Model Reactions for the Biosynthesis of Thyroxine. IV. Synthesis of Analogs of Thyroxine from Derivatives of Tyrosine and of Dibromotyrosine[1,2]

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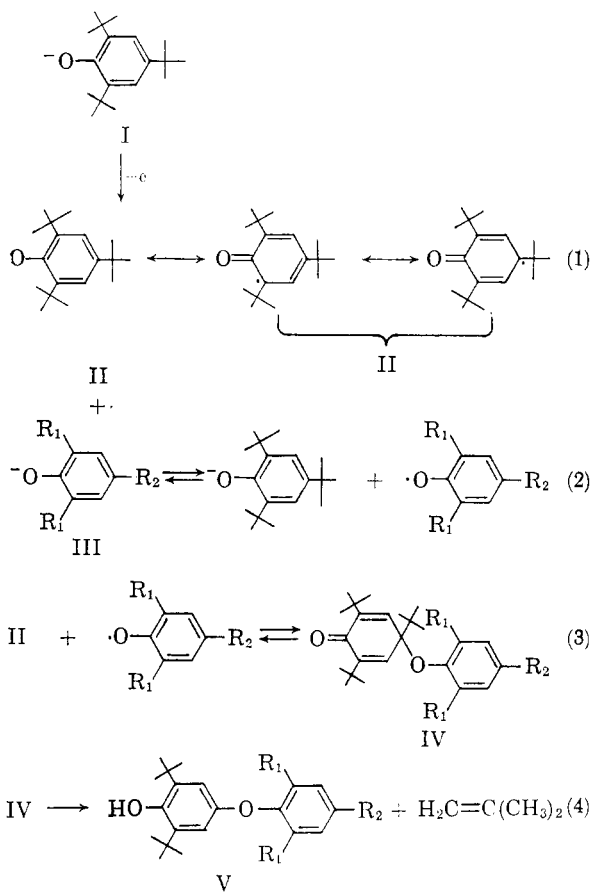
Derivatives of tyrosine and of dibromotyrosine react with the free radical 2,4,6-tri-*t*-butylphenoxyl to form quinol ethers (equations 2 and 3) that can be converted to the corresponding di-*t*-butyl analogs of thyroxine (equation 4). This sequence of reactions represents a nonenzymic model for the conversion of diiodotyrosine to thyroxine *in vivo*.

The synthesis of various quinol ethers of type IV from desamino analogs of tyrosine and of halogenated tyrosines in a free radical reaction has been reported previously.[1] Some of these quinol ethers were converted by pyrolysis or acid catalysis to the corresponding analogs (V) of thyroxine. This sequence of reactions represents a model for the hypothetical mechanism which has been postulated by Johnson and Tewkesbury[3] for the synthesis of thyroxine *in vivo*. This model has, however, various shortcomings. One of them is that the side chain R_2 of the synthesized quinol ethers is not an alanine side chain as in the case of the hypothetical quinol ether intermediate VI of Johnson and Tewkesbury. Consequently, these quinol ethers could only be converted to desamino analogs of thyroxine. The synthesis of quinol ethers of type IV in which R_2 is an alanine side chain, as well as their conversion to analogs of thyroxine, is described in the present paper.

A solution of the relatively stable free radical II was prepared by oxidation of 2,4,6-tri-*t*-butylphenol (I) with potassium ferricyanide[4,5] (equation 1). When one mole of a derivative of tyrosine (IIIa or IIIb or IIIc) was added to the blue solution of the free radical, the color became greenish yellow. The corresponding quinol ether (IVa or IVb or IVc) and tri-*t*-butylphenol (I) were isolated from the reaction mixture in good yield (equations 2 and 3). The infrared spectra of the quinol ethers show semiaromatic ether bands at 1250 and 1000 cm.$^{-1}$ and a doublet of about 1650 cm.$^{-1}$ which is typical for the dienone structure.[6] The ultraviolet spectra show phenol ether maxima[6] at 228, 273–274, and 281–284 mμ and a dienone maximum[4b,6] at 243–244 mμ.

