1-DEHYDROHEXESTROL. SYNTHESIS OF A PRECURSOR FOR THE PREPARATION OF TRITIUM-LABELED HEXESTROL DERIVATIVES AND ITS USE IN A NEW, CONVENIENT SYNTHESIS OF TRITIUM-LABELED o-AZIDO-HEXESTROL.

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SUMMARY

Erythro-1-dehydrohexestrol (4a), an analog of the non-steroidal estrogen *meso*-hexestrol containing a double bond in the side chain, has been synthesized as a general precursor for the preparation of tritium-labeled hexestrol derivatives. It can be functionalized further as needed, and upon catalytic hydrogenation with tritium gas, it furnishes the desired *erythro* or *meso* diastereomer of the hexestrol derivatives. Its use is exemplified in the synthesis of ^{3}H-o-azidohexestrol (9c) with high specific activity.

Key Words: Hexestrol, Estrogen, o-Azidohexestrol, Carrier-Free Tritium, Photoaffinity Label

INTRODUCTION

In the course of our studies on affinity labeling agents for estrogen receptors[1] and estrogen receptor-binding radiopharmaceuticals for imaging of breast tumors,[2,3] we have prepared numerous derivatives of the non-steroidal estrogen *meso*-hexestrol (1a). We have also prepared a number of these derivatives in tritium-labeled form, starting from tritium-labeled *meso*-hexestrol.[2,4] The classical Williams and Ronzio procedure[5] for tritium labeling of *meso*-hexestrol involves the catalytic hydrogenation of dienstrol (3). This method is capable of giving material with very high specific activity, but it does require the separation of the diastereomeric *meso*- and *dl*-hexestrols (1a, 2), that are produced in a 1:1 ratio. Separation on a large scale can be achieved by fractional

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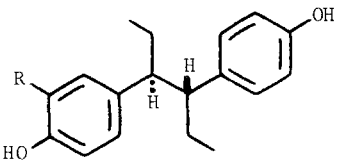
0362-4803/81/030407-12$01.00

Received September 5, 1979
Revised October 22, 1979

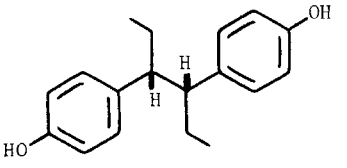
crystallization and on a small scale by chromatography.* Another disadvantage of this method is that for the preparation of hexestrol derivatives, all chemical manipulations must be done after introduction of the radiolabel; this can be a particular problem when chemical reactions on a symmetrical molecule such as hexestrol produce the desired monosubstituted derivative admixed with unreacted and disubstituted material.

Scheme 1

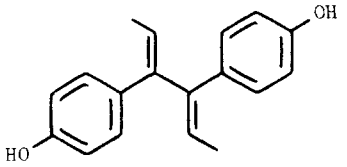


1a R=H *meso*-hexestrol

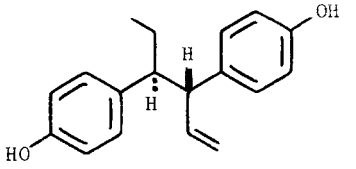
1b R=N_3 *erythro*-o-azidohexestrol



2 dl-hexestrol



3 dienstrol



4a *erythro*-1-dehydrohexestrol

In connection with other work on the synthesis of estrogen receptor-binding radiopharmaceuticals,[3b] we have prepared hexestrol derivatives that can be converted conveniently into *erythro*-1-dehydrohexestrol (4). This molecule is a single diastereomer which upon hydrogenation is converted cleanly into *meso*-hexestrol (1a). It is also a suitable intermediate for derivatization, so that in many cases several reactions and isomer separations can be done prior to the

*Incomplete catalytic hydrogenation of dienstrol can produce diethylstilbestrol (R. Goswami, unpublished). In this case, the properties of the product mixture can be misleading, as cis- and trans-diethylstilbestrol co-migrate on silica gel thin layer chromatography with *dl*- and *meso*-hexestrol, respectively, and diethylstilbestrol co-crystallizes with *meso*-hexestrol (R. Goswami, unpublished).[6]

introduction of the label. We present here a description of the synthesis of 1-dehydrohexestrol (4) and an example of its utility in the preparation of tritium-labeled o-azido-hexestrol (9c), a photosensitive estrogen that we have used as a photoaffinity label for the estrogen receptor from lamb uterus.[4b]

EXPERIMENTAL

Materials.

