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APPLICATION OF ION-EXCLUSION AND ION-EXCHANGE TECHNIQUES IN PREPARING α,β,β' -TRIHYDROXYISOBUTYRAMIDE AND α,β,β' -TRIHYDROXYISOBUTYRIC ACID FROM 1,3-DIHYDROXY-2-PROPANONE VIA THE CYANOHYDRIN SYNTHESIS

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SUMMARY

α,β,β' -Trihydroxyisobutyramide (2,3-dihydroxy-2-hydroxymethylpropanamide) melting point 107.5–108°, has been prepared from 1,3-dihydroxy-2-propanone via formation and partial hydrolysis of its cyanohydrin. After isolation by ion-exclusion techniques and crystallization from water and ethanol–water mixtures, the amide was converted nearly quantitatively to α,β,β' -trihydroxyisobutyric acid (2,3-dihydroxy-2-hydroxymethylpropanoic acid), melting point 117–117.5°, by boiling with excess aqueous NaOH followed by cation-exchange elimination of Na⁺ and any unevolved NH₃ on H⁺-form Dowex 50. Proton NMR spectra for both amide and acid were recorded.

INTRODUCTION

The success reported by Powell *et al.*^{1,2} in preparing similar polyhydroxy amides and acids via the cyanohydrin synthesis (using ion exclusion for isolation of the amides as intermediates in preparing the acids) led us to attempt to prepare α,β,β' -trihydroxyisobutyramide and α,β,β' -trihydroxyisobutyric acid by the same route. No synthesis of the former has been reported previously, although the latter has been prepared several times³⁻⁵.

EXPERIMENTAL

α,β,β' -Trihydroxyisobutyramide

To 144 g (1.60 moles) of 1,3-dihydroxy-2-propanone in a 3-l, three-neck, round-bottom flask, immersed in an ice-bath and fitted with an ice-water-cooled reflux condenser, a thermometer and a stirrer, was added 147 g (5.5 moles) of ice-cold, freshly-prepared, anhydrous liquid HCN. Prior to the reaction, 2 g of solid KCN catalyst were added to the 1,3-dihydroxy-2-propanone. After all the HCN had been added, the flask was raised just out of the ice-bath, whereupon the temperature

of the reaction mixture rose, slowly at first and then rapidly. The reaction was quenched and held at 22° (by dipping the reaction flask partially into the ice-bath) until all the 1,3-dihydroxy-2-propanone had dissolved in the HCN. After the temperature had dropped to 10°, one more mole (90 g) of 1,3-dihydroxy-2-propanone and 1 g of KCN were introduced. And again, the temperature of the reaction mixture was allowed to increase by lifting the flask out of the ice-bath, but this time the temperature rose more slowly and the 1,3-dihydroxy-2-propanone dissolved under 20°. The temperature was maintained about 1.5 h at 36° by judicious dipping of the reaction flask momentarily into the ice-bath or a warmer bath, and more catalyst was added as needed.

After the temperature of the mixture had been maintained at room temperature for about 3 h, the color of the solution changed from light yellow to dark brown. At this point, the flask assembly with reaction mixture was weighed (the assembly had been weighed alone previously), and about 1 g of the mixture was transferred and weighed into a 50-ml volumetric flask containing 2 ml of concentrated nitric acid in some water and then diluted to volume with distilled water. The reaction thus "frozen"⁶ permitted an analysis for the constituents, HCN and α,β,β' -trihydroxyisobutyronitrile, (and 1,3-hydroxypropanone by difference) 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 excess silver in the filtrate plus rinse water with standard potassium thiocyanate solution. The α,β,β' -trihydroxyisobutyronitrile content was next determined by difference between the CN⁻ titer of this aliquot and that of an identical portion which was first made strongly basic (to convert the cyanohydrin to the original ketone and CN⁻) and then added with vigorous stirring to a known amount of silver nitrate solution containing sufficient nitric acid to more than neutralize all of the base. The decomposition of the cyanohydrin was found to occur almost instantaneously and quantitatively¹. By virtue of these analyses it was established that 2.45 moles out of 2.60 moles of 1,3-trihydroxy-2-propanone originally present were converted to α,β,β' -trihydroxyisobutyronitrile, and that only 1.78 moles of HCN and 0.15 moles of 1,3-trihydroxy-2-propanone remained unreacted.

The reaction mixture was then cooled to 8° and treated with 460 ml of chilled 12 N HCl (5.5 moles), whereupon the temperature rose rapidly. The temperature was again controlled by means of the ice-bath between 20 and 22° for 1 h and then between 28 and 30° for 1.5 h. After 15-h standing at room temperature, the solution was saturated with respect to HCl by bubbling in anhydrous HCl at such a rate that the temperature of the mixture (in an ice-bath) did not exceed 29°. After 1 h of such treatment, the mixture was allowed to stand 3 h at room temperature.

