boiling water-bath until all the solid went into solution. The excess oxychloride was removed by distillation under reduced pressure and the oily liquid was poured over crushed ice. A white precipitate appeared immediately which was filtered, washed with water and finally crystallized from aqueous acetone; yield 900 mg. IIId decomposes above 260°.

Anal. Calcd. for $C_{16}H_{11}N_4Cl_3$ C, 52.53; H, 3.00; N, 15.32. Found C, 52.49; H, 2.90; N, 15.26.

2,4-Bis(p-chloroanilino)-5-nitroso-6-hydroxypyrimidine (IIIe). Compound IIIc was finely pulverized and suspended in 30 ml. of 95% ethanol. Concentrated hydrochloric acid was added to this mixture until the *p*H went down to 3. Sodium nitrite (200 mg.) in 10 ml. of water was added drop by drop with stirring at room temperature maintaining the *p*H of the solution at about 3, until the nitrosation was complete. A deep brown colored precipitate was formed during nitrosation. The reaction mixture was cooled, filtered, and the residue washed thoroughly with water and then with cold alcohol. The product could not be satisfactorily crystallized; yield 850 mg. It does not melt below 310°.

Anal. Calcd. for $C_{16}H_{11}N_5O_2Cl_2$: C, 51.06; H, 2.92; N, 18.61. Found: C, 51.00; H, 2.86; N, 18.57.

2-(p-Nitrophenylguanidino)-4-amino-6-hydroxypyrimidine (IVd). *p*-Nitrophenylbiguanide (9 g., 0.04 mole) was added to a solution of sodium ethoxide (0.92 g., 0.04 mole of sodium in 100 ml. of absolute ethanol), and to this mixture was added slowly with stirring ethyl cyanoacetate (11.3 g., 0.1 mole) while the temperature was maintained below 20°. The mixture was heated under reflux for 16 hr. The mass became deep yellow and some precipitate appeared immediately on refluxing. The reaction mixture was cooled, filtered, and the precipitate washed first with water and then with alcohol. The product could be crystallized from *N,N*-dimethylformamide. The crystals appeared as fine yellow needles.

2-(Phenylguanidino)-4-amino-6-hydroxypyrimidine (IVa). A solution of sodium ethoxide (3 g., 0.13 mole of sodium in 75 ml. of absolute ethanol) was treated with phenylbiguanide hydrochloride (10.7 g., 0.05 mole) in an ice bath. This was shaken well until the reaction was complete. The precipitated sodium chloride was filtered and to the filtrate ethyl cyanoacetate (11.3 g., 0.1 mole) was added with shaking, taking care that the temperature of the mixture did not rise above 30°. Some precipitate appeared immediately and the amount increased on standing. The mixture was left at room temperature (25–28°) for 24 hr. The heavy precipitate formed was filtered and washed with cold absolute alcohol. This was suspended in water when most of the precipitate went into solution. The mixture was acidified with hydrochloric acid, cooled to 2°, filtered, and the residue washed with cold water. The residue could be crystallized from aqueous acetone.

2-(p-Methoxyphenylguanidino)-4-amino 6-hydroxypyrimidine (IVb). A mixture of *p*-anisylbiguanide hydrochloride (12.2 g., 0.05 mole), sodium ethoxide (2.3 g. sodium in 50 ml. absolute ethanol), and ethyl cyanoacetate (5.7 g., 0.05 mole) was refluxed for about 2 hr. The precipitate obtained was washed with alcohol, suspended in water (50 ml.), and neutralized with hydrochloric acid. After cooling, the product was filtered, washed with cold water, and crystallized from water as white needles.

2-(p-Methylphenylguanidino)-4-amino-6-hydroxypyrimidine (IVc). A mixture of *p*-methylphenylbiguanide hydrochloride (11.4 g., 0.05 mole), ethyl cyanoacetate (11.3 g., 0.1 mole) and sodium ethoxide (3.5 g. of sodium in 100 ml. of absolute ethanol) was refluxed for 4 hr. The product obtained was isolated in the same way as described under IVb.

