

The Synthesis of γ, δ -Dimethyl- γ -(2-carboxyethyl)- δ -valerolactone*

By Toshihiro TAKATA, Kazunori SAYAMA, Yukihide FURUTSU
and Masahiko TAKIGAWA

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The present paper describes a synthesis of γ, δ -dimethyl- γ -(2-carboxyethyl)- δ -valerolactone, through the scheme shown below, from γ -acetyl- γ -methylpimelonitrile derived from ethyl methyl ketone by cyanoethylation with acrylonitrile¹⁾.

The cyanoethylation of ethyl methyl ketone was carried out according to the method of Bruson and Riener¹⁾ to give γ -acetyl- γ -methylpimelonitrile (I), which was then hydrolyzed to γ -acetyl- γ -methyl pimeric acid (II)¹⁾. Compound II was hydrogenated, in the presence of a Raney-nickel catalyst in an aqueous sodium hydroxide solution, to sodium γ -methyl- γ -(1-hydroxyethyl)-pimelate (III), which was not isolated and which, after treatment with hydrochloric acid, gave γ, δ -dimethyl- γ -(2-carboxyethyl)- δ -valerolactone (IV).

Though δ -valerolactone gives an associated molecule²⁾, compound IV gives no associated molecule, as was detected by the cryoscopic method.

As another route, compound I was esterified with ethanol, water and sulfuric acid to give diethyl- γ -methyl- γ -acetyl- γ -pimelate, which was then hydrogenated to γ, δ -dimethyl- γ -(2-carboxyethyl)- δ -valerolactone (VII) through di-

ethyl- γ -methyl- γ -(1-hydroxyethyl)-pimelate (VI), which was not isolated.

On the other hand, I was hydrogenated with sodium borohydride to give γ -methyl- γ -(1-hydroxyethyl)-pimelonitrile (VIII). In this procedure the nitrile group was not attacked, but the carbonyl group hydrogenated to the hydroxyl group, as is shown in Fig. 1. The absorption bands at 1095 and 1075 cm^{-1} of compound VII are probably due to the formation of the hydroxyl group, while the absorption band at 1705 cm^{-1} , being due to the carbonyl group of I, is absent in VIII. The band at 2250 cm^{-1} , being due to the nitrile group, is present in both I and VIII.

Then, compound VIII was treated with concentrated sulfuric acid in order to obtain γ -methyl- γ -(1-hydroxyethyl)-pimelic acid diamide

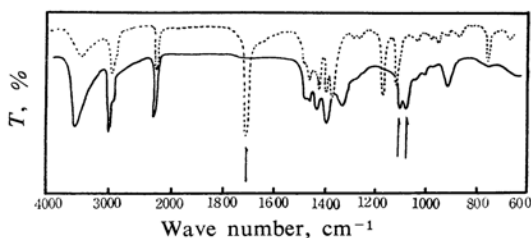
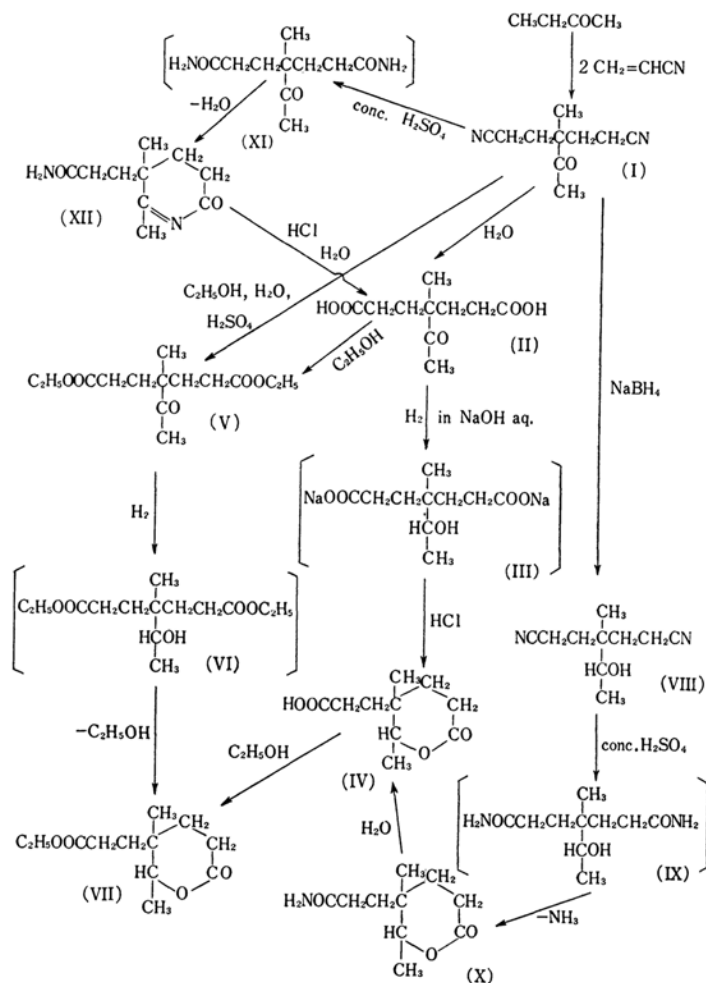


