I. An Attempt to Determine the Absolute Configurations of α- and β-d-Glucose.

II. The Synthesis of dl-1,2-Octadecanediol and Several of Its Homologues

III. The Relation of Chemical Structure to Thyroxine-Like Activity; The Role of the Side-Chain and the Hydroxyl.

Thesis by

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Acknowledgment

I wish to record my grateful appreciation for the help and guidance which Dr. Carl Niemann has given me during my work on these research problems. I also wish to thank the other members of this laboratory who have contributed many helpful suggestions.

Part I

An Attempt to Determine the Absolute Configurations of α- and β-d-Glucose

The work on this problem was done in collaboration with Mr. John T. Hays under the supervision of Dr. Carl Niemann.

Theory

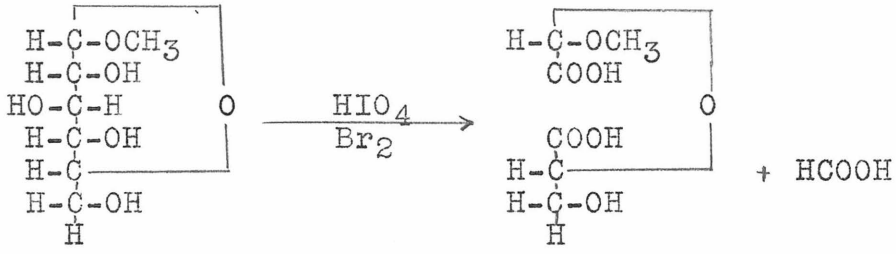
Böeseken(1) proved the configurations of α-and β-glucose around carbon atom one in an indirect physical way. He measured the conductivities of a boric acid solution containing α-glucose and one containing β-glucose as the conductivities changed with time until mutarotation was complete. The solution containing α-glucose had the higher conductivity, and with time the two conductivities approached a common value between the conductivities at the start. Because cis hydroxyls in polyalcohols have been found to form boric acid complexes which increase the acid strength of the solution, it is claimed that the α-compound is the cis form. However, it would be very desirable to prove the configurations directly in a chemical way.

Armstrong(2) hydrolyzed α-and β-methyl glucosides with maltase and emulsin respectively, and by observing polarimetrically he found that α-methyl glucoside produced the higher rotating form of glucose, or α-glucose, and that β-methyl glucoside hydrolyzed to β-glucose.

Neuberger and Rivers(3) have proved that α-and β-methyl glucosaminides have respectively the cis and trans configurations

of the methoxyl group with reference to the adjacent amino group by comparing the rates of hydrolysis of these compounds with those to be expected theoretically.

According to Jackson and Hudson(4), a methyl glucoside when treated with periodic acid followed by bromine yields a hydroxymethyl diglycollic acid.



At the time this work was started, Nicolet and Shinn(5) had published a note that periodic acid splits certain amino alcohols in the same manner. Thus, serine yielded formaldehyde, and the reaction rate indicated that glyoxylic acid and ammonia were also produced. From that, we might expect a methyl glucosaminide to be split in a like manner, to give the same compound as did methyl glucoside. By correlating the properties of the products, the two forms of methyl glucoside, and therefore, also glucose, might then be identified as to configuration around carbon atom one with the α-and β-methyl glucosaminides.

The four compounds needed were first synthesized, α-methyl glucoside by the method of Patterson and Robertson(6) and the glucosaminides according to the method of Neuberger and Rivers (loc. cit.). The physical constants of the latter compounds differed considerably from the values reported by Neuberger and Rivers:

	α			β				
	m.p.	α_D	M_D	m.p.	α_D	M_D	2A	2B
N-carbobenzoxymethyl glucosaminide	161°	+101.5°	+33200	167°	-34.8°	-11380	44580	21820
" reported by Neuberger & Rivers	155°	+80°	+26200	168°	-38°	-12420	38620	13780
Methyl glucosaminide Hydrochloride	190°	+145°	+33300	193°	-26.6°	-6110	39410	27190
" reported by Neuberger & Rivers	119°	+127°	+29150		-24°	-5510	34660	23640
Methyl Glucoside							34760	
d Glucosamine Hydrochloride								25860

From this table it can be seen that the new physical constants of the glucosaminides give a better value for 2B and a poorer one for 2A than the old constants did (as shown by comparison with these values for the reference compounds--methyl glucoside and glucosamine hydrochloride). However, Hudson's rules of optical superposition do not seem to apply very well to these glucosamine derivatives.

The compounds were turned over to Mr. Hays for the oxidation procedure and identification of the common compounds. He attempted to oxidize the glucosaminides in the usual manner with periodic acid, but an immediate precipitation of iodine took place, the periodic acid was almost immediately destroyed, and the solution

became optically inactive. Normally several hours are required for the reaction to go to completion. Because of this result, the project was discontinued.

Since that time, Neuberger(7) has observed a similar effect in the oxidation of ethyl N-benzoyl glucosamate, glucosamic acid, and N-acetyl- and N-benzoyl- α-methyl glucosaminide with periodic acid and sodium periodate. In acid solution the compounds reacted to produce iodine at various rates. In neutral solution, N-benzoyl α-methyl glucosaminide reacted to take up one atom of oxygen without the production of iodine.

Van Slyke, et al.(8) , in November, 1941, reported a method of determination of certain hydroxyamino acids based upon the amount of ammonia liberated when alkaline periodate reacts with these compounds. Periodic acid reacts more slowly than alkaline periodate upon such compounds, whereas it generally reacts more rapidly upon glycols, a fact which suggests different mechanisms of reaction on the two types of compounds. They also discovered that with glucosamine only 32% of the calculated amount of nitrogen was liberated as ammonia by the action of alkaline periodate. Ethanolamine produced 85% of its nitrogen as ammonia. It was found that periodic acid reacts slowly with ammonium salts. These later findings indicate that the proposed method of oxidation cannot be used until the reactions are understood more completely.

Experimental

The four compounds were first prepared:

1. α-Methyl Glucoside.

Two hundred grams was prepared of accepted physical constants by the action of methanolic hydrogen chloride on dry glucose according to the method of Patterson and Robertson(loc.cit.)

2. β-Methyl Glucoside.

One hundred grams of acetobromglucose was ~~first~~ prepared by the usual method of the action of gaseous hydrogen bromide on acetylated glucose in acetic anhydride, ~~but~~ and with the aid of the very useful modifications developed by Dr. C.E. Redemann in this laboratory.

The acetobromglucose was treated with methyl alcohol and silver oxide (with cooling at first followed by five hours shaking). The resulting tetraacetyl β-methyl glucoside was hydrolyzed in ethyl alcohol by barium hydroxide in the cold for eighteen hours, yielding after isolation and crystallization twenty grams of β-methyl glucoside of accepted physical constants.

3. Methyl Glucosaminide Hydrochlorides.

The method of Neuberger and Rivers was used(3).

Glucosamine hydrochloride in sodium bicarbonate solution was first treated with carbobenzoxy chloride to yield carbobenzoxy glucosamine(9).

This product was divided into two portions and mixed with 0.7% hydrogen chloride in methanol. One portion was stored at 40°, the other at room temperature (22°). At intervals of twenty-

four hours their specific rotations were taken. That portion kept at 40° reached a constant value of +76.3° in 188 hours, and that at 22° became constant at +15.3° in 188 hours. The compounds were isolated and each was recrystallized alternately from water and normal propyl alcohol until the alpha compound had a constant melting point of 160°-161° and a rotation of +101.5° and the beta compound had a melting point of 167° and a rotation of -34.8°. The rotations were taken in pyridine.

