

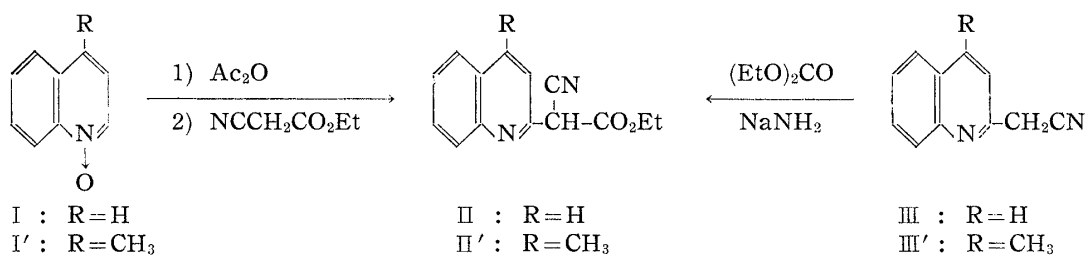
**74. Masatomo Hamana and Motoyoshi Yamazaki : Studies on Tertiary
Amine Oxides. XVI.*¹ Reactions of Quinoline 1-Oxides
with Compounds Containing Reactive Hydrogens
in the Presence of Acetic Anhydride.**

(Institute of Pharmaceutical Sciences, Faculty of Medicine, Kyushu University*²)

In the preceding paper*¹ it was shown that acetyl cyanide reacted as an active hydrogen compound with quinoline 1-oxide in the presence of acetic anhydride to give 2-quinolinepyruvonnitrile. This reaction suggests a promising new method for introduction of a carbon-substituent into the quinoline ring. In order to examine the applicability of the reaction some compounds containing reactive hydrogens were applied to quinoline 1-oxide and its analogues in the presence of acetic anhydride.

When ethyl cyanoacetate was added dropwise to a solution of quinoline 1-oxide (I) in acetic anhydride, an exothermic reaction occurred and crystals separated from the reaction mixture in the similar manner as the reaction of acetyl cyanide. After allowing the reaction to proceed at 30~40° for further 7 hours, crystals were filtered and recrystallized from methanol to give ethyl α -cyano-2-quinolineacetate (II) as yellow crystals, m.p. 166~167°, in 88% yield. The structure of II was established by direct comparison with an authentic specimen prepared from 2-quinolineacetonitrile (III) and diethyl carbonate.¹⁾ In view of the failure²⁾ of its formation from 2-chloroquinoline and ethyl cyanoacetate, this reaction has proved to be very excellent for the synthetic method for II.

From lepidine 1-oxide (I') ethyl α -cyano-4-methyl-2-quinolineacetate (II'), m.p. 176~177°, was similarly obtained, but in considerably lower yield (40%). Its characterization was accomplished in the same way.



The preparation of 4-methyl-2-quinolineacetonitrile (III') necessary for the attempted synthesis of II' was effected by the application of potassium cyanide to 2-chlorolepidine obtained from 2,4-dimethylquinoline 1-oxide and tosyl chloride. Although lepidine 1-oxide reacts with tosyl chloride to yield 4-chloromethylquinoline,³⁾ 2,4-dimethylquinoline 1-oxide gave no 4-chloromethyl derivative but exclusively 2-chloromethyllepidine, which was identified with a sample prepared from 4-methyl-2-quinolinemethanol⁴⁾ and phosphoryl chloride. This result is similar to that of the reaction with acetic anhydride.⁴⁾

*¹ Part XV : This Bulletin, 11, 411 (1963).

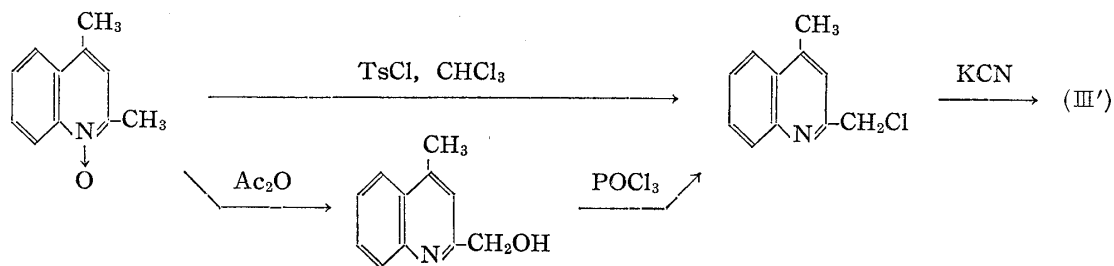
*² Katakasu, Fukuoka (浜名政和, 山崎企善).

1) W. Borsche, R. Mateuffel : Ann., 526, 22 (1936).