The synthesis of the bromide 7b has been described in our earlier publication.[3b] The following chemicals were obtained from Aldrich: diphenyl diselenide, 1-butanethiol, hexamethylphosphoramide (HMPA).

Methods.

Analytical thin layer chromatography was performed using 0.25 mm silica gel glass-backed plates containing F-254 indicator (Pre-Coated TLC Plates silica gel 60 F-254, Merck), and spots were visualized by 254 nm ultraviolet light. Preparative thin layer chromatography was carried out using 2 mm silica gel glass-backed plates with F-254 indicator (Pre-Coated PLC Plates silica gelF-254, Merck).

Tetrahydrofuran was dried by distillation from benzophenone ketyl in a recirculating still.

Melting points were determined on a Fischer-Johns apparatus and are uncorrected. Infrared spectra were determined as KBr pellets or neat films using a Beckman Model IR-12 Instrument. The data are presented in cm^{-1} and only the important diagnostic bands are reported. Proton magnetic resonance (^{1}H-NMR) spectra were taken on a Varian Associates Model EM-390 spectrometer. Chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). The ^{1}H-NMR data are presented in the form: (solvent in which spectra were taken), δ value of signal (peak multiplicity, integrated number of protons, coupling constant (if any), and assignment). Mass spectra were recorded from Varian MAT CH-5 and 731 (high resolution mass spectra) spectrometers, at

the ionization voltage expressed in the parentheses. Only the peaks of high relative intensity or of diagnostic importance are presented in the form: m/e (intensity relative to base peak).

Radiochemical purity was measured on plastic-backed silica gel thin layer plates (Eastman chromatogram Sheet No. 6061, without fluorescent indicator). The labeled material was spotted on top of unlabeled carrier. After development in the solvent system indicated the chromatogram was cut into ten strips, which were then placed in minivials with 5 mL of a xylene-base scintillation fluid containing 0.55% 2,5-diphenyloxazole, 0.01% p-bis[2-(5-phenyloxazolyl)] benzene, and 25% Triton X-114. Radioactivity was determined in a Nuclear Chicago Isocap 300 Liquid Scintillation Counter. Specific activity was determined by radioreceptor assay using lamb uterine cytosol, as described previously.[2a]

erythro-1-Phenylselenyl-3,4-bis(4-methoxyphenyl)-hexane (7c) - In a 50 mL three neck flask equipped with a reflux condenser, diphenyl diselenide (320 mg, 1.02 mmol, 1.2 equiv PhSeNa) and 20 mL of absolute ethanol were stirred at reflux under nitrogen atmosphere. Powdered sodium borohydride was added in small portions to the hot solution until the yellow solution turned colorless.[7] An additional 5 mg of $NaBH_4$ was added and the solution was stirred at reflux as a solution of methoxy bromide 7b (640 mg, 1.69 mmol in 10 mL of ethanol) was slowly added over a period of 10 min. The resulting mixture was stirred at room temperature for 2 h, followed by heating at 60° for 6 h. During this period, whenever the solution turned yellow a small additional amount of $NaBH_4$ was added to the reaction mixture. The mixture was cooled, and 50 mL of 1 N HCl solution added. A white solid that precipitated was collected by filtration. The filtrate contained mostly unreacted diphenyl diselenide, and the precipitate, obtained in 92% yield (705 mg), was the desired pure phenyl selenide 7c. ^1H NMR ($CDCl_3$) δ 0.50 (t, 3, J = 7 Hz, $-CH_2-\underline{CH}_3$), 1.15-1.40 (m, 2, $>CH-\underline{CH}_2-CH_3$), 1.50-1.70 (m,

