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Reduction of Unsaturated Aliphatic Mono- and Dicarboxylic Acids and Brominated Aliphatic Acids with Raney Alloys in an Alkaline Solution, Affording the Corresponding Saturated Aliphatic Acids

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The reduction of *trans*-2-pentenoic acid (**1a**), 4-pentynoic acid (**5**), and 2-bromopentanoic acid (**6**) with Ni-Al and Cu-Al alloys in 10% NaOH solution afforded the expected pentanoic acid (**4**) in good yields. Under the above conditions, *trans*-3- and 4-pentenoic acids, (**2**) and (**3**), were not reduced. But, the reduction in the presence of 10% Pd/C catalyst (43 weight % of the alloys) gave **4**. In 10% Na₂CO₃ solution, the treatment of **5** with Cu-Al afforded pentenoic acid (**3**) as a major product. The reduction of 2,3-dibromopentanoic acid (**8**) gave **4** or a mixture of **4**, **1a**, and *cis*-2-pentenoic acid (**1b**) upon the conditions employed. Fumaric acid (**10**), maleic anhydride (**11**), and acetylenedicarboxylic acid (**12**), and 2,3-dibromosuccinic acid (**13**) afforded the expected succinic acid (**14**) in 71–80% yields in the reduction with the alloys in 10% NaOH solution.

It has been previously reported that the reduction of halogenated phenols,¹⁾ benzoic acids,²⁾ acetophenones,³⁾ and cyanobenzenes,⁴⁾ with Raney alloys in an alkaline solution afforded phenol, benzoic acid, 1-phenylethanol, and benzylamine, respectively. In addition, deuteriated phenols, benzoic acids, and 1-phenylethanols were prepared by the same reduction in NaOD–D₂O solution.

In the present paper, the reduction of aliphatic carboxylic acids with Raney alloys in an alkaline solution was investigated as a preliminary work for the preparation of deuteriated aliphatic acids, which are important for metabolic study.⁵⁾

Results and Discussion

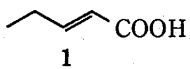
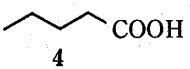
The reduction of *trans*-2-, *trans*-3-, and 4-pentenoic acids, (**1a**), (**2**), and (**3**), with Raney alloys in an alkaline solution was carried out under various conditions and the results are

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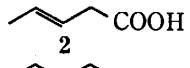
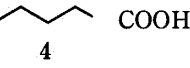
Reduction of Unsaturated and Brominated Aliphatic Acids with Raney Alloys

Table 1 Reduction of 2-Pentenoic Acid (**1**) with Raney Alloys and Al and Zn powders in an Alkaline Solution at 50°C.^{a)}

 1		Metal 10% Alkaline aq.		 4	
Run	Alloy (g)	Time (h)	4 (%) ^{b)}	Recovered 1 (%) ^{b)}	
1	Cu-Al (0.7)	1	79	0	
2	Cu-Al (0.5)	1	72	8	
3	Co-Al (0.7)	1	69	0	
4	Ni-Al (0.7)	1	71	0	
5 ^{c)}	Cu-Al (1.5)	2	11	72	
6	Zn (0.6)	1	0	83	
7	Al (0.3)	2	0	77	

a) The acid; 10mmol, 10% NaOH; 16ml. b) Isolated yields are shown. c) 10% Na₂CO₃ Solution; 37ml.

Table 2 Reduction of 3-Pentenoic Acid (**2**) and 4-Pentenoic Acid (**3**) with Raney Alloys in 10% NaOH Solution at 50°C for 1h.^{a)}

 2		Raney Alloy 10% NaOH aq.		 4	
Run	Alloy (g)	Substrate	Additive Cat. (g)	4 (%) ^{b)}	Recovered 2 or 3 (%) ^{b)}
1	Cu-Al (0.7)	2	none	0	81
2	Cu-Al (1.0)	2	none	0	75
3	Ni-Al (0.7)	2	none	0	73
4	Ni-Al (1.3)	2	none	13	61
5	Cu-Al (0.7)	2	10% Pd/C (0.3)	79	7
6	Cu-Al (0.7)	3	none	0	82
7	Ni-Al (1.3)	3	none	72	13
8	Cu-Al (0.7)	3	10% Pd/C (0.3)	79	0

a) Substrate; 10mmol, 10% NaOH solution; 10ml. b) Isolated yields are shown.

