = CH_2CH_3

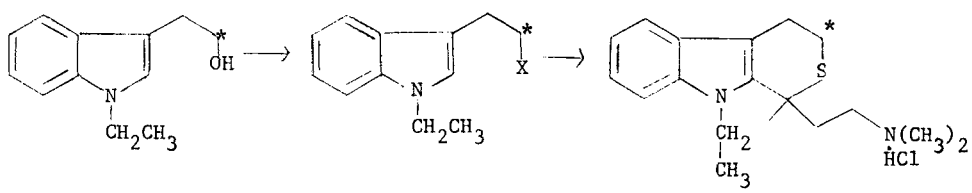
* [^{14}C] label

*This yield of the tryptophol 6a was based on the reduction of commercially available indole-3-[1'-^{14}C]acetic acid.

due to the formation of a hydroperoxide (6). Recrystallization of the acids in the presence of an antioxidant (6), e.g. 2,6-di-tert-butyl-4-methylphenol and storage at -10^{o} inhibited hydroperoxide formation.

The tryptophol 6c was converted to the tetrahydrothiopyranoindole 10 (3a) by the sequence of reactions shown in Scheme 3: reaction of 6c with phosphorous tribromide gave the bromide 9a which was converted to the thiosulfate (Bunte salt) 9b with sodium thiosulfate. Condensation of 9b with 1-(N,N-dimethylamino)-butan-3-one using BF_3 etherate as catalyst gave tandamine 10 (as free

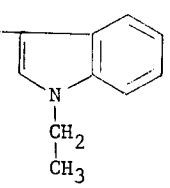
Scheme 3



6c 9 a X = Br 10

b X = SSO_3Na

c X = $S_2(CH_2)_2$

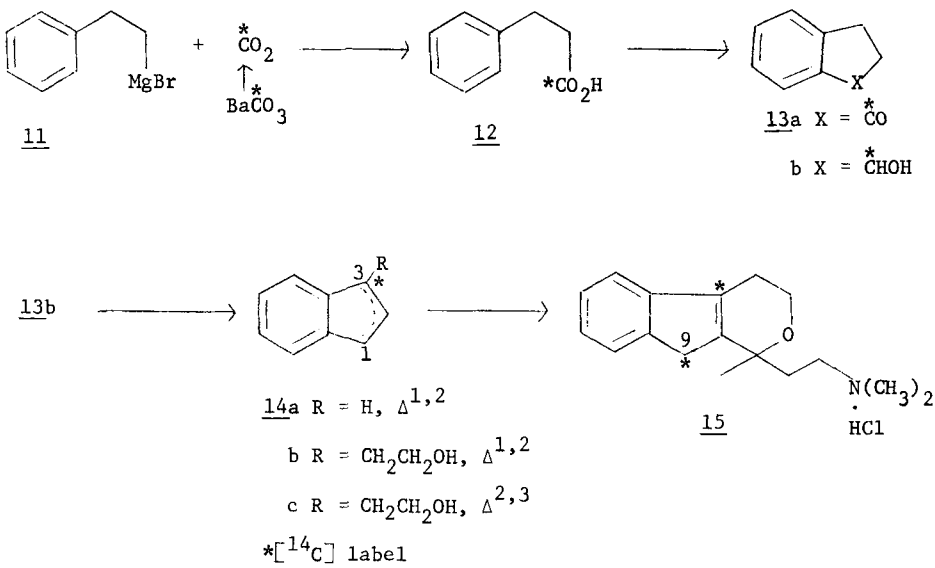


*[^{14}C] label

amine) in 10% yield. The low yield was due to the formation of the disulfide 9c (3a) as a by-product in the reaction. Once formed, the disulfide does not undergo the desired condensation reaction to form 10.

