Thyroxine Analogues: Synthesis of 3,3',5,5'-Tetramethyl-L-thyronine

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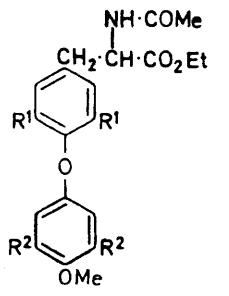
The optically active thyroxine analogue, 3,3',5,5'-tetramethyl-L-thyronine (VI), in which the iodine atoms of thryoxine have been replaced by methyl groups, is of considerable biological interest. Its synthesis *via* the catalytic hydrogenation of *N*-acetyl-3,5-dicyano-(4-methoxy-3,5-dimethylphenoxy)-L-phenylalanine ethyl ester (II) in *p*-cymene under reflux is described. 3,5-Dimethyl-L-thyronine (VII) was also prepared by reduction of *N*-acetyl-3,5-dicyano-4-(4-methoxyphenoxy)-L-phenylalanine ethyl ester (IV).

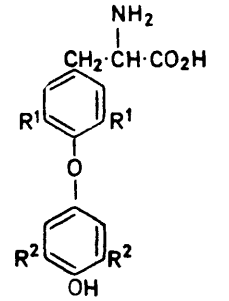
BIELIG and LÜTZEL reported [1] the synthesis of racemic tetramethylthyronine from a chloromethylated diphenyl ether intermediate. However, recent results [2,3] have demonstrated conclusively that the synthetic route employed gives an isomer of the tetramethyl compound in which the amino-acid side-chain is in the wrong position. No authentic tetramethyl analogue has, therefore, been previously prepared or tested for biological activity. Previous methods [4,5] for the synthesis of the dimethylthyronine gave racemic mixtures of products in low yields.

Kindler and Lührs have described [6] the reduction of several aliphatic and aromatic nitriles to the corresponding methyl derivatives by catalytic hydrogenation in an inert solvent under reflux. In our present work, their reaction has been extended to suitable aromatic dicyano-compounds, the reduction of which has led to the preparation of the required methylthyronines.

The di-iodo-ester (I) was prepared by coupling *N*-acetyl-3,5-di-iodo-L-tyrosine ethyl ester [7] with 3,5-dimethyl-4-methoxyphenyliodonium iodide under standard conditions.[8] Reaction with copper(I) cyanide in pyridine under reflux [9] gave the dicyano-compound (II), which



(I) $R^1 = I$, $R^2 = Me$
(II) $R^1 = CN$, $R^2 = Me$
(III) $R^1 = R^2 = Me$
(IV) $R^1 = CN$, $R^2 = H$
(V) $R^1 = Me$, $R^2 = H$



(VI) $R^1 = R^2 = Me$
(VII) $R^1 = Me$, $R^2 = H$

was reduced by bubbling hydrogen through its solution in *p*-cymene (*p*-isopropyltoluene), under reflux, containing palladium on charcoal. The progress of the reaction was followed by titrating the ammonia evolved against standard hydrochloric acid. The methyl analogue (III) was obtained in almost quantitative yield with no evidence of degradation of the amino-acid side-chain. Removal, by acid hydrolysis, of the protecting groups gave the tetramethylthyronine (VI).

The dicyano-compound (IV) [9] was readily reduced by the procedure already described to yield the protected dimethyl-compound (V). Acid hydrolysis gave the required dimethylthyronine (VII) in excellent yield.

EXPERIMENTAL

M.p.s were taken in a Hershberg apparatus. Optical rotations were measured with a Bellingham and Stanley P1 polarimeter. Analytical data were supplied by Huffman Laboratories, Inc., Wheatridge, Colorado 80033.

Reagents.—Terpene-free *p*-cymene was shaken with concentrated sulphuric acid and washed with water and sodium carbonate solution. It was dried first with magnesium sulphate and finally with sodium, and distilled. Either commercial 10% palladium on carbon or, preferably, a catalyst described by Pearlman [10] containing 20% palladium, was employed. The latter was more active and, in view of the high catalyst-to-compound ratio, the reduction in carbon content was advantageous. In evaluating the hydrogenation technique and apparatus 1,3-dicyanobenzene (Aldrich) was used as a standard reactant. Without further purification, it was reduced readily to give the expected *m*-xylene.

Bis-(4-methoxy-3,5-dimethylphenoxy)iodonium Iodide.—A solution of iodine(III) trifluoroacetate in acetic anhydride (150 ml) was prepared from iodine (15·26 g) by the method of Beringer.[11] To the solution at −10°, 2,6-dimethylanisole (28·19 g) in acetic anhydride (40 ml) and trifluoroacetic acid (16 ml) were added slowly with stirring (1 h). After being stirred at 5° (2 h), the solution was brought to room temperature and the solvents were removed *in vacuo*. The residual oil was dissolved in methanol (350 ml) and treated with 10% sodium hydrogen sulphite (50 ml) followed by potassium iodide (60 g) in water (300 ml). The greasy, yellow precipitate was filtered off and crystallized from ethanol–dimethylformamide to give the *iodonium iodide*

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(13·50 g, 23%). Final purification [12] was effected by conversion into the water-soluble sulphate and reprecipitation with iodide (Found: I, 48·3. $C_{18}H_{22}I_2O_2$ requires I, 48·4%).

