The rate of alkaline hydrolysis was followed by paper chromatography in Solvent A. The substance was hydrolyzed to the extent of 50% in 2 hr. at 100° in 1 *N* sodium hydroxide. The product of hydrolysis corresponded to about 80% thymidine-3′ phosphate and about 20% thymidine-5′ phosphate, as judged by the extent of dephosphorylation by the specific 5′-nucleotidase in snake venom.

The substance was hydrolyzed completely in 0.1 *N* hydrochloric acid at 100° within five minutes, whereas at room temperature it hydrolyzed to the extent of about 50% in 24 hr. The sole ultraviolet adsorbing product formed was found to be thymine.

The substance (30 optical density units at 267 mμ) was incubated in tris buffer (*p*H 8.5) with crude snake venom (*ca.* 5 mg). After incubation at 37° for 12 hr., the products were examined by paper chromatography in Solvent A. Approximately one-half of the starting material had disappeared and a spot with the same R_f as thymidylic acid (presumably, thymidine-3′ phosphate) and thymidine had appeared. The latter material obviously arose by the action of the 5′-nucleotidase on the initially formed thymidine-5′ phosphate. The ratio of thymidine-3′ phosphate to thymidine was about one.

General Analytical Methods.—Paper chromatography was carried out by the descending technique and using Whatman No. 1, 4 or 3 MM paper. The solvents which proved useful in this work were isopropyl alcohol–ammonia–water (7–1–2, v./v.) (solvent A), *n*-butyl alcohol–acetic acid–water (5–2–3, v./v.) (solvent B) and the new solvent system isopropyl alcohol–ammonia–acetic acid–water (4–1–2–2, v./v.) (solvent C), which is especially suited for the separation of the homologous series of oligonucleotides. The R_f's of the various compounds in these solvent systems are listed in Table II.

Paper electrophoresis was carried out on Whatman 3 MM strips using the buffers 0.05 *M* ammonium acetate (*p*H 4.5), 0.05 *M* potassium phosphate buffer (*p*H 7.5) and 0.05 *M* sodium borate buffer (*p*H 9.2).

Phosphorus analysis was carried out using the method of E. J. King.[33]

Enzyme Experiments.—Crude snake venom was purchased from Ross Allen's Reptile Institute, Florida. The Experiments using venom were carried out in 0.05 M tris buffer (*p*H 8.2–9.9). The snake venom diesterase used in some experiments was prepared using acetone fractionation procedure of Koerner and Sinsheimer.[34] We are grateful to Dr. W. E. Razzell for this preparation and for performing several of the enzymic experiments.

Prostate phosphomonoesterase was prepared as described by Markham and Smith.[14] It was virtually free from diesterase activity as tested against thymidylyl-(5′→3′)-thymidine.[1] The standard procedure used for removal of phosphomonoester end groups was based on the rate of dephosphorylation of linear thymidine dinucleotide. This rate was determined by adding one volume of a solution of the monoesterase (5–10 mg./ml.) in 1 *M* ammonium acetate buffer, *p*H 5.0, to three volumes of the dinucleotide (about 25 optical density units at 267 mμ) solution in water. Dephosphorylation of the oligonucleotides was followed by paper chromatography and was usually complete in a few hours at 37°.

The spleen diesterase was used according to the procedure of Heppel and Hilmoe,[35] the hydrolysis being followed by paper chromatography.

Acidic Hydrolysis of Cyclic Oligonucleotides.—The oligonucleotides were heated in 1 *N* hydrochloric acid at 100° for about 45 minutes, during which some 20–30% of the starting material had disappeared. The products then were separated on paper chromatograms, run in solvent A for 24–48 hours and the slowest band, which corresponded to dithymidine triphosphate or trithymidine tetraphosphate, etc., was eluted with water containing 0.5% Versene. The eluate was evaporated under reduced pressure and dephosphorylated with prostate monoesterase as described above except that incubation was usually prolonged to several hours. The resulting compounds V, dithymidine monophosphate, trithymidine diphosphate, etc., were compared on paper chromatograms with the corresponding samples obtained by monoesterase treatment of the linear oligonucleotide. The R_f values are listed in Table II.

