EXPERIMENTAL[2]

Reaction of 2-vinylpyridine with ammonium chloride. (A). Freshly distilled (b.p. 48°/9 mm.) 2-vinylpyridine (32.97 g.; 0.314 mole) was heated for 8 hr. under reflux with 33.6 g. (0.628 mole) of ammonium chloride in 95 ml. of water and 15 ml. of methanol according to the method of Magnus and Levine.[1c] The cooled mixture was poured onto ice and made strongly basic with 30% sodium hydroxide solution. Extraction with four 50-ml. portions of chloroform followed by concentration of the chloroform solution after drying over magnesium sulfate left a residue which was vacuum distilled to give 2.43 g. (6.4%) of 2-(2-aminoethyl)pyridine,[1c] b.p. 88–89°/8 mm.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.80; H, 8.25; N, 22.94. Found: C, 68.73; H, 8.23; N, 22.70.

The main product was 18.40 g. (51.6%) of bis[2-(2-pyridyl)ethyl]amine,[3] b.p. 142°/0.1 mm.

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 73.91; H, 7.71; N, 18.72.

(B). A solution of 80.25 g. (1.5 moles) of ammonium chloride in 200 ml. of water was treated with 52.57 g. (0.50 mole) of freshly distilled 2-vinylpyridine. Enough methanol (200 ml.) was added to make the mixture homogeneous. After being heated for 8 hr. under reflux, the mixture was cooled to room temperature, made basic with 30% sodium hydroxide solution and extracted with five 100-ml. portions of chloroform. The chloroform solution was dried over magnesium sulfate, concentrated and distilled to give 20.95 g. (34.4%) of 2-(2-aminoethyl)pyridine.

A similar experiment with 4-vinylpyridine gave 50.6% conversion to 4-(2-aminoethyl)pyridine,[1c] b.p. 104°/9 mm.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.80; H, 8.25; N, 22.94. Found: C, 69.01; H, 8.23; N, 22.80.

This compound formed a monopicrate, m.p. 152°, from 95% ethanol (Magnus and Levine report[1c] the dipicrate, m.p. 186–187°).

Anal. Calcd. for $C_{13}H_{13}N_5O_7$: C, 44.44; H, 3.73; N, 19.94; O, 31.88. Found: C, 44.34; H, 3.51; N, 20.26; O, 31.51.

2-(2-Isopropylaminoethyl)pyridine. A solution of 21.03 g. (0.20 mole) of freshly distilled 2-vinylpyridine and 11.82 g. (0.20 mole) of isopropylamine in 80 ml. of methanol was treated with 12.01 g. (0.20 mole) of glacial acetic acid then heated under reflux for 8 hr. The mixture was evaporated to dryness and the residue was dissolved in a few milliliters of water, made strongly basic with 10% sodium hydroxide solution, and extracted with three 75-ml. portions of ether. The ethereal solution was dried over magnesium sulfate, concentrated, and distilled to give 5.19 g. (15.8%) of product, b.p. 91–92°/7 mm.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.14; H, 9.82; N, 17.06. Found: C, 72.78; H, 9.64; N, 17.04.

2-(2-Dibenzylaminoethyl)pyridine. A solution of 24.58 g. (0.234 mole) of freshly distilled 2-vinylpyridine and 46.20 g. (0.234 mole) of dibenzylamine in 100 ml. of methanol was treated with 28.0 g. (0.468 mole) of glacial acetic acid then heated under reflux for 15 hr. The mixture was evaporated and the residue dissolved in 50 ml. of water. This solution was made strongly basic with 30% sodium hydroxide solution and extracted with four 75-ml. portions of chloroform. The chloroform solution was dried over magnesium sulfate, concentrated, and distilled to give 31.1 g. (44.0%) of product, b.p. 179°/0.1 mm.

Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.27. Found: C, 83.62; H, 7.37; N, 9.24.

