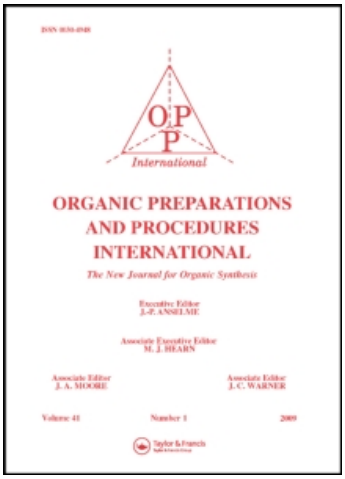

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SYNTHESIS OF THREE NEW ANALOGS OF DL-THYROXINE

George A. Brine[a]; Karl G. Boldt[a]; Michael L. Coleman[a]
[a] Chemistry and Life Sciences Unit, Research Triangle Institute, Research Triangle Park, NC

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SYNTHESIS OF THREE NEW ANALOGS OF DL-THYROXINE

George A. Brine,* Karl G. Boldt and Michael L. Coleman

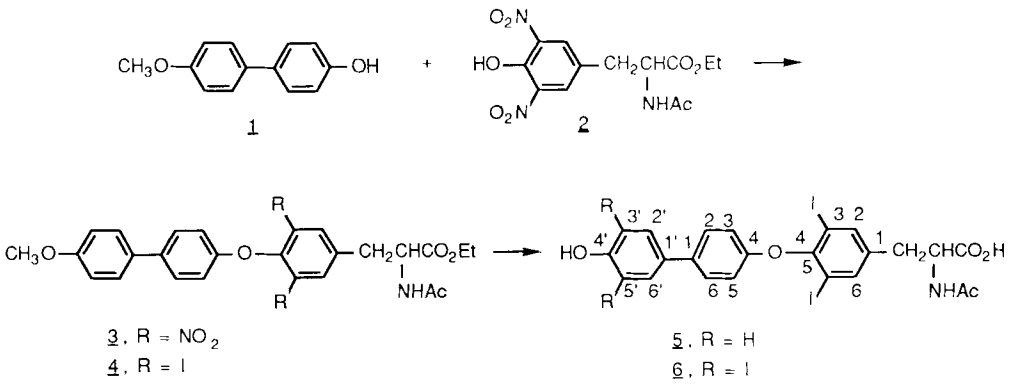
Chemistry and Life Sciences Unit
Research Triangle Institute
Research Triangle Park, NC 27709

Previously we described the evaluation of seven DL-thyroxine analogs as potential internal standards for the reversed-phase HPLC analysis of thyroidal amino acids.[1] Three of these analogs, 3,5-diiodo-4-(4'-hydroxy-4-biphenoxy)-DL-phenylalanine (5), 3,5-diiodo-4-(3',5'-diiodo-4'-hydroxy-4-biphenoxy)-DL-phenylalanine (6), and 3',5'-diiodo-3,5-diisopropyl-DL-thyronine (9), were reported for the first time. We now wish to present the details for the preparation of these three new analogs of DL-thyroxine.

Condensation of 4-hydroxy-4'-methoxybiphenyl (1)[2] with the pyridinium salt derived from N-acetyl-3,5-dinitro-DL-tyrosine ethyl ester (2)[3] using the procedure of Meltzer and co-workers[4] afforded N-acetyl-3,5-dinitro-4-(4'-methoxy-4-biphenoxy)-DL-phenylalanine ethyl ester (3) (cf. Scheme 1). Subsequent reduction, tetrazotization and iodination yielded N-acetyl-3,5-diiodo-4-(4'-methoxy-4-biphenoxy)-DL-phenylalanine ethyl ester (4). Acid cleavage of the protecting groups gave 3,5-diiodo-4-(4'-hydroxy-4-biphenoxy)-DL-phenylalanine (5). Iodination of 5 provided 3,5-diiodo-4-(3',5'-diiodo-4'-hydroxy-4-biphenoxy)-DL-phenylalanine (6). The overall yield of 6 from 2 was 22%.

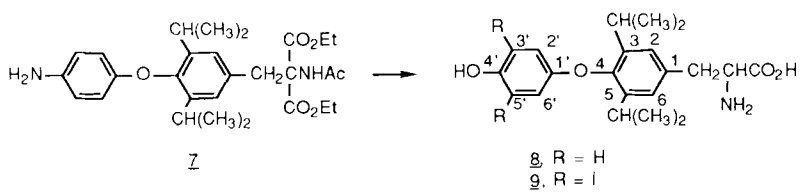
Although 3,5-diisopropyl-DL-thyronine (8),[5] 3,5-diisopropyl-3'-iodo-DL-thyronine[5,6] and 3,5-diiodo-3',5'-diisopropyl-DL-thyronine[7] are known.

