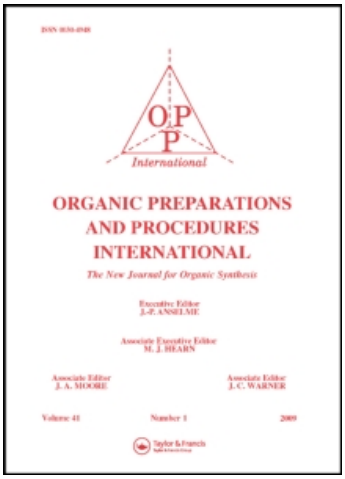

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EFFICIENT SYNTHESIS OF DL-THYROXINE-p-HYDROXYPHENYL ETHER

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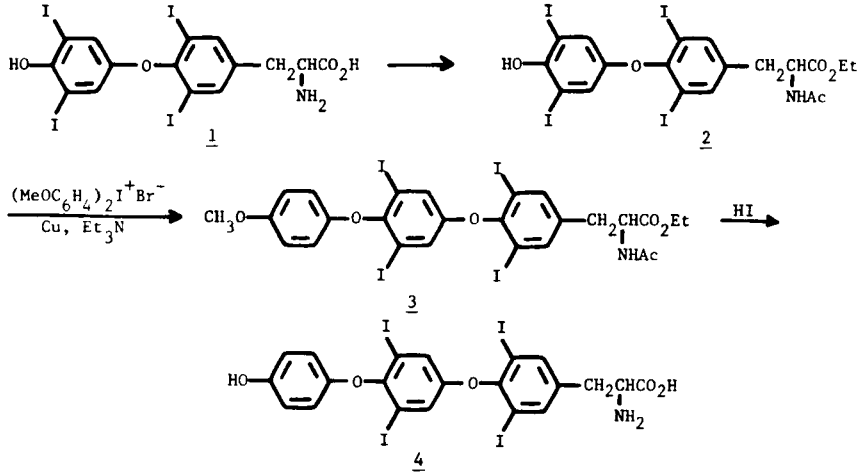
Several authors have described the feasibility of analyzing liothyronine sodium, levothyroxine sodium and liotrix tablets using reversed-phase HPLC procedures.[1-3] However, a problem of this approach has been the lack of suitable internal standards for the analysis of thyroidal amino acids. On the basis of the structure/retention time correlations observed by Hearn and co-workers[4] for the reversed-phase HPLC analysis of pure iodoamino acids, DL-thyroxine-p-hydroxyphenyl ether (4) was considered a possible candidate for use as an internal standard.

The original synthesis of DL-thyroxine-p-hydroxyphenyl ether (4) was reported by Bovarnick and co-workers.[5] The major drawback to the synthesis was that the overall yield was less than 1%. Other drawbacks included the length of the synthesis, the use of hazardous materials such as benzene and asbestos, and the involvement of at least one intermediate which had been reported to be extremely irritating.[6] Since the original synthesis, newer synthetic routes to thyroxine and other thyronine analogs using diaryliodonium salts have been reported.[7-10] Therefore, the more efficient and less hazardous route shown was used to prepare DL-thyroxine-p-hydroxyphenyl ether (4).

Commercially available DL-thyroxine (1) was converted to DL-thyroxine methyl ester hydrochloride and then to DL-thyroxine methyl ester using the procedures described by Ashley and Harington.[11] An attempt to acetylate

the methyl ester using one equivalent of acetyl chloride in the presence of triethylamine[12] resulted in an incomplete reaction. The use of three equivalents of acetyl chloride and triethylamine afforded O,N-diacetyl-DL-thyroxine methyl ester.



Attempts to selectively cleave the O-acetyl group with 2N NH_4OH or 2N Na_2CO_3 to provide N-acetyl-DL-thyroxine methyl ester failed. The use of 2N NaOH converted the O,N-diacetyl-DL-thyroxine methyl ester to N-acetyl-DL-thyroxine as reported by Ashley and Harington.[13] The crude N-acetyl-DL-thyroxine was esterified with ethanol in the presence of p-toluenesulfonic acid to give N-acetyl-DL-thyroxine ethyl ester (2) in 92% overall crude yield from DL-thyroxine (1).

Treatment of N-acetyl-DL-thyroxine ethyl ester (2) with 4,4'-dimethoxydiphenyliodonium bromide[8,14] in methanol with copper and triethylamine[15] gave N-acetyl-DL-thyroxine-p-methoxyphenyl ether ethyl ester (3) in 55% yield after column chromatography and recrystallization. This intermediate was characterized by melting point, NMR, IR, and elemental analysis. Deprotection of the N-acetyl-DL-thyroxine-p-methoxyphenyl ether ethyl ester (3) was carried out using 57% hydriodic acid in glacial acetic acid at 130°[3] to give crude DL-thyroxine-p-hydroxyphenyl ether (4) in 83% yield.

