EXPERIMENTAL

Melting points were determined in soft glass capillary tubes and are uncorrected.

9-Hydroxy-7,9-dimethyl-Δ^{10}-ergolene. Methyllithium in ether solution was prepared by dropwise addition of methyl iodide (148 g., 1.04 mol.) to a stirred suspension of 14.6 g. (2.08 mol.) of lithium ribbon in 350 ml. of dry ether. The solution was stirred for 0.5 hr. after the addition was complete and then with ice-bath cooling there was added slowly a solution of 10 g. (0.042 mol.) of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole. The reaction mixture was stirred for several hours at room temperature, allowed to stand overnight, and then decomposed by slow addition of 150 ml. of ice water. Part of the product which was insoluble in both the organic and aqueous phases separated at this point and was removed by filtration and crystallized from methanol; yield, 3.72 g., m.p. 206–208°. Another crop was obtained from the ether-anisole layer by extraction with dilute hydrochloric acid, neutralization of the extract with sodium bicarbonate and extraction with chloroform. The chloroform extract on evaporation gave 0.63 g. of the methyl carbinol. The total yield was 4.35 g. (41%). A sample was recrystallized from methanol for analysis, m.p. 209–212°.

Anal. Calcd. for $C_{16}H_{29}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.01; H, 7.98; N, 10.82.

9-Ethyl-9-hydroxy-7-methyl-Δ^{10}-ergolene. Ethylmagnesium bromide was prepared in the usual fashion in a 1 l. 3-necked flask using 113 g. of ethyl bromide, 25.4 g. of magnesium, and 350 ml. of ether. After addition of the ethyl bromide was complete, the solution was stirred for 30 min. and then cooled in an ice bath. A solution of 10 g. of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole was then added during 20 min. and the reaction mixture was allowed to stir for 2 hr. at room temperature and then to stand overnight. Decomposition of the complex was carried out by the addition of 140 ml. of saturated aqueous ammonium chloride solution at 0°. The organic layer was decanted and the sludge was extracted with chloroform. About 25 ml. of 50% aqueous sodium hydroxide was added and the sludge was again extracted with chloroform. The combined chloroform extract was washed with water and then extracted with three portions of dilute hydrochloric acid, each containing 5 ml. of the concentrated acid. The acid extracts were carboned and neutralized with an excess of sodium bicarbonate and then extracted with four 75 ml. portions of warm chloroform. The extracts were warmed to keep the product in solution, dried quickly over magnesium sulfate, and concentrated *in vacuo*. The residue was taken up in a little methanol, and the ethyl carbinol was filtered and washed with methanol and ether; yield, 2.67 g. (24%). A sample for analysis was recrystallized from methanol containing a little water, m.p. 204–206° (dec.).

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.80; H, 8.77; N, 10.29.

9-Allyl-9-hydroxy-7-methyl-Δ^{10}-ergolene. The allyl Grignard reagent was prepared in a 3 l. 3-necked flask by the addition during 5–6 hours of a solution of 126 g. (1.1 mol.) of allyl bromide in 625 ml. of dry ether to a stirred suspension of 76 g. (3.1 mol.) of magnesium in 250 ml. of ether. Stirring was continued for 15 min., after which the reaction mixture was cooled in an ice bath. A solution of 10 g. of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole was then added during 10 min. Stirring was continued at room temperature for 3 hr., and the mixture was allowed to stand overnight. It was then cooled and decomposed by addition of 140 ml. of saturated aqueous ammonium chloride solution. Ethyl acetate (300 ml.) was added and the organic layer was decanted. The sludge was extracted with ethyl acetate and then with chloroform. Fifty milliliters of 50% aqueous sodium hydroxide was then added, and the sludge was again extracted with chloroform. The chloroform extracts were combined and extracted five times with dilute hydrochloric acid (each portion containing 5 ml. of concentrated acid). The combined acid extract was neutralized with an excess of sodium bicarbonate and the allyl carbinol was extracted with three 200 ml. portions of chloroform. The combined extract was dried over magnesium sulfate and evaporated *in vacuo*. The product was digested with methanol, filtered and washed with methanol and ether; yield, 6.64 g. (62%). A sample was recrystallized from ethanol containing a little water, m.p. 198–202° (dec.).

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.75; H, 8.34; N, 9.59.

9-Hydroxy-7-methyl-9-phenyl-Δ^{10}-ergolene. Phenylmagnesium bromide was prepared in the usual way from 15.7 g. (0.1 mol.) of bromobenzene and 2.9 g. (0.12 mol.) of magnesium in 200 ml. of absolute ether. A solution of 4.8 g. (0.02 mol.) of 9-keto-7-methyl-Δ^{10}-ergolene in 50 ml. of pure dioxane was then added with stirring during 10 min. Stirring was continued for 2 hr. and then the solution was allowed to stand at room temperature overnight. Saturated aqueous ammonium chloride solution (27 ml.) was added to decompose the complex and the ether layer was decanted. The residual sludge was extracted once with ether and twice with chloroform, and the combined extract was dried over magnesium sulfate and concentrated *in vacuo*. The residual phenyl carbinol, 0.7 g. (11%), was crystallized from ethanol, m.p. 219–220° (dec.).

