Synthesis of *meta* Analogs of Thyroxine

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N-acetyl-3-(3-hydroxy-4,6-diiodophenyl)-DL-alanine (I) was converted to its ethyl ester II, whose etherification gave the diphenyl ether III. Treatment of III with hydriodic acid yielded the isomer IV of thyronine, and treatment with hydrobromic acid yielded the isomer V of diiodothyronine. Iodination of V gave the isomer VI of thyroxine. A similar sequence of reactions converted N-acetyl-3-(3-hydroxy-2,4,6-triiodophenyl)-DL-alanine (VIII) to the isomer XI of triiodothyronine and to the pentaiodinated analog XII of thyronine. The N-acetyl derivative VII of VI was formed in a reaction between 4-hydroxy-3,5-diiodophenylpyruvic acid and I. Similarly the N-acetyl derivative XIII of XII was formed from 4-hydroxy-3,5-diiodophenylpyruvic acid and VIII. Deacetylation of VII gave VI, that of XIII gave XII.

In most of the numerous analogs of thyroxine that have been synthesized, one or more of the iodine atoms or the phenolic hydroxyl group of thyroxine are eliminated or replaced with other functional groups, or the alanine side chain is modified either by lengthening or shortening, or by addition or elimination of functional groups. Two position isomers of thyroxine, *o*- and *m*-thyroxine, which differ from thyroxine in the position of the phenolic hydroxyl with respect to the diphenyl ether bridge, have been described by Niemann, *et al.*,[2-4] and the desamino (propionic acid) analog of *m*-thyroxine has been described by Bruice.[5] Attempts by Jackson to synthesize another position isomer (VI) of thyroxine, in which the alanine side chain is in the position *meta* and not *para* to the diphenyl ether bridge, either failed[6] or had to be discontinued.[7] After Jackson's death, his efforts to synthesize this *meta* isomer of thyroxine were resumed in this laboratory, as he had requested.

Jackson's failure to synthesize VI is due to the fact that he prepared intermediates having nitro groups in the place of iodine with the intention to reduce them to amino groups, which in turn were to be replaced with iodine in a Sandmeyer reaction. Reduction of the nitro compounds, however, did not yield the desired amino compounds but hydrocarbostyrils by ring closure between the methoxycarbonyl group of the aliphatic side chain and an aromatic amino group *ortho* to the side chain. We have avoided this complication by choosing a synthetic approach which does not involve aromatic amines as intermediates. The intermediates in this synthesis already contain iodine atoms *ortho* and *para* to the aliphatic side chain. They show much less tendency for ring formation which could be completely avoided under appropriate experimental conditions.[8]

The starting material for the synthesis was *m*-DL-tyrosine[9] which, upon iodination,[10] gave 3-(3-hydroxy-4,6-diiodophenyl)-DL-alanine.[6] Unless the conditions for the iodination described in the Experimental section were observed, appreciable amounts of other iodination products, mainly 3-(3-hydroxy-2,4,6-triiodophenyl)-DL-alanine, were formed which could not be separated easily from the desired product. The latter was converted to its N-acetyl derivative, I.[6] The further sequence of reactions, leading over II, III, and V to the tetraiodinated *meta* analog VI of thyronine, is shown in Chart I.

A similar sequence of reactions was carried out with the triiodo compound VIII, obtained by further iodination of I. This led to the formation of the pentaiodinated *meta* analog XII of thyronine.

While the etherification of IX with di-*p*-methoxyphenyliodonium bromide[11] took place smoothly, that of II gave III in only 35% yield. In the latter case, hydrolyzed starting material (I) could be isolated from the reaction mixture in about 40% yield.

When III was heated with hydriodic acid in acetic acid in order to remove the various blocking groups, complete deiodination took place and the *meta* analog IV of thyronine was obtained. When the hydriodic acid was replaced with hydrobromic acid, and the other conditions described in the Experimental section were observed, practically no deiodination took place. The ease with which III is deiodinated and the resistance of X to deiodination under similar conditions is in accordance with the findings of Meltzer, *et al.*,[12] and of Matsuura and Nishinaga.[13] Analogs of thyroxine, in whose nonphenolic ring only one of the *ortho* positions with respect to the ether bridge is substituted with iodine, are easily deiodinated, while substitution of both *ortho* positions with iodine or another bulky substituent provides protection against deiodination. Explanations for this difference in behavior have recently been offered.[13,14] These explanations are based on the postulate that unrestricted rotation at the ether bridge is a prerequisite for deiodination.

