

TABLE I
 PREPARATION, PROPERTIES AND ANALYSIS OF BIS-(SUBSTITUTED PHENOXY)-METHANES^o

Substituent and position	Reflux period, hours	Crystallizing solvent	Yield, %	Melting point, °C. (cor.) ^b	Carbon, %		Hydrogen, %		Halogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
<i>p</i> -Phenyl	2	Acetone	63	180.2–180.9	85.20	85.28	5.72	5.81		
<i>o</i> -Phenyl	3	70% ethanol	54	104.0–104.8	85.20	85.20	5.72	5.82		
<i>p</i> - <i>t</i> -Amyl	8	^d	64 ^d	41.5–41.9 ^e	81.13	81.17	9.47	9.36		
<i>o</i> -Cyclohexyl	5	85% ethanol	53	95.8–96.6	82.39	82.46	8.85	9.00		
<i>p</i> -Benzyl	6	95% ethanol	59	74.8–75.4	85.21	85.40	6.36	6.53		
<i>p</i> -Chloro ^{f,h,i}	6	Pet. ether	62	69.7–70.2 ^{f,i}					26.34 ^j	26.45 ^j
<i>o</i> -Chloro ^{g,h}	6	Pet. ether	57	87.8–88.6					26.34 ^j	26.37 ^j
2,4-Dichloro ^h	4 ^{1/2}	80% ethanol	74	100.4–100.8	46.19	46.12	2.38	2.41		
<i>p</i> -Bromo ^{h,i}	3	80% ethanol	62	74.0–74.5 ⁱ	43.59	43.58	2.82	2.89	44.63 ^k	45.09 ^k
<i>p</i> -Formyl	12	50% ethanol	60	84–85 ⁱ	70.35	70.26	4.72	4.89		

^a All compounds are new except those indicated by footnotes, *f*, *g*, *h* and *i*. ^b All melting points were run on samples which were recrystallized several times, generally from different solvents. ^c Average of two values. ^d This low melting product was distilled at 1 mm. pressure, and the yield was based on a fraction boiling within a 3° range. ^e Boiling point 185–186° at 1 mm. pressure. ^f Patented as an insect toxicant by the Dow Chemical Co., Brit. Appl. 16,328, filed June 20, 1947, conv. date May 1, 1942. Melting point listed as 67–69°. ^g The Dow patent cited in footnote *f* states that bis-(2-chlorophenoxy)-methane may be used as an insect toxicant, but no properties of the compound are presented. ^h E. E. Kenaga, *J. Econ. Entomol.*, **42**, 996 (1949) mentions that bis-(*p*-chlorophenoxy)-methane, bis-(*o*-chlorophenoxy)-methane, bis-(2,4-dichlorophenoxy)-methane and bis-(*p*-bromophenoxy)-methane were tested for acaricidal activity, but no properties of the compounds are presented. ⁱ R. L. Metcalf, *J. Econ. Entomol.*, **41**, No. 6, 875 (1948) lists the melting point of bis-(*p*-chlorophenoxy)-methane as 70–72°, and that of bis-(*p*-bromophenoxy)-methane as 74–75°. ^j Chlorine. ^k Bromine. ^l On rapid heating the m.p. is 84–85°. On slow heating the compound softens at about 82° and shrinks to a turbid, jelly-like mass which eventually melts to a clear, isotropic liquid, then solidifies at a higher temperature, and finally remelts (dec.) above 240°. Complete resolidification results after keeping the compound at 115° for about an hour; b.p. (1 mm.), 218–219°, b.p. (2 mm.) 233–234°.

Table I summarizes the data on preparation, analysis and melting point of ten bis-(substituted phenoxy)-methanes prepared by the above procedure, yields being based upon the once-crystallized product. These compounds are new with the exception of the four which are indicated in the table, and which are included because their preparation and properties are incompletely described in the literature.⁴

The compounds listed in Table I are insoluble in water, but soluble in acetone, 95% ethanol, benzene, petroleum ether and glacial acetic acid. In the presence of hot, concentrated sulfuric acid they give rise to deep red, green, orange or brown solutions.

Bis-(*p*-phenylphenoxy)-methane is quite stable to the action of alkali, either in aqueous or ethanolic solution, no detectable change being produced by two hours of refluxing with a 50% solution of potassium hydroxide in 95% ethanol. It is also inert to potassium permanganate in neutral medium; a sample shows no change after 100 hours of refluxing in the presence of 2% aqueous potassium permanganate. In acid solution, on the other hand, the compound appears to be completely oxidized by the permanganate.