Fig. 1. Infrared absorption spectrum of γ -acetyl- γ -methylpimelonitrile (I) (---, KBr disk) and of γ -methyl- γ -(1-hydroxyethyl)-pimelonitrile (VIII) (—, liquid film).

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1) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **64**, 2850 (1942).

2) K. Sayama, T. Takata and M. Taniyama, *J. Chem. Soc. Japan, Ind. Chem. Sec. (Kōgyō Kagaku Zasshi)*, **58**, 112 (1955).



(IX). However, IX was not obtained, and γ , δ -dimethyl- γ -(2-carbamoyl-ethyl)- δ -valerolactone (X) was obtained; it was converted to IV by hydrolysis. The infrared spectrum of X, shown in Fig. 2, has absorption bands at 1730 cm^{-1} and 1675 cm^{-1} , which are, respectively, due to the structures of the six-membered lactone and of the amide group.

Moreover, compound I was treated with concentrated sulfuric acid in order to obtain γ -methyl- γ -acetylpinelic acid diamide (XI). In

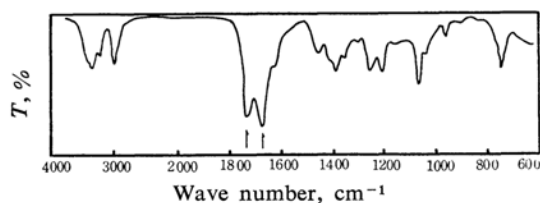
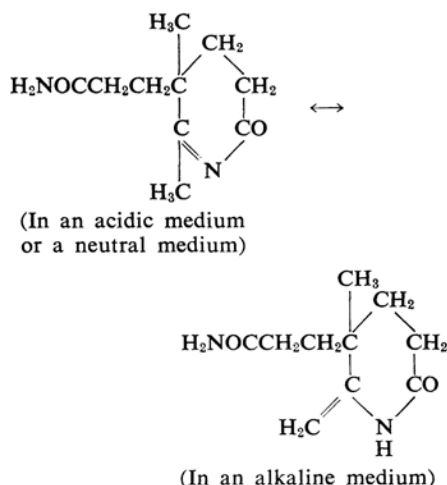


Fig. 2. Infrared absorption spectrum of γ , δ -dimethyl- γ -(2-carbamoyl-ethyl)- δ -valerolactone (X) (liquid film).

this case XI was not obtained, but 2-keto-5,6-dimethyl-5-(2-carbamoyl-ethyl)-2,3,4,5-tetrahydropyridine (XII) was obtained; it was converted to II by hydrolysis, but it could not be hydrogenated under high hydrogen pressure in the presence of a Raney-nickel catalyst nor by sodium borohydride. The infrared absorption spectrum of XII shown in Fig. 3 has absorption bands at 1685, 1660 and 1640 cm^{-1} which are due to the structures of the carbonyl in the ring, of the double bond between C and N in the ring, and of the amide group in the side chain. Moreover, the ultraviolet absorption spectra shown in Fig. 4 has absorption maxima at $201.5 \text{ m}\mu$ (ϵ , 11900) and $282.5 \text{ m}\mu$ (ϵ , 5) in water, at $210 \text{ m}\mu$ (ϵ , 4067) and $280 \text{ m}\mu$ (ϵ , 8) in ethanol, at $202.5 \text{ m}\mu$ (ϵ , 20810) and $282.5 \text{ m}\mu$ (ϵ , 6) in 0.5 N aqueous sulfuric acid, and at $222 \text{ m}\mu$ (ϵ , 2165) and $291 \text{ m}\mu$ (ϵ , 6) in 0.5 N aqueous sodium hydroxide. Such a shift of ultraviolet absorption bands according to the pH value of the

medium suggests the possibility of such tautomerism as the following.



