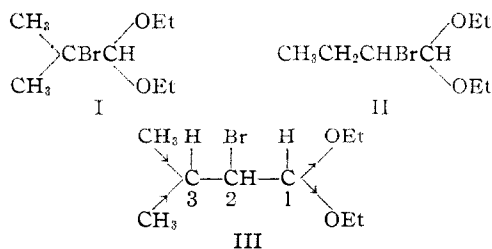


[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

**Ketene Acetals. X. The Elimination of Hydrogen Bromide from the Acetals of  $\alpha$ -Bromoaldehydes. Isopropyl- and *n*-Propylketene Diethylacetal**BY S. M. McELVAIN, ROBERT L. CLARKE<sup>1</sup> AND GIFFIN D. JONES

The preparation of ketene diethylacetal by the elimination of a molecule of halogen acid from the iodo- or bromo-acetal<sup>2</sup> raised the question as to the applicability of this reaction to the  $\alpha$ -bromoacetals of the higher homologs of acetaldehyde. From a purely statistical consideration, such an acetal as  $\alpha$ -bromoisobutyraldehyde acetal (I) with six  $\beta$ -hydrogens would seem much more likely to lose hydrogen bromide between the  $\alpha$ - and one of the  $\beta$ -carbon atoms and yield the acetal of the unsaturated aldehyde. Similarly, the acetal of  $\alpha$ -bromo-*n*-butyraldehyde (II) contains two  $\beta$ -hydrogens to compete with the single hydrogen of the acetal carbon atom. In the case of the acetal of  $\alpha$ -bromoisovaleraldehyde (III), however, the single hydrogen in the  $\beta$ -position would indicate an even statistical chance that some of the ketene acetal as well as the unsaturated acetal would be formed. A consideration of the electronic nature of the groups of III would seem to lead more surely to the prediction that the ketene acetal rather than the unsaturated aldehyde acetal would be produced by the elimination of hydrogen bromide. If the mechanism of the elimination reaction involves, as is generally believed, first the removal of a proton<sup>3</sup> from the molecule by the base, followed by the emission of the bromide ion, then the inductive effects of the groups attached to carbons 1 and 3 of III should make the hydrogen on carbon 1 much more labile and consequently more likely to be removed with the bromine than the hydrogen on carbon 3.



As a matter of fact, each of the bromo-acetals, I, II and III is converted by both sodium ethoxide

(1) Wisconsin Alumni Foundation Research Scholar and Research Assistant, 1940-1942.

(2) (a) Beyerstedt and McElvain, *THIS JOURNAL*, **58**, 529 (1936); (b) Johnson, Barnes and McElvain, *ibid.*, **62**, 968 (1940).

(3) Hauser, *THIS JOURNAL*, **62**, 933 (1940); Drake and McElvain, *ibid.*, **56**, 697 (1934).

in alcohol and potassium *t*-butoxide in *t*-butyl alcohol into the corresponding unsaturated acetals. There is no indication that a ketene acetal is produced in any of these reactions. An explanation of these results led to a consideration of (a) the validity of the proton-removal mechanism of the elimination reaction, (b) the possibility that the ketene acetal really was initially formed from III and then rearranged under the reaction conditions into the acetal of the  $\alpha,\beta$ -unsaturated aldehyde.

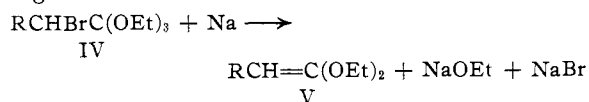
Relative to the mechanism of the elimination reaction, Hughes, Ingold, Masterman and McNulty<sup>4</sup> in a recent paper have pointed out that there are two mechanisms by which hydrogen bromide may be eliminated from such a compound as III. The first of these involves the emission (or ionization) of the bromide ion from the molecule as the rate controlling step which is then followed by the rapid loss of a proton. Such a mechanism requires that the elimination be a first order reaction. The other alternative is the generally accepted proton-removal mechanism which postulates that the rate controlling step is the removal of a proton by the base followed by the rapid emission of the bromide ion. This mechanism requires that the reaction be second order. A third possibility that might be considered involves the intermediate formation of a  $\beta$ -alkoxy acetal with the subsequent loss of an alcohol molecule to form the unsaturated aldehyde acetal. It would be predicted that the *t*-butoxide ion should, due to steric effects, react more slowly than the ethoxide ion to form this intermediate were this the correct mechanism. This mechanism also requires that the reaction be second order unless the loss of the alcohol molecule be the controlling step.