Scheme 1



3', 5'-diiodo-3,5-diisopropyl-DL-thyronine (9) is unknown.[8] Our synthesis of 9 involved the intermediacy of diethyl 4-(4'-aminophenoxy)-3,5-diisopropylbenzylacetamidomalonate (7), which we prepared in 29% overall yield using reported procedures.[5,9] Due to the susceptibility of 7 to oxidative decomposition, we found it advantageous to use the crude compound directly in the next reaction. Subsequent diazotization and diazonium salt decomposition in a refluxing mixture of sulfuric and acetic acids[5] provided 3,5-diisopropyl-DL-thyronine (8) (cf. Scheme 2). Iodination of 8 gave 3',5'-diiodo-3,5-diisopropyl-DL-thyronine (9). The yield of 9 from 7 was 5%.

Scheme 2



In our hands the conversion of 7 to 8 invariably yielded a multicomponent mixture from which product isolation was not possible using repeated isoelectric precipitations as reported.[5,10] We found that the

major impurities were easily removed by column chromatography on silica gel. Subjection of the recovered sample to a combination of isoelectric precipitation/charcoal treatment followed by recrystallization provided analytically pure 3,5-diisopropyl-DL-thyronine (8).

EXPERIMENTAL SECTION

Melting points were taken in capillary tubes using a Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 467 grating spectrometer, and ^1H NMR spectra were obtained on a Bruker WM-250 high resolution spectrometer. All ^1H NMR chemical shifts are reported in ppm downfield from TMS. Elemental analyses were performed 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 analytical silica gel plates (E. Merck). The following solvent systems were used: system A - $CHCl_3$:$(CH_3)_2CO$ (9:1); system B - n-BuOH:HOAc: H_2O (4:1:1); system C - $CHCl_3$:MeOH:HOAc (18:6:1). Spots were visualized with phosphomolybdic acid spray followed by $Ce(SO_4)_2$ spray, or with ninhydrin spray.

4-Hydroxy-4'-methoxybiphenyl (1).- The title compound was prepared in 51% yield from commercially available p,p'-biphenol using the literature[2] procedure.

N-Acetyl-3,5-dinitro-DL-tyrosine Ethyl Ester (2).- The title compound was prepared in 24% yield by a modification of the reported[3] sequence. Thus, commercially available DL-tyrosine was subjected to nitration (HNO_3, H_2SO_4)[3], esterification (EtOH, benzene, HCl gas)[11] and N-acetylation (acetyl chloride, triethylamine, EtOAc)[12]. The desired product was isolated by column chromatography [silica gel, $CHCl_3$:MeOH (95:5)] and recrystallized from EtOH/hexanes to obtain yellow crystals, mp 126-129°, lit.[3] 129-130°.

N-Acetyl-3,5-dinitro-4-(4'-methoxy-4-biphenoxy)-DL-phenylalanine Ethyl Ester (3).- N-Acetyl-3,5-dinitro-DL-tyrosine ethyl ester (4.77 g, 0.014 mol) was dissolved in dry pyridine (28 mL), and the solution was brought to a gentle reflux under a nitrogen atmosphere. Methanesulfonyl chloride (1.76 g, 0.015 mol) was added, and the solution was refluxed 2 min. The

4-hydroxy-4'-methoxybiphenyl (8.29 g, 0.041 mol) was added, and the resultant solution was refluxed for an additional 6 min. The hot reaction mixture was poured into crushed ice (84 g) then extracted with EtOAc (3 x 150 mL). The combined EtOAc extracts were washed with 2N HCl (3 x 210 mL), H_2O (3 x 150 mL), 0.3N NaOH (5 x 50 mL) and H_2O (3 x 280 mL). The organic layer was dried (Na_2SO_4) and evaporated to give 11.71 g of a mixture of product and 4-hydroxy-4'-methoxybiphenyl. The mixture was chromatographed on silica gel (520 g) using a CH_2Cl_2 → 5% acetone/CH_2Cl_2 gradient to obtain 5.79 g of chromatographically pure 3. Subsequent recrystallization from absolute EtOH afforded 4.99 g (68%) of yellow solid, mp 154.5-156°; TLC (system A) single spot, R_f 0.47; IR (CH_2Cl_2) 3430, 1735, 1675, 1545, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3H, t, CH_2CH_3), 2.06 (3H, s, $NHCOCH_3$), 3.21 and 3.40 (1H each, two dd, $ArCH_2CH$), 3.83 (3H, s, OCH_3), 4.27 (2H, q, CH_2CH_3), 4.86 (1H, q, $ArCH_2CH$), 6.20 and 6.22 (1H, two s, $NHCOCH_3$), 6.90 and 7.43 (4H each, two m, biphenyl ArH), 7.96 (2H, s, phenylalanine ArH). An analytical sample recrystallized a second time from absolute EtOH had mp 155-156°.