An attempt to convert the quinol ethers to the corresponding analog of thyroxine by pyrolysis



+ = *t*-butyl

IIIa, IVa, Va R_1 = H R_2 = —$CH_2CH(NH_2)COOC_2H_5$

IIIb, IVb, Vb R_1 = H R_2 = —$CH_2CH(NHCOCH_3)COOH$

IIIc, IVc, Vc R_1 = H R_2 = —$CH_2CH(NHCOCH_3)COOCH_3$

IIId, IVd, Vd R_1 = Br R_2 = —$CH_2CH(NH_2)COOCH_3$

IIIe, IVe, Ve R_1 = Br R_2 = —$CH_2CH(NHCOCH_3)COOH$

IIIf, IVf, Vf R_1 = I R_2 = —$CH_2CH(NHCOCH_2Cl)COOH$

Vg R_1 = H R_2 = —$CH_2CH(NH_2)COOH$

Vh R_1 = Br R_2 = —$CH_2CH(NH_2)COOH$

was not successful. The conversion could, however, be accomplished by treatment of the quinol ethers with an acid catalyst in boiling ethyl acetate (equation 4). This treatment also hydrolyzes the ester groups of IVa and IVc. Thus IVa

(1) Paper III, T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1960).

(2) A preliminary report of this work has been presented at the 14th Annual Meeting of the Chemical Society of Japan, April, 1961, Tokyo, Japan.

(3) T. B. Johnson and L. B. Tewkesbury, Jr., *Proc. Natl. Acad. Sci. U. S.*, **28**, 73 (1942).

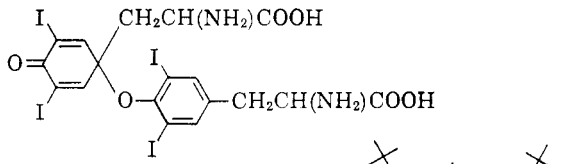
(4) (a) C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953); (b) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

(5) (a) E. Müller and K. Ley, *Chem. Ber.*, **87**, 922 (1954); (b) E. Müller, K. Ley, and W. Kiedaisch, *ibid.*, **87**, 1605 (1954).

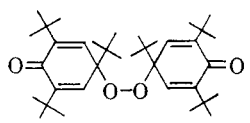
(6) E. Müller, K. Ley, and G. Schlechte, *ibid.*, **90**, 2660 (1957).

yields 3′,5′-di-*t*-butylthyronine (Vg), and both IVb and IVc yield N-acetyl-3′,5′-di-*t*-butylthyronine (Vb), whose acetyl group is hydrolyzed by a more drastic acid treatment.

In contrast to the unsubstituted derivatives of tyrosine the halogenated derivatives IIId, IIIe, and IIIf react with a solution of the free radical II without complete disappearance of the blue color. This is due to a displacement of the equilibrium in equation 3 toward the left which is apparently caused by the steric repulsion of the bulky groups (R_1 and *t*-butyl) in the quinol ethers IVd, IVe, and IVf. The only products that could be isolated from the reaction mixture were the starting phenols (IIId, IIIe, IIIf) and the peroxide VII. The formation of the phenols is certainly due to a displacement of the equilibria in equations 3 and 2 toward the left, the formation of the peroxide to the reaction of the free radical II with atmospheric oxygen in the course of the isolation of the reaction products. Although the brominated quinol ethers IVd and IVe could not be isolated, their formation could be shown by their conversion to the corresponding analogs of thyroxine (Vd, Ve), when the reaction mixture was treated with an acidic catalyst. These analogs of thyroxine gave on hydrolysis the free amino acid Vh. When N-chloroacetyl-3′,5-diiodotyrosine (IIIf) was added to a solution of the free radical II, the quinol ether IVf was probably formed,[1] but this could not be proven since attempts to isolate the corresponding analog of thyroxine (Vf) after treatment of the reaction mixture with an acidic catalyst were unsuccessful.



VI



VII

All analogs of thyroxine obtained from the corresponding quinol ethers gave infrared and ultraviolet spectra that are characteristic for diaryl ethers[1,7] and color tests that are typical for hindered phenols.