Bis-(*p*-formylphenoxy)-methane exhibits most of the characteristic properties of aldehydes. It immediately reddens Schiff reagent in aldehyde-free ethanol solution, produces a good silver mirror with Tollens reagent, forms a crystalline compound with sodium bisulfite, and reduces an acetone solution of potassium permanganate in the cold. Fehling solution, on the other hand, is only slightly reduced after prolonged heating.

The melting behavior of bis-(*p*-formylphenoxy)-methane, described in footnote (1) of Table I, is

(4) All ten compounds were new at the time this work was completed [cf. *University of Pittsburgh Bulletin*, **38**, No. 2, 294–300 (1942)] but priority for the synthesis of four of them was forfeited because of delay in submitting the work for publication.

unusual. A somewhat similar phenomenon has been observed by Neish⁵ in an analogous compound, 4,4'-tetramethylene dioxydibenzaldehyde, which was reported to melt with turbidity at 110° and to clear up at 130–140°. Neish suggested that this behavior was caused by partial oxidation at the melting point.

The cleavage of the methylenedioxy group for characterization purposes was accomplished for the ten compounds of Table I by a modification of the procedure of Clowes and Tollens,⁶ using phloroglucinol as a formaldehyde binder. A mixture of 0.0019 mole of the compound, 0.0019 mole (0.30 g.) of phloroglucinol, 8.0 ml. of 12 *N* HCl, and 30–40 ml. of glacial acetic acid was refluxed for 12 hours. A red precipitate of the formaldehyde phloroglucide generally formed within a few minutes. Distillation of the mixture under reduced pressure left a solid residue consisting chiefly of the phloroglucide and liberated phenolic compound. The phenol was separated from the cleavage residue by steam distillation or solvent extraction, and was identified by its properties and by the formation of a suitable derivative. Yields of recovered phenols varied from 4 to 40%.

(5) W. J. P. Neish, *Rec. trav. chim.*, **66**, 433 (1947).

(6) G. H. A. Clowes and B. Tollens, *Ber.*, **32**, 2841 (1899).

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Synthesis in the Pyridazine Series. I. Pyridazine and 3,6-Dichloropyridazine

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Existing methods for the preparation of pyridazine are in the main cumbersome and characterized by poor yields. The first recorded syn-

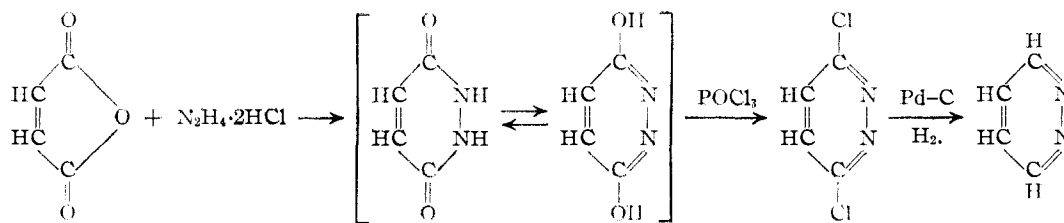


Fig. 1.

thesis is that of Tauber¹ involving oxidation of 3,4,5,6-dibenzopyridazine and decarboxylation of the resultant pyridazinetracarboxylic acid. Gabriel and Colman² started with 2-(*p*-ethoxybenzoyl)-propionic acid and obtained the parent 1,2-diazine in low yield. In more recent times the lengthy procedure of Gabriel,³ a six-step synthesis from α -ketoglutaric acid, was the preferred method.⁴ Evans and Wiselogle⁴ modified this procedure with a resultant increase in yield.

The object of the present work was to seek a less elaborate procedure which would give good yields of pyridazine. The process investigated, which employs the readily available maleic anhydride, is shown schematically in Fig. 1.

Maleic hydrazide, a tautomer of 3,6-pyridazine diol, has been prepared by interaction of hydrazine hydrate and maleic anhydride in alcoholic solution.⁵ Considerable amounts of the monohydrazone of maleic anhydride are formed as a side product. A significant improvement in yield results by allowing maleic anhydride and a mineral acid salt of hydrazine to react in boiling aqueous solution. Substitution of maleic acid for the anhydride is almost as effective in the preparation of the cyclic hydrazone.

The chlorination of 3,6-pyridazine diol is accomplished by boiling with phosphorus oxychloride. 3,6-Dichloropyridazine is a stable crystalline solid which is purified readily by sublimation or distillation. Hydrogenolysis of this substance with palladium-charcoal catalyst in the presence of sodium hydroxide at atmospheric pressure results in low yields of pyridazine. Similar results are encountered in the absence of alkali with pyridazine monohydrochloride being isolated. The use of palladium-charcoal, hydrogen at three atmospheres pressure, and aqueous alcoholic ammonia was found to improve the yield to 60%.

