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125. Tetsuzo Kato and Yukio Kubota : Structure of the Product from the Reaction of Acetonedicarboxylic Acid with Acetic Anhydride.

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In 1893, Pechmann and Neger[1] reported the reaction of acetonedicarboxylic acid (I) with acetic anhydride giving 2-methyl-5-acetyl-4,6-dioxo-4,5-dihydro-2*H*-pyran-3-carboxylic acid (II), which reacted with aniline easily to give its anilide (III), and vacuum distillation of III afforded 1-phenyl-3-acetyl-6-methyl-2,4(1*H*,3*H*)-pyridinedione (IV). Since then, this reaction has been quoted in several literatures.[2]

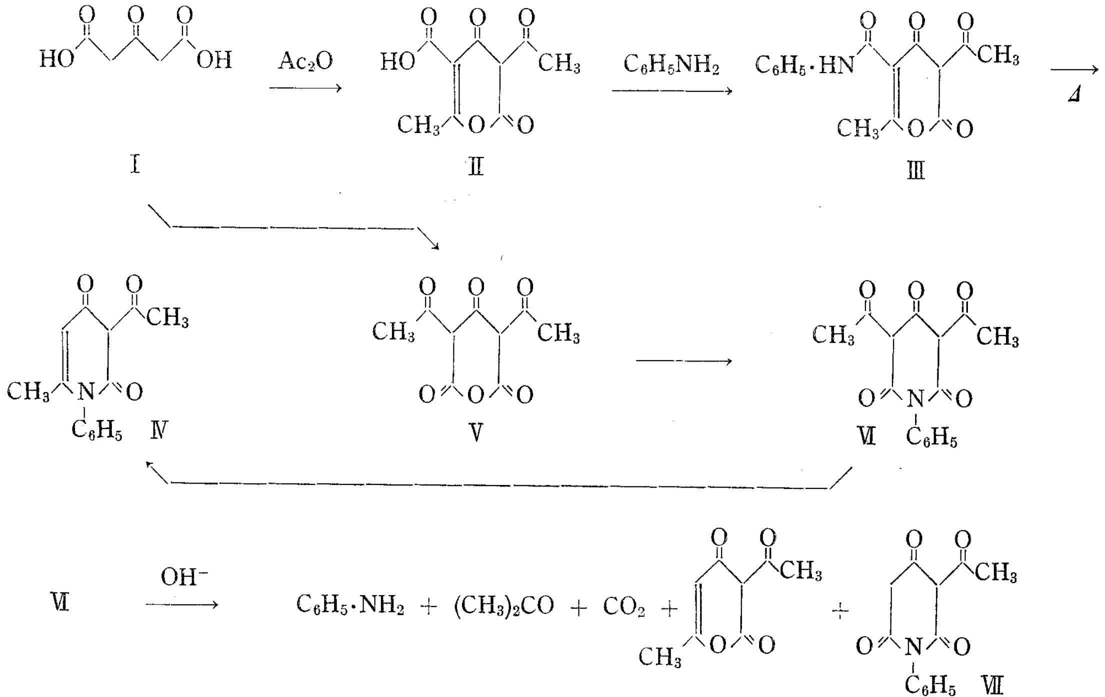

Chart 1.

When this reaction re-examined in our laboratory in an effort to obtain a sample of IV, the results obtained were at variance with those noted by Pechmann and Neger. Although the structure of the final product (IV) leaves no doubt, those of II and III were incorrectly proposed. In this paper we show the preferable structures of these intermediates are not II and III but V and VI respectively.

Following the procedure described in the literature, the reaction of I with acetic anhydride gave colorless plates of m.p. 154~155°, $C_9H_8O_6$ (A). Treatment of A with aniline afforded colorless needles of m.p. 184~185°, $C_{15}H_{13}O_5N$ (B). Physical properties of these two such as solubilities are quite same with those described in the literature.[1]

Hydrolysis of B with 20% sodium hydroxide gave aniline, dehydroacetic acid, carbon dioxide, acetone and a very small amount of colorless needles, m.p. 265~266° (decomp.), $C_{13}H_{11}O_4N$, presumed to be 1-phenyl-3-acetyl-2,4,6-piperidinetrione (VII).

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1) H. Pechmann, F. Neger : Ann., **273**, 194 (1893).

2) *e.g.*, L. Vanino : Handbuch der Preparativen Chemie, II Bd., Org. Teil, 163 (1937); R. Willstätter, A. Pfannenstiel : Ann., **422**, 6 (1921); R. Kaushal : J. Indian Chem. Soc., **17**, 138 (1940); A. Mallams : J. Org. Chem., **29**, 3555 (1964).

