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63. Yoshinobu Sato and Takuzo Nishimura : Synthesis of 5-Hydroxymethylquinoline-4-carboxylic Acid Lactone.

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It has been shown earlier[1] that on boiling 1-cyano-3-ethoxycarbonyl- or 1,3-bis(ethoxycarbonyl)-9-methoxymethyl-4-oxo-4*H*-quinolizine with 18~20% hydrochloric acid, the δ-lactone compound, i.e. 3,6-dioxo-1*H*, 3*H*, 6*H*-pyrano[3,4,5-*i*, *j*]quinolizine, is easily formed.

In this instance, the cyano or ethoxycarbonyl group in 1-position of 4-oxo-4*H*-quinolizine compound was saponified to the carboxyl, and at the same time methanol was liberated from that and methoxymethyl group in 9-position to form a δ-lactone. Examinations were therefore made to see if such a reaction would occur in compounds other than quinolizine, such as in quinoline.

The alcohol compound (II), formed by reduction of 5-ethoxycarbonylquinoline (I) with lithium aluminum hydride, was converted to a chloro compound by application of thionyl chloride, reacted with sodium methoxide, and 5-methoxymethylquinoline (III) was obtained. 4-Cyano-5-methoxymethylquinoline (VII) was prepared from (III) according to the method of Kaufmann[2] by the route shown in Chart 1.

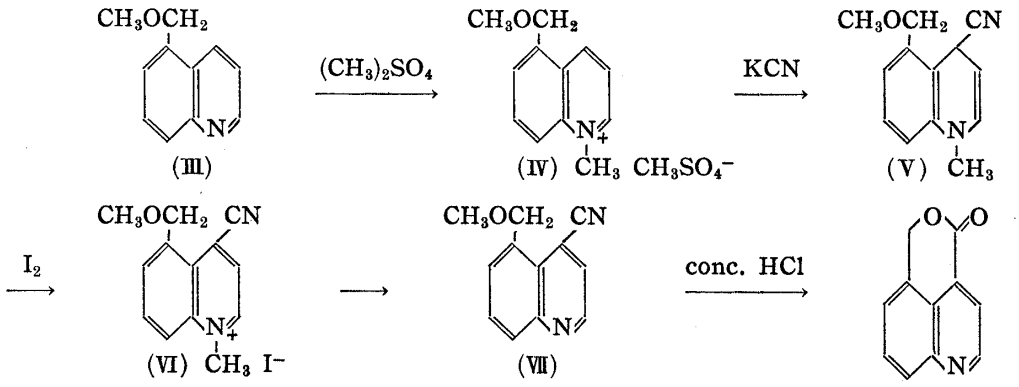

Chart 1.

Saponification of this compound (VII) by boiling with 20% hydrochloric acid for 4 hours afforded colorless crystals, m.p. 156°, whose infrared spectrum exhibited an absorption for δ-lactone at 1724 cm^{-1}, but no absorption for carboxyl. The analytical values of this compound agreed with $C_{11}H_7O_2N$ and it was determined as the δ-lactone compound, i.e. 5-hydroxymethylquinoline-4-carboxylic acid lactone (VIII).

In the compound (VII), the bonds at 4- and 5-positions are on the same plane as that of the quinoline ring and its steric configuration is similar to that of 4-oxo-4*H*-quinolizine.[1] It was thereby proved that a δ-lactone compound is formed with concurrent saponification of the cyano to carboxyl group even in the case of a quinoline compound.

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1) Y. Sato : This Bulletin, **6**, 222(1958); *ibid.*, **7**, 241, 247(1959).
2) A. Kaufmann : Ber., **45**, 1805(1912); *ibid.*, **51**, 116(1918).

Experimental

5-Ethoxycarbonylquinoline (I)—To a mixture of 115.5 g. of quinoline-5-carboxylic acid, prepared by the method of Bradford, *et al.*,[3] and 3500 cc. of EtOH (99%), dry HCl gas was introduced under chilling with ice. After HCl was saturated, the mixture was allowed to stand over night at room temperature. The solvent was distilled off under a reduced pressure, the residue was dissolved in water, neutralized with K_2CO_3, and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4, the solvent was distilled off, and the residue was distilled under a reduced pressure to give a pale yellow oil, b.p_7 170°. Yield, 109.8 g.(83%). *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.44; H, 5.35; N, 7.11.

