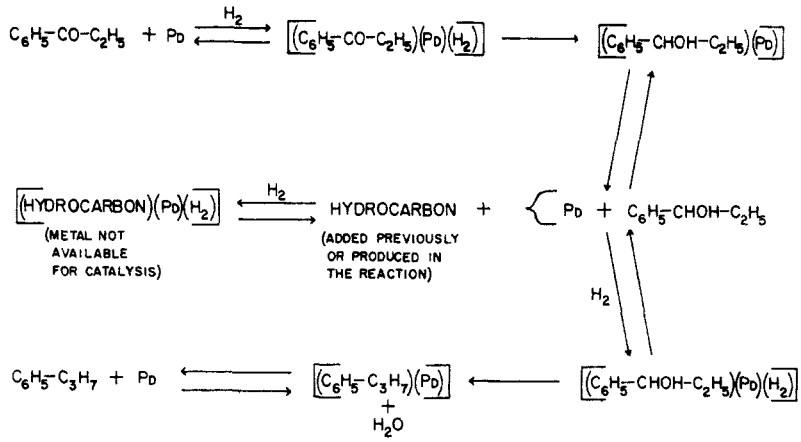

Fig. 7. Mechanism of inhibition

The catalysts were prepared as described in earlier papers of this series.

Acknowledgment. The authors are grateful to the American Platinum Works, now part of Engelhard Industries, Inc., for graciously supplying pure $PdCl_2$.

DEPARTMENT OF CHEMISTRY AND
PHARMACEUTICAL CHEMISTRY
MEDICAL COLLEGE OF VIRGINIA
RICHMOND, VA.

o-Hydroxyphenylphosphonic Acid

LEON D. FREEDMAN, G. O. DOAK, AND EDWARD L. PETIT

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Although a number of hydroxy-substituted arylphosphonic acids are known,[1] the preparation of *o*-hydroxyphenylphosphonic acid, the phosphorus analog of salicylic acid, has not previously been accomplished. Kennedy, Lane, and Willans[2] have investigated two possible methods for the synthesis of this phosphonic acid. They found that attempts to demethylate *o*-methoxyphenylphosphonic acid caused cleavage of the carbon-phosphorus bond; and they reported that the diazo reaction could not be used to convert *o*-benzyloxyaniline to *o*-benzyloxyphenylphosphonic acid (which they planned to debenzylate by hydrogenation). The present study was undertaken in the hope of developing a satisfactory method for the preparation of *o*-hydroxyphenylphosphonic acid and related compounds.

As noted by Kennedy, Lane, and Willans,[2] the demethylation of *o*-methoxyphenylphosphonic acid is not a promising route to the synthesis of the corresponding hydroxy compound. In this laboratory we found that after the *o*-methoxy compound was refluxed with 42% hydrobromic acid for 24 hr., over 90% of the phosphorus had been converted to inorganic phosphate. Attempts to replace the bromine in *o*-bromophenylphosphonic acid with the hydroxyl group were also unsuccessful. Thus, heating the *o*-bromo compound with 4*N* sodium hydroxide in an autoclave at 120° resulted in splitting little or no bromine from the ring. In the presence of cuprous oxide the bromine could be replaced by the hydroxyl group. In the process, however, a certain amount of phosphorus was also cleaved from the ring, and we were never able to isolate any *o*-hydroxyphenylphosphonic acid from the reaction mixture. In brief, the results we obtained in trying to convert *o*-methoxy- or *o*-bromophenylphosphonic acid into the hydroxy compound were similar to those reported[3] for the corresponding *para*-substituted acids.

We were successful, however, in obtaining *o*-hydroxyphenylphosphonic acid by the catalytic hydrogenolysis of *o*-benzyloxyphenylphosphonic acid. Several methods for preparing the latter compound were examined. We first investigated the preparation of the acid from the corresponding diazonium fluoborate. Although the diazonium compound could not be prepared by diazotizing *o*-benzyloxyaniline in fluoboric acid, the amine was readily diazotized in hydrochloric acid and the diazonium fluoborate precipitated by the addition of sodium fluoborate. The diazonium salt was then suspended in ethyl acetate and treated with phosphorus trichloride and cuprous bromide under the usual conditions.[4] Steam distillation of the reaction mixture in the customary manner, however, resulted in cleavage of the ether linkage. Accordingly, the conditions were modified to avoid debenzylation; details of the procedure used for iso-

(1) (a) G. B. Arnold and C. S. Hamilton, *J. Am. Chem. Soc.*, **63**, 2637 (1941); (b) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 753 (1952); (c) R. W. Bost and L. D. Quin, *J. Org. Chem.*, **18**, 358 (1953); (d) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **75**, 6307 (1953).

(2) J. Kennedy, E. S. Lane, and J. L. Willans, *J. Chem. Soc.*, 4670 (1956).

