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APPLICATION OF ION-EXCLUSION AND ION-EXCHANGE TECHNIQUES  
IN PREPARING  $\alpha,\beta$ -DIHYDROXYISOBUTYRAMIDE AND  
 $\alpha,\beta$ -DIHYDROXYISOBUTYRIC ACID FROM ACETOL VIA THE  
CYANOHYDRIN SYNTHESIS\*

J. E. POWELL, H. R. BURKHOLDER AND J. L. FARRELL

*Institute for Atomic Research and Department of Chemistry, Iowa State University, Ames, Iowa  
50010 (U.S.A.)*

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**SUMMARY**

The techniques of ion-exclusion and ion-exchange have been exploited to obtain substantial yields of  $\alpha,\beta$ -dihydroxyisobutyramide and  $\alpha,\beta$ -dihydroxyisobutyric acid, respectively, following acid hydrolysis of acetol cyanohydrin.

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**INTRODUCTION**

During studies of lanthanide chelate formation, it was desired to evaluate stabilities of species formed between rare earth cations and the anion of  $\alpha,\beta$ -dihydroxyisobutyric acid. A search subsequently revealed that the ligand acid was not commercially available, and that the preparative procedures reported to date<sup>1,2</sup> were subject to some difficulties. Although GLATTFELD AND SHERMAN<sup>2</sup> investigated three alternatives (including that of MELIKOFF<sup>1</sup>), they did not cite the preparation of  $\alpha,\beta$ -dihydroxyisobutyric acid directly from what appears to be the most obvious intermediate, acetol, *via* formation and subsequent acid hydrolysis of acetol cyanohydrin. The intermediate  $\alpha,\beta$ -dihydroxyisobutyramide has not been described previously.

When attempts were made in this laboratory to prepare  $\alpha,\beta$ -dihydroxyisobutyric acid by combining acetol and anhydrous hydrogen cyanide (in the presence of a trace of KCN) and then hydrolyzing the resulting acetol cyanohydrin with concentrated hydrochloric acid, removal of the mineral acid presented a problem. It was found that heating the reaction mixture to remove the HCl and water (as is frequently done in preparing  $\alpha$ -hydroxy acids) produced a dark-brown gummy residue which could not be induced to yield a crystalline product. The intractability of this residue was attributed to incomplete removal of mineral acid, water and unreacted acetol; and to the likely presence of a host of reaction by-products formed by esterification, decomposition and polymerization of the desired acid. Accordingly,

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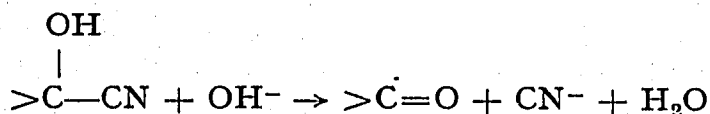
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it was contrived to effect removal of the mineral acid after a limited hydrolysis period by the technique of ion-exclusion<sup>3</sup> to avoid heating the reaction products in the presence of strong mineral acid. In order to follow the course of the reaction and separation, several analytical procedures, outlined below, were utilized.

#### EXPERIMENTAL

124 g (4.6 moles) of freshly prepared anhydrous liquid HCN (0°) was added in an efficient hood to 296 g (3.61 moles) of 90.6% acetol at 0° contained in a 2-l, 3-neck, round-bottom flask, fitted with an icewater-cooled reflux condenser, a thermometer and a stirrer. After thoroughly mixing the reactants, the flask was raised just out of the ice-bath and solid KCN catalyst was added in 0.2 g portions to initiate and sustain the reaction. After adding 0.4 g of catalyst, the temperature of the reaction mixture was observed to rise, slowly at first and then rapidly, until the mixture began to boil and HCN began to return from the condenser. The temperature was maintained between 45–50° by judicious dipping of the reaction flask momentarily into the ice-bath or by adding catalyst, as needed. In all, 2 g of catalyst were added to the mixture to ensure establishment of equilibrium within a reasonable time.