4-(2-Aminoethyl)piperidine. A solution of 12.8 g. (0.1 mole) of 4-(2-aminoethyl)pyridine in 100 ml. of methanol with 13 ml. (0.2 mole) of glacial acetic acid was shaken at room temperature under 2.5 atm. of hydrogen pressure in the presence of 2.4 g. of 5% rhodium on alumina catalyst. The hydrogen uptake was 12.5% after 8 hr. The solution was filtered and rehydrogenated in the presence of 3.0 g. of fresh catalyst. Hydrogen uptake was complete in 24 hr. After filtration, the solution was treated with 0.2 mole of ethanolic hydrogen chloride and evaporated to dryness. The residue was washed with acetone and recrystallized from absolute ethanol, yield 10.7 g. (53%) of the dihydrochloride, m.p. 243°.

Anal. Calcd. for $C_7H_{16}N_2 \cdot 2HCl$: C, 41.79; H, 9.01; N, 13.93. Found: C, 41.86; H, 8.81; N, 13.92.

Bis[2-(2-piperidyl)ethyl]amine. A solution of 13.6 g. (0.06 mole) of bis[2-(2-pyridyl)ethyl]amine in 50 ml. of methanol was shaken at room temperature under 2.5 atm. of hydrogen pressure in the presence of 2.72 g. of 5% rhodium on alumina. Hydrogen consumption was 60% of theory after 18 hr. Filtration of the solution and further hydrogenation with 5.4 g. of fresh catalyst for 8 hr. was necessary to complete the reaction. The mixture was filtered, concentrated, and distilled to give 10.3 g. (72%) of product, b.p. 145°/0.5 mm.

Anal. Calcd. for $C_{14}H_{29}N_3$: C, 70.23; H, 12.21; N, 17.55. Found: C, 70.37; H, 12.38; N, 17.14.

2-(2-Isopropylaminoethyl)piperidine. A solution of 2-(2-isopropylaminoethyl)pyridine (5.19 g.; 0.0316 mole) in 100 ml. of 95% ethanol containing 4.0 ml. (0.063 mole) of glacial acetic acid was hydrogenated under 2.0 atm. pressure with 1.0 g. of 5% rhodium on alumina. Hydrogen uptake was complete after 3 hr. The solution was filtered, treated with 0.063 mole of ethanolic hydrogen chloride, and evaporated to dryness. The residue was recrystallized from ethanol-ether to give 6.4 g. (91%) of material, m.p. 296–300°.

Anal. Calcd. for $C_{10}H_{22}N_2 \cdot 2HCl$: C, 49.58; H, 9.98; N, 11.57. Found: C, 49.75; H, 10.15; N, 11.73.

2-(2-Cyclohexylaminoethyl)piperidine. A solution of 5.23 g. (0.0256 mole) of 2-(2-cyclohexylaminoethyl)pyridine[1b] in 150 ml. of glacial acetic acid was shaken under 2 atm. of hydrogen pressure at room temperature with 0.175 g. of platinum oxide. At the end of 24 hr., uptake was 60%. Filtration, addition of 0.5 g. of fresh catalyst and further hydrogenation (2 atm.; 60°) for 15 hr. led to complete reduction. The mixture was filtered, treated with 0.0513 mole of ethanolic hydrogen chloride, and evaporated to dryness. The residue was washed with acetone and recrystallized from ethanolic hydrogen chloride solution by addition of ether to yield 6.30 g. (87.6%) of the dihydrochloride, m.p. 305°.

Anal. Calcd. for $C_{13}H_{26}N_2 \cdot 2HCl$: C, 55.31; H, 9.99; N, 9.92. Found: C, 55.32; H, 10.02; N, 9.83.

Acknowledgment. We are indebted to Mr. E. F. Shelberg and his staff at Abbott Laboratories for microanalytical data.

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(2) All melting and boiling points are uncorrected.

(3) K. Loffler, *Chem. Ber.*, **37**, 161 (1904).

