SYNTHESIS OF [14-^{14}C]DEXCLAMOL HYDROCHLORIDE AND [14-^{14}C]BUTACLAMOL HYDROCHLORIDE

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SUMMARY

The synthesis of two [^{14}C]labelled compounds, dexclamol and butaclamol hydrochloride, having the octahydrobenzocycloheptapyridoisoquinoline structure is described. Both compounds were prepared by the same synthetic route starting from silver [^{14}C]-cyanide and were labelled in the 14-position. Butaclamol (specific activity 1.23 mCi/mmole) was obtained in 13% overall yield while dexclamol (specific activity 17.8 mCi/mmole), an optically active compound requiring resolution in its preparation, was obtained in 2% overall yield.

Key Words: [^{14}C]Butaclamol Hydrochloride, [^{14}C]Dexclamol Hydrochloride

INTRODUCTION

Dexclamol hydrochloride* (AY-24,169) 5c and butaclamol hydrochloride* (AY-23,028) 4 are two members of the novel benzocycloheptapyridoisoquinoline class of neuroleptic agents (1). The compounds differ in their alkyl substituent in the 3-position. In addition, butaclamol is a racemate and dexclamol is the (+)-enantiomer. For both compounds, the pharmacological activity resides solely in the (+)-enantiomer (2a, b).

The synthesis of the [^{14}C]labelled compounds, described herewith, is based on the previously described preparation of this class of compounds (1).

DISCUSSION

As shown below, the sequence of reactions starting from 5-chloro-10,11-dihydrobenzo[a,d]cycloheptene 1a to the pentacyclic ketone 3 was the same for both compounds. The label was introduced by the reaction of silver [^{14}C]cyanide with

*Nonproprietary names selected by the U.S. Adopted Names Council.

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The reaction of the Shiff base 2a with methylvinylketone in N,N-dimethylformamide-toluene gave the quaternary amine 2b which on treatment with aqueous sodium acetate cyclised to the ketone 3. The resulting ketone was a mixture of cis(4a, 13b) 3a and trans(4a, 13b) 3b isomers (7), of which the latter was the major and desired product. After separation by crystallization and chromatography of the mother liquor, the trans ketone 3b was obtained in 43% overall yield from silver [^{14}C]cyanide.

The reaction of the trans ketone 3b with the appropriate Grignard reagent gave either butaclamol 4 (with tert-butyl magnesium chloride) or the unresolved dexclamol 5a (with isopropyl magnesium chloride). As was previously suggested (1) and subsequently confirmed by crystallographic studies on butaclamol and dexclamol hydrochlorides (9), the addition of the Grignard reagent to the molecule, because of its unique sterochemistry, occurs exclusively equatorially to afford a tertiary carbinol in which the hydroxyl group is axial. Moderate yields of both 4 and 5a: 31 and 42% respectively, were obtained after chromatographic purification and recrystallization. [^{14}C]Butaclamol hydrochloride (specific activity 1.23 mCi/mmole) was obtained in 13% overall yield.

The final step in the preparation of [^{14}C]dexclamol hydrochloride was the resolution of the d,l-carbinol 5a. This was achieved by formation and recrystallization to constant optical rotation of the (+)-tartrate 5b. Conversion of this tartrate to the hydrochloride salt gave [^{14}C]dexclamol ·HCl (specific activity 17.8 mCi/mmole, $[\alpha]_{589}$ + 215°) in 2% overall yield from silver [^{14}C]cyanide.

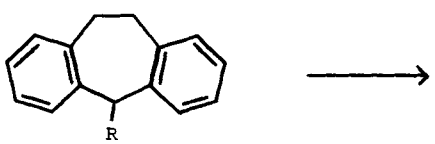
The radiochemical purity, as determined by thin layer chromatography-autoradiography in three different solvent systems, was higher than 99% for [^{14}C]butaclamol ·HCl and 98% for [^{14}C]dexclamol ·HCl. In the solid state, [^{14}C]-dexclamol ·HCl was found to undergo autoradiolysis. This decomposition was minimized when the compound was stored in methanol at -10°.

