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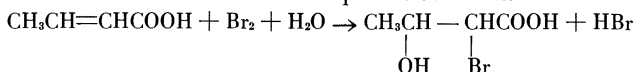
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## The Addition of Bromine to Crotonic Acid and to Ethyl Crotonate under Various Conditions

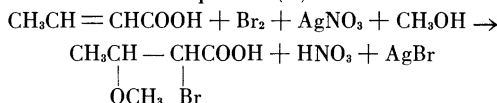
By ROBERT E. BUCKLES, ARNE LANGSJOEN, REX E. SELK,  
AND ROBERT J. COONS

Addition of bromine to ethyl crotonate in the absence of solvent has been reported (1) to give a high yield of ethyl  $\alpha, \beta$ -dibromobutyrate. This result was verified in the present work. Neither ethyl crotonate nor crotonic acid, however, gave a positive test with bromine in carbon tetrachloride at room temperature. In fact bromine could be added to sizable quantities of crotonic acid in a non-polar solvent in a relatively short time only by a method such as that already described for the addition of bromine to tiglic acid (2) in which the latter stages of the addition were forced by heat. The product of such a synthesis was the isomer of  $\alpha, \beta$ -dibromobutyric acid of m.p. 87-88°.

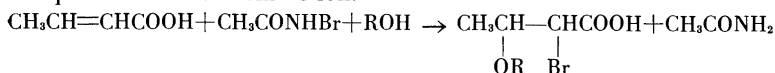
Addition of bromine to an olefinic compound in a hydroxylic solvent gives rise to the incorporation of the solvent in the reaction, so that, in effect, the elements of hypobromous acid or of a derivative thereof are added to the double bond. Excellent yields of  $\alpha$ -bromo- $\beta$ -hydroxybutyric acid have recently been reported (3) for the addition of bromine to crotonic acid in aqueous solution.



Often, however, substantial yields of the dibromide accompany such an addition reaction. The formation of dibromide can be suppressed by the removal of the bromide ion from the reaction mixture as fast as it is formed. The use of silver nitrate to remove bromide ion during the reaction of bromine with crotonic acid in methanol has been described (4), and a similar method using lead salts has been mentioned in a patent (5).

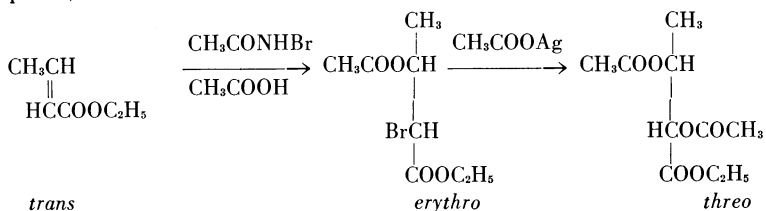


Also the same effect can be achieved by the use of a source of positive bromine other than molecular bromine, such as N-bromo-acetamide (6, 7, 8). In this case there is little bromide ion present so that the hydroxylic solvent can take part in the addition without the competition of the bromide ion.



In the present work several of these methods were investigated for the addition of positive bromine to crotonic acid and to ethyl crotonate in water, methanol and glacial acetic acid. The results are given in Table I. None of the methods was completely satisfactory in general. The esters prepared were contaminated with small amounts of the corresponding dibromides. No amount of careful fractional distillation would completely remove this impurity; therefore, none of these ester samples gave satisfactory analytical results. The identity of the bulk of each ester preparation was established by the hydrolysis of a sample to the corresponding acid.

The action of bromine and mercuric oxide in glacial acetic acid on ethyl crotonate gave rise to a product which was mostly ethyl  $\alpha, \beta$ -diacetoxybutyrate. Presumably mercuric acetate displaced the bromine in the expected product, ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate, as silver acetate was also observed to do. In fact in acetic acid containing small amounts of water a 60% yield of ethyl  $\alpha, \beta$ -diacetoxybutyrate was obtained from the reaction of silver acetate on ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate. This diacetoxy product was shown by saponification to contain the *threo* isomer. Under the conditions of reaction; *i.e.* in the presence of small amounts of water, the *threo* isomer would be expected (9) to be formed from the *erythro*-ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate by an inversion mechanism. This result is consistent with the fact that *erythro*-ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate would be formed from *trans*-ethyl crotonate by the usual, polar, *trans* addition.