4,6-Dimethoxy-2,2-dimethyl-3[2*H*]benzofuranone and Its Halogenated Derivatives

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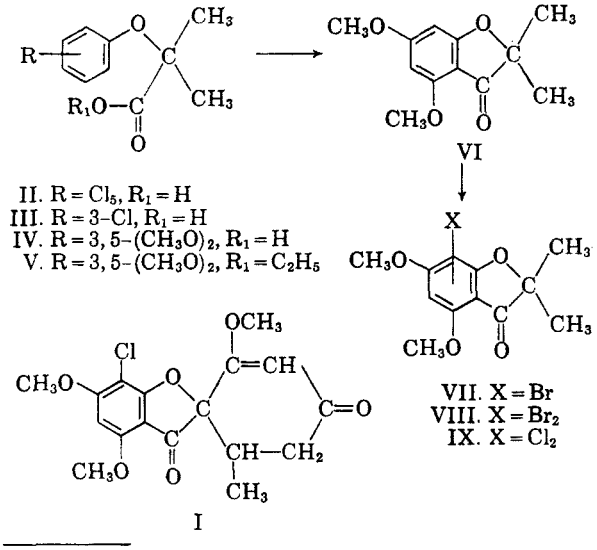
Received May 22, 1961

The antifungal antibiotic griseofulvin[1,2,3] has the structure I which is a derivative of 2,2-disubsti-

(1) For a review of the chemistry of griseofulvin, see W. B. Walley, *Progress in Organic Chemistry*, Vol. 4, J. W. Cook, ed., Academic Press Inc., New York, 1958, p. 98.

tuted 3[2*H*]benzofuranone. This can be further considered as a cyclized derivative of α,α-disubstituted phenoxyacetic acids, some of which are known to have fungicidal activity; *e.g.*, 2-methyl-2-(pentachlorophenoxy)propionic acid[4] (II) and 2-(*m*-chlorophenoxy)-2-methylpropionic acid[5] (III). It is therefore of interest to see whether or not simple 2,2-dialkyl-3[2*H*]benzofuranones show fungicidal activity.[6] This paper reports the synthesis of 4,6-dimethoxy-2,2-dimethyl-3[2*H*]benzofuranone (VI) and its halogenated derivatives.

2-(3,5-Dimethoxyphenoxy)-2-methylpropionic acid (IV) was prepared from 3,5-dimethoxyphenol by: (1) its reaction with a mixture of acetone, chloroform, and sodium hydroxide[7]; (2) its condensation with ethyl 2-bromo-2-methylpropionate and subsequent hydrolysis of the ester V. Cyclization of IV by means of trifluoroacetic anhydride[8] yielded the desired 3(2*H*)benzofuranone VI in 47% yield. Similar reaction of IV with polyphosphoric acid gave a lower yield (26%) of VI.



II. R = Cl_5, R_1 = H
III. R = 3-Cl, R_1 = H
IV. R = 3,5-$(CH_3O)_2$, R_1 = H
V. R = 3,5-$(CH_3O)_2$, R_1 = C_2H_5

VI

VII. X = Br
VIII. X = Br_2
IX. X = Cl_2

I

Bromination of VI afforded two products: a monobromo derivative VII when 1:1 mole ratio of bromine to VI was used, and a dibromo derivative VIII when more than two moles of bromine was employed. The position of the bromine atom in the monobromo derivative has not been established. Reaction of VI with excess sulfuryl chloride yielded the dichloro derivative IX. The isolation of the monochloro derivative from the reaction of equimolar quantities of VI and sulfuryl chloride was unsuccessful and was not pursued further.

The fungitoxicity of the four 4,6-dimethoxy-2,2-dimethyl-3-[2*H*]benzofuranones (VI, VII, VIII, and IX) was evaluated by the slide-germination method[9] against *Monilinia fructicola* and *Stemphylirim sarcinaeforme*. All show negligible activity, having ED_{90} values of greater than 1000 p.p.m. against both organisms.