Compound VIII and the analogs V, VI, XI, and XII of thyroxine showed a tendency to retain solvent when dried at room temperature. A check for the identity of the tetra- and pentaiodo compounds VI and XII was provided by the comparison of their infrared spectra and R_f values in paper chromatograms with those of the same compounds prepared by a different and un-

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(2) C. Niemann, *Fortschr. Chem. Org. Naturstoffe*, **7**, 167 (1950).

(3) C. Niemann and C. E. Redemann, *J. Am. Chem. Soc.*, **63**, 1549 (1941).

(4) C. Niemann and J. F. Mead, *ibid.*, **63**, 2685 (1941).

(5) T. C. Bruice, *J. Org. Chem.*, **19**, 333 (1954).

(6) E. L. Jackson, *ibid.*, **77**, 4860 (1955).

(7) E. L. Jackson, *ibid.*, **25**, 2227 (1960).

(8) *Cf.* footnote 27.

(9) R. R. Sealock, M. E. Speeter, and R. S. Schweet, *J. Am. Chem. Soc.*, **73**, 5386 (1951).

(10) W. P. Dickinson and P. G. Marshall, *J. Chem. Soc.*, 2289 (1930).

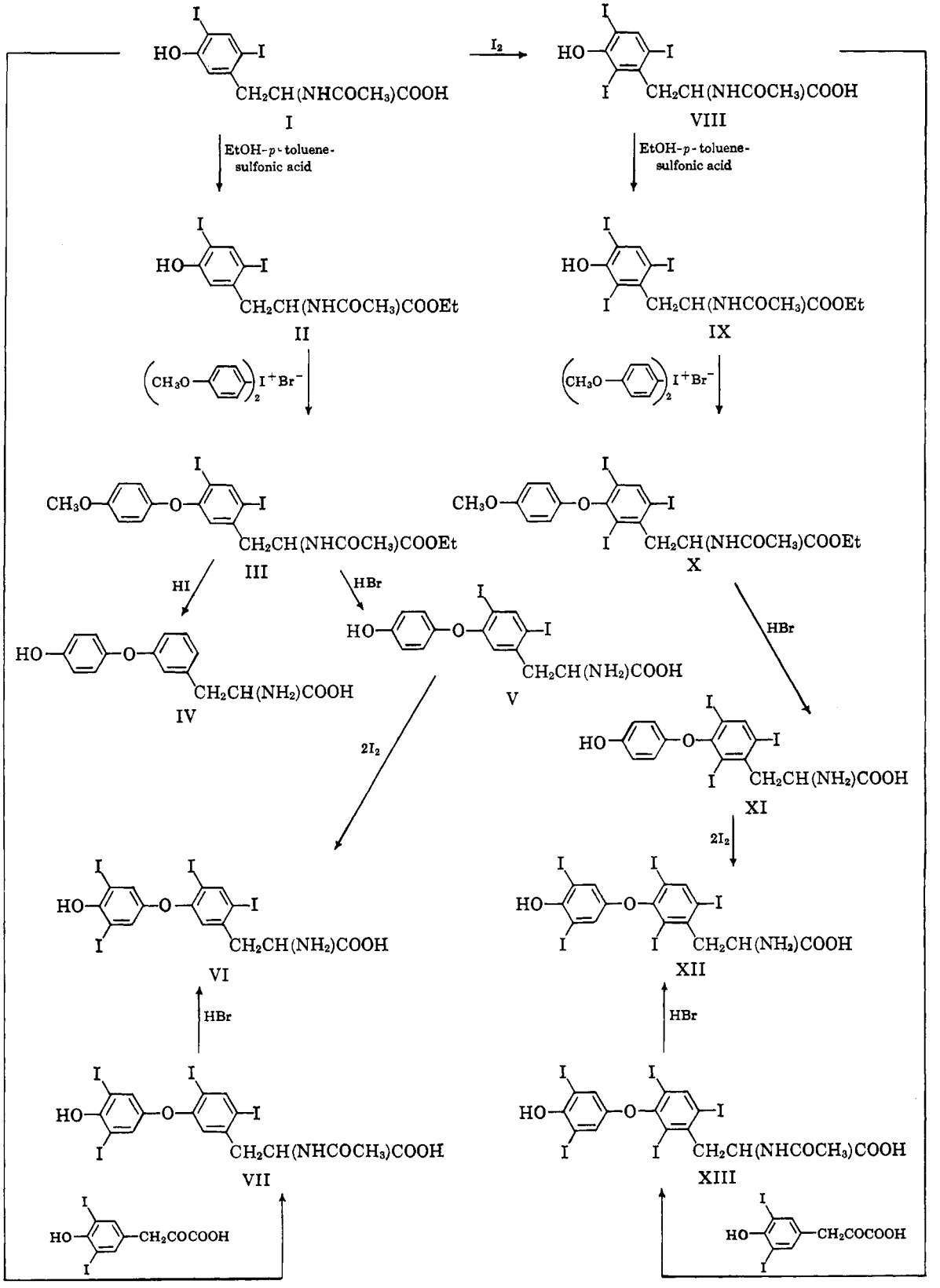
(11) *Cf.* P. F. Bevilacqua and J. T. Plati, U. S. Patent 2,895,927 (July 21, 1959).

