Notes

Model Reactions for the Biosynthesis of Thyroxine. VIII. The Reaction of Various Analogs of 4-Hydroxy-3,5-diiodophenylpyruvic Acid with 3,5-Diiodotyrosine[1,2]

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Thyroxine is formed in about 20% yield when DIHPPA[4] is permitted to react with DIT[4] at room temperature in a neutral or slightly alkaline solution.[5] Analogs of thyroxine are formed when in this reaction the amino acid is replaced with certain analogs of DIT. The influence of structural changes in the DIT molecule upon the yield of the corresponding analog of thyroxine has been investigated.[6,7] The present Note deals with the influence of structural changes in the keto acid component of this coupling reaction upon the yield of the coupling product.

Various compounds structurally related to DIHPPA were permitted to react with DIT (and in a few cases with desamino analogs of DIT) following the usual procedure described in the previous papers of this series. The yield of thyroxine (or its analogs) was determined by isolation and weighing or, in the case of very poor yields, by paper chromatography.

The syntheses of most of the analogs of DIHPPA used have not been previously reported and are therefore described in the Experimental part.

The yields obtained in the various coupling reactions are reported in Table I. It has been shown[5-8] that in the reaction between DIHPPA and DIT, the latter can be replaced with various analogs of DIT, without a drastic reduction in the coupling yield. In contrast, the requirement for DIHPPA is much more specific. It can be seen from Table I that no coupling took place in most instances when DIHPPA was replaced with analogs of this keto acid. Only with a few analogs was a coupling product obtained, and then only in poor or modest yield. In these cases, the analog used had the same aliphatic side chain as DIHPPA, and the phenolic ring still contained one iodine atom or two bromine atoms in *ortho* position to the phenolic hydroxyl. 4-Hydroxy-3,5-diiodophenylacetaldehyde (X) did not react with DIHPPA. Upon alkalinization of the mixture, the aldehyde apparently underwent an aldol condensation leading to the tetraiodo aldehyde XII.

Experimental[9]

5-Iodovanillin.—A solution of 16.2 g. (0.1 mole) of iodine monochloride in 20 ml. of 20% HCl was added at once to a warm solution (50°) of 14.2 g. (0.1 mole) of vanillin in 400 ml. of 20% HCl. After 1 week, the precipitate formed (21.6 g., 81%), was collected, and recrystallized from aqueous ethanol yielding needles, m.p. 182–183° (lit.[10] m.p. 181–182°).

4-Hydroxy-3-iodo-5-methoxyphenylpyruvic Acid (IV).—Iodovanillin was converted to 4-(4-acetoxy-3-iodo-5-methoxybenzal)-2-methyl-5-oxazolone following a procedure similar to the one described below for the synthesis of 4-(4-acetoxy-3,5-dibromobenzal)-2-methyl-5-oxazolone; m.p. 192–194° (lit.[11] m.p. 196–197°), yield 86% (lit.[11] 27%). This azlactone was converted to IV by acid hydrolysis as described for the synthesis of DIHPPA.[5] Recrystallization of the crude keto acid from ethanol–acetic acid gave needles, m.p. 241–243° dec., in 58% yield.

Anal. Calcd. for $C_{10}H_9IO_5$: C, 35.75; H, 2.70. Found: C, 36.26; H, 3.00.

4-(4-Acetoxy-3,5-dibromobenzal)-2-methyl-5-oxazolone.—A mixture of 22.6 g. (0.08 mole) of 3,5-dibromo-4-hydroxybenzaldehyde,[12] 10 g. (0.08 mole) of acetylglycine, 7 g. (0.08 mole) of freshly fused sodium acetate, and 75 ml. of acetic anhydride was heated on a boiling water bath for 2 hr. After cooling, 10 ml. of petroleum ether (b.p. 40–60°) and 10 ml. of water were added to the reaction mixture which was then broken up by means of a glass rod. The crystalline mass was filtered and washed with water, dried, and recrystallized from benzene to give needles, m.p. 180–185°, yield 27 g. (86%). An analytical sample was recrystallized a second time; m.p. 187–189°.