After the reaction had subsided and the temperature returned to 25° (about 2 h); the flask assembly with reaction mixture was weighed (the assembly had been weighed alone previously) and about a gram of the mixture was weighed into a 100-ml volumetric flask containing 2 ml of concentrated nitric acid and about 50 ml of distilled water and finally diluted to volume. This procedure "froze" the reaction (see LAPWORTH AND MANSKE<sup>4</sup>) and permitted an analysis for the constituents HCN and acetol cyanohydrin present at equilibrium. HCN was estimated in one aliquot of the diluted reaction mixture by adding a known amount of silver nitrate, filtering off and rinsing the AgCN precipitate, and finally titrating the soluble silver in the filtrate plus rinse water with standard potassium thiocyanate solution. The acetol cyanohydrin content was determined by the difference between the CN<sup>-</sup> titers in this aliquot and an identical portion which was first made strongly basic to convert the cyanohydrin to the original ketone and CN<sup>-</sup> and then added with vigorous stirring to a known amount of excess silver nitrate solution containing sufficient nitric acid to neutralize all of the base. The reaction



was found to occur instantaneously and quantitatively. By virtue of these analyses it was established that 3.41 moles out of 3.61 moles of acetol originally present were converted to acetol cyanohydrin, and that only 0.81 moles of HCN and 0.20 moles of acetol remained unreacted.

The reaction mixture was then cooled to 0°, treated with 400 ml of cold concentrated hydrochloric acid, and saturated with respect to HCl by bubbling in anhydrous HCl at such a rate that the temperature of the mixture did not exceed 40° while being stirred in an ice bath. Within an hour a large amount of NH<sub>4</sub>Cl had formed and the reaction was allowed to proceed at room temperature overnight with no further

addition of HCl. After 16 h of hydrolysis, the mixture was sampled and analyzed again for cyanohydrin. The same technique was used to determine the concentration of cyanohydrin in the presence of chloride as was used to estimate cyanohydrin in the presence of excess cyanide. At this point only 0.06 moles of cyanohydrin remained. Analysis for nitrogen (Kjeldahl), after removing ammonium ion from an aliquot by cation exchange and correcting for cyanohydrin, revealed that the reaction mixture contained 2.86 moles of  $\alpha,\beta$ -dihydroxyisobutyramide at this point.

The reaction mixture was then diluted to a volume of 8 l, passed into and eluted (with distilled water) through an ion-exchange column system (consisting of three 6-in. diameter  $\times$  48-in. long beds of H<sup>+</sup>-form, 40–50 mesh, Dowex 50W X8, cation-exchange resin) at a rate of about 1.8 l/h. The effluent solution was collected in a series of 80, 900-ml fractions. The individual samples were analyzed for total acidity, chloride (HCl), displaceable NH<sub>3</sub> (amide), and volatile weak acid (formic acid). The first strong acid (HCl) appeared in the 27th fraction, peaked at about the 45th fraction and then fell off sharply (see Fig. 1). Amide and weak acids were detected in samples 50 through 76. Samples 50 through 60 contained varying proportions of HCl, amide and  $\alpha,\beta$ -dihydroxyisobutyric acid, but only a little formic acid. Most of the formic acid (from hydrolysis of HCN) eluted in fractions 61 through 75.

Elution curves for the several constituents of the mixture are somewhat irregular. The occurrence of shoulders was unexpected, but reproducible, and remains to be explained. Integration of the areas under these analytical curves revealed a total of 2.55 moles of  $\alpha,\beta$ -dihydroxyisobutyramide, 0.84 moles of  $\alpha,\beta$ -dihydroxyisobutyric acid and 0.76 moles of formic acid. Since 3.41 moles of acetol cyanohydrin and 0.81 moles of HCN were indicated before hydrolysis, material balances reveal that virtually all of the excess HCN ended up as formic acid and 3/4 and 1/4 of the acetol cyanohydrin intermediate yielded amide and acid respectively.