(12) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, **26**, 1413 (1961).

(13) T. Matsuura and A. Nishinaga, *ibid.*, **29**, 3168 (1964).

(14) E. C. Jorgensen and J. A. W. Reid, *ibid.*, **29**, 3396 (1964).

CHART I



equivocal route, the reaction of 4-hydroxy-3,5-diiodophenylpyruvic acid with I and VIII, respectively, followed by deacetylation of the reaction products VII and XIII. In view of the low yields obtained in these coupling reactions, this synthetic approach is not of preparative interest but throws further light on the structural requirements of the reaction partners in this interesting coupling reaction.[15]

The purification of the various intermediate and end products of the syntheses described in this paper was followed routinely by paper chromatography in 1-butanol–dioxane–2 *N* ammonium hydroxide (4:1:5) and in 1-butanol–acetic acid–water (78:10:12). R_f values in the former solvent, which usually gave more

(15) These structural requirements and the mechanism of the coupling reaction have been discussed in previous publications.[22-26]

TABLE I

R_f VALUES IN 1-BUTANOL–DIOXANE–2 N AMMONIUM HYDROXIDE[a]

Compound[b]	R_f	Color[c]
3-(3-Hydroxy-4,6-diiodophenyl)-DL-alanine	0.28	Brownish orange
I	0.30	Yellowish orange
II	0.79	Yellowish brown
IV	0.45	Bluish orange
V	0.59	Bluish purple
VI	0.44	Grayish purple
VII	0.37	Grayish purple
VIII	0.34	Reddish orange
IX	0.81	Grayish orange
XI	0.57	Bluish purple
XII	0.41	Grayish purple
XIII	0.47	Grayish purple

[a] Solvent ratio, 4:1:5; ascending method; Toyo paper 51 (Whatman paper 3MM gives somewhat higher R_f values); color reagent, diazotized N^1,N^1-diethylsulfanilamide.[16] [b] Numerals refer to Chart I. [c] The colors vary somewhat with the concentration of the substance, the amount of reagent used, and the amount of residual solvent in the paper.

compact spots and better separations, are listed in Table I. Other previously mentioned solvent systems[16] were used occasionally.

Experimental[17]

3-(3-Hydroxy-4,6-diiodophenyl)-DL-alanine.—A solution of 12.0 g. (66 mmoles) of *m*-DL-tyrosine in 230 ml. of concentrated ammonium hydroxide[18] (~15 M) was centrifuged in order to remove some insoluble material. The clear supernatant was cooled in an ice bath and a solution of 34.0 g. (134 mmoles) of iodine and 50 g. of potassium iodide in 100 ml. of water was added with stirring over a period of 1 hr. The reaction mixture was permitted to stand overnight in an open beaker. This resulted in the evaporation of most of the ammonia and in the formation of a precipitate. The remainder of the ammonia was removed by concentrating the reaction mixture under reduced pressure to about 200 ml. The residue was centrifuged and the precipitate was washed with water and dried, yielding 23.9 g. (83%), m.p. 228–229° dec.

This material was used without purification for the subsequent acetylation. A small amount was purified by filtration of a solution in dilute hydrochloric acid, alkalinization of the clear filtrate with ammonium hydroxide, and precipitation at pH 4 with acetic acid: m.p. 233° dec., lit.[10] m.p. 230°.

N-Acetyl-3-(3-hydroxy-4,6-diiodophenyl)-DL-alanine Ethyl Ester (II).—The conversion of 3-(3-hydroxy-4,6-diiodophenyl)-DL-alanine to its O,N-diacetyl derivative by alternate treatment with sodium hydroxide and freshly distilled acetic anhydride, and the subsequent O-deacetylation were carried out according to Jackson.[6] The crude N-acetyl derivative (I), m.p. 192–193° dec., was used for the conversion to the ethyl ester II. After recrystallization, the melting point rose to 195–196°, lit.[6] m.p. 200°.