EXPERIMENTAL

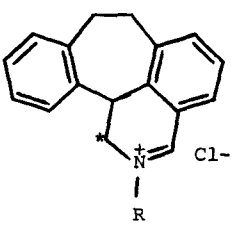
All the procedures were validated in preliminary experiments using unlabelled compounds. Except for the final products in the synthesis, the reported analytical data were obtained with unlabelled compounds. Where possible, the reactions in the labelled synthesis were monitored by thin layer chromatography (TLC)

the chloride 1a in refluxing benzene (3). Attempts to introduce the cyano group by reaction of the chloride 1a with sodium cyanide in dimethyl sulfoxide (4) or cuprous cyanide in refluxing chloroform (5) were unsuccessful.

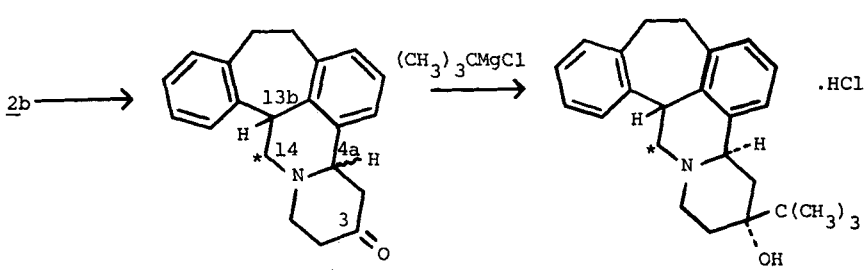
The nitrile 1b, obtained in 95% yield from silver cyanide, was reduced with lithium aluminum hydride-aluminum chloride to the amine hydrochloride 1c·HCl (6) in 78% yield. Formylation of the amine 1c, followed by reaction with polyphosphoric acid (PPA), gave the Shiff base 2a which was obtained in good yield when the reaction temperature was carefully maintained at 150°.



1a R = Cl
b R = *CN
c R = *CH_2NH_2
d R = *CH_2NHCHO

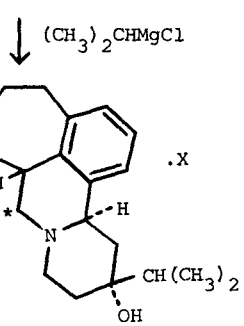


2a R = H
b R = $CH_2CH_2COCH_3$



3a 13b, 4a (cis)
b 13b, 4a (trans)

4



5a X = HCl (d, l mixture)
b X = (+)tartrate
c X = (+)HCl

using the appropriate unlabelled compound as a reference. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Radioactivity was measured on a Packard Tri-Carb 3375 liquid scintillation spectrometer. [^{14}C]Silver cyanide, 177.6 mCi, specific activity 17.18 mCi/mmole, was purchased from New England Nuclear, Boston.

5-[^{14}C]Cyano-10,11-dihydrobenzo[a,d]cycloheptene, 1b.

The [^{14}C]silver cyanide (1.383 g, 10.2 mmole) was placed in a 250 ml flask along with 125 ml anhydrous benzene and the chloride 1a (2.49 g, 10.9 mmole), and the resulting slurry was refluxed for 12 hr with vigorous stirring. After cooling, the reaction mixture was filtered through Celite and concentrated. Although part of the nitrile 1b crystallized out from ethanol, the material was not sufficiently pure; purification was ahcieved by column chromatography using silica gel (100 g) and benzene-hexane 70:30 as the eluting system. The nitrile 1b (2.14 g) was obtained as a white solid in 95% yield: m.p. 90-92°; i.r. ($CHCl_3$) 225 cm^{-1}; n.m.r. ($CDCl_3$) δ 5.5 (1H, s, CHCN).

10,11-Dihydrobenzo[a,d]cyclohepten-5-yl-[^{14}C]methylamine, 1c.

