verized and then extracted for several hours with 250 ml. of ether in a Soxhlet apparatus.[13] The material in the thimble was then extracted for 8 hr. with 250 ml. of absolute ethanol. The alcoholic solution was evaporated to dryness, and the residue was recrystallized from 6*N* hydrochloric acid. The yield of pure *2,2'-diphosphonodiphenyl ether* was 2.0 g. (32%); m.p. 233–235°.

Anal. Calcd. for $C_{12}H_{12}O_7P_2$: C, 43.65; H, 3.66; P, 18.76; neut. equiv. (for two ionizable hydrogens per molecule), 165.1. Found: C, 43.46; H, 3.96; P, 18.50; neut. equiv. (to *p*H 4.3), 168.2.

o-Hydroxyphenylphosphonic acid. A solution of 5.28 g. of *o*-benzyloxyphenylphosphonic acid in 50 ml. of 95% ethanol was shaken with 5.0 g. of 10% palladium-on-carbon[14] under an initial hydrogen pressure of 40 lb. After the uptake of hydrogen ceased, the catalyst was removed by filtration and the solvent distilled off under vacuum. The resulting sirup solidified when dried in a desiccator over calcium chloride. The crystals obtained were further dried *in vacuo* at 100°. The yield was quantitative, m.p. 124–127°.

Anal. Calcd. for $C_6H_7O_4P$: C, 41.39; H, 4.05; P, 17.79. Found: C, 41.17; H, 4.27: P, 17.51.

Absorption spectra measurements. The ultraviolet absorption spectra were determined in 95% ethyl alcohol by the procedure previously described.[15]

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9-Substituted-9-hydroxy-Δ^{10}-ergolenes

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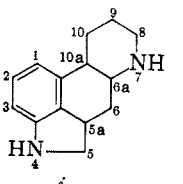
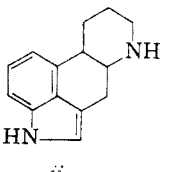
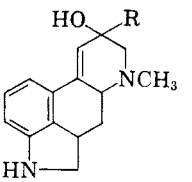
Numerous times during the course of our work on the total synthesis of lysergic acid[1] we found it appropriate to submit certain of the intermediates for pharmacological evaluation. On one such occasion we became interested in some 9-substituted-9-hydroxy-7-methyl-Δ^{10}-ergolenes (I).[2]



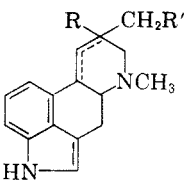
i



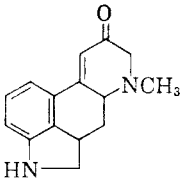
ii



I



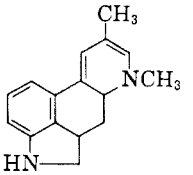
II



III

We were further intrigued by the possibility of synthesizing several new alkaloids which have been obtained by other workers during their studies on the fermentation of various strains of the ergot fungus.[3] Several members of this group of alkaloids are agroclavine (II, Δ^9, R′ = H), elymoclavine (II, Δ^9, R′ = OH), penniclavine (II, Δ^{10}, R = R′ = OH), and setoclavine (II, Δ^{10}, R = OH, R′ = H). The desired synthetic compounds, I (R = methyl, ethyl, allyl, phenyl), were prepared by the action of the appropriate organo-lithium compound or Grignard reagent on 9-keto-7-methyl-Δ^{10}-ergolene (III).[1] Except in the case of the phenyl substituted compound, it was necessary to employ an extremely large excess of reagent in order to obtain the product. Subsequent efforts to convert I (R = CH_3) to setoclavine by dehydrogenation were unrewarding.

The dehydration of I (R = CH_3) to 7,9-dimethyl-$\Delta^{8,10}$-ergoladiene (IV) was accomplished by the use



IV

of boron trifluoride. Evidence for the endocyclic position of the newly introduced double bond was the absence of terminal methylene absorption in the infrared spectrum.

Pharmacologically, these materials are characterized by their oxytocic, hypothermic, and central nervous system activity. Details of these studies will be published elsewhere.

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(2) In order to avoid the cumbersome nomenclature of this multi-ring system, we have assigned the generic name ergolane to 4, 5, 5a, 6, 6a, 7, 8, 9, 10,10a-decahydroindolo-[4,3-*fg*]quinoline (*i*). The name ergoline has geen assigned to the corresponding Δ^5-compound (ii) by W. A. Jacobs and R. G. Gould, Jr., *J. Biol. Chem.*, **120,** 142 (1937).

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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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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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