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The Synthesis of 3,5,3′-Triisopropyl-D,L-thyronine

Teruo Matsuura, Tomoaki Nagamachi, and Akira Nishinaga

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University[1]

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In view of the fact that a replacement of the 3′-iodine atom in 3,5,3′-triiodothyronine (T_3) with an isopropyl group, which has nearly the same size as an iodine atom, results in a considerable increase in biological activity,[2–6] it is of interest to determine whether a similar replacement of the 3- and 5-iodine atoms also enhances the biological activity of T_3 or abolishes it as in the case of other analogs of T_3 which have no halogen atom in the nonphenolic ring. In connection with the high biological activity of 3,5-diiodo-3′-isopropylthyronine, we reported the synthesis of 3,5-diisopropyl-3′-iodo-D,L-thyronine.[7] In this paper the synthesis of 3,5,3′-

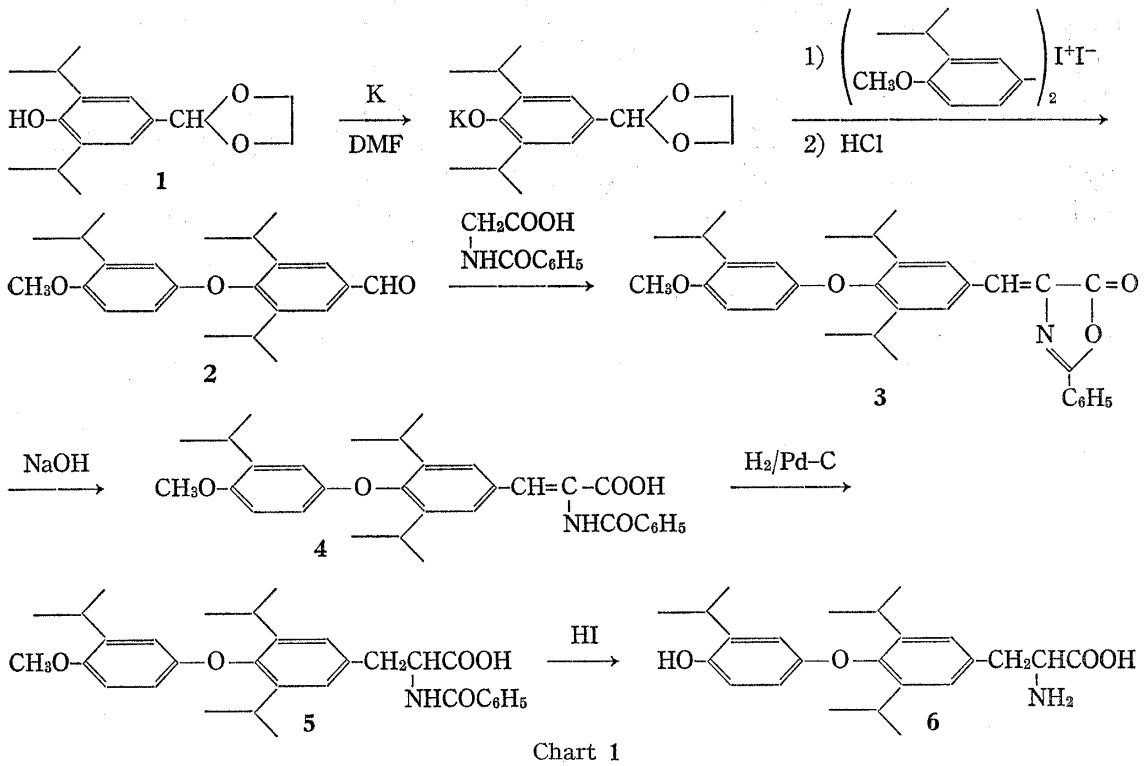

Chart 1

1) Location: *Yoshidahonmachi, Sakyo-ku, Kyoto.*
2) B. Blank, F.R. Pfeiffer, C.M. Greenberg, and J.F. Kerwin, *J. Med. Chem.*, **6**, 554, 560 (1963).
3) B. Blank, C.M. Greenberg, and J.F. Kerwin, *J. Med. Chem.*, **7**, 53 (1964).
4) C.M. Greenberg, B. Blank, F.R. Pfeiffer, and J.F. Pauls, *Am. J. Physiol.*, **205**, 821 (1963).
5) S.B. Barker, M. Shimada, and M. Makiuchi, *Endocrinology*, **76**, 115 (1965).
6) M. Wool, V.S. Fong, and H.A. Selenkow, *Endocrinology*, **78**, 29 (1966).
7) T. Matsuura, T. Nagamachi, K. Matsuo, and A. Nishinaga, *J. Med. Chem.*, **11**, 899 (1968). The thyromimetic activity of 3,5-diisopropyl-3′-iodo-D,L-thyronine was shown to be less than 1% of triiodothyronine using the tadpole urea excretion test [Ashely, Katti, and Frieden, *Dev. Biol.*, **17**, 293—307 (1968)] and the tail decrease test [Wahlborg, Bright, and Frieden, *Endocrinol.*, **75**, 561—564 (1964)]. The authors wish to thank Drs. A.K. Medda and E. Frieden of Florida State University for the testing of this compound.

triisopropyl-D,L-thyronine which failed to be synthesized so far[8] is described. The synthetic route was similar to that of 3,5-diisopropyl-3'-iodo-D,L-thyronine as summarized in Chart 1.