2, >CH-C<u>H</u>$_2$-CH$_2$-), 2.10-2.80 (m, 4, -CH-$_2$C<u>H</u>$_2$-SePh and both methine H's), 3.70 (s, 6, ArOC<u>H</u>$_3$), 6.60-7.10 (m, 8, all Ar<u>H</u> except the Ar<u>H</u>'s adjacent to Se) and 7.00 (broad singlet, 5, Ar<u>H</u>'s in SePh).

erythro-3,4-bis (4-Methoxyphenyl)-1-hexene (4b) - Methoxy phenyl selenide 7c (350 mg, 0.77 mmol) was dissolved in 15 mL of dry THF, cooled to -15° (ice-acetone-dry ice), and a nitrogen atmosphere was introduced. m-Chloroperbenzoic acid (200 mg, 75% purity, 0.86 mmol, 1.13 equivalent) was added in one portion, and the resulting mixture was stirred for 20 min at -15°.[8] (It is important to not use a large excess of MCPBA in this reaction). The cold reaction mixture was then slowly pipetted into a stirred solution of 2 mL of diisopropylamine in 150 mL of refluxing hexane. After the addition was complete (∿ 15 min), the resulting mixture was refluxed for an additional 5 min. Twenty mL of 10% Na_2CO_3 solution was added, and the organic layer was separated, combined with two ether extracts of the aqueous layer, washed with 1 N HCl followed by saturated NaCl solution, and then dried (Na_2SO_4). Solvents were removed under reduced pressure, and the residue purified by preparative tlc (silica gel, 20% ether in hexane) to give 223 mg (quantitative yield) of methoxy vinyl compound (4b) as a white solid: mp 118°; ^{1}H NMR ($CDCl_3$) δ 0.60 (t, 3, J = 7 Hz, -CH$_2$-C<u>H</u>$_3$), 1.20-1.70 (m, 2, >CH-C<u>H</u>$_2$-CH$_3$), 2.50-2.80 (m, 1, J = 5 Hz, CH-C<u>H</u>-CH$_2$CH$_3$), 3.40 (t, 1, J = 9 Hz, >CH-C<u>H</u>-CH=CH$_2$), 3.80 (s, 6, ArOC<u>H</u>$_3$), 4.60-4.90 (m, 2, -CH=C<u>H</u>$_2$), 5.60-6.00 (m, 1, J = 8 Hz, CH-C<u>H</u>=CH$_2$) and 6.80-7.15 (m, AA'XX' pattern, 8, Ar<u>H</u>); Mass spectrum (70 ev) <u>m/e</u> (rel intensity) 296 (2.5, M^+), 150 (11), 149 (100), 146 (10.6), 122 (3), 121 (33.8), and 115 (5.7); <u>Anal</u>. Exact mass determination. Calcd for $C_{20}H_{24}O_2$ 296.1770. Found 296.1782.

erythro-3,4-bis(4-Hydroxy phenyl)-1-hexene (4a) - Freshly distilled 1-butanethiol (642 µL, 4 mmol) was added to 10 mL of HMPA (freshly distilled from CaH_2). This solution was cooled using an ice bath, a nitrogen atmosphere was introduced, and 2 mL of 2.2 N n-butyl lithium was slowly added. A solution of 280 mg (0.95 mmol) methoxy vinyl compound 4b in 2 mL of HMPA was slowly added, and the result-

