

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

 **$\alpha$ -Bromination of Dicarboxylic Acids<sup>1</sup>**

BY ERWIN SCHWENK AND DOMENICK PAPA

The method commonly employed for the  $\alpha$ -bromination of carboxylic acids consists of the addition of bromine to a mixture of the acid and red phosphorus or phosphorus halide. In place of the free acid, the corresponding ester may be used. This method, with minor variations, has been found satisfactory, even with acids of considerable molecular weight. Occasionally, the reaction has been reported to be violently exothermic, particularly when large amounts of phosphorus and bromine were used.

A rather ingenious method for the  $\alpha$ -bromination of aliphatic monocarboxylic acids was described by Bagard.<sup>2</sup> It consists of the preparation of the acid chloride from the aliphatic acid and phosphorus trichloride and the subsequent addition of 1.25 molecular proportions of bromine to the acid chloride mixture. Thionyl chloride has been used by Ingold in place of phosphorus trichloride in preparing  $\alpha$ -mono- and  $\alpha,\alpha'$ -di-halogenated dicarboxylic acid.<sup>3</sup>

In general, the preparation of  $\alpha$ -monobromodicarboxylic acids is, however, difficult. They are prepared either by the addition of one mole of bromine to the dicarboxylic acid at elevated temperatures or to the corresponding acid chloride.<sup>3,4</sup> In certain cases,  $\alpha$ -monobromination has been secured by using the dicarboxylic acids in the form of their anhydrides. All these procedures, as well as their modifications, give, in addition to the desired  $\alpha$ -monobromo derivative, considerable amounts of the corresponding  $\alpha,\alpha'$ -dibromo acids which in most instances are difficult to remove completely from the monobrominated product.

In a recent patent,<sup>5</sup> a simplified method for the preparation of  $\alpha$ -monobromo derivatives of aliphatic dicarboxylic acids has been described. It consists of the addition of slightly more than one molecular proportion of bromine to the ester-acid chloride of a dibasic acid in the presence of catalytic amounts of red phosphorus. It is recommended that the reaction be conducted at 90–100°.

(1) Presented in abstract before the Division of Organic Chemistry at the Chicago Meeting of the American Chemical Society, April 19, 1948.

(2) Bagard, *Bull. chim. soc.*, [4] 1, 310 (1907).

(3) Ingold, *J. Chem. Soc.*, 119, 316 (1921), describes the mono- and dibromination of glutaric acid as follows: "A mixture of glutaric acid (200 g.) and thionyl chloride (280 cc.) was warmed until no more sulfur dioxide was generated. The product was heated at 60° before a naked arc light while dry bromine (87 cc. or 174 cc.) was added in six equal portions." It is not possible to ascertain from this description whether any thionyl chloride remains as solvent for the halogenation reaction. However, only a 50% yield of ethyl  $\alpha$ -bromoglutarate was obtained.

(4) Compare Baker, Querry, Bernstein, Safir and SubbaRow, *J. Org. Chem.*, 12, 169 (1947).

(5) British Patent 577,877; *C. A.*, 41, 2087 (1947). The principle of the patented method is mentioned without any experimental detail in *Nature*, 154, 459 (1944).

The  $\alpha$ -monobromo half-esters so formed are converted to the diesters; and, after purification by distillation, the latter may be converted to the corresponding  $\alpha$ -monobromo dicarboxylic acids by hydrolysis.

A method which appears as an advantageous modification of this procedure has been used in our laboratories for several years. It comprises the use of thionyl chloride not only as a reagent for forming the ester-acid chlorides, but also as a solvent for the subsequent halogenation reaction. In the presence of thionyl chloride, the use of red phosphorus has been found to be unnecessary. The halogenation of the ester-acid chlorides failed when ether was used as solvent. The reaction proceeds rapidly at reflux temperature, particularly in the presence of light. The half-ester of the dicarboxylic acid is added to an excess of thionyl chloride, the mixture refluxed for a short time; and, at reflux temperature, 1.05 moles of bromine is added. The bromine is usually rapidly consumed, and the reaction mixture then cautiously added to an excess of the desired alcohol to yield the  $\alpha$ -monobromo diesters. The reaction mixture may also be worked up by distilling off the excess thionyl chloride and adding the residue to the alcohol. The  $\alpha$ -monobromo diesters are obtained in excellent yields by fractional distillation. In this manner, it is also possible to prepare  $\alpha$ -monobromo mixed esters of dicarboxylic acids.