Experimental[8]

4-[*p*-(2-Amino-2-carbethoxyethyl)phenoxy]-2,4,6-tri-*t*-butyl-2,5-cyclohexadien-1-one (IVa).—A solution of 5.25 g. (20 mmoles) of 2,4,6-tri-*t*-butylphenol[9] in 200 ml. of benzene was stirred at room temperature with a solution of 20 g. of potassium ferricyanide and 11 g. of potassium hydroxide in 100 ml. of water for 2 hr. in an atmosphere of oxygen-free nitrogen.[10] A previously described reaction flask[11] was used. The alkaline layer was removed and the deep blue organic layer was washed five times with water. To the washed benzene solution was added a solution of 2.1 g. (10 mmoles) of L-tyrosine ethyl ester[12] in 50 ml. of ethyl acetate and the mixture was stirred for 20 min. The greenish yellow solution was dried over anhydrous sodium sulfate and evaporated *in vacuo* at room temperature to a sirup which was dissolved in benzene and chromatographed on a silica gel column (100 g.). After elution of 2,4,6-tri-*t*-butylphenol with petroleum ether, elution with benzene–ether (1:1) yielded 3.6 g. (77%) of the quinol ether IVa as a pale yellow sirup. Crystallization from methanol gave yellow needles, m.p. 42–43°, which kept the crystalline form only in the presence of methanol or in an atmosphere of methanol. The crystals lost methanol of crystallization in air or in a vacuum desiccator and changed to a pale yellow sirup. Microanalyses and the infrared spectrum were determined on this sirup. Infrared spectrum (liquid film): 3420, 1732, 1670, 1648, 1233, 977 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 228 mμ (log ε 4.13), 244 mμ (3.98), 274 mμ (3.45), 284 mμ (3.35).

Anal. Calcd. for $C_{29}H_{43}O_4N$: C, 74.16; H, 9.23; N, 2.98. Found: C, 74.21; H, 9.28; N, 3.12.

4-[*p*-(2-Acetylamino-2-carboxyethyl)phenoxy]-2,4,6-tri-*t*-butyl-2,5-cyclohexadien-1-one (IVb).—A blue free radical solution was prepared from 1.05 g. (4 mmoles) of 2,4,6-tri-*t*-butylphenol as described in the preceding paragraph. A suspension of 0.45 g. (2 mmoles) of *N*-acetyl-L-tyrosine[13] in 20 ml. of ethyl acetate was added with stirring. Stirring was continued until a clear greenish yellow solution was obtained which was then dried over anhydrous sodium sulfate and evaporated *in vacuo* to a small volume. After standing for 1 hr. at 2°, the crystals formed were filtered and recrystallized from benzene–petroleum ether; yellow plates (0.75 g., 77%) m.p. 144–144.5°. Infrared spectrum (Nujol): 3300, 1714, 1666, 1645, 1610, 1544, 1234, 978 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 228 mμ (log ε 4.20), 243 mμ (3.98), 274 mμ (3.39) 281 mμ (3.28).

Anal. Calcd. for $C_{29}H_{41}O_5N$: C, 72.02; H, 8.55; N, 2.90. Found: C, 72.37; H, 8.82; N, 3.00.

4-[*p*-(2-Acetylamino-2-carbomethoxyethyl)phenoxy]-2,4,6-tri-*t*-butyl-2,5-cyclohexadien-1-one (IVc).—A blue free radical solution was prepared from 2.62 g. (10 mmoles) of 2,4,6-tri-*t*-butylphenol as described above. A suspension of 1.18 g. (5 mmoles) of N-acetyl-L-tyrosine methyl ester[13] (1.18 g., 5 mmoles) in 50 ml. of ethyl acetate was added with stirring. After stirring for 40 min., the resulting greenish yellow solution was dried over anhydrous sodium sulfate and evaporated *in vacuo* to a sirup which was dissolved in benzene and chromatographed on a silica gel column (60 g.). After elution of 2,4,6-tri-*t*-butylphenol with benzene, the quinol ether IVc was obtained as a yellow sirup which did not crystallize (2.29 g., 92%). Infrared spectrum (liquid film): 3270, 1736, 1666, 1645, 1235, 982 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 228 mμ (log ε 4.22), 243 mμ (3.98), 273 mμ (3.39), 281 mμ (3.28).

