Reduction of Aliphatic α -Hydroxycarbonyl Compounds

Part II. α -Hydroxyisobutyraldehyde

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α -Hydroxyisobutyraldehyde, one of model compounds for α -aldol structure of streptose moiety of streptomycin, was reduced at controlled-potential mercury cathode to give isobutyl alcohol and 1,1-dimethylethyleneglycol. Reduction ratio of α -hydroxyl group was dependent on the cathode potential and pH, as was seen in the reduction of streptomycin. Results of reduction of α -hydroxyisobutyraldehyde with sodium or aluminum amalgam suggests that their mode of action on the aldehyde is determined by the magnitudes of negative potential that they respectively retain in the reaction media, and by pH, as in the cases of electroreduction. Isobutyraldehyde was isolated as an intermediate product of reduction to isobutyl alcohol, in both cases.

Controlled-potential electroreduction of streptomycin was reported in the preceding paper¹⁾, in which the effect of cathode potential and pH upon the reduction mode of α -aldol moiety was clarified. At cathode potential slightly more negative than the polaro-

graphic half-wave potential of streptomycin the reduction gave dihydrodesoxystreptomycin as dominant product, whereas at more negative cathode potential the yield of dihydrostreptomycin, another reduction product, increased at the expense of that of dihydrodesoxystrepto-

1) K. Tsuji, *This Journal*, **25**, 432 (1961).

mycin. In either case the formation of dihydrodesoxy derivative was favored by higher hydrogen ion concentration in the media. It was pointed out that, in this case, the action of sodium²⁾ or aluminum³⁾ amalgam was not different from that of mercury cathode maintained at the same negative potential as that of the amalgam.

In this study α -hydroxyisobutyraldehyde was chosen as one of the model compounds because it represents the aldol moiety of streptose with tertiary hydroxyl group. This compound is known to behave in alkaline media in a similar manner to that of alkaline decomposition of streptomycin⁴⁾. Formation of isobutyl alcohol by reduction of this compound has been hitherto unknown.

Polarography of this compound showed that reduction waves of α -hydroxyisobutyraldehyde appear only in alkaline media or in concentrated calcium chloride solution. In view of the common structure between this aldehyde and streptomycin, it is interesting that both give distinct double waves in calcium chloride media. Half-wave potentials obtained are listed in Table I.

TABLE I. HALF-WAVE POTENTIALS OF α -HYDROXYISOBUTYRALDEHYDE (I) AND STREPTOMYCIN (II), VOLT vs SCE

	0.1 N NaOH	1.0 N NaOH	Saturated CaCl ₂
I	-1.66	-1.74	-1.37 -1.61
II	-1.54	-1.63	-1.21 -1.38

Reduction experiments on α -hydroxyisobutyraldehyde revealed that potential- or pH-dependence of reduction ratio of α -hydroxyl group was the same as that was found in the reduction of streptomycin. As expected, products of reduction with metal amalgams or by controlled-potential electroreduction were isobutyl alcohol and 1,1-dimethylethyleneglycol. There was no evidence of bimolecular reduction. Formation of isobutylalcohol was characteristic to these methods of reduction, i.e., reduction at metal surfaces; catalytic hydrogenation or reduction with sodium borohydride yielded only 1,1-dimethylethyleneglycol. Reduction ratios of hydroxyl group (per cent, estimated by determination of consumption of periodic acid) by controlled-potential electrolysis are graphically summar-

FIG. 1. Polarograms of Streptomycin and α -Hydroxyisobutyraldehyde.

(I) Streptomycin, 1×10^{-3} M/L. (II) α -Hydroxyisobutyraldehyde, 1×10^{-3} M/L. 0.005% gelatin added.

2) H. Ikeda et al., unpublished data.

3) H. Ikeda et al., *Proc. of the Japan Acad.*, **32**, 48, 53 (1956).

4) E. Bricker and A. Vail, *J. Am. Chem. Soc.*, **73**, 585 (1951).

ized in Fig. 2. Table II shows the results by reduction with metal amalgams.

FIG. 2. Cathode Potential and Reduction Ratio of Hydroxyl Group.

