Hydrolysis of 3-Hydroxy-3-methylglutaronitrile; A Convenient Synthesis of 3-Hydroxy-3-methylglutaric Acid

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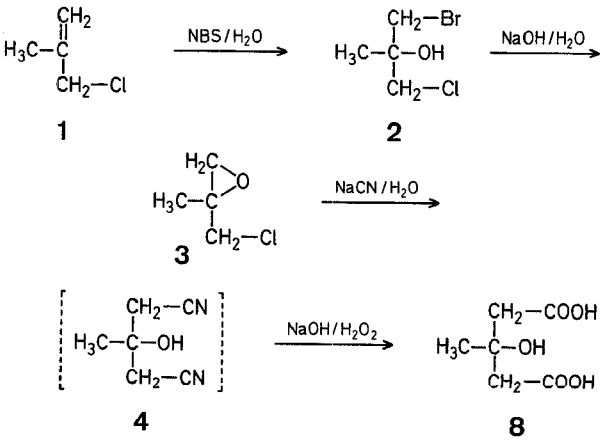
Syntheses of the biologically important isoprene unit precursor 3-hydroxy-3-methylglutaric acid (HMG, **8**) have been accomplished by:

- oxidation of diallylmethyl carbinol or 3-hydroxy-3-methylhex-5-enoic acid with ozone and hydrogen peroxide[1,2];
- Reformatsky reaction[3] between ethyl acetoacetate and ethyl bromoacetate.

An alternate synthesis of 3-hydroxy-3-methylglutaric acid **(8)** is reported here which has been found more suitable for large-scale syntheses[4]. In addition, we have prepared and characterized 3-hydroxy-3-methylglutaric amide nitrile **(5)**, 3-hydroxy-3-methylglutaramide **(6)**, and 3-hydroxy-3-methylglutaric acid monoamide **(7)**, the expected intermediates formed during the hydrolysis of **4** to **8**.

Methallyl chloride **(1)** was converted to 3-bromo-1-chloro-2-methyl-2-propanol **(2)** by reaction with *N*-bromosuccinimide in water. *N*-Bromosuccinimide was found to give a much



1 **2** **3** **4** **8**

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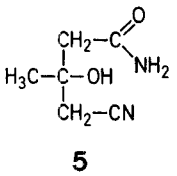
cleaner reaction than bromine/water[5]. Conversion to 1-chloro-2,3-epoxy-2-methylpropane **(3)** could be achieved without isolation of the bromohydrin **2**. The reaction of **3** with an aqueous solution of sodium cyanide buffered by magnesium sulfate or acetic acid to pH 9.5 gave 1,3-dicyano-2-methyl-2-propanol[6] **(4)**. Hydrolysis of **4** to 3-hydroxy-3-methylglutaric acid **(8)** could be easily accomplished in good yield with aqueous 50% sodium hydroxide/30% hydrogen peroxide[7].

Compounds **5, 6,** and **7** could be obtained from the hydrolysis mixture in low yield if a strongly basic ion-exchange resin was used in place of sodium hydroxide.



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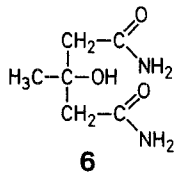

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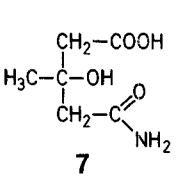

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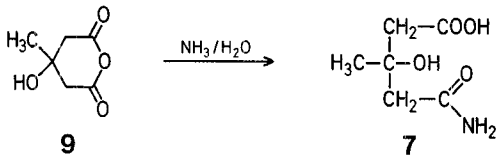
Authentic **7** was prepared for comparison by reaction of 3-hydroxy-3-methylglutaric anhydride[8] **(9)** with ammonia.



9 **7**

Attempts to prepare **8** by acid hydrolysis of **6** resulted in the formation of 3-methylglutaconic acid as the major product.