In contrast to the other compounds, pirandamine hydrochloride 15 was more easily labelled in the indene nucleus than in the tetrahydropyrano ring. The sequence of reactions used to prepare the labelled indenopyran 15 from [^{14}C]barium carbonate is shown in Scheme 4. 2-Phenylethylmagnesium bromide 11 was allowed to react with [^{14}C]CO_2 to give the carboxylic acid 12. Ring closure with hydrofluoric acid (7) gave [1-^{14}C]indan-1-one 13a which was then reduced to the alcohol 13b with sodium borohydride.

Scheme 4



The conversion of 1-indanol 13b to indene 14a was, initially, not successful; dehydrating agents such as p-toluenesulfonic acid, sulfuric acid, oxalic acid, phosphorous oxychloride and thionyl chloride did not effect the conversion; florisil in refluxing benzene (8) caused some dehydration of the alcohol but the reaction was not efficient. Only after applying the method of Melton and Eisenbraun (9), i.e. by refluxing 1-indanol 13b in cyclohexane in the presence of a small amount of the strong cation exchange resin Amberlyst 15, a near quantitative conversion to indene 14a was achieved. [1-^{14}C]Indene was obtained in 60% overall yield from [^{14}C]$BaCO_3$.

The treatment of indene 14a with ethylmagnesium bromide gave the exchanged Grignard 14a (R = MgBr) which on reaction with ethylene oxide gave the indene-1-ethanol 14b (11). Isomerization of the double bond to 14c was effected by refluxing 14a in 20% aqueous alcholic KOH. The product, isolated by column chromatography, was obtained in 67% yield.

Condensation of the indene-3-ethanol 14c with 1-(N,N-dimethylamino)-butan-3-one using BF_3-etherate as the catalyst gave the free amine 15 which was purified by preparative thin-layer chromatography (TLC) and converted to the hydrochloride salt.

The radiochemical purity of the final [^{14}C] labelled compounds was determined by TLC-autoradiography in two or three different solvent systems. The results are summarized in Table 1.

Table I. Specifications for [^{14}C]prodolic acid 8a, [^{14}C]etodolic acid 8b, [^{14}C]tandamine hydrochloride 10 and [^{14}C]pirandamine hydrochloride 15.

Name	Specific activity, mCi/mmole	% Radiochem. purity	Solvent system
Prodolic acid, 8a	1.56	99	methylcyclohexane-acetone acetic acid 70:30:0.5
			benzene-ethanol acetic acid 80:12:5
Etodolic acid, 8b	3.03	99	hexane-acetone acetic acid 70:30:0.5
			benzene-ethanol acetic acid 80:12:0.5
			petroleum ether (30-60)-ethyl acetate-acetic acid 50:50:0.5
Tandamine hydrochloride 10	2.15	99	chloroform-methanol 9:1
			benzene-acetone-triethylamine 60:30:10
Pirandamine hydrochloride 15	4.70	99.5	chloroform-methanol 87:13
			benzene-acetone-triethylamine 70:30:10

EXPERIMENTAL

The experimental details in this section are those used for the labelled synthesis. The reactions were monitored by TLC (0.25 mm silica gel F_{254} plates from E.M. Laboratories) using the appropriate unlabelled compound as the reference. Autoradiograms were obtained with manually developed Kodak RP/R14 medical X-ray film. Radioactivity was measured with a Packard Tri-Carb 3375 liquid scintillation spectrometer.

[^{14}C]Potassium cyanide, [^{14}C]barium carbonate and indole-3-[1'-^{14}C]acetic acid were purchased from New England Nuclear Corp., Boston, Massachusetts.

3-(N,N-Dimethylaminomethyl)-7-ethylindole, 1b.

7-Ethylindole (5.37 g, 0.037 mole), prepared from 7-ethylisatin (2a), was dissolved in dioxane (25 ml) and added under a nitrogen atmosphere to a solution consisting of dioxane (35 ml), glacial acetic acid (35 ml), formaldehyde (3.48 ml) and dimethylamine (7.62 ml). The reaction mixture was then stirred at room temperature under nitrogen for 24 hr.

