

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MONTANA STATE UNIVERSITY]

## Cathodic Reduction of Negatively Substituted Ketones: $\alpha$ -Ketoacids and $\beta$ -Ketoesters

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Received December 16, 1957

The cathodic reduction of  $\alpha$ -ketoacids and  $\beta$ -ketoesters has been studied. The  $\alpha$ -carboxyl group in  $\alpha$ -ketoacids has been found to promote reduction but not pinacol formation compared with a phenyl group. It also has a pronounced effect upon the stereoisomeric identity of the pinacol product, unlike unsubstituted ketones. The carbethoxy group in  $\beta$ -ketoesters inhibits pinacol formation in acid medium and favors hydroxy acid in alkaline medium.

Since it has been shown that the presence of an alpha aryl group in ketones promotes pinacol type reduction by either chemical or electrochemical methods,<sup>1</sup> it was of interest to study the effect of other negative groups such as carboxyl and carbethoxyl groups located in the alpha and beta positions on the course of cathodic reduction.

The reductions were carried out at mercury or mercury plated copper gauze cathodes at constant cathode potential.<sup>2</sup> In general, it was found necessary to use the mercury cathode when the product was insoluble to avoid clogging of the cathode with subsequent loss of current efficiency.

The compounds studied were pyruvic, and benzoylformic acids, ethyl acetoacetate, and ethyl benzoylacetate. Pyruvic acid has previously been reduced electrolytically to lactic acid in aqueous sulfuric acid but no pinacol was reported.<sup>3</sup> In the present work, in addition to lactic acid a small amount of one isomer of dimethyltartaric acid was isolated from reductions in aqueous sulfuric acid. The best yields of the latter product were obtained when the reaction was carried out in aqueous acetic acid or in solutions of pyruvic acid buffered to pH 2-6 with ammonia.

Benzoylformic acid was readily reduced in acid, buffered acid, or alkaline media. Maximum yields (50-60%) of the mixed diphenyltartaric acids were obtained in alkaline solution. In addition to the pinacol, a small amount of mandelic acid was isolated from acid reductions. The crude pinacol could be separated into *racemic* and *meso* fractions. Applying the rule of Stern,<sup>4</sup> the *meso* configuration may be tentatively assigned to the higher melting isomer. The *meso* isomer was the principal one formed in alkaline solution while the *racemic* form was the main product in acid solution. The latter

isomer appeared to be the one isolated by Schonberg<sup>5</sup> by photochemical reduction of benzoylformic acid. On vacuum sublimation, the *meso* isomer disproportionated to mandelic acid and benzoylformic acid.

Benzoyl cyanide failed to reduce in acid solution. Methyl benzoylacetate was readily reduced in alkaline solution but the yield of dimethyl diphenyltartrate was low due to partial hydrolysis of the esters during the reaction.

Ethyl acetoacetate failed to reduce in either acid or alkaline media at either of the cathodes.

Reduction of ethyl benzoylacetate in acid or buffered acid solutions produced a 1:1 mixture of *racemic* and *meso*-diethyl 3,4-diphenyl-3,4-dihydroxyglutarate in 50-60% yields. However, considerable unreacted starting material was recovered and it was noted that the concentration of the ester in the catholyte had to be about 5% before any reduction would occur at all. Also, addition of the reductant to the catholyte produced a 10-20% rise in the cathode potential instead of the drop that occurred with the  $\alpha$ -ketoacids (50%) and acetophenone (30%). Only  $\beta$ -phenyl- $\beta$ -hydroxypropionic acid was isolated from alkaline reductions.

