201. *A New Synthesis of Thyronine.*

By C. R. Harington and Rosalind V. Pitt Rivers.

The limiting factor in the synthesis of thyronine is the accessibility of 4-(4′-methoxyphenoxy)benzaldehyde. An improved method of preparation of this aldehyde is described, starting from ethyl *p*-hydroxybenzoate and *p*-bromoanisole.

The preparation and properties of hitherto undescribed derivatives of thyronine are recorded.

In connection with some experiments on the formation of thyronine from iodinated proteins and the possible conversion of tyrosine into thyroxine (compare Harington and Pitt Rivers, *Nature*, 1939, **144**, 205), it became desirable to have a quantity of thyronine [4-(4′-hydroxyphenoxy)phenylalanine]. The existing syntheses of this amino-acid (Harington, *Biochem. J.*, 1926, **20**, 300; Harington and McCartney, *ibid.*, 1927, **21**, 852) are tedious and unsatisfactory for preparative purposes, the limiting factor being the difficulty of obtaining the necessary 4-(4′-methoxyphenoxy)benzaldehyde.

Attempts to obtain a direct synthesis of *N*-benzoyl-*O*-methylthyronine ethyl ester by the condensation of *p*-bromoanisole with the potassium salt of *N*-benzoyltyrosine ethyl ester have failed; by heating *p*-bromoanisole with ethyl *p*-hydroxybenzoate and potassium hydroxide in presence of copper bronze we have, however, been able to obtain a satisfactory yield of *ethyl* 4-(4′-*methoxyphenoxy*)*benzoate*. The latter ester can readily be converted into the *hydrazide*, the p-*toluenesulphonyl* derivative of which, on heating with anhydrous sodium carbonate in ethylene glycol solution (compare McFadyen and Stevens, J., 1936, 584), reacts smoothly to give the desired aldehyde.

The amino-acid itself is conveniently prepared by direct treatment with hydriodic acid and red phosphorus of the azlactone obtained from the aldehyde and hippuric acid (compare Harington and McCartney, *loc. cit.*).

The opportunity is taken to record below the preparation and properties of some hitherto undescribed derivatives of thyronine.

Experimental.

Ethyl 4-(4′-*Methoxyphenoxy*)*benzoate*.—*p*-Bromoanisole (42 g.; 1·5 mols.), ethyl *p*-hydroxybenzoate (24 g.; 1 mol.), powdered potassium hydroxide (8·4 g.; 1 mol.), and copper bronze (300 mg.) were heated together on a metal-bath. A vigorous reaction occurred at about 150°; after this was over, the temperature was raised rapidly to 240° and maintained at that level for 1 hour. The reaction mixture was cooled, shaken with water and ether, and filtered; the ethereal layer was separated, washed three times with ice-cold N/2-sodium hydroxide and

once with water, and dried over calcium chloride. The ether was removed, and the residue distilled at about 15 mm.; the fraction distilling between 210° and 240° formed a colourless oil which solidified in a cooling mixture. Yield, 21·5 g. or 53% of the theoretical. After two recrystallisations from light petroleum (b. p. 60—80°) the *product* had m. p. 23—24° (Found: C, 71·5; H, 6·1. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

4-(4′-*Methoxyphenoxy*)*benzhydrazide*.—Ethyl 4-(4′-methoxyphenoxy)benzoate (36 g.), hydrazine hydrate (18 c.c.), and alcohol (55 c.c.) were heated in a pressure bottle for 13 hours at 100°; the warm mixture was poured into a beaker and crystallised on cooling; after keeping for a short time at 0° the solid was collected, and a further crop obtained by diluting the mother-liquor with water. The yield was 25 g. (74%) of a product which was pure enough for the next reaction. After two recrystallisations from alcohol the *compound* formed long colourless needles, m. p. 136—136·5° (Found: C, 66·1; H, 5·4; N, 12·0. $C_{14}H_{14}O_3N_2$ requires C, 65·1; H, 5·4; N, 11·8%).

p-*Toluenesulphonyl*-4-(4′-*methoxyphenoxy*)*benzhydrazide*.—The above hydrazide (25·8 g.) was dissolved in dry pyridine (200 c.c.), and the solution treated with *p*-toluenesulphonyl chloride (20 g.) in small portions with ice-cooling; the mixture was kept at the ordinary temperature for 2 hours and then poured into a slight excess of ice-cold 5N-hydrochloric acid; the precipitate was collected and crystallised from acetic acid. Yield, 34 g. (88%). After a second crystallisation from acetic acid the *compound* had m. p. 172—173° (Found: S, 8·2. $C_{21}H_{20}O_5N_2S$ requires S, 7·9%).