Picrate: m.p. 166°(from EtOH). *Anal.* Calcd. for $C_{18}H_{14}O_9N_4$: C, 50.24; H, 3.28; N, 13.02. Found: C, 50.42; H, 3.49; N, 13.27.

5-Hydroxymethylquinoline (II)—A mixture of 99.7 g. of (I) in 400 cc. of Et_2O was added dropwise into a solution of 27.5 g. of $LiAlH_4$ in 2700 cc. of Et_2O under chilling and agitation. After the addition was completed, the mixture was refluxed for 1 hr., hydr. Et_2O was added to decompose the excess Li-salt, and inorganic salt was filtered off. The inorganic salt was extracted with MeOH and the combined MeOH extract and the above filtrate was evaporated to give colorless prisms, m.p. 137~138°(from EtOH). *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.45; H, 5.70; O, 10.05; N, 8.80. Found: C, 75.61; H, 5.83. O, 10.10; N, 8.79. UV λ_{max}^{EtOH} mμ(log ε): 228.5(4.54), 231(4.53), 290(3.66), 302(3.61), 315(3.55).

Picrate: m.p. 188~190°(from EtOH). *Anal.* Calcd. for $C_{16}H_{12}O_8N_4$: C, 49.47; H, 3.12; O, 32.97; N, 14.43. Found: C, 49.45; H, 3.08; O, 33.09; N, 14.46.

5-Methoxymethylquinoline (III)—To a mixture of 9 g. of (II) and 500 cc. of benzene, 30 g. of $SOCl_2$ was added dropwise under chilling and agitation. After the addition was completed, the mixture was refluxed for 2.5 hr., the solvent and excess $SOCl_2$ were distilled off under a reduced pressure, and the residual 5-chloromethylquinoline was dissolved in 30 cc. of MeOH. The MeOH solution was added to a solution of NaOMe (prepared from 5.5 g. of Na) in 150 cc. of MeOH and the mixture was refluxed for 4 hr. The solvent was distilled off under a reduced pressure, the residue was dissolved in water, and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4, Et_2O was distilled off, and the residual oil was distilled under a reduced pressure to give a pale yellow oil, b.p_5 110~125°. Yield, 3.3 g.(32.3%). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.42; N, 8.09. Found: C, 76.13; H, 6.59; N, 8.08. UV λ_{max}^{EtOH} mμ(log ε): 231(4.52), 275(4.55), 284(3.67), 302(3.60), 315(3.60).

Picrate: m.p. 178° (from EtOH). *Anal.* Calcd. for $C_{17}H_{14}O_8N_4$: C, 50.75; H, 3.51; N, 13.93. Found: C, 51.02; H, 3.55; N, 14.01.

1-Methyl-4-cyano-5-methoxymethyl-1,4-dihydroquinoline (V)—A solution of 3.3 g. of (III) in 20 cc. of benzene was added dropwise to a solution of 29 g. of Me_2SO_4 in 40 cc. of benzene under agitation. After the addition was completed, the mixture was refluxed for 3 hr. Oily 1-methyl-5-methoxymethylquinoline methosulfate (IV) that separated from the benzene solution was washed with benzene and Et_2O, and dissolved in 10 cc. of water. To the mixture of this aqueous solution and 100 cc. of Et_2O, a saturated aq. solution of 15.5 g. of KCN was added dropwise during 2 hr. under agitation. The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The combined Et_2O solution was dried over anhyd. Na_2SO_4 and the solvent was distilled off to give fine colorless crystals, m.p. 82~83°. Yield, 3.22 g. (79%). *Anal.* Calcd. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.59; O, 7.47; N, 13.08. Found: C, 73.13; H, 6.42; O, 7.60; N, 13.15. UV λ_{max}^{EtOH} mμ(log ε): 237(3.98), 299(3.84). IR $\nu_{max}^{CHCl_3}$: 2247 cm^{-1}(-C≡N).

