

### Experimental

**Homophthalic Acid.**—Several 1500-g. batches of phthalonic acid were reduced to homophthalic acid by the method of Graebe and Truempy.<sup>5</sup> The purified product melted at 181° and the average yield obtained was 65%.

**Homophthalimide.**—One kilogram (5.55 moles) of homophthalic acid and 1100 ml. (ca. 16.5 moles) of 28% ammonium hydroxide were placed in a flask. The water and ammonia were distilled until the salt solidified, then the heating was continued, using a soft flame, until all the salt had decomposed to the imide, which was obtained as a dark orange viscous liquid. The imide was recrystallized from acetic acid. The product melted at 230–233°, and was obtained in 83% yield.

**N-Ethyl Homophthalimide.**—One hundred and eighty grams (1.0 mole) of homophthalic acid and 405 g. (3.0 moles) of 33% aqueous monoethylamine were treated as in the preparation of homophthalimide.

**4,4-Diethyl Homophthalimide.**—A solution of 38.4 g. (0.96 mole) of sodium hydroxide in 100 ml. of water was added to a suspension of 77.5 g. (0.48 mole) of homophthalimide in 700 ml. of alcohol. After solution was complete, 150 g. (0.96 mole) of ethyl iodide was added and the mixture was refluxed for one-half hour and allowed to stand overnight. The solution was evaporated to incipient cloudiness. On cooling crystals were obtained; m. p. 130–138°. When the filtrate was evaporated, the liquid separated into two layers, the lower of which was an aqueous solution of sodium iodide. The upper layer was evaporated to dryness and the residue combined with the first crop of crystals. This mixture was recrystallized from alcohol, then treated with charcoal in ether. The product was precipitated by the addition of petroleum ether.

**N-Ethyl-4,4-diethyl Homophthalimide.**—Fifty grams (0.264 mole) of N-ethyl homophthalimide suspended in 300 ml. of alcohol was mixed with a solution of 21.6 g.

(0.54 mole) of sodium hydroxide in 50 ml. of water. To this was added 82.8 g. (0.53 mole) of ethyl iodide and the mixture was refluxed eight hours. Then the alcohol was distilled and the residue diluted with water. The precipitated oil slowly crystallized. The product was collected by filtration, treated with charcoal in ether, and reprecipitated as white crystals by the addition of petroleum ether.

**4,4-Dibenzyl Homophthalimide.**—Fifty grams (0.31 mole) of homophthalimide suspended in 500 ml. of alcohol, 52.3 g. (0.62 mole) of sodium bicarbonate dissolved in 500 ml. of water, and 78.7 g. (0.62 mole) of benzyl chloride were refluxed together for sixteen hours, at the end of which time a considerable quantity of crystals had separated. These were collected by filtration, dissolved in hot methanol and reprecipitated by the addition of water. The precipitate was collected by filtration and treated with charcoal in ether. The other compounds listed in Table I were obtained by one or another of the methods just described.

### Summary

A series of 4,4-dialkyl derivatives of homophthalimide has been prepared and tested orally for hypnotic activity. No activity was found in any of the compounds in this group, which included the diethyl, di-*n*-propyl, diallyl, di-*n*-butyl, di-*i*-butyl, di-*n*-amyl, dibenzyl, and *i*-propyl benzyl derivatives. The N-ethyl, N-ethyl-4,4-diethyl and 4-*i*-propyl derivatives of homophthalimide also have no apparent hypnotic activity.

CINCINNATI, OHIO

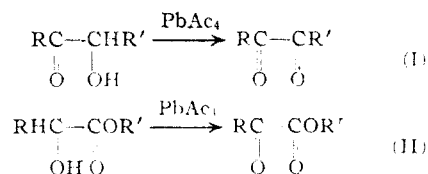
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

## A New Method of Preparing Phenylglyoxylic Acid and its Methyl Ester

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$\alpha$ -Keto alcohols are readily oxidized to the corresponding  $\alpha$ -diketones by means of lead tetracetate (L.T.A.):<sup>2</sup> The oxidation of the tetracetate alcohol is obviously facilitated by the presence of the carbonyl group in  $\alpha$ -position. The similar, although not quite identical arrangement of groups existing in esters of  $\alpha$ -hydroxy acids suggested the extension of reaction I to this class of compounds.