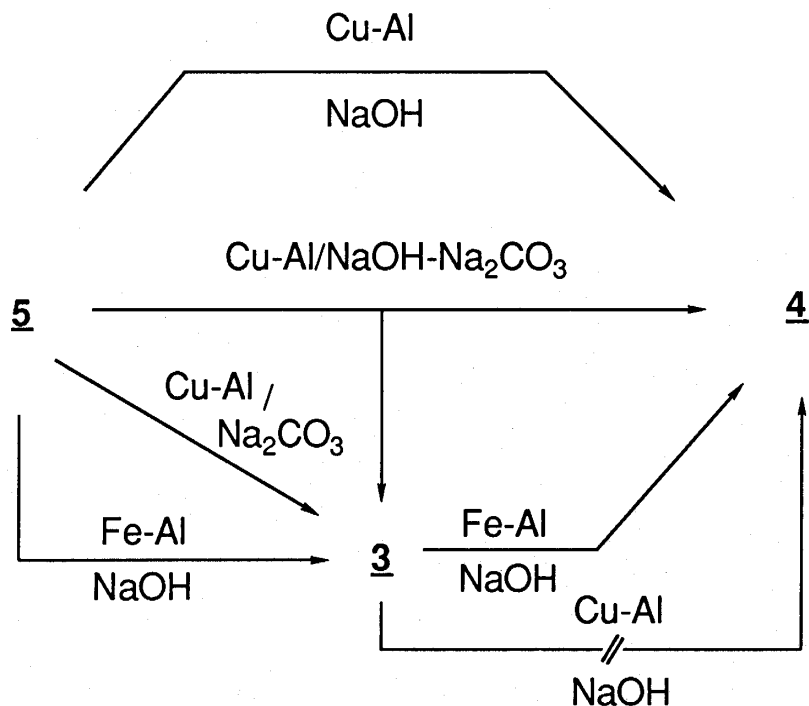
summarized in Tables 1 and 2.

Compound **1a** was reduced with Raney Cu-Al, Co-Al, and Ni-Al alloys in 10% NaOH solution, giving the expected **4**, in good yields. The reduction of **1a** with Cu-Al in 10% Na₂CO₃ solution gave **4** only in 11% yield and **1a** was recovered in 72% yield. When **1a** was treated with Al or Zn powder in 10% NaOH solution, **4** was not obtained and **1a** was recovered in 77 or 83% yield.

The above results mean that Cu, Co, and Ni catalysts generated from the corresponding Raney alloys during the reaction are necessary for the reduction of **1a** in 10% NaOH solution.

As shown in Table 2, pentenoic acids, **2** and **3**, were not reduced with Raney alloys under same conditions and unchanged **2** and **3** were recovered. However, when 10% Pd/C catalyst was added in the reaction system, **2** and **3** were reduced smoothly, giving **4** in good yields.