EXPERIMENTAL[10]

3,5-Dimethoxyphenol was prepared according to Nakazawa and Matsuura[11] in 38% yield.

Ethyl 2-(3,5-dimethoxyphenoxy)-2-methylpropionate (V). 3,5-Dimethoxyphenol (56 g.) was added to a sodium ethoxide solution prepared from 9.2 g. of metallic sodium and 210 ml. of anhydrous ethanol. The mixture was warmed to a clear solution, and 74 g. of ethyl 2-bromo-methylpropionate was added. The whole mixture was stirred and refluxed for 20 hr. The solid was separated by filtration, and the filtrate was concentrated *in vacuo* to about half of its original volume. The solid was again separated. (The total weight of sodium bromide isolated was 36.8 g.; theory, 37.1 g.) The filtrate was further concentrated, and the residue distilled under reduced pressure. There was obtained 66.3 g. (69%) of V, boiling at 118–138° (0.5 mm.). The analytical sample had a boiling point of 126–128° (0.5 mm.), n_D^{21} 1.5167.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.66; H, 7.51. Found: C, 62.77; H, 7.15.

2-(3,5-Dimethoxyphenoxy)-2-methylpropionic acid (IV). *Method A.* A mixture of V (56 g.), 10% aqueous sodium hydroxide solution (100 ml.), and ethanol (100 ml.) was heated under reflux on a steam bath for 2 hr. Most of the ethanol was removed by vacuum distillation. The remaining solution was diluted with 100 ml. of water and acidified with 6*N* hydrochloric acid. The oil which separated was taken up in ether. The ether solution was extracted four times with 10% sodium bicarbonate solution (125 ml. each time). The combined aqueous solution was acidified with 6*N* hydrochloric acid. The oil was taken up in ether, washed with water, and dried over magnesium sulfate. Removal of the ether yielded 24.6 g. (49%) of a viscous oil.[12] This was

(2) The synthesis of griseofulvin was recently reported: (a) A. C. Day, J. Nabney, and A. I. Scott, *Proc. Chem. Soc.*, 284 (1960); (b) A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 1444 (1960).

(3) For fungitoxic activity of griseofulvin see, among others, P. W. Brain, J. M. Wright, J. Stubbs, and A. M. Way, *Nature*, **167**, 347 (1951); E. J. Napier, D. I. Turner, and A. Rhodes, *Ann. Botany*, **20**, 461 (1956); D. Davis and J. W. Rothrock, *Plant Disease Reptr.*, **40**, 328 (1956); A. Rhodes, R. Crosse, R. McWilliam, J. P. R. Toothill, and A. T. Dunn, *Ann. Appl. Biol.*, **45**, 215 (1957).

(4) S. H. Crowdy and R. L. Wain, *Nature*, **165**, 937 (1950).

(5) C. H. Fawcett, D. M. Spencer, and R. L. Wain, *Ann. Appl. Biol.*, **43**, 553 (1955).

(6) Chloro-3[2*H*]benzofuranones have been synthesized for herbicidal testing; see M. L. Kalinowski and L. W. Kalinowski, *J. Am. Chem. Soc.*, **70**, 1970 (1948); D. Stefange and W. L. Howard, *J. Org. Chem.*, **20**, 813 (1955).

(7) This is a general method of preparation of 2-substituted 2-methylpropionic acids of the structures $ROC(CH_3)_2COOH$ or $RSC(CH_3)_2COOH$. For more recent work, see H. Gilman and G. R. Wilder, *J. Am. Chem. Soc.*, **77**, 6644 (1955); M. Julia, M. Baillarge, and G. Tchernoff, *Bull. soc. chim. France*, 776 (1956).

(8) The use of this reagent was suggested by Dr. R. M. Ross.

(9) Published by the American Phytopathological Society, *Phytopathology*, **33**, 627 (1943).