(I) pH 6~7, (II) pH 2~3

TABLE II. REDUCTION RATIO OF HYDROXYL GROUP BY REDUCTION WITH AMALGAMS

Metal	pH	
	2~3	6~8
Al	99~100	100
Na	45	1

Paper chromatographic separation of mixture of 2,4-dinitrophenylhydrazones prepared from partly reduced solution of α -hydroxyisobutyraldehyde gave an evidence to the formation of isobutyraldehyde during the course of reduction. It corresponds to the formation of methylethylketone from acetoin⁵). The fact, that Kling isolated the ketone as one of reduction products, in spite of the present author's finding the aldehyde only in minor amount, is explained by smaller reducibility of methyl ethyl ketone than that of isobutyraldehyde.

Peculiar transformations of polarogram patterns, observed during the reduction of streptomycin and after neutralization of the reduced solution¹), were not found in the reduction of α -hydroxyisobutyraldehyde.

EXPERIMENTAL

Preparation of α -Hydroxyisobutyraldehyde.

This compound was prepared by hydrolysis of 1,1',2,2'-tetrabromo-isobutylether which was described by Dworzak and Prodinger⁶. This method of preparation was preferred to more widely used hydrolysis of α -bromoisobutyraldehyde or its acetal because it was found to be more convenient and gave higher yield of pure product by choice of conditions. Owing to difficulties encountered in the extraction and preservation of pure aldehyde its aqueous solution was used for all experiments, after confirmation on its purity and exact content. When tetrabromoisobutylether was hydrolyzed by refluxing it with water alone according to Dworzak, it was found that the product was considerably contaminated with acetoin, butan-2-ol-3-one. Evidently rearrangement took place during hydrolysis by prolonged contact with hot hydrobromic acid. The method was modified to give purer product by the use of barium carbonate.

Procedure: In a 500 ml three-necked flask equipped with thermometer, mechanical stirrer and a dropping funnel containing 240 g of bromine, is placed 108 g of pure isobutyraldehyde (b.p. 63~64°C). The content is cooled to -10°C and ten drops of bromine is added. Stirring and cooling is continued until polymerization is complete. Under efficient stirring bromine is added dropwise at 10~20°C, which takes about three hrs. After standing overnight, 300 ml of ethanol is added to the brominated mixture below 10°C with stirring. Shiny white crystal separates when it is kept in refrigerator overnight. The crystal is filtered, washed with cold ethanol and is recrystallized twice from the same solvent containing some water. Yield 80 mg, m.p. 83°C. Anal. Found: Br, 72.17. Calcd. for $C_4H_6OBr_4$: Br, 72.71%.

A mixture of 13.4 g of tetrabromoisobutylether, 12.0 g of barium carbonate and 134 ml of water is refluxed under vigorous stirring. A bubble counter containing some water is connected to the top opening of reflux condenser. The reaction proceeds faster than in the case without barium carbonate and is complete within three hrs; by the time bubbles of carbon dioxide is no longer observed in the counter. Potentiometric titration shows that bromine is quantitatively ionized into the solution. The solution is then distilled under ordinary pressure to nearly dryness, during which α -hydroxyisobutyraldehyde passes over in the distil-

5) H. Kling, *Ann. Chim. Phys.* (8), 5, 506, 553 (1906).

6) R. Dworzak u, W. Prodinger, *Monat.*, 53/54, 588 (1929).

late.

The distillate is assayed for consumption of periodic acid⁷⁾. Consumption is 80~90% of theoretical amount based on tetrabromoisobutylether and agrees with the result of carbonyl determination with 2,4-dinitrophenylhydrazine. Quantitative amount of acid is liberated by oxidation with sodium periodate and also reduces mercuric chloride quantitatively, which proves the acid is formic acid⁹⁾. Absence of acetoin was proved by this fact and also by the absence of aldehyde in the oxidized product.