The N-carbobenzoxy methyl glucosaminides were reduced in methanol at one atmosphere of hydrogen in the presence of palladium black with the calculated amount of hydrogen chloride added gradually during the reaction. After fifty-eight hours with the alpha and twenty-four hours with the beta compound, the reactions had ceased as indicated by the lack of carbon dioxide evolution. The catalyst and solvent were removed and the compounds were crystallized from methyl alcohol yielding nice crystals. The α-methyl glucosaminide hydrochloride melted at 190° and had a specific rotation of +145° in water. The β-methyl glucosaminide hydrochloride had a melting point of 193° and its specific rotation equalled -26.6°. The alpha compound was very hygroscopic.

Analysis of α-Methyl Glucosaminide Hydrochloride

		C	H	Cl	N (Kjeldahl)
Calc. for $C_7H_{16}O_5NCl$	(229.7)	36.6	6.97	15.46	6.1
Found		36.9	6.93	15.82	6.0

Summary

The methyl glucosides and methyl glucosaminides were prepared in pure form. When attempts were made to oxidize the two types of substances to a pair of common products, and thus to correlate their configurations about carbon atom one, a reaction took place which prevented the correlation and which was undoubtedly another manifestation of the effects noted by other investigators since this work was done.

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Part II

The Synthesis of dl-1,2-Octadecanediol and Several of Its Homologues

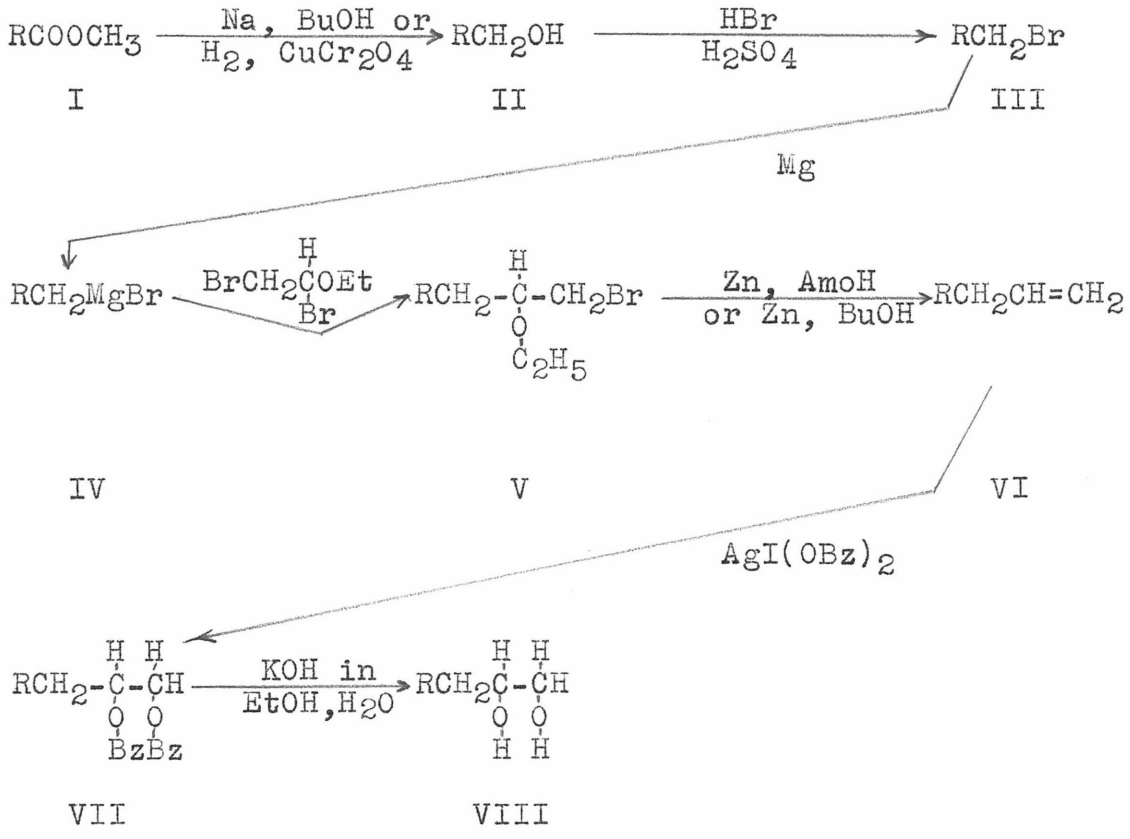
In 1901, Thudichum published an account(1) of the work done on compounds isolated from brain and spinal cord tissue. When sphingomyelin was treated with barium hydroxide at only slightly elevated temperatures for three to five hours, "sphingomyelinic acid," $C_{48}H_{95}NPO_{12}$, was formed. When this was heated with more barium hydroxide at 100° for ten hours, a compound was isolated which he called sphingol. This substance is a neutral alcohol with an empirical formula of $C_{18.5}H_{36.6}O_2$ obtained by analysis. If it were desamino sphingosine, it would have the empirical formula of $C_{18}H_{36}O_2$, with the two hydroxyls occupying the 1,2; 1,3; or 2,3 positions of octadecene-4.

Stetten and Schoenheimer (2) and Waelsch and Sperry (3) have shown that a fatty acid and a high molecular weight alcohol are interconvertible in the animal body. Therefore it seems likely that 1,2 glycols and alpha hydroxy acids might have the same relationship.

In view of these facts, it was deemed of value to prepare 1,2-hexadecanediol, 1,2-octadecanediol, and 1,2-eicosanediol, noting the physical properties of the compounds both in the pure state and in mixtures of the homologues. Also, it might prove valuable to resolve one of the racemic mixtures into its

optical antipodes sometime in the future.

The general method of synthesis used is represented schematically thus:



In order to obtain final products free of homologues and in the highest possible state of purity, intermediate products were fractionated carefully wherever possible. For this purpose also, the technical methyl stearate which was used as starting material for the preparation of 1,2 eicosanediol was hydrogenated completely over Raney nickel to saturate methyl oleate and other unsaturated compounds.

The olefines were prepared by the application of the excellent procedure developed by Boord and his co-workers(4) for the preparation of alkenes from alkyl bromides having two

less carbon atoms. The olefines were oxidized to the glycols[1] through the dibenzoates by silver iodine dibenzoate(5). Of the three glycols, one, 1,2-hexadecanediol, has been prepared before (6-8).

In order further to assure high purity, the glycols were converted to the isopropylidene derivatives. These were purified by distillation, and the glycols were regenerated by acid hydrolysis. The melting points of the cruder glycol fractions rose to those exhibited by the pure fractions, while the melting points of the pure samples did not change in the purification process.

Melting point-composition diagrams of mixtures of the homologues were made and the melting point depressions were sufficient to furnish a means of detecting the admixture of more than five percent of a homologue in a pure glycol. As in the case of many other similar compounds, polymorphism exists in these three long-chain glycols.

For the purpose of characterization, the diacetates and the di (N-phenylcarbamate) derivatives were prepared.

In order to prove conclusively that the substance prepared was an alpha glycol, a small sample of octadecanediol was oxidized with lead tetraacetate and a practically quantitative yield of formaldehyde was isolated as the dimedon derivative.

[1] The method described by Milas and Sussman(8) for the oxidation of hexadecene-1 to the glycol was attempted, but the use of osmium tetroxide in tert.butyl peroxide gave only a 40-50% yield of crude glycol which was very difficult to purify. It is probable that some splitting occurred with the formation of aldehyde. The silver iodine dibenzoate method(5) did not suffer from this disadvantage and seemed to be an excellent method.

