

[CONTRIBUTION FROM THE INSTITUTE OF APPLIED CHEMISTRY, KYUSHU UNIVERSITY]

The Synthesis of  $\alpha$ -Alkoxy- $\beta$ -haloethyl Acetates and 2-Aminothiazole

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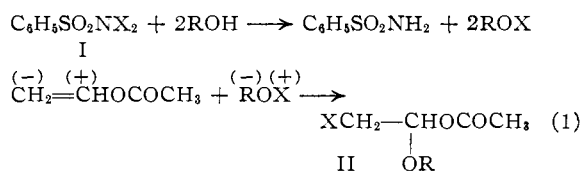
$\alpha$ -Alkoxy- $\beta$ -haloethyl acetates, not previously known, have been synthesized by three different methods. These new compounds react with thiourea to give 2-aminothiazole in good yield.

$\alpha$ -Alkoxy- $\beta$ -haloethyl acetates have been assumed to be intermediates in the synthesis of  $\beta$ -haloacetals from vinyl acetate,<sup>1</sup> but they have been neither isolated from the reaction mixture nor synthesized by other methods.

Our isolation of one of these compounds as an intermediate for bromoacetal made further investigation possible. This paper describes the synthesis of several  $\alpha$ -alkoxy- $\beta$ -haloethyl acetates along with a new synthesis of 2-aminothiazole starting from these materials.

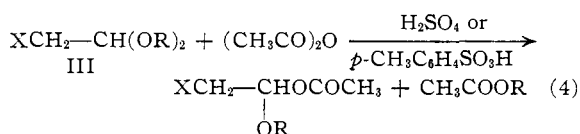
$\alpha$ -Ethoxy- $\beta$ -bromoethyl acetate can be separated from the reaction product of  $\alpha,\beta$ -dibromoethyl acetate with equimolar ethanol in the presence of calcium carbonate, or from the reaction product of the pyridine complex of halogenated vinyl acetate with equimolar ethanol. The yields, however, are poor (7–10%), and the compound is hard to purify owing to the presence of bromoacetal. Further investigation led to the preparation of this compound by the three following methods.

The first consists of the addition of alkyl hypohalites to vinyl acetate in the presence of *N,N*-dihalobenzenesulfonamides<sup>2,3</sup> as shown below.

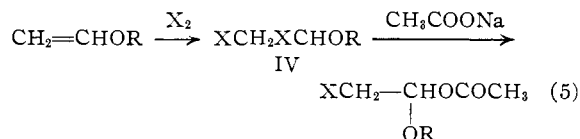


*N,N*-Dibromobenzenesulfonamide can be synthesized from benzenesulfonamide and hypobromic acid which is prepared by shaking bromine with an aqueous suspension of precipitated mercuric oxide.<sup>4</sup> We have succeeded in brominating benzenesulfonamide directly in sodium carbonate or bicarbonate solution; this method is less expensive and gives an almost quantitative yield of the pure product. The reaction seems to proceed in two steps,  $\text{C}_6\text{H}_5\text{SO}_2\text{NBrNa}$  first dissolving to give a yellow solution; then the second step occurs, and yellow dibromide precipitates out. *N,N*-Dichlorobenzenesulfonamide can be prepared by the same method.

The second method consists of the reaction of haloacetals (III) with acetic anhydride using sulfuric acid or *p*-toluenesulfonic acid as a catalyst.

(1) E. M. Filachione, *THIS JOURNAL*, **61**, 1705 (1939).(2) M. v. Lihosherstov and V. A. Sklyarov, *C. A.*, **32**, 4524 (1938).(3) A. A. Petrov, *ibid.*, **32**, 5370 (1938).(4) F. D. Chattaway, *J. Chem. Soc. Trans.*, **87**, 145 (1905).

The third method is the addition of halogen to vinyl ether, followed by reaction with sodium acetate.



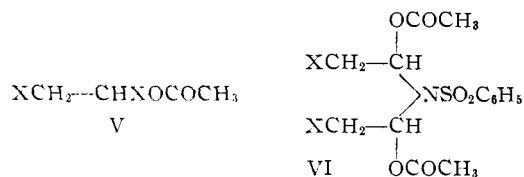
The yields, physical constants and analytical data of these compounds are given in Table I.