Anal. Calcd for $C_{26}H_{25}N_3O_9$: C, 59.65; H, 4.81; N, 8.03

Found: C, 59.82; H, 4.87; N, 8.01

N-Acetyl-3,5-diiodo-4-(4'-methoxy-4-biphenoxy)-DL-phenylalanine Ethyl Ester (4).- Compound 3 (4.50 g, 0.0086 mol) was dissolved in HOAc (85 mL) and 10% Pd/C (0.85 g) was added. The resultant mixture was shaken 2 h on a Parr hydrogenator at 45 psi, then filtered and diluted with H_2SO_4 (22 mL). The green filtrate was added dropwise over 15 min to a freshly prepared solution of nitrosylsulfuric acid [$NaNO_2$ (2.38 g, 0.034 mol) added portionwise to H_2SO_4 (26 mL) at 70°, then cooled to -10° (ice/salt bath) and diluted with HOAc (26 mL) followed by H_2SO_4 (18 mL)] at -10°. After addition, the mixture was stirred 90 min at -10°.

The purple tetrazonium solution was poured into a well-stirred mixture of iodine (9.17 g, 0.036 mol), NaI (12.36 g, 0.082 mol) and urea (1.34 g, 0.022 mol) in H_2O (130 mL) underlayered with $CHCl_3$ (130 mL) and maintained at 0°. After stirring 1 h at 0°, the mixture was stirred 1 h with warming to room temperature and then 30 min at 40°. The layers were separated when cool and the aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were washed with H_2O (2 x 500 mL), 10% $NaHSO_3$ (2 x 500 mL), H_2O (500 mL), saturated $NaHCO_3$ (2 x 500 mL) and saturated NaCl (500 mL). The organic layer was dried (Na_2SO_4) and evaporated to obtain a residue (5.13 g) which was flushed through a column of silica gel (250 g) using $CHCl_3$, affording 4.44 g of yellow solid. Recrystallization from CH_2Cl_2/hexanes gave 4.01 g (68%) of 4 as an off-white solid, mp 162-165°; TLC (system A) single spot, R_f 0.68; IR (CH_2Cl_2) 3440, 1740, 1680, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3H, t, CH_2CH_3), 2.06 (3H, s, $NHCOCH_3$), 3.08 (2H, m, $ArCH_2CH$), 3.84 (3H, s, OCH_3), 4.23 (2H, m, CH_2CH_3), 4.83 (1H, q, $ArCH_2CH$), 6.10 and 6.14 (1H, two s, $NHCOCH_3$), 6.88 and 7.48 (4H each, two dd, biphenyl ArH), 7.64 (2H, s, phenylalanine ArH).

Anal. Calcd for $C_{26}H_{25}I_2NO_5$: C, 45.57; H, 3.68; N, 2.04; I, 37.04

Found: C, 45.57; H, 3.68; N, 2.15; I, 36.72

3,5-Diiodo-4-(4'-hydroxy-4-biphenoxy)-DL-phenylalanine (5).- A mixture of 4 (2.00 g, 0.0029 mol), HOAc (23 mL) and 57% HI (17 mL) was heated 5 h under nitrogen at 125-130° (oil bath). Solution was affected as soon as heating was begun. Afterwards, the reaction mixture was allowed to cool to room temperature, then was refrigerated (5°) overnight. The resultant precipitate was collected and washed with H_2O (3 x 10 mL), then MeOH (10 mL) containing a small amount of petroleum ether. The solid was dissolved in acetone and the solution stored at -15° overnight. When no

crystallization occurred, the acetone was evaporated to give 1.60 g of yellow solid. Meanwhile, the original filtrate was combined with the H_2O wash, diluted to 400 mL with H_2O, and refrigerated (5°) overnight. This process yielded an additional 0.36 g of pale yellow solid, which was collected and washed with H_2O (50 mL).

