

CHROM. 6280

APPLICATION OF ION-EXCLUSION AND ION-EXCHANGE TECHNIQUES IN PREPARING 2,3-DIHYDROXY-2-METHYLBUTANAMIDE AND 2,3-DIHYDROXY-2-METHYLBUTANOIC ACID FROM ACETOIN VIA THE CYANOHYDRIN SYNTHESIS

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(Received August 1st, 1972)

SUMMARY

The techniques of ion exclusion and ion exchange have been exploited to obtain substantial yields of 2,3-dihydroxy-2-methylbutanamide and 2,3-dihydroxy-2-methylbutanoic acid, respectively, following acid hydrolysis of acetoin cyanohydrin. The reaction of acetoin with anhydrous HCN appears to be stereospecific, since the overall process yields an unexpectedly high percentage of only one of two possible diastereomeric *dl*-acid mixtures, namely, the racemate comprised of (2*S*,3*R*)-2,3-dihydroxy-2-methylbutanoic and (2*R*,3*S*)-2,3-dihydroxy-2-methylbutanoic acids.

INTRODUCTION

The facile synthesis of 2,3-dihydroxy-2-methylbutanoic acid has posed a problem since two forms of this reagent were characterized^{1,2} in 1886 and 1890. Due to two asymmetric carbon atoms, 2,3-dihydroxy-2-methylbutanoic acid has four optical isomers or two pairs of enantiomeric modifications, *i.e.*, it can be separated by common crystallization procedures into diastereomers. One of the *dl*-mixtures melts at 110–111° and the other at 88°³. The high-melting diastereomer has been prepared successfully from *cis*-2-methyl-2-butenic acid (angelic acid) by hydroxylating with aqueous alkaline KMnO_4 ³ (*cis*-addition) and from *trans*-2-methyl-2-butenic acid (tiglic acid) by hydroxylating via peracetic acid⁴ (*trans*-addition) and from tiglic acid via treatment with HOCl followed by alcoholic KOH and subsequent hydrolysis¹. The lower-melting diastereomer has been obtained from tiglic acid via the hydroxylating action of alkaline KMnO_4 ^{3,4} at 0°. In all cases the yields were unspectacular and the intermediates (angelic and tiglic acids) costly.

Because of the cost factor and recent success in synthesizing the homologous 2,3-dihydroxy-2-methylpropanoic acid from acetol via acetol cyanohydrin and 2,3-dihydroxy-2-methylpropanamide⁵, it was decided to investigate preparation of 2,3-

dihydroxy-2-methylbutanoic acid from relatively inexpensive acetoin via acetoin cyanohydrin and 2,3-dihydroxy-2-methylbutanamide.

EXPERIMENTAL

2,3-Dihydroxy-2-methylbutanamide

Ninety-four grams (3.5 moles) of freshly prepared anhydrous liquid HCN (0°) was added in an efficient hood to 259 g (2.5 moles) of 85% 3-hydroxy-2-butanone (acetoin) at 0° contained in a 2-l, three-neck, round-bottom flask, fitted with an ice-water-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 0.1-g portions to initiate and sustain the reaction. After adding a total of 0.8 g of KCN, the temperature was observed to rise, slowly at first and then rapidly. When the temperature reached 40°, the reaction was quenched and maintained between 30 and 32°, either by judiciously dipping of the reaction flask momentarily into the ice-bath or by adding a bit more KCN. In all, 2.0 g of solid KCN catalyst was used. After the reaction subsided and the temperature had dropped to 25° (2.5 h), the mixture was allowed to stand overnight at room temperature.

The mixture was then cooled to 2° and treated with 282 ml of chilled 12 *N* HCl, (3.5 moles), whereupon the temperature rose rapidly. The temperature was again controlled by means of the ice-bath between 30 and 32°, and (after about an hour) the solution was saturated with respect to HCl by bubbling in anhydrous HCl at such a rate that the temperature of the mixture did not exceed 30° while being stirred in the ice-bath. After 5 h of such treatment, the mixture was allowed to stand overnight at room temperature.

After 20 h, the light-brown reaction mixture was diluted to a volume of 4.5 l, then passed into and eluted (with distilled water) through an ion-exchange column system (comprised of six 6-in.-diameter × 48-in.-long cylindrical beds of 40–50 mesh Dowex 50W-X8 (H⁺ form) cation-exchange resin) at a rate of 1.2 l/h. The effluent solution was collected in a series of fifty-five 1.2-l fractions and the pH of each sample was measured to monitor the separation achieved. The strong acid (HCl) was observed to pass through the system (at pH 0.9) in fractions 19–36, and 2,3-dihydroxy-2-methylbutanamide was detected (accompanied by some formic and 2,3-dihydroxy-2-methylbutanoic acids) in fractions 40–49 (which had a pH of about 2.4).