Anal. Calcd. for $C_{13}H_9Br_2NO_4$: C, 38.74; H, 2.25; Br, 39.66; N, 3.48. Found: C, 38.50; H, 2.47; Br, 39.51; N, 3.62.

3,5-Dibromo-4-hydroxyphenylpyruvic Acid (V).—The oxazolone was converted to V by acid hydrolysis as described for the synthesis of IV. Recrystallization of the crude keto acid from aqueous ethanol gave needles, m.p. 208° dec., in 61% yield.

Anal. Calcd. for $C_9H_6Br_2O_4$: C, 31.71; H, 2.23. Found: C, 31.98; H, 1.79.

N-(α-Acetamido-4-acetoxy-3,5-diiodocinnamoyl)glycine.—To a suspension of 3.3 g. (6.6 mmoles) of 4-(4-acetoxy-3,5-diiodobenzal)-2-methyl-5-oxazolone[5] and 0.5 g. (6.6 mmoles) of glycine in 30 ml. of acetone was added 13.2 ml. of 0.5 *N* NaOH. After standing for 1.5 hr., 6.6 ml. of 1 *N* HCl was added; the reaction mixture was concentrated to about 10 ml. and then kept overnight at 4°. The precipitate formed was recrystallized from aqueous ethanol yielding 3.0 g. (78%), m.p. 222–223°.

Anal. Calcd. for $C_{15}H_{14}I_2N_2O_6$: C, 31.49; H, 2.47; I, 44.66; N, 4.90. Found: C, 31.28; H, 2.59; I, 44.59; N, 4.80.

N-(α-Acetamido-4-hydroxy-3,5-diiodocinnamoyl)glycine.—This product can be obtained by mild alkaline hydrolysis of the corresponding acetoxy compound described in the preceding

(1) Paper VII: T. Matsuura, H. Kon, and H. J. Cahnmann, *J. Org. Chem.*, **29**, 3058 (1964).

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(4) Abbreviations: DIHPPA, 4-hydroxy-3,5-diiodophenylpyruvic acid; DIT, 3,5-diiodotyrosine.

(5) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).

(6) A. Nishinaga and T. Matsuura, *ibid.*, **29**, 1812 (1964).

(7) T. Shiba and H. J. Cahnmann, *ibid.*, **29**, 1652 (1964).

(8) T. Shiba and H. J. Cahnmann, *ibid.*, **29**, 3063 (1964).

(9) The elemental analyses were carried out by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by Mr. J. Goda and his associates of the Faculty of Science, Osaka City University, Osaka, Japan. Melting points were determined in capillary tubes and are uncorrected.

(10) G. D. Thorn and C. B. Purves, *Can. J. Chem.*, **32**, 373 (1954).

(11) L. C. Raiford and C. H. Buurman, *J. Org. Chem.*, **8**, 466 (1943).

(12) C. Paal, *Ber.*, **28**, 2407 (1895).

TABLE I

YIELDS OBTAINED IN VARIOUS COUPLING REACTIONS

Compd.	DIHPPA and analogs: R_1	R_2	R_3	DIT and analogs: R_1	R_2	Yield of thyroxine or its analogs, %
I	I	I	$CH_2COCOOH$	I	NH_2	20[a]
II	I	H	$CH_2COCOOH$	I	NH_2	2[b]
III	H	H	$CH_2COCOOH$	I	NH_2	None[a]
IV	I	CH_3O	$CH_2COCOOH$	I	NH_2	4
				I	H	1
V	Br	Br	$CH_2COCOOH$	I	NH_2	9
				I	H	3
				Br	H	1
VI	I	I	$CH_2COCONHCH_2COOH$	I	NH_2	Trace
VII	I	I	$CH_2C(COOH)=NOH$	I	NH_2	Trace
VIII	I	I	$CH=C(COOH)NHCOCH_3$	I	NH_2	None
IX	I	I	$COCOOH$[c]	I	NH_2	None
X	I	I	CH_2CHO	I	NH_2	None
XI	I	I	CHO[c]	I	NH_2	None

[a] See ref. 5. [b] See ref. 7. [c] See ref. 18.