2-(p-Chlorophenylguanidino)-4-amino-6-hydroxypyrimidine (IVe). A mixture of *p*-chlorophenylbiguanide hydrochloride (12.5 g., 0.05 mole), ethyl cyanoacetate (5.7 g., 0.05 mole), and sodium ethoxide (1.3 g. of sodium in 50 ml. of absolute ethanol) was refluxed for 2 hr. The product was then isolated in the same way as described under IVb.

[Added in proof]

2-Amino-4-(p-chloroanilino)-6-hydroxypyrimidine (IIc). A mixture of 2-amino-4-chloro-6-hydroxypyrimidine (2.9 g., 0.02 mole), *p*-chloroaniline, (2.6 g., 0.02 mole), glacial acetic acid (30 ml.), and concentrated hydrochloric acid (0.4 ml.) was heated at refluxing temperature for about 4 hr. The resulting solution was treated with charcoal for decolorization and filtered hot. The desired product precipitated partially on cooling, but for complete precipitation the solution was diluted with 200 ml. of water and then neutralized partially with 20 ml. of 10*N* sodium hydroxide. The precipitate was filtered, thoroughly washed with water, and crystallized from 60% alcohol.

2-Amino-4-(p-toluidino)-6-hydroxypyrimidine (IIb) *and 2-amino-4-(anilino)-6-hydroxypyrimidine* (IIa) were prepared by the same general method as given for IIc.

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CALCUTTA, INDIA

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of Some Vicinal Trimethoxyphenyl Derivatives of Heterocyclic Nitrogen Bases

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A number of vicinal trimethoxy analogs of compounds possessing psychopharmacological activity were synthesized to examine the influence of vicinal trimethoxy groups on this type of activity.

In a continuation of our investigation of correlations between chemical structure and psychopharmacological activity, we have undertaken the synthesis of several new compounds in which vicinal trimethoxy groups are present on the phenyl rings of a number of useful synthetic drugs which affect mood and behavior of human subjects. It is well known that the presence of vicinal trimethoxy groups on a phenyl ring can alter pro-

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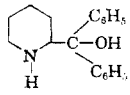
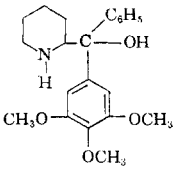
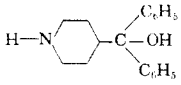
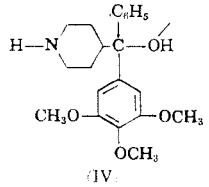
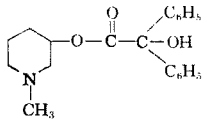
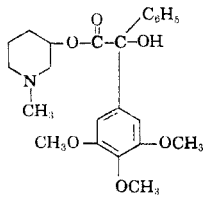
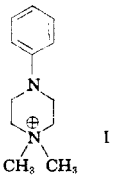
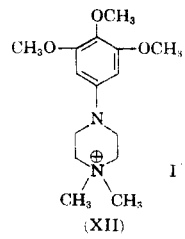
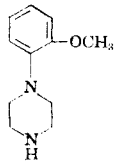
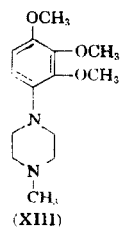
foundly the psychopharmacological action of certain amines. For example, 3,4,5-trimethoxy-β-phenethylamine and DL-3,4,5-trimethoxy-β-phenylisopropylamine both exhibit psychotomimetic activity whereas the unalkoxylated amines are inactive in this respect at comparable dose levels.

Table I shows the parent compound, its type of activity, and the structure of the desired trimethoxy analog.