A suspension of 4.75 g. (10 mmoles) of I and 0.3 g. of *p*-toluenesulfonic acid monohydrate in a mixture of 3 ml. of ethanol and 30 ml. of chloroform was refluxed, and water was removed azeotropically. After 6 hr., the reaction mixture was washed successively with an aqueous solution of sodium bicarbonate, dilute hydrochloric acid, and water. The chloroform was evaporated under reduced pressure, after the addition of a few drops of 6 N hydrochloric acid.[19] Water was added to a solution of the residue in hot ethanol containing a few drops of 6 N hydrochloric acid, until a precipitate began to form which was redissolved by slight heating. When the solution was then permitted to cool very slowly, heavy crystals formed which, after washing with water and drying, melted at 149–151°. When the solution was cooled rapidly in an ice bath, with scratching or seeding, different crystals, melting at 83–85°, were obtained. The yield, based on I, ranged from 81 to 93% in both cases. When the melt obtained by heating the lower melting crystals was cooled, crystals formed which, on reheating, melted at 150–151°. When an ethanolic solution of either the low- or the high-melting crystals was treated with an equal volume of 1 N NaOH at room temperature for 25 min., chromatographically pure I was obtained. The infrared solution spectra and the elemental analyses of the two crystal forms were identical within the experimental error.

Anal. Calcd. for $C_{13}H_{15}I_2NO_4$: C, 31.04; H, 3.01; I, 50.45; N, 2.78. Found: C, 30.95; H, 2.97; I, 50.18; N, 2.92.

N-Acetyl-3-[3-(4-methoxyphenoxy)-4,6-diiodophenyl]-DL-alanine Ethyl Ester (III).—To a solution of 2.12 g. (4.2 mmoles) of II in 100 ml. of methanol were added 4.21 g. (10 mmoles) of di-*p*-methoxyphenyliodonium bromide,[20] 1.4 ml. (10 mmoles) of triethylamine, and 0.5 g. of copper powder (electrolytic dust). The reaction mixture was stirred at room temperature for 20 hr. The greenish precipitate formed was removed by filtration and washed with benzene. The combined filtrates were evaporated to dryness, the residue was dissolved in hot benzene, and the solution obtained was clarified by filtration. The filtrate was washed successively with an aqueous solution of sodium bicarbonate, water, dilute hydrochloric acid, and again water, then dried. The residue obtained after evaporation of the solvent was crystallized from ethyl acetate–petroleum ether, to give 0.90 g. (35%) of crystals, m.p. 174–175.5°.

Anal. Calcd. for $C_{20}H_{21}I_2NO_5$: C, 39.43; H, 3.47; I, 41.66, N, 2.30. Found: C, 39.30; H, 3.37; I, 41.74; N, 2.33.

3-[3-(4-Hydroxyphenoxy)phenyl]-DL-alanine (IV).—A mixture of 1.18 g. (1.94 mmoles) of III, 10 ml. of glacial acetic acid, and 10 ml. of 57% hydriodic acid (containing 1% of hypophosphorous acid) was heated for 3 hr. in an oil bath at 130–140°, while a slow stream of carbon dioxide was bubbled through the solution.[21] The reaction mixture was cooled to room temperature, then evaporated to dryness under reduced pressure. The residue was dissolved in 3 ml. of hot ethanol, and a hot solution of 1 g. of sodium acetate in 1.5 ml. of water was added. The mixture was permitted to stand overnight at 2°. The crystals formed were collected by filtration, washed with a small amount of ice-cold aqueous ethanol, and dried, yielding 0.43 g. (81%), m.p. 217–218° dec. An analytical sample was recrystallized by dissolving it in very dilute hydrochloric acid and adding a solution of sodium acetate, or by letting a solution in methanol containing a few drops of concentrated ammonium hydroxide stand in an open beaker; m.p. 222–223° dec.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.54; H, 5.85; N, 5.09.

3-[3-(4-Hydroxyphenoxy)-4,6-diiodophenyl]-DL-alanine (V).—A mixture of 1.40 g. (2.3 mmoles) of III, 25 ml. of glacial acetic acid, and 2.7 ml. of 47% hydrobromic acid was heated for 2 hr. in an oil bath at 130–140°. The reaction mixture was allowed to stand overnight in an open beaker. The crystals formed were collected by filtration and washed with water, yielding 0.82 g. (68%), m.p. 230–232° dec. A solution of this crude product in methanol containing a few drops of ammonium hydroxide was decolorized with charcoal, then permitted to stand overnight in an open beaker. The crystals formed were collected by filtration,

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

(17) Elemental analyses were carried out by Mr. M. Okumiya and his associates of the Department of Chemistry, Faculty of Science, Osaka University, and by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points were taken in capillary tubes and are uncorrected. Melting points determined on the Kofler stage differed only slightly from those taken in capillary tubes. This is in contrast to the behavior of certain other iodinated compounds which have lower melting points on the Kofler stage. The most striking example for such a compound is 4-hydroxy-3,5-diiodobenzaldehyde which melts at 203° in a capillary and at 191° on the Kofler stage.

