Reductive Amination of 12-Ketostearic Acid[1]

BERNARD FREEDMAN and GLENN FULLER,
Western Regional Research Laboratory,[2] Albany, California 94710

Abstract

In the preparation of 12-aminostearic acid by reductive amination of 12-ketostearic acid, the keto acid is first contacted with ammonia under pressure to produce an intermediate, not isolated, which is then hydrogenated to give the product. Variables such as time and temperature of reaction, hydrogen pressure, and amount and type of catalyst were examined to find optimum conditions for high yield and purity of 12-aminostearic acid. With a hydrogenation pressure of 500 psi and 10% Raney nickel catalyst an essentially quantitative yield of product was obtained having a purity of 94%. With 34% catalyst and 260 psi hydrogen, a 98% yield of 98% pure product was obtained.

Introduction

The preparation of 12-aminostearic acid from 12-ketostearic acid was examined because 12-aminostearic acid has potential as a monomer, as a surface active agent, and as a chemical intermediate for other industrial products. A laboratory method has been reported for preparing this amino acid by sodium-alcohol reduction of the oxime of 12-ketostearic acid (1). An economically more attractive process is reductive amination of 12-ketostearic acid to 12-aminostearic acid (2,3). We have reexamined the reductive amination of 12-ketostearic acid as described with a twofold objective: 1) to raise the reported yield of 62% and purity of 82% (estimated) and 2) to lower the hydrogenation pressure of 2000 psi to pressures more easily obtainable.

Experimental Procedures

Materials

12-Ketostearic acid was obtained by saponification of methyl 12-ketostearate prepared by dehydrogenation of methyl 12-hydroxystearate (4). Raney nickel and Raney Cobalt catalysts were purchased from W. R. Grace and Co., Raney Catalyst Division, Chattanooga, Tenn.

Thin Layer (TLC) and Gas Liquid Chromatography (GLC)

Crude reaction mixtures containing the amino acid were examined by TLC. The amino acid was also converted to its trifluroacetylated methyl ester which was then examined by TLC and GLC (5). These analyses were used to determine extent of conversion and product purity.

Reductive Amination Procedure

An example of the reductive amination procedure is as follows. A 300 ml stirred autoclave (Magnedrive, Autoclave Engineers) was charged with 10 g of ketostearic acid, 0.17 g of ammonium chloride, 2.4 g of potassium hydroxide dissolved in methanol, and 3.4 g of Raney nickel catalyst washed three times with methanol to remove most of the water. The catalyst was washed into the autoclave with methanol so that the total volume of methanol was 110 ml. After the autoclave was cooled in an ice bath to 1 C, ammonia was added to the stirred, cooled solution until 16.6 g was introduced (20 molar excess).

The autoclave was then heated to 100 C and kept at this temperature for 4 hr during which the pressure rose to 150 psig. Hydrogen was then added until the total pressure was 260 psi at 100 C. Even though the pressure leveled after stirring for 1.3 hr (pressure drop was 35 psi) heating was continued for a total of 2.75 hr to insure complete reaction. After the autoclave was cooled and vented, catalyst was separated from product by filtration with Celite. The Celite was washed with a total of 600 ml hot methanol, and the filtrate was evaporated to dryness. The residue was redissolved in 74 ml hot methanol, and this solution was added to 756 ml distilled water in a 2 liter beaker. The addition of 16.2 ml of 10% aqueous acetic acid brought the pH to 7.0 and caused the precipitation of 12-aminostearic acid. The amino acid was filtered, washed thoroughly with water, and dried, giving 9.8 g (98%) of product melting at 136.1–136.5 C. Based on a correlation between a number of melting point determinations and GLC purity, the crude product was ca. 98% pure. Recrystallization, when required, is best effected with *t*-butyl alcohol-water (80:20) v/v.

To obtain an analytically pure sample, the amino acid was recrystallized until the melting point was 137.0 to 137.1 C. Calculated for $C_{18}H_{37}NO_2$: C, 72.18; H, 12.46; N, 4.68. Found: C, 72.0; H, 12.3; N, 4.62. The reported melting point for 12-aminostearic acid is 137 to 138 C (3). TLC and GLC (5) as well as IR, NMR and mass spectra further confirmed the purity and structure of the 12-aminostearic acid.

Results and Discussion

Reductive Amination of 12-Ketostearic Acid to 12-Aminostearic Acid

The potassium salt of the keto acid is allowed to react with ammonia under pressure causing ammonia to add to the carbonyl group to give a hydroxyamino intermediate which is not isolated (6,7). This intermediate may undergo dehydration to give an imino intermediate (also not isolated) which is then hydrogenated to the amino acid salt, or the hydroxyamino intermediate may be hydrogenated directly to the amino acid salt. Neutralization of the potassium salt with acetic acid gives free 12-aminostearic acid. In one experiment the reaction was stopped after the amination stage in an attempt to isolate the intermediate(s). The only compound obtained was the starting keto acid indicating intermediate formation was reversible.

Sodium 12-ketostearate may be used in place of the potassium salt and would be less expensive. In the laboratory preparation, however, potassium hydroxide was used rather than sodium hydroxide because it is more soluble in methanol. Ammonium chloride is claimed to aid the replacement of a keto group by an imino group (8); otherwise the keto group would be reduced to a hydroxyl function.

A competing reaction is the formation of a secondary amino dicarboxylic acid. It has been proposed that secondary amines are formed during the prepara-

---

[1] Presented at the AOCS Meeting, San Francisco, April 1969.
[2] W. Utiliz. Res. Dev. Div., ARS, USDA.