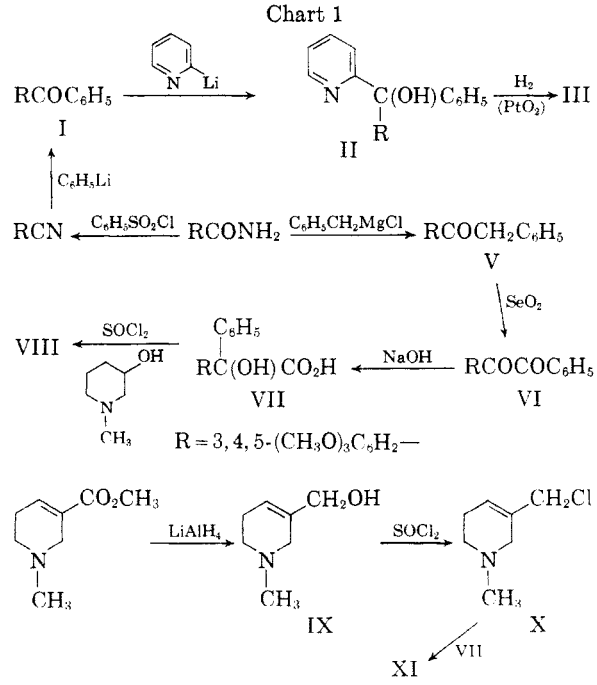
TABLE I

VICINAL TRIMETHOXY DERIVATIVES

Parent Compound	Type of Activity	Desired Trimethoxy Analog
	CNS Stimulant[3]	 (III)
	Ataractic[4]	 (IV)
	Psychotogenic[5]	 (VIII)
 I	Sympathetic ganglian stimulator[6]	 I (XII)
	Antihypotensive causing dream activity[6]	 (XIII)

As shown in Chart 1, 3,4,5-trimethoxybenzonitrile, obtained from the dehydration of the corresponding amide with benzenesulphonyl chloride,[7] reacted readily with a solution of phenyllithium in absolute ether to obtain 3,4,5-trimethoxybenzophenone (I) in 86% yield. Previous work in this laboratory had shown that extensive ether cleavage occurs when the preparation of I is attempted by means of a Friedel-Crafts reaction between 3,4,5-trimethoxybenzoyl chloride and benzene in the presence of aluminum chloride. The preparation of I through the action of phenylmagnesium bromide on 3,4,5-trimethoxybenzonitrile was not attempted because Grignard reagents usually attack the 4-methoxy group and also cause ether cleavage.[8] Our use of the organo - lithium reaction was prompted by the fact that many nitriles give better yields of ketones with this reagent than with organomagnesium halides.[9] 2-Lithiopyridine, obtained from the interchange of *n*-butyllithium with 2-bromopyridine at −50°, was allowed to react with the ketone I to obtain DL-phenyl-2-pyridyl-3,4,5-trimethoxyphenylcarbinol (II) in 72% yield.

Chart 1



Catalytic hydrogenation of II, as a methanol solution containing some hydrochloric acid, in the presence of Adams catalyst[10] brought about the

(3) B. B. Brown and H. W. Werner, *J. Pharmacol. Exptl. Therap.*, **110**, 180 (1954).

(4) B. B. Brown, D. L. Braun, and R. G. Feldman, *J. Pharmacol. Exptl. Therap.*, **118**, 153 (1956).

(5) L. G. Abood, A. Ostfeld, and J. H. Biel, *Arch. intern. pharmacodynamie*, **120**, (2), 186 (1959).

(6) I. H. Page, *Science*, **125**, 721 (1957).

(7) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **64**, 2085 (1942).

(8) In the preparation of 3,4,5-trimethoxyphenyl isobutyl ketone from the corresponding nitrile and isobutylmagnesium bromide, C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, **64**, 2085 (1942), found that this cleavage occurred at temperatures above 40°. Although lower reaction temperatures prevented this side reaction, the yield of ketone was unsatisfactory.

(9) H. Gilman, private communication (1957).

(10) H. W. Warner and C. H. Tilford, U. S. Patent **2,624,739** (1953).

selective reduction of the heterocyclic ring and gave the desired DL-phenyl-2-piperidyl-3,4,5-trimethoxyphenylcarbinol (III); this compound was isolated as its water-soluble hydrochloride.