These results indicate that, under similar conditions the presence of the alpha carboxyl group facilitates reduction (acetone fails to reduce under conditions effective with pyruvic acid) it is not as effective in promoting pinacol formation as a phenyl group.<sup>6</sup> However, it does have a pronounced effect in upsetting the 1:1 ratio of the stereoisomeric pinacols formed in contrast to the beta carbethoxy group and unsubstituted ketones,<sup>7</sup> where the two isomers are formed in about equal amounts. The beta carbethoxyl group not only does not favor pinacol formation but actually inhibits reduction as shown by the rise in cathode potential and recovery of unreacted starting material. The larger yield of pinacol formed from

(1) The method of M. Gomber and W. E. Bachmann [*J. Am. Chem. Soc.*, **49**, 236 (1927)] using magnesium subiodide is effective only on diaryl ketones. Michler's ketone is reduced at a copper cathode [F. Escherich and M. Moest, *Z. Elektrochem.*, **8**, 849 (1902)] while acetone fails to reduce even when the copper cathode is mercury plated (*loc. cit.*).

(2) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 114 (1950).

(3) G. W. Rockwell, *J. Am. Chem. Soc.*, **24**, 719 (1902).

(4) R. Stern, Abstracts of Papers 131st Meeting American Chemical Society, Miami, Fla., April 7-12, 1957.

(5) A. Schonberg, N. Latif, R. Moubasher, and A. Sina, *J. Chem. Soc.*, 1364 (1951).

(6) Compare results of runs 1,2,3 with 4 and 5 Table I. Also note that alkyl aryl ketones frequently give higher pinacol yields<sup>7,14</sup> than benzoylformic acid.

(7) R. E. Juday and W. J. Sullivan, *J. Org. Chem.*, **20**, 617 (1955).

TABLE I

Run	Initial C.d./Cm. <sup>2</sup>	Cathode	Cathode Potential	Electrolyte	Products (% Yield)	
					Pinacol	Alcohol
Pyruvic Acid						
1	0.018	Cu(Hg)	1.1	H <sub>2</sub> SO <sub>4</sub>	4	45
2	0.012	Cu(Hg)	1.1	Acetic acid	7	—
3	0.014	Cu(Hg)	0.7	Ammonia pH 2-5	11	—
Benzoylformic Acid						
4	0.0078	Cu(Hg)	0.75	NaOH	60 (mostly <i>meso</i> )	—
5	0.0078	Cu(Hg)	0.5	H <sub>2</sub> SO <sub>4</sub>	20 (mostly <i>dl</i> )	7
6	0.0078	Cu(Hg)	0.8	NaOH pH 4-6	trace	—
Ethyl Benzoylacetate						
7	0.058	Cu(Hg)	1.4	NaOH	0	44
8	0.037	Hg	4.2	H <sub>2</sub> SO <sub>4</sub>	60 (1:1 <i>dl, meso</i> )	0
9	0.037	Hg	6.5	H <sub>2</sub> SO <sub>4</sub>	61	0
10	0.037	Hg	3.0	HCl	50	0
11	0.037	Hg	3.4	HClO <sub>4</sub>	35	0

benzoylformic acid in alkaline solution is in agreement with results obtained with other ketones.<sup>7</sup> The failure of ethyl benzoylacetate to form the pinacol in alkaline solution may be due to the fact that reduction of the enolate anion present produces only the alcohol while the pinacol is produced primarily from the keto form.

## EXPERIMENTAL

**Benzoyl cyanide.** The procedure in *Organic Syntheses*<sup>8</sup> was used except that 15 g. of powdered potassium iodide was added to the reaction mixture and the crude product was purified by recrystallization from petroleum ether rather than by fractional distillation.

**Benzoylformic acid.** Benzoyl cyanide was hydrolyzed using the procedure in *Organic Syntheses*.<sup>9</sup>

**Reductions. Apparatus.** Reactions were run in a 200-ml. Berzelius beaker using the anode, diaphragm, and cathodes as previously outlined.<sup>7</sup> In addition, a calomel electrode was placed in the cell close to the cathode in order to measure cathode potential. Current was passed through the cell containing all of the components but the reductant until the cathode potential was constant. The reductant was then added and its effect on the cathode potential noted. The potential was then maintained throughout the run by manual adjustment<sup>10</sup> of the current with a rheostat until gassing indicated that the reaction was completed. In general, there was little change in the potential until near the end of the run. All reactions were run between 15° and 25°.