1-Chloro-2,3-epoxy-2-methylpropane (2-Chloromethyl-2-methyloxirane, 3):

N-Bromosuccinimide (534 g, 3.0 mol) is added to a vigorously stirred suspension of methallyl chloride (294 ml, 3.0 mol) in water (1.5 l) at room temperature. The mixture is stirred for 16 h, then cooled to 10 °C, and 50% aqueous sodium hydroxide (3 mol) is added at such a rate that the temperature remains at ~25 °C. After stirring for 2 h, the lower organic phase is separated, dried with magnesium sulfate (20 g), and evaporated; yield: 266 g (84%) of crude **3**. Extraction of the aqueous phase with chloroform (250 ml) gives an additional 50 g (12%). The product can be used directly in the next step, but distillation to remove the last traces of succinimide is preferable (b.p. 65 °C/40 torr).

1,3-Dicyano-2-methyl-2-propanol (4):

To a solution containing sodium cyanide (147 g, 3 mol) in water (1000 ml) is added glacial acetic acid (70 ml) while stirring in an ice bath (*Caution:* This should be done under a fume hood). Allow the solution to cool to 24 °C, then add distilled **3** (160 g, 1.5 mol) with good stirring. After 15 min, the temperature will begin to rise and should be maintained at 35–40 °C with an ice/water bath. The pH should be maintained at 9.5 with acetic acid (5 ml). The cooling bath is removed when the temperature begins to drop, and stirring is continued for 3 h. The resulting dark solution is treated with activated carbon (10 g) and filtered through Celite. The cake is washed with water (100 ml). The filtrate is used directly for the hydrolysis to **8**. [Alternatively, **4** can be isolated by extraction with ether (4 × 250 ml). After drying with magnesium sulfate (30 g) and filtration, the solvent is removed and the resulting oil distilled; yield: 127 g (68%); b.p. 125–135 °C/0.3 torr].

3-Hydroxy-3-methylglutaric Acid (8):

The above filtrate containing **4** is diluted to a total volume of 2000 ml with ice and water, and 50% aqueous sodium hydroxide (275 ml, 5 mol) is added with stirring at a temperature below 20 °C (ice bath). The mixture is then cooled to 5 °C and ice (1000 g) is added. With continuous stirring and cooling, 30% hydrogen peroxide (320 ml, 3.7 mol) is cautiously added at such a rate that the temperature does not exceed 25 °C. (*Caution:* The reaction should be done in a large open beaker to allow for foaming). After the addition, the mixture is allowed to stand overnight at room temperature. Additional 30% hydrogen peroxide (100 ml) is added and after 1 h the solution is slowly heated to boiling over a 6 h period while keeping the volume above 2000 ml by addition of water as necessary. The solution is cooled and neutralized to pH 1 with conc. hydrochloric acid (700 ml), keeping the temperature below 25 °C. The acidic solution is evaporated under reduced pressure at 45 °C to a solid residue, which is further dried by addition and evaporation of benzene (300 ml). The dried cake is vigorously stirred with acetone (1000 ml). The salt is removed by filtration and washed with acetone (2 × 250 ml). The combined acetone extracts are evaporated under reduced pressure and the residue dried by addition and evaporation of benzene (100 ml). The residue is dissolved in boiling ethyl acetate (300 ml) and treated with activated carbon (10 g) and anhydrous magnesium sulfate (10 g). After filtration, the solution is cooled to 0 °C and the resulting crystals are collected and washed with ethyl acetate/hexane (1/1). Recrystallization from ethyl acetate (200 ml) affords pure **8**; yield: 70 g (29%, based on **3**); m.p. 106–108 °C (Ref.[1], m.p. 108–109 °C). Work-up of the supernatants gives an additional 20 g (8%); total yield of **8**: 37% (based on **3**).