4-Cyano-5-methoxymethylquinoline (VII)—To a cold solution of 5 g. of (V) in 10 g. of dehyd. pyridine, a solution of 5.5 g. of I_2 in 48 cc. of EtOH was added. The dark red crystals that separated were heated at 170~210° for 3 hr. under a reduced pressure (2 mm. Hg) and the residue was extracted with benzene. The benzene extract was chromatographed over Al_2O_3 to give pale yellow crystals, m.p. 85~87.5°. Yield, 0.5 g. *Anal.* Calcd. for $C_{12}H_{10}ON_2$: N, 14.13. Found: N, 13.96. UV λ_{max}^{EtOH} mμ(log ε): 242(4.41), 316(3.78), 329(3.76). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1096(ether), 2247(-C≡N).

5-Hydroxymethylquinoline-4-carboxylic Acid Lactone (VIII)—A solution of 0.522 g. of (VII) in 35 cc. of 20% HCl was refluxed for 4 hr., adjusted to pH 3.8 with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and the solvent was distilled off to give colorless crystals, m.p. 169° (from Et_2O-EtOH). Yield, 0.407 g. *Anal.* Calcd. for $C_{11}H_7O_2N$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.68; H, 4.31; N, 7.70. UV λ_{max}^{EtOH} mμ(log ε): 242(4.28), 248.5(4.26), 319(3.72), 330(3.74). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724(>C=O), 1171(-C-O-C-).

Picrate: m.p. 194~196° (from EtOH). *Anal.* Calcd. for $C_{11}H_{10}O_9N_4$: C, 49.3; H, 2.44; O, 34.8; N, 13.5. Found: C, 49.48; H, 2.51; O, 34.98; N, 13.45.

3) L. Bradford, T. J. Elliot, F. M. Rowe: J. Chem. Soc., **1947**, 443.

Summary

4-Cyano-5-methoxymethylquinoline was prepared from quinoline-5-carboxylic acid through several steps. This quinoline compound was found to easily form a δ-lactone compound on boiling with conc. hydrochloric acid.

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64. Hisashi Nogami, Jun Hasegawa, and Yoshinobu Nakai*: Studies on Powdered Preparations. II. Studies on Tablet Disintegration of Calcium Carbonate by Thermal Analysis.

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Disintegration time of a tablet is the most important characteristic by which the quality of a tablet is evaluated. The pharmacopoeiae of several countries contain the method of testing this value. The Japanease Pharmacopoeia VI specifies time of disintegration of a tablet in water at 37° under specific conditions; a test tablet is placed in a 100-cc. Erlenmeyer flask, 50 cc. of water is added and shaken occasionally, and the end of disintegration is recognized when the original form of the tablet disappears completely. A testing apparatus is specified in U.S.P. XV and the time necessary for all particles of the tested tablet to pass through a 10-mesh sieve attached to the bottom of a basket assembly is measured.

The end-point of disintegration is not clear by the method of J. P. VI, the deviation may increase by the difference of shaking, the determination is subjective, and moreover, the deviation is not small. The determination of disintegration is more clear and objective by the U.S.P. method, but true determination may not be known exactly.

These methods are very simple in finding the outline of tablet disintegration, but the values are not related directly to physical phenomena such as the increase of surface area and the solution of crystalline medicine contained in a tablet during its disintegration, and details of the phenomena cannot be elucidated.

The process of solution, absorption through the gastric tissues, and the effect on blood concentration were examined by Nelson[2] on theophylline salts and derivatives and he concluded that the rate of solution was determinant. Edward[3] discussed the solution rate of Aspirin crystal after disintegration of the tablet and referred to the effect of absorption.

As can be seen from these reports, disintegration of a tablet is directly responsible for the appearance of medicinal effect. Since the most widely used method is to compress granules into a tablet, the tablet has a secondary structure and is not a simple assembly of microcrystals. Therefore, it is considered that examination of tablet disintegration and its physical process is very important and is required for the elucidation of mechanism of disintegration.

A new method using thermal analysis for the detailed investigation of tablet disintegration is proposed. By this means continuous variation in the surface area of solid medicine can be studied and each stage of disintegration and physical process are easily and distinctly recognized. This method was applied to the tablet of calcium

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1) Part I: Yakuzai-gaku, **18**, 167(1958).
2) E. Nelson: J. Am. Pharm. Assoc., **46**, 607(1957).
3) L. J. Edward: Proc. Roy. Soc., **47**, 1191(1951).