Anal. Calcd. for $C_{14}H_{23}ClN_2O_3$: C, 55.5; H, 7.6; Cl, 11.7. Found: C, 55.2; H, 7.4; Cl, 11.9.

N-(2,3,4-Trimethoxyphenyl)-N',N'-dimethylpiperazinium iodide (XIV). The free base was liberated by treating 10.5 g. of XIII hydrochloride with aqueous alkali and extracting with ether. After drying over anhydrous magnesium sulfate, the ether solution was concentrated to a volume of 25 ml. and treated with 5.7 g. of methyl iodide. A white precipitate began to form almost immediately. After standing overnight, the solid product was collected on a suction filter, washed with ether, and air dried. The resulting XIV weighed 15 g. (93%); m.p. 170–171°.

Anal. Calcd. for $C_{15}H_{25}IN_2O_3$: C, 44.2; H, 6.1; I, 31.2. Found: C, 44.1; H, 6.3; I, 30.9.

Acknowledgment. This research was supported by Battelle Memorial Institute funds and by Public Grant M-1588.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

n-Butyl 5-Chloro-2-pyrimidoxyacetate—A Plant Growth Regulator Analog

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Received February 15, 1960

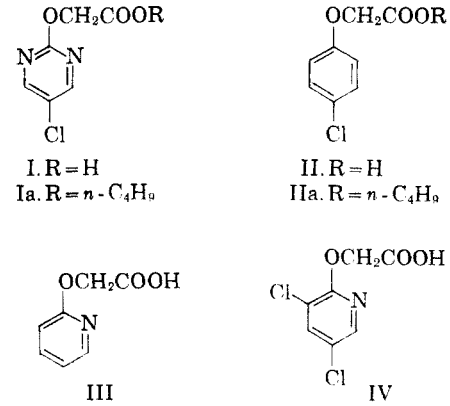
In order to provide a further comparative test of the present theories concerning the relation of structure to chemical stimulation of plant growth, *n*-butyl 5-chloro-2-pyrimidoxyacetate was prepared as an analog of the active 4-chlorophenoxyacetic ester. Although very similar in shape and physical properties to the phenyl compound, the analog was inactive as a growth stimulant.

The stimulation of plant growth by substituted phenoxyacetic acids was first reported by Zimmerman and Hitchcock in 1942.[1] Since then these compounds have received much attention in an attempt to correlate the position and type of substituent with observed effects on growth. The results of the many investigations directed toward elucidation of the mechanism of growth regulator action have been resolved into three general theories.

One theory[2] supposes that the regulator undergoes a chemical reaction with appropriate groups, probably nucleophilic, at some site within the cell with the resulting formation of new covalent bonds. The most probable point of reaction on the phenyl ring is indicated to be at a position *ortho* to the ether oxygen. Another theory[3,4] ascribes major importance to the shape of the regulator molecule and the specificity of its fit onto some receptor within the plant. In this case, the phenyl nucleus with its substituents acts as a whole at a locus or point of attachment, and chemical reactions at the ring are considered unlikely. The third and most recent theory,[5,6] unlike the other two, is not particularly concerned with the relation of the regulator to an active site. It holds, instead, that the growth-regulating activity of a compound is primarily associated with its ability to chelate metal ions such as calcium or magnesium.

In order to offer a further test of these hypotheses, it was thought desirable to attempt the synthesis of an analog of a simple aromatic growth-promoting compound in which the possibility of reaction at the positions *ortho* to the side chain was negligible. The compound chosen was 5-chloro-2-pyrimidoxyacetic acid (I) which, although expected to be very similar in many respects to the powerful growth stimulant 4-chlorophenoxyacetic acid (II), would not be susceptible to the usual form of nucleophilic attack at the *ortho* positions.