3′,5′-Di-*t*-butyl-N-acetylthyronine (Vb).—A. From the Quinol Ether IVb.—A solution of 0.30 g. (0.62 mmole) of the quinol ether IVb in 30 ml. of ethyl acetate was refluxed with 30 mg. of *p*-toluenesulfonic acid for 1.5 hr. After evaporation of the solvent, the residue was triturated with water. The resulting solid mass was removed by filtration and dried. Crystallization from benzene–ethyl acetate gave 87 mg. (33%) of colorless prisms, m.p. 186–187° dec. In-

(7) S. Kimoto, *J. Pharm. Soc., Japan*, **75**, 763 (1955).

(8) Melting points were determined in capillary tubes and are uncorrected. The infrared spectra were determined in a Nippon Bunko recording spectrophotometer, Model IR-S. The ultraviolet spectra were determined in a Hitachi recording spectrophotometer, Model EPS-2. The microanalyses were made by Mr. J. Goda and his associates, of this faculty.

(9) Kindly supplied by the Koppers Co., Inc., m.p. 130–131°.

(10) L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

(11) *Cf.* ref. 1, footnote 27.

(12) M.p. 103–105°, prepared by Fischer esterification of L-tyrosine.

(13) D. G. Doherty and F. Vaslow, *J. Am. Chem. Soc.*, **74**, 931 (1952).

frared spectrum (Nujol): 3520, 3340, 2700–2400, 1698, 1624, 1544, 960 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 220 mμ (log, ε 4.39), 275 mμ (3.58), 281 mμ (3.57).

Anal. Calcd. for $C_{25}H_{33}O_5N$: C, 70.23; H, 7.78; N, 3.28. Found: C, 70.14; H, 7.99; N, 3.20.

This substance gives a negative color test with ferric chloride reaction but a positive one with ferricyanide–ferric chloride reagent.[14]

B. From the Quinol Ether IVc.—A solution of 0.43 g. (0.86 mmole) of the quinol ether IVc in 40 ml. of ethyl acetate was refluxed with 40 mg. of *p*-toluenesulfonic acid for 30 min. The solvent was evaporated *in vacuo*, the residue dissolved in ether, and the solution extracted with a 5% aqueous solution of sodium bicarbonate. The aqueous layer was acidified with 1 *N* hydrochloric acid and extracted with ether. The ether layer was evaporated and the residue dissolved in benzene and chromatographed on a silica gel column (6.0 g.). Elution with ether yielded 29 mg. (7.9%) of colorless prisms, m.p. 186–187°, whose infrared spectrum was identical with that of the 3′,5′-di-*t*-butylthyronine obtained in procedure A.

3,5′-Di-*t*-butylthyronine (Vg). A. By Acid-Catalyzed Decomposition of the Quinol Ether IVa.—A solution of 2.0 g. (4.3 mmoles) of the quinol ether IVa in 20 ml. of ethyl acetate was refluxed with 1 g. of *p*-toluenesulfonic acid for 1 hr. The pale yellow solution turned green, then reddish violet. On cooling the reaction mixture deposited 1.06 g. (65%) of violet needles of the *p*-toluenesulfonic acid salt of L-tyrosine ethyl ester, m.p. 184–186.5°.

Anal. Calcd. for $C_{18}H_{23}O_6NS$: C, 56.68; H, 6.08; N, 3.67. Found: C, 56.55; H, 6.02; N, 3.69.

This salt, on decomposition with a 5% aqueous solution of sodium bicarbonate gave L-tyrosine ethyl ester which was identical with an authentic sample (mixed melting point and infrared spectra).

The reddish violet filtrate from the *p*-toluenesulfonic acid salt was evaporated. A solution of the residue in ether was washed with a 5% aqueous solution of sodium bicarbonate to remove *p*-toluenesulfonic acid, and then with water. At this point a solid material, which was insoluble in the ether and in the water layer was formed. It was separated by filtration (58 mg., 3.5%) and recrystallized from methanol to give 33 mg. of 3,5-di-*t*-butylthyronine as colorless plates, m.p. 227–228°. Infrared spectrum (Nujol): 3400, 3130, 2800–2400, 964 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 220 mμ (log ε 4.36), 275 mμ (3.61), 281 mμ (3.57).