The dark brown reaction mixture was diluted to a volume of 5 l, then passed into, and eluted (with distilled water) through, an ion-exchange column system (comprised of six, 6-in.-diameter \times 48-in.-long, cylindrical beds of 40–50 mesh, H⁺-form, Dowex 50W-X8, cation-exchange resin) at a rate of 1 l/h. The effluent solution was collected in sixty-five 1-l fractions. The individual samples were analyzed for total weak acids (formic and α,β,β' -trihydroxyisobutyric acids), strong acid (HCl), α,β,β' -trihydroxyisobutyronitrile and α,β,β' -trihydroxyisobutyramide. The first strong acid (HCl) appeared in the 28th fraction and disappeared at the 47th fraction (Fig. 1). The weak acids (formic acid from hydrolysis of HCN and α,β,β' -trihydroxyisobutyric acid from hydrolysis of α,β,β' -trihydroxyisobutyramide) were detected in the 45th

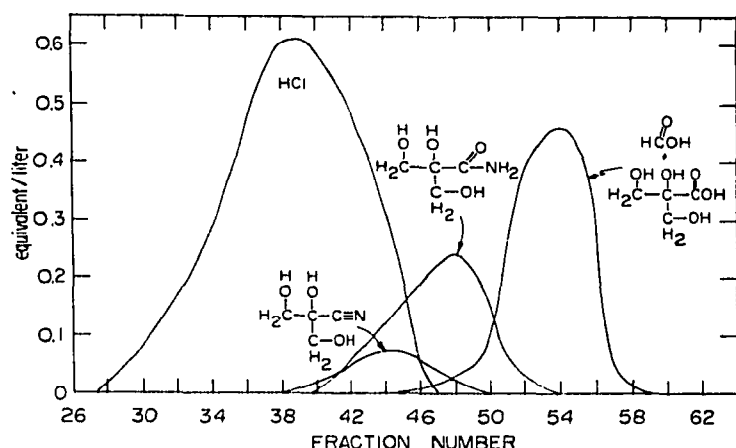


Fig. 1. Partial resolution of the reaction mixture by ion-exclusion elution on Dowex 50 resin.

through 59th fractions. The product α,β,β' -trihydroxyisobutyramide, first found in the 40th fraction, peaked at the 48th fraction and vanished in the 54th fraction. Unreacted α,β,β' -trihydroxyisobutyronitrile was detected in fractions 38 through 50.

Integration of areas under the analytical curves showed a total of 6.1 moles of HCl, 1.40 moles of α,β,β' -trihydroxyisobutyramide, 0.50 moles of α,β,β' -trihydroxyisobutyronitrile, and 2.30 moles of combined weak acids. Since 2.45 moles of α,β,β' -trihydroxyisobutyronitrile and 1.78 moles of HCN were indicated before hydrolysis, material balances revealed that 0.55 moles of the α,β,β' -trihydroxyisobutyronitrile intermediate yielded α,β,β' -trihydroxyisobutyric acid and that all excess HCN ended up as formic acid. These two weak acids were not separated from each other. From the total moles of HCl, it was determined that 0.6 moles of HCl came from anhydrous HCl gas added.

An anion-exchange technique was used to improve the principal α,β,β' -trihydroxyisobutyramide fractions. Each fraction (45 through 51) was neutralized to pH 6 by stirring with 40–50 mesh, OH^- -form, IR-400 anion-exchange resin. In this process, unwanted acids were retained by the anion resin. Fractions 40 through 44 and 52 through 54 were not treated with anion-exchange resin because of the relatively high concentrations of such acids present. They will be combined with a future synthesis to improve the yields of α,β,β' -trihydroxyisobutyramide and α,β,β' -trihydroxyisobutyric acid in the ion-exclusion process. When the combined, strong and weak acid- (also nitrile-) free, amide-bearing solutions (45 through 51), containing 1 mole of amide, were evaporated to near dryness and allowed to cool, large crystals of α,β,β' -trihydroxyisobutyramide separated. These crystals were filtered off, rinsed with a small portion of cold 1:1 ethanol–water mixture and dried. The recovered amide, weighing 94.5 g (0.7 moles) and melting at $107.5\text{--}108^\circ$, was found to contain 10.30% N, 35.09% C and 6.59% H (theoretical analysis: 10.37% N; 35.58% C; 6.66% H; 47.39% O). The NMR spectrum consisted of a quartet at 3.67 ppm in D_2O solvent with Tier's salt as reference (Fig. 2). The spectrum was interpreted as an AB pattern resulting from non-equivalent protons on the β -methylene carbons.