Purification using a slightly modified literature procedure[5] gave pure DL-thyroxine-p-hydroxyphenyl ether (4) in 72% yield.

In summary a new seven-step synthesis of DL-thyroxine-p-hydroxyphenyl ether (4) from DL-thyroxine (1) was developed. The key step of the new synthesis was the reaction of N-acetyl-DL-thyroxine ethyl ester (2) with 4,4'-dimethoxydiphenyliodonium bromide to form N-acetyl-DL-thyroxine-p-methoxyphenyl ether ethyl ester (3). The overall yield from DL-thyroxine was 36%, a considerable improvement over the less than 1% yield previously reported.[5]

EXPERIMENTAL SECTION

Melting points were taken in capillary tubes using either a Thomas Hoover or a Büchi model 510 apparatus. UV spectra were recorded on a Cary model 14 spectrometer, and IR spectra were obtained on a Perkin-Elmer model 467 grating spectrometer. ^{1}H-NMR spectra were run on either a Varian EM-360 spectrometer or a Bruker WM-250 high resolution spectrometer. All ^{1}H-NMR chemical shifts are reported in ppm downfield from TMS. Elemental analyses were performed by Micro-Tech Laboratories Inc., Skokie, IL, and by Galbraith Laboratories, Inc., Knoxville, TN. All operations on compounds containing iodine were carried out in glassware wrapped with foil to protect the samples from light. TLC analyses were routinely carried out using commercially available silica gel plates (E. Merck). The following solvent systems were used: system A - EtOAc:MeOH:2N NH_4OH (100:40:60, top layer); system B - $CHCl_3$:$(CH_3)_2CO$ (9:1); system C - n-BuOH:i-PrOH:H_2O:2N HOAc (50:20:20:5); system D - n-PrOH:$(CH_3)_2CO$:HOAc:5% NH_4OH:H_2O (9:3:2:2:4). Spots were visualized with I_2, with phosphomolybdic acid spray followed by $Ce(SO_4)_2$ spray, or with ninhydrin spray.

DL-Thyroxine Methyl Ester Hydrochloride.- A stirred suspension of DL-thyroxine (3.00 g, 3.86 mmoles) in MeOH (30 ml) was bubbled with HCl gas for 30 min then cooled to room temperature. The suspension was again bubbled with HCl gas for 30 min. Afterwards, the cooled mixture was evaporated to dryness, and the solid was vacuum dried to give 3.17 g (99%) of DL-thyroxine methyl ester hydrochloride as an off-white solid, mp. 219-220° (dec.), lit.[11] 221° (dec.); TLC (system A) single spot, R_f 0.49.

DL-Thyroxine Methyl Ester.- The crude DL-thyroxine methyl ester hydrochloride (3.17 g, 3.83 mmoles) was suspended in 50% EtOH/H_2O (240 ml) and 2N NaOH (1.92 ml, 3.84 mmoles) was added. The reaction mixture was stirred

20 hrs at room temperature, then stored at -20° overnight. The solid was collected, washed with EtOH and vacuum dried to give 2.94 g (97%) of DL-thyroxine methyl ester as a white powdery solid, mp. 152-154° (dec.), lit.[11] 156°; TLC (system A) single spot, R_f 0.51.

O,N-Diacetyl-DL-thyroxine Methyl Ester.- The crude DL-thyroxine methyl ester (2.84 g, 3.59 mmoles) was suspended in dry EtOAc (240 ml), and the flask was immersed in an oil bath at 50°. To the stirred suspension was added triethylamine (0.726 g, 7.17 mmoles) followed by a solution of acetyl chloride (0.563 g, 7.17 mmoles) in EtOAc (148 ml). The resultant mixture was stirred at 50° for 6 1/2 hrs and then cooled to room temperature overnight. Subsequent TLC analysis (system A) showed incomplete reaction. Consequently, additional triethylamine (0.368 g, 3.64 mmoles) and acetyl chloride (0.281 g, 3.58 mmoles) were added, and the reaction mixture was stirred at room temperature for 72 hrs, after which TLC showed complete reaction. The triethylamine hydrochloride was separated by filtration and washed with EtOAc. The filtrate and washings were stripped to give 3.25 g (103.5%) of O,N-diacetyl-DL-thyroxine methyl ester as an off-white, smelly solid, mp. 208-210°; TLC (system B) major spot, R_f 0.53.