ing yellow solution was heated (bath temp. 125-155°C) for 30 h. Hydrochloric acid (20 mL of 1 N) was added to the resulting yellow suspension, which was then extracted with 30 mL of a 4:1 EtOAc:THF mixture. The organic layer was washed (5N NaOH, water, sat. NaCl solution), dried (Na_2SO_4), and then evaporated under reduced pressure to give a residue that was purified by preparative tlc (silica gel, 2:1 CH_2Cl_2:EtOAc, 2 developments) furnishing 200 mg of 4a. An additional 50 mg of 4a was obtained by extraction of the alkaline aqueous fractions after acidification with conc. HCl, giving a combined yield of 250 mg of 4a (98%): mp 174°; ^{1}H NMR (acetone-d_6) δ 0.60 (t, 3, J = 7 Hz, $-CH_2-\underline{CH_3}$), 1.20-.160 (m, 2, $>CH-\underline{CH_2}-CH_3$), 2.50-2.90 (m, 1, $>CH-\underline{CH}-CH_2-CH_3$), 3.37 (t, 1, J = 9 Hz, $>CH-\underline{CH}-CH=CH_2$), 4.55 (doublet of doublets, 1, J = 6 Hz and 1.5 Hz, $-CH=C\langle^{H}_{\underline{H}}$), 4.70 (broad singlet, 1, $-CH=C\langle^{H}_{\underline{H}}$), 5.50-6.00 (m, 1, $CH-\underline{CH}=CH_2$), 6.80 (m, AA'XX' pattern, 8, Ar<u>H</u>) and 7.95 (broad, 2, ArO<u>H</u>); Mass spectrum (70 ev) m/e (rel intensity) 268 (2.7, M^+), 136 (11.2), 135 (100), 133 (17.7), and 107 (53.6).

erythro-3-(4-Hydroxy phenyl)-4-(3-nitro-4-hydroxy phenyl)-1-hexene (8a) - Cupric nitrate trihydrate (45 mg, 0.186 mmol, 0.5 equiv) was mixed with 0.5 mL of acetic anhydride; 3 mL of glacial acetic acid was added, the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 15 min. and then slowly added to a solution containing 100 mg (0.37 mmol) of diphenolic vinyl compound 4a in 5 mL of glacial acetic acid and 2 mL of dry THF at 0°. The resulting mixture was stirred at 0° under nitrogen atmosphere. After 13 min, 5 mL of water was added, and the reaction mixture was neutralized with $NaHCO_3$. The aqueous suspension was extracted twice with 50 mL of EtOAc:THF (5:1) mixture. The organic layers were combined, washed (twice with water and once with sat. NaCl solution), dried (Na_2SO_4) and evaporated under reduced pressure. Cyclohexane was added to the residue and then evaporated under reduced pressure to remove the last traces of acetic acid as an azeotrope. The yellow residue was subjected to preparative TLC (silica gel, 10% EtOAc in CH_2Cl_2, two developments), but the

separation between the mono- and dinitro products was only partial. This partially purified material was again subjected to preparative TLC (silica gel, $CHCl_3$, two developments, then 1% EtOH in $CHCl_3$). In this case the separation between mono- and dinitro derivatives was very good. A 34% yield (40 mg) of mixture of the two possible mononitro derivatives was obtained. No attempts were made to separate them, because upon reduction (tritiation) of the double bond, they produce the same compound: ^{1}H NMR ($CDCl_3$) δ 0.65 (two overlapping triplets, J = 7 Hz, $CH_2\underline{CH}_3$), 1.2-1.8 (m, 2H, CH-$\underline{CH}_2$-CH_3), 2.5-2.9 (m, 1H, CH-$\underline{CH}$-CH_2CH_3), 3.3-3.6 (m, 1H, CH-CH-CH=CH_2), 4.6-5.05 (m, 2H, CH=$\underline{CH}_2$), 5.05-6.15 (m, 1H, CH-$\underline{CH}$=CH_2), 6.7-7.4 (m, 7H, Ar$\underline{H}$), and 7.8 (m, 1H, Ar$\underline{H}$ *ortho* to $-NO_2$).