Pentadecanal was also isolated and identified as the semicarbazone.

Another homologue, 1,2-hexanediol, was prepared, since it could be prepared relatively easily in larger quantities and can be used in the future as a compound upon which to try new reactions (such as resolution, formation of glycol galactosides).

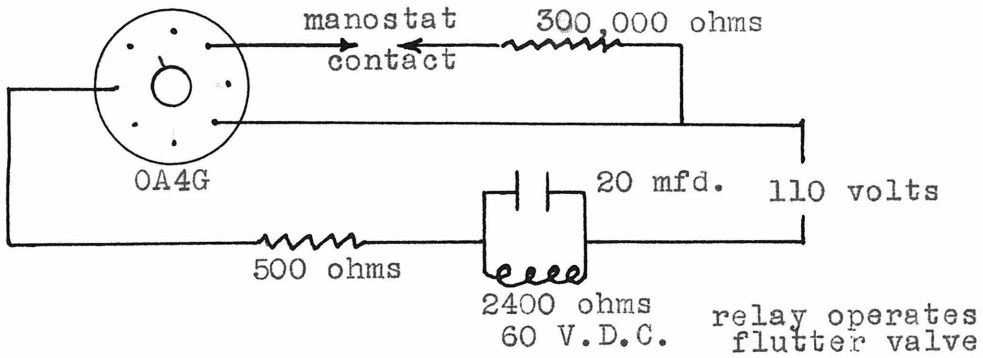
Experimental

I. Apparatus

A. Fractionating Still

A special column was built for the distillation of the compounds prepared in this work. The column itself was a Vigreux type, 100 cm. long and 2.5 cm. in diameter, covered with asbestos cord. Three copper-constantan thermocouples of ten junctions each for the purpose of measuring the temperatures at various parts of the column were placed underneath the asbestos cord against the glass. Around the asbestos was wound a spiral of chromel heating wire, and the whole was covered by magnesia pipe covering. Ground glass joints joined the column to both the distilling flask and the total reflux, variable takeoff head. The three inch immersion thermometer in the head was read by means of a periscope. The heating bath was an oil bath in a cylindrical asbestos-insulated can over a hot plate, the whole bath assembly being raised or lowered by means of an automobile jack. A variable transformer and a variac regulated the current in the bath and column heater respectively.

The vacuum was regulated at constant pressure well within 0.1 mm. by a sulfuric acid manostat (9) which actuated a flutter valve through a vacuum tube circuit.



Most of the distillations were carried out at from three to five millimeters at 130°-180°.

B. Melting Point Apparatus.

For precise melting point measurements, an instrument similar to that described by Hershberg(10) was used.

II. Syntheses

A. 1,2-Hexadecanediol.

1. Methyl Myristate.

2000 g. of technical myristic acid was esterified by refluxing it with 12 l. of 2% methanolic hydrogen chloride. The product was isolated, distilled, and fractionated at 5 mm. 882 g. (42%) was obtained, b.p./5 mm. 141.5°-142.5°, f.p. 19.2°, n_D^{20} 1.4351. Sauer, Hain, and Boutwell(11) report f.p. 19.0° and n_D^{20} 1.4353 for methyl myristate prepared from bayberry wax.

2. 1-Tetradecanol.

Four reduction runs (12) were made on 880 g. of pure methyl myristate. Each 220 g. of the ester was mixed with

2 l. of dry n-butyl alcohol in a 5 l. flask fitted with three efficient condensers, heated to 55°, and 105 g. of sodium in large lumps was added quickly. After the initial vigorous reaction had slackened, a vigorous reflux was maintained by a flame until the sodium had completely reacted. (The evolved gas was led from the top of the condensers by a rubber tube). 100 ml. of water was added cautiously, the mixture was refluxed one hour, and then 700 ml. more of water was added. The mixture was shaken vigorously and the lower layer was separated and discarded. 125 g. of sodium chloride was added and the butanol was removed by steam distillation. With the aid of a heated separatory funnel, the lower layer was separated and discarded. In order to remove the sodium myristate present as a troublesome impurity, a modification in Reid's procedure was made at this point. The hot product was poured into excess hot calcium chloride solution with vigorous stirring and allowed to cool. The solid product was collected, washed well with water, dried, and pulverized. The total mass from the four runs was suspended in 2 l. of ethanol and stirred vigorously for two hours, then filtered, and the solid was washed with hot alcohol. Removal of the solvent from the combined filtrate and washings gave nearly pure 1-tetradecanol, which was distilled at 3 mm. to yield 464 g. (59%) of 1-tetradecanol boiling at 128°-132° at this pressure and melting at 38.5° in a capillary tube. Meyer and Reid(13) report a melting point of 37.62° for 1-tetradecanol.

When the calcium myristate was treated with hydrochloric acid and extracted with ether, 192 g. of myristic acid was obtained as a by-product.

3. n-Tetradecyl Bromide.

461 g. of 1-tetradecanol was added to a mixture of 500 ml. of 48% hydrobromic acid and 125 ml. of concentrated sulfuric acid(14). The mixture was warmed cautiously until liquid, then refluxed for six hours in an oil bath. The lower layer was separated and discarded while still hot, and the hot bromide layer was washed twice with more 48% hydrobromic acid and allowed to cool. An equal volume of ether was added. The ethereal solution was washed several times with sodium chloride solution and dried over anhydrous potassium carbonate. After filtration, the ether was removed and the bromide was distilled at 3 mm. to give 540 g. of crude bromide. This was fractionated once at 5 mm. to yield a product boiling at 146°-147° but containing a crystalline solid impurity. The melting point of the liquid in the mixture was 5.5°, and Meyer and Reid(13) report a melting point of 5.67° for the bromide, so it was assumed that the impurity was practically insoluble in the bromide at its melting point. The solid was filtered off after storing the mixture for some time at 6°, and the filtrate was refractionated, to give 423 g.(71%) of tetradecyl bromide, b.p./5 mm. 146°-146.5°, f.p. 5.5°, n_D^{20} 1.4608, n_D^{30} 1.4565.

The solid impurity was purified and shown to be unreacted 1-tetradecanol by a mixed melting point with an authentic specimen.

4. α-Tetradecyl β-Bromoethyl Ethyl Ether

423 g. of tetradecyl bromide was converted to the Grignard reagent in a three-neck 5 l. flask by the usual method,

using 1300 ml. of ether and 37 g. of magnesium. After the reaction mixture was stirred at 50° for 15 minutes, it was cooled to below 25° and 300 g. of pure, freshly distilled α,β-dibromoethyl ethyl ether(4) in 500 ml. of ether was added with stirring at such a rate that the temperature was maintained at or below 25°. Stirring was continued for several minutes after the addition, then the two phase mixture was poured onto 4 kg. of ice and acidified with dilute hydrochloric acid.

Petroleum ether was added to the mixture and the whole shaken until the white solid dissolved. The ether layer was washed with dilute hydrochloric acid once, by water twice, and dried over calcium chloride. The ether was removed, leaving a viscous liquid containing a waxy crystalline solid. This solid was filtered off at room temperature, and the filtrate was distilled at 200 microns to yield 318 g. (60%) of α-tetradecyl β-bromoethyl ethyl ether, b.p./0.2 mm. 145°-165°, f.p. 23.5°. In this distillation 50 g. of a liquid boiling at 100°-145° at 200 microns was obtained which was not further investigated.

The crystalline precipitate was recrystallized from isopropyl ether and was found to be octacosane[2], m.p. 61.5°. Egloff(15) gives the melting point of octacosane as 61.6°.