Anal. Calcd. for $C_{23}H_{31}O_4N$; C, 71.66; H, 8.11; N, 3.63. Found: C, 71.91; H, 8.08; N, 3.66.

This substance gives positive color tests with ninhydrin and with ferricyanide–ferric chloride reagent.[14]

The ether layer was dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in petroleum ether and chromatographed on a silica gel column (10 g.). Elution with petroleum ether gave 0.65 g. of 2,4,6-tri-*t*-butylphenol. Elution with petroleum ether–benzene (9:1) yielded 0.15 g. of 2,6-di-*t*-butylbenzophenone which, upon recrystallization from ethanol, gave 33 mg. of yellow prisms, m.p. 68–68.5°. The infrared spectrum and melting point were identical with those described in the literature.[15]

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.56; H, 9.18.

B. By Hydrolysis of 3′,5′-Di-*t*-butyl-N-acetylthyronine (Vb).—A solution of 100 mg. (0.24 mmole) of 3′,5′-di-*t*-butyl-N-acetylthyronine in 4 ml. of acetic acid and 1 ml. of water was refluxed with 2 ml. of conc. hydrochloric acid for 5 hr. The reaction mixture was evaporated *in vacuo* to dryness, the residue dissolved in a small volume of water, and the solution adjusted to pH 7 with a 5% aqueous solution of sodium bicarbonate. The precipitate formed was collected by filtration and dried; yield 80 mg. (89%). Crystallization from methanol gave colorless plates, m.p. 227–228°, which were identical with the 3′,5′-di-*t*-butylthyronine obtained in procedure A (mixed melting point and infrared spectra).

Reaction of Derivatives of 3,5-Dibromo-L-tyrosine with 2,4,6-Tri-*t*-butylphenoxyl.—A solution of 3.67 g. (10 mmoles) of 3,5-dibromo-L-tyrosine ethyl ester[16] in 200 ml. of ethyl acetate was added with stirring to a free radical solution which was prepared from 5.25 g. (20 mmoles) of 2,4,6-tri-*t*-butylphenol as described above. The mixture was stirred in an atmosphere of oxygen-free nitrogen for 1.5 hr. The color of the solution remained blue. After evaporation of the solvent *in vacuo*, petroleum ether was added to the residue. The resulting precipitate was collected, and identified as 3,5-dibromo-L-tyrosine ethyl ester (mixed melting point and infrared spectra); wt. 2.79 g. (94% recovery).

On evaporation of the remaining petroleum ether solution yellow crystals were obtained. Recrystallization from ethanol gave 5.3 g. (95%) of yellow prisms, m.p. 145–146° dec., which were identical with an authentic sample of the peroxide VII.[4b]

In the reactions of N-acetyl-3,5-dibromo-L-tyrosine,[13] of its methyl ester,[13] and of N-chloroacetyl-3,5-diiodo-L-tyrosine[17] with 2,4,6-tri-*t*-butylphenoxyl similar results were obtained.

3,5-Dibromo-3′,5′-di-*t*-butylthyronine Methyl Ester (Vd).—A solution of 1.05 g. (2.9 mmoles) of 3,5-dibromo-L-tyrosine methyl ester[18] in 30 ml. of ethyl acetate was added with stirring to a free radical solution which was prepared from 1.66 g. (6.3 mmoles) of 2,4,6-tri-*t*-butylphenol as described above and the mixture was stirred for 3 hr. in an atmosphere of oxygen-free nitrogen. After drying over anhydrous sodium sulfate, the reaction mixture was refluxed for 1 hr. with 1 g. of *p*-toluenesulfonic acid in an atmosphere of oxygen-free nitrogen. When the mixture was evaporated *in vacuo* and then diluted with petroleum ether, a solid mass was obtained. This was treated with a 5% aqueous solution of sodium bicarbonate. After filtration the solid mass was dried and triturated with benzene. The remaining insoluble material (225 mg.) was collected. It was identified as 3,5-dibromo-L-tyrosine methyl ester. From the filtrate, crystals separated on standing overnight at 2°. These were recrystallized from benzene to give 0.19 g. (12%) of 3,5-dibromo-3′,5′-di-*t*-butylthyronine methyl ester as colorless plates, m.p. 171–172°. Infrared spectrum (Nujol): 3520, 3300, 1725, 960 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 220 mμ (log ε 4.51), 280 mμ (3.59).