A preliminary investigation to test the feasibility of reaction II was carried out using as substrates the methyl esters of  $\alpha$ -hydroxypalmitic acid, lactic acid and mandelic acid. The oxida-

tion of the  $\alpha$ -hydroxypalmitic acid ester in glacial acetic acid, benzene and cyclohexane did not proceed as anticipated. Attempts to isolate  $\alpha$ -keto palmitic acid ester from the oxidation product were unsuccessful. Somewhat more encouraging were the results of the oxidation of lactic acid methyl ester with L.T.A. in boiling benzene, cyclohexane or dioxane. In these solvents the pyruvic acid methyl ester was formed to the extent of 28, 11 and 9%, respectively. Only traces of the keto ester were produced in boiling acetic acid or ethyl acetate. The oxidation of mandelic acid methyl ester in boiling benzene, however, proceeded fully as expected and forms the basis of a new method for the practical preparation of phenylglyoxylic acid and its ester.

The synthesis is carried out according to the following sequence of reactions: mandelic acid  $\rightarrow$  mandelic acid methyl ester  $\rightarrow$  phenylglyoxylic acid methyl ester  $\rightarrow$  phenylglyoxylic acid. Calculated on the basis of mandelic acid the over-all yield of phenylglyoxylic acid methyl ester is 74% and that of phenylglyoxylic acid 67%.

The results of the present investigation show that an  $\alpha$ -hydroxy acid in the form of its ester

(1) This paper forms part of a thesis submitted to the Department of Chemistry of the University of Toronto by M. Kates in partial fulfillment of the requirements for the degree of Bachelor of Arts, May, 1945.

(2) E. Baer, *THIS JOURNAL*, **62**, 1597 (1940).

can be oxidized successfully by means of L.T.A. to the corresponding  $\alpha$ -keto acid ester, if no other groups or combinations of groups are present which react with the lead (IV) salt. The difference in the rate of oxidation of an  $\alpha$ -hydroxy acid ester as compared to that of an  $\alpha$ -keto alcohol is due to the difference in the chemical nature of the carbonyl group and the carboxyl CO-group. Further investigations with the object of determining the range of application of reaction II are in progress.

### Experimental

**Mandelic Acid Methyl Ester.**<sup>3</sup>—To a solution of 200 g. of mandelic acid in 1500 cc. of dry methanol containing 70 cc. of concd. sulfuric acid was added 400 g. of anhydrous calcium sulfate and the mixture, protected against the intrusion of moisture, was boiled under reflux for a period of twenty-four hours. After cooling to room temperature, the mixture was neutralized to litmus by adding cautiously a saturated aqueous solution of potassium carbonate and was filtered with suction using a filter coated with supercel. The residue of drierite and filter-aid was washed with several portions of hot methanol, totalling 400 cc. The combined filtrates were freed from a small amount of potassium salts and concentrated *in vacuo* to approximately 500 cc. The concentrate was mixed with an equal amount of water and extracted five times with 250-cc. portions of ether. The combined ether extracts, after drying with anhydrous sodium sulfate, were concentrated under diminished pressure and the residue distilled in a high vacuum using a distilling flask with sealed-on receiver.<sup>4</sup> The yield was 190 g. (87%) of mandelic acid methyl ester, b. p. (0.01 mm.) 96–101°, bath temperature 110–120°; m. p. 55–56°, reported 58°.