The solution was concentrated on a rotary-evaporator and the residue diluted with water (100 ml), made alkaline with 6N NaOH and extracted with chloroform (2 x 50 ml); the extracts were dried over anhydrous sodium sulfate (Na_2SO_4) and evaporated. The crude product was obtained as a light brown oil (8.76 g): i.r. ($CHCl_3$) 3460 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.27 (t, J = 7.0 Hz; 3H, $-CH_2CH_3$), 2.27 (s, 6H, $N(CH_3)_2$), 2.75 (q, J = 7.0 Hz, 2H, $-CH_2CH_3$), 3.62 (s, 2H, $-CH_2N$), 7.0 (m, 3H, aromatic), 7.5 (m, 1H, aromatic), 8.61 (b.s., 1H, NH). The compound was used without further purification in the preparation of the quaternary amine 2b.

3-(N,N-Dimethylaminomethyl)-1-ethylindole, 1c.

3-(N,N-Dimelthylaminomethyl)indole (10) (75 g, 0.49 mole) was dissolved in anhydrous dimethylformamide (DMF) (1.0 l). Benzene (50 ml) was added and distilled off to remove any traces of water. The solution was then cooled to 0° and sodium hydride (22 g of a 59% dispersion) was added. The mixture was stirred at 0° for 1 hr, then ethyl bromide (40 ml) was added dropwise. After stirring for 30 min at 0°, the reaction mixture was poured on crushed ice and extracted with chloroform. The chloroform extract was washed with water and extracted with 10% HCl. The combined acidic extract was made alkaline with 6N NaOH and extracted with ether. The ether extract was washed with water, dried over Na_2SO_4 and the solvent evaporated to give a brown oil (40 g): i.r. ($CHCl_3$) showed no ν (NH) vibration; n.m.r. ($CDCl_3$): δ1.38 (t, J 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 3.90 (q, J 7.5 Hz, 2H, $\underline{CH_2}CH_3$). The compound was used without further purification in the formation of the quaternary amine 2c.

7-Ethyl-3-(N,N,N-trimethylaminomethyl)indole methylsulfate, 2b.

The crude gramine 1b, (8.26 g, 50.6 mmole) was dissolved in tetrahydrofuran (THF) (190 ml) containing glacial acetic acid (5.75 ml) and cooled to 0°. A solution of dimethylsulfate (18.2 ml) and acetic acid (5.75 ml) in tetrahydro-

furan (16 ml) was added dropwise. The reaction mixture was allowed to warm to and remain at room temperature for 24 hr.

The resulting solid was collected by filtration and washed with THF and recrystallized several times from ethanol. The pure product was obtained as a white crystalline compound (8.65 g, 64%): m.p. 152-153°; i.r. (nujol) 3250, 1195 cm^{-1}; n.m.r. (DMSO) δ 1.3 (t, J = 7.0 Hz, 3H, $-CH_2\underline{CH_3}$), 2.9 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 3.05 (s, 9H, $N(CH_3)_3$), 3.4 (s, 3H, OCH_3), 4.7 (s, 2H, CH_2 - N), 7.1 - 7.7 (m, 4H, aromatic).

1-Ethyl-3-(N,N,N-trimethylaminomethyl)indole methyl sulfate, 2c.

The gramine 1c, (40 g, 0.25 moles) was treated with dimethylsulfate (100 ml) as described above and the title compound was obtained as a white crystalline solid (38.7 g, 69%): m.p. 156-8°; i.r. (nujol) 1245 cm^{-1}; n.m.r. (DMSO) δ 1.42 (t, J = 7Hz, 3H, CH_2CH_3), 3.09 (s, 9H, $N(CH_3)_3$, 3.45 (s, 3H, CH_3OSO_3), 4.3 (q, J = 7Hz, 2H, $\underline{CH_2}CH_3$), 4.73 (s, 2H, CH_2N).

7-Ethylindole-3-[1'-^{14}C]acetonitrile, 3b.