TABLE II

R_f VALUES OF THYMIDINE OLIGONUCLEOTIDES AND RELATED COMPOUNDS

Compound	Solvent A	Solvent B	Solvent C
Thymidylic	0.15	0.36	0.69
Linear dithymidylic	.08	.21	.51
Linear trithymidylic	.045	.14	.41
Linear tetrathymidylic	.02	.09	.31
Linear pentathymidylic	.01	.06	.21
Thymidine	.67	.60	
Dithymidine monophosphate (V, $n = 0$)	.42		
Trithymidine diphosphate (V, $n = 1$)	.21		
Tetrathymidine triphosphate (V, $n = 2$)	.11		
Pentathymidine tetraphosphate (V. $n = 3$)	.045		
Thymidine-3′,5′ cyclic phosphate (IV)	.45	.31	.78
Cyclic dithymidylic	.28	.21	.56
Cyclic trithymidylic	.12	.16	.48
Cyclic tetrathymidylic	.051	.13	.32
Cyclic pentathymidylic	.026	.08	.22

(33) E. J. King, *Biochem. J.*, **26**, 292 (1932).

(34) J. F. Koerner and R. L. Sinsheimer, *J. Biol. Chem.*, **228**, 1039 (1957).

(35) L. A. Heppel and R. J. Hilmoe, in "Methods in Enzymology." Vol. II, Academic Press, Inc., New York, N. Y., 1955. p. 565.

VANCOUVER 8, CANADA

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND THE INSTITUTE FOR ENZYME RESEARCH, UNIVERSITY OF WISCONSIN]

3′-Hydroxy-3,5-diiodo-L-thyronine[1]

BY RAYMOND W. DOSKOTCH AND HENRY A. LARDY

RECEIVED JULY 14, 1958

The synthesis of 3′-hydroxy-3,5-diiodo-L-thyronine is described. This compound has but little thyroid hormone activity.

Because the thyroid hormones and the adrenal medullary hormones augment one another,[2] and because thyroid hormones appear to interfere with catechol amine destruction,[3] the possibility exists that metabolic hydroxylation of the partially iodinated thyronine molecule forms a compound which is competitively antagonistic to catechol amine destruction. To test this hypothesis, the synthesis of

(1) Taken in part from the M.S. Thesis submitted by Raymond W. Doskotch, 1957. Presented at the 132nd National Meeting of the American Chemical Society, New York, 1957. Supported by grants from the U. S. Public Health Service and the Office of Naval Research.

(2) R. M. Morris, M. S. Witter and S. Weiss, *Proc. Soc. Exptl. Biol. Med.*, **21**, 149 (1924); J. Schaeffer and O. Thibault. *Compt. rend. soc. biol.*, **139**, 855 (1945); H. W. Swanson. *Endocrinol.*, **59**, 217 (1956).

(3) Z. M. Bacq, *J. Physiol. (London)*, **87**, 87P (1936); M. Zile, M.S. Thesis, University of Wisconsin, 1956.

3' - hydroxy - 3,5 - diiodo-L-thyronine was undertaken.[4] This compound has served as a model for the attempted synthesis of 5'-hydroxy - 3,5,3' - triiodothyronine. The latter and 3'-hydroxy-3,5-diiodo-L-thyronine are possible products of the aerobic deiodination by liver homogenates[5] of thyroxine and triiodothyronine, respectively.

The synthetic route (Fig. 1) leading to the formation of 3'-hydroxy-3,5-diiodo-L-thyronine was based on the sequence of reactions developed by Hems and his group[6] which culminated in a commercial synthesis of thyroxine. The necessary intermediate, 3,5-dinitro - N - acetyl - L - tyrosine ethyl ester, was synthesized from L-tyrosine by previously reported methods.[6,7] Condensation of the substituted amino acid with 3,4-dimethoxyphenol[8] in the presence of *p*-toluenesulfonyl chloride in pyridine afforded 3,5-dinitro-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine ethyl ester (I), which was hydrogenated to the diamine II with Pd-on-charcoal catalyst. The difficulty encountered in purifying this compound for analysis was circumvented by forming the diacetyl derivative III with acetic anhydride. Replacement of the nitro groups by iodine was accomplished by catalytic reduction of I, diazotization of the formed amino groups and treatment of the diazonium salt with sodium iodide without isolation of the intermediate products. Crystallization of 3,5-diiodo-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine ethyl ester (IV) was possible only when the crude product was passed through a short alumina column, which removed the dark impurities, allowing easy crystallization of the material in the effluent.

