UDC 615.778:547.747.07

187. **Kazuo Kariyone**: Studies on Insecticides. VI. Synthesis of Proline Derivatives. (4).

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A previous paper[1] in this series described the preparation of alkyl-2-piperidones from alkyl-2(1*H*)-pyridones by catalytic hydrogenation.

This paper deals with the synthesis of 2- and 4-methylproline, which were derived from 3- and 5-methyl-2-piperidone, and the investigation of the structure of 3-methyl-2-piperidone, which was reported in the previous paper to be prepared from 3-methyl-2(1*H*)-pyridone by the method of Boekelheide, *et al.*[2]

(I) (derived from 3-methyl-2(1*H*)-pyridone) (II) (III)

Chart 1.

When 3-methyl-2-piperidone, derived from 3-methyl-2(1*H*)-pyridone, was treated with phosphorus pentachloride and sulfuryl chloride in chloroform, two products, (II), m.p. 120°, and (III), m.p. 130°, were obtained in ca. 30:1 ratio. According to analysis, (II) seemed to be 3-methyl-3-chloro-2-piperidone and (III) was presumed to be 3,3-dichloro-5-methyl-2-piperidone. The structure of each was identified by another route as will be described below.

It is clear that in the process from 3-picoline 1-oxide to 3-methyl-2(1*H*)-pyridone, 5-methyl-2(1*H*)-pyridone is produced as a by-product, because in this reaction two products (II and III) were isolated as shown in Chart 1. The preparation of (III) is shown in Chart 2.

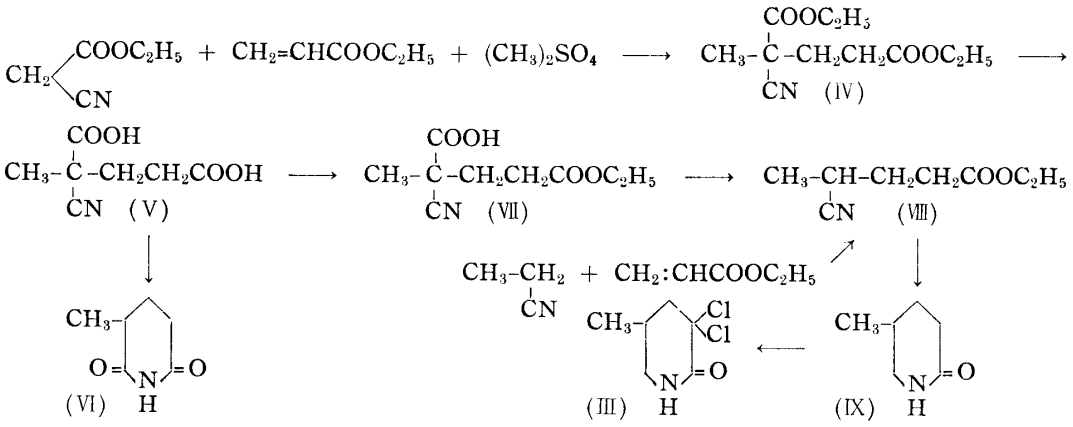

Chart 2.

Diethyl 2-cyano-2-methylglutarate (IV) was obtained in an excellent yield by the Michael condensation of ethyl cyanoacetate and ethyl acrylate in the presence of sodium ethoxide,[3] followed by methylation with dimethyl sulfate. Hydrolysis of (IV) by boiling with equimolar amount of potassium hydroxide, yielded crude 2-cyano-2-methylglutaric acid (V),

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1) T. Takahashi, K. Kariyone: This Bulletin, **8**, 1106(1960).
2) V. Boekelheide, *et al.*: J. Am. Chem. Soc., **76**, 1286(1954).
3) K. Osugi: Yakugaku Zasshi, **78**, 1318(1958).

which gave 3-methylglutarimide (VI) by decarboxylation in the usual manner. Selective esterification and decarboxylation of (V) afforded ethyl 4-cyanovalerate (VIII) which was also obtained from propionitrile and ethyl acrylate with potassium *tert*-butoxide by the Michael condensation. 5-Methyl-2-piperidone (IX), obtained by reduction of (VIII) over Raney nickel in ethanol, was chlorinated successively with phosphorus pentachloride and sulfuryl chloride to (III).