The quaternary amine 2b (3.26 g, 9.93 mmole), was dissolved in water (50 ml) and [^{14}C]potassium cyanide (30.0 mCi, 0.648 g, 9.93 mmole), dissolved in water (5 ml), was added. The reaction mixture was refluxed for 5 hr and stirred at room temperature for 16 hr. The reaction mixture was extracted with ether (3 x 70 ml) and the combined ether extracts washed with water (70 ml), dried over anhydrous magnesium sulfate ($MgSO_4$) and evaporated to dryness. The crude product was obtained as a light brown solid (1.83 g, 100%) and did not require further purification for the next reaction.

The nitrile when recrystallized from ether-hexane gave the following data: m.p. 105-105.5°; i.r. ($CHCl_3$) 3450, 2240 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.35 (t, J 7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.88 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 3.8 (s, 2H, CH_2CN), 7.3 (m, 4H aromatic), 8.2 (b.s., 1H, NH).

1-Ethylindole-3-[1'-^{14}C]acetonitrile, 3c.

The pure quaternary gramine 2c (8.11 g, 24.7 mmole) was allowed to react with [^{14}C]KCN (50 mCi, 1.50 g, 23.1 mmole) as described above. The product (4.34 g), a mixture of the two isomeric nitriles 3c and 4, was hydrolyzed without purification to the indoleacetic acid 5c; the nitrile 4 did not hydrolyze under

those conditions and could be removed in the work-up.

In a preparation using unlabelled KCN, the two nitriles were separated by column chromatography on silica gel using 30% acetone in hexane. The minor product, 2-cyano-1-ethyl-3-methylindole 4 was eluted first and obtained in 35% yield: i.r. ($CHCl_3$) 2200 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.37 (t, J = 7HZ, 3H, $CH_2\underline{CH_3}$), 2.44 (s, 3H, CH_3), 4.17 (q, J 7Hz, 2H, $\underline{CH_2}CH_3$), 7.0 - 7.7 (m, 4H, aromatic). The major component of the mixture was the desired nitrile 3c, obtained in 65% yield: i.r. ($CHCl_3$) 2250 cm^{-1}; n.m.r. ($CDCl_3$) δ 1.38 (t, J = 7Hz, 3H, $CH_2\underline{CH_3}$), 3.75 (s, 2H, CH_2CN), 4.10 (q, J = 7Hz, 2H, $\underline{CH_2}CH_3$), 7.1 (m, 1H, NCH), 7.2 - 7.7 (m, 4H, aromatic).

7-Ethylindole-3-[1'-^{14}C]acetic acid, 5b.

The crude nitrile 3b (1.83 g 8.9 mmole) was refluxed in 6N sodium hydroxide solution (45 ml) for 6 hr. The reaction mixture was cooled to room temperature, extracted with ether (2 x 50 ml) and the extracts discarded. The aqueous phase was then acidified with cold concentrated hydrochloric acid and extracted with ether (3 x 50 ml). The ether extracts were combined, washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was dried further by azeotropic distillation with benzene (3 x 70 ml) and used without further purification. The crude acid weighed 2.22 g (100%).

A sample of the unlabelled acid when recrystallized from ether-hexane gave the following data: m.p. 158-159°; i.r. (nujol) 3380, 1695 cm^{-1}; n.m.r. (DMSO) δ 1.25 (t, J = 7.0 Hz, 3H, $CH_2\underline{CH_3}$), 2.8 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 3.59 (s, 2H, CH_2), 7.0 (m, 4H, aromatic), 10.0 (b.s., 1H, COOH), 10.6 (b.s., 1H, NH).

1-Ethylindole-3-[1'-^{14}C]acetic acid, 5c.

The crude nitrile 3c (4.34 g, 21.4 mmole) was hydrolyzed to the title compound in 70 ml refluxing 20% aqueous KOH as described above. The acid 5c (2.94 g) was obtained as a light brown oil that crystallized on standing.