Analysis	C	H
Calc. for $C_{28}H_{58}$ (394.7)	85.3	14.7
Found	85.2	14.4

[2] These hydrocarbons were evidently by-products occurring by "Wurtzing" during the preparation of the Grignard.

$$RMgBr + RBr \longrightarrow R\text{-}R + MgBr_2$$

5. Hexadecene-1.

285 g. of α-tetradecyl β-bromoethyl ethyl ether, 600 g. of zinc dust, and 600 ml. of n-butyl alcohol were refluxed with stirring for 24 hours[3]. The mixture was cooled, centrifuged, the precipitate washed with ether, and the washings and supernatant liquid combined. The solution was shaken with 75 ml. of water[4], filtered, the filtrate dried, and the butanol and ether removed in vacuo to give, after cooling, a residue of two phases. The upper phase was separated and distilled at 0.5 mm. to give a distillate which was then fractionally distilled at 3 mm. to give 120 g. of hexadecene-1, b.p. 122°-122.5°. This product contained a small amount of tetradecanol as an impurity, but here, as in the case of tetradecyl bromide, the alcohol appeared to be insoluble at a temperature just above the melting point of the desired compound. Accordingly, it was filtered off at 4° to yield 114 g.(62.5%) of hexadecene-1, f.p. 4.0°, b.p./3 mm. 122.0°-122.5°, n_D^{20} 1.4410, n_D^{30} 1.4372. Egloff(15) gives the following constants for hexadecene-1; m.p. 4°, b.p./3 mm. 123°, n_D^{20} 1.4417. The tetradecanol impurity was identified after purification by a mixed melting point with an authentic specimen.

6. Dibenzoate of 1,2-Hexadecanediol.

The method of Prevost(5) was used for this oxidation.

[3] The reaction mixture must be stirred vigorously during the refluxing, for the heavy zinc will otherwise settle out almost completely to a hard mass.

[4] Much of the zinc ethoxy bromide product of the reaction seems to dissolve in the alcohol. The addition of water to the centrate hydrolyzes this compound fairly rapidly. Some evidence was found for the presence of a small amount of an organo-zinc compound with a long carbon chain in the hydrolysate.

10.6 g. of iodine in 100 ml. of dry benzene was added in portions with shaking to a suspension of 26.5 g. of dry silver benzoate in 150 ml. of dry benzene. To this slightly reddish mixture was added slowly, with shaking, 10.5 g. of hexadecene-1 in 50 ml. of dry benzene. The red iodine color disappeared immediately, and during the addition the pasty mixture became more fluid. It was refluxed one hour, cooled, filtered, and the filtrate was freed of solvent, leaving the viscous residue consisting of the crude dibenzoate of the glycol.

7. 1,2-Hexadecanediol.

The crude glycol dibenzoate was refluxed for three hours with 12 g. of potassium hydroxide in 75 ml. of ethanol and 25 ml. of water. The mixture was then poured into 500 ml. of hot water with good stirring. After cooling, the crude glycol was collected, recrystallized from methanol twice, then from ligroin (b.p. 60°-70°), and finally from methanol to give 4 g. (33% from hexadecene) of 1,2-hexadecanediol, m.p. 73.1°-73.6°.[5,6]

[5] The melting point as recorded here was taken in the precision melting point apparatus described by Hershberg(10), and the temperature was raised at about one-fourth of a degree per minute. If an ordinary melting point device is used with a temperature change of one degree per minute, a melting point of 76°-77° is obtained, which agrees closely with the values reported by Kraft and Grosjean(6) (75°-76°), and Milas and Sussman(8) (75°).

[6] As in the case of the long chain alcohols(11), the glycols exhibit polymorphism. As noted by Kraft and Grosjean(6), when hexadecanediol, which has been crystallized from a solvent, is melted and allowed to cool, it solidifies to a semi-opaque mass which melts about two degrees lower than the original form. Recrystallization of the lower melting form changes it back to the higher melting form.

Analysis	C	H
Calc. for $C_{16}H_{34}O_2$ (258.4)	74.4	13.3
Found	74.4	13.3

B. 1,2-Octadecanediol.

1. Methyl Palmitate.

9 kg. of bayberry wax was alcoholyzed with methanol containing 4% sulfuric acid according to the method of Sauer, Hain, and Boutwell(11). The mixtures, each consisting of 1 kg. of bayberry wax and 1500 ml. of the methanolic sulfuric acid, were refluxed on the water bath for forty-eight hours each. 800 ml. of methanol was then distilled off, 1000 ml. of water was added, and the mixture was allowed to cool. The ester was separated, washed with water four times, dried over anhydrous sodium sulfate, and distilled to give a deep green distillate, b.p./3 mm. 143°-170°.

The distillates were fractionated at 5 mm. to yield the following approximate fractions:

5%	--- -140.0°	a light green liquid with a terpene-like odor.
40%	140.0°-141.5°	methyl myristate
15%	141.5°-163.0°	methyl myristate and methyl palmitate
35%	163.0°-163.5°	methyl palmitate
5%	163.5°- ---	high boiling residue

A total of 2934 g. of methyl palmitate was obtained, f.p. 29.0°. Sauer, Hain, and Boutwell report a melting point of 29.5°.

2. 1-Hexadecanol.

The 2934 g. of methyl palmitate was reduced in twelve portions by the same method as that used on the methyl myristate,

except that the mixture was heated to 80° before the sodium was added. 1760 g. (67%) of 1-hexadecanol was obtained, b.p./3 mm. 144°-146°, m.p. 49.0°. Meyer and Reid(13) and J.C. Smith(16) report a melting point of 49.27°. 420 g. of palmitic acid was recovered as a by-product.

3. n-Hexadecyl Bromide.

1760 g. of 1-hexadecanol, 1680 ml. of 50% hydrobromic acid, and 420 ml. of concentrated sulfuric acid were used in three portions in the same procedure as that used in the preparation of tetradecyl bromide(14). As noted in that preparation, some unreacted alcohol was present in the fractionated product. It was filtered off at the melting point of the bromide, and the bromide was refractionated to yield 1670 g.(75%) of n-hexadecyl bromide, b.p./1.5 mm. 153°-154°, f.p. 17.8° n_D^{20} 1.4627, n_D^{30} 1.4592. Meyer and Reid(13) report a melting point of 17.54°.

4. α-Hexadecyl β-Bromoethyl Ethyl Ether.

1667 g. of n-hexadecyl bromide, 134 g. of magnesium, and 4 l. of ether were used in three portions to prepare the Grignard reagent. To each portion was added 370 g. of α,β-dibromoethyl ethyl ether(4) in 500 ml. of ether as described in the preparation of α-tetradecyl β-bromoethyl ethyl ether. Crystalline dotriacontane was filtered from the viscous, reddish, crude product and was recrystallized several times from isopropyl ether to yield a total of 32 g., m.p. 69.0°. Egloff(15) gives 70.3° as the m.p. of dotriacontane.

Analysis	C	H
Calc. for $C_{32}H_{66}$ (450.8)	85.3	14.7
Found	85.4	14.6

The crude bromoether was distilled in three portions at 0.2 mm. There was some forerun distilling up to 150°, and the product was collected at 160°-180°. Slight decomposition occurred when it was heated for very long at this temperature. 1430 g.(70.5%) was obtained, f.p. 28.5°-29.5°.