Experimental

3,5-Diisopropyl-4-(3-isopropyl-4-methoxyphenoxy)benzaldehyde (2)——To a solution of 3.8 g (0.015 mole) of acetal **1** in 50 ml of dry dimethylformamide (dried over BaO) was added 0.58 g (0.015 mole) of potassium. To the green solution was added 7.1 g (0.0128 mole) of di-(3-isopropyl-4-methoxyphenyl)iodonium iodide[2,9] and 0.5 g of copper powder. The mixture was heated at 150—180° for 5 hr with stirring and under exclusion of moisture. The reaction mixture was cooled to room temperature, then taken up with ether and water. The ether layer was washed with dilute NaOH, then with water, and evaporated. The residue was dissolved in 70 ml of ethanol containing *ca.* 2 ml of concentrated HCl, then refluxed for 30 min. The reaction mixture was evaporated *in vacuo* to dryness and the residue was taken up with ether and water. The ether layer was washed with water, dried, and evaporated *in vacuo* to dryness. The residue (4.1 g) was chromatographed on a column of 80 g of silica gel (Mallinckrodt 100 mesh). Elution with benzene gave 890 mg (19.7%) of **2**, which was distilled at 170—200° (10^{-3} mm). IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR (in CCl_4) τ: 8.88 (6H, doublet, J=6.1 cps, $CH(CH_3)_2$), 8.85 (12H, doublet, J=6.1 cps, $2CH(CH_3)_2$), 6.97 (3H, septet, J=6.1 cps, $3CH(CH_3)_2$), 6.35 (3H, singlet, OCH_3) 4.0—3.5 (3H, unresolved, 1,2,4-substituted aromatic protons), 2.61 (2H, singlet aromatic protons adjacent to formyl group), 0.44 (1H, singlet, CHO). *Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.55; H, 8.78.

2-Phenyl-4-[3,5-diisopropyl-4-(3-isopropyl-4-methoxyphenoxy)benzal]-5-oxazolone (3)——A mixture of 2.47 g (7 mmoles) of aldehyde **2**, 1.61 g (9 mmoles) of hippuric acid, 0.74 g (9 mmoles) of anhydrous sodium acetate, and 10 ml (98 mmoles) of acetic anhydride was heated at 100° for 5 hr. The reaction mixture was kept overnight at 2° to give a semisolid material, which was pressed on a suction filter and washed with cold water yielding 990 mg of yellow crystals. Recrystallization from ethanol gave 880 mg (25.3%) of azlactone **3** as pale yellow needles, mp 136—138°. UV $\lambda_{max}^{ethanol}$ mμ (ε): 362 (37900), 373 (47400), 390 (39200); IR ν_{max}^{Nujol} cm^{-1}: 1795, 1770, and 1655. *Anal.* Calcd. for $C_{32}H_{35}O_4N$: C, 77.23; H, 7.09; N, 2.82. Found: C, 77.17; H, 7.22; N, 2.96.

α-Benzamido-3,5-diisopropyl-4-(3-isopropyl-4-methoxyphenoxy)cinnamic Acid (4)——A solution of 350 mg (0.705 mmole) of azlactone **3** in 100 ml of ethanol and 5 ml of 2N NaOH was heated at 60° for 30 min. The reaction mixture, after cooling, was acidified with chilled dilute HCl and concentrated *in vacuo* at room temperature to yield a brown solid residue. Crystallization from benzene–ligroin gave 160 mg (44.1%) of acid **4** as colorless needles, mp 214—216°. UV $\lambda_{max}^{ethanol}$ mμ (ε): 227 (31000) and 293 (23300). IR ν_{max}^{Nujol} cm^{-1}: 2500—2700 (COOH), 1685, and 1630. NMR (in $CDCl_3$), τ: 8.95 (12H, doublet, J=6.1 cps, $2CH(CH_3)_2$), 8.89 (6H, doublet, J=6.1 cps, $CH(CH_3)_2$), 6.93 (3H, septet, J=6.1 cps, $3CH(CH_3)_2$), 6.25 (3H, singlet, OCH_3), 3.7—3.1 (3H, multiplet, aromatic H), 2.99 (2H, singlet, aromatic H), 2.85—2.10 (5H, multiplet, aromatic H), 0.79 (1H, singlet, COOH). *Anal.* Calcd. for $C_{32}H_{37}O_5N$: C, 74.54; H, 7.23; N, 2.72. Found: C, 74.81; H, 7.21; N, 3.02.

3,5,3'-Triisopropyl-D,L-thyronine (6)——A solution of 400 mg (0.77 mmole) of **5** prepared by catalytic hydrogenation (Pd-C, methanol, 1 mole H_2-uptake) of **4** in 12 ml of hydroiodic acid (sp. gr 1.7) and 20 ml of acetic acid was refluxed for 4 hr under nitrogen. The reaction mixture was evaporated *in vacuo*, and acetic acid was completely removed by repeated additions and evaporations *in vacuo* of water. The residue was dissolved in dilute NaOH. The solution was decolorized with Norit, then neutralized (pH 7.0) with dilute HCl. Fine crystals of 3,5,3'-triisopropyl-D,L-thyronine (152 mg, 49.5%) were obtained which were collected by centrifugation, washed with water, and dried. Paper chromatography (1-BuOH–conc. NH_4OH–H_2O, 5:1:1, *Rf* 0.80) showed a single spot, mp 155—158°, NMR (in CD_3OD) τ: 8.88 (18H, doublet, J=6.1 cps, $3CH(CH_3)_2$), 3.80—2.65 (5H, unresolved, aromatic H).

A sample for elemental analysis was prepared by reprecipitation with water from a solution in methanol and dried at 100° (10^{-3} mm) for 7 hr. *Anal.* Calcd. for $C_{24}H_{33}O_4N \cdot 1/2\ H_2O$: C, 70.56; H, 8.34; N, 3.43. Found: Found: C, 70.23; H, 8.21; N, 3.33.

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