A displacement reaction of silver acetate with ethyl  $\alpha, \beta$ -dibromobutyrate, which would be expected (9) to give results similar to those obtained with ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate, gave instead an impure, unsaturated product which contained bromine. Presumably elimination of the  $\alpha$ - or  $\beta$ -bromine as hydrogen bromide took place.

#### EXPERIMENTAL PART

*Ethyl Crotonate.*—A mixture of 430 g. (5 moles) of *trans*-crotonic acid (Shawinigan), 583 ml. of absolute ethanol, 20 ml. of concentrated sulfuric acid and 1 l. of benzene was boiled under reflux in

Table 1

Comparison of the Various Methods of preparation of the Derivatives of  $\alpha$ -Bromo- $\beta$ -hydroxybutyric Acid

$$\text{CH}_3\text{CH}=\text{CHCOOR} \xrightarrow[\text{R' OH}]{\text{Source of Br}} \text{CH}_3\underset{\text{OR}'}{\text{CH}}-\underset{\text{Br}}{\text{CHCOOR}}$$

R	R'	Source of Br	Yield %	m.p. <sup>1</sup>		B.p.	
				$[\alpha]_D$	$[\alpha]_C$	Pres., m.m.	
H	H	AcNHBr	48	85-87	....	....	
H	H	Br <sub>2</sub> + AgNO <sub>3</sub>	14	85-87	100-150	3	
H	H	HOBBr <sup>2</sup>	20	86-88	....	....	
H	Me	AcNHBr	54	53 <sup>3</sup>	120-130	11	
H	Me	Br <sub>2</sub> + AgNO <sub>3</sub> (4)	47	52-55	116-120	4	
H	Me	Br <sub>2</sub> + HgOAc <sup>4</sup>	66	....	120-150	6-10	
H	Ac	AcNHBr	....	....	decomp <sup>5</sup>	....	
Et	H	AcNHBr	46	....	76-78	6	
Et	H	Br <sub>2</sub> + AgNO <sub>3</sub>	34	....	110-115	20	
Et	H	Br <sub>2</sub> + HgO	42	....	103-106	12	
Et	Me	AcNHBr	72	....	93-95	18	
Et	Me	Br <sub>2</sub> + AgNO <sub>3</sub>	51	....	82-88	14	
Et	Me	Br <sub>2</sub> + HgO	30	....	94-96	17	
Et	Ac	AcNHBr	44	....	120-126	18	
Et	Ac	Br <sub>2</sub> + AgNO <sub>3</sub>	24	....	112-120	14	
Et	Ac	Br <sub>2</sub> + HgO	24	....	126-130 <sup>6</sup>	18	
Et	Ac	Br <sub>2</sub> + HgO <sup>7</sup>	47	....	117-120 <sup>8</sup>	18	
			23	....	125-130 <sup>9</sup>	18	

1. All m.p.'s corrected.

2. Direct addition of hypobromous acid as described in Reference (10).

3. Crystallization from chloroform-carbon tetrachloride gave m.p. 61-62°.

4. Addition of mercuric acetate in methanol followed by bromination as described in Reference (11).

5. The product could not be isolated in crystalline form. Distillation yielded volatile decomposition products and a tarry residue.