5. Octadecene-1.

940 g. of α-hexadecyl β-bromoethyl ethyl ether and 2 kg. of zinc dust in 2 l. of n-amyl alcohol[7] was refluxed with stirring for twenty-four ~~more~~ hours. The reaction mixture was cooled, centrifuged, and 800 ml. of water was added to the supernatant liquid. When precipitation was complete, the mixture was filtered and the alcohol phase was dried over sodium sulfate. The solvent was removed and the crude octadecene-1 was distilled, then fractionated to give 289 g.(46%) of octadecene-1, b.p./3 mm. 144°-146°, f.p. 17.5°, n_D^{20} 1.4448, n_D^{30} 1.4412. Egloff(15) gives m.p. 18°, n_D^{22} 1.4443, n_D^{32} 1.4411 for this compound.

No impurity of hexadecanol was noted in this distilled product in contrast to the presence of tetradecanol in the crude hexadecene.

6. Dibenzoate of 1,2-Octadecanediol.

Prevost's(5) method was also used in this preparation. 288 g. of octadecene-1, 620 g. of silver benzoate, and 290 g.

[7] Shoemaker and Boord(4c) state that use of a higher alcohol in place of ethanol for the preparation of heptenes seems to increase the yield, and they made use of propyl alcohol. The higher temperature of reflux and greater solubility of the organo-zinc compound undoubtedly are the reasons. For these compounds, n-butyl alcohol and then n-amyl alcohol were used, the latter being more satisfactory. Markedly poorer yields resulted as the carbon chain of the desired olefine was increased two and then four carbon atoms, indicating that the use of even a longer chain alcohol might be desirable.

of iodine were used in the same manner as in the preparation of hexadecanediol to yield the crude product as a viscous liquid.

7. 1,2-Octadecanediol.

The crude dibenzoate was hydrolyzed as in the preparation of 1,2-hexadecanediol with 300 g. of potassium hydroxide in 2 l. of ethanol and 700 ml. of water. 239 g. (73% from octadecene) of the pure glycol was obtained after alternate crystallizations from methanol and ligroin, m.p. 79.0°-79.5°[6].

Analysis	C	H
Calc. for $C_{18}H_{38}O_2$ (286.5)	75.5	13.4
Found	75.3	13.2

C. 1,2 Eicosanediol.

1. Methyl Stearate.

1500 g. of technical methyl stearate was hydrogenated in two runs at 120° and 140 atmospheres of hydrogen over 25 g. of Raney nickel for two hours each. The Raney nickel was filtered off and the esters fractionated at 1.5 mm. to yield the following fractions:

--- - 135°	0	
135° - 140°	50 g.	
140° - 145°	450 g.	(methyl palmitate)
145° - 164°	350 g.	
164° - 167°	350 g.	(methyl stearate, m.p. 37.0°)
167° - ---	300 g.	

2. 1-Octadecanol.

350 g. of methyl stearate dissolved in ethanol was hydrogenated at 250° and 225 atmospheres of hydrogen over 20 g.

of copper chromite(17) to give, after removal of the catalyst and solvent, distillation, and crystallization from isopropyl ether, 270 g. (85%) of 1-octadecanol, b.p./5 mm. 165°-170°, m.p. 58.0°. Meyer and Reid(13) give a melting point of 57.85°, J.C. Smith(16), 57.93°, for this compound.

3. n-Octadecyl Bromide.

A mixture of 270 g. of 1-octadecanol, 230 ml. of 48% hydrobromic acid, and 55 ml. of concentrated sulfuric acid was refluxed for 20 hours, and the bromide product was isolated and distilled in the usual manner(14). The bromide was fractionated to yield 247 g. (74%) of pure n-octadecyl bromide, b.p./1.5 mm. 168.0°-169.5°, f.p. 27.4°. Meyer and Reid(13) report a melting point of 27.35° for octadecyl bromide. No unreacted alcohol was noted.

4. α-Octadecyl β-Bromoethyl Ethyl Ether.

247 g. of octadecyl bromide and 18.1 g. of magnesium were used to prepare the Grignard reagent in 1 l. of ether. 170 g. of α,β-dibromoethyl ethyl ether(4) in 500 ml. of ether was added in the usual manner. After hydrolysis of the reaction mixture with ice and dilute hydrochloric acid, the ethereal phase was washed with saturated aqueous sodium sulfate, then with water. The hexatriacontane by-product was filtered off and the filtrate was dried over calcium chloride. After the ether was removed, a dark colored viscous residue was obtained, which was dissolved in twice its volume of isopropyl ether and decolorized with alumina to give a light red solution. Removal of the solvent gave 190 g. of crude bromoether which could not

be distilled without decomposition.

The hexatriacontane by-product was recrystallized from isopropyl ether, giving 14 g., m.p. 76°. Egloff(15) gives 76° as the melting point also.

5. Eicosene-1.

190 g. of crude α-octadecyl β-bromoethyl ethyl ether in 800 ml. of n-amyl alcohol was refluxed with 400 g. of zinc dust for twenty hours; then between the twentieth and forty-eighth hour of refluxing 500 additional grams of zinc dust was added in three portions. The mixture was then cooled, centrifuged, the precipitate washed with isopropyl ether, and the washings and supernatant liquid were combined and added to 100 ml. of water. The suspension was shaken, filtered, and the alcoholic layer dried. The alcohol was removed and the residue distilled and fractionated to give 22 g. of eicosene-1 containing a small amount of 1-octadecanol, which was removed by filtration at 30° leaving 18.2 g. of eicosene-1, b.p./1.5 mm. 151°, f.p. 28.5°, n_D^{30} 1.4440. The overall yield from n-octadecyl bromide to eicosene-1 was 8.7%[7].

6. Dibenzoate of 1,2-Eicosanediol.

The glycol dibenzoate was prepared as a viscous liquid in the usual manner(5) from 18.2 g. of eicosene-1, 29.8 g. of silver benzoate, and 16.4 g. of iodine.

7. 1,2-Eicosanediol.

The glycol dibenzoate was saponified in the usual manner to yield, after alternate recrystallization from methanol and ligroin(b.p. 60°-70°), 14.2 g. (70% from eicosene) of 1,2

eicosanediol, m.p. 84.3°-84.8°[6].

Analysis	C	H
Calc. for $C_{20}H_{42}O_2$ (314.5)	76.4	13.5
Found	76.5	13.4

III. Purification of the Glycols[8].

The general procedure used in the purification was as follows: One gram of the glycol in 10 ml. of acetone was shaken for six hours with 1.2 g. of anhydrous cupric sulfate[9]. After filtering the suspension, the excess acetone was removed and the residue distilled at a pressure not greater than 0.2 mm. The distillate was allowed to stand at a temperature one degree above its melting point for five hours and then was filtered to remove any glycol present. For analysis, the isopropylidene compound was recrystallized from isopropyl ether. The yield of pure isopropylidene glycol was generally about 90%.

Table I

Glycol-Acetone Condensation Products.

Compound	m.p.	b.p./0.1 mm.	Analysis Calc. C	Calc. H	Found C	Found H
isopropylidene-1,2-hexadecanediol	22.9°	135°	76.5	12.8	76.7	13.0
isopropylidene-1,2-octadecanediol	31.3°	150°	77.2	13.0	77.1	13.0
isopropylidene-1,2-eicosanediol	36.7°	165°	77.9	13.1	77.7	13.1

[8] Other means of purification were also tried. Preparation of the diacetate from a crude 1,2-octadecanediol sample, followed by recrystallization and gentle hydrolysis to the glycol, did not raise the melting point. Preparations of cyclic acetals, such as the benzylidene and benzhydrylidene compounds, were attempted, but the products were too difficult to isolate.