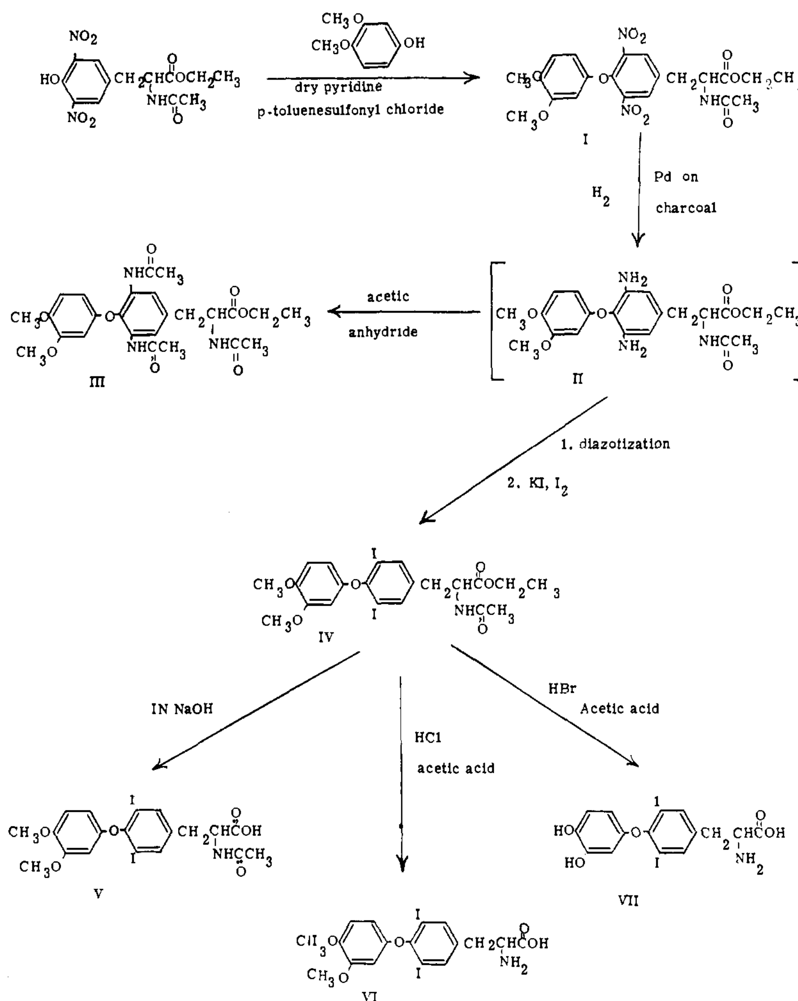


Fig. 1.

Alkaline hydrolysis of IV at room temperature produced 3,5-diiodo-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine (V), while HCl hydrolysis gave the free amino acid, 3,5-diiodo-4-(3',4'-dimethoxyphenoxy)-L-phenylalanine (VI). Cleavage of the two methoxy groups in addition to the groups protecting the amino acid portion of IV was accomplished with 48% HBr. The product 3,5-diiodo-4-(3',4'-dihydroxyphenoxy)-L-phenylalanine or 3'-hydroxy-3,5-diiodo-L-thyronine (VII) could be obtained in white crystalline form, but the use of Versene[9] and sodium metabisulfite in the crystallization was obligatory to prevent oxidation of the compound. However, this treatment resulted in contamination as witnessed by the quantitative elemental analysis. Decomposition of VII in solution was extremely rapid above *p*H 5. The hydrochloride salt was formed readily without addition of other reagents and allowed for considerable purification. Wilkinson[10] has reported the attempted synthesis of VII, starting with 3,4-methylenedioxyphenol and found it very difficult to purify; his best preparation was colored and low in iodine.

Qualitative tests support the structure proposed for this compound. The ninhydrin test for the amino acid portion was positive, while the catechol portion accounts for its ability to reduce rapidly a 5% phosphomolybdic acid solution,[11] and to form an orange precipitate with titanium(III) chloride.[12]

Catalytic reduction of 3,5-diiodo-4-(3',4'-dimeth-

(4) G. E. W. Wolstenholme and E. C. P. Millar, Editors, "Ciba Foundation Colloquia on Endocrinology," Vol. 10, J. and A. Churchill Ltd., London, 1957, p. 154.

(5) N. F. Maclagen and W. E. Sprott, *Lancet*, **2**, 368 (1954); W. E. Sprott and N. F. Maclagen, *Biochem. J.*, **59**, 288 (1955).