Formation of (II) is shown in Chart 3.

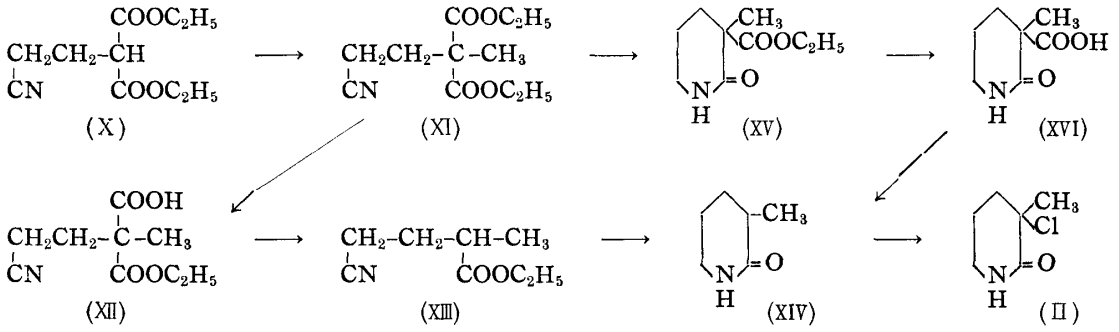

Chart 3.

Diethyl 2-(2-cyanoethyl)malonate (X) was converted with dimethyl sulfate to diethyl 2-(2-cyanoethyl)-2-methylmalonate (XI). The crude ester-acid (XII), prepared by partial hydrolysis of (XI), was decarboxylated by distillation to give ethyl 2-cyano-2-methylbutyrate (XIII). The reduction of (XIII) to 3-methyl-2-piperidone (XIV) was effected easily under above-mentioned condition. (XIV) was prepared in a good yield from (XI) through another route, which included catalytic reduction of (XI) and hydrolysis and decarboxylation of the resulting (XV). When (XIII) was treated with phosphorus pentachloride and sulfuryl chloride, (II) was produced. (III) gave (XVII) by catalytic hydrogenation over Raney nickel in the presence of equimolar amount of triethylamine at atmospheric pressure.

Preparation of 4-methylproline (XVIII) and 2-methylproline (XIX) from (XVII) and (II) was carried out by hydrolysis with barium hydroxide.

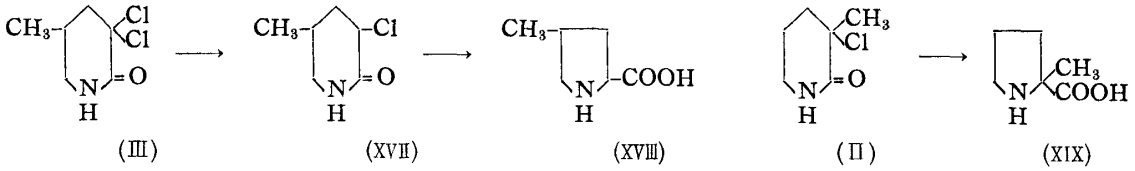

Chart 4.

Experimental

3,3-Dichloro-5-methyl-2-piperidone (III) and 3-Chloro-2-piperidone (II)—i) (II) and (III) from (I): A solution of 2.3 g. of (I) dissolved in $CHCl_3$ (70 cc.) was added, by stirring, with PCl_5 (4.1 g.) and a solution of SO_2Cl_2 (5.4 g. in 10 cc. of $CHCl_3$). The mixture was refluxed gently for 8 hr. and kept standing overnight at room temperature. After addition of cold K_2CO_3 solution to this reaction mixture, organic layer was separated, dried, and evaporated *in vacuo*. By fractional recrystallization with Me_2CO-petr. benzine, two crystalline products were obtained; (II), colorless cubes, m.p. 120° and (III), colorless needles, m.p. 130°, in ca. 30:1 ratio. *Anal.* Calcd. for $C_6H_{10}ONCl$: C, 48.82; H, 6.82; N, 9.41. Found (for II): C, 48.22; H, 6.67; N, 8.90. *Anal.* Calcd. for $C_6H_9ONCl_2$: C, 39.8; H, 6.38. Found (for III): C, 40.9; H, 6.78.