α,β,β' -Trihydroxyisobutyric acid

94 g (0.7 moles) of the α,β,β' -trihydroxyisobutyramide were dissolved in 2 l of water and treated with 50 g (1.25 moles) of NaOH pellets. The solution was boiled until evolution of ammonia ceased (about 3 h) and some 600 ml of light-yellow solution remained. The solution was divided into 4 equal parts, and each part was passed through a 1-in., H⁺-form, 40–50 mesh, Dowex 50W-X8, cation-exchange resin bed, 24-in. long, to obtain a clear solution of α,β,β' -trihydroxyisobutyric acid, which was subsequently concentrated to a thick syrup by vacuum evaporation below 35°. The syrup precipitated as small white crystals immediately after removing the rotative flask from the warm water bath. The acid product was recrystallized from a hot mixture of ethyl acetate and absolute ethanol (1:1), yielding 92.5 g (0.68 moles) of α,β,β' -trihydroxyisobutyric acid melting at 117–117.5°. Coleman and Glattfeld³ and Widiger⁴ reported the m.p. as 117° and Fischer and Tafel⁵ as 116°. The equivalent weight was found to be 137.02 (calculated 136.1) and the C and H analyses to be 34.13% C and 5.61% H (theoretical analysis: 35.32% C; 5.88% H; 58.80% O). Coleman and Glattfeld³ reported equivalent weights of 138.0 and 137.7 (C and H analyses: 35.71% C and 5.90% H). The NMR spectrum of α,β,β' -trihydroxyisobutyric acid in D₂O solvent (with Tier's salt as reference) was similar to the spectrum of α,β,β' -trihydroxyisobutyramide as shown in Fig. 2, except that the quartet was shifted from 3.67 ppm in the amide to 3.73 ppm in the acid. It is clear, of course, that the change in the two functional groups (–COOH and –CONH₂) caused this change in the absorption frequency.

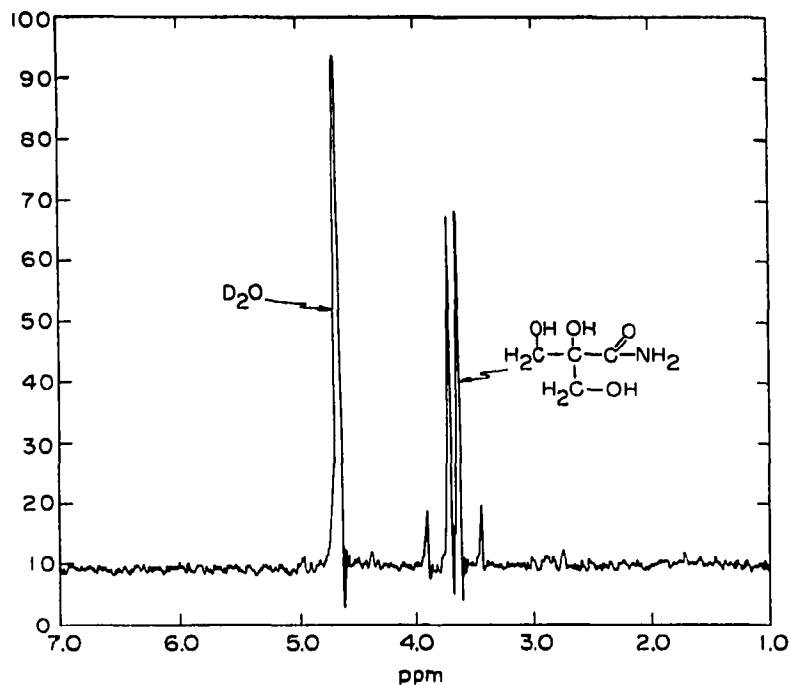


Fig. 2. Proton NMR spectrum of α,β,β' -trihydroxyisobutyramide (in D₂O).

CONCLUSIONS

α,β,β' -Trihydroxybutyramide appears to be more difficult to prepare and isolate than either 2,3-dihydroxy-2-methylpropanamide¹ or 2,3-dihydroxy-2-methylbutanamide². Conversion of α,β,β' -trihydroxyisobutyronitrile to amide proceeded more slowly and hydrolysis of α,β,β' -trihydroxybutyramide to α,β,β' -trihydroxyisobutyric acid occurred more extensively during the conversion of nitrile to amide. The amide obtained, however, was isolated in a high state of purity and was subsequently converted to acid nearly quantitatively via basic hydrolysis followed by removal of the Na⁺ (and any NH₃) via cation exchange for H⁺.

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