**Reduction of pyruvic acid to dimethyltartaric acid and lactic acid.** The catholyte contained 90 ml. of water and 7-10 g. of pyruvic acid. In acid reductions 2-4 g. of sulfuric acid or 5-10 g. of acetic acid was added. In buffered solutions enough ammonia was added to maintain the pH between 2 and 5 during the reaction. If necessary a small amount of acetic acid could be added near the end of the reaction to keep the solution acidic. Mercury plated copper gauze cathodes were used throughout. The yields obtained in typical runs are summarized in Table I.

(8) T. S. Oakwood and C. A. Weissberger, *Org. Syntheses*, **Coll. Vol. 3**, 112 (1955).

(9) T. S. Oakwood and C. A. Weissberger, *Org. Syntheses*, **Coll. Vol. 3**, 114 (1955).

(10) R. Pasternak, *Helv. Chim. Acta*, **31**, 753 (1948) and private communication.

The dimethyltartaric acid was first separated as the barium salt. When sulfuric acid was used as electrolyte, an amount of barium hydroxide equivalent to the sulfuric acid was first added and the suspension filtered. Extra barium hydroxide was then added and the product separated. When ammonia was used as buffer, the catholyte was first made alkaline with ammonia, concentrated *in vacuo*, and diluted with alcohol to precipitate the ammonium salt which was then dissolved in water and treated with barium hydroxide. To isolate the free acid, the barium salt was suspended in water and treated with an equivalent amount of sulfuric acid. The suspension was filtered and concentrated to about a 40% solution *in vacuo*. Removal of water was completed in a vacuum desiccator over phosphorus pentoxide. A yield of 6 g. of the acid melting at 174-175° (177-178°<sup>11</sup>) was obtained starting with 9 g. of the ammonium salt. The acid was converted to the dimethyl ester with diazomethane and recrystallized from ligroin, m.p. 50-51.7°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>O<sub>6</sub>: C, 46.60; H, 6.80. Found: C, 46.72; H, 6.70.

Lactic acid was isolated from the catholyte after removal of the sulfuric acid by evaporating and distilling the residue *in vacuo*. It was identified by conversion to the *p*-bromophenacyl ester, m.p. 110-112°.

**Reduction of benzoylformic acid to diphenyltartaric acid and mandelic acid.** The catholyte contained 90 ml. of water, 5-7 g. of benzoylformic acid, and 2 g. of sulfuric acid or 3-5 g. of sodium hydroxide. In buffered solution enough base was added to neutralize partially the benzoylformic acid. Mercury plated copper gauze cathodes were used as yields with the mercury cathode were very low. The yields of products obtained in typical runs are summarized in Table I.

When sulfuric acid was used as electrolyte, it was first removed by adding excess barium chloride and filtering. The filtrate was neutralized with sodium hydroxide and a 100% excess of barium hydroxide added to precipitate the barium salts of the diphenyltartaric acids. When sodium hydroxide was used as electrolyte the barium hydroxide could be added directly. The barium salts were suspended in water and treated with excess 20% hydrochloric acid. The precipitated acid was filtered, washed with water, and dried *in vacuo* over phosphorus pentoxide. The isomers could be separated by fractional crystallization of the sodium salts from dilute sodium chloride solution. The product from acid reduction contained about 90% of the *dl* isomer, m.p. 153.5-155° (155°).<sup>5</sup>

(11) C. Bottinger, *Ber.*, **25**, 397 (1892).

*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  $\beta,\beta'$ -diphenyl- $\beta,\beta'$ -dihydroxyadipate and  $\beta$ -phenyl- $\beta$ -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  $\beta,\beta'$ -diphenyl- $\beta,\beta'$ -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°)<sup>12</sup> 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°).<sup>12</sup>

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  $\beta$ -phenyl- $\beta$ -hydroxypropionic acid, m.p. 89–91° (92–93°),<sup>13</sup> was obtained from 11 g. of starting material. No pinacol could be isolated from the reaction mixture.

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(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,  
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## Preparation of the Chrysanthemumates of 6-Bromo- and 6-Chloropiperonyl Alcohols

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Received December 12, 1957

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<sup>2,3</sup> 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<sup>4</sup> which are among the most effective of these compounds.

(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).

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