In Table 3, the results of the reduction of 4-pentynoic acid (**5**) with Raney alloys in alkaline



Scheme 1

Table 3 Reduction of 4-Pentynoic Acid (5) with Raney Alloys in an Alkaline Solution at 50°C for 1h.^{a)}

Run	Alloy (g)	Alkaline (ml)	Product (%) ^{b)}	Recovered 5 (%) ^{b)}
1	Cu-Al (0.3)	10% NaOH (5)	4 (86)	0
2	Cu-Al (0.3)	10% Na ₂ CO ₃ (8)		69
3	Cu-Al (0.6)	10% Na ₂ CO ₃ (8)	3 (42)	30
4	Cu-Al (0.6)	10% Na ₂ CO ₃ (15)	3 (78)	0
5	Cu-Al (0.6)	10% NaOH (5)	3 (3), 4 (79)	0
		10% Na ₂ CO ₃ (5)		0
6	Fe-Al (0.3)	10% NaOH (5)	3 (72), 4 (7)	0

a) The acid (5); 10mmol. b) Isolated yields are shown.

solutions are summarized. Although 3 did not give any products on the treatment with Cu-Al alloy in 10% NaOH solution as mentioned above, 5 afforded 4 in 86% yield under similar conditions. This suggests that 3 is not an intermediate in the formation of 4 (Scheme 1).

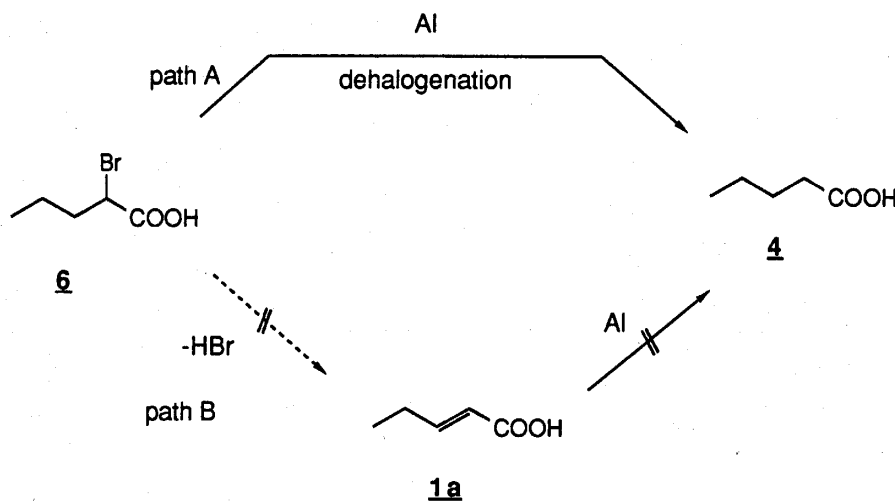
The reduction of 5 with Cu-Al alloy (0.3g/10 mmol of 5) in 10% Na₂CO₃ solution (8ml) did not afford any products. When amounts of the alloy and the alkaline solution were increased, the formation of 3 was observed. Compound 3 was obtained as a sole product in 78% yield in the reduction with the alloy (0.6g/10 mmol of 5) in 15ml of 10% Na₂CO₃ solution. The reduction with the alloy in a 1:1-mixture of 10% NaOH and 10% Na₂CO₃ solutions afforded 4 in 79%

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Table 4 Reduction of 2-Bromopentanoic Acid (**6**) with Raney Alloy and Al and Zn powders in 10% NaOH Solution at 50°C for 1h.^{a)}

Run	Alloy (g)	Alkaline (ml)	Product (%) ^{b)}
1	Cu-Al (0.75)	27	4(67)
2	Cu-Al (0.6)	16	4(80), 6(1), 7(5)
3	Cu-Al (0.6)	12	4(71), 6(2), 7(8)
4 ^{c)}	Cu-Al (0.6)	12	4(65), 7(18)
5	Co-Al (0.6)	16	4(23), 6(45)
6	Ni-Al (0.6)	16	4(69)
7 ^{d)}	Al (0.3)	12	4(88)
8	Zn (1.5)	12	4(5), 6(69)

a) Two grams (11 mmol) of **6** were used. b) Isolated yields are shown. c) Under ultrasonic irradiation. d) Reaction time: 3h.


Scheme 2

yield, together with **3** in 3% yield. The use of a mixture of 10% NaOH and 10% Na₂CO₃ solutions is valuable for the preparation of deuteriated pentanoic acids, since NaOD is expensive.