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.12; H, 7.05; N, 8.67.

7,9-Dimethyl-$\Delta^{8,10}$-ergoladiene. 7,9-Dimethyl-9-hydroxy-Δ^{10}-ergolene, 0.5 g., was mixed with 20 ml. of acetonitrile and 5 ml. of boron trifluoride–etherate. The solution was allowed to stand at room temperature for 24 hr. and then poured into an excess of ice and water. The mixture was neutralized with sodium bicarbonate and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from methanol containing a little ethyl acetate; yield, 0.34 g. (74%), m.p. 122–126°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.21; H, 7.60; N, 12.09.

Ultraviolet absorption maxima are at 253, 293 and 306 mμ (neutral) and 213, 222, 230, 238, 288, and 309 mμ (acidic).

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Biologically Active 2,4-Dichlorophenoxyacetylated Amino Acids

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Received August 7, 1959

This report on amino acid derivatives of 2,4-dichlorophenoxyacetic acid, designated 2,4-D, is an extension of previous studies[2–8] which have dem-

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TABLE I

PHYSICAL AND ANALYTICAL DATA OF AMINO ACID DERIVATIVES OF 2,4-DICHLOROPHENOXYACETIC ACID

N-(2,4-Dichlorophenoxyacetyl)-	M.P., °C. (Corr.)[a]	Yield, %		Formula	Analyses[b]					
					Cl, %		N, %		Optical rotation	
		Crude	Refined		Calcd.	Found	Calcd.	Found	$[\alpha]_D^{25}$	C, g./100 ml[c]
D-alanine	203.7–204.7	73.8	51.6	$C_{11}H_{11}Cl_2NO_4$	24.28	24.24	4.80	4.84	−12.8 ± 0.4	5.77
β-alanine	172.8–174.0[d]	82.5	72.6		24.28	24.27	4.80	4.79		
L-asparagine	186.4–187.4	73.2	57.1	$C_{12}H_{12}Cl_2N_2O_5$	21.15	21.14	8.36	8.27	+17.4 ± 0.5	4.46
D-asparagine	183.3–184.3	82.6	60.6		21.16	21.24	8.36	8.14	−18.5 ± 0.4	4.56
DL-asparagine	180.2 181.3[e]	82.8	47.1		21.16	21.21	8.36	8.11		
D-glutamic acid	184.0–185.0[f,g]	17.1	12.4	$C_{13}H_{13}Cl_2NO_5$	20.25	20.10	4.00	4.09	−12.5 ± 1.5	0.89
Glycylglycine	184.0–185.0[g]	74.4	48.8	$C_{12}H_{12}Cl_2N_2O_5$	21.16	20.80	8.36	8.11		
L-isoleucine	143.4–143.9	71.7	41.4	$C_{14}H_{17}Cl_2NO_4$	21.22	21.23	4.19	4.21	+10.0 ± 0.3	7.80
D-isoleucine	143.9–145.1	71.1	59.9		21.22	21.19	4.19	4.22	−10.1 ± 0.3	8.96
D-leucine	155.7–156.7	82.4	70.6		21.22	21.14	4.19	4.21	+16.0 ± 0.4	5.19
L-serine	180.0–183.0[h]		19.5	$C_{11}H_{11}Cl_2NO_5$	23.02	23.07	4.55	4.51	+22.2 ± 0.4	2.00[i]
D-serine	171.8–172.8[j]	58.7	13.6		23.02	22.38	4.55	4.67	−25.3 ± 0.4	5.29
L-threonine	131.0–132.5[k]		20.0	$C_{12}H_{13}Cl_2NO_5$	22.01	21.82	4.34	4.62	+13.8 ± 0.6	2.00
D-threonine	131.0–132.0[f]	62.2	42.6		22.01	21.92	4.34	4.32	−13.1 ± 0.4	5.47
L-tryptophane	152.2–153.4	98.9	70.1	$C_{19}H_{16}Cl_2N_2O_4$	17.40	17.32	6.88	6.88	−13.0 ± 0.3	8.22
D-tryptophane	177.2–178.2	89.2	79.2		17.40	17.41	6.88	6.86	+13.0 ± 0.3	9.09
L-valine	164.2–164.7	79.8	69.4	$C_{13}H_{15}Cl_2NO_4$	22.15	22.14	4.38	4.40	+13.8 ± 0.4	5.15
D-valine	164.2–164.7	80.0	70.6		22.15	22.15	4.38	4.39	−14.3 ± 0.4	5.33
N,N'-bis-(2,4-Dichlorophenoxyacetyl)-										
D-cystine	217.0–220.0[h]		32.8	$C_{22}H_{20}Cl_4N_2O_8S_2$	21.94	21.85	4.33	4.30	+109.2 ± 0.4	1.00[l]
DL-cystine	214.0–217.0[h]		40.0		21.94	21.64	4.33	4.35		