(6) J. R. Chalmers, G. T. Dickson, J. Elks and B. A. Hems, *J. Chem. Soc.*, 3424 (1949).

(7) T. C. Bruice, N. K. Kharasch and R. J. Winzler, *J. Org. Chem.*, **18**, 83 (1953).

(8) R. I. Meltzer and J. Doczi, THIS JOURNAL, **72**, 4986 (1950).

(9) Disodium ethylenediaminetetraacetic acid produced by Bersworth Chemical Co., Framingham, Mass.

(10) J. H. Wilkinson, *Biochem. J.*, **63**, 601 (1956).

(11) F. Feigl, "Spot Tests," Vol. II, Elsevier Publishing Co., New York, N. Y., 1954, p. 102 pp. 305-306.

(12) F. Weygand and E. Csendes, *Chem. Ber.*, **85**, 45 (1952).

oxyphenoxy)-L-phenylalanine removed the iodines to give 4-(3',4'-dimethoxyphenoxy)-L-phenylalanine (VIII). Hydrolysis of VIII with HI or HBr gave a product which was not purified but possessed, in the crude state, the same reducing ability as did VII.

Biological assays[13] for thyroxine-like activity were carried out on compounds IV, V, VI and VII. In the rat goiter prevention assay 3'-hydroxy-3,5-diiodo-L-thyronine (VII) was 1.5% as active as L-thyroxine, while all other compounds were inactive. The tadpole metamorphosis assay indicated 3,5-diiodo-4-(3',4'-dimethoxyphenoxy)-L-phenylalanine (VI) to be approximately 10% as active as L-thyroxine. 3'-Hydroxy-3,5-diiodo-L-thyronine was slightly more active than VI.

Experimental[14]

3,5-Dinitro-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine Ethyl Ester (I).—A solution of 34.1 g. (0.10 mole) of 3,5-dinitro-N-acetyl-L-tyrosine ethyl ester in 40 ml. of dry pyridine, in a dry system, was treated with 21.0 g. (0.11 mole) of *p*-toluenesulfonyl chloride and heated 30 minutes at 100°; 3,4-dimethoxyphenol (46.2 g., 0.30 mole) was added and the mixture was refluxed for one hour. Pyridine was removed at reduced pressure and the residue taken up in 300 ml. of chloroform. The chloroform solution was extracted successively with 2 *N* HCl, 2 *N* NaOH and water, then dried over anhydrous sodium sulfate. Removal of the chloroform *in vacuo* and recrystallization of the residue from ethanol–water afforded 24 g. (50%) of orange colored needles, m.p. 125–126.5°, $[\alpha]^{22.5}D$ −14.1 ± 0.4° (*c* 1.13 in dioxane).

Anal. Calcd. for $C_{21}H_{23}N_3O_{10}$ (477.4): C, 52.8; H, 4.85; N, 8.80. Found: C, 53.0; H, 4.73; N, 9.05.

3,5-Diacetamino-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine Ethyl Ester (III).—Compound I (1.0 g., 2.1 mmoles) was hydrogenated in 60 ml. of methanol at room temperature and atmospheric pressure with 0.1 g. of 10% Pd-on-charcoal as catalyst. The hydrogen uptake ceased in two hours. The catalyst was separated by filtration and the solvent was removed completely at reduced pressure. These operations were conducted under a CO_2 atmosphere. The crude diamine was dissolved in 30 ml. of acetic anhydride from which the product crystallized. In two hours it was collected, washed with water and dried. Recrystallization from ethanol gave 0.70 g. (65%) of long white lances, m.p. 209.5–210.0°, $[\alpha]^{23}D$ +72.3 ± 0.9° (*c* 1.05 in chloroform).

Anal. Calcd. for $C_{25}H_{31}N_3O_8$ (501.6): C, 59.9; H, 6.23; N, 8.38. Found: C, 59.9; H, 5.96; N, 8.50.