The reduction of **5** with Fe-Al alloy afforded **3** and **4** in 72 and 7% yields, respectively.

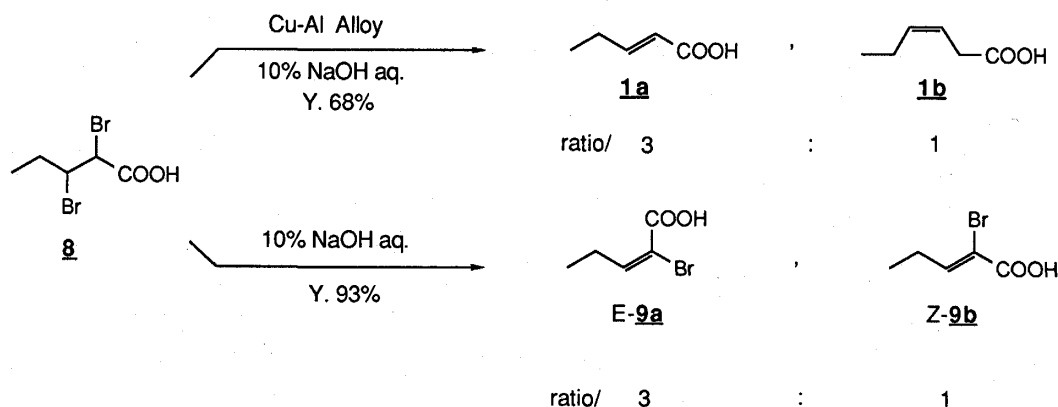
Table 4 shows the results of the reduction of 2-bromopentanoic acid (**6**) with Raney alloys and Al and Zn powders in 10% NaOH solution.

The reduction with alloys, such as Ni-Al, Cu-Al, and Co-Al, afforded the expected **4**. Interestingly, Raney Cu-Al alloy gave dl-2,3-dipropylsuccinic acid (**7**)¹⁰⁾ as a by-product (5% yield). Powdered Al-metal reduced **6** affording **4** in 88% yield, while the reduction with Zinc powder gave **4** only in 5% yield. These results mean that **4** was directly formed by the reductive debromination of **6** and not via **1a** as an intermediate, since **1a** was not reduced with Al powder in 10% NaOH solution as shown in Table 1 (Scheme 2). Ultrasonic irradiation increased the

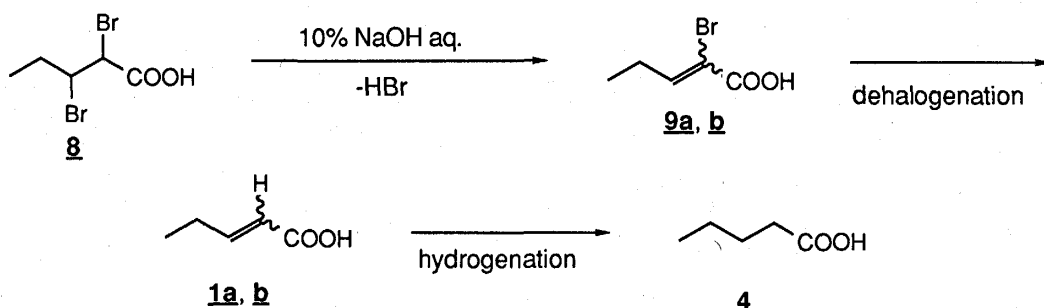
Table 5 Reduction of 2, 3-Dibromopentanoic Acid (8) with Raney Alloys and Al powder in 10% NaOH solution at 50°C for 1h.^{a)}

Run	Metal (g)	Product (%) ^{b)}
1	Cu-Al (1.2)	4 (86)
2	Cu-Al (0.6)	4 (3), 1a+1b (68) ^{c)}
3	Ni-Al (1.2)	4 (79)
4	Ni-Al (0.6)	4 (14), 1a+1b (61) ^{c)}
5 ^{d)}	Al (0.3)	1a+1b (66) ^{c)}

a) Two grams (7.7 mmol) of 8 and 12 ml of 10% NaOH solution were used. b) Isolated yields are shown. c) 1a : 1b = 3 : 1. d) Reaction time; 3h.