(10) Boiling points and melting points are uncorrected.

(11) K. Nakazawa and S. Matsuura, *J. Pharm. Soc. Japan*, **73**, 751 (1953); *Chem. Abstr.*, **48**, 7007 (1954).

(12) This oil had the correct analysis of IV. Calcd.: C, 59.98; H, 6.71; Acid No., 233.1. Found: C, 59.73; H, 6.63; Acid No., 232.2. Attempted distillation (at 0.5 mm.) of this material yielded an oil which had a lower acid number (115.2). The thermal decomposition of 2-phenoxy-2-methylpropionic acid into phenol and methacrylic acid has been reported by C. A. Bischoff, *Ber.*, **33**, 931 (1900). The decomposition of IV was not investigated further.

used without further purification in the cyclization reaction.

Method B. To a mixture of 3,5-dimethoxyphenol (59 g.), solid sodium hydroxide (72 g.), and acetone (340 ml.) was slowly (45 min.) added 55 g. of chloroform. The mixture was stirred and heated under reflux on a steam bath for 3 hr. After the removal of acetone, the residue was dissolved in water. The solution was worked up as above to afford 50.4 g. (54.7%) of a viscous oil.[13] This was used as such in the cyclization reaction.

A portion (25 g.) of the above product was dissolved in 200 ml. of ether and extracted with 10% sodium bicarbonate solution. Extraction of the combined and acidified aqueous solution with ether yielded 23 g. of solid IV. After recrystallization from a mixture of hexane and toluene, the solid had a melting point of 65–68°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.71; CH_3O, 25.83; neut. equiv., 240.2. Found: C, 59.85; H, 6.64; CH_3O, 25.60; neut. equiv., 233.3.

4,6-Dimethoxy-2,2-dimethyl-3[2H]benzofuranone (VI). *Method A.* 2-(3,5-Dimethoxyphenoxy)-2-methylpropionic acid (12 g.) was mixed with trifluoroacetic anhydride (21 g.). The exothermic reaction was moderated by cooling at 40°. After the initial reaction subsided, the mixture was heated at 90° for 30 min. and concentrated under reduced pressure. The residue was recrystallized from anhydrous ethanol to afford 5.25 g. (47.3%) of VI, m.p. 123–125°.

Method B. A mixture of IV (16 g.) and polyphosphoric acid (130 g.) was stirred and heated at 90–100° for 2 hr. After being cooled, the reaction mixture was poured into 300 ml. of water and extracted with ethyl acetate. The ethyl acetate solution was washed with 10% sodium bicarbonate, then with water, dried over magnesium sulfate, and concentrated *in vacuo*. The solid was recrystallized from anhydrous ethanol to give 3.8 g. (25.5%) of VI, m.p. and mixture m.p. with above, 123–125°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; CH_3O, 27.93. Found: C, 64.98; H, 6.39; CH_3O, 27.95.

Monobromo-4,6-dimethoxy-2,2-dimethyl-3[2H]benzofuranone (VII). Liquid bromine (2.2 g.) was added to a solution of VI (3 g.) in glacial acetic acid (10 ml.). The mixture was allowed to stand at room temperature for 15 min. and then concentrated *in vacuo*. The residue was crystallized from anhydrous ethanol to afford 3 g. (74%) of VII, m.p. 191–193°.

Anal. Calcd. for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.83; H, 4.37.

5,7-Dibromo-4,6-dimethoxy-2,2-dimethyl-3[2H]benzofuranone (VIII). Liquid bromine (5 g.) was slowly added to a solution of VI (1 g.) in glacial acetic acid (15 ml.). The mixture was heated under reflux on a steam bath for 30 min. and concentrated *in vacuo*. The residue was crystallized from ethanol to give 1.2 g. (70.5%) of VIII, m.p. 126–129°.

Anal. Calcd. for $C_{12}H_{12}Br_2O_4$: C, 37.91; H, 3.18; CH_3O, 16.33. Found: C, 38.30; H, 2.97; CH_3O, 16.35.