Aluminum chloride (1.45 g) was added to 50 ml anhydrous ether, cooled to -5° under dry nitrogen and lithium aluminum hydride (410 g) slowly added. The nitrile 1b (2.14 g, 9.77 mmole), dissolved 50 ml anhydrous ether, was then added to the solution. The ice bath was removed and the reaction mixture was refluxed for 2 hr. After cooling, the mixed hydride complex was destroyed with 50 ml 6N HCl and the ether was removed by distillation using a Dean-Stark separator. An additional 50 ml water was added to the residue and the solution was heated to reflux. Water was added until all the residue had dissolved. On cooling, a thick oily residue settled out. The aqueous solution was decanted, and on further cooling to room temperature gave the amine hydrochloride 1c·HCl as a white solid precipitate (1.45 g). The aqueous mother liquor was made alkaline with 40% NaOH and extracted with benzene. The combined benzene extract was washed with water, saturated saline, dried over anhydrous magnesium sulfate ($MgSO_4$) and concentrated. This gave an additional 460 mg of the amine 1c. The total yield for the reduction of the nitrile 1b was 1.69 g (78%): m.p. (amine hydrochloride 290-5°; i.r. ($CHCl_3$) 3340, 3160 cm^{-1} (NH); n.m.r. ($CDCl_3$) δ 1.3 (2H, s, NH_2); 3.2 (6H, m, CH_2), 4.0 (1H, m, C_5H).

N-Formyl-10,11-dihydrobenzo[a,d]cyclohepten-5-yl-[^{14}C]methylamine, 1d.

Formic acid (2.82 ml) was added dropwise under nitrogen to acetic anhydride (6.35 ml). The solution was heated to 50° for 2 hr then cooled to room temperature. The free amine 1c (1.69 g, 7.61 mmole) dissolved in 10 ml toluene was added dropwise so that the temperature did not exceed 30°. The reaction, after stirring for 2 hr at room temperature, was quenched by the addition of 25 ml water. The aqueous phase was separated and extracted several times with benzene. The combined organic phase was washed with water, 10% NaOH and water again, dried over $MgSO_4$ and concentrated. On cooling, the crude reaction product (1.83 g) crystallized. Careful recrystallization from benzene-petroleum ether 30-60° gave 1.35 g or 71% of the formamide 1d: m.p. 106-8°. The mother liquor was concentrated giving 352 mg of an oil which was treated separately in the next reaction.

[1-^{14}C]-1,7,8,12b-Tetrahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline hydrochloride, 2a.

The formamide 1d (1.35 g, 5.38 mmole) was added portion-wise to 35 g of polyphosphoric acid (PPA) heated to 130°. The reaction was carried out under an atmosphere of dry nitrogen with careful monitoring of the temperature. When the addition was completed, the reaction temperature was raised to 150° and maintained there for 3 hr. The reaction mixture was then cooled to 90° and water (60 ml) was added dropwise. After further cooking the resulting solid free Shiff base of 2a was filtered, washed with a minimum of water and air dired (0.898 g, 72%). An additional 388 mg (ca. 25%) of less pure free base of 2a was obtained from the reaction of the crude formamide and extraction of the aqueous mother liquor with benzene. The two batches were treated separately in the next step.

Both batches were converted to the hydrochloride 2a by addition of excess ethereal HCl to a benzene solution of the free Shiff base. Excess HCl gas was removed with nitrogen and the solvent was evaporated under vacuum.

2-(3-Oxobutyl-[1-^{14}C]-1,7,8,12b-tetrahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline, 2b.

The hydrochloride 2a (1.09 g, 4.02 mmole) was dissolved in 4 ml N,N-dimethylformamide (DMF)-toluene 1.5:2 and methylvinylketone (0.675 ml, 9.6 mmole) was added. The solution was heated on a steam bath until it started to turn dark.

The heating was continued for 2 hr at 95° in an oil bath. After cooling, 35 ml toluene was added and the reaction mixture was filtered. The quaternary amine 2b crystallized from the filtrate on cooling to 0°. The pure Shiff base gave 1.53 g, and the less pure material 0.319 g, of the quaternary amine 2b, for a combined yield of 95%.