^{1}H-NMR ($CDCl_3$): δ 2.05 (3H, broad s, $NHCOC\underline{H}_3$), 2.39 (3H, s, $ArOCOC\underline{H}_3$), 3.06 (2H, dd, $ArC\underline{H}_2CH$), 3.77 (3H, s, $CO_2C\underline{H}_3$), 4.84 (1H, ABq, $ArCH_2C\underline{H}$), 6.10 and 6.13 (1H, two s, $N\underline{H}COCH_3$), 7.18 and 7.63 (2H each, two s, $Ar\underline{H}$); IR (CH_2Cl_2) 3440, 1775, 1745, 1685, 1170 cm^{-1}.

Recrystallization of an analytical sample (0.25 g) from MeOH afforded 0.14 g of off-white crystals, mp. 220-222° (dec.).

Anal. Calcd. for $C_{20}H_{17}I_4NO_6$: C, 27.46; H, 1.96; N, 1.60.

Found: C, 27.32; H, 1.99; N, 1.63.

N-Acetyl-DL-thyroxine.- To a suspension of crude O,N-diacetyl-DL-thyroxine methyl ester (3.00 g, 3.43 mmoles) in absolute EtOH (60 ml) was added 2N NaOH (6.0 ml, 12.0 mmoles), and the mixture was stirred at room temperature

for 4 hrs. To the yellow solution was added 1N HCl (12.0 ml, 12.0 mmoles), causing a solid to precipitate. The mixture was evaporated to dryness and the solid vacuum dried to give 3.66 g (130%) of N-acetyl-DL-thyroxine as an off-white solid; TLC (system C) single spot, R_f 0.61. The excessive weight was due to contamination with inorganic salts. Precipitation of a sample from $HOAc/H_2O$ afforded a coarse white powder, mp. 211-214° (dec.), lit.[13] 210-215° (dec.); IR (KBr) 1722, 1640, 1586, 1530, 1452, 1433 cm^{-1}; TLC (system C) single spot, R_f 0.61.

N-Acetyl-DL-thyroxine Ethyl Ester (2).- To a suspension of crude N-acetyl-DL-thyroxine (3.41 g) in absolute EtOH (400 ml) was added p-toluenesulfonic acid monohydrate (0.48 g), and the mixture was refluxed under a Dean Stark trap for 21 hrs. The reaction was cooled and the solid removed by filtration. The yellow filtrate was evaporated to obtain a pale yellow solid. The solid was suspended in $CHCl_3$ (500 ml), and the suspension was washed with saturated $NaHCO_3$ (2 x 400 ml), 0.1N HCl (2 x 400 ml), and saturated NaCl (2 x 400 ml). The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to give 2.60 g of (2) as a yellow solid, mp. 187-189° (dec.); TLC (system A) major spot, R_f 0.78, and two slower moving trace impurities (R_f 0.66 and R_f 0.48). When corrected for a small amount of N-acetyl-DL-thyroxine saved back, the overall yield from O,N-diacetyl-DL-thyroxine methyl ester was 96%.

^{1}H-NMR ($CDCl_3$): δ 1.29 (3H, t, $CH_2\underline{CH_3}$), 2.06 (3H, s, $NHCO\underline{CH_3}$), 3.06 (2H, d, $Ar\underline{CH_2}CH$), 4.20 (2H, m, $\underline{CH_2}CH_3$), 4.80 (1H, ABq, $ArCH_2\underline{CH}$), 6.06 and 6.09 (1H, two s, $\underline{NH}COCH_3$), 7.08 and 7.61 (2H each, two s, $Ar\underline{H}$); IR (CH_2Cl_2) 3500, 3440, 1740, 1680 cm^{-1}.

Recrystallization of an analytical sample (0.11 g) from $EtOH/H_2O$ afforded 0.09 g of an off-white powdery solid, mp. 187-189° (dec.).

Anal. Calcd for $C_{19}H_{17}I_4NO_5$: C, 26.94; H, 2.02; I, 59.93; N, 1.65.
Found: C, 26.93; H, 1.89; I, 60.20; N, 1.58.