erythro-3-(4-Acetoxy phenyl)-4-(3-acetamido-4-acetoxy phenyl)-1-hexene (8c) - The mononitro derivative 8a (115 mg) was dissolved in 5 mL of acetone and 2 mL of 5 N NaOH and 3 mL of water were added. The red solution was then heated to reflux under nitrogen atmosphere, and 150 mg of sodium dithionite was added. The reaction mixture was refluxed an additional 30 min, and then 60 mg of sodium dithionite followed by 3 mL of 5 N NaOH were added. The mixture was refluxed for an additional 30 min; at which point it was almost colorless. The cooled reaction mixture was neutralized with glacial acetic acid, and the product, which precipitated as white solid, was extracted into a 4:1 EtOAc:THF mixture. The organic layer was then washed (water, sat. NaCl solution) dried and evaporated to give a pale yellow solid that was subjected to acetylation without further purification. Acetic anhydride (2 mL) was added, followed by 3 drops of conc. H_2SO_4. The reaction mixture warmed rapidly; it was stirred for 5 min and then poured into 10 mL of ice-water mixture. The product was extracted (2:1 EtOAc:THF) and was purified by preparative TLC (silica gel 5% EtOH in $CHCl_3$) to give 46.5 mg (31%) of a white solid that was recrystallized from methylene chloride-hexane: mp 154-156°. The nmr sample sample contains two possible monosubstituted isomers: ^{1}H NMR ($CDCl_3$) δ 0.65 (two overlapping triplets, 3, J = 7 Hz, $-CH_2-\underline{CH}_3$), 1.20-1.70

(m, 2, $\geq$CH-C$\underline{H}_2$-CH$_3$), 2.15 (two broad singlets, 3, ArNHCOC$\underline{H}_3$), 2.30 (overlapping singlets, 6, both Ar-OCOC$\underline{H}_3$), 2.50-2.90 (m, 1 $\geq$CH-C$\underline{H}$CH$_2$-CH$_3$), 3.30-3.60 (m, 1, CH-C$\underline{H}$-CH=CH$_2$), 4.60-5.05 (m, 2, -CH=C$\underline{H}_2$), 5.50-6.15 (m, 1, $\geq$CH-C$\underline{H}$=CH$_2$), 6.95 (m, 7, Ar$\underline{H}$) and two broad peaks at 7.80 and 8.70 (Ar-N$\underline{H}$COCH$_3$); Mass spec (70 eV) m/e (rel int) 409 (2.4, M^+), 367 (4), 349 (4), 234 (22), 192 (100).

Anal. Exact mass determination. Calcd for $C_{24}H_{27}NO_5$: 409.1882. Found: 409.1884.

[^3H] *erythro-3-(4-Acetoxy phenyl)-4-(3-acetamido-4-acetoxy phenyl)hexane* (9a) - (This procedure was carried out at New England Nuclear.) A solution of the vinylic precursor 8c (20 mg, 48.9 μmol) and 12 mg of 5% Pd/C in 5 mL of ethyl-acetate was stirred under an atmosphere of tritium gas for 2 h at room temperature. Labile tritium was removed in vacuo using ethanol as solvent. The catalyst was removed by filtration and the solvents were evaporated in vacuo. The residue was taken up in 10 mL of benzene:ethanol 10:1. Total radioactivity incorporated was 2.924 Ci, corresponding to an overall specific activity of 60 Ci per mmole. The radiochemical purity was determined by TLC (silica gel, 2% ethanol in chloroform) to be 83%.

[^3H]*3-Azidohexestrol* (9c) - A solution of [^{3}H]*erythro*-3-(4-acetoxyphenyl)-4-(3-acetamido-4-acetoxyphenyl)hexane (9a, 50 mCi, 0.35 mg, 0.9 nmol) in 0.4 mL of ethanol, 2 drops of water, and 2 drops of conc hydrochloric acid was refluxed for 30 h under a nitrogen atmosphere. The solution was cooled; ethanol was evaporated with a stream of nitrogen, and 1 mL of water, 0.5 mL of acetone, and one drop of hydrochloric acid were added. The aqueous solution was placed in an ice-water bath; a nitrogen atmosphere was re-introduced, and sodium nitrite (5 mg, 70 μmol) was added in small portions. The diazonium salt solution was stirred for 15 min at 0-5° and then decomposed by addition of a solution of sodium azide (100 mg, 1.5 mmol) in 1 mL of water. The aqueous solution was overlayed with 2 mL of diethyl ether and stirred an additional 1 h at 0-5°. The ether layer was drawn