(3) V. L. Bell, Jr., and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 4901 (1953).

(4) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951).

lating the desired acid are described in the Experimental section.

We also were able to obtain *o*-benzyloxyphenylphosphonic acid by the reaction between *o*-bromophenylphosphonic acid, benzyl alcohol, and anhydrous potassium carbonate. The desired compound was obtained in only 10% yield. However, we were able to isolate from the reaction mixture a second phosphonic acid in 32% yield. The analysis and ultraviolet absorption spectrum (*cf.* Table I) of this unknown phosphonic acid indicated that it was either 2,2′-diphosphonodiphenyl ether[5] or a hydrate of 2,2′-biphenylenediphosphonic acid. The second possibility was effectively eliminated when we found that the compound lost no weight when heated to 200° for 1 hr. When the compound was heated to 240°, it decomposed to give a 69% yield of diphenyl ether (identified by its b.p. and ultraviolet absorption spectrum) and a residue of inorganic phosphate.[6] There seems little doubt, therefore, that the unknown phosphonic acid must be 2,2′-diphosphonodiphenyl ether.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA

Compound	λ_{max}, mμ	ϵ_{max}
Phenyl ether[a]	221–225[b]	10,000
	265	1,570
	271	1,850
	278	1,630
o-Phenoxyphenylphosphonic acid[c]	229	9,110
	278.5	3,410
o-Biphenylylphosphonic acid[d]	237	8,220
	274.5	2,030
Unknown phosphonic acid[e]	235.5	7,840
	278.0	3,920

[a] Reagent grade material (Eastman Kodak Co. 104). [b] Shoulder. [c] Prepared as described by L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **23**, 769 (1958). [d] Taken from L. D. Freedman, *J. Am. Chem. Soc.*, **77**, 6223 (1955). [e] Shown to be 2,2′-diphosphonodiphenyl ether (see text). The ε values were calculated on this basis.

o-Hydroxyphenylphosphonic acid at a concentration of 0.01*M* showed significant activity (*i.e.*, at least 50% inhibition compared to the controls) *in vitro* against one strain of *Escherichia coli* and three strains of pathogenic *Staphylococcus aureus:* slight activity at this concentration was found against one strain of *Aerobacter aerogenes.*[7]

EXPERIMENTAL[8]

o-Benzyloxyphenylphosphonic acid. A. From the diazonium fluoborate and phosphorus trichloride. *o*-Nitrophenyl benzyl ether[9] (23.0 g.) was dissolved in 200 ml. of 95% ethanol and shaken for about 2 hr. with Raney nickel and hydrogen at 40 lb. pressure. After the catalyst was removed by filtration, the amine was isolated by evaporating the filtrate to about 20 ml. and cooling in the deep freeze at −25°. The crystals obtained were washed with 5 ml. of petroleum ether and dried *in vacuo*. The yield of *o*-benzyloxyaniline was 87%; m.p. 36.5–37° (lit.[9] 39–40°).

A mixture of 0.2 mol. of the above amine and 150 ml. of 6*N* hydrochloric acid was boiled, with stirring, for about 5 min. to form the amine hydrochloride. The resulting suspension was quickly cooled to 0° and then diazotized with a solution of sodium nitrite. During this reaction, the temperature was kept below 5°. The diazonium fluoborate was then precipitated with a cold solution of sodium fluoborate.[10] The yield was 87%, decomposition temperature about 135°.

o-Benzyloxybenzenediazonium fluoborate (149 g., 0.5 mol.) was suspended in dry ethyl acetate and treated with phosphorus trichloride and cuprous bromide in the usual manner.[4] No evolution of nitrogen occurred until the mixture was warmed to about 55°. After nitrogen evolution had ceased, the reaction mixture was cooled to 5° and hydrolyzed by the dropwise addition of 200 ml. of water. The solution was then concentrated to 400 ml. *in vacuo* at a temperature below 45° and extracted with four 200-ml. portions of ether. The combined ether solutions were then extracted with 1 l. of 10% sodium carbonate solution. The aqueous alkaline solution was then treated with Darco and acidified with concentrated hydrochloric acid to *p*H 0.4, whereupon crude *o*-benzyloxyphenylphosphonic acid crystallized from solution. After recrystallization from aqueous acetone, the yield was 21%; m.p. 156–157°.

Anal. Calcd. for $C_{13}H_{13}PO_4$: C, 59.10; H, 4.96; P, 11.72. Found: C, 59.11; H, 5.25; P, 11.97.

B. From o-bromophenylphosphonic acid and benzyl alcohol. An intimate mixture of 10.0 g. of *o*-bromophenylphosphonic acid,[11] 20 ml. of redistilled benzyl alcohol, 10.0 g. of anhydrous potassium carbonate, and 0.2 g. of copper powder was heated under reflux for a period of 16 hr. The reaction mixture was then diluted with about 35 ml. of water, and the excess benzyl alcohol was removed by steam distillation. The residual liquid[12] from the steam distillation was treated with Darco and then acidified to *p*H 0.4 to obtain crude *o*-benzyloxyphenylphosphonic acid. The yield of the pure acid, after recrystallization, was 1.1 g. (10%).