For our purposes, it was not only desirable but necessary for the chlorine and nitrogens to have this particular structural relationship to each other and to the side chain, as the 5-position is the only one



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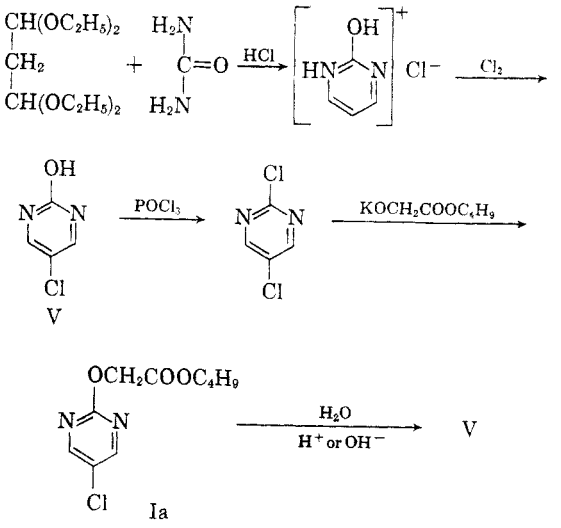

Fig. 1. Preparation of *n*-butyl 5-chloro-2-pyrimidoxyacetate (Ia)

on the pyrimidine nucleus in which a halogen substituent could be expected to be inert under the conditions of bioassay.

Consideration of satisfactory synthetic routes to the pyrimidine led to the conclusion that an ester would be more convenient to prepare and handle than the acid itself. The *n*-butyl ester was chosen because of the ease with which these derivatives are made and the high degree of plant growth stimulation previously shown by *n*-butyl 4-chlorophenoxyacetate (IIa).

The reaction sequence followed for the preparation of *n*-butyl 5-chloro-2-pyrimidoxyacetate (Ia) is shown in Fig. 1.

2-Hydroxypyrimidine hydrochloride was obtained by reaction of a malonaldehyde derivative such as 1,1,3,3-tetraethoxypropane or 1,3,3-triethoxy-1-propene with urea in the presence of alcoholic hydrogen chloride. The reaction mixture must be boiled in order for the desired compound to be formed. Otherwise, the only product isolated was a high-melting material which, from analysis and infrared spectrum, appeared to be identical with the complex substance obtained by Dornow and Peterlein[7] from the reaction of triethoxypropene with two equivalents of urea. The preparation of 2-hydroxypyrimidine from tetraethoxypropane and urea at room temperature in the presence of aqueous hydrochloric acid, described by Protopopova and Skoldinov[8] during the course of our work, could not be repeated. Under conditions satisfactory for our synthesis of 2-hydroxypyrimidine hydrochloride, sulfuric acid provided a good yield of 2-hydroxypyrimidine bisulfate, while syrupy phosphoric acid gave monobasic 2-hydroxypyrimidine phosphate. Both the bisulfate and the phosphate were readily converted to free 2-hydroxypyrimidine.

2-Hydroxypyrimidine hydrochloride was converted into 2-hydroxy-5-chloropyrimidine by reaction with chlorine in aqueous solution, analogous to the chlorination of 2-aminopyrimidine reported in the literature.[9] A large excess of chlorine was very detrimental to the yield of the desired product. In a similar manner, 2-hydroxy-5-bromopyrimidine was prepared by bromination of 2-hydroxypyrimidine in aqueous solution. The monochloropyrimidine formed 2,5-dichloropyrimidine upon heating with phosphoryl chloride,[10] and the product was recovered by steam distillation.

The preparation of 2-alkoxypyrimidines by reaction of 2-chloropyrimidine with the appropriate sodium alkoxide has been reported previously.[11,12] Reaction of 2,5-dichloropyrimidine with the potassium or sodium alkoxide of *n*-butyl glycolate in dry toluene provided a 52% yield of an almost colorless liquid product which was assumed to be the desired ester Ia.

The compound contained the anticipated amounts of carbon, hydrogen, and nitrogen corresponding to the formula $C_9H_{13}ClN_2O_3$. Its ultraviolet spectrum was typical of simple 2,5-disubstituted pyrimidines,[11] as shown in Table I.

TABLE I

PYRIMIDINE SPECTRA[a]

Compound	*p*H	λ_{max}	log ϵ
(Ia)	—[b]	219, 282	4.10, 3.55
	0.7	218, 281	4.08, 3.54
	5.0	218, 281	4.03, 3.54
	13.0	222, 283	4.05, 3.52
2,5-Dichloropyrimidine[11]	—[c]	219, 268	4.20, 3.49
	7.0	219, 272	4.23, 3.51
2-Methyl-5-bromopyrimidine[11]	7.0	219, 267	4.09, 3.48

[a] Spectra measured in a Cary Model 11 spectrophotometer. [b] Anhydrous methanol solution. [c] Ethanol solution.