An exploratory attempt to prepare the isomeric DL-phenyl-4-piperidyl-3,4,5-trimethoxyphenylcarbinol (IV) *via* the above route using 4-pyridyllithium was unsuccessful since the latter reagent could not be prepared. When 4-bromopyridine was interchanged with *n*-butyllithium at −75°, the only reaction product which could be isolated was an oil which was identified as 4-*n*-butylpyridine. Wibaut and Heeringa[11] state that 4-pyridyllithium results when the above interchange is carried out at this reaction temperature.

The synthesis of DL-*N*-methyl-3-piperidyl 3,4,5-trimethoxybenzilate (VIII) required DL-3,4,5-trimethoxybenzilic acid (VII) as an intermediate. 3,4,5-Trimethoxybenzamide was first treated with benzylmagnesium chloride to obtain 3,4,5-trimethoxyphenyl benzyl ketone (V) in 41% yield. Oxidation of V to 3,4,5-trimethoxybenzil (VI) by means of selenium dioxide in acetic anhydride as a solvent[12] gave a somewhat lower yield than might have been expected. Clark[13] has pointed out that it is often not advantageous to carry out the oxidation of desoxybenzoins, such as V, in the presence of acetic anhydride because of the formation of high-boiling selenium-containing compounds as side products. The conversion of the benzil VI to a high yield of DL-3,4,5-trimethoxybenzilic acid (VII) was carried out using the anaerobic technique described by Schoenberg and Keller.[14] These workers have shown that alkoxybenzils are converted to undesirable oxidation products when their alkaline solutions are exposed to air under the conditions usually employed in the benzilic acid rearrangement. DL-*N*-Methyl-3-piperidyl 3,4,5-trimethoxybenzilate (VIII) resulted from the reaction of VII with *dl*-1-methyl-3-chloropiperidine in isopropyl alcohol.[15] Treatment of VIII in dry ether solution with anhydrous hydrogen chloride gave an oily salt which could not be induced to crystallize. Accordingly, VIII was isolated as the maleate.

In the course of this investigation, it was desired to obtain DL-*N*-methyl-1,2,5,6-tetrahydro-3-pyridylmethyl benzilate (XI) for making pharmacological comparisons with DL-*N*-methyl-3-piperidyl benzilate. The commercially available alkaloid arecoline was reduced to *N*-methyl-3-hydroxymethyl-1,2,5,6-tetrahydropyridine[16] (IX) by means of lithium aluminum hydride. Treatment of IX with thionyl chloride afforded *N*-methyl-3-chloromethyl-1,2,5,6-tetrahydropyridine (X) hydrochloride, which was subsequently treated with benzilic acid under the conditions already given for the preparation of VIII. The resulting ester base XI was isolated as the hydrochloride.

In an attempt to obtain *N*-(3,4,5-trimethoxyphenyl)-*N'*,*N'*-dimethylpiperazinium iodide (XII), 3,4,5-trimethoxyaniline was first treated with *N*-methyl-bis(β-chloroethyl)amine hydrochloride under the conditions given by Prelog and Driza[17] for aniline. However, none of the expected intermediate *N*-(3,4,5-trimethoxyphenyl)-*N'*-methylpiperazine could be isolated from the tar which formed during the reaction. It was of interest to note, however, that 2,3,4-trimethoxyaniline reacted smoothly with this chloroethylamine derivative to give a 46.5% yield of *N*-(2,3,4-trimethoxyphenyl)-*N*-methylpiperazine (XIII) with no formation of tar. By treating XIII with a limited quantity of methyl iodide, *N*-(2,3,4-trimethoxyphenyl)-*N'*,*N'*-dimethylpiperazinium iodide was obtained in high yield.

Detailed results concerning the psychopharmacology of these compounds will be published elsewhere.