preparation. It is, however more conveniently prepared directly from 4-(4-acetoxy-3,5-diiodobenzal)-2-methyl-5-oxazolone. A solution of 1.65 g. (22 mmoles) of glycine in 22 ml. of 1 *N* NaOH was added to a suspension of 9.94 g. (20 mmoles) of this oxazolone[5] in 60 ml. of acetone. After stirring for 4.5 hr. the oxazolone was completely dissolved. Then 20 ml. of 2 *N* NaOH was added and stirring was continued for 1 hr. The precipitate, formed after acidification with 2 *N* HCl and cooling, was recrystallized from ethanol yielding 6.73 g. (63%), m.p. 240–242° dec.

Anal. Calcd. for $C_{13}H_{12}I_2N_2O_5$: C, 29.45; H, 2.28; I, 47.88; N, 5.29. Found: C, 29.67; H, 2.46; I, 47.71; N, 5.04.

N-(4-Hydroxy-3,5-diiodophenylpyruvyl)glycine (VI).—A mixture of 1.06 g. (2 mmoles) of N-(α-acetamido-4-hydroxy-3,5-diiodocinnamoyl)glycine, 15 ml. of acetic acid, and 6 ml. of 1 *N* HCl was heated for 2 hr. on a steam bath. The reaction mixture was clarified by filtration, and the filtrate was evaporated. The residue was triturated five times with 20 ml. of ether. The combined ether extracts were mixed with petroleum ether (1:1). The precipitate obtained (0.12 g., 12.3%) melted at 219–223°.

Anal. Calcd. for $C_{11}H_9I_2NO_5$: C, 27.02; H, 1.86; I, 51.90; N, 2.86. Found: C, 27.26; H, 2.16; I, 52.19; N, 2.63.

2-Oximino-3-(4-hydroxy-3,5-diiodophenyl)propionic Acid (VII).—Hydrogen was bubbled through a solution of 10 g. (0.14 mole) of hydroxylamine hydrochloride in 60 ml. of water and 150 ml. of 2 *N* NaOH, in order to remove oxygen. Then 4.7 g. (11 mmoles) of DIHPPA[13] was added and the mixture was heated in an atmosphere of hydrogen[14] on a steam bath for 20 min., then cooled and acidified with 4 *N* HCl to about pH 4. On standing overnight at 4° a crystalline precipitate formed, which, on recrystallization from aqueous ethanol, gave 2.6 g. (52%) of crystals, m.p. 173–176°.

Anal. Calcd. for $C_9H_7I_2NO_4 \cdot 1.5H_2O$: C, 22.81; H, 2.13; I, 53.55; N, 2.96. Found: C, 22.83; H, 2.59; I, 53.35; N, 3.07.

α-Acetamido-4-hydroxy-3,5-diiodophenylcinnamic Acid (VIII).—A suspension of 2.49 g. (5 mmoles) of 4-(4-acetoxy-3,5-diiodobenzal)-2-methyl-5-oxazolone[5] in 15 ml. of 20% aqueous KOH was heated for 20 min. on a steam bath. The reaction mixture was cooled and acidified (congo red) with 1 *N* HCl. The crystals formed were recrystallized from aqueous ethanol yielding 1.56 g. (66%), m.p. 245–247° dec. (lit.[15] m.p. 234–235°).

Anal. Calcd. for $C_{11}H_9I_2NO_4$: C, 27.93; H, 1.92; I, 53.66; N, 2.96. Found: C, 28.15; H, 2.06; I, 53.43; N, 2.95.