The glycols were regenerated from the isopropylidene compounds by dissolving the latter in four times their weight of methanol, adding a 300% molar excess of water and a drop of concentrated hydrochloric acid, and heating the mixtures until they were homogeneous. Upon cooling, the glycols crystallized out, were recovered by filtration, and recrystallized from methanol in about 90% yield.

IV. Derivatives of the Glycols.[10]

A. Glycol Di(N-Phenylcarbamates).

Two g. of the glycol in 10 ml. of benzene was refluxed for six hours with 3.5 ml. of phenylisocyanate, the excess benzene and phenylisocyanate were removed by distillation and the residue was recrystallized from isopropyl ether to constant melting point.

Table II

Glycol-Di(N-Phenylcarbamates)

Compound	m.p.	Analysis					
		Calc.			Found		
		C	H	N	C	H	N
1,2-Hexadecanediol-Di(N-phenylcarbamate)	95°	72.6	8.9	5.6	72.8	9.2	5.9
1,2-Octadecanediol-Di(N-phenylcarbamate)	99.5°	73.2	9.2	5.3	73.4	9.3	5.5
1,2-Eicosanediol-Di(N-phenylcarbamate)	103.5°	73.9	9.5	5.1	74.0	9.4	5.2

[9] The isopropylidene compound can also be prepared by the use of a solution of anhydrous zinc chloride in acetone. However, the best yield obtained in this way was only about 50%. This was possibly due to hydrolysis from the use of aqueous potassium carbonate in removing the zinc chloride.

B. Glycol Diacetates.

One gram of the glycol in 4 ml. of pyridine and 4 ml. of acetic anhydride was heated to boiling and then was allowed to stand at room temperature for twenty-four hours. The mixture was then poured into an aqueous solution of 10 g. of sodium carbonate. After this mixture was extracted three times with ether, the ether extract was washed twice with water and dried over drierite. The solvent was removed and the residue consisting of the crude diacetate was recrystallized twice from methanol at 4°.

Table III

Glycol-Diacetates

Compound	m.p.	Analysis Calc. C	Calc. H	Found C	Found H
1,2-Diacetoxyhexadecane[11]	30°	70.1	11.2	70.1	11.0
1,2-Diacetoxyoctadecane	40°	71.3	11.4	71.4	11.7
1,2-Diacetoxyeicosane	47°	72.4	11.6	72.4	11.8

[10] Preparations of other derivatives were also attempted. 3,5-dinitrobenzoyl chloride gave no crystalline compound. p-nitrobenzoyl chloride also gave no acceptable derivative. A 6-naphthoate of octadecanediol which melted at 135°-138° was prepared with difficulty.

[11] Kraft and Grosjean(6) reported a melting point of 1,2-diacetoxyhexadecane of 56°-57°. Their procedure was the addition of bromine to hexadecene-1 followed by treatment with silver acetate in acetic acid. We repeated their work, having in mind the possibility of an orthoacetate structure in the diacetate prepared by us.

Pure hexadecene was treated with bromine in carbon disulfide, and an 86% yield of dibromohexadecane was obtained, b.p./0.3 mm. 145°, m.p. 12.5°. They report a melting point of 13.5°.

The dibromide was refluxed in acetic acid with silver acetate, and a product was isolated which proved identical with the diacetate prepared by acetylation of the glycol with acetic anhydride, m.p. 30°.

V. Melting Points of Glycol Mixtures

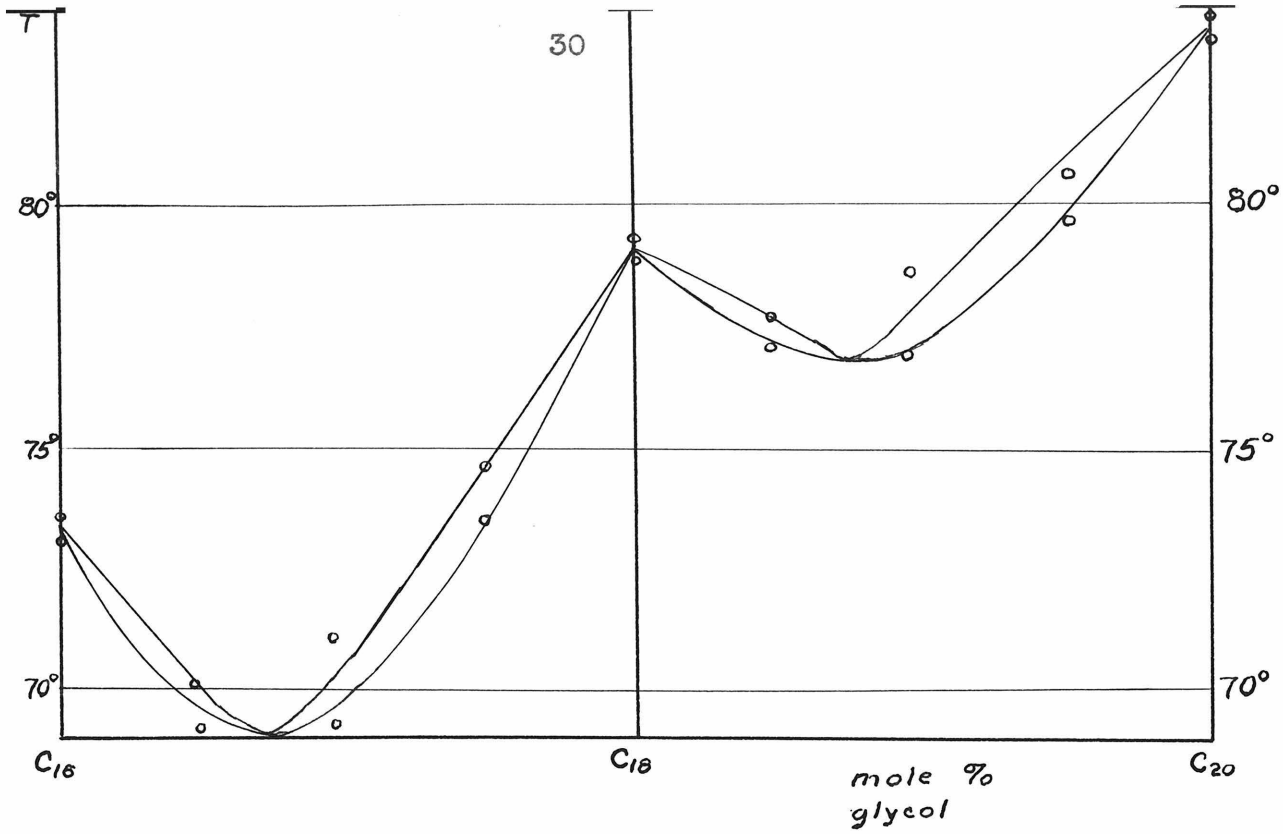
The melting points of the ~~pure~~ glycols were taken in the Hershberg melting point apparatus(10) mentioned above. The initial temperature in the ranges given indicate the temperature at which liquid was first observed on the crystals, while the final temperature is that at which the last crystal has just melted. The rate of heating was about one-fourth of a degree per minute.

In order to insure uniformity of crystal form, the pure glycols and mixtures were dissolved in warm methanol, and the solvent was allowed to evaporate leaving the crystals. The percentages given are per cent by weight.