(18) In contrast to the iodination of the diphenyl ethers V and XI where the use of concentrated ammonium hydroxide or of an aqueous solution of methylamine as the proton acceptor gave similar yields, the former base gave a better yield of the desired product in the case of the iodination of I and of *m*-tyrosine.

(19) Without the addition of hydrochloric acid some deiodination occurs; *cf.* J. H. Barnes, E. T. Borrows, J. Elks, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, 2824 (1950).

(20) H. Ziegler and C. Marr, *J. Org. Chem.*, **27**, 3335 (1962).

(21) The transient formation of an intermediate was revealed by short-path paper chromatography. This intermediate gave color reactions with diazotized N^1,N^1-diethylsulfanilamide and with ninhydrin, and is therefore believed to be V.

washed with aqueous methanol and dried, yielding 0.62 g. (50%), m.p. 239–241° dec.

Anal. Calcd. for $C_{15}H_{13}I_2NO_4 \cdot H_2O$: C, 33.17; H, 2.78; I, 46.73; N, 2.58. Found: C, 33.38; H, 2.79; I, 46.84; N, 2.86.

3-[3-(4-Hydroxy-3,5-diiodophenoxy)-4,6-diiodophenyl]-DL-alanine (VI). A. By Iodination of 3-[3-(4-Hydroxyphenoxy)-4,6-diiodophenyl]-DL-alanine.—A solution of 0.51 g. (2 mmoles) of iodine and 1 g. of potassium iodide in 8 ml. of water was added over a period of 5 min. to a stirred solution of 0.52 g. (1 mmole) of V in 25 ml. of 30% aqueous methylamine. Stirring was continued for 2 hr.; then 30 ml. of methanol was added to the reaction mixture and the pH was brought to 5 with acetic acid. The precipitate formed was collected by filtration, washed with aqueous methanol, and dried, yielding 0.63 g. (81%), m.p. 203–204° dec. Reprecipitation with aqueous acetic acid from a solution in aqueous methanol containing some ammonium hydroxide, followed by washing with methanol, water, and acetone, gave 0.48 g. (62%) of practically pure VI, melting at 207.5–208.5° dec. An analytical sample was obtained by permitting a solution, in glacial acetic acid containing some dilute hydrochloric acid, to evaporate slowly.

Anal. Calcd. for $C_{15}H_{11}I_4NO_4 \cdot 0.5CH_3COOH$: C, 23.81; H, 1.62; I, 62.91; N, 1.74. Found: C, 23.98; H, 1.58; I, 62.68; N, 2.08.

Removal of the acetic acid by heating the sample at 80° over potassium hydroxide for 16 hr. was accompanied by some loss of iodine.

Anal. Calcd. for $C_{15}H_{11}I_4NO_4$: C, 23.19; H, 1.43; I, 65.34; N, 1.80. Found: C, 23.36; H, 1.55; I, 64.64; N, 2.01.

B. By Reaction of N-Acetyl-3-(3-hydroxy-4,6-diiodophenyl)-DL-alanine with 4-Hydroxy-3,5-diiodophenylpyruvic Acid and Oxygen, Followed by Deacetylation.—The reaction was carried out with 4.3 g. (9 mmoles) of I at pH 7.6 (phosphate buffer) and in the presence of sodium sulfate and of a small amount of *t*-butyl hydroperoxide, essentially as described previously for similar coupling reactions.[22-26] The precipitate formed upon acidification of the reaction mixture was dissolved in 1 *N* sodium hydroxide, the alkaline solution was extracted with 1-butanol, and the butanol extract was evaporated. Acidification of an aqueous solution of the residue gave a precipitate which was washed with water and dried, yielding 0.52 g. (7%). After another reprecipitation from ethyl acetate–petroleum ether, an aliquot of the still not pure N-acetyl-3-[3-(4-hydroxy-3,5-diiodophenoxy)-4,6-diiodophenyl]-DL-alanine (VII) was deacetylated without further purification.