ii) (II) from (XIV): To a mixture of (XIV) (6.0 g.), PCl_5 (10.0 g.), and $CHCl_3$ (50 cc.), a solution of SO_2Cl_2 (7.5 g. in 15 cc. of $CHCl_3$) was added dropwise with stirring during 30 min. The mixture was refluxed gently for 8 hr., allowed to stand overnight, and worked up as above. Yield, 7.5 g., m.p. 120° (from Me_2CO). *Anal.* Calcd. for $C_6H_{10}ONCl$: C, 48.82; H, 6.82; N, 9.41. Found: C, 48.42; H, 6.68; N, 9.10.

iii) (III) from (IX): To a mixture of (XI) (6.5 g.), PCl_5 (10.4 g.), and $CHCl_3$ (150 cc.), a solution of

SO_2Cl_2 (16 g. in 20 cc. of $CHCl_3$) was added dropwise with stirring during 30 min. The reaction mixture was worked up as above, giving (III) (9.0 g.), as colorless needles, m.p. 134°. *Anal.* Calcd. for $C_6H_9ONCl_2$: C, 39.8; H, 4.99; N, 7.69. Found: C, 39.6; H, 5.25; N, 7.99.

Diethyl 2-Cyano-2-methylglutarate (IV)—In a solution of NaOEt (23 g. of metallic Na in 350 cc. of EtOH) ethyl cyanoacetate (120 g.) was added with stirring, then ethyl acrylate (100 g.) was added in small portions under the surface of the mixture. During the addition, the reaction mixture was kept below 45°. When addition of ethyl acrylate was completed, the reaction mixture was heated gently to 85°, maintained there for 2.5 hr., Me_2SO_4 (120 g.) was added, and the mixture was refluxed for 2.5 hr. After cool, the precipitate was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in benzene, which was washed with 10% NaOH solution and H_2O, dried, and distilled fractionally, giving 69 g. of (IV), b.$p_{0.25}$ 116°. *Anal.* Calcd. for $C_{11}H_{17}O_4N$: C, 57.88; H, 7.57; N, 6.16. Found: C, 57.85; H, 7.62; N, 6.45.

2-Cyano-2-methylglutaric Acid (V)—A mixture of the ester (IV) (65 g.), EtOH (300 cc.), and KOH (77 g. in 77 cc. of H_2O) was refluxed on a steam bath for 2 hr. After removal of EtOH by distillation *in vacuo*, the colorless solid residue was dissolved in ca. 100 cc. of H_2O and the solution was shaken with EtOAc. The aqueous layer was acidified with conc. HCl under cooling, (V) was extracted with EtOAc, which was dried and evaporated, giving 40 g. of the crude acid. The crude product was used directly in the next step.

3-Methylglutarimide (VI)—When the above acid (2.0 g.) was heated in an oil bath for 2 hr. at 180°, (VI) was obtained as a caramel-like solid. It gave colorless minute leaflets, m.p. 97°, from Me_2CO–petr. benzine. *Anal.* Calcd. for $C_6H_9O_2N$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56,44; H, 7.30; N, 11.27.