(±)-(4a,13b-trans)[14-^{14}C]-1,2,4,4a,8,9,13b,14-Octahydro-1H-benzo[6,7]cyclohepta-[1,2,3-de]pyrido[2,1-a]isoquinolin-3-one, 3b.

The quaternary amine 2 (1.53 g, 4.5 mmole) was added portionwise to a solution of sodium acetate (585 mg) in 3.5 ml water and 40 ml toluene. The solution was stirred at room temperature for 45 min then at 45-55° for 45 min. The reaction mixture was then cooled, 15 ml water added, the organic layer was separated and washed with warm water. The combined organic fraction was dried over $MgSO_4$ and concentrated to give 1.29 g of crude ketone; 675 mg of the desired ketone 3b was obtained by recrystallization from toluene-hexane.

The mother liquor from this crystallization and the product from the cyclization of the impure quaternary amine gave 880 mg of crude product, a mixture of the cis- and trans-ketones (3a and b) by TLC (hexane-ethylacetate 8:2). This crude product was chromatographed on a column of silica gel (180 g) using hexane-ethyl acetate 8:2 as the eluant. The cis isomer of ketone 3a (120 mg) was eluted first, followed by 120 mg of a cis- and trans-mixture and finally 260 mg of the pure trans ketone 3b. The combined yield of the ketone 3b was 57%, and the overall yield from [^{14}C]silver cyanide was 43%.

(±)-(4a,13b-trans)[3(OH),13b(H)-trans]-[14-^{14}C]-2,3,4,4a,8,9,13b,14-Octahydro-3-tert-butyl-1H-benzo[6,7]cyclohepta 1,2,3-de pyrido[2,1-a]isoquinolin-3-ol hydrochloride, (butaclamol hydrochloride) 4.

Tert-butyl magnesium chloride was prepared by the addition of tert-butyl chloride (2.13 g, 22.5 mmole) to magnesium turnings (540 mg, 22.5 mmole) activated by iodine, using anhydrous tetrahydrofuran (THF) as solvent (30 ml). After stirring the reaction for 4 hr at room temperature, a portion of the THF was distilled off (ca 20 ml); 30 ml toluene was then added and the solution was cooled to -15°. The ketone 3b (1.89 g, 6.25 mmole, specific activity 1.2 mCi/mmole) was added portionwise so that the temperature did not exceed -15°. After the addition the temperature was maintained at -15° for 30 min, then slowly brought to room

temperature and kept there for 15 hr. Methanol (5 ml), followed by 15% ammonium sulfate (20 ml), was slowly added to quench the reaction. The solution was filtered through Celite, and the aqueous fraction was separated and extracted several times with benzene. The combined organic extract was washed with water until neutral, dried over $MgSO_4$ and concentrated. Methanolic HCl was added to an methanol solution of the reaction product and the resulting salt was filtered. Butaclamol hydrochloride (800 mg, sp. act. 1.23 mCi/mmole), after several recrystallizations from 5% aqueous methanol, was obtained in 32% yield.

The radiochemical purity of the compound was at least 99% as determined by TLC-autoradiography in three different solvent systems: A) benzene-methanol-ether-NH_4OH 80:0.5:20:1; B) benzene-methanol-NH_4OH 80:20:1; C) benzene-dioxane-ethanol-NH_4OH 50:40:5:5. After development, the TLC plates were exposed to Kodak RP/R14 medical X-ray film and the radioactive zone on each plate was located from the resulting autoradiogram. Each plate was scraped in 1 cm strips into counting vials and the silica gel, after treatment with 0.2 ml water and 0.2 ml 50% hydrofluoric acid, was counted in Aquasol (8).

(±)-(4a,13b-trans)[3(OH),13b(H)-trans] [14-^{14}C]-2,3,4a,8,9,13b,14-Octahydro-3-isopropyl-1H-benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolin-3-ol, 5a.