Anal. Calcd. for $C_{24}H_{31}NBr_2$: C, 51.72; H, 5.56; N, 2.52. Found: C, 52.08; H, 5.96; N, 2.58.

This substance gives a positive color test with ferricyanide–ferric chloride reagent.[14]

N-Acetyl-3,5-dibromo-3′,5′-di-*t*-butylthyronine (Ve).—A solution of 1.42 g. (4 mmoles) of N-acetyl-3,5-dibromo-L-tyrosine[13] in 40 ml. of ethyl acetate was added with stirring to a free radical solution which was prepared from 2.1 g. (8 mmoles) of 2,4,6-tri-*t*-butylphenol as described above. Stirring was continued for 2.5 hr. After drying over anhydrous sodium sulfate the mixture was refluxed for 1 hr. with 150 mg. of *p*-toluenesulfonic acid in an atmosphere of oxygen-free nitrogen. The residue obtained after evaporation *in vacuo* was triturated with petroleum ether. The solid material (0.52 g.) was dissolved in benzene and chromatographed on a silica gel column (12 g.). Elution with benzene and then with benzene–ether (1:1) yielded 0.42 g. of crystals which on recrystallization from benzene 0.37 g. (16%) of colorless needles, m.p. 102–103° dec. Infrared spectrum (Nujol):3500, 3290, 1732, 1620, 1550, 960 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{max}^{C_2H_5OH}$ 220 mμ (log ε 4.49), 280 mμ (3.53).

(14) G. M. Barton, R. S. Evans, and J. A. F. Gardner, *Nature*, **170**, 249 (1952).

(15) E. Müller and K. Ley, *Chem. Ber.*, **88**, 606 (1955).

(16) M.p. 161–163°, prepared by Fischer esterification of 3,5-dibromo-L-tyrosine.

(17) E. Ronwin, *J. Org. Chem.*, **18**, 1546 (1953).

(18) M.p. 196–198°, prepared by Fischer esterification of 3,5-dibromo-L-tyrosine.

Anal. Calcd. for $C_{25}H_{31}O_5NBr_2$: N, 2.40. Found: N, 2.59.

This substance gives a positive color test with ferricyanide–ferric chloride reagent.[14]

3,5-Dibromo-3′,5′-di-*t*-butylthyronine (Vh). A. By Acid Hydrolysis of N-Acetyl-3,5-dibromo-3′,5′-di-*t*-butylthyronine (Ve).—A solution of 100 mg. (0.17 mmole) of Ve in a mixture of 4 ml. of acetic acid, 2 ml. of concentrated hydrochloric acid and 1 ml. of water was refluxed for 3.5 hr. The precipitate formed upon neutralization with a 5% aqueous solution of sodium bicarbonate was dissolved in 2 ml. of 2 *N* sodium hydroxide and the solution was extracted with 1-butanol. The butanol layer was evaporated *in vacuo* and the residue was dissolved in aqueous tetrahydrofuran. The solution was acidified with acetic acid and evaporated *in vacuo* to give a sirup which solidified on treatment with water. Recrystallization from methanol gave 12 mg. (13%) of Vh as colorless prisms, m.p. 233–234°. Infrared spectrum (Nujol): 3600, 3380, 3110, *ca.* 1620, 954 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_4NBr_2$: C, 50.82; H, 5.38; N, 2.58. Found: C, 51.08. H, 5.90; N, 2.58.

This substance shows positive color tests with ninhydrin and with ferricyanide–ferric chloride reagent.[14]

B. By Alkaline Hydrolysis of 3,5-Dibromo-3′,5′-di-*t*-butylthyronine Methyl Ester (Vd).—A solution of 75 mg. (0.14 mmole) of Vd in 3 ml. of ethanol was refluxed with 2.6 ml. of 0.1 *N* sodium hydroxide for 30 min. Upon neutralization of the hydrolyzate with 2.6 ml. of 0.1 *N* sulfuric acid a precipitate formed. Crystallization from methanol gave 27 mg. (37%) of colorless prisms, m.p. 233–234°, identical with the 3,5-dibromo-3′,5′-di-*t*-butylthyronine obtained in procedure A.