Ethyl 4-Cyanovalerate (VIII)—i) A mixture of (V) (60 g.), dehyd. EtOH (300 cc.), and conc. H_2SO_4 (11 cc.) was refluxed on a steam bath for 3 hr. After EtOH was evaporated, the residue was dissolved in H_2O, and made alkaline with K_2CO_3. In order to isolate (IV), this aqueous solution was extracted with EtOAc, the H_2O layer was acidified with conc. HCl under cooling, and again extracted with EtOAc. The EtOAc solution was dried and evaporated under a reduced pressure. The residue was decarboxylated by distillation at b.p_{13} 116° to (VIII) as a colorless liquid; yield, 10.5 g, which was redistilled for analysis at b.p_{13} 114°. *Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.09. Found: C, 61.65; H, 8.62; N, 8.97.

ii) A mixture of propionitrile (8.0 g.), ethyl acrylate (15 g.), and *tert*-BuOK solution (0.3 g. of metallic K, 70 cc. of *tert*-BuOH) was heated in a sealed tube at 180° for 10 hr. After cooling, the content was poured into H_2O, and extracted with benzene. Benzene solution was dried, evaporated, and the oily residue was distilled. (VIII) was obtained as a fraction of b.p_{10} 113° (colorless liquid). Yield, 1.5 g. *Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.09. Found: C, 61.57; H, 8.77; N, 8.92.

5-Methyl-2-piperidone (XI)—To a solution of 11.0 g. of (VIII) in 20 cc. of EtOH, 10 cc. of triethylamine was added. The solution was reduced over Raney Ni at an initial pressure of 80 atm. at 130° for 3 hr. After cool, the reaction mixture was filtered and the filtrate was evaporated to dryness. (XI) distilled at b.p_{17} 154~157°. Yield, 6.9 g. Colorless plates (from Me_2CO–petr. benzine), m.p. 51°. *Anal.* Calcd. for $C_6H_{11}ON$: C, 63.68; H, 9.80; N, 12.39. Found: C, 62.99; H, 10.19; N, 11.81.

Diethyl 2-(2-Cyanoethyl)-2-methylmalonate (XI)—To a solution of 70 g. of diethyl 2-(2-cyanoethyl)-malonate and equimolar amount of NaOEt in 300 cc. of EtOH, 42 g. of Me_2SO_4 was added. After 3 hr., the reaction mixture was concentrated, poured into H_2O, and extracted with Et_2O. The Et_2O layer was washed with 10% NaOH and H_2O, dried, and distilled. Yield, 53 g. of colorless viscous liquid, b.$p_{0.4}$ 128°. *Anal.* Calcd. for $C_{11}H_{17}O_4N$: C, 58.13; H, 7.54; N, 6.16. Found: C, 57.88; H, 7.57; N, 6.39.

Ethyl 4-Cyano-2-methylbutyrate (XIII)—A solution of (XI) (5.0 g.) dissolved in a solution of 1.5 g. of KOH in 50 cc. of EtOH was refluxed for 4 hr., the mixture was evaporated, 10 cc. of H_2O was added to the residue, and the solution was shaken with EtOAc. The organic layer was dried and concentrated *in vacuo*. The residual crude acid was decarboxylated by distillation in reduced pressure; yield, 3.0 g. of colorless liquid, redistilled for analysis. *Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.62; H, 8.42; N, 9.01.

3-Methyl-2-piperidone (XIV)—i) A solution of (XIII) (3.0 g.) dissolved in a mixture of 3 cc. of triethylamine and 20 cc. of EtOH was hydrogenated over Raney Ni at an initial pressure of 80 atm. at 130° for 3 hr. After cool, the reaction mixture was filtered and the filtrate was distilled. (XIX) was obtained as a fraction of b.p_{16} 132°. Yield, 1.8 g. of colorless plates, m.p. 46°. *Anal.* Calcd. for $C_{16}H_{11}$-ON: C, 63.68; H, 9.80; N, 12.39. Found: C, 63.56; H, 10.11; N, 12.52.

ii) When crude (XVI) (11 g.) was decarboxylated slowly by distillation, 6.0 g. of (XIV) distilled at b.p_{16} 132°. On cooling, the products solidified to colorless plates, m.p. 46°. *Anal.* Calcd. for $C_6H_{11}ON$: C, 63.68; H, 9.80; N, 12.39. Found: C, 63.42; H, 10.09; N, 12.46.