Further experiments may be necessary to establish this phenomenon completely.

Experimental

γ , δ -Dimethyl- γ -(2-carboxyethyl)- δ -valerolactone (IV).—In a 220 ml. autoclave, compound II (40 g. in 90 g. of a 20% aqueous sodium hydroxide solution) was hydrogenated under about 80 atm. of hydrogen pressure at 104–120°C in the presence of a Raney-nickel catalyst (from 20 g. of Ni-Al alloy 50:50) for 4.3 hr. The reaction mixture was evaporated and acidified with concentrated hydrochloric acid, and extracted with ether. From the ether extract IV was obtained as a viscous liquid (b. p., 200–202°C/1 mmHg), which after standing became crystalline; m. p., 60–62°C; yield, 35.2 g. (95.0%).

Found: C, 59.92; H, 8.15; N, 0.00. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_4$: C, 59.98; H, 8.06; N, 0.00%.

Neutralization and saponification equivalent, 100.3. Calcd. for IV, 100.1.

Mol. wt., 196.5 (cryoscopic method in acetic acid). Calcd. for IV, 200.2.

Diethyl γ -Methyl- γ -acetylpielate (V).—Compound I (17.8 g.) was dissolved in a mixture of ethanol (36.8 g.) and concentrated (96%) sulfuric acid (25.6 g.), and the mixture was heated under reflux at a bath temperature of 140–143°C for 3.5 hr. The reaction mixture was washed with

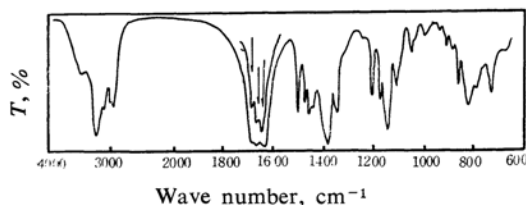


Fig. 3. Infrared absorption spectrum of 2-keto-5, 6-dimethyl-5-(2-carbamoyl-ethyl)-2, 3, 4, 5-tetrahydropyridine (XII) (KBr-disk).

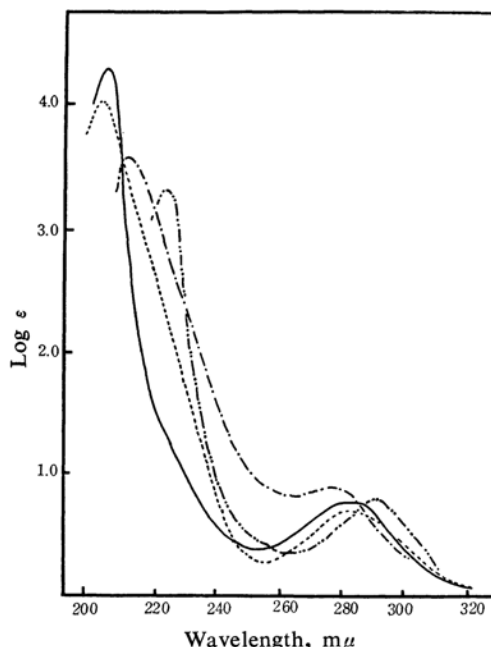


Fig. 4. Ultraviolet absorption spectra of 2-keto-5, 6-dimethyl-5-(2-carbamoyl-ethyl)-2, 3, 4, 5-tetrahydropyridine (XII).

--- In water
 - · - · - In ethanol
 — In 2N aqueous sulfuric acid
 · · · · In 2N aqueous sodium hydroxide

water, and the oily layer was extracted with ether, dried with sodium sulfate, and distilled to give V; b. p., 158°C/2 mmHg, d_4^{20} 1.0522, n_D^{20} 1.4562; yield, 20.9 g. (76.7%).