3-Hydroxy-3-methylglutaric Amide Nitrile (5) and 3-Hydroxy-3-methylglutaramide (6):

A mixture of compound **4** (20 g), water (100 ml), Dowex 2 (hydroxide form; 100 ml), and 30% hydrogen peroxide (20 ml) is heated under reflux for 1 h. Another portion (20 ml) of 30% hydrogen peroxide is then added and reflux is continued for 1 h. The cooled solution is filtered, concentrated to a small volume, and applied to a 4 × 50 cm column of Dowex 2 (hydroxide form, 200–400 mesh). The column is then eluted with water; compound **6** is eluted between 500 and 700 ml and compound **5** between 1000 and 1400 ml. The fractions containing **5** are concentrated under vacuum and the residue is crystallized from ethyl acetate after first removing some insoluble materials by filtration. Recrystallization affords pure *3-hydroxy-3-methylglutaric amide nitrile (3-hydroxy-3-methyl-5-nitrilopentanamide,* **5**); yield: 2 g (8%); m.p. 72–73 °C.

$C_6H_{10}N_2O_2$	calc.	C 50.69	H 7.09	N 19.71
(142.2)	found	50.76	7.17	19.64

I.R. (KBr): $\nu = 2250$ (CN); 1660 ($CONH_2$) cm^{-1}.

^{1}H-N.M.R. (D_2O/TMS_{ext}): $\delta = 2.8$ (s, 2H, —CH_2—CN); 2.5 (s, 2H, —CH_2—$CONH_2$); 1.4 ppm (s, 3H, CH_3).

The fractions containing **6** are concentrated under vacuum and the residue is crystallized from methanol/acetone to give *3-hydroxy-3-methylglutaramide (3-hydroxy-3-methylpentanediamide,* **6**); yield: 0.5 g (2%); m.p. 134–135 °C.

$C_6H_{12}N_2O_3$	calc.	C 44.99	H 7.55	N 17.49
(160.2)	found	44.71	7.58	16.66

I.R. (KBr): $\nu = 1660$ cm^{-1} ($CONH_2$).

^{1}H-N.M.R. (D_2O/TMS_{ext}): $\delta = 2.5$ (s, 4H, —CH_2—$CONH_2$); 1.4 ppm (s, 3H, CH_3).

3-Hydroxy-3-methylglutaric Acid Monoamide (7):

Method A, **7** Ammonium Salt from Anhydride **9**: A solution of 3-hydroxy-3-methylglutaric anhydride[8] (**9**; 1.7 g, 0.01 mol) in conc. aqueous ammonia (30 ml) is allowed to stand at room temperature for 10 min and then evaporated to dryness under reduced pressure. The gummy residue is dissolved in warm methanol (10 ml) and crystallized by the slow addition of ethyl acetate (10 ml); yield: 1.5 g (71%); m.p. 135–138 °C (ammonium salt).

$C_6H_{14}N_2O_4$	calc.	C 40.45	H 7.87	N 15.73
(178.2)	found	40.55	7.90	15.60

^{1}H-N.M.R. (D_2O/TMS_{ext}): $\delta = 2.83$ (s, 2H, CH_2); 2.90 (s, 2H, CH_2); 1.75 ppm (s, 3H, CH_3).

Method B, **7** from **4**: A solution of 1,3-dicyano-2-methyl-2-propanol (**4**; 12.4 g, 0.1 mol) in water (100 ml) and 19 normal aqueous sodium hydroxide (7.0 ml) is stirred at 25 °C while 30% hydrogen peroxide (17.4 ml, 0.2 mol) is added slowly. The mixture is heated to boiling during 3 h. The mixture is then cooled, diluted to 1000 ml with water, and passed through a 200 ml bed of Dowex 2 resin in the formate form. The bed is washed with water, and **7** is then eluted off with 0.1

normal formic acid. The eluate is evaporated, neutralized with ammonia, and crystallized twice from methanol/ethyl acetate; yield: 3.0 g (16%) of pure **7**. [The product was shown to be identical to that prepared above].

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