In the hope of gaining some information as to which of these mechanisms is followed in the process of elimination of hydrogen bromide from III, three series of reaction rate determinations between this bromo-acetal and 0.75 *N* and 2.0 *N* sodium ethoxide in absolute alcohol and 0.75 *N* potassium *t*-butoxide in *t*-butyl alcohol were

(4) Hughes, Ingold, Masterman and McNulty, *J. Chem. Soc.*, 899 (1940).

carried out. Plots of the reciprocal of the concentration against time are shown in Fig. 1. It is seen that these curves approximate the straight lines characteristic of a second order reaction in each case. It may also be seen from these plots that potassium *t*-butoxide causes a more rapid elimination of hydrogen bromide from III than does sodium ethoxide, a fact which eliminates the third possible reaction mechanism mentioned above. These facts lead to the rather contradictory conclusions that the elimination of hydrogen bromide from III follows the proton-removal mechanism and that the least labile proton is removed, unless it be that the proton of carbon 1 of III is really removed and the resulting ketene acetal, by a prototropic change, rearranges into the acetal of the unsaturated aldehyde which actually was isolated from the reaction.

In order to test this latter possibility it was necessary to prepare the ketene acetal in question. Both the isopropyl- and *n*-propylketene diethylacetals (V, R is isopropyl and *n*-propyl) were prepared by the action of sodium on the corresponding  $\alpha$ -bromo-orthoesters,<sup>5</sup> thus



Both of these ketene acetals add water readily to give the corresponding esters and show no tendency to rearrange into the unsaturated acetals when refluxed in a *t*-butyl alcohol solution of potassium *t*-butoxide. In these respects their behavior is similar to that of methylketene diethyl acetal.<sup>5,6</sup>

It is seen from the results outlined above that the hydrogen on carbon 3 rather than the one on carbon 1 of  $\alpha$ -bromoisovaleraldehyde acetal (III) is the more active and that electronic factors other than simple inductive effects are operative in the basic elimination of hydrogen bromide from this acetal. In this connection it might be noted that a halogen on a carbon carrying an ethoxyl group, *i. e.*, an  $\alpha$ -chloro-ether, is very reactive, presumably on account of an electromeric polarization,  $\text{EtO} \overset{\curvearrowright}{\text{C}} \text{---} \overset{\curvearrowleft}{\text{C}} \text{---} \text{Cl}$ , that facilitates the removal of the chloride ion. If the ethoxy group is thus able to facilitate the removal of an anion from a carbon to which it is attached, it would seem reasonable to believe that it would impede the separation of a

(5) Walters and McElvain, *THIS JOURNAL*, **62**, 1482 (1940).

(6) Rothstein, *J. Chem. Soc.*, 1558 (1940).

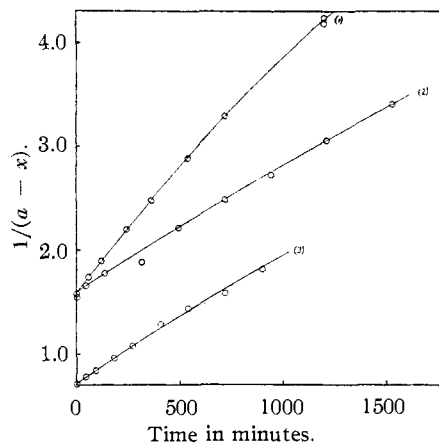


Fig. 1.—(1) 0.760 N KOBu (*t*); (2) 0.771 N NaOEt; (3) 2.040 N NaOEt.

positive proton. That is to say, the failure of the acetal (III) to lose hydrogen bromide between carbons 1 and 2 is another case of the more potent electromeric (E) effect of an alkoxy group overshadowing an inductive (I) effect of opposite direction.<sup>7</sup> It must be admitted, however, that an illustration of the electromeric hindrance of the ethoxy groups of III to the loss of a proton from carbon 1 is difficult to imagine without some increase in this carbon's octet of electrons.

The authors wish to acknowledge their indebtedness to Professor Farrington Daniels for suggestions relative to the kinetic studies reported in this paper.