6. Mostly ethyl  $\alpha$ ,  $\beta$ -diacetoxybutyrate:  $n_D^{25}$  1.4310,  $d_4^{20}$  1.147.

7. Only 5 g. of HgO was used.

8. Mostly ethyl  $\alpha$ ,  $\beta$ -dibromobutyrate:  $n_D^{25}$  1.4800,  $d_4^{20}$  1.570.

9. Acetoxybromide contaminated by dibromide:  $n_D^{25}$  1.4680,  $d_4^{20}$  1.485.

a Soxhlet apparatus in which the thimble was filled to two-thirds of capacity with calcium carbide chips. The heating was continued until fresh calcium carbide no longer reacted with the condensate. The reaction mixture was washed with water, and the ester layer was removed. Ether extraction of the water layer gave an ether solution which was combined with the ester. The solution was washed with 10% sodium carbonate, dried over anhydrous potassium carbonate,

and distilled. A yield of 425 g. (75%) of ethyl crotonate, b.p. 134-138°, was obtained. The general method of esterification is that of Thielepape (12).

*N-Bromoacetamide*.—This material of m.p. 98° or higher was prepared by the bromination of acetamide in basic solution as previously described (13).

*Ethyl  $\alpha$ ,  $\beta$ -Dibromobutyrate*.—The reaction of 57 g. (0.50 mole) of ethyl crotonate with 80 g. (0.50 mole) of bromine as described by Carter and Ney (1) yielded 115 g. (84%) of ethyl  $\alpha$ ,  $\beta$ -dibromobutyrate, b.p. 110-112° (20 mm.).

*$\alpha$ ,  $\beta$ -Dibromobutyric Acid*.—To a solution of 160 g. (52 ml., 1.0 mole) of bromine in 200 ml. of carbon tetrachloride was added 86 g. (1.0 mole) of *trans*-crotonic acid in small portions. At first it was necessary to cool the solution after each addition. When all of the acid had been added the reaction mixture was allowed to stand until it was at room temperature. It was then boiled under reflux until the solution was light orange. The solution was treated with 500 ml. of ligroin (Skellysolve H). Cooling yielded 200 g. (81%) of  $\alpha$ ,  $\beta$ -dibromobutyric acid, m.p. 87-88°. This method is that used with tiglic acid (2) and is comparable to the method (14) using carbon disulfide as a solvent.

*Ethyl  $\alpha$ ,  $\beta$ -Diacetoxybutyrate*.—To 200 ml. of glacial acetic acid containing 0.5% water was added 5.5 ml. of freshly distilled acetic anhydride. The mixture was allowed to stand overnight, and 50.6 g. (0.20 mole) of ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate was added. Freshly made silver acetate (from 0.25 mole of silver nitrate), which had been washed with glacial acetic acid, but which still contained sizable amounts of water, was added a little at a time to the stirred, reaction mixture which was heated to 80°. After the addition was complete the reaction temperature was raised to 120-130° and maintained there for 24 hours. The reaction mixture was filtered, concentrated by distillation, and again filtered to remove silver acetate. Distillation yielded 32 g. (68%) of ethyl  $\alpha$ ,  $\beta$ -diacetoxybutyrate, b.p. 138-144° (21 mm.).

*Anal.* Calcd. for  $C_{10}H_{16}O_6$ : C, 51.7; H, 6.94. Found: C, 51.7; H, 6.89.

A similar experiment in which 3.6 g. of water was added instead of the acetic anhydride yielded 30.0 g. of an ester of nearly identical properties.

*Saponification of Ethyl  $\alpha$ ,  $\beta$ -Diacetoxybutyrate*.—A mixture of 30 g. (0.13 mole) of  $\alpha$ ,  $\beta$ -diacetoxybutyrate, 27 g. (0.47 mole) of potassium hydroxide and 200 ml. of 95% ethanol was boiled under

reflux for one hour. The solution was cooled and acidified exactly to the Congo red end point. Distillation at reduced pressure removed most of the solvent. Ether was added and the potassium chloride precipitate was removed by filtration. The ether was removed by distillation, and the residual material was dissolved in absolute ethanol. The ethanol solution was filtered, treated with 22.5 g. (0.21 mole) of phenylhydrazine at 70-75°, and cooled in an ice-water bath. The crude product was crystallized from absolute alcohol to yield 3.0 g. (10%) of the phenylhydrazine salt of *threo*- $\alpha$ ,  $\beta$ -dihydroxybutyric acid (15), m.p. 128-129°. This was shown to be the salt rather than the phenylhydrazide (16) by tests for the phenylhydrazinium ion (17). The  $\alpha$ ,  $\beta$ -dihydroxybutyric acid could not be obtained in the crystalline state from the saponification reaction.