off, and the aqueous layer was extracted with 2 mL of ether. The ether layers were combined, dried ($MgSO_4$) and evaporated with a stream of nitrogen to yield 15.1 mCi of crude azide. Purification by TLC (silica gel, diethyl ether, 2 developments) yielded 5.25 mCi (11% radiochemical yield) of [^{3}H]3-azidohexestrol (9c) with 96% radiochemical purity.

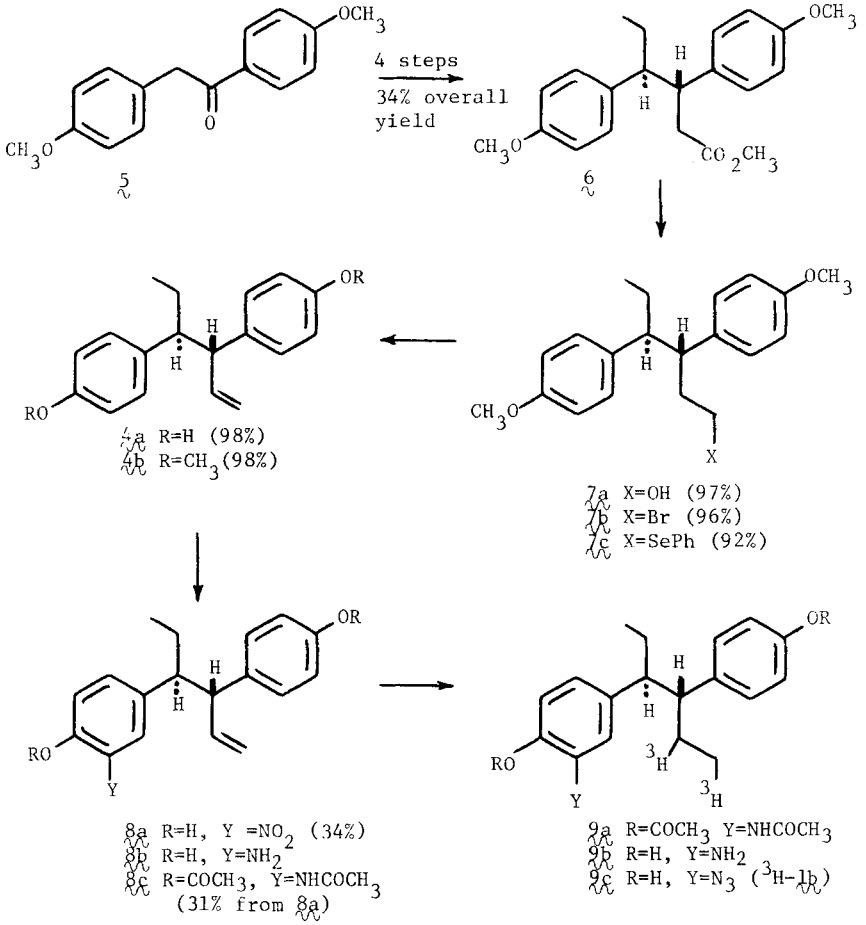
RESULTS AND DISCUSSION

Synthesis of 1-Dehydrohexestrol (4a)

The protected *erythro*-hexestrol carboxylic acid methyl ester 6 was prepared in 34% yield from deoxyanisoin (5) by a procedure that we have recently described.[3b] This ester was reduced to the alcohol 7a with lithium aluminum hydride and converted in quantitative yield to the corresponding bromide 7b by treatment with triphenylphosphine and carbon tetrabromide. This bromide proved to be quite resistant to base-induced elimination (unaffected by alcoholic potassium tert-butoxide or potassium hydroxide), but low yields (20%) of dehydrohexestrol dimethyl ether (4b) could be obtained using the bicyclic base 1,5-diazobicyclo[5.4.0]undec-5-ene(DBU). This olefin could be prepared much more efficiently by conversion of the bromide to the phenylselenide 7c,[7] which undergoes facile elimination upon treatment with one equivalent of m-chloroperoxybenzoic acid.[8]