Scheme 3



Scheme 4

yield of 7 up to 18%.

The results of the reduction of 2,3-dibromopentanoic acid (8) in 10% NaOH solution are summarized in Table 5.

The treatment of 8 with 1.2g of Cu-Al or Ni-Al alloy per 2.0g (7.7 mmol) of the substrate afforded the reduced product, 4, in good yields. When 0.6g of the alloys were used, the expected 4 was obtained only in small amounts. The major products were trans- and cis-2-pentenoic acids, (1a) and (1b). The ratio of 1a/1b was 3/1. The treatment of 8 with Al powder also

Table 6 Preparation of Succinic Acid (**14**) from Unsaturated Carboxylic Acids (**10**), (**11**), and (**12**) and Dibromosuccinic acid (**13**) with Raney Alloys in 10% NaOH Solution.^{a)}

Run	Substrate	Alloy (g)	Yield (%) ^{b)} of 14
1	10	Cu-Al (0.3)	78
2	11	Cu-Al (0.35)	80
3	12	Ni-Al (0.6)	73
4	13	Ni-Al (0.6)	71

a) Five mmol of the substrate and 10ml of 10% NaOH solution were used. b) Isolated yields are shown.

afforded a 3:1-mixture of **1a** and **1b**, but without Al powder in 10% NaOH solution, **8** afforded a 3:1-mixture of trans- and cis-2-bromo-2-pentenoic acids, (**9a**) and (**9b**).¹³⁾

The observed ratios of trans- and cis-isomers of **1** and **9** are identical. From the above results, the pathway of the reduction of **8** is proposed as following Scheme 4.

The reductive method described above was applied to the preparation of aliphatic dicarboxylic acid, **14**, from fumaric acid (**10**), maleic anhydride (**11**), acetylenedicarboxylic acid (**12**), and meso-2,3-dibromosuccinic acid (**13**). The expected **14** was formed in good yields, respectively (Table 6).

In conclusion, the reductive method with Raney alloys in an alkaline solution is convenient and effective for the preparation of saturated aliphatic acids from unsaturated and brominated aliphatic acids. Preparation of deuteriated aliphatic acids using this method is now in progress and will be reported elsewhere.

Experimental

Melting points were determined on a Yanagimoto microapparatus and are uncorrected. ¹H-NMR spectra were taken on a Nippon Denshi JEOL FT-100 NMR spectrometer with Me₄Si as an internal reference in CDCl₃.

Materials

Compound **1a** was prepared by the modified method.⁶⁾ To a stirred solution of 30g (417 mmol) of malonic acid in 50ml (618 mmol) of pyridine was added gradually 15g (259 mmol) of propionaldehyde. After the reaction mixture was stirred at room temperature for 1 day, it was heated at 45°C for 16h and then at 70°C for 2h. It was cooled to room temperature,

acidified with 6N H₂SO₄ to pH.1, and extracted with ether. The extract was washed with water, dried over Na₂SO₄, and evaporated in vacuo. The residue was distilled under reduced pressure to afford 16.3g (63%) of **1a** as a colorless liquid, bp 61–64°C/1.5 mmHg (lit.⁶⁾ 105–108°C/17 mmHg).

Compounds, **2**, **5**, **6**, **8**, and **13**, were prepared according to the reported methods. Compounds, **3**, **10**, **11**, and **12**, were commercially available.

