Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.63. Found: C, 63.42; H, 4.74.

The product from alkaline reduction contained about 90% of the *meso* isomer, m.p. 217–219°,

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.63. Found: C, 63.39; H, 4.75.

The acids were converted to the dimethyl esters with diazomethane and recrystallized from alcohol. The ester of the *dl* acid melted at 119–121°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.60; H, 5.30.

The ester of the *meso* acid melted at 151.5–153°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.35; H, 5.48.

The catholyte from the acid reduction of benzoylformic acid was treated with an equivalent amount of barium hydroxide to remove sulfate. The solution was evaporated to dryness *in vacuo* and the residue treated with a little warm water. Filtration followed by concentration produced 0.4 g. of mandelic acid, m.p. 116–117°. The yield of pinacol was 1.9 g.

Pyrolysis of meso-diphenyltartaric acid. The acid vacuum sublimed with decomposition at 140–160°/0.1 mm. The product was dissolved in ether and most of the ether evaporated. On standing partial crystallization occurred. The solid was filtered and washed with ligroin, ether. It melted at 116–117° and showed no depression when mixed with *dl*-mandelic acid. The residual oil was treated with dinitrophenylhydrazine. The dinitrophenylhydrazone melted at 194–196° and showed no depression when mixed with benzoylformic acid dinitrophenylhydrazone.

Reduction of ethyl acetoacetate. Aqueous alcohol solutions of the ester with sodium hydroxide or sulfuric acid added as electrolyte were used. No reduction products were isolated with either of the cathodes.

Reduction of ethyl benzoylacetate to diethyl β,β'-diphenyl-β,β'-dihydroxyadipate and β-phenyl-β-hydroxypropionic acid. The catholyte contained 50 ml. of alcohol, 25 ml. of dioxane, 30 ml. of water, and 3–4 g. of acid. Sulfuric, hydrochloric, and perchloric acids were used with sulfuric and hydrochloric giving the best results. A minimum of 5 g. of ester was necessary to get reduction with 14–15 g. being used in most runs. In buffered acid, the catholyte consisted of 75 ml. of acetic acid, 40 ml. of water, and 5 g. of sodium acetate. In alkaline medium the catholyte contained 45 ml. of alcohol, 45 ml. of water, and 4 g. of sodium hydroxide. The ester was mostly hydrolyzed during the run, so the product recovered was the acid rather than the ester. Because of the insolubility of the pinacol it was necessary to use the mercury cathode in all acid reductions. Since no pinacol was formed in alkaline solution the mercury plated copper gauze cathode was used. The yields of products obtained in typical runs are summarized in Table I, and are based on reacted starting material.

dl- and *meso*-Diethyl β,β'-diphenyl-β,β'-dihydroxyadipate were isolated from the catholyte from the acid reductions by filtration. The filtrate was concentrated *in vacuo* and the residue distilled *in vacuo* to recover the unreacted ester. The residue from the distillation crystallized and was added to the yield of pinacol after washing with a little alcohol. The *dl* isomer was separated from the *meso* by dissolving in cold benzene. It was purified by recrystallizing from ethanol. A yield of 3.1 g., m.p. 131–135° (137°)[12] was obtained from 6.5 g. of the mixed pinacols. The residue left after the treatment with cold benzene was recrystallized from butanone to give 3.2 g. of the *meso* isomer, m.p. 166–168.5° (168°).[12]

The catholyte from the alkaline reduction was acidified with hydrochloric acid and evaporated *in vacuo* until all of the alcohol was removed. The residue was extracted twice with ether and the ether solution evaporated to dryness. The residue was decolorized with Norit and recrystallized from benzene. A yield of 4.2 g. of β-phenyl-β-hydroxypropionic acid, m.p. 89–91°(92–93°),[13] was obtained from 11 g. of starting material. No pinacol could be isolated from the reaction mixture.

MISSOULA, MONT.

(12) E. Beschke, *Ann.*, **384**, 143 (1911).

(13) E. Erlenmeyer and G. Hilgendorff, *Biochem. Z.*, **35**, 140.

(14) S. Swann, P. Ambrose, R. Dale, R. Rowe, H. Ward, H. Kerfman, and S. Axelrod, *Trans. Electrochem. Soc.*, **85**, 231 (1944).

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Preparation of the Chrysanthemumates of 6-Bromo- and 6-Chloropiperonyl Alcohols

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An over-all synthesis in high yield of two esters, 6-bromo- and 6-chloropiperonyl chrysanthemumates which have high toxicity to insects and low toxicity to mammals, is reported.