The combined crude product samples were suspended in MeOH (30 mL) and H_2O (5 mL). Concentrated NH_4OH was added dropwise until pH 10, then HOAc was added until pH 6. The resultant suspension was centrifuged and the supernatant removed. The solid was washed with MeOH (50 mL), H_2O (50 mL) and MeOH (50 mL), then vacuum dried at room temperature. The precipitation afforded 1.59 g (91%) of 5 as a white solid, mp 224-227° foaming; TLC (system B) single spot, R_f 0.60; IR (KBr) 3470, 1641, 1620, 1602, 1492, 1436, 1250, 1243, 819 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.88 and 3.15 (1H each, two dd, $ArCH_2CH$), 6.81 and 7.47 (4H each, two dd, biphenyl ArH), 7.84 (2H, s, phenylalanine ArH). The $ArCH_2CH$ signal was obscured by solvent signals. This material was suitable for synthetic use.

An analytical sample was obtained by suspending 0.25 g of 5 in MeOH (25 mL), adding 1N NaOH until solution was achieved, centrifuging and decanting away from the residue, and reprecipitating by addition of HOAc until pH 6. The collected solid was washed with H_2O (3x) and MeOH (2x), then vacuum dried at 60-70° until constant weight (6 h). The recovered white solid (0.20 g) had mp 227.5-230.5°.

Anal. Calcd for $C_{21}H_{17}I_2NO_4 \cdot 0.5\ H_2O$: C, 41.34; H, 2.97; N, 2.30; I, 41.60

Found: C, 41.51; H, 2.99; N, 2.14; I, 41.88

3,5-Diiodo-4-(3',5'-diiodo-4'-hydroxy-4-biphenoxy)-DL-phenylalanine (6).- To a stirred solution of 5 (0.25 g, 0.42 mmol) in 40% aqueous methylamine (10 mL) was added dropwise a solution of iodine (0.21 g, 0.83 mmol) and KI (0.414 g, 2.50 mmol) in H_2O (6 mL). Following the addition, the

mixture was stirred 4 h at room temperature. Concentrated HCl was added dropwise until pH 6 and the mixture refrigerated (5°) overnight. The precipitated solid was collected, washed with H_2O (20 mL) and dried to obtain 0.28 g of crude product. This was suspended in MeOH (15 mL) and H_2O (15 mL) and the suspension treated with 50% NaOH until pH 13. Undissolved solid was separated by centrifugation and the clear supernatant was adjusted to pH 6 using HOAc. The precipitated solid was collected and washed with H_2O (2 x 30 mL) and MeOH (2 x 30 mL). The precipitation was repeated to afford 0.19 g (53%) of 6 as an off-white solid, mp 225-227° foaming; TLC (system B) single spot, R_f 0.61; IR (KBr) 3470, 1628, 1610, 1452, 1438, 1245, 1168, 822 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.88 and 3.13 (1H each, two dd, $ArCH_2CH$), 3.50 (1H, m, $ArCH_2CH$), 6.81 and 7.54 (2H each, two d, biphenyl ArH), 7.85 (2H, s, phenylalanine ArH), 7.94 (2H, s, biphenyl ArH).

Anal. Calcd for $C_{21}H_{15}I_4NO_4$: C, 29.57; H, 1.77; N, 1.64; I, 59.51

Found: C, 29.85; H, 1.68; N, 1.61; I, 59.29

Initial attempts to iodinate 5 using either concentrated NH_4OH or 2N NaOH as the reaction medium were largely unsuccessful. Although small amounts of 6 were formed, pure product could not be isolated from either reaction mixture.

Diethyl 4-(4'-Aminophenoxy)-3,5-diisopropylbenzylacetamidomalonate (7).- The title compound was prepared in 29% overall yield from commercially available 2,6-diisopropylphenol and p-chloronitrobenzene using literature[5,9] procedures. The crude product was used directly in the next reaction.

3,5-Diisopropyl-DL-thyronine (8).- Crude 7 (7.50 g, 0.015 mol) was dissolved with heating in a mixture of 20% H_2SO_4 (6 mL), H_2O (12 mL) and HOAc (12 mL). The resultant solution was cooled to 10° in an ice bath.