Attempts to deprotect the phenolic functions in 4b using trimethylsilyl iodide[9] gave a mixture of products that lacked the characteristic terminal vinyl signals in ^{1}H-NMR, suggesting that the olefinic function was quite sensitive to the usual acid or Lewis acid reagents commonly employed in methyl ether cleavages. Demethylation proceeded cleanly, however, under basic conditions; heating 4b with lithium n-butylmercaptide in hexamethyl phosphoramide in an oxygen-free atmosphere[10] gave the phenolic vinyl compound 4a in high yield. Catalytic hydrogenation of 1-dehydrohexestrol over palladium on charcoal gave a quantitative yield of *meso*-hexestrol.

Scheme 2



Synthesis of ^{3}H-o-azidohexestrol (9c)

Our previous preparation of ^{3}H-o-azidohexestrol involved three reactions on ^{3}H-hexestrol:[4a] nitration (followed by careful chromatographic separation of unreacted, mononitro and dinitro material), reduction to the amine, and finally diazotization followed by trapping of the diazonium ion with azide ion (done in one pot). Difficulties were encountered on a tracer scale in controlling the extent of nitration so as to maximize the fraction of mononitro product produced,

in separating the three products from the nitration reaction, and in handling the amino compound under basic conditions where it is sensitive to oxidation.

These difficulties were avoided starting with 1-dehydrohexestrol (4a); since this compound is nitrated prior to the introduction of the label, this reaction can be done on a macroscopic scale and thus can easily be controlled to produce the mononitro product 8a in a 34% yield. (Mononitro-dehydrohexestrol is actually a mixture of isomers in terms of which side chain bears the double bond; since these isomers are not separable chromatographically, and since the isomerism disappears when the double bond is saturated, this isomerism is of no concern.) The nitro compound (8a) was reduced with dithionite to the amino compound (8b) which was converted to the triacetyl derivative (8c) with acetic anhydride and sulfuric acid. Acetylation protects the aminophenol (8b) from oxidative degradation.

A portion of acetamidodehydrohexestrol diacetate (8c) was subjected to catalytic reduction over palladium on carbon using carrier-free tritium gas (reaction done at New England Nuclear). The crude hydrogenation product (9a) showed an overall specific activity of 60 Ci per mmole and a radiochemical purity of 83%. It was used without further purification.

The final conversions could be done in one reaction flask. Hydrolysis of the triacetyl compound 9a to aminohexestrol (9b) was accomplished by refluxing with hydrochloric acid in ethanol-water solution. Diazotization followed by the addition of azide ion gave 9c as a crude product in 30% yield; purification by thin layer chromatography produced ^{3}H-o-azidohexestrol 9c (in 11% overall yield from 9a) with a radiochemical purity of 96%. The specific activity of this material, determined by radioreceptor assay,[2a] was 48 Ci per mmole.

This method for the synthesis of ^{3}H-o-azidohexestrol represents a substantial improvement over the sequence previously employed, in that the majority of reactions and separations are done prior to introduction of the tritium label,

the post labeling procedures involving only two reactions (done in one pot) and a single chromatographic purification. Thus, *erythro*-1-dehydrohexestrol is a versatile precursor that should find utility in the preparation of a variety of tritium-labeled derivatives of the non-steroidal estrogen hexestrol.

ACKNOWLEDGMENT

This research was supported by grants from the National Institutes of Health (AM 15556 and CA 18119) and from the American Cancer Society (BA-223). J.A.K. is a Camille and Henry Dreyfus Teacher Scholar.

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