2: colorless liquid; bp 105–108°C/30 mmHg (lit.⁷⁾ bp 191–192°C)

5: colorless needles; mp 55–57°C (lit.⁸⁾ mp 57.5°C)

6: pale yellow liquid; bp 90–92°C/2.4 mmHg (lit.⁹⁾ bp 132–136°C/25 mmHg)

8: colorless prisms; mp 55–57°C (lit.⁸⁾ mp 57°C)

13: colorless needles; mp 260°C (decomp.) (lit.¹⁰⁾ mp 255–256°C (decomp.)

Reduction of monocarboxylic acid.

Two typical procedures are given below.

Reduction of 2-bromopentanoic acid (6).: To a stirred mixture of 2.0g (11 mmol) of **6** in 12ml of 10% aqueous NaOH was gradually added 600mg of Raney Cu-Al alloy at room temperature, then the reaction mixture was heated at 50°C for 1h. After it was cooled to room temperature, the Cu powder produced and unchanged Raney alloy were removed by filtration. The filtrate was acidified with conc. HCl to pH.1 under cooling and extracted with ether. The extract was washed with water, then brine, dried over MgSO₄, and evaporated in vacuo. The residue was distilled by using Kugelrohr distilling apparatus to afford 903mg (80%) of pentanoic acid (**4**) as a colorless liquid, bp 70–75°C/2.8 mmHg (lit.¹¹⁾ 187–189°C). The residue was treated with hexane to give white solids which, on recrystallization from a mixture of benzene and petr. ether, afforded 56mg (5%) of dl-2,3-dipropylsuccinic acid (**7**) as colorless needles, mp 184.5°C (lit.¹²⁾ 182–183°C).

Reduction of 2,3-dibromopentanoic acid (8).: To a solution of 2.0g (7.7 mmol) of **8** in 12ml of 10% NaOH solution was added gradually 600mg of Raney Cu-Al alloy at room temperature. After the reaction mixture was heated at 50°C for 1h, it was worked up as described above to give 524mg (68%) of a 3:1-mixture of trans- and cis-2-pentenoic acids, (**1a**) and (**1b**), bp 60–70°C/3.0 mmHg and 24mg (3%), bp 65–70°C/2.3 mmHg of **4** as colorless liquid. Compound **1b** could not be isolated, but its structure was determined on the ¹H-NMR spectra of the mixture.

Dehydrobromination of (8).: After a solution of 2.0g (7.7 mmol) of **8** in 20ml of 10% NaOH solution was heated at 50°C for 1.5h, the reaction mixture was cooled to room temperature and it was acidified with conc. HCl solution to pH.1 and then extracted with dichloromethane. The extract was washed with water, dried over MgSO₄, and evaporated in vacuo. The residue was distilled under a reduced pressure to give 1.28g (93%), bp 145–150°C/14 mmHg of a 3:1-mixture of trans- and cis-2-bromo-2-pentenoic acids, (**9a**) and (**9b**), as colorless liquid. Although **9a** solidified as colorless needles of mp 47–50°C lit.¹³⁾ 49–50°C) from the mixture by standing for

several days, **9b** could not be obtained in a pure form. However, the structure of **9b** was determined on the ^1H -NMR spectra of the mixture.

Reduction of Dicarboxylic acid. Typical Procedure.: To a solution of 490mg (5 mmol) of maleic anhydride (**11**) in 10% aqueous NaOH was gradually added 350mg of Raney Cu-Al alloy in a period of 30min, then the reaction mixture was heated at 50°C for 1h. After the mixture was cooled to room temperature and then the Cu powder produced and unchanged Raney alloy were removed by filtration. The filtrate was acidified with conc. HCl to pH.1 and extracted with ether. The ether extract was washed with water, dried over MgSO_4 , and evaporated in vacuo. The residue was recrystallized from ethyl acetate to afford 472mg (80%) of succinic acid (**14**) as colorless needles, mp 185–187°C (lit.¹⁴⁾ 184–185°C).

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