**Phenylglyoxylic Acid Methyl Ester.**—A solution of 166 g. of mandelic acid methyl ester in two liters of dry benzene together with 443 g. of lead tetraacetate was boiled under reflux (CaCl<sub>2</sub>-tube) for at least a period of eight hours. The contents of the flask should be shaken at frequent intervals to prevent decomposition due to local overheating. The cooled mixture was filtered with suction and the lead diacetate washed with several portions of ether, totalling 500 cc. To the combined vigorously stirred filtrates was added first 400 cc. of a saturated aqueous solution of sodium bicarbonate and then solid sodium bicarbonate until the evolution of carbon dioxide ceased. The mixture was filtered with suction through a filter coated with supercel and the brown sludge washed with 200 cc. of ether. The two layers of the filtrate were separated and the aqueous solution was extracted with 300 cc. of ether. The combined organic solutions were dried with anhydrous sodium sulfate and concentrated to a volume of approximately one liter. The rest of the solvent was removed under diminished pressure. The fractionated vacuum

distillation of the residue in a distilling flask with sealed-on receiver<sup>4</sup> yielded (a) 5.0 g. of a precursor, mainly benzaldehyde, b. p. (10 mm.) 85–100°, and (b) 140 g. (85.4%) of pure phenylglyoxylic acid methyl ester, b. p. (6 mm.) 110–111°,  $n_D^{20}$  1.5261. *Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>O<sub>3</sub> (164): C, 65.85; H, 4.92. Found: C, 66.20; H, 4.96.

**Phenylglyoxylic Acid Methyl Ester Phenylhydrazone.**—The hydrazone was prepared in the customary way, yield 92%. The crude hydrazone was purified by washing with a dilute aqueous solution of sodium bicarbonate and repeated recrystallization from low boiling petroleum ether (b. p. 40–60°); m. p. 86–88°. *Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> (254): C, 70.86; H, 5.55. Found: C, 70.56; H, 5.58.

**Phenylglyoxylic Acid.**—A suspension of 140 g. of phenylglyoxylic acid methyl ester in 700 cc. of 2 *N* sodium hydroxide was shaken until most of the ester was dissolved (approx. ten minutes). The saponification was completed by heating the slightly yellow solution on the steam-bath for half an hour. Traces of an undissolved oil were removed by extracting the cooled solution twice with 100-cc. portions of ether. On acidification with 350 cc. of 5 *N* hydrochloric acid the phenylglyoxylic acid precipitated as a heavy oil which was separated by extracting twice with 200-cc. portions of ether. The combined ether extracts, after drying with anhydrous sodium sulfate, were concentrated under diminished pressure. The residue was distilled in a high vacuum using a distilling flask with sealed-on receiver and yielded 115.5 g. (90%) of almost pure phenylglyoxylic acid, b. p. (0.1 mm.) 105°, m. p. 60.5–61.5°. Washing the crude acid with petroleum ether raised the m. p. to 63°. A more effective purification was achieved by recrystallizing the keto acid from carbon tetrachloride: 115 g. of phenylglyoxylic acid was dissolved in 170 cc. of warm carbon tetrachloride and the solution cooled to –5°. The colorless and well-crystallized acid was filtered off, washed with a small volume of cold carbon tetrachloride and dried *in vacuo* over phosphorus pentoxide: yield 92.5 g. of pure phenylglyoxylic acid, m. p. 64.5–65.5°; reported m. p. 65–66°.

**Phenylglyoxylic Acid Phenylhydrazone.**—The hydrazone was obtained in almost the theoretical yield. After recrystallization from ethanol m. p. (dec.) 163–164°; reported m. p. 163°. *Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub> (240): C, 70.00; H, 5.00. Found: C, 69.92; H, 5.08.

### Summary

It has been found that the methyl esters of certain  $\alpha$ -hydroxy acids can be oxidized with lead tetraacetate to the corresponding esters of  $\alpha$ -keto acids. This reaction is an extension of the previously reported oxidation of  $\alpha$ -keto alcohols to the corresponding  $\alpha$ -diketones by means of lead tetraacetate.

A new and convenient method of preparing phenylglyoxylic acid and its methyl ester by oxidation of mandelic acid methyl ester with lead tetraacetate is described.

(3) The esterification of mandelic acid as described above follows the procedure reported by Acree (*Ber.*, **37**, 2767 (1904)) with the exception that anhydrous calcium sulfate is added to remove the water of reaction.

(4) E. Baer, *Ind. Eng. Chem., Anal. Ed.*, **16**, 399 (1944).