When the HCl-free amide-bearing fractions (40–49) were combined and evaporated to a small volume (at 98°) and allowed to cool, large crystals of 2,3-dihydroxy-2-methylbutanamide separated from the aqueous medium. The crystals were filtered off, washed with a small portion of cold acetone and dried. The recovered amide, weighing 288 g (86% yield), melted at 139–140° and was found to contain 45.25% C, 8.20% H and 10.50% N (theoretical analysis: 45.11% C; 8.27% H; 10.53% N; 36.09% O). On two prior occasions, when the temperature was controlled less carefully, the amide was obtained in yields of 53 and 71%.

2,3-Dihydroxy-2-methylbutanoic acid

Two moles (266 g) of the amide were dissolved in 2.5 l of water and treated with 100 g (2.5 moles) of NaOH pellets. The solution was simmered at 98° (while water was added occasionally) until evolution of NH₃ ceased; then it was cooled and passed into

and eluted (with distilled water) through an ion-exchange column system (comprised of three 6-in.-diameter \times 48-in.-long cylindrical beds of 40–50 mesh Dowex 50W-X8 (H^+ form) cation-exchange resin) at a rate of about 1.2 l/h. The effluent solution was collected in a series of thirty 1.2-l fractions. Fractions 18 through 25 (pH 2.13) were found to contain the bulk of the 2,3-dihydroxy-2-methylbutanoic acid. These were concentrated by vacuum evaporation (under 40°) to a thick syrup, which was dissolved in hot ethyl acetate and allowed to cool; whereupon, 2,3-dihydroxy-2-methylbutanoic acid separated in crystalline form and was recovered by filtration. This crude acid product was recrystallized from a warm mixture of acetone and carbon tetrachloride, yielding 204 g (76% yield) of 2,3-dihydroxy-2-methylbutanoic acid melting at $109\text{--}110^\circ$ and having an equivalent weight of 135.39 (calculated 134.14). The product was found to contain 44.54% C and 7.50% H (theoretical analysis: 44.71% C; 7.46% H; 47.83% O).

CONCLUSIONS

It is clear from the above that either 2,3-dihydroxy-2-methylbutanamide or 2,3-dihydroxy-2-butanoic acid can be obtained conveniently from the intermediate acetoin via formation and (partial or complete) hydrolysis of acetoin cyanohydrin. As with the preparation of 2,3-dihydroxy-2-methylpropanoic acid from acetol, it was expedient to isolate 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.

Although one might anticipate production of equal amounts of the two possible diastereoisomeric modifications of acetoin cyanohydrin from *dl*-acetoin (with subsequent yields of neither the higher-melting nor the lower-melting diastereomeric forms of either 2,3-dihydroxy-2-methylbutanamide and 2,3-dihydroxy-2-methylbutanoic acid exceeding 50%), it appears from the unexpectedly high recovery of the higher-melting diastereomeric modifications of amide and acid that the reaction between racemic acetoin and CN^- anion is essentially stereospecific. One can rationalize such stereospecificity by postulating formation of a strong hydrogen bond in acetoin between the hydroxyl hydrogen atom and the adjacent carbonyl oxygen atom. This mechanism would fix the terminal methyl group at the carbonyl end of the molecule in the plane of the five-membered hydrogen-bonded ring since the carbonyl carbon is sp^2 -hybridized. The terminal methyl group attached to the sp^3 -hybridized carbinol C atom, however, would lie above the plane of the ring in the case of one acetoin enantiomer and below the plane of the ring with the other. It is clear then (from the above argument and the observed yields) that the approach of CN^- to the carbon end of the $C=O$ π bond is hindered from one side (but not the other) with this planar conformation in each case, so that only a single pair of enantiomers forms easily. The reader will see that, by approaching only from the side of the plane opposite the out-of-plane methyl group, the CN^- group adds in such a way that subsequent mechanistic events yield only the (2*S*,3*S*)-2,3-dihydroxy-2-methylbutyronitrile and (2*R*,3*R*)-2,3-dihydroxy-2-methylbutyronitrile enantiomeric configurations which are consistent with the stereospecific syntheses of a (2*R*,3*S*)-2,3-dihydroxy-2-methylbutanoic acid

plus (2S,3R)-2,3-dihydroxy-2-methylbutanoic acid enantiomeric pair from angelic acid by *cis*-addition of two hydroxyl groups (KMnO₄) or from tiglic acid by *trans*-addition of two hydroxyl groups (peracetic acid).

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