TABLE I

Preparation of 12-Aminostearic Acid[a]

Run No.	Reaction temperature, C	NH_3/keto acid mole ratio	Catalyst, wt %	Time, hr		Hydrogen pressure, psig	Product purity by GLC, %	Melting point, C
				NH_3	H_2			
1[b]	150	10:1	34	2	3	2000	82	128.0–128.5
2	150	10:1	34	2	3	2000	86	128.8–129.2
3[c]	150	20:1	34	4	3	2000	89	129.5–129.8
4[d]	100	20:1	34	4	1.5	2000	97	136.0–136.2
5	100	10:1	17	2	3	2000	94	134.0–134.5
6	100	10:1	17	4	3	2000	93	133.5–134.0
7	100	20:1	34	2 (125 C)	1.5	2000	94[e]	134.2–134.8
8	100	20:1	34	4	1.5	1000	96[e]	135.8–136.0
9	100	20:1	34	4	1.5	500	95[e]	135.0–135.1
10	100	20:1	34	4	2.75	260	98[e]	136.1–136.5
11	100	20:1	10	4	3.5	500	94	134.6–135.0

[a] 10 g Ketostearic acid, Raney nickel catalyst.

[b] Solvent was 45% H_2O–55% CH_3OH, v/v. Solvent for all subsequent runs was 100% CH_3OH.

[c] An identical run with Raney cobalt in place of Raney nickel gave 87% product purity.

[d] Catalyst for this run was two years old. A repeat run with fresh catalyst gave identical product purity.

[e] Product purity estimated from melting point. Accuracy is approximately ±1%.

tion of primary amines by addition of the primary amine to the imino intermediate followed by hydrogenation with loss of ammonia (9):

$$RCH_2NH_2 + RCH{=}NH \rightarrow$$

$$RCH(NH_2)NHCH_2R \xrightarrow{H_2} RCH_2NHCH_2R + NH_3$$

TLC analysis of the crude reductive amination reaction mixtures did show the presence of slight amounts of a compound with lower R_f than 12-aminostearic acid which may have been the secondary amino dicarboxylic acid. Under favorable reaction conditions, however, this by-product is almost completely eliminated.

Study of Reaction Variables

Table I shows modifications of the reductive amination procedure designed to achieve milder reaction conditions while improving yield and purity of product. Run 1 uses the conditions described by Hanford (3) as a starting point for systematic variation of conditions. In the runs shown crude yields of product were 90–100% once we acquired skill in avoiding mechanical losses during product isolation. Therefore crude yields are not reported.

Since water is a product of reaction, decreasing its concentration in the system could improve product yield. As shown in Run 2 where no water was used product yield increased slightly, so no water was added in subsequent runs. Doubling the ammonia concentration and amination time (Run 3) further improved product purity. No improvement was noted when Raney cobalt was used in place of Raney nickel although the former has been claimed to produce less secondary amine by-product (10).

The remaining runs illustrate the effects of several variables at 100 C compared to 150 C. In general, this decrease in temperature was beneficial because fewer side reactions took place. Thus significantly purer product was obtained in Run 4 compared to Run 3. Identical product purity was obtained when a new batch of catalyst was used in place of the two-year-old catalyst of Run 4. Decreased catalyst and lower ammonia concentration (Runs 5 and 6) caused longer reaction times for hydrogenation and some decrease in product purity. The purpose of Run 7 was to determine if the amination time could be shortened. In Run 7, 2 hr at 125 C was used instead of 4 hr at 100 C. The purity in Run 7, however, was not as great as in Run 4, so aminations in all subsequent runs were conducted for 4 hr at 100 C.

Runs 8–11 represent attempts to achieve adequate reductive amination at lower hydrogen pressures. Although a somewhat longer hydrogenation time was needed below 500 psi excellent products were produced. Even lower pressures might be employed if one is willing to trade time for pressure.

The final run, Run 11, was carried out to determine if 10% Raney nickel could replace the 34% nickel used above. At this lower catalyst level the hydrogenation required 3.5 hr, but gave a product of 94% purity. To remove impurities from this product, mainly 12-ketostearic acid and 12-hydroxystearic acid, the crude material was slurried first with acetone and then with chloroform followed by filtration. This raised the purity to 98% with only a 9% loss in gross yield. To further purify the product, it was recrystallized from *t*-butyl alcohol-water giving finally a 99% pure product in 89% yield.

ACKNOWLEDGMENT

Carbon-hydrogen analysis by G. Secor, NMR by R. Lundin and mass spectrometry by D. Black.

REFERENCES

1. Colonge, J., and P. Guyot, Bull. Soc. Chim. France *1954*, 339–342.
2. Floyd, D. E. (General Mills) U.S. Patent 2,610,212 (1952).
3. Hanford, W. E. (DuPont Co.) U.S. Patent 2,312,967 (1943).
4. Freedman, B., and T. H. Applewhite, JAOCS *43*, 342–344 (1966).
5. Freedman, B., in press, JAOCS.
6. Astle, J. M., "Industrial Organic Nitrogen Compounds," Reinhold Publishing Corp., New York, 1961, p. 10.
7. Lieber, E., and F. L. Morritz, "Advances in Catalysis," Vol. V, Academic Press Inc., New York, 1953, p. 435.
8. Howk, B. W., and Rigby, G. W. (DuPont Co.) U.S. Patent 2,309,509 (1943).
9. Schwoegler, E. J., and H. Adkins, J. Am. Chem. Soc. *61*, 3499–3502 (1939).
10. Schroter, R., "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, 1948, p. 77.

[Received April 10, 1970]