Found: C, 61.88; H, 8.83; O, 28.99. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_5$: C, 61.74; H, 8.88; O, 29.38%.

Saponification value, 414.4. Calcd. for V, 412.0.

This compound was obtained in an 82.3% yield by the esterification of II (50 g.) with ethanol (200 g.) in the presence of sulfuric acid (9 g.) at a bath temperature of 130–140°C for 5 hr.

γ , δ -Dimethyl- γ -(2-carboethoxyethyl)- δ -valerolactone (VII).—Compound IV (10 g., in 10 ml. of ethanol) was hydrogenated under about 85 atm. of hydrogen pressure at 140–150°C in the presence of a Raney-nickel catalyst (from 5 g. of Ni-Al alloy 50:50) for 2 hr. From this reaction mixture VII was obtained by distillation; b. p., 155°C/2 mmHg, d_4^{20} 1.0579, n_D^{20} 1.4640; yield, 6.3 g. (75.2%).

Found: C, 63.07; H, 8.90; O, 27.80. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_4$: C, 63.13; H, 8.83; O, 28.04%.

Saponification value, 487.2. Calcd. for VII, 491.2.

This compound was obtained in a 76.3% yield by the esterification of IV (5 g.) with ethanol (50 g.) in the presence of sulfuric acid (2 g.) at a bath temperature of 130–140°C for 5 hr.

γ -Methyl- γ -(1-hydroxyethyl)-pielonitrile (VIII).—Into a solution of I (90 g.) in methanol (500 ml.) sodium borohydride (9.6 g.) was slowly stirred below 30°C; after it had been left standing for 2.5 hr. at room temperature, this mixture was

neutralized with concentrated hydrochloric acid, evaporated, separated from the precipitate by filtration, and dried in vacuum to give a viscous substance which was identified as VIII by the infrared spectrum shown in Fig. 1 and by elementary analysis as follows. Yield, 90 g. (quantitatively), n_D^{20} 1.4800.

Found: N, 15.48. Calcd. for $C_{10}H_{15}N_2O$: N, 15.55%.

γ , δ -Dimethyl- γ -(2-carbamoylethyl)- δ -valerolactone (X).—A mixture of VIII (10 g.) and 90% sulfuric acid (20 g.) was heated at 60°C for 1 hr., neutralized with concentrated aqueous ammonia while being vigorously stirred and externally cooled, and extracted with chloroform. From this extract after evaporating, X was obtained as a viscous liquid, n_D^{20} 1.4945; yield, 11 g. (99.6%). The infrared spectrum of X is shown in Fig. 2.

Found: N, 7.01. Calcd. for $C_{10}H_{17}NO_3$: N, 7.03%.

The Hydrolysis of X.—Compound X was treated with sodium hydroxide (4 g., in 40 g. of water) on a water bath for 3 hr., acidified with hydrochloric acid, evaporated, and extracted with ether. From the ether extracts IV was obtained; yield 2.2 g. (54.7%).

2-Keto-5, 6-dimethyl-5-(2-carbamoylethyl)-2, 3, 4, 5-terahydropyridine (XII).—By a method similar to that described for X, XII was obtained from I (10 g.) and 90% sulfuric acid (20 g.) in the form of colorless crystals; m. p., 237~238°C (from

ethanol); yield, 5.1 g (42.4%). The infrared spectrum of XII is shown in Fig. 3, while the ultraviolet absorption spectra are shown in Fig. 4.

Found: C, 61.64; H, 8.26; N, 14.29. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28%.

The Hydrolysis of XII.—Compound XII was treated with 20% aqueous hydrochloric acid on a boiling water bath for 2.7 hr. and then extracted with ethylene dichloride. From the ethylene dichloride extract II was obtained; yield, 1.85 g. (84.1%); m. p., 124~125°C (from ethylene dichloride), undepressed on admixture with the authentic specimen derived from I.

Found: C, 55.39; H, 7.33; N, 0.00. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46; N, 0.00%.

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*The Research Institute, Toho Rayon Co., Ltd.
Itano-gun, Tokushima*