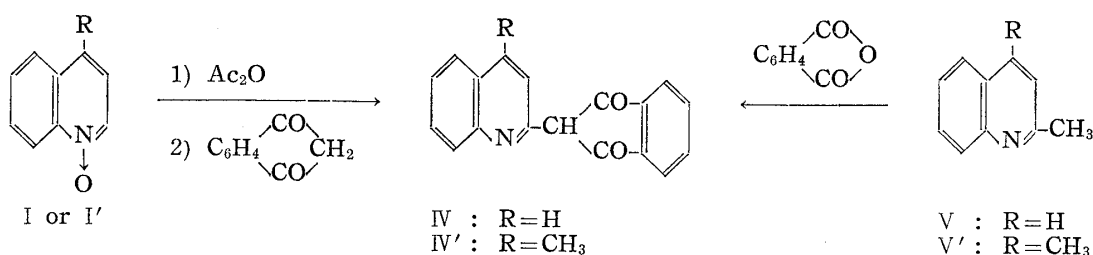
2) Y. Mizuno, K. Adachi, K. Ikeda : This Bulletin, 2, 225 (1954).

3) H. Tanida : Yakugaku Zasshi, 78, 611 (1958).

4) S. Furukawa : This Bulletin, 3, 413 (1955).

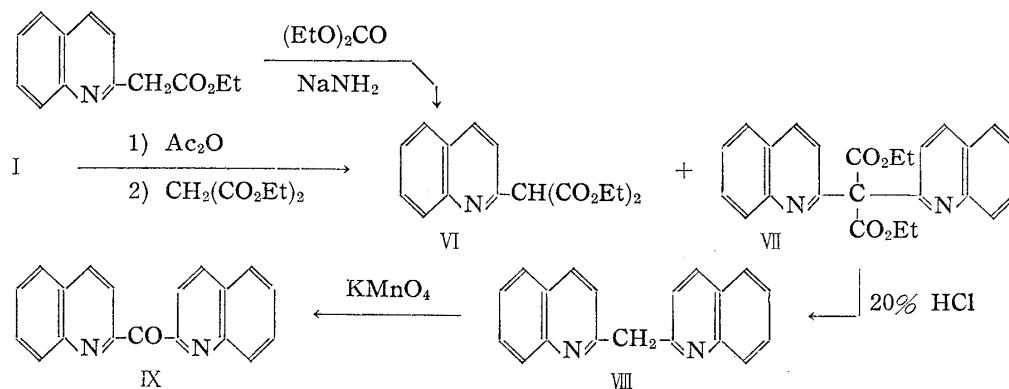


The reactions of 1,3-indandione with I and I' proceeded also smoothly, and quino-phthalone (IV) of m.p. 238~239° and 2-(4-methyl-2-quinolyl)-1,3-indandione (IV') of m.p. 240~241° were obtained in 73% and 55% yields, respectively. They were identified with the samples prepared from the corresponding 2-methylquinolines, V and V', and phthalic anhydride.⁵⁾



Similar application of diethyl malonate to I unexpectedly resulted in preferential formation of a disubstituted product, diethyl di-(2-quinolyl)malonate (VII), colorless scales, m.p. 174~175°, in 34% yield, accompanied by only 7% of diethyl 2-quinolinemalonate (VI), yellow pillars, m.p. 73~74°. Although Lowmann⁶⁾ described that I reacted with benzoyl chloride and sodium derivative of diethyl malonate in dioxane to give VI in 30% yield, the detailed data are not available. Accordingly, the structure of VI was confirmed by the synthesis as shown below.

The structure of VII was deduced from the following facts. VII was a neutral substance of an empirical formula $C_{25}H_{22}O_4N_2$, and its infrared absorption spectrum showed the ester band at 1754 cm^{-1} . Heating VII with hydrochloric acid gave a base, $C_{19}H_{14}N_2$ (VIII), which formed light brown needles of m.p. 107° and lacked an absorption band for ester; VIII was subsequently oxidized with potassium permanganate to another base, $C_{19}H_{12}ON_2$ (IX), of m.p. 165~166°, which showed an infrared absorption band characteristic of a ketone at 1681 cm^{-1} . The properties of VIII and IX agreed with those recorded



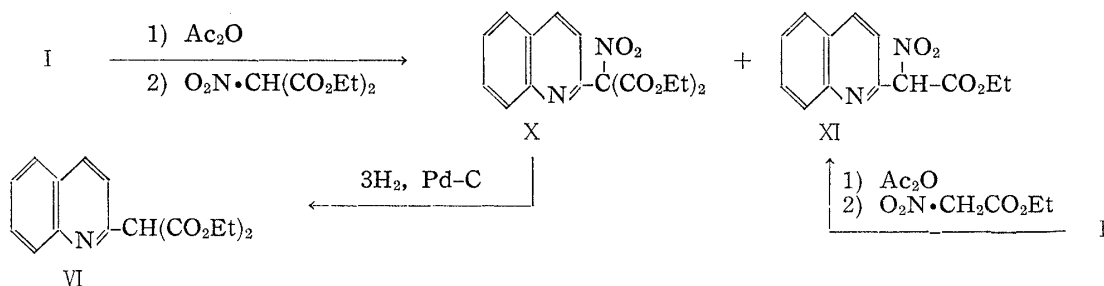
5) A. Eibner, *et. al.*: *Ber.*, **37**, 3006 (1904).

