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Syntheses of α-Hydroxyamino Acids from α-Keto Acids

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Synopsis. A new general method for the synthesis of α-hydroxyamino acids has been developed. Lithium cyanohydridoborate reduces α-keto acid oximes to the corresponding α-hydroxyamino acids and not to the corresponding α-amino acids.

During the course of investigations into the chemical and biological oxidation of α-amino acids it was considered essential to study the chemistry of analogous α-hydroxyamino acids. α-Hydroxyamino acids had been prepared earlier by several methods,[1-6] most of which gave contaminated products showing considerable discrepancies in their physical and chemical properties. One approach which appeared attractive entailed the synthesis of α-oximino acids from α-keto acids as the first step with a subsequent controlled reduction to obtain α-hydroxyamino acids as final products. All attempts, using methods to generate a stoichiometric amount of active hydrogen to convert α-oximino acid into the corresponding α-hydroxyamino acid resulted in complete failure. In every case a mixture of the corresponding α-amino acid and unchanged α-oximino acid was recovered.

Borch and Durst[7] have demonstrated a reaction of an aldehyde or ketone with ammonia in the presence of lithium cyanohydridoborate ($LiBH_3CN$) under neutral conditions in absolute methanol to give good yields of the corresponding amines. On application of this reaction, it was observed that when excess lithium cyanohydridoborate was stirred with α-oximino acids in aqueous medium at pH 5 for 48 hr at room temperature, α-hydroxyamino acids were also obtained in good yields. It was also found that in this reaction α-oximino acid could be replaced by the corresponding α-keto acid and hydroxylamine in equimolar quantities.

$$\mathrm{R{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}COOH} + NH_2OH \text{ or } \mathrm{R{-}\overset{\overset{\mathrm{NOH}}{\|}}{C}{-}COOH} \xrightarrow{LiBH_3CN} \mathrm{R{-}\underset{\underset{\mathrm{NHOH}}{|}}{CH}{-}COOH}$$

α-Hydroxyamino acids prepared by this method are listed in Table 1. They are colorless crystalline compounds, having dipolar ion structure, and can be titrated with both acids and alkalies. pK_1 (2.05—2.45) and pK_2 (5.20—5.95) were measured in aqueous solutions and their isoelectric points calculated (pH 3.6—4.1). When they were titrated with sodium hydroxide in the presence of formaldehyde (Sørensen formal titration) a considerable decrease in the apparent values of pK_2 was observed. The dissociation constant pK_2 should therefore be associated with the hydroxyamino group ($R{-}NH_2^+OH \rightleftharpoons R{-}NHOH + H^+$), and constant pK_1 should thus be associated with the dissociation of carboxylic group ($R{-}COOH \rightleftharpoons R{-}COO^- + H^+$). An additional evidence in favor of the dipolar structure came from IR absorption studies. Like α-amino acids α-hydroxyamino acids show two characteristic bands for $-COO^-$ group, a prominent one occurring in the region 1580—1620 cm^{-1} and a weak one near 1410 cm^{-1}. Absorption band due to NH_2^+ deformation also appears near or coincident with the ionized carboxyl (1600 cm^{-1}) resulting in the broadening of the peak in this region. A complex series of medium scale continuous absorptions in the range 2400—2800 cm^{-1} were also observed in all cases.[8] Persistant absorption bands near 1300 cm^{-1} (NH_2 deformation) and 800 cm^{-1} (NH_2 rock) were displayed by all α-hydroxyamino acids.

Experimental

α-Keto Acids. Most of the α-keto acids were commercial products. Phenylglyoxylic acid[9] and phenylpyruvic acid[10] were prepared by known methods.

α-Oximino Acids. These were prepared by well-established methods, either from suitably substituted α-keto or malonic ester or malonic acids, by nitrosation with freshly prepared butyl nitrite,[11] or from α-keto acids and hydroxylamine.

α-Hydroxyamino Acids. A General Procedure: Either

Table 1.

α-Hydroxyamino acids $RCH(\overset{+}{N}H_2OH)COO^-$ R=	Yield[a] (%) from α-Keto acids	Yield[a] (%) from α-Oximino acids	Mp (°C) (decomp.)	Analysis (%) Found C	Found H	Found N	Calcd C	Calcd H	Calcd N
H–	53	71	135(139)[b]	26.43	5.49	15.40	26.38	5.53	15.38
CH_3–	38	55	146—147(194—195)[c]	34.32	6.79	13.28	34.29	6.71	13.34
CH_3CH_2–	45	68	173(193—194)[c]	40.48	7.51	11.81	40.35	7.62	11.76
$CH_3(CH_2)_2$–	49	70	167(194—195)[c]	45.31	8.39	10.75	45.11	8.27	10.53
$(CH_3)_2CH$–	43	57	193—194(192—193)[c]	45.32	8.41	10.35	45.11	8.27	10.53
$HOOC(CH_2)_2$–	41	48	138(138)[b]	36.73	5.71	8.48	36.81	5.56	8.59
C_6H_5–	47	59	135(133)[b]	57.51	5.38	8.29	57.48	5.43	8.38
$C_6H_5CH_2$–	41	54	159(159—160)[c]	59.77	6.21	7.83	59.69	6.12	7.73

a) Reaction time 48 hr in each case. b) Reported Mps.[9] c) Reported Mps.[5]

α-oximino acid (0.001 mol) or a mixture of the corresponding α-keto acid (0.001 mol) and $NH_2OH \cdot HCl$ (0.001 mol) is taken in water (10 ml). Enough alkali (NaOH) is added to raise the pH of the solution to approximately pH 5. A large excess of lithium cyanohydridoborate ($LiBH_3CN$) (0.002—0.003 mol) is added and the solution is stirred at room temperature for 48 hr. The reaction is interrupted by decomposing the unreacted $LiBH_3CN$ by adding concd HCl dropwise. The pH of the reaction mixture is adjusted to 1. The solution is filtered and the clear filtrate is evaporated to dryness under vacuum at room temperature. The residue so obtained is taken in water (10 ml) and evaporated again as before to remove free acid. The brown residue is then taken up in water (5 ml) and passed through a column (1×10 cm) of cation exchange resin (Bio-rad., Ag 50 W-x8, H^+ form). After thorough washing of the column with distilled water, α-hydroxyamino acid is taken off the column with aqueous ammonia (2%). The eluate is evaporated to dryness under vacuum at room temperature to give almost pure α-hydroxyamino acid. Further purification is achieved by crystallization from aqueous ethanol. Occasionally it was found necessary to purify α-hydroxyamino acids by passing through a column of anion exchange resin (Bio-Rad., Ag 1-x8, OH^- form) also. α-Hydroxyamino acids prepared by this method are recorded in Table 1. The IR spectrum of α-hydroxyaminopropionic acid is given (cm^{-1}) as a specimen: 655(s), 790(s), 895(s), 960(w), 1000(s), 1060(m), 1090(s), 1140(s), 1260(s), 1305(s), 1370—1620 (strong and broad), 2350(sh.) and 2400—2800 (a continuous medium absorption).

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