[a] Recrystallized twice from 50% ethanol unless otherwise indicated. [b] The authors are indebted to J. S. Ard of this laboratory for the analyses. [c] In 10% molar excess of sodium hydroxide. [d] Recrystallized once from 50% ethanol. [e] Sample sealed under nitrogen. [f] Recrystallized twice from ethyl acetate–hexane. [g] Prepared by C. H. H. Neufeld. [h] Prepared by J. F. Carmichael. [i] In pyridine. [j] Recrystallized twice from methyl ethyl ketone–hexane. [k] Prepared by T. F. Drake. [l] In dimethyl formamide.

onstrated that amino acid coupling can have a marked effect upon the growth-regulating properties of a compound. Such properties are also modified by combination with inexpensive protein hydrolyzates prepared from animal and vegetable sources.[9]

A previous report on the synthesis of 28 amino acid derivatives of 2,4-D appeared in 1952;[10] this note extends the 2,4-D series to 48 amino acid derivatives. The 20 new derivatives were prepared to elucidate further the mode of action and specificity of aryloxyalkylcarboxylic acids as plant growth regulators, as well as to investigate further the use of amino acids as bioactive formulating agents. Many of the compounds from the various series have been submitted to various cooperating agencies for evaluation as plant growth regulators, herbicides, fungicides, anticancer agents, insect repellents, and nematocides. One report[2] on herbicidal evaluation describes *N*-(2,4-dichlorophenoxyacetyl)-D-asparagine as effective in killing pigweed, mustard, and broadleaf weeds without effect on corn and gladiolus in postemergence sprays at $^1/_2$ to 1 pound per acre application rates. Details on the specific biological properties of these compounds will be reported elsewhere.

EXPERIMENTAL

The compounds listed in Table I were prepared by Schotten-Baumann techniques in accordance with descriptions outlined in previous publications. No special directives are necessary here in view of earlier descriptions and the absence of any particular preparative difficulties.

Some of the D-amino acids used in this work were obtained through the courtesy of the late Dr. Jesse P. Greenstein of the National Institutes of Health, Bethesda, Md.; others, and the 2,4-D used, were purchased from commercial sources and utilized without further purification. The 2,4-D was converted to its acyl chloride by the method of Freed[11] and also described by us.[10]

In general the yields of reaction products were fairly high but appreciably losses were taken in the purification processes because it was essential that traces of free acid be removed from the derivatives and that optical purity be obtained. The optical values received were essentially equal and opposite for the D- and L-isomeric compounds. The special variations used in the purification techniques are indicated in the footnotes of Table I.

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The Structure of the Addition Product from Hydrogen Cyanide and a 2-Vinyldihydro-1,3-oxazine

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Received August 10, 1959

A recent article[1] described the preparation of several 2-alkenyl-4,6,6-trimethyldihydro-1,3-oxazines from unsaturated nitriles and 2-methyl-2,4-pentanediol and the reaction of one of these dihydro-1,3-oxazines with hydrogen cyanide. The heterocyclic bases were prepared according to the general method first described by Tillmanns and Ritter[2] who condensed a series of nitriles with 2-methyl-2,4-pentanediol in cold 92% sulfuric acid.

Treatment of I with hydrogen cyanide in glacial acetic acid yielded an addition product which could possess structure II or III as a result of either 1,4- or 3,4- addition, respectively. On the basis of the infrared spectrum of the adduct, II was concluded to represent the true structure. This reaction has now been re-examined and III is claimed to be the correct structure of the adduct. This claim is based upon an alternate synthesis of III, alkaline hydrolysis of the addition product, and a revised interpretation of the infrared spectrum in the light of recent studies.[3]

The alternate method of synthesis of the addition compound was accomplished by treating 2-methyl-2,4-pentanediol with succinonitrile in cold concentrated sulfuric acid. Comparison of this product with that obtained by treating I with hydrogen cyanide according to the method of Lynn[1] showed that both compounds were identical in every respect. This method of obtaining III is one which is currently under investigation in our laboratory for the preparation of a wide variety of *N*-heterocycles of the type, IV. It has been found possible, however, to limit the reaction of the dinitriles to only one of the nitrile groups, thus enabling the facile preparation of III. Other *N*-heterocycles such as 1-pyrrolines, 2-thiazolines, and dihydropyridines have already been reported.[4] Extension

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