3,5-Diiodo-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine Ethyl Ester (IV).—Compound I (4.0 g., 8.4 mmoles) was hydrogenated in 100 ml. of acetic acid at room temperature and atmospheric pressure over 0.4 g. of 10% Pd-on-charcoal. The catalyst was removed by filtration under a CO_2 atmosphere and the filtrate was added dropwise (1 hr.) to a well-stirred mixture of 70 ml. of concd. H_2SO_4, 1.8 g. $NaNO_2$ and 70 ml. of acetic acid maintained between −3 and 0°. The resulting orange diazonium salt solution was stirred one additional hour at 0°, then added fairly rapidly from a cooled dropping funnel to a well-stirred solution of 8.0 g. of NaI, 7.0 g. of I_2 and 1.0 g. of urea in 125 ml. of water, covering 200 ml. of chloroform. The chloroform layer was separated after two hours stirring and the aqueous layer extracted with chloroform. The combined dark chloroform extracts were covered by a 10% sodium sulfite solution and SO_2 was bubbled through until the iodine was reduced, then washed well with water and dried over anhydrous sodium sulfate. Removal of the chloroform at reduced pressure left a dark oil which yielded 3.5 g. (66%) of tiny rosettes of white needles from ethanol–water after decolorizing with charcoal and seeding,[15] m.p. 133–134.7°, $[\alpha]^{23.5}D$ +10.2 ± 0.5° (*c* 0.98 in ethanol).

Anal. Calcd. for $C_{21}H_{23}O_6NI_2$ (639.2): C, 39.5; H, 3.63; N, 2.19; I, 39.7. Found: C, 39.8; H, 4.00; N, 2.34; I, 39.3.

3,5-Diiodo-4-(3',4'-dimethoxyphenoxy)-N-acetyl-L-phenylalanine (V).—Compound IV (0.50 g., 0.78 mmole) was stirred in 7 ml. of ethanol and 7 ml. of 1 *N* NaOH for 30 minutes at room temperature, the small amount of insoluble material was removed by filtration and the filtrate acidified slowly to about *p*H 4 (multi-range *p*H paper) with concd. HCl. Addition of 10 ml. of water induced crystallization and the product was collected after two hours cooling in the refrigerator. Recrystallization was accomplished by diluting 10 ml. of the hot ethanol solution with 20 ml. of hot water and cooling, resulting in rosettes of white needles, 0.43 g. (90%), m.p. 237–239° dec., with slight browning at 225°, $[\alpha]^{25}D$ +5.8 ± 0.5° (*c* 1.04 in acetone), $[\alpha]^{25}D$ +53.7 ± 0.8° (*c* 1.30 in 0.05 *N* NaOH).

Anal. Calcd. for $C_{19}H_{19}O_6NI_2$ (611.2): C, 37.3; H, 3.13; N, 2.29; I, 41.5. Found: C, 37.5; H, 3.10; N, 2.54; I, 41.2.

3,5-Diiodo-4-(3',4'-dimethoxyphenoxy)-L-phenylalanine (VI).—Compound IV (0.51 g., 0.80 mmole), 7 ml. of acetic acid and 7 ml. of concd. HCl were refluxed for 2.5 hours, then diluted with 20 ml. of water and cooled. The tiny white needles which formed were recrystallized by dissolving in 0.3 *N* HCl in 60% ethanol and, while hot, adding 10% sodium acetate to *p*H 4. After crystallization was nearly complete, the mixture was placed in the refrigerator for a few hours before collecting the product, 0.35 g. (77%) m.p. 217–219° dec., $[\alpha]^{23}D$ +27.2 ± 0.5° (*c* 1.05 in 1:1 ethanol–1 *N* HCl).

Anal. Calcd. for $C_{17}H_{17}O_5NI_2$ (569.2): C, 35.9; H, 3.01; N, 2.46; I, 44.6. Calcd. for $C_{17}H_{17}NI_2 \cdot H_2O$ (587.2): C, 34.8; H, 3.26; N, 2.39; I, 43.2. Found: C, 34.8; H, 3.33; N, 2.57; I, 42.8 (the average of analyses performed on three different preparations).

3,5-Diiodo-4-(3',4'-dihydroxyphenoxy)-L-phenylalanine or 3'-Hydroxy-3,5-diiodo-L-thyronine (VII).—Compound IV (0.50 g., 0.78 mmole), 10 ml. of acetic acid and 10 ml. of 48% HBr were refluxed four hours, diluted with 20 ml. of water, decolorized once with charcoal and neutralized to *p*H 4 while hot with solid sodium carbonate. On cooling, 0.32 g. (75%) of long buff colored needles appeared which were collected, and washed well with water. The compound was recrystallized by dissolving in 1 *N* HCl and ethanol (1:2) containing a few drops of 5% Versene and 10% sodium metabisulfite, decolorizing with charcoal and neutralizing while hot to *p*H 4 with 10% sodium acetate. The almost colorless product was recrystallized again without addition of Versene or metabisulfite. On heating, the compound slowly darkened at about 260° and decomposed around 290° as manifested by a burst of iodine vapor. Above *p*H 5 solutions of this compound decompose readily; $[\alpha]^{23}D$ +23.6 ± 0.5° (*c* 0.997 in 1 *N* HCl–ethanol (1:2)).