The ethyl  $\alpha$ ,  $\beta$ -diacetoxybutyrate from the reaction mixture containing added water gave 3.1 g. (10%) of the hydrazine salt of *threo*- $\alpha$ ,  $\beta$ -dihydroxybutyric acid.

*Reaction of Ethyl  $\alpha$ ,  $\beta$ -Dibromobutyrate with Silver Acetate.*—The reaction of 27.4 g. (0.10 mole) of ethyl  $\alpha$ ,  $\beta$ -dibromobutyrate with a little more than 0.2 mole of freshly prepared silver acetate in anhydrous acetic acid was carried out for eight hours as described for this type of reaction by Winstein and Buckles (9). From the reaction mixture 14.0 g. (0.075 mole) of silver bromide was obtained by filtration after the unchanged silver acetate was dissolved in dilute nitric acid. The filtrate yielded 18.0 g. (0.125 mole) of silver chloride which represents the silver acetate, when treated with hydrochloric acid. These results indicate that the displacement or elimination of total available bromine was 38% complete. Distillation yielded 7.0 g. (35% based on ethyl bromocrotonate as the product) of a fraction of b.p. 83-90 (17 mm.),  $n_D^{25}$  1.4747, and 7.8 g. of a fraction of b.p. 90 (17.4 mm.)  $n_D^{25}$  1.4838. Both fractions behaved as mixtures. Tests with bromine in carbon tetrachloride were negative in both cases as well as the similar tests of ethyl crotonate and crotonic acid. Tests with potassium permanganate in acetone were positive in all of these cases. Ethyl  $\alpha$ ,  $\beta$ -dibromobutyrate gave negative tests to both reagents. Both fractions as well as ethyl  $\alpha$ ,  $\beta$ -dibromobutyrate gave precipitates within five minutes with cold alcoholic silver nitrate and gave brown solutions with sodium iodide in acetone.

*Additions with N-Bromoacetamide as the Source of Bromine.*—One-tenth mole of crotonic acid or ethyl crotonate was mixed with 13.8 g. (0.1 mole) of N-bromoacetamide in 60-75 ml. of water.

methanol or glacial acetic acid. When the ester was used in water or methanol a few drops of 6 *N* sulfuric acid was added to start the reaction. In the other cases the carboxylic acids present exerted sufficient catalytic activity. As the reaction started a mild evolution of heat was always observed. It was necessary to stir the two phase reaction mixture of ethyl crotonate in water in order to obtain satisfactory results. The reaction mixture was allowed to stand over night after the initial heat effect was observed. The solvent (except for water) was removed by distillation, and the residue was mixed with water. Extraction with ether yielded a solution from which the product was isolated. The results are listed in Table I.

*Additions with Bromine and Silver Nitrate as a Source of Bromine.*—A quarter of a mole of crotonic acid or ester in 30 ml. of solvent was added slowly to a stirred solution of 42.5 g. (0.25 mole) of silver nitrate in 250 ml. of the solvent. At the same time 40.0 g. (0.25 mole) of bromine was added dropwise to the reaction mixture. The silver bromide (virtually quantitative yield) was removed by filtration; a small amount of excess bromine was removed by sodium bisulfite, and the nitric acid was neutralized by sodium hydroxide. Most of the solvent was removed by distillation. The residue was acidified when acid products were expected. Ether extraction gave a solution from which the product was isolated by distillation or crystallization. The results of these addition reactions are given in Table 1. This type of addition has previously been described for the synthesis of  $\alpha$ -bromo- $\beta$ -methoxybutyric acid (4).

