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Synthesis of the Butyric Acid Analog of Thyroxine[1]

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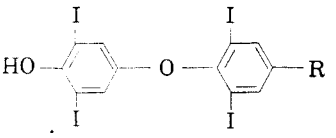
The synthesis of the butyric acid analog of throxine is reported.

It has been amply demonstrated[2,3,4] that the nature of the side-chain, R, in diphenyl ethers related to thyroxine (I) is one of the major factors in determining the thyromimetic activity of a particular

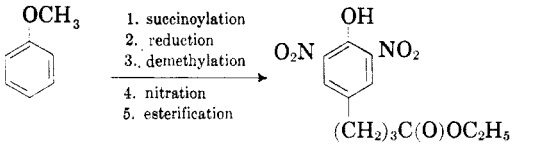


I, R = L-alanyl
II, R = —COOH
III, R = —CH_2—COOH
IV, R = —CH_2CH_2COOH
V, R = CH_2—CH_2—CH_2—COOH

analog. However, while some suggestions[4] have been made as to the possible rôle of the side-chain in promoting activity, there is as yet no fully substantiated explanation of the relation between the structure of the side-chain and activities of thyroxine analogs. Further studies to elucidate this relationship are therefore indicated.

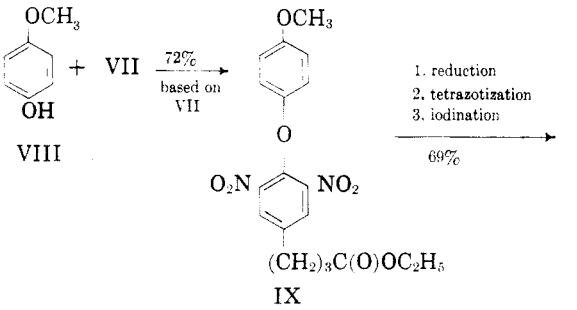
In view of the special interest in the acetic acid (III)[5] and propionic acid (IV)[4] analogs, and the reports[2,3,4,5] that thyromimetic activity, in certain assays, increases *markedly* in passing from II to IV, it seemed desirable to prepare the butyric acid analog, V. The synthesis of this substance is now reported.[6]

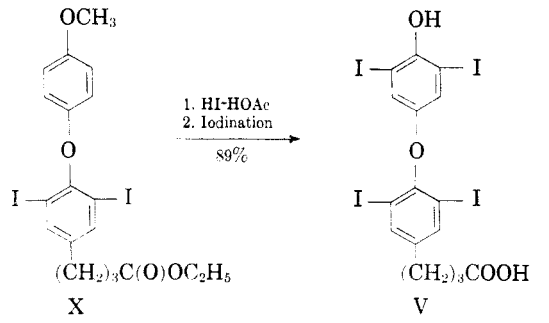
Methods similar to those used to prepare the propionic acid analog[7,8,9] were employed for the synthesis of V. The required precursor, VII, ethyl γ-(3,5-dinitro-4-hydroxyphenyl)butyrate, was obtained as shown in the following sequence.



VI VII

The conversion of VII to V involved the following steps:





EXPERIMENTAL[10]

ETHYL γ-(3,5-DINITRO-4-HYDROXYPHENYL)BUTYRATE (VII)

β-(4-Methoxybenzoyl) propionic acid, m.p. 148–149°, was prepared (84% yield) from anisole by the method of Fieser and Hershberg,[11] who reported m.p. 146.5–147.5° and this was reduced (92% yield) to *γ-(4-methoxyphenyl)butyric acid*, m.p. 62°, lit.,[11] 62°, by the Martin modification of the Clemmenson reduction.[12] The latter product (5 g.) was demethylated by refluxing with 40 ml. of a 1:1 mixture, by volume, of acetic acid and hydriodic acid (47%). After 4 hours, the mixture was cooled to 70° and part of the solvent was aspirated. On cooling and addition of water, crystals of *γ-(4-hydroxyphenyl)butyric acid* separated. Recrystallization from benzene–petroleum ether (b.p. 63–69°) gave 4.4 g. (94%) of product;

(1) This study was carried out, in part, under Public Health Service Research Grant A-703 from the National Institutes of Health, Public Health Service.

(2) Selenkow and Asper, *Physiol. Revs.*, **35**, 426 (1955).

(3) Bruice, Winzler, and Kharasch, *J. Biochem.*, **210**, 1 (1954).

(4) Bruice, Kharasch, and Winzler, *Archives of Biochem. and Biophys.*, in press (1956).

(5) Pitt-Rivers, *Lancet*, 234 (1953).

(6) Compound V has been submitted for bio-assay and the results will be reported separately.

(7) Kharasch, Kalfayan, and Arterberry, *J. Org. Chem.*, 21, 925 (1956).

(8) Clayton, Green, and Hems, *J. Chem. Soc.*, 2467 (1951).

(9) The designation "desaminothyroxine" has also been used.[4] The systematic names for IV and V are employed in the experimental part.

(10) Melting points were made on a Fischer-Johns block. The analyses were kindly performed by Mr. W. J. Schenck.

(11) Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2315 (1936).

(12) Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

m.p. 107–108°. The latter product was nitrated, by a method previously described for the propionic acid analog,[7] to give *γ-(3,5-dinitro-4-hydroxyphenyl)butyric acid*, in 78% yield; m.p. 132–133°. Esterification of 5 g. of the acid[7] gave 5 g. (90%) of the ester, VII, m.p. 38°.

3,5-DIIODO-4-(3′,5′-DIIODO-4-HYDROXYPHENOXY)-γ-PHENYLBUTYRIC ACID (V)

Ethyl γ-[3,5-dinitro-4-(4′-methoxyphenoxy)phenyl]butyrate was obtained by condensing VII and VIII, through the pyridinium tosylate,[7,8] in 70–75% yields of pure product, which melted at 72–73° after recrystallization from 70% ethanol.

Anal. Calc'd for $C_{19}H_{20}N_2O_8$: C, 56.40; H, 4.95; N, 6.93. Found: C, 56.20; H, 4.91; N, 6.71.

γ-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl)butyric acid. Reduction, tetrazotization, and iodination of IX as described for IV[7] gave the intermediate ethyl *γ-[3,5-diiodo-4-(4′-methoxyphenoxy)phenyl]butyrate*, in 69% yield, as an oil that could not be induced to crystallize from alcohol or alcohol-water mixtures. This product (4.1 g.) was refluxed with a mixture of acetic acid (25 ml.) and 47% hydriodic acid (20 ml.) for 3 hours. On cooling, and addition of water, white crystals separated. Yield: 3.65 g. (96%); m.p. 223–224°.

Anal. Calc'd for $C_{16}H_{14}I_2O_4$: C, 36.60; H, 2.70; I, 48.40. Found: C, 36.90; H, 2.95; I, 47.67.

To obtain V, the above compound (2.0 g.) was dissolved in aqueous ethylamine (35 ml., 33%) and iodinated, below 20°, by adding—during 30 min., an aqueous solution of iodine in potassium iodide (8.5 ml. soln.; 1.9*N* in iodine). After stirring one hour, the solution was acidified with 15% hydrochloric acid and precipitated V was recrystallized from aqueous acetone. Two more recrystallizations from the same solvent yielded 2.8 g. (93%) of product, m.p. 195–196°.

Anal. Calc'd for $C_{16}H_{12}I_4O_4$: C, 24.74; H, 1.55; I, 65.4. Found: C, 24.31; H, 1.20; I, 66.53.

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