The distillate of the hydrolysate was thus regarded as pure aqueous α -hydroxyisobutyraldehyde. This solution was fairly stable in a refrigerator but showed sign of deterioration, a decrease in consumption of periodic acid, after one week. Two derivatives of the aldehyde were prepared from the solution. 2,4-Dinitrophenylhydrazone, m.p. 182~183°C. *Anal.* Found: C, 44.24; H, 4.15; N, 20.73. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_6\text{N}_4$: C, 44.78; H, 4.41; N, 20.89%. $\lambda_{\text{max}}=354 \text{ m}\mu$, $\epsilon=28,100$ (ethanol). Thiosemicarbazone, *Anal.* Found: C, 37.19; H, 6.67. Calcd. for $\text{C}_6\text{H}_{11}\text{ON}_3\text{S}$: C, 37.25; H, 6.87%. $\lambda_{\text{max}}=270.5 \mu$, $\epsilon=25,900$ (ethanol).

Reduction with Aluminum Amalgam.

i) At pH 2~3: To 100 ml of aqueous solution of α -hydroxyisobutyraldehyde (13.6 millimole, 1.20 g) was added 2 g of aluminum amalgam, prepared as described in previous paper. Reduction was carried out at 40°C with stirring, while pH of the solution was maintained between 2 and 3 by addition of 10% sulfuric acid. The reaction was very slow and several times of interruption were necessary until the reduction was complete. After each interruption the solution was decanted from the amalgam, and reaction was recommenced by addition of 2 g of fresh amalgam. Total reaction time of 20 hrs was required until Fehling's test proved the absence of reducing substances. The solution was cleared by filtration and was assayed for consumption of periodic acid. Consumption was only a trace. The body of the reduced solution was saturated with sodium sulfate and was repeatedly extracted with ether. Combined extracts

was dried and ether was removed by distillation through fractionating column. About 0.1 g of clear liquid that remained was taken up with 2 ml of water to be esterified with 3,5-dinitrobenzoyl chloride by the method of Lipscomb⁹⁾. White crystalline mass was recrystallized from petroleum ether, m.p. 86~87°C. *Anal.* Found: C, 49.02; H, 4.23, N, 10.29. Calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_6\text{N}_2$: C, 49.25; H, 4.51; N, 10.45%. α -Naphthylamine complex of the ester was orange-red crystal, m.p. 107°C. The ester was identified as isobutyl 3,5-dinitrobenzoate.

ii) At pH 8: Under the same conditions, except that pH of the solution was allowed to rise to 8, reduction of aqueous solution of α -hydroxyisobutyraldehyde proceeded with considerable speed, and was complete after five hrs of reduction. Consumption of periodic acid by reduced solution was 1% of the original solution. The solution was filtered from aluminum hydroxide, which was washed with plenty of water. Ether extracts of combined filtrate and washings was distilled to remove the solvent to give 0.53 g of clear liquid with characteristic odour, which distilled at 100~110°C in a micro apparatus. $n_D^{12}=1.3964$. Its 3,5-dinitrobenzoyl ester melted at 86°C, α -naphthylamine complex of the ester at 106°C. The liquid was identified as isobutyl alcohol.

iii) Isolation of isobutyraldehyde 2,4-dinitrophenylhydrazone.

Twenty ml of aqueous α -hydroxyisobutyraldehyde (3.16 millimoles) was mixed with 100 ml of phosphate buffer (0.5 molar, pH 2.1) and with 80 ml of water. The solution was stirred at 40°C, to which 1 g of aluminum amalgam was added. pH of the solution was maintained at 2.2~2.5 by occasional addition of 5% phosphoric acid. At intervals of thirty min single aliquots of 1 ml were taken out and each was treated as follows: An aliquot was mixed with 2 ml of saturated solution of 2,4-dinitrophenylhydrazine in 2N hydrochloric acid, in a loosely stoppered test tube, and was warmed at 60°C for three min. After cooling in ice bath the mixture was extracted with 1 ml of chloroform which was pipetted out, dried briefly on anhydrous sodium sulfate, and was spotted on chromatographic filter paper by means of a micropipette. Procedure by Rice¹⁰⁾ for paper chromatography of 2,4-dinitrophenylhydrazones was follow-

7) "Organic Analysis", Edited by J. Mitchell et al., Interscience, Vol. I, 1953, p. 41.

8) "Methods of Biochemical Analysis", Edited by Glick, Interscience, Vol. III, 1956, p. 131.

9) W.N. Lipscomb and R.H. Baker, *J. Am. Chem. Soc.* **64**, 179 (1942).