Indole-3-[1'-^{14}C]ethanol, 6a.

Indole-3-[1'-^{14}C]acetic acid 5a (5 mCi, 565 mg, 3.23 mmole) dissolved in anhydrous THF was added to a stirred suspension of lithium aluminum hydride (LAH) (245 mg) in 10 ml THF at 0°. The reaction mixture was brought to room temperature and stirred for 3 hr. The mixture was cooled to 0° and the excess LAH was

destroyed by addition of wet THF. The inorganic salts were removed by filtration and washed with chloroform. The filtrate was washed with saturated saline solution, dried over Na_2SO_4 and evaporated to dryness. The tryptophol 6a (415 mg), obtained as an oil, was homogeneous by TLC (hexane-acetone 7:3) and spectrally identical to the material prepared by an alternative route (1, 2a).

7-Ethylindole-3-[1'-^{14}C]ethanol, 6b.

The procedure described above was also used to reduce the acid 5b (2.22 g, 10 mmole) with LAH (1.54 g, 40 mmole) in 40 ml anhydrous THF. The title compound (1.89 g) was obtained as an oil, homogeneous by TLC (hexane-acetone 7:3) and identical to the tryptophol prepared by an alternative route (2a).

1-Ethylindole-3-[1'-^{14}C]ethanol, 6c.

The same procedure was used to reduce the acid 5c (2.94 g, 15.1 mmole) with LAH (2.5 g, 66 mmole) in anhydrous THF (70 ml). The title compound (2.69 g), homogeneous by TLC (hexane-acetone 7:3), was identical to the tryptophol prepared by an alternative route (3a).

[3-^{14}C]-1-n-Propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (prodolic acid), 8a.

The tryptophol 6a (415 mg, 2.58 mmole), ethyl butyrylacetate (532 mg, 337 mmole), and benzene (50 ml) were refluxed for 10 min in a Dean-Stark apparatus. Boron trifluoride etherate (10 drops) was added dropwise to the boiling mixture and the refluxing was continued for 2 hr. After cooling, the benzene solution was washed with water, 5% sodium bicarbonate, water, dried over Na_2SO_4 and concentrated.

The resulting ester 7a (400 mg) was dissolved in 40 ml methanol and refluxed after addition of the antioxidant, 2,6-di-tert-butyl-4-methylphenol (BHT) (0.1 mg) and potassium hydroxide (250 mg) dissolved in 2 ml of water. Upon completion of the hydrolysis, as determined by TLC (hexane-ethylacetate 8:2), the methanolic solution was concentrated, the residue was dissolved in 20 ml water, cooled to 0°, acidified with 6N hydrochloric acid and extracted with benzene. The organic layer was dried over Na_2SO_4 and concentrated. The resulting solid was recrystallized from benzene; a trace of BHT was added to the benzene to inhibit hydroperoxide formation during the recrystallization.

[^{14}C]Prodolic acid (233 mg, specific activity 1.56 mCi/mmole), recrystallized to constant melting point (150-151°), was obtained in 26% overall yield. The compound was 99% radiochemically pure as determined by TLC-autoradiography (12) in two solvent systems, viz. methylcyclohexane-acetone-acetic acid 70:30:0.5, and benzene-ethanol-acetic acid 80:12:5.

[3-^{14}C]-9-Ethyl-1,3,4,9-tetrahydro-N,N,1-trimethylthiopyrano[3,4-b]indole-1-ethanamine (tandamine hydrochloride) 10.

To the thiosulfate 9b (1.80 g, 5.67 mmole) was added (1-N,N-dimethylamino)-butan-3-one (1.2 g) dissolved in 20 ml anhydrous toluene and BF_3-etherate (5 ml). The reaction mixture was stirred at room temperature for 18 hr, then quenched by the addition of 5% aqueous $NaHCO_3$ (20 ml) and extracted with chloroform. The organic extract was dried over Na_2SO_4, concentrated, dissolved in 50 ml ether and extracted with 10% aqueous HCl; the aqueous layer was separated, made alkaline with 10% aqueous NaOH and extracted with ether. The extract was dried over Na_2SO_4 and evaporated to give 320 mg of the crude amine 10. The amine was purified by preparative TLC (chloroform-methanol 9:1), converted to the hydrochloride salt with etheral HCl and recrystallized from methanol.