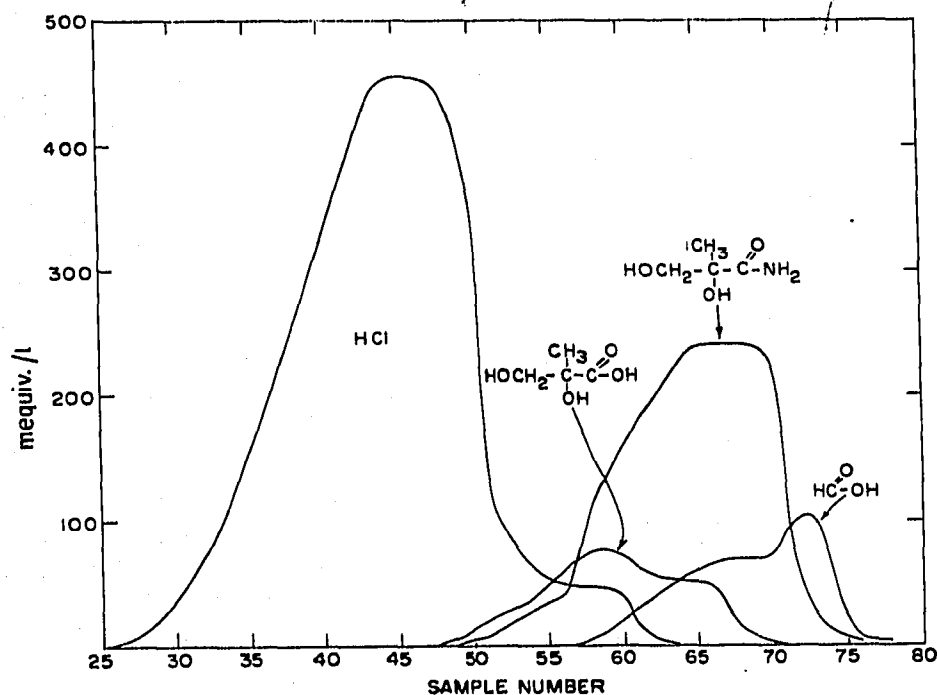


Fig. 1. Ion exclusion separation of mineral acid from reaction products.

When the HCl-free amide-bearing solutions (61 through 73), containing 233 g of amide, were evaporated to near dryness and allowed to cool, large crystals of  $\alpha,\beta$ -dihydroxyisobutyramide separated from the aqueous medium. These crystals were filtered off subsequently and rinsed with a small portion of cold acetone. The recovered amide, melting at 123–127°, weighed 202 g. When recrystallized from water, the pure amide melted at 128.5–129.5°. It is clear, of course, that additional ion-exclusion operations performed on the HCl-containing samples, 50 through 61, as well as appropriate retreatment of the mother liquor from amide recovery, would have enhanced the yield of  $\alpha,\beta$ -dihydroxyisobutyramide. Subsequently, 155 g of the recovered amide was dissolved in a liter of water and treated with 60 g of NaOH pellets. The solution was boiled (while water was added occasionally) until evolution of  $\text{NH}_3$  ceased; then it was cooled and passed through a 2-in.,  $\text{H}^+$ -form, 40–50 mesh, Dowex 50W X8, cation-exchange resin bed, 4 ft. long, to obtain a dilute solution of  $\alpha,\beta$ -dihydroxyisobutyric acid which was subsequently concentrated to a thick syrup by vacuum evaporation below 30°. The syrup was dissolved in 3 parts of warm ethyl acetate and allowed to cool. Crystallization of  $\alpha,\beta$ -dihydroxyisobutyric acid was induced and the mixture was cooled in ice before filtering. Two crops of crystals totalling 115.4 g and melting at 104–104.5° were obtained. The melting point noted by GLATTFELD AND SHERMAN<sup>2</sup> was 104°.

#### CONCLUSIONS

It is clear from the above that either  $\alpha,\beta$ -dihydroxyisobutyramide or  $\alpha,\beta$ -dihydroxyisobutyric acid can be prepared readily from the intermediate acetol *via* formation and subsequent hydrolysis of acetol cyanohydrin. The key to obtaining reasonable yields of either product is to separate the amide and/or the weak acid from the strong mineral acid (used to hydrolyze the cyanohydrin) before attempting to concentrate and recover the acid sensitive products. The indicated separation was accomplished readily by ion-exclusion elution on cation-exchange resin.

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