$\alpha$ -Alkoxy- $\beta$ -haloethyl acetates are powerful lachrymators, give resinous material upon reaction with magnesium or zinc, and are sensitive to heat. When distilled at atmospheric pressure, they decompose into  $\beta$ -halovinyl ethers and acetic acid.<sup>5</sup>

$\alpha,\beta$ -Dihaloethyl acetates (V),  $\alpha,\beta$ -dihaloethyl ethers (IV) and  $\beta$ -haloacetals (III) have been reported to react with thiourea to give 2-aminothiazole in yields of 50, 80 and 70%, respectively.<sup>6</sup> Similarly,  $\alpha$ -alkoxy- $\beta$ -haloethyl acetates (II) reacted with thiourea to give an almost quantitative yield of 2-aminothiazole of high purity.<sup>7</sup> For comparison, 2-aminothiazole was prepared from haloacetals and from halogenated vinyl acetates under similar conditions; the results are shown in Table II.

The halogen atom of  $\alpha$ -alkoxy- $\beta$ -haloethyl acetate is more reactive than that of  $\beta$ -haloacetal, as shown in their condensation with thiourea. The former reacts instantaneously at 50°; the latter requires more than a half hour at 80°.

Since the addition products of *N,N*-dihalobenzenesulfonamides and vinyl acetate are easily decomposed by acid, they can also be used as starting material for 2-aminothiazole, but the yield is poor (about 10%) and a large amount of resinous material is obtained.



The chloro derivative of adduct VI, when hydrolyzed by dilute hydrochloric acid, and allowed to react with thiourea gave a colorless substance melting at 155°. As the product is soluble in acid and can be reprecipitated with alkali, it seems to be

(5) From the bromo derivative, about 25% of  $\beta$ -bromovinyl ether was obtained, b.p. 135–139°,  $n_D^{20}$  1.4729,  $d_4^{20}$  1.4139.(6) A. E. Favorskii and M. N. Shchukina, *C. A.*, **40**, 4347 (1946).

(7) The procedure is described by L. H. Wiley, D. C. England and L. C. Behr, "Organic Reaction," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., p. 379.

(8) From 20 g. of vinyl acetate, 26.7 g. of  $\text{C}_6\text{H}_5\text{SO}_2\text{NCl}_2$  and 18 g. of thiourea, 15 g. of this compound was obtained.

TABLE I

X	R	$n_D^{20}$	$d_4^{17}$	B.p. (2 mm.) °C.	Yield, %			Carbon, %		Hydrogen, %	
					1	2	3	Calcd.	Found	Calcd.	Found
Cl	Me	1.4277	1.176	37-38	48	82	..	39.36	39.42	5.94	5.88
Cl	Et	1.4237	1.125	43-44	42	80	40	43.25	43.31	6.66	6.78
Br	Me	1.4472	1.437	45-46	86	81	..	30.48	30.21	4.59	4.59
Br	Et	1.4420	1.309	53-54	83	78	40	34.14	34.08	5.25	5.31

<sup>a</sup>1, From vinyl acetate; 2, from haloacetal; 3, from vinyl ether.

TABLE II

Reactants	Yield of 2-aminothiazole, %
$\begin{array}{l} \text{ClCH}_2-\text{CH} \\ \begin{array}{l} \diagup \text{OCOCH}_3 \\ \diagdown \text{OCH}_3 \end{array} \end{array}$	93-95
$\begin{array}{l} \text{ClCH}_2-\text{CH} \\ \begin{array}{l} \diagup \text{OCOCH}_3 \\ \diagdown \text{OC}_2\text{H}_5 \end{array} \end{array}$	93-95
$\begin{array}{l} \text{BrCH}_2-\text{CH} \\ \begin{array}{l} \diagup \text{OCOCH}_3 \\ \diagdown \text{OCH}_3 \end{array} \end{array}$	88-92
$\begin{array}{l} \text{BrCH}_2-\text{CH} \\ \begin{array}{l} \diagup \text{OCOCH}_3 \\ \diagdown \text{OC}_2\text{H}_5 \end{array} \end{array}$	85-90
$\text{ClCH}_2-\text{CH}(\text{OCH}_3)_2$	75-80
$\text{ClCH}_2-\text{CH}(\text{OC}_2\text{H}_5)_2$	75-80
$\text{BrCH}_2-\text{CH}(\text{OCH}_3)_2$	75
$\text{BrCH}_2-\text{CH}(\text{OC}_2\text{H}_5)_2$	75
$\text{ICH}_2-\text{CH}(\text{OC}_2\text{H}_5)_2$	70
$\text{ClCH}_2-\text{CHClOCOCH}_3$	45-50
$\text{BrCH}_2-\text{CHBrOCOCH}_3$	40

an amino compound; benzenesulfonamide is not involved since it can be almost completely recovered from the reaction mixture.