The wave length of maximum absorption and the extinction coefficients were not greatly affected by changes in *p*H of the solvent, indicating a probably low order of basicity in the nitrogen atoms.

The infrared spectrum was consistent with the proposed structure and exhibited absorption bands characteristic of the pyrimidine ring (795 cm.$^{-1}$, 1560 cm.$^{-1}$), ester (1748 cm.$^{-1}$), and ether (1270 cm.$^{-1}$). Although thermal rearrangement of alkoxypyrimidines and alkoxypyridines to the corresponding *N*-alkylated pyrimidinones and pyri-

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TABLE II

COMPARATIVE PROPERTIES OF (Ia) AND (IIa)

Compound	Mol. Wt.	M.P.	B.P./1 Mm.	n_D^{45}	Ring	Halogen
n-Butyl 5-chloro-2-pyrimidoxyacetate (Ia)	244.7	14°	119–125°	1.492	Planar	Aromatic
n-Butyl 4-chlorophenoxyacetate (IIa)	242.7	41°	122–123°	1.501	Planar	Aromatic

dones has been reported on several occasions,[13,14] the possibility of such a reaction having taken place in the present instance to give butyl 5-chloro-2-pyrimidinone-1-acetate is removed by the absence of any infrared absorption attributable to this type of amide (1600–1700 cm.$^{-1}$ in 5-chloro-2-pyrimidinone). Brown and Short[12] have discussed this difference in the case of 2-pyrimidinone (2-hydroxypyrimidine) and 2-methoxypyrimidine.

In a closely analogous reaction, Hill and McGraw[15] obtained ethyl 2-pyridoxyacetate from 2-bromopyridine and sodium ethyl glycoxide. The structure of their ester was confirmed by synthesis of both it and the corresponding *N*-substituted compound from 2-hydroxypyridine and ethyl diazoacetate.[16] However, unlike the pyridine derivative, butyl 5-chloro-2-pyrimidoxyacetate was not converted to the free acid upon hydrolysis. Instead, 2-hydroxy-5-chloropyrimidine was produced in the presence of either hot alkali or hot acid, offering further evidence of *O*-alkylation rather than *N*-alkylation.

The similarity between butyl *p*-chlorophenoxyacetate and its pyrimidine analog is shown in Fig. 2 and Table II. Molecules of the two substances are of almost identical shape and size. Although the pyrimidine must differ slightly in shape from the benzene derivative,[17] the difference may be considered negligible for most purposes. Dipole moment measurements on pyrimidine and 2,5-disubstituted pyrimidines[18] indicate that the ring is planar, as it is in the phenoxy acid. The halogen in position 5 is similar in its reactivity to a phenyl halogen, and the reactivity of the ester would not be expected to differ appreciably from that of the same group in butyl 4-chlorophenoxyacetate.

The plant growth regulatory activities of the *n*-butyl esters of 4-chlorophenoxyacetic acid and 5-chloro-2-pyrimidoxyacetic acid were measured by Dr. A. J. Vlitos of the Boyce Thompson Institute for Plant Research, Inc., in Yonkers, N. Y. Four different bioassays were employed: elongation of wheat and oat (*Avena*) coleoptiles, elongation of oat first internodes,[19] and curvature of slit pea stems. In each test, the phenoxy derivative was highly active while the pyrimidine was completely inactive.[20]