[^{14}C]Tandamine hydrochloride 10 (145 mg, specific activity 2.15 mCi/mmole) was obtained in 3% overall yield from the tryptophol 6c. The radiochemical purity was 99% as determined (12) by TLC-autoradiography in two different solvent systems, viz. chloroform-methanol 9:1 and benzene-acetone-triethylamine 6:13:1.

[1-^{14}C]-3-Phenylpropionic acid, 12.

The carbonation reaction was carried out on a vacuum line according to the general procedure described by Dauben et al. (13). 2-Phenylethyl magnesium bromide 11, was generated by careful addition of 2-phenylethylbromide (2.13 g, 11.5 mmole) to magnesium turnings (280 mg, 11.5 mmole) with ether as solvent. On completion of the reaction, the reagent was frozen with liquid nitrogen and the entire system including the CO_2-generator (a flask containing 50 mCi, 1.975 g or 10 mmole [^{14}C]$BaCO_3$ fitted with a dropping funnel containing 10 ml sulfuric acid) was evacuated to 0.4 mm of Hg.

After degassing the solution (by raising the temperature to -25° followed by cooling to -195° and repeating this 3 times) the vacuum system was disconnected from the pump and the temperature of the reaction mixture was brought to -25°. The sulfuric acid was then added dropwise to the [^{14}C]$BaCO_3$ to generate CO_2. Upon completion of the reaction between $BaCO_3$ and sulfuric acid, the temperature of the reaction mixture was again reduced to -195° to trap all the [^{14}C]CO_2 in the system. The flask was then disconnected from the system, the temperature raised to -25° and the solution was stirred for 45 min.

After releasing the vacuum, 10% HCl was added to the reaction mixture and extracted with ether. The ether fraction was then extracted with 10% aqueous NaOH which was acidified with concentrated HCl at 0° and reextracted with ether. The final ether extract was washed with saturated saline solution, dried over $MgSO_4$ and concentrated. [1-^{14}C]-3-Phenylpropionic acid 12 was obtained as a crystalline solid (1.297 g, 86%). In another experiment, an additional 0.546 g of the labelled acid 12 was prepared.

[1-^{14}C]Indan-1-one, 13a (7).

The [1-^{14}C]phenylpropionic acid 12 (1.85 g, 12.3 mmole) was transferred to a 15 ml plastic vial containing a magnetic stirrer. Hydrogen fluoride (10 ml) from a precooled cylinder was condensed into the vial. The vial was capped and the solution was stirred at room temperature for 20 hr. The cap was removed and most of the HF was blown off with a stream of nitrogen. The remainder was dissolved in ether and poured into ice-cold 10% aqueous NaOH. The alkaline solution was extracted with ether and the combined ether extracts were washed with water, saline, dried over $MgSO_4$ and concentrated. The indanone was obtained as a crystalline solid (1.12 g).

Unreacted acid was recovered by extraction of the acidified aqueous phase with ether and the condensation reaction was repeated giving more of ketone 13a. The final yield of [1-^{14}C]-1-indanone was 1.42 g (87%).

[1-^{14}C]-1-Indanol, 13b.

The [1-^{14}C]indan-1-one 13a (1.42 g, 10.7 mmole) was dissolved in methanol (25 ml) and cooled to 0°. Sodium borohydride (1.5 g) was added portion-wise and the solution was stirred at room temperature for 1 hr. The reaction

mixture was then cooled, diluted with 100 ml water and extracted with ether. The combined ether extracts were washed with water, dried over Na_2SO_4 and concentrated. The alcohol 13b was obtained as an oil (1.49 g) and was homogeneous as determined by TLC (chloroform): i.r. ($CHCl_3$) 3560, 3390 cm^{-1}.

