

The Preparation and Properties of Some Ethoxy Compounds

NED GUTHRIE, Hanover College

This work is the result of an attempt to prepare alpha-amino-beta-hydroxy-acids by the following reactions:

- (1) $\text{CH}_3\text{CHO} + \text{C}_2\text{H}_5\text{OH} + \text{HCl} \rightarrow \text{CH}_3\text{CHClOC}_2\text{H}_5 + \text{H}_2\text{O}$
- (2) $\text{CH}_3\text{CHClOC}_2\text{H}_5 + \text{Br}_2 \rightarrow \text{CH}_2\text{BrCHBrOC}_2\text{H}_5 + \text{HCl}$
- (3) $\text{CH}_2\text{BrCHBrOC}_2\text{H}_5 + \text{RMgBr} \rightarrow \text{CH}_2\text{BrCH}(\text{OC}_2\text{H}_5)\text{R} + \text{MgBr}_2$
- (4) $\text{RCH}(\text{OC}_2\text{H}_5)\text{CH}_2\text{Br} + \text{NaCN} \rightarrow \text{RCH}(\text{OC}_2\text{H}_5)\text{CH}_2\text{CN} + \text{NaBr}$
- (5) $\text{RCH}(\text{OC}_2\text{H}_5)\text{CH}_2\text{CN} + 2\text{HOH} \xrightarrow{\text{HCl}} \text{RCH}(\text{OC}_2\text{H}_5)\text{CH}_2\text{COOH} + \text{NH}_4\text{Cl}$
- (6) $\text{RCH}(\text{OC}_2\text{H}_5)\text{CH}_2\text{COOH} + \text{Br}_2 \rightarrow \text{RCH}(\text{OC}_2\text{H}_5)\text{CHBrCOOH} + \text{HBr}$
- (7) $\text{RCH}(\text{OC}_2\text{H}_5)\text{CHBrCOOH} + \text{NH}_3 \rightarrow \text{RCH}(\text{OC}_2\text{H}_5)\text{CHNH}_2\text{COOH} + \text{NH}_4\text{Br}$
- (8) $\text{RCH}(\text{OC}_2\text{H}_5)\text{CHNH}_2\text{COOH} + \text{HBr} \rightarrow \text{RCH}(\text{OH})\text{CHNH}_2\text{COOH} + \text{C}_2\text{H}_5\text{Br}$

The first three reactions were carried out according to Boord. The first reaction was carried out by passing 100 g. of hydrogen chloride gas, dried over anhydrous calcium chloride, into an ice-cold mixture of paraldehyde and absolute ethyl alcohol. This requires about two hours time. The reaction mixture separated into two layers. The lower layer was discarded, and the upper layer was dried over anhydrous calcium chloride. Suction was used to remove any excess hydrogen chloride gas. This crude product was not distilled since distillation would cause too much decomposition.

The second reaction was carried out by treating the crude product from the first reaction with the theoretical amount of bromine in an ice bath kept at a temperature between 0° and 5°C. Hydrogen chloride gas was evolved. Calcium chloride was added, and the product was kept under suction for several hours to remove the hydrogen chloride gas which was formed. The product, a pale straw-colored liquid, was not distilled but was used directly in the third reaction.

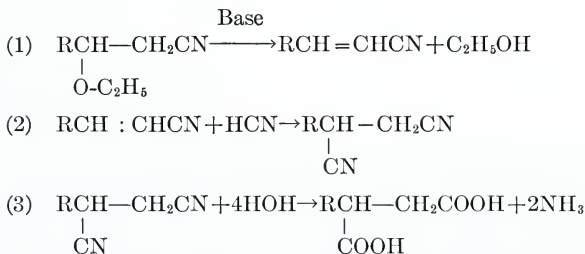
The product of the second reaction was mixed with twice its volume of dry ether, cooled, and added slowly to a slight excess of alkyl magnesium bromide. After this reaction had taken place, the mixture was decomposed by pouring on ice and acidifying with hydrochloric acid. The ether layer separated. The ether extract of the aqueous layer was added to the ether layer and both dried over anhydrous sodium sulfate. The

ether was removed by distillation, and the remaining liquid was purified by steam distillation and then separated from the upper aqueous layer and dried over anhydrous sodium sulfate. This treatment destroyed any unchanged dibromo-ether, which was the product of the second reaction.