5,7-Dichloro-4,6-dimethoxy-2,2-dimethyl-3[2H]benzofuranone (IX). A mixture of VI (5 g.), chloroform (40 ml.), and sulfuryl chloride (6 g.) was allowed to stand at room temperature overnight and concentrated under reduced pressure. The residue was crystallized from ethanol to afford 4.2 g. (57.5%) of IX, m.p. 95–97°.

Anal. Calcd. for $C_{12}H_{12}Cl_2O_4$: C, 49.50; H, 4.16; Cl, 24.36; CH_3O, 21.32. Found: C, 49.64; H, 4.33; Cl, 24.41; CH_3O, 21.40.

(13) This oil had the correct analysis of IV. Calcd.: C, 59.98; H, 6.71; Acid No., 233.1. Found: C, 59.78; H, 6.41; Acid No., 238.7. Distillation of this material at 0.4 mm. also resulted in partial decomposition. The distillate had an acid number of 140.9 after one distillation and of 89.5 after a second distillation.

Acknowledgment. We wish to thank Dr. R. M. Ross for his encouragement and interest in this work, Mr. C. W. Nash and his staff for chemical analyses, and Dr. H. L. Keil and his associates for fungicidal evaluation.

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Oxidation-Reduction Concomitant with Molecular Complexing

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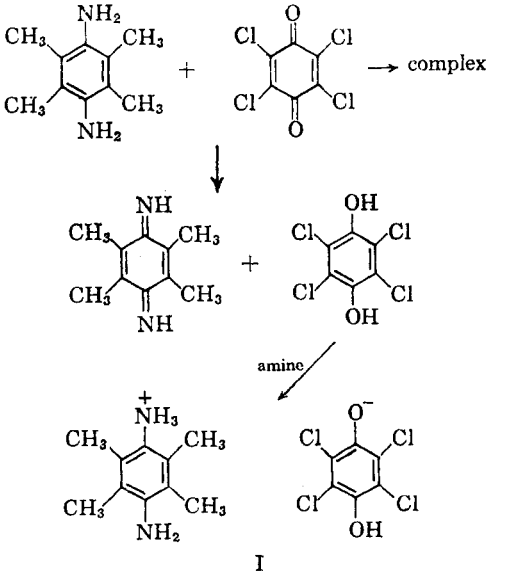
Received May 23, 1961

In the course of studying the electronic properties of solid molecular complexes,[1] attempts at growth of single crystals of diaminodurene-chloranil from chloroform gave well developed small crystals, $\rho \sim 10^4$ Ω cm.,[1a,b] while from benzene only irregular-shaped crystals of poor quality, and duller in color could be obtained. None of our crystals were suitable for electrical measurements, but it has been reported that these benzene-grown crystals have a higher resistivity.[2] It was noted, however, that a crystalline, off-white colored solid was formed in conjunction with the complex in very dilute solution.

The reaction is apparently a case of oxidation-reduction under extremely mild conditions, followed by formation of the salt I:



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(1)(a) P. L. Kronick and M. M. Labes, *J. Chem. Phys., in press;* (b) M. M. Labes, R. Sehr, and M. Bose, *Proc. International Conference on Semiconductor Physics*, Prague, Czechoslovakia, Aug. 29–Sept. 2, 1960, *in press;* (c) R. Sehr, M. M. Labes, M. Bose, F. Wilhelm, and H. Ur, *Proc. Conference on Electronic Conductivity in Organic Solids*, Duke University, April 1960, Interscience Publishers, Inc., New York, *in press;* (d) M. M. Labes, R. Sehr, and M. Bose, *J. Chem. Phys.*, **33**, 868 (1960); (e) M. M. Labes, R. Sehr, and M. Bose, *J. Chem. Phys.*, **32**, 1570 (1960).

(2) R. G. Kepler, private communication.