The search for new insecticides of low mammalian toxicity is part of the research program of the Entomology Research Division. Of particular interest in this respect have been esters of chrysanthemumic acid[2,3] and about two hundred of these have been prepared at the Beltsville, Md., laboratory and tested for insecticidal activity at the Orlando, Fla., laboratory of the Division. This paper reports the preparation of the 6-bromo- and 6-chloropiperonyl chrysanthemumates[4] which are among the most effective of these compounds.

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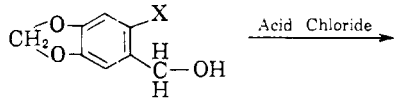
(2) Y. L. Chen and W. F. Barthel, *J. Am. Chem. Soc.*, **75**, 4287 (1953); U. S. Dept. of Agr., ARS-33-23 (1956).

(3) W. F. Barthel and B. H. Alexander, U. S. Dept. of Agr., ARS-33-42 (1957).

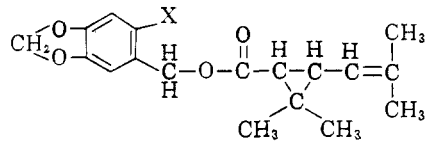
(4) W. F. Barthel, B. H. Alexander, P. G. Piquett, and J. B. Gahan, U. S. patent pending.

The esters are highly toxic to both mosquito larvae and house flies *Musca domestica* (L.); they have, though, an extremely low order of mammalian toxicity.[5]

The chrysanthemumates were prepared by treating the halogenated piperonyl alcohols (II)[6] with chrysanthemumic acid chloride. II was

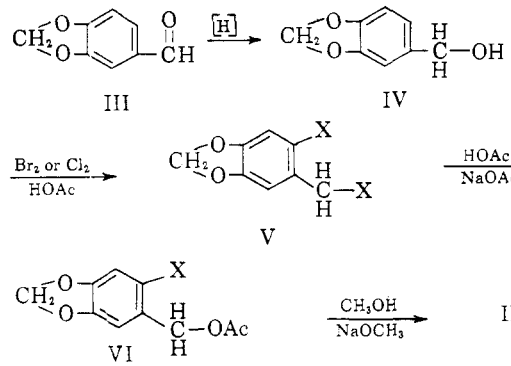


II (X = Cl or Br)



I

initially prepared by the following series of reactions, in which each intermediate was isolated and characterized:



When larger quantities of I were needed for additional testing, a high yield four-step synthesis was devised without the isolation of intermediates. As a check on the purity and identity of II, the alcohols were prepared by way of the aldehyde through lithium aluminum hydride reduction.

Also described is another procedure for the synthesis of I (X = Cl) by transesterification in which II (X = Cl) was treated with ethyl chrysanthemumate[7] with sodium metal as the catalyst.

EXPERIMENTAL

6-Bromopiperonyl bromide (V, X = Br).[6] Bromine (24 ml.) in glacial acetic acid (60 ml.) was slowly added to piperonyl alcohol (60 g.) in glacial acetic acid (120 ml.), with mechanical stirring and cooling (15–25°). Crystallization occurred on standing overnight at 25°, and the crude crystals (84 g.) melted at 91–93°. After recrystallization from methyl alcohol, the melting point was 92–93° (lit. 94°); yield 75%.

Acetate of 6-bromopiperonyl alcohol (VI, X = Br). The above bromide (74 g.), anhydrous sodium acetate (41 g.), and glacial acetic acid (300 ml.) were refluxed for 4 hr. The solution was poured into ice and water and kept at 5° for several hours. The crude product (66 g.) melted at 80–82°, and after one recrystallization from ethyl alcohol melted at 81–82°; yield 96%.

Anal. Calcd. for $C_{10}H_9BrO_4$: Br, 29.3%. Found: Br, 29.7%.

6-Bromopiperonyl alcohol (II, X = Br). (A) The above acetate (50 g.) and 2*N* sodium methylate in methanol (100 ml.) were refluxed for 4 hr. and then poured into cold water. The crude crystals (43 g.) melted at 89–90°, and after recrystallization from ethyl alcohol melted at the same temperature (lit. 90°); yield was quantitative.

(B) 6-Bromopiperonal (40 g.), prepared according to Orr *et al.*,[8] was reduced with lithium aluminum hydride (9 g.) by the extraction method of Nystrom and Brown.[9] The crude product (35 g.), after recrystallization from ethyl alcohol, melted at 89–90°; yield 90%. A mixture of these crystals with those from (A) melted at 89–90°.