Table IV

Melting Points of Glycol Mixtures

Glycol A		Glycol B		m.p.
100%	C_{16}			73.1°-73.6°
75%	C_{16}	25%	C_{18}	69.2°-70.2°
50%	C_{16}	50%	C_{18}	69.3°-71.2°
25%	C_{16}	75%	C_{18}	73.7°-74.7°
		100%	C_{18}	79.0°-79.5°
25%	C_{20}	75%	C_{18}	77.2°-77.8°
50%	C_{20}	50%	C_{18}	77.0°-78.7°
75%	C_{20}	25%	C_{18}	79.8°-80.8°
100%	C_{20}			84.3°-84.8°



VI. Degradation of 1,2-Octadecanediol.

A mixture of 3.75 g. of pure 1,2-octadecanediol, 6 g. of lead tetraacetate, and 20 ml. of glacial acetic acid was shaken for five hours at 25°. The clear solution was distilled into 25 ml. of cold water until the vapor temperature reached 120°. 3.5 g. of dimedon (dimethyl dihydroresorcinol) in 20 ml. of alcohol was added to the distillate, and the mixture was heated to 70° and allowed to cool. The crystals were collected, washed with water, and dried. 2.85 g.(80%) of the formaldehyde-dimedon condensation product was obtained, m.p. 190°.(18).

The residue remaining in the flask from the distillation was neutralized with dilute sodium hydroxide solution with stirring and cooling, and the mixture was extracted with ether. After the ethereal extract was washed and dried over drierite, the solvent was removed. The residue was dissolved in alcohol

and a mixture of 0.6 g. semicarbazide hydrochloride and 0.8 g. of potassium acetate in 50% alcohol was added; the solution was heated until clear, and was then allowed to cool. The crystals were collected and recrystallized from alcohol, m.p. 107°. Le Seuer(19) reported a melting point of 106.5°for pentadecanal semicarbazone.

VII. Preparation of 1,2-Hexanediol.

A. Hexene-1.

337 g. of n-propyl bromide was converted to the Grignard reagent in 900 ml. of dry di-n-butyl ether with 80 g. of magnesium. The milky liquid was decanted into another similar apparatus. 264 g. of allyl bromide in 600 ml. of butyl ether was then added with stirring at such a rate that the temperature remained below 100°, and the mixture was allowed to stand overnight. It was then poured with stirring onto ice and dilute sulfuric acid, the phases were separated, and the ether layer was washed with water, sodium bicarbonate solution, and water again, and dried over calcium chloride.

The ether solution was then distilled and the fraction collected up to 100°. This was dried over calcium chloride again and refractionated to yield 118 g.(52%) of hexene-1, b.p. 60.5°-63.5°.

B. 1,2 Hexanediol.

In three portions, 105 g. of hexene-1, 722 g. of dry silver benzoate, 346 g. of iodine, and 7 l. of dry benzene were used in the same manner as that used in preparing the

other glycol dibenzoates from the olefines(5). In three portions also, 320 g. of potassium hydroxide, 300 ml. of ethanol, 900 ml. of water, and the crude dibenzoate were refluxed for from three to six hours. The mixtures were cooled and combined and extracted continously with ether in a liquid-liquid extractor for fifteen hours.

The ether extract was dried over drierite, the solvent was removed, and the residue was distilled and fractionated at 5 mm. 43.5 g. of a very slightly straw-colored viscous liquid was obtained, b.p./5 mm. 98.5°, m.p. 0.0° to +2.0°.

Summary

1. The Boord alkene-1 synthesis has been extended to members of a homologous series containing sixteen, eighteen, and twenty carbon atoms. The synthesis of eicosene-1 is described for the first time.

2. 1,2-Hexadecanediol, 1,2-octadecanediol, 1,2-eicosanediol, and 1,2-hexanediol have been synthesized, the eighteen- and twenty-carbon chain glycols for the first time.

3. An excellent method for the isolation and purification of such glycols was found, involving the conversion to the isopropylidene compounds and subsequent regeneration to the glycols. Melting point-composition curves of mixtures of the pure homologues were plotted.

4. An account is given of some of their derivatives which are suitable for their characterization.

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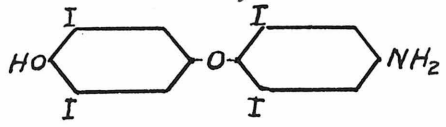
Part III.

The Relation of Chemical Structure to Thyroxine-Like Activity; The Role of the Side-chain and the Hydroxyl.

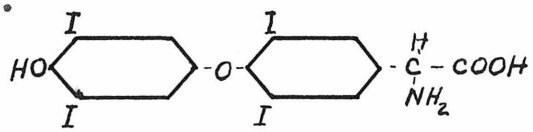
Much work on the relation between physiological activity and the chemical structure of thyroxine has already been done. In order to extend the knowledge along these lines, it is proposed in this research to replace the typical alanine side chain with other groups and to test their biological activity to see if the alanine side chain is necessary for thyroxine-like activity. The compounds to be prepared are listed below:

1. 3,5-diiodo-4-(3',5'-diiodo-4'-hydroxyphenoxy) aniline.

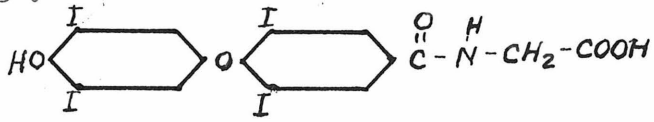


This amine is to be diazotized and coupled to a protein such as gelatin. The resulting substance will then be tested for its physiological activity.

2. 3,5-diiodo-4-(3',5'-diiodo-4'-hydroxyphenoxy) phenylglycine.



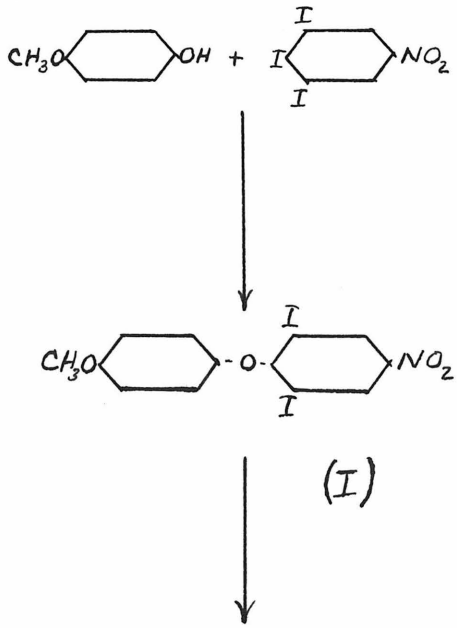
3. N-3,5-diiodo-4-(3',5'-diiodo-4'-hydroxyphenoxy) benzoylglycine.