The original filtrate from the crude *o*-benzyloxyphenylphosphonic acid was acidified further with 10 ml. of concentrated hydrochloric acid and then evaporated to dryness on a steam bath. The residue was further dried in a desiccator over sodium hydroxide. The solid thus obtained was pul-

(5) This possibility was first suggested to us by Professor Robert L. McKee of the University of North Carolina.

(6) It has been known for a long time that heating phosphonic acids at relatively high temperatures may result in splitting of the carbon-phosphorus bond. Thus, A. Michaelis and C. Mathias [*Ber.*, **7**, 1070 (1874)] found that phenylphosphonic acid decomposes at 250° into benzene and metaphosphoric acid. More recently, H. Z. Lecher, T. H. Chao, K. C. Whitehouse, and R. A. Greenwood [*J. Am. Chem. Soc.*, **76**, 1045 (1954)] have reported that 2-naphthylphosphonic acid, when heated in a sealed tube at 275° for 24 hr., gives naphthalene and metaphosphoric acid. Unpublished work from this laboratory indicates that phenylphosphonic acids containing alkyl, aryl, alkoxy, phenoxy, or halogen substituents undergo a similar type of decomposition at 240°.

(7) We are grateful to Dr. J. D. Thayer, Chief of the Biology Section of our laboratory, for testing this compound.

(8) Melting points were taken as previously described; *cf.* ref. 4. Phosphorus was determined by the method of B. C. Stanley, S. H. Vannier, L. D. Freedman, and G. O. Doak, *Anal. Chem.*, **27**, 474 (1955).

(9) A. Sieglitz and H. Koch, *Ber.*, **58B**, 78 (1925).

(10) A. Roe, *Org. Reactions*, **V**, 203 (1949).

(11) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **75**, 683 (1953).

(12) Bromide ion analyses on aliquots of this liquid showed that all the bromine had been split from the ring.

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]

Acknowledgment. The authors wish to acknowledge the assistance given by Mrs. Betty Pegram Herring throughout the course of this research.

VENEREAL DISEASE EXPERIMENTAL LABORATORY
COMMUNICABLE DISEASE CENTER
U. S. PUBLIC HEALTH SERVICE
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C.

(13) This step served to remove a small amount of colored material.

(14) R. Mozingo, *Org. Syntheses*, **Col. Vol. III,** 687 (1955).

(15) H. H. Jaffé and L. D. Freedman, *J. Am. Chem. Soc.*, **74,** 1069 (1952).

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

G. BRUCE KLINE, EUGENE J. FORNEFELD, ROBERT R. CHAUVETTE, AND EDMUND C. KORNFELD

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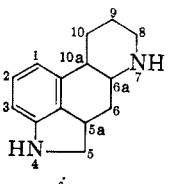
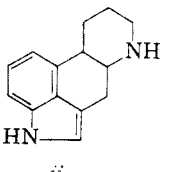
Numerous times during the course of our work on the total synthesis of lysergic acid[1] we found it appropriate to submit certain of the intermediates for pharmacological evaluation. On one such occasion we became interested in some 9-substituted-9-hydroxy-7-methyl-Δ^{10}-ergolenes (I).[2]



i



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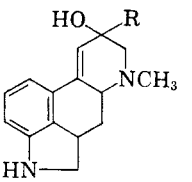

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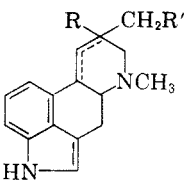

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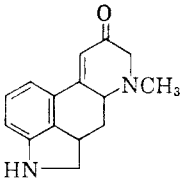
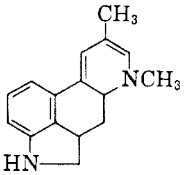


III

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.

(1) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78,** 3087 (1956).

(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).

(3) M. Abe, T. Yamano, Y. Kozu, and M. Kusumoto, *J. Agr. Chem. Soc. Japan*, **25,** 458 (1952); **29,** 364, 697 (1955); M. Abe, and S. Yamatodani, *J. Agr. Chem. Soc. Japan*, **28,** 501 (1954); *Bull. Agr. Chem. Soc. Japan*, **19,** 92, 94, 161 (1955); M. Pöhm, *Die Pharmazie*, **11,** 110 (1956); A. Stoll, A. Brack, H. Kobel, A. Hofmann, and R. Brunner, *Helv. Chim. Acta*, **37,** 1815 (1954); A. Hofmann, R. Brunner, H. Kobel, and A. Brack, *Helv. Chim. Acta*, **40,** 1358 (1957).