10) R.G. Rice et al., *Anal. Chem.*, **23**, 194 (1951).

ed, employing 5% diethyl ether in ligroin as developing agent. From the second and the third spottings (30 and 60 min of reduction) were developed spots of R_F 0.9, besides those of 2,4-dinitrophenylhydrazine (R_F 0.0) and those of α -hydroxyisobutyraldehyde 2,4-dinitrophenylhydrazone (R_F 0.1). Spots of R_F 0.9 matched with those of pure isobutyraldehyde 2,4-dinitrophenylhydrazone in the parallel run. They were cut out from the strip and were extracted with warm ethanol. The extract showed its absorption maxima at 358 $m\mu$, which agreed with that of ethanol solution of standard specimen of isobutyraldehyde 2,4-dinitrophenylhydrazone.

Reduction with Sodium Amalgam.

i) At pH 2~3: In a 500 ml three-necked flask is placed a mixture of aqueous α -hydroxyisobutyraldehyde (130 ml, 43.3 millimoles) and 20 ml of 0.2 molar solution of potassium dihydrogen phosphate, to which 690 g of 1% sodium amalgam, freshly prepared, was added in small portions. pH of the solution was maintained between 2 and 3 by addition of 5 *N* sulfuric acid, and temperature kept below 30°C. After addition was complete the solution was assayed for consumption of periodic acid. Consumption calculated for total volume was 45% of the original solution. By usual method isobutyl alcohol was isolated and was identified as its 3,5-dinitrobenzoate. Infrared spectrum of the ester matched with that of standard specimen of isobutyl 3,5-dinitrobenzoate but differed much from that of *n*-butyl ester. The fact eliminates the possibility of rearrangement of α -hydroxyisobutyraldehyde to acetoin during the reaction.

ii) At pH 6~7: Aqueous α -hydroxyisobutyraldehyde (13.2 millimoles) was reduced with 1% sodium amalgam in a similar manner as in the previous experiment, except that pH of the solution was maintained at 6~7. Consumption of periodic acid by reduced solution was 13.1 millimoles, 99% of original solution. The solution was removed under reduced pressure and the residue was repeatedly extracted with warm acetone. Upon evaporation of acetone 0.4 g of syrupy liquid remained in the flask. It strongly reduced periodic acid, with formation of formaldehyde, which was evidenced by reaction with chromotropic acid. The product was regarded as 1,1-dimethyl-ethylenglycol and was not further investigated.

Reduction at Controlled-potential Cathode.

The same method and apparatus were adopted as described in the previous paper, except that the cell

was modified to permit working with larger quantity of electrolytes. Electrolysis of α -hydroxyisobutyraldehyde was always attended by evolution of hydrogen which made the potential control less accurate.

i) At pH 2~3: Five hundred ml of catholyte, containing 50.3 millimoles of α -hydroxyisobutyraldehyde and was buffered with phosphate and phosphoric acid (0.2 molar) at pH 2.5, was reduced at stirred mercury cathode maintained at -1.4 – -1.5 V*, at 40°C. The reaction proceeded very slowly and after 16 hrs there remained some unreduced carbonyl compounds, during which pH of the solution was maintained between 2 and 3 by addition of dilute sulfuric acid. Taking the loss of reduction products into account the reaction was arrested here. Consumption of periodic acid by the reduced solution was, corrected for change in the volume, 13.5% of that by original solution. By usual method 0.8 g of ether-soluble substance was isolated and was esterified with 3,5-dinitrobenzoyl chloride, m.p. 86°C. Analysis and infrared spectrum of the ester proved the identity of the ester as isobutyl 3,5-dinitrobenzoate. The fact also eliminates the possibility of rearrangement of α -hydroxyisobutyraldehyde to acetoin, during the reduction.

Similar experiments were carried out in smaller scale, this time nearly to completion of reduction, with 100 ml of 0.03 molar solution of α -hydroxyisobutyraldehyde. At cathode potential of -1.4 V, consumption of periodic acid by the reduced solution decreased to 2.8% of that by original solution.

Formation of isobutyraldehyde was also evidenced by paper chromatography and UV spectroscopy, employing the solution reduced for 4 hrs at 40°C, cathode potential at -1.4 V.