### Experimental

**Acetals.**—The diethyl acetals of isobutyraldehyde, *n*-butyraldehyde and isovaleraldehyde were prepared by the Tschitschibabin reaction from ethyl orthoformate and the appropriate Grignard reagent according to the procedure for the preparation of the acetal of hexaldehyde.<sup>8</sup> The following modifications were found to give considerable improvements in yield. After the addition of the ethyl orthoformate and a refluxing period of sixteen hours, crushed ice was added to decompose the excess of Grignard reagent. The ether layer was decanted and washed with water. The aqueous layer was covered with ether, cooled and treated slowly and with stirring with a 10% solution of acetic acid that contained 80% of the acetic acid required for the neutralization of the basic magnesium bromide produced in the reaction. Since all of the solids did not dissolve, the supernatant liquids were decanted, the ether layer separated, washed with water and a 10% sodium carbonate solution. The aqueous layer was extracted twice with ether and, after washing, the ether layers were combined, dried over potassium carbonate and fraction-

(7) Cf. the dissociation constants of benzoic acid with those of the *m*- and *p*-methoxybenzoic acids, Watson, "Modern Theories of Organic Chemistry," Oxford Press, New York, N. Y., 1937, p. 36.

(8) "Organic Syntheses," **16**, 41 (1936).

ated. Using these modifications of procedure and two-mole quantities of reactants isobutyraldehyde diethylacetal, b. p. 133-136°, *n*-butyraldehyde diethylacetal, b. p. 143-144°, and isovaleraldehyde diethylacetal, b. p. 156-158°, were obtained in yields of 83, 80 and 90% of the theoretical, respectively.

**$\alpha$ -Bromo-acetals.**—The three acetals mentioned above were brominated by the procedure of Hartung and Adkins.<sup>9</sup> The yields of  $\alpha$ -bromoisobutyraldehyde diethylacetal, b. p. 63-64° (7 mm.),  $\alpha$ -bromo-*n*-butyraldehyde diethylacetal, b. p. 82-84° (12 mm.), and  $\alpha$ -bromoisovaleraldehyde diethylacetal, b. p. 87-88° (14 mm.), were 36, 20 and 40% of the theoretical, respectively.

Since the  $\alpha$ -bromoisovaleraldehyde acetal was to be used for kinetic studies it was further purified, particularly since it was found that the product obtained from the bromination reaction gave low ethoxyl values as well as about 8% immediate reaction with an alcoholic solution of sodium ethoxide. In an attempt to hydrolyze the bromo-acetal to the corresponding bromo-aldehyde, it was accidentally discovered that the unchanged bromo-acetal recovered from the incomplete hydrolysis showed the correct ethoxyl content and gave a quite low (2%) zero-time reaction with sodium ethoxide. Apparently the lower boiling bromo-aldehyde had carried with it, as an azeotropic mixture, the unknown contaminants of the bromo-acetal leaving the unhydrolyzed acetal quite pure. Since as high a purity as possible for the acetal was desired, the following rather wasteful purification procedure was adopted: a mixture of 25 g. of the bromo-acetal from the bromination reaction and 7 ml. of dilute (1:10) sulfuric acid was heated on a steam-bath with occasional shaking for ten minutes. Then 10 ml. of ether was added, the layers separated and the ether layer washed with 7 ml. of a 10% potassium carbonate solution. After drying over anhydrous potassium carbonate, the ether layer was fractionated. After removal of the ether and the lower boiling fractions, 12 g. of  $\alpha$ -bromoisovaleraldehyde diethyl acetal, b. p. 55-56° (3 mm.), or 92-95° (14 mm.);  $n_D^{20}$  1.4438;  $d_4^{20}$  1.163 was obtained.

*Anal.* Calcd. for  $C_9H_{19}O_2Br$ :  $C_2H_5O$ , 37.7; Br, 33.5. Found:  $C_2H_5O$ , 37.5; Br, 33.2.

$\alpha$ -Bromoisovaleraldehyde diethylacetal has been prepared by Fischer, Ertel and Löwenberg,<sup>10</sup> who reported it to have the following properties: b. p. 88-89° (13 mm.);  $n_D^{20}$  1.4489;  $d_4^{20}$  1.177.

**Preparation of Isobutenal-, *n*-Butenal- and Isopentenaldiethylacetal.**—Each of these unsaturated acetals was obtained when the corresponding bromo-acetal was heated with an equivalent amount of 1.4 *N* potassium *t*-butoxide in *t*-butyl alcohol solution in the manner described<sup>21</sup> for the preparation of ketene acetal from bromo-acetal. When the reactions were carried out in 0.2-mole quantities the yields of the isobutenal acetal,<sup>11</sup> b. p. 136-137°, *n*-butenal acetal,<sup>12</sup> b. p. 48-49° (21 mm.), and isopentenal acetal,<sup>9,10</sup> b. p. 59-60° (16 mm.), were 64, 41 and 62% of the theoretical, respectively.