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Experimental⁶

3,6-Pyridazinediol.—To a boiling solution of 75.6 g. (0.7 mole) of hydrazine dihydrochloride in 500 cc. of water there was added in one lot 68.6 g. (0.7 mole) of maleic anhydride, with stirring. The mixture was maintained at the boiling point for 3 hours. During this period the solution was reduced to a small volume, and water was added from

time to time to prevent evaporation to dryness. After dilution to ca. 500 cc., crystallization was allowed to proceed in the cold. A white solid (66.8 g., 85.4%) melting at 299.5–300° was obtained and identified as 3,6-pyridazine diol. Recrystallization from hot water did not alter the melting point.

Anal. Calcd. for $C_4H_4N_2O_2$: C, 42.86; H, 3.60; N, 25.00. Found: C, 43.01; H, 3.50; N, 25.62.

3,6-Dichloropyridazine.—Twenty-five grams of 3,6-pyridazine diol was refluxed with 300 cc. of phosphorus oxychloride for 5 hours. Excess reagent was distilled *in vacuo* and the cooled residue poured onto ice. Ammonium hydroxide (28%) was added until the suspension was slightly alkaline to litmus. The light tan solid was filtered off and dried *in vacuo*. The combined filtrates were extracted once with chloroform and the extract was dried over anhydrous magnesium sulfate. The solid obtained after filtration of this solution and removal of the solvent was combined with that obtained first. After thorough drying this substance melted at 59–63° (29 g., 87%). Purification was effected by sublimation. The m.p. of this material was 68–69° (27 g., 81%).

Anal. Calcd. for $C_4H_2Cl_2N_2$: C, 32.24; H, 1.35; N, 18.81; Cl, 47.60. Found: C, 32.42; H, 1.59; N, 18.72; Cl, 47.35.

Hydrogenolysis of 3,6-Dichloropyridazine. (A).—A mixture of 12 g. of 3,6-dichloropyridazine, 6 g. of palladium-charcoal (10%) and 50 cc. of absolute alcohol was hydrogenated at atmospheric pressure over a 4-hour period. The suspension was filtered and the residue was washed with alcohol. The combined filtrate and washings were treated with ca. one volume of ether which was added slowly. The hygroscopic yellow solid was dried over phosphorus pentoxide and then purified by sublimation. A yield of 2.6 g. (27.8%) of pyridazine monohydrochloride was obtained, m.p. 161–163° (sealed tube).

Anal. Calcd. for $C_4H_5ClN_2$: N, 24.04; Cl, 30.42. Found: N, 23.85; Cl, 30.11.

(B).—A mixture of 29.6 g. of 3,6-dichloropyridazine, 40 cc. of ammonium hydroxide (28%), 2 g. of palladium-charcoal (5%) and 70 cc. of alcohol was hydrogenated at 3 atmospheres pressure. Uptake of hydrogen was rapid, and the reaction was complete in 45 minutes. Two such runs were combined and filtered. The filtrate was made strongly alkaline by the addition of sodium hydroxide pellets, with cooling after each addition. The solution was extracted continuously with ether. The extract was dried with anhydrous potassium carbonate. Solvent was removed *in vacuo* and the residue distilled *in vacuo*, b.p. 86–87° at 14 mm. (19.4 g., 60.7%).

Anal. Calcd. for $C_4H_4N_2$: C, 59.98; H, 5.03; N, 34.99. Found: C, 59.87; H, 5.13; N, 34.99.

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The Action of Formaldehyde on L-Ascorbic Acid-1-C¹⁴

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The reaction of ascorbic acid with formaldehyde results in a complex mixture of compounds which have not been identified.^{1,2} Reithel and West

(1) Reithel and West, *THIS JOURNAL*, **70**, 898 (1948).

(2) Snow and Zilva, *Biochem. J.*, **37**, 630 (1943).

(1) E. Tauber, *Ber.*, **28**, 45 (1895).

(2) S. Gabriel and J. Colman, *ibid.*, **32**, 395 (1899).

(3) S. Gabriel, *ibid.*, **42**, 654 (1909).

(4) R. C. Evans and F. Y. Wiselogle, *THIS JOURNAL*, **67**, 60 (1945).

(5) T. Curtius and H. A. Foersterling, *J. prakt. Chem.*, [2] **51**, 391 (1895).

(6) Melting points are uncorrected.