The product of the third reaction was refluxed with very slight excess of sodium cyanide, with sufficient quantities of ethyl alcohol and water to dissolve the ethoxybromide and also the sodium cyanide. The time of refluxing was 24 hours. Longer periods of refluxing did not increase the yields to any appreciable extent. The reaction mixture was then cooled and made neutral to litmus with hydrochloric acid and the alcohol removed through a fractionating column. The remaining liquid was again cooled and acidified and then extracted several times with ether. The ether extract was washed with sodium bicarbonate to remove any acids. The ether extract was then dried over anhydrous sodium sulfate and the ether removed by distillation. The nitrile was then fractionated under a pressure of one millimeter of mercury, the ethoxybromide distilling first and the ethoxy-nitrile distilling at a higher temperature.

The sodium bicarbonate washing was acidified and then extracted with ether and dried and the ether removed by distillation. Very little residue was left, thus showing that no acids were formed under these conditions.

When the alcohol was removed through a fractionating column in the fourth reaction, without the mixture being made neutral, some nitrile was formed and also some dibasic acid. When the alkyl group was ethyl, a yield of 18% of the nitrile was obtained, and a solid acid was identified as ethyl succinic acid by its melting point, neutral equivalent, and solubility. The melting point found was 95-96; that reported in the literature is 98. The neutral equivalent was 73, which checks with the calculated value. The compound was very soluble in water and insoluble in petroleum ether, as would be expected. The possible mechanism for this reaction is being further investigated. The following is suggested:



The hydrogen cyanide and the base for these reactions are formed by the hydrolysis of sodium cyanide.

In the fifth reaction, the product of reaction four was hydrolyzed with concentrated hydrochloric acid at 100°C. for two and one-half hours. On cooling, a white solid, ammonium chloride, separated out. Water was added to dissolve the ammonium chloride, and the mixture was extracted with ether. The ether extract was washed with water to remove hydrochloric acid and dried and the ether removed by distillation. The beta

ethoxy-acid distilled at 112-113°C. under a pressure of one millimeter of mercury. The neutral equivalent checked with the calculated value when the alkyl group was ethyl. When the hydrolysis was carried out at 60°C., a solid melting at 88-89°C. was isolated, which was the amide of the acid.

For the bromination of the ethoxy-acid, three attempts were made when the alkyl group was ethyl. In the first attempt, bromine and the acid were mixed and heated to 70°C., when some hydrogen bromide was evolved. The liquid remaining was extracted with chloroform, treated with sodium sulfite to remove excess bromine, and dried over anhydrous sodium sulfate. The chloroform was removed by distillation under reduced pressure. Only decomposition products of low boiling point were obtained. In the second attempt to brominate the ethoxy-acid, the bromine was mixed with the acid and kept in ultra-violet light. Hydrogen bromide was evolved, and decomposition products were again formed. In the third attempt to brominate the ethoxy-acid, the acid chloride was prepared by using thionyl chloride. The acid chloride was then brominated, hydrolyzed, extracted with ether, and dried and the ether removed by distillation. A liquid boiling at 98-100°C. under a pressure of one millimeter of mercury was obtained. The neutral equivalent of the acid was found to be 182.8, which corresponds to alpha-bromo-valeric acid, which has a neutral equivalent of 181.

Bromination was given up at this point and work with various Grignard's started in order to prepare following compounds and observe data listed below:

Alkyl Group Used	Ethyl	Propyl	Butyl
Yield of Nitrile.....	50%	35%	30%
Boiling Point of Nitrile (1mm.).....	47-48°C.	64-66°C.	78-80°C.
Index of Refraction of Light.....	1.4200	1.4252	1.4260
Melting Point of Amide.....	88-89°C.		
Boiling Point of Acid (1 mm.).....	112-113°C.		
Melting Point of Alkyl Succinic Acid..	96°C.		81°C.

Further work is being carried out to improve and also determine the yields for other groups besides the ethyl.

Bibliography

- Jour. Amer. Chem. Soc. 52:651, 3396.
 Jour. Amer. Chem. Soc. 53:1505, 1533, 2427.