Anal. Calcd. for $C_{15}H_{13}O_5NI_2$ (541.1): C, 33.3; H, 2.42; N, 2.59; I, 46.9. Found: C, 33.0; H, 3.11; N, 2.77; I, 44.5.

The hydrochloride was obtained in the form of colorless elongated hexagonal plates on cooling a solution of the compound in 2 *N* HCl, m.p. 198–200° dec.

Anal. Calcd. for $C_{15}H_{13}O_5NI_2 \cdot HCl$ (577.6): C, 31.2; H, 2.44; N, 2.43; halogen, 50.1. Found: C, 31.0; H, 2.68; N, 2.51; halogen, 48.9.

4-(3',4'-Dimethoxyphenoxy)-L-phenylalanine (VIII).—The iodine was removed from VI (1.14 g., 2.0 mmoles) by hydrogenation in 25 ml. of 2 *N* NaOH and 25 ml. of ethanol in the presence of 1.0 g. of 2% Pd-on-calcium carbonate.[16] The catalyst, which turns black on completion of the reaction, was removed by filtration and the filtrate was acidified to *p*H 5 with acetic acid. Reduction of the volume at reduced pressure to 20 ml. induced crystallization and diluting with 50 ml. of water brought out 0.63 g. (81%) of tiny white lances. To recrystallize, it was dissolved in 300 ml. of

(13) K. Tomita and H. A. Lardy, *J. Biol. Chem.*, **219**, 595 (1956).

(14) Melting points are corrected. Elemental analyses by Micro-Tech Laboratories, 8000 Lincoln Ave., Skokie, Ill., on samples dried *in vacuo* at 56° and 0.05 mm. for 2–3 hours over P_2O_5.

(15) Original crystals were obtained by passing a benzene solution of the crude product through a short alumina column, eluting with 10% methanol in benzene, evaporating the solvents, and crystallizing the light colored material from ethanol.

(16) A. T. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1956, pp. 391–392.

ethanol, the volume was reduced to one-third by boiling, and the solution then was cooled, m.p. 204.5–206.0° (with effervescence to a clear red melt), $[\alpha]^{23}D$ +16.2 ± 0.2° (*c* 1.01 in 1 *N* HCl–ethanol (1:1)).

Anal. Calcd. for $C_{17}H_{19}O_5N$ (317.3): C, 64.3; H, 6.03; N, 4.42. Found: C, 63.7; H, 6.15; N, 4.34.

MADISON 5, WISC.

[CONTRIBUTION FROM THE ORGANIC DIVISION, MONSANTO CHEMICAL CO.]

α-Halogenation Products of ε-Caprolactam and their Transformation to DL-Lysine[1]