However, refluxing of B with 30% hydrochloric acid resulted in the recovery of the starting material in a quantitative yield.

If the anilide structure (III) is correct, it will be difficult to explain why the hydrolysis in an acidic condition was unsuccessful, and it seemed to be reasonable to assume the correct structure being 1-phenyl-3,5-diacetyl-2,4,6-piperidinetrione (VI) instead of the anilide structure (III). Conclusive structural assignments were made on the basis of infrared absorption spectral data. As shown in Fig. 1a and b, the infrared spectra of these compounds exhibit characteristic peaks at 1757, 1727 (shoulder), 1658, 1585 for A and 1736, 1706 (shoulder), 1653, 1567 for B (cm^{-1}, CHCl$_3$). If the acid type structure (II) were correct, the absorption at 1757 (acid carbonyl of II) would eliminate in the spectrum of B at such a high frequency. However, the spectra of these two are essentially similar, and in the spectrum of B the absorption band owing to NH is not observed. The most significant fact is that in the spectrum of A no absorption band due to COOH appears in the region 3000~2500 cm^{-1}. As shown in Fig. 1c, in the spectrum of 2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic acid the band in the region 3000~2500 cm^{-1} is clearly observed.

These data above described are consisted with the 3,5-diacetyl-2*H*-pyran-2,4,6-(3*H*, 5*H*)-trione (V) and 1-phenyl-3,5-diacetyl-2,4,6-piperidinetrione (VI), but not with the structures proposed by Pechmann and Neger (II and III).

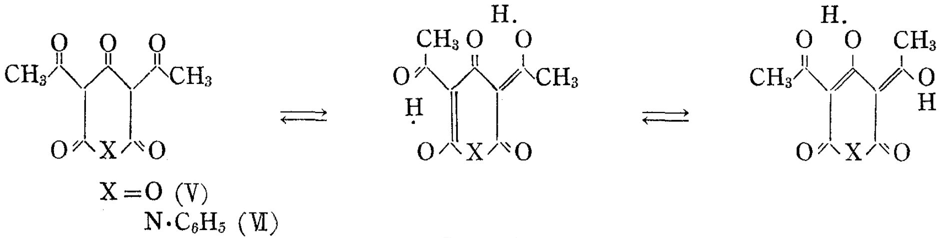

Chart 2.

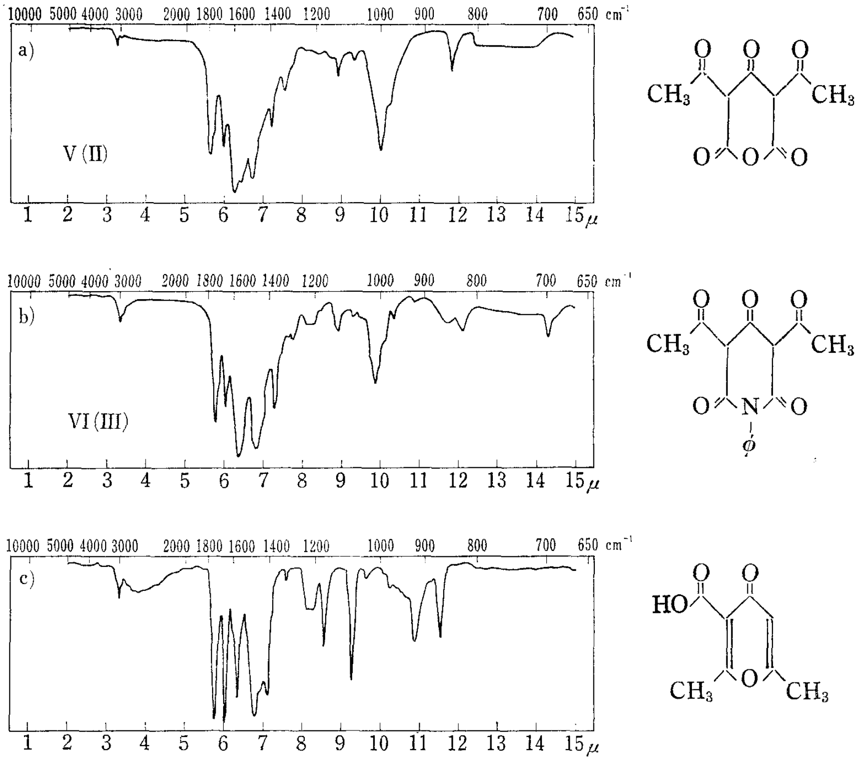

Fig. 1.