Ultraviolet Spectra of 3′,5′-Di-*t*-butylthyropropionic Acid and of 3,5-Dibromo-3′,5′-di-*t*-butylthyropropionic Acid.—3′,5′-Di-*t*-butylthyropropionic acid[1]: $\lambda_{max}^{C_2H_5OH}$ 211 mμ (log ε 4.54), 275.5 mμ (3.62), 282 mμ (3.55). 3,5-Dibromo-3′,5′-di-*t*-butylthyropropionic acid[1]: $\lambda_{max}^{C_2H_5OH}$ 210 mμ (log ε 4.76), 281 mμ (3.55).

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Enols of 4-Bromo- and 4-Methyl-2,3-dioxopyrrolidines. Ketone α-Monomethylation under Acidic or Neutral Conditions[1]

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The 1-benzyl- and 1-cyclohexyl-2,3-dioxopyrrolidines (Ia and Ib) yielded enols of corresponding 4-bromo-2,3-dioxopyrrolidines (IIa and IIb) when brominated in chloroform solution. The bromo derivatives underwent condensation with two moles of formaldehyde to yield crystalline products which appear to be sesquiketals, 6-benzyl- or 6-cyclohexyl-4a-bromo-7a-hydroxy-4,4a,5,7a-tetrahydro-1,3-dioxino[4,5-*c*]pyrrol-7(6*H*)-one (IIIa or IIIb). Acetic acid hydrolysis of the condensation product IIIb yielded 1-cyclohexyl-4-bromo-4-hydroxymethyl-2,3-dioxopyrrolidine (IVb); catalytic hydrogenation of IIIa, IIIb, or IVb in acetic acid solution over a platinum catalyst yielded enols of 1-benzyl- or 1-cyclohexyl-4-methyl-2,3-dioxopyrrolidine (XIa or XIb). Chlorine derivatives (Vb and VIIb) corresponding to IIIb and IVb were also obtained. Infrared and particularly n.m.r. data showed that the 4-bromo and 4-methyl compounds were fully enolized; with respect to ferric chloride colors and acidity the compounds resembled phenols.

Those 2,3-dioxopyrrolidines which are unsubstituted in the 4-position undergo self-condensations of the aldol type very rapidly in alkaline solutions.[3,4b] It has therefore not been feasible to attempt the preparation of 4-monoalkyl-2,3-dioxopyrrolidines by direct alkylation of sodium enolates of 2,3-dioxopyrrolidines, although a few 4-monoalkyl or 4-monoaralkyl derivatives have been made by other synthetic routes.[4,5] In order to obtain 4-methyl-2,3-dioxopyrrolidines we have successfully exploited a new reaction sequence which began with 2,3-dioxopyrrolidines unsubstituted in position 4 and introduced a single methyl group at that position without recourse to any process requiring basic reaction conditions. The steps involved are summarized in Chart I. It is quite possible that other α-bromo ketones which are sufficiently reactive toward formaldehyde might be methylated in a similar way.

The sequence was tested with two initial starting materials (Ia. R = benzyl; Ib. R = cyclohexyl). These compounds were brominated in chloroform to afford the α-bromo compounds IIa or IIb in yields of 70 and 93%, respectively. Formula II depicts these compounds as enols; the infrared spectra showed no ketonic carbonyl absorption at or near 5.67μ, where ketonic absorption in such compounds is normally found,[3-6] but did exhibit hydroxyl absorption at 3.12 to 3.18 μ. Moreover, the compounds gave strong purple ferric chloride colors. The expected lactam carbonyl absorption was observed at *ca.* 6.0 μ, and carbon-carbon double

(1) This investigation was supported by a research grant (RG-4371) from the National Institutes of Health, Public Health Service.

(2) Taken principally from a thesis submitted by Julius A. Vida in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology, December, 1960.

(3) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(4) (a) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98, 1554, 1560 (1957); (b) W. R. Vaughan and I. S. Covey, *J. Am. Chem. Soc.*, **80**, 2197 (1958).

(5) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962).

(6) H. H. Wasserman and R. C. Koch, *Chem. Ind.* (London), 128 (1957); *J. Org. Chem.*, **27**, 35 (1962).