Isopropyl magnesium chloride was prepared by the addition of isopropyl chloride (890 mg, 11.2 mmole) to magnesium turnings (269 mg, 11.2 mmole) activated by iodine, using anhydrous ether as the solvent. After stirring the reaction for 4 hr at room temperature, the ether was evaporated off and replaced with anhydrous toluene. The ketone 3b (675 mg, 2.22 mmole), with a specific activity of 17.8 mCi/mmol) was added portionwise over a period of 15 min and the reaction allowed to stand overnight at room temperature. Methanol (10 ml), followed by 15% ammonium sulfate solution (10 ml), was slowly added to quench the reaction and the resulting solution was filtered through Celite. The aqueous layer was washed with water until neutral, dried over $MgSO_4$ and concentrated. The crude product was chromatographed on a column of basic alumina (10 g, activity II) alcohol (450 mg) eluted from the column was converted to the hydrochloride salt and recrystallized from methanol-ether to give 5a (269 mg) which was homogeneous by TLC (benzene-ether-methanol-NH_4OH 80:15:5:5). An additional 78 mg of the free

base of 5a was obtained by preparative TLC of the mother liquor from the recrystallization. The combined yield of the d,l-alcohol 5a was 42%.

(+)-(4a,13b-trans)[3(OH),13b(H)-trans]-[14-^{14}C]-2,3,4,4a,8,9,13b,14-Octahydro-3-isopropyl-1H-benzo-[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinoline-3-ol tartrate, 5b.

The solid hydrochloride salt 5a (269 mg) was combined with the free base (78 mg) in 10 ml water, made alkaline with conc. NH_4OH, and extracted several times with ether. The ether was dried over $MgSO_4$ and concentrated to give 306 mg (0.882 mmole) of the free base 5a. The base was first treated with l-tartaric acid (136 mg) and the resulting salt was crystallized from isopropanol.

The mother liquor from the above crystallization was concentrated and converted to the free base as described above. Recrystallized d-tartaric acid (136 mg) was then added to an isopropanol solution of the free base and the resulting tartrate salt 5b crystallized out. An additional 31 mg of the tartrate was obtained from the mother liquor. The total (+)-tartrate 5b (134 mg), was recrystallized from isopropanol-methanol to constant optical rotation (50.9 mg, $[\alpha]_{589} = +199^{\circ}$).

(+)(4a,13b-trans)[3(OH),13b(H)-trans]-[14-^{14}C]-2,3,4,4a,8,9,13b,14-Octahydro-3-isopropyl-1H-benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinoline-3-ol hydrochloride ([^{14}C]dexclamol hydrochloride) 5c.

The tartrate 5b (50.9 mg) was converted to the free base as described above. The free base, dissolved in ether and treated with excess ethereal HCl, gave 25 mg of the title compound after recrystallization from methanol-ether: specific activity 17.8 mCi/mmole, $[\alpha]_{589} = +221^{\circ}$, u.v. max ($CH_3OH$) 269 ($\varepsilon$ 760).

All the mother liquors of the recrystallizations including the tartrates were combined and 40 mg pure unlabelled dexclamol was added. This was converted to the free base and the d-tartrate was reformed and recrystallized to constant optical rotation (33 mg, $[\alpha]_{589} = +222$). The tartrate was then converted to the free base, treated with ethereal HCl and the resulting solid was recrystallized to give 16.0 mg of [^{14}C]dexclamol hydrochloride having $[\alpha]_{589} = +215^{\circ}$ and specific activity 12.7 mCi/mmole.

The radiochemical purity of the two batches was determined by TLC-autoradiography in three different solvent systems: A) benzene-ether-methanol-

NH_4OH 80:15:5:5; B) acetone-methylcyclohexane-triethylamine 20:75:5; C) benzene-ethyl acetate-methanol-NH_4OH 90:10:1.2. After development, the purity of the compound on the plate was determined as previously described for ^{14}C butaclamol ·HCl, 4.

The labelled compound in the crystalline form became coloured over a period of 24 hr even when stored at -10°. Since this does not occur with the unlabelled dexclamol ·HCl it was assumed that autoradiolysis was taking place. Indeed TLC-autoradiography indicated that the compound was decomposing. In methanol this decomposition was inhibited and the compound was stored in that solvent at 0°.

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