A solution of 100 mg. (0.12 mmole) of VII in a mixture of 2 ml. of glacial acetic acid and 0.2 ml. of 47% hydrobromic acid was heated for 2 hr. in an oil bath at 130–140°, then permitted to stand in an open vessel overnight. A precipitate formed which was dissolved in methanol containing aqueous ammonium hydroxide. The solution was decolorized with charcoal, then permitted to stand in an open beaker. The crystals formed (45 mg.) melted at 199.5–200.5° dec. Although elemental analyses showed that the product was not pure, it gave a single spot on paper chromatograms after spraying with diazotized N^1,N^1-diethylsulfanilamide or ninhydrin. The R_f values and the infrared spectra of VI synthesized by either method A or B were identical.

N-Acetyl-3-(3-hydroxy-2,4,6-triiodophenyl)-DL-alanine (VIII).—A solution of 3.0 g. (12.0 mmoles) of iodine and 10 g. of potassium iodide in 40 ml. of water was added over a period of 20 min. to a stirred and cooled solution (0–5°) of 5.4 g. (11.4 mmoles) of I in 70 ml. of concentrated ammonium hydroxide (~15 *M*).[18] Stirring was continued at room temperature for another 3 hr., then the reaction mixture was brought to pH 2 with 6 *N* acetic acid, and permitted to stand overnight at 2°. The precipitate formed was collected by filtration and crystallized from aqueous ethanol containing a small amount of hydrochloric acid,[27] yielding 6.21 g. (88%), m.p. 222–223° dec. Recrystallization from the same solvent raised the melting point to 227–228° dec.

Anal. Calcd. for $C_{11}H_{10}I_3NO_4 \cdot 0.5C_2H_5OH$: C, 23.10; H, 2.10; I, 61.02; N, 2.24. Found: C, 23.21; H, 1.89; I, 61.10; N, 2.32.

N-Acetyl-3-(3-hydroxy-2,4,6-triiodophenyl)-DL-alanine Ethyl Ester (IX).—A suspension of 0.60 g. (9.6 mmoles) of VIII and 30 mg. of *p*-toluenesulfonic acid monohydrate in a mixture of 7 ml. of ethanol and 70 ml. of chloroform was refluxed for 7 hr. Water was removed azeotropically. The clear solution was worked up in the same manner as described above for the synthesis of II. A first crop of 0.42 g. of crystals was obtained; acidification of the water washings gave a second crop of 0.20 g.; total yield was 0.62 g. (102%), m.p. 169–173°. A recrystallized sample, m.p. 172–173°, was used for analysis.

Anal. Calcd. for $C_{13}H_{14}I_3NO_4$: C, 24.82; H, 2.24; I, 60.53; N, 2.23. Found: C, 24.93; H, 1.96; I, 60.08; N, 2.38.

N-Acetyl-3[3-(4-methoxyphenoxy)-2,4,6-triiodophenyl]-DL-alanine Ethyl Ester (X).—To a solution of 3.77 g. (6.0 mmoles) of IX in 250 ml. of methanol, were added 5.47 g. (13 mmoles) of di-*p*-methoxyphenyliodonium bromide,[20] 1.8 ml. (13 mmoles) of triethylamine, and 1.0 g. of copper powder (electrolytical dust). After stirring for 24 hr., 200 ml. of benzene was added. A small amount of copper and of a greenish brown precipitate were removed by filtration and washed with methanol–benzene. The filtrate was worked up as described above for III, yielding 3.15 g. (71%), m.p. 155–156.5°.

Anal. Calcd. for $C_{20}H_{20}I_3NO_5$: C, 32.68; H, 2.74; I, 51.79; N, 1.91. Found: C, 32.75; H, 2.56; I, 51.85; N, 1.90.

3-[3-(4-Hydroxyphenoxy)-2,4,6-triiodophenyl]-DL-alanine (XI).—The treatment of 0.74 g. (1 mmole) of X with hydrobromic acid was carried out as described above for the conversion of III to V.[28] During the heating, crystals appeared whose amount increased upon cooling of the reaction mixture. After filtration, washing with a small amount of acetic acid and with water, and drying, 0.55 g. (82%)[29] of crystals melting at 239.5–240.5° dec. were obtained. An analytical sample was recrystallized by letting a solution in methanol containing a few drops of concentrated ammonium hydroxide stand overnight in an open beaker; fine needles formed, melting at 244–245° dec.

Anal. Calcd. for $C_{15}H_{12}I_3NO_2 \cdot H_2O$: C, 26.93; H, 2.11; I, 56.91; N, 2.09. Found: C, 27.16; H, 2.19; I, 56.66; N, 2.06.