N-Acetyl-DL-thyroxine-p-methoxyphenyl Ether Ethyl Ester (3).- To a solution of N-acetyl-DL-thyroxine ethyl ester (2.35 g, 2.77 mmoles) in MeOH (275 ml) was added 4,4'-dimethoxydiphenyliodonium bromide[8] (2.34 g, 5.56 mmoles), Et_3N (0.57 g, 5.63 mmoles), and Cu powder (0.46 g). The mixture was stoppered and stirred at room temperature for 23 hrs. Afterwards, the mixture was filtered through a filter pad, and the pad washed with MeOH. The combined filtrate and washings were evaporated to a brown solid (4.35 g) which was redissolved in EtOAc (500 ml). The solution was washed with saturated $NaHCO_3$ (2 x 250 ml), 0.1N HCl (2 x 250 ml), and saturated NaCl (2 x 250 ml). The EtOAc layer was dried (Na_2SO_4), filtered and evaporated to give a tan solid (3.35 g). The solid was chromatographed on silica gel (670 g) using hexanes/$CHCl_3$ (1:3) and collecting 20 ml fractions. The fractions were monitored by TLC (system B), and similar fractions were combined and evaporated. The chromatography yielded two fractions totaling 1.73 g (66%) of crude (3) as an off-white solid.

Recrystallization of the first fraction (0.34 g, from tubes 430-449) from EtOAc/hexanes afforded 0.25 g (10%) of (3) as a white powdery solid, mp. 158-160°; TLC (system B) major spot, R_f 0.58, and a single trace impurity, R_f 0.64. Recrystallization of the second fraction (1.39 g, from tubes 450-520) from EtOAc/hexanes afforded 1.19 g (45%) of (3) as a white powdery solid, mp. 168-170°; TLC (system B) single spot, R_f 0.58. An analytical sample recrystallized from EtOAc/hexanes and vacuum dried at 60° for 20 hrs had mp. 168-174°.

^{1}H-NMR ($CDCl_3$): δ 1.29 (3H, t, $CH_2\underline{CH}_3$), 2.06 (3H, s, $NHCOC\underline{H}_3$), 3.07 (2H, d, $ArC\underline{H}_2CH$), 3.77 (3H, s, $OC\underline{H}_3$), 4.22 (2H, m, $C\underline{H}_2CH_3$), 4.80 (1H, ABq, $ArCH_2C\underline{H}$), 6.06 and 6.09 (1H, two s, $N\underline{H}COCH_3$), 6.77 (4H, ABq, $Ar\underline{H}$), 7.23 and 7.63 (2H each, two s, $Ar\underline{H}$); IR (CH_2Cl_2) 3430, 1740, 1680 cm^{-1}.

Anal. Calcd. for $C_{26}H_{23}I_4NO_6$: C, 32.77; H, 2.43; I, 53.26; N, 1.47.
Found: C, 32.42; H, 2.47; I, 53.28; N, 1.33.

DL-Thyroxine-p-hydroxyphenyl Ether (4).- A suspension of N-acetyl-DL-thyroxine-p-methoxyphenyl ether ethyl ester (1.00 g, 1.05 mmoles) in 57% HI (9 ml) and glacial HOAc (12 ml) was immersed in a wax bath at 130° and stirred for 4 hrs. Afterwards, the reaction mixture was cooled to room temperature and then refrigerated overnight. The precipitate was collected, washed with H_2O, and dried to give 0.758 g of (4) as an off-white, fluffy solid; mp. 234-237° (dec.).

The crude product (0.756 g) was suspended in a boiling mixture of 95% EtOH (100 ml) and H_2O (30 ml). The suspension was treated with 2N NaOH, added dropwise, until the solid dissolved. The pH was adjusted to 6 by dropwise addition of HOAc. The hot solution was removed from the heat (whereupon a solid began to precipitate), cooled slowly to room temperature, then cooled at -20° for 4 hrs. The precipitate was collected, yielding 0.682 g of (4) as a white fluffy solid, mp. 234-237° (dec.), lit.[5] 267-268° (dec.). After vacuum drying at 85° overnight, the solid weighed 0.658 g (71%), mp. 239-242° (dec.); TLC (system D) single spot, R_f 0.80. A sample immersed in an oil bath preheated to 245° had mp. 248-250° (dec.), lit.[5] 267-268° (dec.).

UV (2% NaOH/MeOH) λ_{max} (ε) 225 (62,000), 240 (sh) (41,600), 301 (10,000) mμ; IR (KBr) 1615, 1575, 1500, 1422 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 6.59 (4H, ABq, ArH), 7.29 and 7.82 (2H each, two s, ArH). The aliphatic proton signals were obscured by a H_2O signal.

Anal. Calcd for $C_{21}H_{15}I_4NO_5 \cdot 3/4\ H_2O$: C, 28.58; H, 1.88; I, 57.52; N, 1.59.
Found: C, 28.23; H, 1.73; I, 58.17; N, 1.47.

A sample vacuum dried at 100° for 10 hrs and redried at 100° just prior to analysis was analyzed.

Anal. Calcd. for $C_{21}H_{15}I_4NO_5 \cdot 1/4\ H_2O$: C, 28.88; H, 1.79; N, 1.60.
Found: C, 28.60; H, 1.75; N, 1.57.

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