BY ROBERT J. WINEMAN, EU-PHANG T. HSU AND CONSTANTINE E. ANAGNOSTOPOULOS

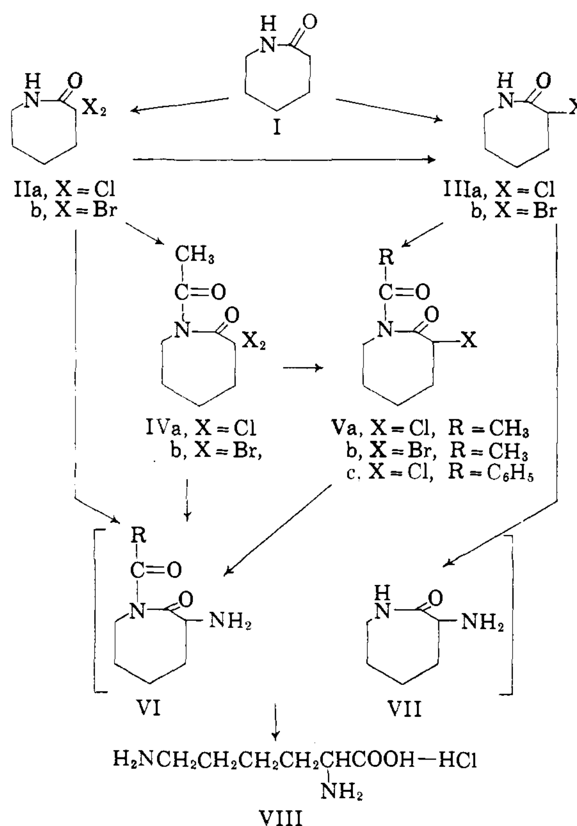
RECEIVED APRIL 11, 1958

Improved methods have been developed for the preparation of 3,3-dihalo-2-oxohexamethyleneimines. Conversions of the dihaloimines to the corresponding 3-halo-2-oxohexamethyleneimines, and transformations of the 3-halo- and 3,3-dihalo-2-oxohexamethyleneimines to DL-lysine by amination or reductive amination and acid hydrolysis are given. The latter reactions were carried out on the corresponding 1-acyl-3-halo- or 1-acyl-3,3-dihalo-2-oxohexamethyleneimines for comparison. Similarly, the transformation of 6-acetamido-2-halo- or 6-acetamido-2,2-dihalohexanoic acids to DL-lysine was made.

For the synthesis of DL-lysine, ε-caprolactam (2-oxohexamethyleneimine) frequently has been chosen as the starting material. In the last decade the increased availability of ε-caprolactam, containing all the carbon atoms and one of the nitrogen atoms required for DL-lysine in their correct state of oxidation, has gained in attractiveness as a starting material for synthetic DL-lysine. Until recently, the lactam ring has been hydrolytically cleaved, prior to halogenations and amination.[2-8] As in the classic synthesis of Eck and Marvel, an additional blocking group is introduced for protection of the ε-amino group.

It seemed apparent that the lactam might provide sufficiently stable acyl blocking of the ε-amino group to prevent its degradation in the halogenation step and to prevent effectively its interaction with an α-halogen. This study deals with the halogenation and subsequent transformations of the halocaprolactams into DL-lysine. After this work was completed, Rickenbacher and Brenner[9] reported using 3-chloro-2-oxohexamethyleneimine as an intermediate for lysine synthesis, introducing the α-amino group by interaction with sodium azide and reduction.

The initial purpose of the present investigation was to study the conversion of ε-caprolactam (I) into 3-chloro-2-oxohexamethyleneimine (IIIa), its amination to 3-amino-2-oxohexamethyleneimine (VII), and the hydrolysis of the latter to DL-lysine (VIII). Since the 3-chloro-2-oxohexamethyleneimine could not be obtained by direct halogenation of ε-caprolactam, use was made of the selective reduction of the 3,3-dichloro-2-oxohexamethyleneimine (IIa). By improved conditions for the halogenation of ε-caprolactam and selective reduction, 3-chloro-2-oxohexamethyleneimine was prepared in yields of over 80% from ε-caprolactam. The best yield of DL-lysine obtained by amination and hydrolysis of 3-chloro-2-oxohexamethyleneimine (IIIa) was 30–33% giving an over-all yield of DL-lysine of 25% from ε-caprolactam. Modifications of this route described below gave yields of 50% over-all.



The chlorination of 2-oxohexamethyleneimine was first reported by von Braun and Heymons.[10] These workers used an excess of phosphorus pentachloride, xylene as solvent and reaction at elevated temperatures. Their procedure involved a high

(1) Presented in part before the Organic Division of the American Chemical Society at the 133rd National Meeting, San Francisco, Calif., April 18, 1958.

(2) J. C. Eck and C. S. Marvel, *J. Biol. Chem.*, **106**, 387 (1934); J. C. Eck and C. S. Marvel, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 74, 76 and 374.

(3) K. Odo and S. Himizu, *J. Soc. Org. Synthet. Chem. Japan*, **11**, 386 (1953); *C. A.*, **48**, 1958 (1954).

(4) D. C. Sayles and E. F. Degering, THIS JOURNAL, **71**, 3161 (1949).

(5) A. Galat, U. S. Patent 2,519,038.

(6) A. Galat, THIS JOURNAL, **69**, 86 (1947).

(7) E. E. Howe and E. W. Pietrusza, *ibid.*, **71**, 2581 (1949).

(8) G. Steinbrunn, German Patent 855,260.

(9) H. R. Rickenbacher and M. Brenner, *Angew. Chem.*, **69**, 688 (1957); M. Brenner and H. R. Rickenbacher, *Helv. Chim. Acta*, **41**, 181 (1958).

(10) J. v. Braun and A. Heymons, *Ber.*, **63**, 502 (1930).