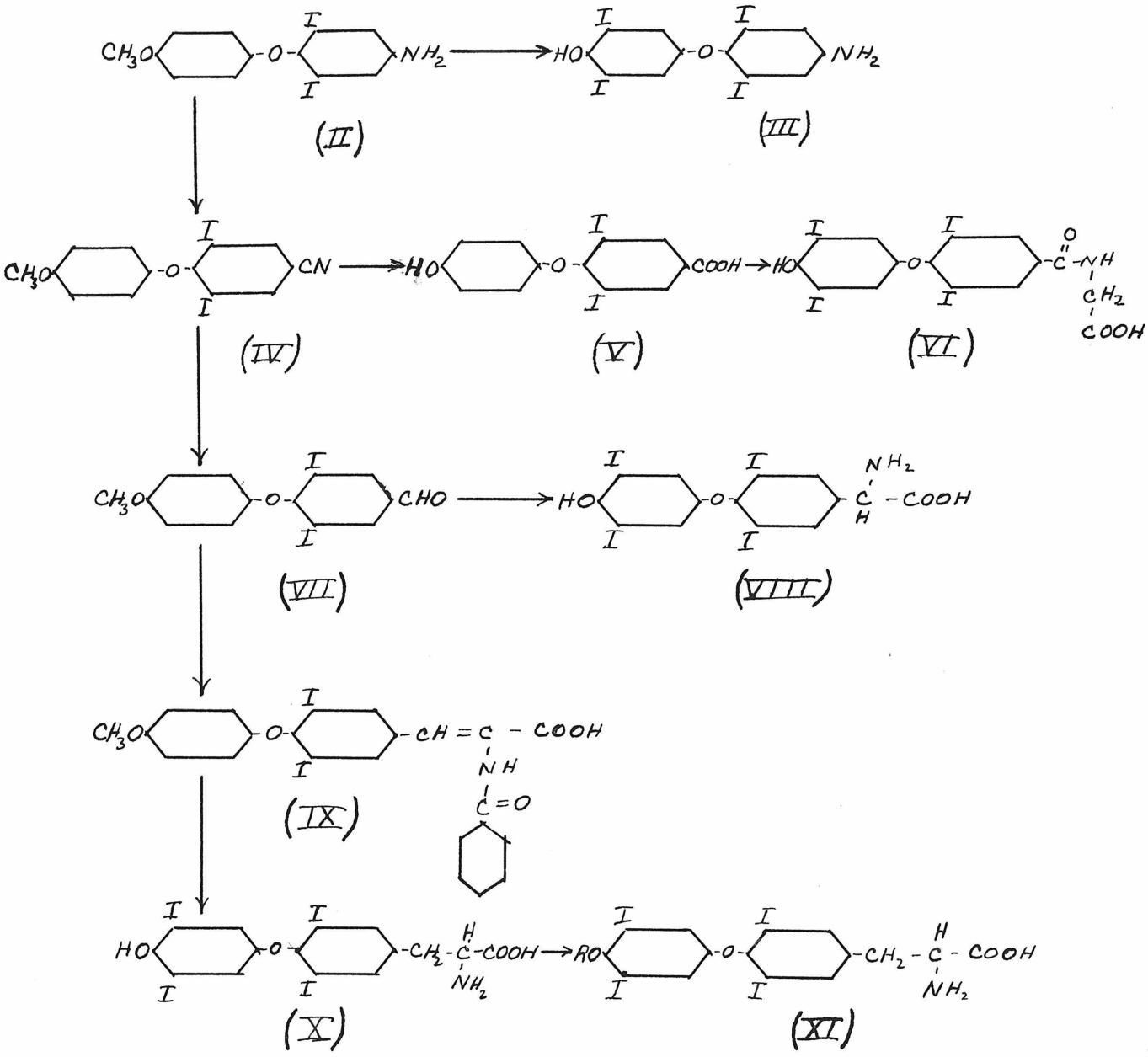


[1] Only preliminary synthetic work on this problem was completed before the author was transferred to defense research. The problem has since been turned over to Mr. Gifford McCasland of this laboratory.

Myers(1) claimed that the methyl ether of thyroxine has no activity, while Loeser, Ruland, and Trikojus(2) state that it has about the same activity as thyroxine itself. In this work, the plan is to make the methyl, ethyl, and propyl ethers and to study their biological activities. If the ethyl and propyl ethers are inactive while the methyl ether is active, it will indicate that the activity of the methyl compound is due to liberated thyroxine, since transmethylation in the body is common, while transethylation, etc., is rare. This result also would be interesting in connection with the theory of Niemann and Redemann(3), which predicts that the formation of quinoid structures in an oxidation-reduction equilibrium, is a requirement for physiological activity.

Accordingly, the synthesis of thyroxine as described by Harington and Barger(4) was undertaken. Portions of certain of the intermediate products were saved for the syntheses of the glycine derivatives described above, and the rest of each intermediate was used for the preparation of thyroxine, which was to be converted to the ethers. The proposed syntheses are given below:





50 g. of the amine (II) in the form of the hydrochloride, 12 g. of the acid(V), 8 g. of the aldehyde(VII), and 14 g. of the α-benzoylamino 3,5-diiodo-4-(4'-methoxyphenoxy) cinnamic acid(IX) were prepared. Small amounts of the cinnamic acid derivative were reduced to diiodothyronine, and this was iodinated, but only amorphous thyroxine was obtained in the preliminary experiments.

Experimental

3,5-diiodo-4-(4'-methoxyphenoxy)-nitrobenzene (I).

Harington's method(4) was followed with certain modifications(3). To one mole of triiodonitrobenzene was used 1.4 moles of hydroquinone monomethyl ether, 2-pentanone was used as the solvent, and the mixture was heated for eight hours. 318 g. (73%) of the product was secured, m.p. 143°-144°.

3,5-diiodo-4-(4'-methoxyphenoxy)-aniline(II).

The nitro compound was reduced(4) to the amine(II) and converted in isopropyl ether into the hydrochloride in 64% yield. 205 g. was obtained, of which 50 g. was saved for diazotization and coupling to a protein. The remainder was used for the preparation of the nitrile(IV).

3,5-diiodo-4-(4'-methoxyphenoxy)-benzonitrile(IV).

The amine(II) was diazotized(4) with butyl nitrite and the diazonium solution was added dropwise to the potassium cuprocyanide solution at room temperature. After one hour, the mixture was heated to 80°, then cooled, and the solid collected. The excess cuprous cyanide was removed by shaking the solid with potassium cyanide solution and toluene. After decolorizing the toluene layer by the use of an alumina Tswett column, the toluene was removed and the nitrile distilled in the usual manner. 72 g. (46%) was obtained, m.p. 174°-177°.

3,5-diiodo-4-(4'-hydroxyphenoxy)-benzoic acid(V).

15 g. of the nitrile(IV) was converted to the acid(V)(4). 11.8 g. (78%) was obtained, m.p. 255°-256°.

3,5-diiodo-4-(4'-methoxyphenoxy)-benzaldehyde(VII).

31 g. (72%) of the aldehyde(VII), m.p. 123°-124.5°, was prepared(4) from the nitrile(IV). 8 g. was saved for the preparation of the glycine derivative (VIII). The rest was used in the preparation of thyroxine (X).

α-benzoylamino-3,5-diiodo-4-(4'-methoxyphenoxy)-cinnamic acid (IX).

23 g. of the aldehyde (VII) was converted(4) to the azlactone. This was hydrolyzed according to the method of Harington and McCartney(5) to give 17 g. of the cinnamic acid derivative (IX), m.p. 239°-241°. This was a 56% yield from the aldehyde.

Ø-(3,5-diiodo-4-(3',5'-diiodo-4'-hydroxyphenoxy)phenyl)-α-amino propionic acid.(X)(thyroxine).

4.5 g. of the cinnamic acid derivative(IX) was reduced and hydrolyzed with hydriodic acid in acetic anhydride(5) to produce 1.8 g. of diiodothyronine, or Ø-(3,5-diiodo-4-(4'-hydroxyphenoxy) phenyl-α-aminopropionic acid, m.p. 238°-242°. Upon recrystallization from sodium hydroxide in dilute alcohol with acetic acid, the melting point decreased to approximately 230°.

0.62 g. of diiodothyronine was iodinated in ammonium hydroxide with potassium triiodide solution (4) to give 0.6 g. of amorphous thyroxine which we were unable to crystallize, probably because we attempted to modify Harington's method of isolation and to purify it in the same manner as we did the diiodothyronine.[1]

Summary

According to the well-known synthetic methods of Harington and his collaborators(4,5), 4 compounds were prepared which will be useful in correlating the chemical structure of compounds with thyroxine-like activity.

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