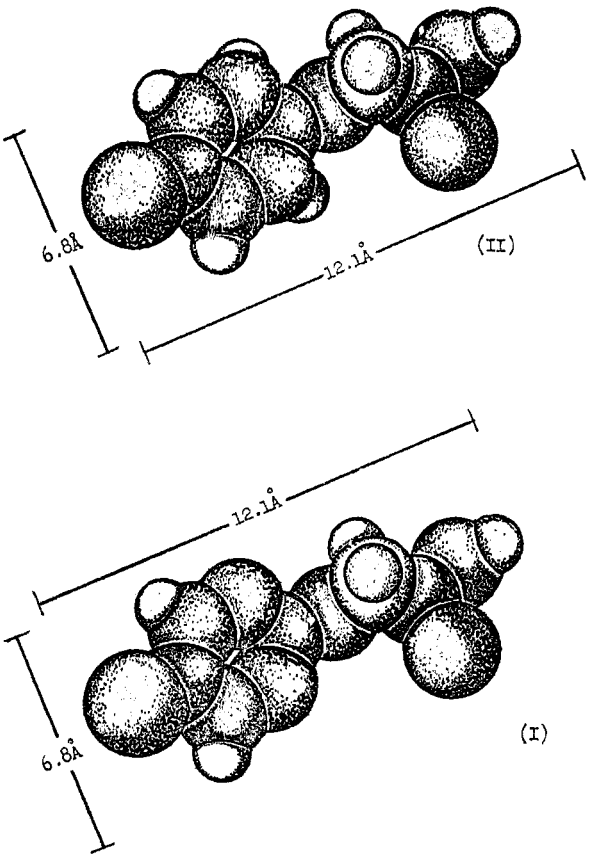

Fig. 2. Similarity between *p*-chlorophenoxyacetate acid (II) and its pyrimidine analog (I)

Gorter[21] has demonstrated the high degree of growth stimulation provided by 2-pyridoxyacetic acid (III) and 3,5-dichloro-2-pyridoxyacetic acid (IV), both of which also are closely related to our pyrimidine. Although the pyridine derivatives were tested as free acids, no difficulty in the *in vivo* hy-

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drolysis of the pyrimidoxy ester Ia to the corresponding acid would be anticipated.

According to the proposal of Hansch, *et al.*,[22] which has received recent theoretical support by Fukui,[23] the pyridines III and IV could derive their biological activity through displacement of hydride ion and chloride ion, respectively, from the the 3-position by some cellular nucleophilic agent. The complete absence of growth-promoting ability in butyl 5-chloro-2-pyrimidoxyacetate, a substance which appears to possess many spatial and chemical characteristics closely resembling those of the corresponding phenyl and pyridyl analogs, strongly suggests that the availability of the positions *ortho* to the side chain toward nucleophilic reaction indeed bears an important relation to growth stimulation by compounds of the phenoxy acid series.

EXPERIMENTAL[24]

2-Hydroxypyrimidine hydrochloride. Urea (360 g., 6.0 moles) was added to 2 l. of dry methanol, and the mixture was chilled to 0° and saturated with hydrogen chloride. While the temperature was maintained at 0°, 1,1,3,3-tetraethoxypropane (1320 g., 6.0 moles) was added dropwise over a period of 1.25 hr. with constant stirring. After standing overnight, the mixture was boiled for 1 hr. under reflux with stirring, cooled, and the product removed by filtration in 88% yield. Crystallization from ethanol gave tan needles, m.p. 205–210° dec. (lit.,[25] m.p. 200–205° dec.).

Under similar conditions, substitution of concd. sulfuric acid for the hydrogen chloride provided a 90% yield of *2-hydroxypyrimidine bisulfate,* which, after crystallization from dilute acetic acid, was recovered as white needles, m.p. 188.5–189°.

Anal. Calcd. for $C_4H_6N_2O_5S$: C, 24.7; H, 3.11; N, 14.4. Found: C, 24.9; H, 3.23; N, 14.6.

Likewise, use of 86% phosphoric acid provided an 80% yield of monobasic *2-hydroxypyrimidine phosphate,* m.p. 179° dec.

Anal. Calcd. for $C_4H_7N_2O_5P$: C, 24.8; H, 3.63; N, 14.4. Found: C, 24.9; H, 3.63; N, 14.6.

2-Hydroxy-5-chloropyrimidine. 2-Hydroxypyrimidine hydrochloride (9.0 g., 0.068 mole) was dissolved in 1 l. of 0.1*M* aqueous chlorine solution and heated to 70° for 30 min. After cooling and standing at room temperature overnight, the crude product was isolated by removal of solvent under reduced pressure at steam-bath temperature. Recrystallization from ethanol afforded a 54% yield of pale yellow crystals m.p. 236° dec. (lit.[9] m.p. 237–238°).

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.8; H, 2.32; N, 21.5. Found: C, 37.1; H, 2.17; N, 21.3.