6-Chloropiperonyl alcohol (II, X = Cl). The lithium aluminum hydride (4.6 g.) reduction of 6-chloropiperonal (74 g.) gave 6-chloropiperonyl alcohol (72 g.) in 96% yield; m.p. 66–69° (lit.[6] 73–74°).

Anal. Calcd. for $C_8H_7ClO_3$: Cl, 18.84%. Found: Cl, 18.97%.

6-Bromopiperonyl chrysanthemumate (I, X = Br). To a stirred solution of bromopiperonyl alcohol (23 g.), low-boiling (30°–40°) petroleum ether (200 ml.), and dry pyridine (9 ml.) maintained at about 45°, chrysanthemumic acid chloride (19 g.) was slowly added and the mixture was stirred for several hours. After remaining at 25° for 18 hr., the mixture was washed with 5% hydrochloric acid, 5% sodium hydroxide, and cold water. The petroleum ether layer was dried over anhydrous sodium sulfate and the solvent was removed. The crude product (32 g., yield 80%) was distilled; b.p. 183–200°/1.1 mm., n_D^{25} 1.5483.

Anal. Calcd. for $C_{18}H_{21}BrO_4$: Br, 20.69%. Found: Br, 20.61%.

6-Chloropiperonyl chrysanthemumate (I, X = Cl) was prepared from 6-chloropiperonyl alcohol in the same manner as the bromo compound; yield 73%; b.p. 184–206°/0.7 mm., n_D^{25} 1.5378.

Anal. Calcd. for $C_{18}H_{21}ClO_4$: Cl, 10.53%. Found: Cl, 10.45%.

4-Step synthesis of 6-bromopiperonyl chrysanthemumate (I, X = Br). A 3-liter flask, equipped with stirrer, dropping funnel, thermometer, and drying tube, and arranged so that it could be cooled with a water bath or heated electrically, was charged with 300 g. of piperonyl alcohol and 1 liter of glacial acetic acid. With the temperature maintained at 15–20°, 340 ml. of bromine was added dropwise over 4 hr. and the mixture was allowed to stand overnight. Then 250 g. of anhydrous sodium acetate was added. The dropping funnel was replaced with a reflux condenser, and the solution heated to reflux. The mixture was mechanically stirred to prevent bumping during the 4-hr. reflux period, then cooled and poured into ice water with stirring. Stirring was continued for 1 hr. while granular crystals formed. The crystals were filtered, pressed dry, and transferred to a 5-liter flask containing 2 liters of methanol. Then 200 g. of sodium hydroxide dissolved in 500 ml. of water was added. The mixture was refluxed for 3 hr. and poured into 4 liters of ice water with vigorous mechanical stirring. After 1 hr. of stirring the crystals were filtered and transferred to a 5-liter flask equipped with a water separator and reflux con-

(5) Personal communication from Dr. Anthony M. Ambrose, Army Environmental Health Lab, Army Chemical Center, Md.

(6) R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).

(7) A sample of the ethyl ester of D,L-*cis,trans*-chrysanthemumic acid was furnished by Fairfield Chemical Div., Food Machinery and Chemical Corp., Baltimore, Md.

(8) A. M. B. Orr, R. Robinson, and M. M. Williams, *J. Chem. Soc.*, 946 (1917).

(9) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, 49, 2548 (1947).

denser. Two liters of benzene were added, and the mixture was refluxed until no more water separated.

The flask was then equipped with a mechanical stirrer, reflux condenser, and dropping funnel. Dry pyridine (200 ml.) was added, followed by dropwise addition of 342 g. (1.8 mole) of chrysanthemumic acid chloride. After the mixture had stood overnight, water was added to dissolve the pyridine hydrochloride. The upper benzene layer was washed consecutively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution, and then dried with sodium sulfate overnight. The benzene was removed and the residue distilled under high vacuum. A small forerun was obtained and then the main fraction; b.p. 183–200°/1.1 mm., n_D^{25} 1.5496; yield 593 g. (78% based on piperonyl alcohol).

The over-all 4-step synthesis for the chloro derivative was similar to the bromo except that chlorination took place at 50° instead of 15–25°.

6-Chloropiperonyl acetate (VI, X = Cl). Hydrolysis of V (X = Cl) in glacial acetic acid and anhydrous sodium acetate in the usual manner gave VI in 83% yield melting at 84–85°.