The cold stirred solution was treated with a solution of $NaNO_2$ (1.20 g, 0.017 mol) in H_2O (1.2 mL). A β-naphthol test was positive. The diazonium salt solution was treated with urea (0.075 g) and refrigerated (5°) for 2 h. The diazonium salt solution was then added dropwise over 30 min to a stirred, refluxing solution of H_2SO_4 (13.5 mL), HOAc (27 mL), and H_2O (30 mL). Following addition, the dark mixture was refluxed 2 h. Afterwards, the dark mixture was cooled to below 10° and treated with concentrated NH_4OH until pH 5. During the neutralization a brown oil formed in the mixture. After overnight refrigeration (5°), the solution was decanted away from the separated brown oil. The oil was dissolved in MeOH (300 mL) and the solution was evaporated to obtain a brown foam (7.95 g) which TLC analysis (system B) showed to be a multicomponent mixture. Subsequent chromatography on silica gel (500 g) using 25% MeOH/$CHCl_3$ afforded 1.51 g of crude 8 as a yellow solid. This was dissolved in warm 2N NaOH and the red solution was treated with neutral Norit. After filtration through a Celite pad, the filtrate was neutralized with 2N HOAc until pH 6-7. The resultant white precipitate was collected by filtration, washed with H_2O and vacuum dried. Recrystallization from EtOAc/ MeOH followed by vacuum drying 18 h at 60° afforded 1.05 g (19%) of 8 as a white solid, mp 210-213° foaming (lit.[5] 225-230°); TLC (system B) single spot, R_f 0.46; ^1H NMR (DMSO-d_6) δ 1.06 (12H, d, CH_3CHCH_3), 2.79 and 3.20 (1H each, two dd, $ArCH_2CH$), 2.95 (2H, m, CH_3CHCH_3), 3.37 (1H, m, $ArCH_2CH$), 6.61 (4H, AB q, ArH), 7.12 (2H, s, ArH).

Anal. Calcd for $C_{21}H_{27}NO_4 \cdot 0.5\ H_2O$: C, 68.82; H, 7.70; N, 3.82

Found: C, 68.54; H, 7.91; N, 3.56

3',5'-Diiodo-3,5-diisopropyl-DL-thyronine (9).- To a stirred solution of 8 (0.25 g, 0.70 mmol) in 40% aqueous methylamine (10 mL) was added

dropwise a solution of iodine (0.36 g, 1.4 mmol) and KI (0.70 g, 4.20 mmol) in H_2O (5.7 mL). Following the addition, the mixture was stirred 3 h at room temperature. Concentrated HCl was added dropwise until pH 6 and the mixture refrigerated (5°) overnight. The precipitated solid was collected, washed with H_2O (30 mL) and dried to obtain 0.37 g of crude product. Recrystallization from EtOAc/MeOH followed by overnight vacuum drying at 65° gave 0.12 g (27%) of 9 as an off-white solid, mp 188-190°; TLC (system C) single spot, R_f 0.44; IR (KBr) 3480, 2982, 1628, 1585, 1454, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.08 (12H, d, CH_3CHCH_3), 2.86 (2H, m, CH_3CHCH_3), 7.13 and 7.17 (2H each, two s, ArH). The remaining aliphatic proton signals were obscured by solvent signals.

Anal. Calcd for $C_{21}H_{25}I_2NO_4$: C, 41.40; H, 4.14; N, 2.30; I, 41.66

Found: C, 41.56; H, 4.29; N, 2.31; I, 41.23

Evaporation of the mother liquors afforded 0.17 g of crude 9 as a yellow solid.

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REFERENCES

1. G. A. Brine, K. G. Boldt, M. L. Coleman and R. S. Rapaka, Anal. Lett., 15 (B11), 923 (1982).

2. J. van Alpen, Rec. Trav. Chim., 50, 657 (1931).

3. J. C. Clayton, G. F. H. Green and B. A. Hems, J. Chem. Soc., 2467 (1951).

4. R. I. Meltzer, D. M. Lustgarten and A. Fischman, J. Org. Chem., 22, 1577 (1957).

5. E. C. Jorgensen and J. Wright, J. Med. Chem., 13, 367 (1970).

6. T. Matsuura, T. Nagamachi, K. Matsuo and A. Nishinaga, J. Med. Chem., 11, 899 (1968).

7. B. Blank, F. R. Pfeiffer, C. M. Greenberg and J. F. Kerwin, J. Med. Chem., 6, 554 (1963).

8. We note that impure 9 was among the samples available from the laboratory of the late Dr. E. C. Jorgensen. We thank Dr. E. N. Cheung for providing this information to us.

9. J. Wright and E. C. Jorgensen, J. Org. Chem., 33, 1245 (1968).

10. We found the literature[5] procedure to be in error with respect to the molar ratio of reagents. A correct procedure is provided in the experimental section.

11. M. Dymicky, E. F. Mellon and J. Naghski, Anal. Biochem., 41, 487 (1971).

12. M. Dymicky, Org. Prep. Proced. Int., 8, 219 (1976).

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