Acetyl-2,6-diiodochavicol (O-Acetyl-4-allyl-2,6-diiodophenol).—A solution of 13 g. (123 mmoles) of Na_2CO_3 in 100 ml. of water was mixed with a solution of 6.7 g. (50 mmoles) of chavicol (4-allylphenol)[16] in 50 ml. of 1 *N* NaOH. The mixture was cooled in an ice bath and a solution of 25.4 g. (0.1 mole) of iodine and 25.5 g. of potassium iodide in 100 ml. of water was added over a period of 1 hr. An aqueous suspension of the precipitate formed was acidified with 4 *N* HCl. An oil formed which solidified in the cold yielding 17.1 g. (78%). A solution of 16.6 g. of this crude diiodochavicol in 50 ml. of pyridine was cooled in an ice bath and 50 ml. of acetic anhydride was added. After standing overnight at room temperature, the mixture was poured into ice–water, acidified with 4 *N* HCl, and extracted with ether. After successive washings with 2 *N* HCl, water, 1 *N* NaOH, and again water, the ether extract was dried and evaporated. Distillation of the residue gave 15.0 g. (82%) of a viscous oil, b.p. 146–148° (0.5 mm.), which crystallized upon standing at 4° for 1 month; m.p. 42–45°.

Anal. Calcd. for $C_{11}H_{10}I_2O_2$: C, 30.86; H, 2.35. Found: C, 30.91; H, 2.50.

Semicarbazone of 4-Acetoxy-3,5-diiodophenylacetaldehyde.—To a mixture of 2.2 g. (5 mmoles) of acetyl-2,6-diiodochavicol, 50 ml. of ether, 50 ml. of water, and 50 mg. (0.2 mmole) of osmium tetroxide, was added 2.3 g. (12 mmoles) of sodium periodate in small portions.[17] After stirring for 4.5 hr., the ether layer was separated and concentrated to about 10 ml. A solution of 2.2 g. (20 mmoles) of semicarbazide hydrochloride in 10 ml. of water was added and the mixture was rendered homogeneous by the addition of about 10 ml. of pyridine. After standing overnight, the mixture was poured into ice–water. The precipitate formed gave, after recrystallization from ethanol, 1.5 g. (62%) of fine prisms, m.p. 177–179°.

Anal. Calcd. for $C_{11}H_{11}I_2N_3O_3$: C, 27.12; H, 2.28; N, 8.63. Found: C, 27.18; H, 2.47; N, 8.65.

The 2,4-dinitrophenylhydrazone was obtained by adding a solution of 2,4-dinitrophenylhydrazine in a mixture of aqueous ethanol and sulfuric acid to the above-mentioned concentrated ether solution. Recrystallization from ethanol gave yellow needles, m.p. 210–213°.

Anal. Calcd. for $C_{16}H_{12}I_2N_4O_6$: C, 31.50; H, 1.98; N, 9.18. Found: C, 31.82; H, 2.14; N, 9.11.

Semicarbazone of 4-Hydroxy-3,5-diiodophenylacetaldehyde.—A suspension of 1.2 g. (2.5 mmoles) of the above-mentioned semicarbazone in a mixture of 10 ml. of ethanol and 10 ml. of 2 *N* NaOH was warmed to 40° in order to obtain a clear solution which was permitted to stand at room temperature for 1.5 hr. Water was then added and the mixture was acidified with 4 *N* HCl. The precipitate formed gave, after recrystallization from ethanol, 0.57 g. (52%) of needles, m.p. 175–176°.

Anal. Calcd. for $C_9H_9I_2N_3O_2$: C, 24.41; H, 2.04; N, 9.44. Found: C, 24.61; H, 2.36; N, 9.42.

(13) Commercially available from Osaka Laboratory of Synthetic Organic Chemicals, 74 Ueda Higashimachi, Nishinomiya, Japan.

(14) In alkaline medium DIHPPA undergoes a rapid breakdown to the aldehyde XI, when oxygen is present.

(15) M. Nakano and S. Tsuchiya, *Gunma J. Med. Sci.*, **10**, 280 (1961).

(16) V. Grignard and J. Ritz, *Bull. soc. chim. France*, [5]**3**, 1181 (1936).

(17) *Cf.* R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

4-Hydroxy-3,5-diiodophenylacetaldehyde (X).—To a solution of 1.18 g. (3.1 mmoles) of the semicarbazone of 4-hydroxy-3,5-diiodophenylacetaldehyde in 30 ml. of acetic acid and 15 ml. of water, was added 3 ml. (43 mmoles) of pyruvic acid. The solution was kept for 20 hr. at 40° in an atmosphere of nitrogen. Water was then added until a slight turbidity persisted. On standing overnight at 4°, 0.81 g. of crystals were obtained. The mother liquors yielded another crop of 0.11 g. The crude product was recrystallized from aqueous acetic acid yielding 0.29 g. (28%) of needles, m.p. 111–113°.