EXPERIMENTAL[18]

3,4,5-Trimethoxybenzophenone (I). To a stirred suspension of 35 g. of 3,4,5-trimethoxybenzamide in 70 ml. of pyridine was added slowly 34.2 g. of benzenesulphonyl chloride. The warm reaction mixture was heated to 70° for 0.5 hr. (stirring), cooled to room temperature, and finally poured into 400 ml. of cold water. The solid product was collected on a Büchner funnel and washed with dilute hydrochloric acid and then with water. After air drying, the crude 3,4,5-trimethoxybenzonitrile amounted to 29.2 g. (91%); m.p. 94–95° (reported,[7] m.p. 90–92°).

To a stirred solution of phenyllithium, prepared from 2.8 g. of lithium wire and 31.4 g. of bromobenzene in 150 ml. of dry ether, was added a solution of 29 g. of 3,4,5-trimethoxybenzonitrile in 125 ml. of dry benzene. The mixture was stirred at room temperature overnight and then hydrolyzed by the addition of water and cold dilute hydrochloric acid. The resulting insoluble ketimine hydrochloride of I was converted to 35 g. (86%) of nearly colorless 3,4,5-trimethoxybenzophenone (I) by boiling with very dilute hydrochloric acid; m.p. 75–76°, after recrystallization from alcohol.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.5; H, 5.9. Found: C, 70.6; H, 5.8.

DL-*Phenyl-2-pyridyl-3,4,5-trimethoxyphenylcarbinol* (II). A solution of *n*-butyllithium was prepared by treating a stirred suspension of 2.8 g. of lithium wire (2-mm. pieces) in 200 ml. of dry ether with 30 g. of *n*-butyl bromide under a dry nitrogen atmosphere. When dissolution of the metal was complete, the solution was cooled to −60° (Dry Ice-acetone bath) and 30 g. of 2-bromopyridine was added at such a rate that the temperature did not rise above −50°. To the re-

(11) J. P. Wibaut and L. G. Heeringa, *Rec. trav. chim.*, **74**, 1003 (1955).

(12) H. H. Hatt, A. Pilgrim, and W. J. Hurran, *J. Chem. Soc.*, 93 (1936).

(13) M. T. Clark, E. C. Hendly, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955).

(14) A. Schoenberg and K. T. Keller, *Ber.*, **36B**, 1638 (1923).

(15) F. F. Blicke and C. E. Maxwell, *J. Am. Chem. Soc.*, **64**, 428 (1942).

(16) P. Karrer and P. Portmann, *Helv. Chim. Acta*, **31**, 2088 (1948).

(17) V. Prelog and G. J. Driza, *Collection Czechoslov. Chem. Communs*, **5**, 497 (1933).

(18) All melting points uncorrected.

sulting deep-orange solution was added 12.9 g. of I in 25 ml. of dry benzene; during this addition the temperature of the reaction mixture was kept below +10°. After refluxing for 45 min. and cooling to room temperature, the reaction mixture was hydrolyzed by adding 80–90 ml. of water. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and quickly evaporated to a small volume. Treatment of the residue with petroleum ether (30–60°) precipitated II (12 g.; 72%) as nearly colorless prisms; m.p. 134–135°. An analytical specimen recrystallized from boiling ether melted at 137–137.5°.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.9; H, 5.99. Found: C, 71.8; H, 5.8.

DL-*Phenyl-2-piperidyl-3,4,5-trimethoxyphenylcarbinol* (III). To a solution of II (14 g.) in 100 ml. of reagent methanol was added 200 mg. of Adams' catalyst and 20 ml. of 10% aqueous hydrochloric acid. The mixture was shaken with hydrogen in a Parr apparatus at about 60 p.s.i.g. until hydrogen was no longer absorbed (final pressure 56.5 p.s.i.g. after 3.3 hr.). After adding both another 200-mg. portion of catalyst and 5 ml. of 10% hydrochloric acid, the apparatus was repressurized to 60 p.s.i.g. and hydrogenation continued until the total gas uptake had reached that calculated for total hydrogenation of the pyridine ring. The resulting mixture was treated with Norit, filtered, and evaporated *in vacuo*. A sample of the crude free base III thus obtained melted at 169–170°. The residue was taken up in a dry ether-benzene mixture and treated with dry hydrogen chloride to precipitate DL-phenyl-2-piperidyl-3,4,5-trimethoxyphenylcarbinol (III) hydrochloride. Recrystallization from hot ether-ethanol gave 9.5 g. (61%) of the purified salt as colorless prisms, m.p. 265–266°.