The procedure is also applicable for the  $\alpha$ -monochlorination of dicarboxylic acids. To a solution of acid chloride ester in thionyl chloride, there is added an excess of sulfuryl chloride.<sup>6</sup> After refluxing for a few hours, the thionyl chloride and excess sulfuryl chloride is distilled off. The residue is then added to the anhydrous alcohol and the  $\alpha$ -monochloro diester distilled.

TABLE I

$\alpha$ -Halogen ester	Yield <sup>a</sup> %	B. p., °C.	Mm.	Literature °C.	Mm.
Ethyl $\alpha$ -bromoglutarate <sup>b</sup>	92	122–124	2		
Ethyl $\alpha$ -bromoadipate	90	133–135	5	161–163	11 <sup>c</sup>
Ethyl $\alpha$ -bromosebacate <sup>d</sup>	88	170–172	2		
Ethyl $\alpha$ -bromocyclohexyl acetate <sup>e</sup>	98	96–98	1	131–135	15 <sup>f</sup>
Ethyl $\alpha$ -bromophenyl acetate	96	110–113	1.5	175	25 <sup>g</sup>
Ethyl $\alpha$ -chloroadipate	90	120–121	5	129–131	10 <sup>h</sup>
Ethyl $\alpha$ -chlorophenyl acetate	92	130–132	8	142	18 <sup>i</sup>

<sup>a</sup> The yields reported are for the distilled products. <sup>b</sup> Calcd. for C<sub>8</sub>H<sub>10</sub>O<sub>4</sub>Br: Br, 29.95. Found: Br, 29.62. <sup>c</sup> Ethyl hydrogen glutarate prepared as described by Bachmann, Kushner and Stevenson, *THIS JOURNAL*, 64, 977 (1942). <sup>d</sup> Ingold, *J. Chem. Soc.*, 119, 961 (1921). <sup>e</sup> Calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>4</sub>Br: Br, 23.41. Found: Br, 23.66. <sup>f</sup> Cyclohexylacetic acid obtained from Dow Chemical. <sup>g</sup> J. v. Braun, *Ber.*, 56, 2184 (1923); <sup>h</sup> Hill and Weinzly, *Ber.*, 28, 2446 (1895). <sup>i</sup> Ingold, *J. Chem. Soc.*, 119, 962 (1921). <sup>j</sup> Wheeler, *Am. Chem. J.*, 26, 352 (1901).

(6) Galat, *THIS JOURNAL*, 69, 86 (1947).

This halogenation procedure has also been used with monocarboxylic acids and has given practically quantitative yields of ethyl  $\alpha$ -bromocyclohexyl acetate, ethyl  $\alpha$ -bromophenyl acetate and ethyl  $\alpha$ -chlorophenyl acetate. Table I represents the data for several  $\alpha$ -bromo and  $\alpha$ -chloro acids which have been prepared.

### Experimental

The preparation of ethyl  $\alpha$ -bromoadipate will illustrate the procedure for  $\alpha$ -monobromination of dicarboxylic acids: In a 500-cc., round-bottom flask fitted with an adapter carrying a condenser protected by a calcium chloride tube and dropping funnel,<sup>7</sup> there was placed 174 g. (1.0 mole) of ethyl hydrogen adipate and 300 cc. of purified thionyl chloride.<sup>8</sup> The mixture was refluxed for approximately two hours and 168 g. (1.05 moles) of bromine added over a period of two to three hours. Gentle refluxing was maintained during the addition, and the mixture, after standing overnight, was poured cautiously into 500 cc. of commercial absolute ethyl alcohol. The resulting alcoholic solution was kept at room temperature for two to three hours, then poured into water and extracted with three 150-cc. portions of ether. The combined ether extracts were washed with water, dilute sodium bicarbonate solution and finally washed neutral with water. After drying over sodium sulfate, the ether was removed and the residue fractionated *in vacuo* in a 28-cm. Vigreux column.

The reaction mixture may be worked up by removing

(7) All glass apparatus was used for the reaction.