2-Hydroxy-5-bromopyrimidine. Free 2-hydroxypyrimidine was prepared by dissolving 20 g. (0.1 mole) of its bisulfate in 150 ml. of water, adding a solution of an equivalent quantity of barium acetate in 200 ml. water, treatment with carbon dioxide, and filtration. The filtrate was evaporated to dryness to provide an 87% yield of pure 2-hydroxypyrimidine, m.p. 180–181°.

This product (5 g., 0.05 mole) was added with stirring to a solution of 9 g. (0.056 mole) bromine in 2 l. water. Solvent was removed under vacuum and the residue was crystallized from 90% aqueous ethanol. The yield of 2-hydroxy-5-bromopyrimidine, m.p. 234–235° dec., was 5 g. (55%).

Anal. Calcd. for $C_4H_3BrN_2O$: C, 27.5; H, 1.73; N, 16.0. Found: C, 27.8; H, 1.83; N, 16.3.

2,5-Dichloropyrimidine was prepared by the method of English, *et al.*,[10] by reaction of 2-hydroxy-5-chloropyrimidine with excess phosphoryl chloride. The yield of product melting at 58.5–59.5° (lit. m.p. 57–57.5°) was 47%.

n-Butyl glycolate. Glycolic acid (300 g., 4 moles), *n*-butyl alcohol (600 g., 8 moles), 300 ml. of dibutyl ether, and 5 g. of tetrabutyl titanate were mixed and heated to boiling under reflux in apparatus permitting the separation of water as it distilled azeotropically. After about 5 hr., the theoretical volume of water had been collected. The ether solution was washed with water and distilled to give an almost quantitative yield of product, b.p. 56–59° (5 mm.), n_D^{30} 1.4225.[26]

Butyl (5-chloro-2-pyrimidoxy)acetate. Metallic potassium (5.9 g., 0.15 mole) in the form of sand was suspended in 300 ml. of dry toluene under a nitrogen atmosphere. Butyl glycolate (22.8 g., 0.17 mole) was added dropwise over a period of 45 min. with rapid stirring, and stirring was continued for 3 hr. after the ester addition was complete. A solution of 22 g. (0.15 mole) 2,5-dichloropyrimidine was then added dropwise, the mixture was boiled under reflux for 1 hr., and, when cool, it was treated with 25 ml. of absolute ethanol. After washing with water, the dark toluene solution was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residual oil was distilled to give 18 g. (52%) of colorless liquid, b.p. 119–125° (1 mm.).

Redistillation gave an analytically pure sample, b.p. 110° (0.8 mm.), n_D^{20} 1.4998, n_D^{45} 1.492, m.p. 10–14°.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3$: C, 49.1; H, 5.35; N, 11.5. Found: C, 49.2; H, 5.49; N, 11.5.

Hydrolysis of butyl (5-chloro-2-pyrimidoxy)acetate. The ester (9.0 g., 0.037 mole) was heated with stirring at about 95° for 1 hr. with 10% aqueous sodium hydroxide solution, cooled, and acidified with hydrochloric acid. The precipitated solid was filtered, washed with water, and dried in air to give 5.0 g. (84%) of yellowish crystals of 2-hydroxy-5-chloropyrimidine. After recrystallization from ethanol, the compound melted at 236.5–237.5°.

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.8; H, 2.32; N, 21.5. Found C, 37.0; H, 2.32; N, 21.5.

Hydrolysis with dilute aqueous hydrochloric acid at 95° resulted in the same product.

Butyl p-chlorophenoxyacetate. Commercial *p*-chlorophenoxyacetic acid was esterified with *n*-butyl alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid, and water was removed azeotropically with toluene. Distillation provided a 93% yield of the desired ester boiling at 122–123° (1 mm.), m.p. 41°, n_D^{45} 1.501.

Anal. Calcd. for $C_{12}H_{15}ClO_3$: C, 59.4; H, 6.23. Found: C, 59.7; H, 6.05.

Acknowledgment. We wish to express our gratitude to Mr. Quentin Quick and his group for infrared spectra and microanalyses, Dr. A. J. Vlitos and his group for bioassays, and Mr. F. G. Bollinger and Miss Celeste Holswade for their assistance.

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(26) The authors are indebted to Mr. T. F. Carruthers for the preparation of this compound.