[1-^{14}C]-Indene, 14a (9).

The [1-^{14}C]-indanol 13b (1.49 g, 10.7 mmole) was refluxed with stirring, for 1 hr in cyclohexane (50 ml) containing a suspension of 150 mg Amberlyst 15 (BDH Laboratory Reagents), a strong cation exchange resin (4). The reaction mixture was then cooled, filtered through celite, washed with water and concentrated. The resulting indene 14a (1.4 g) was homogeneous by TLC (benzene): i.r. ($CHCl_3$) no (OH) absorption; identical with indene reference spectrum.

Indene-3-[1'-^{14}C]ethanol, 14c.

The [1-^{14}C]indene 14a (1.4 g) was dissolved in 3 ml of dry toluene and added under dry nitrogen to a cold solution of ethylmagnesium bromide (5.2 ml of 3M solution in ether) in 7 ml of dry toluene. The ether was distilled off under reduced pressure and the reaction mixture was slowly brought to 95°, kept at this temperature for 15 min, then raised and maintained at 109°, with stirring, for 2 hr during which time a precipitate was formed. The reaction mixture was then cooled to -10° and ethylene oxide (1.1 g), dissolved in 4 ml anhydrous ether, was slowly added. The mixture was stirred at room temperature for 18 hr, cooled to 0° and quenched with a saturated ammonium sulfate solution (3.3 ml) followed by 9 ml of 10% sulfuric acid; the temperature was always kept below 10°. The aqueous phase was extracted with ether and the combined ether extracts were washed with water, dried over Na_2SO_4 and concentrated.

The product (2.0 g) consisted primarily of the indenethanol 14b [(n.m.r. ($CDCl_3$) δ 3.5 (m, 1H, =CCH), 6.6 (m, 2H, CH=CH)], which was isomerized to the title compound in the following manner. The crude product was refluxed in 8% aqueous methanolic KOH for 5.5 hr. The methanol solution was concentrated, diluted with water (50 ml) and extracted with ether. The combined ether extracts were washed with dilute aqueous HCl, dried over Na_2SO_4 and concentrated to give a pale brown oil (1.49 g). This was chromatographed on a silica gel column (100 g) using chloroform-methanol (95:5) as the eluant and the title compound 14c (600 mg)

was isolated: n.m.r. ($CDCl_3$) δ 3.3 (m, 2H, CH_2 indene), 6.30 (m, 1H, =CH).

[^{14}C]-1,3,4,9-Tetrahydro-N,N-1-trimethylindeno[2,1-c]pyran-1-ethylamine hydrochloride, (pirandamine hydrochloride) 15.

The purified indenethanol 14c was dissolved in 20 ml anhydrous toluene; 1-(N,N-dimethylamino)-butan-3-one (1.8 ml) and BF_3-etherate (10 ml) were then added and the solution was stirred at room temperature for 24 hr. The reaction was quenched by slow addition of 10% aqueous NaOH and extracted with ether. The combined ether phases was extracted with 10% aqueous HCl which, in turn, was washed with ether to remove all neutral material. The acidic aqueous phase was made alkaline with cold 10% aqueous NaOH and extracted with ether. The ether extract was dried over Na_2SO_4 and concentrated to give 510 mg of the crude amine 15.

The amine was purified by preparative TLC (chloroform-methanol 9:1) and converted to the hydrochloride salt with etheral HCl. After two recrystallizations from ethanol, [^{14}C]pirandamine hydrochloride 15 (170 mg, specific activity 4.70 mCi/mmole) was obtained in 5% overall yield from [^{14}C]$BaCO_3$. The radiochemical purity of the final product was 99% as determined (12) by TLC-autoradiography in two different solvent systems, viz. chloroform-methanol 87:13, and benzene-acetone-triethylamine 7:3:1.

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