3-[3-(4-Hydroxy-3,5-diiodophenoxy)-2,4,6-triiodophenyl]-DL-alanine (XII). A. By Iodination of 3-[3-(4-Hydroxyphenoxy)-2,4,6-triiodophenyl]-DL-alanine.—Iodination of 0.65 g. (1 mmole) of XI was carried out in the same manner as described for the iodination of V, except that the reaction mixture was stirred for 3 instead of 2 hr. The precipitate formed upon addition of methanol and acetic acid was a gel. It was washed with aqueous methanol, then crystallized by adding some dilute hydrochloric acid to a solution in glacial acetic acid and permitting the mixture to evaporate slowly in an open beaker, yielding 0.56 g. (63%), m.p. 218–219° dec.

Anal. Calcd. for $C_{15}H_{10}I_5NO_4 \cdot H_2O$: C, 19.57; H, 1.31; I, 68.91; N, 1.52. Found: C, 19.31; H, 1.40; I, 68.22; N, 1.75.

B. By Reaction of N-Acetyl-3-(3-hydroxy-2,4,6-triiodophenyl)-DL-alanine with 4-Hydroxy-3,5-diiodophenylpyruvic Acid and Oxygen, Followed by Deacetylation.—The coupling reaction was carried out in the usual manner (*cf.* preparation of VI, method B) with 3.0 g. (5 mmoles) of VIII. A precipitate formed already during the addition of the keto acid. The reaction mixture was permitted to stand at 2° overnight; then the precipitate was collected and dissolved in dilute ammonium hydroxide. Adjustment of the pH to 8 with acetic acid resulted in the formation of a precipitate (probably the ammonium or sodium salt of XIII). The addition of petroleum ether to a solution of this precipitate in ethyl acetate containing a few drops of 6 *N* hydrochloric acid gave 40 mg. (0.9%) of crystals melting at 209–211° dec. This still not pure N-acetyl-3-[3-(4-hydroxy-3,5-diiodophenoxy)-2,4,6-

(22) R. I. Meltzer and R. J. Stanaback, *J. Org. Chem.*, **26**, 1977 (1961).
(23) T. Shiba and H. J. Cahnmann, *ibid.*, **27**, 1773 (1962).
(24) A. Nishinaga and T. Matsuura, *ibid.*, **29**, 1812 (1964).
(25) T. Shiba, H. J. Cahnmann, T. Matsuura, A. Nishinaga, and H. Sakamoto, *ibid.*, **29**, 3061 (1964).
(26) T. Shiba and H. J. Cahnmann, *ibid.*, **29**, 3063 (1964).

(27) Without the addition of hydrochloric acid, the product lost iodine. On refluxing an ethanolic solution for 5 hr., most of VIII was converted to a new substance having an R_f value of 0.85 in paper chromatograms developed with 1-butanol–dioxane–2 *N* ammonium hydroxide (4:1:5). It is believed to be the lactone formed by reaction of the carboxyl hydrogen with the iodine in the 2-position of the aromatic ring, since the infrared spectrum shows an ester band at 1740 instead of the carboxyl band at 1700 cm.$^{-1}$ present in the spectrum of VIII.

(28) The transient formation of an intermediate was revealed by short-path paper chromatography. This intermediate gave a color reaction with ninhydrin, but not with diazotized N^1,N^1-diethylsulfanilamide and is therefore believed to be the methyl ether of XI.

(29) In a run in which the reaction time was extended from 2 to 5 hr., the yield was 72%.

triiodophenyl]-DL-alanine (XIII) was deacetylated without further purification. Paper chromatography of the precipitate obtained by acidification of the soluble fraction of the reaction mixture (see above) did not reveal the presence of the coupling product XIII. Deacetylation of XIII, carried out as described for that of VII, gave 23 mg. of XII, m.p. 209–211° dec. Although this melting point is slightly lower than that of the material prepared by method A, both substances had identical R_f values in paper chromatograms and gave identical infrared spectra.

Synthesis of 2:3-Benzo-1-silacycloalkenes. I

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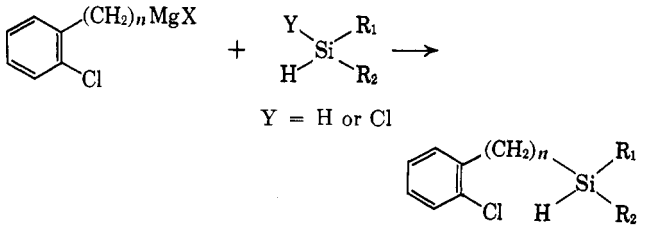
A new class of cyclic silanes, 2:3-benzo-1-silacycloalkenes, have been prepared by ring closure of (*o*-chlorophenyl)alkylsilanes with molten sodium. Two cyclic silicon hydrides were included. Attempts to effect ring closure of two benzyl derivatives were unsuccessful. Some n.m.r. and infrared data of the cyclic compounds are reported.