*Additions with Bromine and Mercuric Oxide as a Source of Bromine.*—A mixture of 14.0 g. (0.123 mole) of ethyl crotonate, 15 g. (0.069 mole) of red mercuric oxide and 100 ml. of solvent was stirred vigorously as 28 g. (0.175 mole) of bromine was slowly added. Stirring was continued one hour after the addition was completed. The solvent (except water) was partially removed by distillation. The residue was mixed with water and the mercuric bromide was removed by filtration. Isolation of the products was completed as described above. The results of these reactions are summarized in Table 1.

*Purification of the Derivatives of  $\alpha$ -Bromo- $\beta$ -hydroxybutyric Acid.*—The esters were carefully fractionated at reduced pressure and then refractionated in some cases in order to produce samples which were as pure as possible. Representative values of the indices of refraction and the specific gravities of these samples are recorded in Table 2. In all cases analyses of the samples for carbon and hydrogen showed the corresponding dibromide as a significant im-

Table 2  
Properties of Purified Esters

Ester	B.p.	$n_D^{25}$	$d_4^{20}$
Ethyl $\alpha, \beta$ -dibromobutyrate (1)	110-112 (20 mm.)	1.4941	1.680
Ethyl $\alpha$ -bromo- $\beta$ -hydroxybutyrate	76-78 ( 6 mm.)	1.4697	1.465
Ethyl $\alpha$ -bromo- $\beta$ -methoxybutyrate (18)	93-95 (18 mm.)	1.4518	1.345
Ethyl $\alpha$ -bromo- $\beta$ -acetoxybutyrate	120-126 (18 mm.)	1.4588	1.418
Ethyl $\alpha, \beta$ -diacetoxybutyrate	138-144 (21 mm.)	1.4268	1.110

purity except for the case of the reaction of ethyl crotonate with bromine and mercuric oxide in acetic acid. Analysis in this case showed the product to be mostly the diacetate.

The acids were crystallized from chloroform-carbon tetrachloride. This solvent pair proved to be quite superior to benzene-petroleum ether (3, 18) or ligroin-ether (10).

*Hydrolysis of Esters.*—Ethyl  $\alpha$ -bromo- $\beta$ -methoxybutyrate was saponified to  $\alpha$ -bromo- $\beta$ -methoxybutyric acid in cold sodium hydroxide solution as described by Wood, Madden and Carter (18).

A mixture of 5.00 g. of ethyl  $\alpha$ -bromo- $\beta$ -hydroxybutyrate in 50 ml. of 1 *N* sulfuric acid was boiled under reflux for eight hours. At the end of this time very little water-insoluble oil remained. The solution was made basic with sodium bicarbonate, washed with ether, and acidified to Congo red. The acid product was extracted into ether, and the ether solution was dried over anhydrous sodium sulfate. After removal of the ether by evaporation the residue was crystallized from chloroform-carbon tetrachloride. A yield of 3.10 g. (72%) of  $\alpha$ -bromo- $\beta$ -hydroxybutyric acid, m.p. 85-87°, was obtained. Similarly 5.00 g. of ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate yielded 2.65 g. (73%) of  $\alpha$ -bromo- $\beta$ -hydroxybutyric acid, and 1.0 g. of the crude  $\alpha$ -bromo- $\beta$ -acetoxybutyric acid yielded 0.51 g. (63%) of this acid.

#### SUMMARY

Various methods for the addition of bromine to crotonic acid and to ethyl crotonate—especially in the hydroxylic solvents, water, methanol, and acetic acid have been investigated. The yields even with *N*-bromoacetamide as a source of bromine were only fair at best, and purity was disappointingly low—especially in the case of the esters. In contrast, addition of bromine in the absence of hydroxylic solvents gave good yields of the corresponding pure dibromides.

The reaction of ethyl  $\alpha$ -bromo- $\beta$ -acetoxybutyrate with silver acetate in acetic acid gave ethyl  $\alpha, \beta$ -diacetoxybutyrate. Ethyl  $\alpha, \beta$ -



dibromobutyrate under similar conditions yielded a mixture of bromine-containing unsaturated esters.

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