Another experiment in small scale, reduction at cathode potential -1.9 V gave reduced solution, of which consumption of periodic acid was 16% of original solution.

ii) At pH 6~7: Reductions were performed by the same principle as before, employing phosphate buffer of pH 6.0. Original concentration of α -hydroxyisobutyraldehyde was 0.03 molar. Cathode potentials were controlled at -1.6 and -2.1 V. Final values of consumption of periodic acid were 23 and 37% of that of original solution, respectively. Combined catholytes were concentrated under reduced pressure and extraction of the residue with acetone gave syrupy

* Cathode potentials are expressed vs. saturated calomel electrode.

liquid, which was identified as 1,1-dimethylethyleneglycol by chemical means.

Reduction with Sodium Borohydride.

Twenty ml of aqueous α -hydroxyisobutyraldehyde (13.2 millimoles) was added dropwise into a solution of 0.05 g of sodium borohydride in 10 ml of water, within 2 hrs. The solution was mechanically stirred during the addition and twenty min more, acidified with dilute acetic acid to pH 4 and was filled up to 50 ml. No carbonyl compounds were detected in the

ethyleneglycol.

CONCLUSION

The mode of reduction of α -hydroxyisobutyraldehyde by controlled-potential electrolysis was dependent on cathode potential and pH, as was found in the reduction of streptomycin. Evidence of formation of isobutyraldehyde supports the following scheme:

reduced solution. Oxidation with periodic acid was carried out on a small portion of this solution. Consumption calculated for total volume was 98% of the original solution.

The body of the solution was oxidized with slight excess of periodic acid and was treated with excess of lead acetate to remove periodate and iodate. The filtrate was distilled with steam and a portion of the distillate was made to react with dimedone to yield formaldimedone, m.p. 185°C. *Anal.* Found: C, 69.29; H, 8.21. Calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_4$: C, 69.83; H, 8.28%. The remaining solution was treated with excess of silver oxide for two hrs at 60°C to oxidize formaldehyde and then filtered. The filtrate was made to react with 2,4-dinitrophenylhydrazine in phosphoric acid solution to yield acetone 2,4-dinitrophenylhydrazone, m.p. 127°C. *Anal.* Found: C, 45.18; H, 4.10; N, 23.44. Calcd. for $\text{C}_9\text{H}_{10}\text{O}_4\text{N}_4$: C, 45.38; H, 4.23; N, 23.52%. Identifications of oxidation products proved the structure of reduction product by sodium borohydride, 1,1-dimethylethyleneglycol.

Catalytic Hydrogenation.

Aqueous solution of α -hydroxyisobutyraldehyde containing 2.90 millimoles of the aldehyde was shaken in a atmosphere of hydrogen, in the presence of 0.1 g of platinum oxide catalyst. The solution absorbed theoretical amount of hydrogen, 1 mole to 1 mole of α -hydroxyisobutyraldehyde. After filtration the solution was assayed for consumption of periodic acid, which was unaltered from that of original solution. It was granted that the product was 1,1-dimethyl-

Recently Kabasakalian and McGlotten¹¹⁾ reported the reduction of 16-hydroxy (or acetoxy)-17-ketosteroids at the dropping mercury electrode; hydroxyl or acetoxy groups give reduction waves at more positive potentials than those of carbonyl groups. Reduction of large-membered cyclic acyloins with zinc and hydrochloric acid¹²⁾ is possibly of the same nature. These facts support the present view about α -hydroxycarbonyl compounds but question remains how hydroxyl groups, otherwise utterly unreducible under mild conditions, are reduced prior to or at least concurrently with the carbonyl groups. The fact that higher hydrogen ion concentration favors the reduction of hydroxyl groups is to be remarked.

Parallelism between controlled-potential electroreduction and reduction with active metal amalgams, observed in the reduction of streptomycin or α -hydroxyisobutyraldehyde, is also significant.

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- 11) P. Kabasakalian and J. McGlotten, *Anal. Chem.*, **31**, 1091 (1959).
 12) V. Prelog et al., *Helv. Chim. Acta*, **30**, 1741 (1947).