Anal. Calcd. for $C_{21}H_{28}ClNO_4$: C, 64.1; H, 7.12; Cl, 9.03. Found: C, 63.8; H, 7.2; Cl, 9.0.

3,4,5-Trimethoxyphenyl benzyl ketone (V). To a stirred solution of benzylmagnesium chloride (prepared from 101 g. of benzyl chloride and 19.4 g. of magnesium turnings) in 500 ml. of dry absolute ether was added 42 g. of finely powdered 3,4,5-trimethoxybenzamide. The mixture was refluxed for 2 hr., allowed to stand overnight, and then poured into 800 g. of an ice-water mixture containing 44 ml. of concd. sulfuric acid. An insoluble precipitate of unchanged amide (20.5 g.; 49% recovery) was collected. The ether layer from the filtrate was washed with 5% aqueous sodium bicarbonate and then with water. After drying over anhydrous magnesium sulfate, and concentrating *in vacuo*, the residue was induced to crystallize by adding an ether–petroleum ether (b.p. 30–60°) mixture. The crude product (20.4 g.) yielded 13.1 g. of 3,4,5-trimethoxyphenyl benzyl ketone (V) as light-yellow prisms, m.p. 97–98°. An additional 4.4 g. of purified V was obtained by treating the recovered amide in suspension in dry benzene with benzylmagnesium chloride. A total yield of 17.5 g. (41%) of pure V was thus obtained.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3. Found: C, 71.3; H, 6.2.

3,4,5-Trimethoxybenzil (VI). To a solution of 35 g. of V in 75 ml. of acetic anhydride was added 19.2 g. of selenium dioxide. After refluxing for 3.5 hr., the reaction mixture was poured onto crushed ice and brought to *p*H 8 by the addition of aqueous ammonia. The yellow semisolid precipitate was collected and recrystallized from hot ethanol to give 13 g. (39%) of VI as yellow prisms; m.p. 110–111°; an analytical specimen out of ethanol-ether melted at 115–116°. No additional benzil could be obtained by evaporating the mother liquor; instead, an intractable orange oil was obtained.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.34. Found: C, 68.0; H, 5.2.

DL-*3,4,5-Trimethoxybenzilic acid* (VII). A solution of 4.3 g. of sodium hydroxide in a minimum volume of water was first diluted with 45 ml. of absolute ethanol and cooled in an ice bath, and then 9.2 g. of 3,4,5-trimethoxybenzil (VI) was added in one portion. The mixture was placed in a 125-ml. flask and sufficient ether added to fill the neck. After securing a rubber stopper closure by means of a wire, the flask was placed in the refrigerator for 2 days. The resulting solution of the sodium salt of VII was diluted with ice water and extracted with ether to remove traces of unchanged ketone. Upon acidification of the aqueous liquid with hydrochloric acid, the crude benzilic acid (VII) precipitated as an oil which solidified on cooling and scratching. There was obtained 9.2 g. (97%) of DL-3,4,5-trimethoxybenzilic acid as colorless prisms; m.p. 148°. The melting point was unchanged after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.2; H, 5.7. Found: C, 64.3; H, 5.7.

DL-*N-Methyl-3-piperidyl 3,4,5-trimethoxybenzilate* (VIII). A mixture of 8.7 g. of *N*-methyl-3-chloropiperidine[18] and 10.6 g. of VII in 50 ml. of isopropyl alcohol was refluxed for 2 days and then the solvent removed by evaporation *in vacuo*. The viscous oily residue was first treated with 10% aqueous sodium carbonate to remove unchanged VII and then extracted with three 50-ml. portions of ether. Treatment of the dried ether extracts with anhydrous hydrogen chloride gave an oily precipitate which did not crystallize, and therefore the base was again liberated by the addition of alkali. The crude base, amounting to 11.1 g. of a colorless oil, was taken up in hot ethyl acetate and treated with a boiling solution of 3.5 g. of maleic acid in the same solvent. Upon cooling and adding ether dropwise, III maleate crystallized from the solution as small colorless needles. Recrystallization from an ethanol–ethyl acetate mixture containing a little water afforded 2.5 g. of the pure salt, m.p. 196–197°.