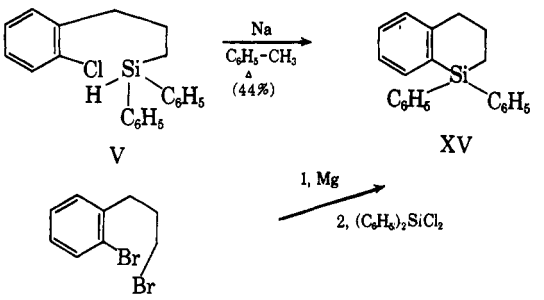
A class of compounds which may be of broad interest is that of the perhydro-1,2-cyclopentanophenanthrene ring system that has a silicon atom incorporated into the ring. Compounds which may serve as precursors to such derivatives are the benzosilacycloalkenes.

Only two compounds containing the benzosilacycloalkene nucleus, 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-en-4-one (2,3-dihydro-1,1-diphenyl-4H-1-silanaphthalen-4-one)[1] and the seven-membered ring homolog have been reported.[2] These were prepared by an intramolecular acylation reaction of the acid chloride of triphenylsilyl-substituted carboxylic acids. Since this method is limited to the availability of the acid derivatives that were prepared from silylmetallic reagents, improved methods of preparation of these silanes were desirable. The first efforts were directed toward the preparation of the nonfunctional compound 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene (XV). Attempts to prepare XV by ring closure of 3-triphenylsilylpropanol-1 and 3-triphenylsilylpropyl bromide using Lewis acid catalysts were unsuccessful.[2]

The method which appeared to be the most promising was an intramolecular cyclization reaction of (*o*-chlorophenyl)alkyl-substituted silicon hydrides with molten sodium in an inert solvent. Benkeser and Foster[3] have shown that silicon hydrides do not react with sodium, whereas phenylsodium reacts quantitatively with silicon hydrides to give the phenylated silicon compound. Also, Clark, *et al.*,[4] prepared *o*-phenylenebis(trimethylsilane) by coupling *o*-chlorophenyltrimethylsilane and chlorotrimethylsilane with molten sodium in refluxing toluene. Therefore, a series of (*o*-chlorophenyl)alkylsilanes was first prepared from the appropriate (*o*-chlorophenyl)alkylmagnesium halides and monochlorosilanes or silicon hydrides. The physical properties of these compounds are listed in Table I. These compounds were then added to molten sodium in refluxing toluene to give 2:3-benzo-1-silacycloalkenes (Table II). The Grignard reagents were prepared in good yields from the organic halides and were further characterized by carbonation to the corresponding (*o*-chlorophenyl)alkyl acids.



Thus, [3-(*o*-chlorophenyl)propyl]diphenylsilane (V), prepared from chlorodiphenylsilane and 3-(*o*-chlorophenyl)propylmagnesium bromide, was subsequently added to molten sodium in toluene to give 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene (XV) in good yield.



An alternate synthesis of XV was realized by treating the di-Grignard reagent of 3-(*o*-bromophenyl)-propyl bromide with dichlorodiphenylsilane.

To illustrate the versatility of the ring closure with sodium and to make available other precursory benzosilacycloalkenes, the five- (XIII) and seven-membered (XVIII) ring compounds were prepared in good yields. The eight-membered ring homolog (XIX) was similarly synthesized, but in low yield.

By varying R_1 and R_2, the method proved to be applicable for the preparation of other functional and nonfunctional derivatives. For example, treatment of phenylsilane with 2-(*o*-chlorophenyl)ethylmagnesium bromide and 3-(*o*-chlorophenyl)propylmagnesium bromide and then effecting ring closure of the resulting [2-(*o*-chlorophenyl)ethyl]- and [3-(*o*-chlorophenyl)propyl]-phenylsilanes (III or VI) gave 2:3-benzo-1-phenyl-1-silacyclopent-2-ene (XII) and 2:3-benzo-1-phenyl-1-silacyclohex-2-ene (XIV), respectively. These Si–H-containing compounds were converted into the fully phenylated derivatives by reaction with phenyllithium.

(1) The names and numbering system used herein are those recommended by the editorial staff of *Chemical Abstracts*.

(2) D. Wittenberg, P. B. Talukdar, and H. Gilman, *J. Am. Chem. Soc.*, **82**, 3608 (1960).

(3) R. A. Benkeser and D. J. Foster, *ibid.*, **74**, 5314 (1952).

(4) H. A. Clark, A. F. Gordon, C. W. Young, and M. J. Hunter, *ibid.*, **73**, 3798 (1951).