4-(4′-*Methoxyphenoxy*)*benzaldehyde*.—*p*-Toluenesulphonyl-4-(4′-methoxyphenoxy)benzhydrazide (33·8 g.) and ethylene glycol (150 c.c.) were heated in a metal-bath at 160°; the hot solution was treated with anhydrous sodium carbonate (17·5 g.); vigorous effervescence set in and lasted for 30 seconds. Heating was continued for 30 seconds longer and the solution was then rapidly cooled to about 100° and diluted with 1200 c.c. of hot water. The mixture was extracted with ether, and the extract dried over sodium sulphate and evaporated; the crystalline residue was practically pure aldehyde (15·7 g., 80%). After recrystallisation from light petroleum (b. p. 60—80°) the aldehyde had m. p. 60·5°, not depressed on admixture with an authentic specimen prepared according to Harington (*loc. cit.*). The semicarbazone had m. p. 212—213°; Harington (*loc. cit.*) gives m. p. 211°.

Thyronine.—The above aldehyde (15 g.) was converted into the azlactone in the usual manner; the recrystallised product (14·6 g.; cf. Harington and McCartney, *loc. cit.*) was refluxed for 1½ hours with red phosphorus (10 g.) and 75 c.c. of a mixture of equal parts of acetic anhydride and hydriodic acid (*d* 1·7). The solution was filtered through asbestos and evaporated under diminished pressure, and the residue shaken with ether and water; the aqueous layer was treated with a little sodium hydrogen sulphite to remove the excess of iodine and then neutralised at the b. p. to Congo-red with concentrated aqueous ammonia. After keeping in the ice-chest overnight, the amino-acid was collected, washed with alcohol and ether, and dried in the steam-oven. The yield was 7·2 g., or 42% calculated from the aldehyde.

Thyronine Methyl Ester Hydrochloride.—Thyronine (7·2 g.) was suspended in anhydrous methyl alcohol (115 c.c.), and a rapid stream of hydrogen chloride passed in to saturation; the solution was refluxed for a short time and then evaporated under diminished pressure to a thick paste of crystalline material. The latter was taken up in warm alcohol, and the solution diluted with ether; on cooling, there were obtained 5·4 g. of the pure *ester hydrochloride*. By evaporating the mother-liquor, re-esterifying the residue, and working up in a similar manner, a further crop of 1·4 g. was obtained, the total yield thus amounting to 80·6%. The compound had m. p. 215° (Found: N, 4·3; Cl, 11·2. $C_{16}H_{17}O_4N,HCl$ requires N, 4·3; Cl, 11·0%).

ON-*Dibenzoylthyronine Methyl Ester*.—Thyronine methyl ester hydrochloride (0·4 g.), diethylamine (0·15 c.c.), and benzoyl chloride (0·35 c.c.) were dissolved together in dry pyridine (2 c.c.); the solution was heated on the steam-bath for a few minutes, cooled, and poured into 5 c.c. of 5N-hydrochloric acid mixed with ice. The oil which separated rapidly solidified and was crystallised from alcohol; the *product* had m. p. 132—134° (Found: C, 72·5; H, 5·1; N, 3·0. $C_{30}H_{25}O_6N$ requires C, 72·7; H, 5·4; N, 2·8%).

N-p-*Toluenesulphonylthyronine*.—Thyronine methyl ester hydrochloride (0·16 g.) was dissolved in pyridine (2 c.c.) with the aid of diethylamine (0·1 c.c.), and the ice-cold solution treated with *p*-toluenesulphonyl chloride (0·098 g.) in small portions; after 1 hour at the ordinary temperature the mixture was poured into ice and hydrochloric acid, and the resulting precipitate crystallised from aqueous alcohol. Without further purification this product was dissolved in 2 equivs. of N-sodium hydroxide in 50% aqueous alcohol and kept for 40 minutes at the ordinary temperature; addition of 2 equivs. of N-hydrochloric acid produced a precipitate

which crystallised almost at once. Recrystallised from aqueous alcohol, the *compound* had m. p. 141° after sintering (Found: N, 3·3; S, 7·5. $C_{22}H_{21}O_6NS$ requires N, 3·3; S, 7·5%).

N-*Carbobenzyloxythyronine*.—Thyronine methyl ester hydrochloride (1·5 g.) was dissolved in the minimum amount of water; chloroform (25 c.c.) was added, followed, after cooling to 0°, by 2N-sodium carbonate (1 equiv.), and the mixture was vigorously shaken. Benzyl chloroformate (1·5 c.c.) was added in small portions with shaking and finally a further equiv. of 2N-sodium carbonate; the mixture was shaken at 0° for 30 minutes and kept at the ordinary temperature for 1½ hours. The chloroform layer was separated, washed successively with water, 0·1N-hydrochloric acid, and water, dried over sodium sulphate, and evaporated under diminished pressure. The residual gum, which could not be crystallised, was taken up in alcohol (5 c.c.) containing 2N-sodium hydroxide (2 equivs.); after 45 minutes at the ordinary temperature the solution was made acid to Congo-red with hydrochloric acid and the resulting crystalline precipitate was collected, dried, and recrystallised from ether–light petroleum (b. p. 40—50°). The yield was 1·5 g. of a *product*, m. p. 105—106° (Found: C, 67·5; H, 5·15; N, 3·5. $C_{23}H_{21}O_6N$ requires C, 67·8; H, 5·15; N, 3·4%).

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL,
LONDON, W.C. 1.

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