Anal. Calcd. for $C_8H_6I_2O_2$: C, 24.75; H, 1.55. Found: C, 24.92; H, 1.76.

Coupling Reactions of Analogs of DIHPPA with DIT.—These reactions were carried out essentially as described previously[6] with several minor modifications imposed by the nature of the analog used. The amount of analog used in a run ranged from 0.5 to 6 mmoles. The analog VIII was insoluble in butanol and was therefore dissolved in 2 *N* NaOH and the pH was kept at 7.6 by the slow addition of 4 *N* HCl. In several cases, the addition of *t*-butylhydroperoxide was omitted since preliminary tests indicated that it had little if any influence on the yield of the analog of thyroxine. The method of working up the reaction mixture also depended on the nature of the starting material and on the yield of coupling product. In the case of very small yields the thyroxine formed could only be detected by paper chromatography in the usual solvent systems.[18]

3,5,3′-Triiodo-5′-methoxythyronine.—A coupling reaction was carried out with 2.02 g. (6 mmoles) of the keto acid IV and 2.01 g. (4.6 mmoles) of DIT. The crude product was extracted with acetone in order to remove side products of the reaction, mainly 5-iodovanillin. The undissolved material, m.p. 218–219° dec., weighed 0.13 g. (4%). It was chromatographically pure. Crystallization from a 5% sodium carbonate solution gave the sodium salt in the form of fine crystals.

3,5,3′-Triiodo-5′-methoxythyropropionic Acid.—A coupling reaction of 2.02 g. (6 mmoles) of the keto acid IV and 1.94 g. (4.6 mmoles) of 3,5-diiodophloretic acid[18] gave a crude product which was crystallized from benzene to give 17 mg. (1%) of prisms, m.p. 196–198°.

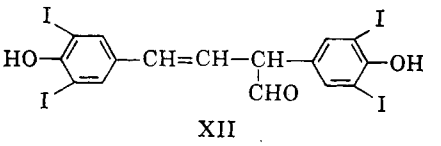
Anal. Calcd. for $C_{16}H_{13}I_3O_5$: C, 28.79; H, 1.97. Found: C, 28.26; H, 2.08.

3′,5′-Dibromo-3,5-diiodothyronine.—A coupling reaction was carried out with 2.02 g. (6 mmoles) of the keto acid V and 2.17 g. (4.6 mmoles) of DIT dihydrate. The crude product was extracted with acetone in order to remove side products of the reaction, mainly 3,5-dibromo-4-hydroxybenzaldehyde. The undissolved material, m.p. 243° dec., weighed 0.28 g. (9%). It was chromatographically pure. Treatment of a solution in methanol–ammonia (95:1) with dilute acetic acid gave a colorless precipitate, m.p. 244° dec. (lit. m.p. 245–246° dec.[19] and 244.5° dec.[20]).

3′,5′-Dibromo-3,5-diiodothyropropionic Acid.—The crude product obtained in a coupling reaction between 2.02 g. (6 mmoles) of keto acid V and 1.94 g. (4.6 mmoles) of 3,5-diiodophloretic acid[18] was crystallized from benzene yielding 0.1 g. (3%) of needles, m.p. 203–205°. The infrared spectrum was identical with that of a sample prepared by a different synthetic route.[21]

3,5,3′,5′-Tetrabromothyropropionic Acid.—A coupling reaction between 1.27 g. (3.5 mmoles) of the keto acid V and 0.59 g. (2.9 mmoles) of 3,5-dibromophloretic acid[22] gave a crude product which, after crystallization from benzene, yielded 18 mg. (1%) of needles, m.p. 184–186°. The infrared spectrum was identical with that of a sample prepared by a different synthetic route.[21]