In the nuclear magnetic resonance (NMR) spectra of these two, the chemical shifts of two methyl groups fall at τ 7.37, 7.25 for V ($CDCl_3$) and 7.4, 7.36 for VI (pyridine), which suggests the structures of these two being consisted with the tautomerism between the keto and the enol forms, and among several considerable forms likely enol forms are shown in Chart 2.

Experimental

Reaction of Acetonedicarboxylic Acid (I) with Acetic Anhydride——According to the procedure described in the literature,[2] 20 g. of acetonedicarboxylic acid (I) was added to 60 ml. of acetic anhydride at ice temperature. After heating on a steam bath for 10 min., the reaction mixture was cooled to 10°, poured into ice-water to give a crystalline solid, which was collected by suction. Recrystallization from MeOH afforded colorless plates of m.p. 155°, 7.6 g. The filtrate was extracted with ether. The ether layer was dried, filtered, evaporated to give another 2.9 g. Total yield, 10.5 g. (35%). *Anal.* Calcd. for $C_9H_8O_6$ (V): C, 50.95; H, 3.80. Found: C, 51.26; H, 4.01.

Reaction of V with Aniline——To a solution of V (5 g.) in ca. 10 ml. of AcOH was added 2.2 g. of aniline. After heating for 10 min. on a steam bath, the reaction mixture was allowed to stand at room temperature to give crystals. Recrystallization from MeOH gave colorless needles of m.p. 185°. Yield, quantitative. *Anal.* Calcd. for $C_{15}H_{13}O_5N$ (VI): C, 62.71; H, 4.56; N, 4.88. Found: C, 62.50; H, 4.87; N, 4.81.

1-Phenyl-3-acetyl-6-methyl-2,4(1*H*,3*H*)-pyridinedione (IV)——According to the procedure reported by Pechmann,[1] 0.5 g. of VI was distilled under reduced pressure to give a crystalline solid, b.p.$_1$ 215~217°, 0.12 g. Recrystallization from acetone gave colorless needles of m.p. 219~220°. *Anal.* Calcd. for $C_{14}H_{13}O_3N$ (IV): C, 69.12; H, 5.39; N, 5.76. Found: C, 68.93, H, 5.34; N, 5.74. IR ν_{max}^{KBr} cm^{-1}: 1647, 1613.

The NMR spectrum (Varian A-60, TMS as standard, $CDCl_3$ as solvent) exhibit CH_3CO singlet at τ 7.35, 2-methyl protons at τ 8.05 (doublet, J=0.65 c.p.s.), olefinic proton at τ 4.1 (doublet, J=0.65 c.p.s.), proton of 5-position (or 4-OH) at τ −5.76, and phenyl protons at τ 2.4~2.91.

Alkaline Hydrolysis of VI——One gram of VI was dissolved in 10 ml. of 20% NaOH, and the solution was refluxed for 20 min., and then condensed. To the distillate was added 2,4-dinitrophenylhydrazine to give yellow crystals of m.p. 148~149° (from EtOH), undepressed on admixture with an authentic sample of acetone 2,4-dinitrophenylhydrazone. The residue was extracted with ether, and the ether soluble fraction was dried over K_2CO_3, condensed to give a yellow oil, diazo color test positive, which was characterized as its HCl salt, m.p. 195~197°, undepressed on admixture with aniline HCl.

The ether insoluble fraction was neutralized with 2*N* HCl to give CO_2 gas (identified as Ba_2CO_3), and a crystalline solid, which was purified by crystallization to give 75 mg. of dehydroacetic acid (m.p. 104~106°) and a small amount of colorless needles of m.p. 265~266° (decomp.). *Anal.* Calcd. for $C_{13}H_{11}O_4N$ (VII): N, 5.71. Found: N, 5.72. IR ν_{max}^{KBr} cm^{-1}: 1715 (shoulder), 1709, 1634, 1595.

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Summary

Pechmann and Neger[1] reported the reaction of acetonedicaboxylic acid with acetic anhydride to give dehydroacetocarboxylic acid (II), which transformed to its anilide (III) by the treatment with aniline. On the basis of chemical behavior and infrared data, we prefer the correct structures of these two being 3,5-diacetyl-2*H*-pyran-2,4,6(3*H*,5*H*)-trione (V) and 1-phenyl-3,5-diacetyl-2,4,6-piperidinetrione (VI) respectively.

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