(9) Hartung and Adkins, *THIS JOURNAL*, **49**, 2520 (1927).

(10) Fischer, Ertel and Löwenberg, *Ber.*, **64**, 30 (1931).

(11) Kinney and Adams, *THIS JOURNAL*, **59**, 897 (1937).

(12) Wohl and Frank, *Ber.*, **35**, 1904 (1902); Düvel, *Ann.*, **410**, 69 (1915).

None of these unsaturated acetals showed the warming characteristic of a ketene acetal when treated with water containing a trace of hydrochloric acid. The isobutenal acetal yielded a resinous solid when hydrolyzed, but the *n*-butenal acetal and isopentenal acetal gave the corresponding unsaturated aldehydes which were identified as the known semicarbazones.

**Rate of Reaction of  $\alpha$ -Bromoisovaleraldehyde Diethyl Acetal with Alkali Alkoxides.**—The determination of the reaction rates between the bromoacetal and sodium ethoxide was attempted at 55°, but the rate was so low (11% reaction in thirteen hours) at this temperature that 80° was used as the reaction temperature. Determinations were made with 0.771 *N* and with 2.040 *N* sodium ethoxide in absolute ethyl alcohol and 0.760 *N* potassium *t*-butoxide in *t*-butyl alcohol.

The alkali solutions were prepared by dissolving the metal in the alcohol and titrating the resulting solutions against standard hydrochloric acid solution.

For each rate determination a series of 10 reaction tubes 7 cm. in length and 1.5 cm. in diameter and constricted at the open end for sealing, was prepared from Pyrex test-tubes. Approximately a 0.5-g. sample of the bromo-acetal was accurately weighed into each of these reaction tubes. Then the volume of the alcoholic alkali solution containing alkoxide equivalent to the bromo-acetal in each tube was rapidly calculated and added to the reaction tube from a buret. Each tube was sealed and immersed in an ice-bath immediately after the addition of the alkali.

At zero time all of the tubes except nos. 1 and 10 (in order of filling) were placed in a constant temperature bath at  $80 \pm 2^\circ$ . Tubes 1 and 10 were then opened in bottles containing 50 ml. of water and 25 ml. of ether. After thorough mixing 1.5 ml. of concentrated nitric acid was added to the mixture, and the bromide ion determined by adding an excess of standard silver nitrate solution and back titrating with potassium thiocyanate. The apparent per cent. reaction at zero time thus obtained was subtracted from the per cent. reaction at each subsequent time interval. The concentration of the reactants at zero time was calculated by multiplying the original concentration in moles per liter after mixing by the per cent. reaction at zero time and subtracting this value from the original concentration.

Plots against time of  $1/(a - x)$ , in which  $a$  represents the original concentration of the reactants in moles per liter and  $x$  represents the moles reacted in time  $t$ , are shown in Fig. 1.

**Isovaleronitrile.**—In a distilling flask of such size that the reactants occupied not more than 0.4 of the volume of the flask were placed 190 g. (1.88 moles) of isovaleramide<sup>13</sup> (which had been dried at 110°) and 230 g. (1.62 moles) of phosphorus pentoxide. The two solids were mixed very thoroughly by shaking and the flask was connected to a condenser for distillation. The solid mixture was heated slowly in an oil-bath to 90° and allowed to stand at this temperature overnight. The bath temperature was then raised to 130° and held there for two hours. The product was then distilled under reduced pressure (200 mm.). The resulting distillate was redistilled from 5 g. of phosphorus pentoxide. A yield of 125 g. (80% of the theoretical) of the isovaleronitrile, b. p. 127-129°,<sup>14</sup> was obtained.

(13) Mailhe, *Bull. soc. chim.*, **37**, 1394 (1925).

(14) Cf. Timmermans and Delacourt, *J. chim. phys.*, **31**, 85 (1934).

**Ethyl Ortho- $\alpha$ -bromoisovalerate.**—This ester was prepared from ethyl orthoisovalerate<sup>15</sup> by the following procedure. A mixture of 33 g. (0.162 mole) of ethyl orthoisovalerate and 13 g. (0.164 mole) of pyridine was introduced into a three neck flask fitted with a stirrer, condenser and dropping funnel. To this mixture was added 26 g. (0.162 mole) of bromine over a period of one hour, after which time the mixture was stirred overnight. Approximately 50 ml. of dry ether was then added and, after mixing and allowing the precipitate to settle, the ether solution was decanted. The solid remaining in the flask was washed by decantation with three 30-ml. portions of dry ether and the combined washings washed once with 25 ml. of 10% potassium carbonate. The ether solution was dried over anhydrous potassium carbonate and after the ether was removed, the product was distilled under reduced pressure. It boiled at 63–64° (1.3 mm.);  $n^{25}_D$  1.4408;  $d^{25}_4$  1.150. The yield amounted to 31 g. (67% of the theoretical). Although this ester possessed a very constant boiling point it showed an unexpectedly high bromine content and low ethoxyl values. The carbon and hydrogen analyses were fairly good.