(8) Fieser, "Experiments in Organic Chemistry," D. C. Heath & Co., Boston, Mass., 1941, p. 381.

the excess thionyl chloride *in vacuo* following the bromination. The  $\alpha$ -bromoester-acid is then added slowly to 200 cc. of commercial absolute alcohol and the  $\alpha$ -bromo diester purified by distillation.

The monocarboxylic acids were brominated in essentially the same manner as described for ethyl  $\alpha$ -bromoadipate: A mixture of one mole of the acid in 200 cc. of thionyl chloride was refluxed for two hours and then 168 g. (1.05 moles) of bromine added. After completion of the reaction, the  $\alpha$ -bromo acid chloride was converted into the  $\alpha$ -bromo ester by either of the two methods outlined.

Ethyl  $\alpha$ -chloroadipate and ethyl  $\alpha$ -chlorophenyl acetate were prepared by the procedure described for the bromination except that 450 cc. of sulfuryl chloride was used in place of the bromine. It was found advantageous to remove both the thionyl chloride and excess sulfuryl chloride *in vacuo* prior to converting the  $\alpha$ -chloro acid chloride to the  $\alpha$ -chloro ester.

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### Summary

A method for the mono- $\alpha$ -bromination of dicarboxylic acids is described wherein excellent yields are obtained. The method has been applied to aryl and cycloalkyl acetic acids with good results. Under similar conditions,  $\alpha$ -chlorination of these acids also can be obtained in good yields with sulfuryl chloride.

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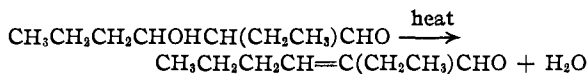
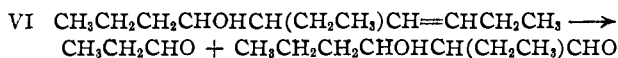
## Condensation of Butanal with 4-Heptanone and 3-Hexanone and Attempted Condensation of 2-Ethyl-2-hexenal with 4-Heptanone

BY S. G. POWELL AND ARNOLD T. NIELSEN<sup>1</sup>

This paper is concerned with three base-catalyzed aldehyde-ketone condensations. The first condensation between butanal and 4-heptanone gave a very low yield (3.6%) of a ketol, 5-ethyl-6-hydroxy-4-nonanone (I), in the presence of *N* alcoholic potassium hydroxide. Much of the 4-heptanone was recovered unreacted and as a result of a side reaction *n*-butyraldol and 2-ethyl-2-hexenal were formed in one run in yields of 26 and 47%, respectively. By heating I with iodine it readily dehydrated to form 5-ethyl-5-nonen-4-one (II), which on hydrogenation gave 5-ethyl-4-nonanone (III). Ketone III was also prepared from 5-ethyl-4-nonanol (IV), which was synthesized from 2-ethyl-1-hexanal and *n*-propylmagnesium bromide. The melting point of a mixture of the hydantoin derivatives formed from each of the two samples of ketone showed no depression.

In a second run, using a slightly different procedure, the unsaturated ketonic material isolated proved to be a mixture of II and 5-ethyl-6-nonen-4-one (V). Treatment of this mixture with an excess of sodium and alcohol reduced II to IV and

V to 5-ethyl-6-nonen-4-ol (VI). Ozonolysis of the mixture formed by reduction yielded 2-ethyl-2-hexenal, the latter resulting from the dehydration of *n*-butyraldol, a possible ozonolysis product of VI. The propionaldehyde was not isolated.



The amount of IV recovered and the yield of ozonide obtained indicate that the original mixture contained about one-third II. The formation of V was probably caused by excessive heating during fractional distillation.<sup>2</sup>

The second study pertains to the condensation of butanal with 3-hexanone. A survey of numerous aldehyde-ketone condensations reveals that in alkaline medium aldehydes condense on the  $\alpha$ -methylene group of methyl ketones ( $\text{CH}_3$ -

(2) Powell and Hagemann (THIS JOURNAL, 66, 372 (1944)) report such a mixture of  $\alpha,\beta$  and  $\beta,\gamma$  unsaturated ketones resulting from the condensation of isobutyraldehyde with 2-heptanone.

(1) From the Ph.D. thesis of Arnold T. Nielsen, June, 1947.