Ethyl 3-Methyl-2-oxonipecotate (XV)—A solution of 44 g. of (XI) in 400 cc. of EtOH added with 10 cc. of triethylamine was reduced over Raney Ni at an initial pressure of 95 atm. at 110° for 7 hr. After cool, the solvent was evaporated in reduced pressure from the filtrate of the reduction mixture,

the residual semisolid was distilled, and 16.0 g. of (XV) was obtained as colorless prisms, m.p. 77°; b.$p_{0.7}$ 188°. *Anal.* Calcd. for $C_8H_{13}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found : C, 57.97; H, 8.37; N, 8.05.

3-Methyl-2-oxonipecotic Acid (XVI)—A cloudy mixture of (XV) (16.0 g.) and KOH (5.7 g.) in 16 cc. of H_2O was refluxed for a short time to give a clear solution and refluxing was continued for 4 hr. After cool, the reaction mixture was neutralized with an equimolar amount of conc. H_2SO_4 with cooling. K_2SO_4 was filtered off and the filtrate was evaporated *in vacuo*. The residual crystalline mass was used in the next step without purification (quantitative yield). The crude acid was recrystallized from EtOH-EtOAc for analysis, m.p. 129° (decomp.). *Anal.* Calcd. for $C_7H_{11}O_3N$: C, 53.49; H, 7.50; N, 8.91. Found : C, 53.69; H, 7.24; N, 8.77.

5-Methyl-3-chloro-2-piperidone (XVII)—A mixture of (III) (4.5 g.), triethylamine (2.5 g.), and EtOH (600 cc.) was hydrogenated over Raney Ni in atmospheric pressure. When equimolar H_2 was absorbed, the reaction mixture was filtered and evaporated *in vacuo* to dryness. The residue was treated with hot toluene, the toluene solution was washed with small portions of H_2O, dried, and the solvent was removed *in vacuo*. The residue was recrystallized from Me_2CO; yield, 2.5 g. of m.p. 116°. *Anal.* Calcd. for $C_6H_{10}ONCl$: C, 48.82; H, 6.83; N, 9.49. Found : C, 49.34; H, 7.06; N, 9.20.

4-Methylproline (XVIII)—(XVII) (2.5 g.) was added to a refluxing solution of 5.7 g. of $Ba(OH)_2$ in 100 cc. of H_2O. After refluxing for 3.5 hr., conc. H_2SO_4 (1.8 g.) was added, the mixture was refluxed for 0.5 hr., and allowed to stand overnight. The filtrate of the reaction mixture was passed through a columm of Amberlite IR-4B (20 cc.), concentrated *in vacuo*, and the residue was recrystallized from EtOH to colorless cubic crystals, m.p. 219° (decomp.). Yield, 1.0 g. *Anal.* Calcd. for $C_6H_{11}O_2N$: C, 55.79; H, 8.58; N, 10.97. Found : C, 55.57; H, 8.66; N, 10.72.

2-Methylproline (XIX)—(II) (2.5 g.), $Ba(OH)_2$ (5.7 g.), and H_2O (100 cc.) were treated in the same manner as above. Residual solid was crystallized from a mixture of iso-PrOH and dioxane to colorless fluffy needles, m.p. 260°. *Anal.* Calcd. for $C_6H_{11}O_2N$: C, 55.79; H, 8.58; N, 10.97. Found: C, 55.52; H, 8.86; N, 10.69.

The author expresses his deep gratitude to Emeritus Prof. T. Takahashi for his kind and unfailing guidance throughout the course of this work. He is grateful to the President of Fujisawa Pharmaceutical Industries, Ltd., who gave great assistance to this work, and thanks the members of the Microanalytical Center of Kyoto University for microanalysis.

Summary

In addition to 3-methyl-2(1*H*)-pyridone, 5-methyl-2(1*H*)-pyridone was also obtained as one of the products from treatment of 3-picoline 1-oxide with acetic anhydride. Two products derived from the above 2(1*H*)-pyridone derivatives were identified as 3,3-dichloro-5-methyl-2-piperidone and 3-methyl-3-chloro-2-piperidone. 2- and 4-Methylproline were obtained from the above 2-piperidone derivatives.

(Received April 16, 1960)