Anal. Calcd. for $C_{27}H_{33}NO_{10}$: C, 61.0; H, 6.22. Found: C, 60.9; H, 6.5.

N-Methyl-1,2,5,6-tetrahydro-3-pyridylmethyl benzilate (XI). Arecoline alkaloid was reduced by means of lithium aluminum hydride to *N*-methyl-3-hydroxymethyl-1,2,5,6-tetrahydropyridine (IX) in 64% yield by the procedure of Karrer and Portmann.[16] To an ice-cooled solution of 17.9 g. of IX in chloroform was added dropwise with swirling 19 g. of thionyl chloride, and the resulting mixture heated on the steam bath for 0.5 hr. After cooling and dilution with ether, the *N*-methyl-3-chloromethyl-1,2,5,6-tetrahydropyridine (X) hydrochloride was collected and washed with ether. The resulting base hydrochloride was dissolved in a small volume of water and made alkaline with saturated potassium carbonate solution to liberate the free base which in turn was taken up in ether. After drying, the ether solution was evaporated to a yellow oil which exhibited some tendency to dimerize. Accordingly, the free base was immediately dissolved in 100 ml. of isopropyl alcohol containing 22.5 g. of benzilic acid and the resulting solution refluxed for 2.5 days. Evaporation of the isopropanol *in vacuo* left a residue which was first treated with saturated potassium carbonate solution and then extracted with ether. By passing anhydrous hydrogen chloride through the resulting dry ether solution, there was obtained the crude ester hydrochloride as a heavy dark oil which gradually solidified (12 g.; 32%). Recrystallization from ethanol gave 8 g. of pure *N*-methyl-1,2,5,6-tetrahydro-3-pyridylmethyl benzilate (XI) hydrochloride as colorless crystals, m.p. 200–201° dec.

Anal. Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.5; H, 6.64; Cl, 9.5. Found: C, 67.6; H, 6.6; Cl, 9.4.

N-(2,3,4-Trimethoxyphenyl)-N'-methylpiperazine (XIII). A mixture of 20 g. of *N*-methylbis(β-chloroethyl)amine hydrochloride,[19] 39 g. of 2,3,4-trimethoxyaniline and 90 ml. of methanol was stirred and refluxed for 17 hr. The solvent was removed at diminished pressure leaving a solid residue which was taken up in a minimum volume of hot methanol. Upon cooling there was deposited 14.1 g. (47%) of pure XIII hydrochloride as small colorless needles, m.p. 239–240° dec.

(19) K. A. Jensen and F. Lundquist, *Dansk. Tiddskri Farm.*, 15, 201 (1941).

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.

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

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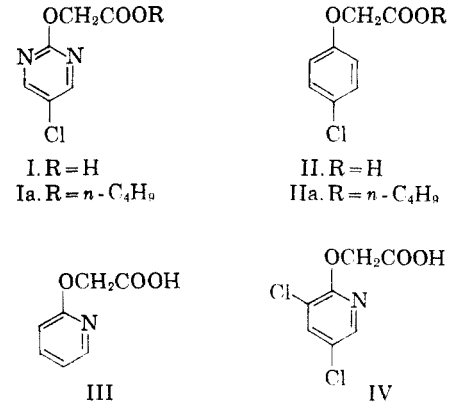
In order to provide a further comparative test of the present theories concerning the relation of structure to chemical stimulation of plant growth, *n*-butyl 5-chloro-2-pyrimidoxyacetate was prepared as an analog of the active 4-chlorophenoxyacetic ester. Although very similar in shape and physical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