Anal. Calcd. for $C_{10}H_9ClO_4$: Cl, 15.48%. Found: Cl, 15.17%.

6-Chloropiperonyl alcohol in 93% yield was prepared from this acetate by sodium hydroxide hydrolysis in methanol; m.p. (from ethanol) 69–70°, mixed melting point with that prepared by reduction of 6-chloropiperonal 69–70.5°.

Anal. Calcd. for $C_8H_7ClO_3$: Cl, 18.84%. Found: Cl, 18.97%.

6-Chloropiperonyl ester of chrysanthemumic acid by transesterification (I, X = Cl). One molar amount of ethyl chrysanthemumate[7] and 6-chloropiperonyl alcohol were heated to 150° in a flask, equipped with a Dean-Starke trap and thermometer. Shortly after addition of 0.25 g. of sodium, ethanol began to distil. When this liberation of ethanol ceased, another 0.25 g. of sodium was added and more alcohol liberated. This procedure was repeated (about eight additions), the temperature being maintained between 150–160°, until the theoretical quantity of ethanol was collected. The mixture was then cooled and dissolved in ether. The solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate, saturated sodium chloride solution, and finally dried over sodium sulfate. After removal of the ether and some forerun of unreacted ethyl chrysanthemumate and 6-chloropiperonyl alcohol, the product distilled; b.p. 155–171°/0.2 mm., n_D^{25} = 1.5375; yield 65%.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Preparation of Some *N*-Substituted Phenothiazines in Tetrahydrofuran

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Tetrahydrofuran was found to be an excellent solvent for the preparation of some *N*-substituted phenothiazine derivatives. 10-(*n*-Decyl)phenothiazine, 10-(*n*-octadecyl)phenothiazine, and 10-(*o*-bromobenzyl)phenothiazine were prepared in high yields using this technique. The sulfoxides and sulfones of 10-(*n*-decyl)phenothiazine and 10-(*n*-octadecyl)phenothiazine were also prepared in very good yields.

N-Substitutions of phenothiazine can be accomplished by a number of techniques. These include the sealed tube reaction such as was used for the preparation of 10-phenothiazinecarbonyl chloride using a mixture of phenothiazine and phosgene in toluene;[1–3] reactions between phenothiazine and a halogen compound in a solvent such as toluene or xylene using a basic condensing agent (*e.g.*, sodium carbonate or sodium hydroxide) and a copper powder catalyst as in the preparation of 10-(*p*-methoxyphenyl)phenothiazine from phenothiazine, *p*-iodoanisole, potassium carbonate, and copper powder in refluxing xylene;[4] reactions similar to that just described in the absence of solvent as in the preparation of 10-phenylphenothiazine by heating a mixture of iodobenzene, phenothiazine, sodium carbonate, and copper powder;[4] and reactions between 10-sodiophenothiazine and an appropriate halide in anhydrous liquid ammonia as in the preparation of 10-ethylphenothiazine from 10-sodiophenothiazine (prepared from phenothiazine and sodium amide in liquid ammonia) and ethyl bromide.[5,6]

10-(*n*-Decyl)phenothiazine and 10-(*n*-octadecyl)-phenothiazine have both been prepared in low yield (10% and 20%, respectively).[7] In these preparations, a mixture of phenothiazine, sodium carbonate, copper powder, and the appropriate alkyl bromide was heated for 11–12 hr. at 180°. Purification was accomplished by extraction with ether, vacuum distillation of the residue after removal of the ether, and, in the case of the *n*-octadecyl derivative, recrystallization of the distilled material from absolute ethanol.

Champaigne[8] prepared 10-(*n*-decyl)phenothiazine

(1) N. Fraenkel, *Ber.*, **18**, 1843 (1885).
(2) S. Paschkowezky, *Ber.*, **24**, 2905 (1891).
(3) R. Dahlbom, *Acta Chem. Scand.*, **7**, 879 (1953).
(4) H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 1214 (1944). For general references on the chemistry of phenothiazine see the excellent article by S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).
(5) H. Gilman, R. D. Nelson, and J. F. Champaigne, Jr., *J.Am. Chem. Soc.*, **74**, 4205 (1952).
(6) H. Gilman, R. K. Ingham, J. F. Champaigne, Jr., J. W. Diehl, and R. O. Ranck, *J. Org. Chem.*, **19**, 560 (1954).
(7) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944).
(8) J. F. Champaigne, Jr., M.S. thesis, Iowa State College (1952).