### Experimental

**N,N-Dibromobenzenesulfonamide.**—In a 2-liter three-necked flask were placed 125 g. of benzenesulfonamide, 90 g. of sodium carbonate (or 160 g. of sodium bicarbonate) and 600 ml. of water; then 255 g. of bromine was added with vigorous stirring. The resulting precipitate of N,N-dibromobenzenesulfonamide was filtered, washed with water, and dried. The yield was 245 g. (98%), m.p. 115° (dec.).

**N,N-Dichlorobenzenesulfonamide.**—Chlorine gas was passed into a mixture of 50 g. of benzenesulfonamide, 40 g. of sodium carbonate and 250 ml. of water in a 1-liter three-necked flask. The yield was 72 g. (100%).

### $\alpha$ -Alkoxy- $\beta$ -haloethyl Acetate (II) from Vinyl Acetate.—

In a three-necked flask fitted with a mechanical stirrer and a dropping funnel 50 ml. of carbon tetrachloride was placed and cooled to  $-10^\circ$  (when X = Cl, the temperature was kept at  $15-20^\circ$ ); 0.12 mole of dihalobenzenesulfonamide (I) and 0.34 mole of alcohol were added; then 0.23 mole of vinyl acetate was added dropwise with stirring. The stirring was continued for another hour after the addition of vinyl acetate. If any benzenesulfonamide precipitated, it was filtered off and washed with 20 ml. of carbon tetrachloride. The combined filtrate was washed with water saturated with calcium chloride to remove excess alcohol, and dried over calcium chloride. Then the carbon tetrachloride was distilled off under slightly reduced pressure, and the residue fractionated *in vacuo*. The results are shown in Table I.

**$\alpha$ -Alkoxy- $\beta$ -haloethyl Acetate (II) from Haloacetal.**—A mixture of 0.15 mole of haloacetal, 40 g. (0.39 mole) of acetic anhydride and a drop of concentrated sulfuric acid was allowed to stand at room temperature for one day. Then the mixture was poured onto ice and extracted with carbon tetrachloride. The organic layer was washed with ice-cold dilute sodium bicarbonate solution, dried over calcium chloride, and then worked up as outlined above. The results are also shown in Table I.

**$\alpha$ -Alkoxy- $\beta$ -haloethyl Acetate (II) from Vinyl Ether.**—A solution of 15 g. of vinyl ethyl ether in 30 ml. of carbon disulfide was cooled to  $-5^\circ$ , and then brominated with 30 g. of bromine. Carbon disulfide was removed under reduced pressure, and 15 g. of sodium acetate and 50 ml. of acetic acid were added to the residue. Then the mixture was warmed on the water-bath for an hour, allowed to stand for a day, filtered and distilled *in vacuo*. The yields are given in Table I.

**2-Aminothiazole.**—When a mixture of 13 g. of  $\beta$ -chloro- $\alpha$ -methoxyethyl acetate, 7 g. of thiourea and 14 ml. of water was stirred and warmed to  $40^\circ$ , the reaction started immediately. The temperature was allowed to rise to  $60^\circ$ . After the mixture became homogeneous, it was kept at  $50^\circ$  for half an hour. The flask was then cooled in an ice-bath and the reaction mixture neutralized with ice-cold 40% sodium hydroxide solution; white crystals of 2-aminothiazole separated. The crude product (m.p.  $86-88^\circ$ ) upon recrystallization from alcohol melted at  $89^\circ$ . A mixed m.p. determination with a sample obtained from bromoacetal gave no depression. The results of similar reactions with various  $\alpha$ -alkoxy- $\beta$ -haloethyl acetates,  $\beta$ -haloacetals and  $\alpha,\beta$ -dihaloethyl acetates are shown in Table II.

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