*Anal.* Calcd. for  $C_{11}H_{23}O_3Br$ :  $C_2H_5O$ , 47.7; Br, 28.2; C, 46.65; H, 8.19. Found:  $C_2H_5O$ , 45.9; Br, 32.0; C, 46.33; H, 7.86.

**Ethyl Ortho- $\alpha$ -bromovalerate.**—This compound was prepared from ethyl orthovalerate<sup>15</sup> by the procedure described above for the preparation of ethyl ortho- $\alpha$ -bromoisovalerate. The yield amounted to 80% of the theoretical and the product boiled at 69–70° (2 mm.);  $n^{25}_D$  1.4390.

*Anal.* Calcd. for  $C_{11}H_{23}O_3Br$ :  $C_2H_5O$ , 47.7. Found:  $C_2H_5O$ , 47.4.

**Isopropylketene Diethylacetal.**—This ketene acetal was prepared from ethyl ortho- $\alpha$ -bromoisovalerate and sodium by the procedure of Walters and McElvain.<sup>5</sup> It boiled at 96–97° (100 mm.) or 156–157° (745 mm.);  $n^{25}_D$  1.4158;  $d^{25}_4$  0.8385. The yield from 25.4 g. of the bromo-ortho-ester was 9.4 g. (65%).

*Anal.* Calcd. for  $C_9H_{18}O_2$ : C, 68.31; H, 11.46;  $C_2H_5O$ , 56.96. Found: C, 68.33; H, 11.64;  $C_2H_5O$ , 54.59.

A 1.7-g. sample of isopropylketene diethylacetal was treated with the theoretical amount of water containing a trace of hydrochloric acid. The reaction mixture under-

went almost spontaneous reaction, the temperature rose rapidly to 60–65° and the ketene acetal was converted quantitatively into ethyl isovalerate. The reaction mixture was dried over anhydrous potassium carbonate and distilled under atmospheric pressure. The ethyl isovalerate thus obtained boiled at 134°;  $n^{25}_D$  1.3947; sap. equiv., 128 (calcd. 130); m. p. of the toluide of the acid, 107°.

***n*-Propylketene Diethylacetal.**—This ketene acetal was prepared as was the isopropylketene diethylacetal. The yield of product boiling at 107–108° (100 mm.) or 167–168° (737 mm.);  $n^{25}_D$  1.4204;  $d^{25}_4$  0.850, amounted to 71% of the theoretical.

*Anal.* Calcd. for  $C_9H_{18}O_2$ : C, 68.31; H, 11.46;  $C_2H_5O$ , 56.96. Found: C, 67.89; H, 11.37;  $C_2H_5O$ , 54.58.

A 1.8-g. sample of *n*-propylketene diethylacetal was treated with the theoretical amount of water and converted quantitatively to ethyl valerate. This reaction was strongly exothermic as was the case with the isopropylketene diethylacetal. The ester so obtained boiled at 144°;  $n^{25}_D$  1.3991; sap. equiv., 133 (calcd. 130); m. p. of the toluide of the acid, 69.5°.

Each of the above described ketene acetals was recovered unchanged when it was refluxed in a 1.4 *N* solution of potassium *t*-butoxide in *t*-butyl alcohol for three hours.

### Summary

The acetals of  $\alpha$ -bromoisobutyraldehyde,  $\alpha$ -bromo-*n*-butyraldehyde and  $\alpha$ -bromoisovaleraldehyde are converted by potassium *t*-butoxide in *t*-butyl alcohol into the corresponding unsaturated acetals rather than into the ketene acetals.

The reactions between  $\alpha$ -bromoisovaleraldehyde diethylacetal and both sodium ethoxide and potassium *t*-butoxide are shown to be second order and the implications of this fact are discussed.

Isopropylketene diethylacetal and *n*-propylketene diethylacetal have been prepared from the corresponding  $\alpha$ -bromo-orthoesters and show no tendency to rearrange into unsaturated aldehyde acetals.

(15) McElvain and Nelson, *THIS JOURNAL*, **64**, 1825 (1942).