N-Acetyl-3,5-di-iodo-4-(4-methoxy-3,5-dimethylphenoxy)-L-phenylalanine Ethyl Ester (I).—*N*-Acetyl-3,5-di-iodo-L-tyrosine ethyl ester (10·00 g) and the foregoing iodonium iodide (13·11 g, 25% excess) were dissolved in anhydrous methanol (100 ml) containing triethylamine (3·0 ml) and copper powder (0·21 g). The mixture was stirred and maintained at 45° (24 h). Extraction with benzene followed by crystallization from ethanol–hexane gave the product (I) (8·92 g, 70%), m.p. 155—156° (lit.,[13] 149—150°).

N-Acetyl-3,5-dicyano-4-(4-methoxy-3,5-dimethylphenoxy)-L-phenylalanine Ethyl Ester (II).—The di-iodo-compound (I) (3·00 g) was converted into the dinitrile under the conditions employed by Barnes *et al.*[9] Two crystallizations from ethanol with addition of activated charcoal normally provided a *compound* (II) (1·35 g, 65%), m.p. 160—161° (Found: C, 66·3; H, 5·8; N, 9·4. $C_{24}H_{25}N_3O_5$ requires C, 66·2; H, 5·8; N, 9·6%) that would not poison the catalyst in the subsequent reduction.

N-Acetyl-4-(4-methoxy-3,5-dimethylphenoxy)-3,5-dimethyl-L-phenylalanine Ethyl Ester (III).—A three-necked flask (100 ml) was fitted with a thermometer, gas dispersion tube, and reflux condenser, the top of which led to a second dispersion tube dipping beneath the surface of water (100 ml) containing Methyl Red indicator. The dicyano-compound (II) (1·30 g) was dissolved in *p*-cymene (35 ml) containing 20% palladium on carbon (0·3 g). Hydrogen was bubbled through the refluxing mixture while the temperature was maintained at 170—175°. The ammonia evolved was absorbed and titrated against hydrochloric acid (1·0N). The reaction became slower at its mid-point and virtually ceased when 92% of the theoretical amount of acid had been neutralized (1·75 h). Catalyst was removed by filtration while hot and washed with acetone. The solvents were removed *in vacuo* and the residue, after treatment with pentane, was kept in the refrigerator (18 h). Filtration then gave the required compound in almost quantitative yield. Crystallization from ethanol–hexane gave the *dimethyl compound* (III) (0·93 g, 75%), m.p. 142—143·5°, $[\alpha]_D^{25}$ +2·5° (*c* 1·73 in EtOH) (Found: C, 69·3; H, 7·4; N, 3·5. $C_{24}H_{31}NO_5$ requires C, 69·7; H, 7·6; N, 3·4%). The ^{1}H n.m.r. spectrum was consistent with the proposed structure.

3,3′,5,5′-Tetramethyl-L-thyronine (VI).—The protected amino-acid (III) (0·93 g) was hydrolysed (7 h) in acetic acid (6·5 ml) and hydroiodic acid (5·5 ml). After partial removal of the acids *in vacuo*, the residue was taken up in 30% ethanol, whereupon neutralization gave the *thyronine* (VI) (0·63 g, 93%). Reprecipitation from a 1% solution in 30% ethanol afforded the free amino-acid, m.p. 238·5—240·5° (heated rapidly from 220°), $[\alpha]_D^{25}$ +17·1° (*c* 1·0 in 0·1N-HCl in 50% EtOH) (Found: C, 69·3; H, 7·0; N, 4·2. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·0; N, 4·3%).

N-Acetyl-4-(4-methoxyphenoxy)-3,5-dimethyl-L-phenylalanine Ethyl Ester (V).—The dicyano-compound (IV) (3·26 g) was dissolved in *p*-cymene (50 ml) containing 20% palladium on charcoal (0·6 g) and hydrogenated by the standard procedure. The reaction, which almost ceased when 92% of the theoretical amount of ammonia had been evolved, gave an almost quantitative yield of crude product. Crystallization from ethanol–hexane gave the *dimethyl compound* (V), m.p. 109·5°, $[\alpha]_D^{22}$ +18·2° (*c* 2·0 in EtOH) (Found: C, 68·8; H, 7·0; N, 3·8. $C_{22}H_{27}NO_5$ requires C, 68·6; H, 7·1; N, 3·6%). The ^{1}H n.m.r. spectrum was consistent with the proposed structure.

3,5-Dimethyl-L-thyronine (VII).—Hydrolysis (5 h) of the dimethyl compound (V) (1·50 g) in acetic acid (22·5 ml) and hydrobromic acid (7·5 ml) gave the free *amino-acid* (0·96 g, 83%), m.p. 251·5—252·5°, $[\alpha]_D^{22}$ +14·1° (*c* 2·0, 0·1N-HCl in 50% EtOH) (Found: C, 68·1; H, 6·5; N, 4·5. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·4; N, 4·6%).

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