Behavior of 4-Hydroxy-3,5-diiodophenylacetaldehyde (X) in the Coupling Reaction with DIT.—The reaction was carried out in the usual manner with 0.25 g. (0.64 mmole) of the aldehyde X and 0.25 g. (0.53 mmole) of DIT. When the residue obtained after evaporation of the butanol extract was acidified, 0.1 g. of a precipitate was obtained which, after crystallization from ethyl acetate, gave fine needles, m.p. 248–249° dec. No thyroxine was detected by paper chromatography of the mother liquor. Further investigation showed that the presence of DIT was not required for the formation of this product which was tentatively identified as the aldehyde XII, formed by aldol condensation of 2 molecules of X. The aldehyde X was fairly stable when it was treated with oxygen at pH 7.6 However, when alkali was added the condensation product XII formed. Structure XII is compatible with the elemental analysis and the infrared spectrum. A carbonyl band at 1730 cm.$^{-1}$ indicated that the carbonyl is not in conjugation with a double bond.[23] The ultraviolet spectrum showed bands at λ_{max}^{EtOH} 220 mμ (ε 37,000), 245 (26,000), 260 (24,000), 348 (28,400), and shoulder at 415 (6300).



XII

Anal. Calcd. for $C_{16}H_{10}I_4O_3$: C, 25.33; H, 1.32. Found: C, 25.21; H, 1.55.

(18) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **81**, 871 (1959).

(19) K. Schuegraf, *Helv. Chim. Acta*, **12**, 405 (1929).

(20) C. R. Harington and W. McCartney, *J. Chem. Soc.*, **892** (1929).

(21) T. Matsuura, unpublished work.

(22) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1962).

(23) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 133.

Model Reactions for the Biosynthesis of Thyroxine. IX. Synthesis of Peptides of L-Thyroxine[1,2]

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Only a few peptides of thyroxine[4,5] have been synthesized.[6] The method used, heating of halogenoacylthyroxine with ammonia, permits the preparation of only a limited number of peptides, leads to racemization, and cannot be applied to the synthesis of those peptides in which the carboxyl group of thyroxine is peptide linked. The numerous methods for the synthesis of peptides published during the last few decades are not easily applicable to the synthesis of peptides of thyroxine since most of them involve the removal of a blocking group by either strong acid or hydrogenolysis, which leads to partial or total deiodination. It is also not possible to synthesize peptides of thyroxine by iodinating peptides of thyronine since this would lead to peptides of 3′,5′-diiodothyronine.

In the present investigation a new principle, etherification of peptides of diiodotyrosine with 4-hydroxy-3,5-diiodophenylpyruvic acid, was applied to the synthesis of peptides of thyroxine. This reaction is analogous to that in which the same keto acid converts diiodotyrosine to thyroxine[7] and various analogs of diiodotyrosine to the corresponding analogs of thyroxine.[8,9] The

(1) Paper VIII: T. Shiba, H. J. Cahnmann, T. Matsuura, A. Nishinaga, and H. Sakamoto, *J. Org. Chem.*, **29**, 3061 (1964).

(2) A preliminary report of this work was presented at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(3) Visiting Scientist from the Department of Chemistry, Faculty of Science, Osaka University, Osaka, Japan.

(4) J. N. Ashley and C. R. Harington, *Biochem. J.*, **22**, 1436 (1928).

(5) E. Abderhalden and E. Schwab, *Fermentforschung.*, **11**, 164 (1930).

(6) The formation of N-acylated peptides of thyroxine in the aerobic incubation of N-acylated peptides of diiodotyrosine was described by R. Pitt-Rivers [*Biochem. J.*, **43**, 223 (1948)] and by R. Pitt-Rivers and A. T. James [*ibid.*, **70**, 173 (1958)]. Attempts to convert these acyl derivatives to the free thyroxine peptides failed, because removal of the acyl group was accompanied by fission of the peptide bond (R. Pitt-Rivers, personal communication).

(7) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).

(8) A. Nishinaga and T. Matsuura, *ibid.*, **29**, 1812 (1964).

(9) T. Shiba and H. J. Cahnmann, *ibid.*, **29**, 1652 (1964).