6) R.C. Elderfield: "Heterocyclic Compounds," Vol. II, 245 (1952), John Wiley & Sons, Inc., New York.

by Scheibe⁷⁾ for 2,2'-methylenediquinoline and di-(2-quinolyl)ketone respectively, and the both compounds were identified by direct comparison with samples prepared by the Scheibe's method.⁷⁾

Preferential formation of the disubstituted product (VII) in this case may be ascribed to the fact that the initial product (VI) is easily soluble in the reaction medium in contrast to II, II', IV or IV', and its reactivity as an active hydrogen compound is inherently higher than diethyl malonate because of the attachment of the electron-withdrawing quinoline nucleus. This view was justified by following experiments. The reaction using excess of both diethyl malonate and acetic anhydride under the same condition did not noticeably affected the relative proportion of the products; on the other hand, the reaction of VI with I in acetic anhydride proceeded by far smoothly and VII was obtained in 69% yield.

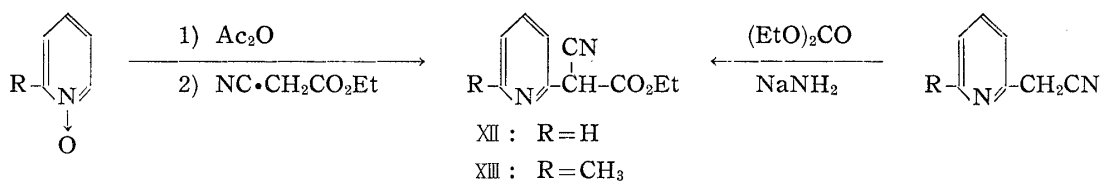
When I was treated with diethyl nitromalonate under the same condition, neither exothermic reaction nor separation of crystals was observed. Separation of the products by passing their chloroform solution through alumina column gave diethyl α -nitro-2-quinolinemalonate (X) in 63% yield and a small amount of ethyl α -nitro-2-quinolineacetate (XI). X, $C_{16}H_{16}O_6N_2$, formed colorless prisms of m.p. 54~55° after recrystallization from petroleum benzin, and its infrared absorption spectrum showed two ester bands at 1779 and 1761 cm^{-1} and two bands for a nitro group at 1508 and 1302 cm^{-1} . When X was hydrogenated over palladium-charcoal, about 3 moles of hydrogen was absorbed and diethyl 2-quinolinemalonate (VI) was obtained. Although not clear in which stage of the reduction it occurred, such a reductive cleavage of carbon-nitrogen linkage has no similar precedent and seems to be very interesting. XI formed yellow needles of an empirical formula $C_{13}H_{12}O_4N_2$, m.p. 124~125°, and its infrared absorption spectrum showed a characteristic ester band at 1724 cm^{-1} and two bands for a nitro group at 1527 and 1314 cm^{-1} . Moreover XI was also able to be obtained in 58% yield from ethyl nitroacetate and I. Therefore, there is no doubt remained about the structure of XI.



Attempted reactions of quinoline 1-oxide with acetone, acetophenone or phenylacetonitrile under similar conditions always failed and the starting materials were recovered almost quantitatively. These results apparently demonstrate that the acidity of a compound containing reactive hydrogens should be considerably high for the initiation of this type of reaction.

When this procedure was applied to pyridine 1-oxide and 2-picoline 1-oxide using ethyl cyanoacetate which had afforded the highest yield in the reactions of quinoline 1-oxide, the corresponding 2-substituted pyridines, XIII and XIII, were obtained in yields of 26 and 17% respectively. Their structures were established by synthesis from the corresponding 2-pyridineacetonitriles as shown below. Comparison of these results with those of quinoline 1-oxides demonstrates favorable activation by the naphthoide structure of quinoline ring in this reaction.

7) C. Scheibe : Ber., 54, 786 (1921).



Finally, quinoline 1-oxide was treated with ethyl cyanoacetate in chloroform or dioxane using benzoyl chloride as the acylating agent. Ethyl α -cyano-2-quinolineacetate (II) was similarly obtained in the both cases, but its yields were consistently lower than 20%. The poor yield would be partly due to the usage of solvent, which was inevitable for smooth formation of the adduct between the N-oxide and benzoyl chloride, but it seems more probable to assume that the nature of acylating agent plays an essential role for the initiation of the reaction.

Experimental

1) Reactions of Quinoline 1-Oxide (I) with Ethyl Cyanoacetate—(a) When ethyl cyanoacetate (1.3 g.) was added dropwise to a mixture of I (1.5 g.) and Ac_2O (1.3 g.) with ice-cooling and stirring, an exothermic reaction occurred and yellowish brown crystals precipitated from the reaction mixture. After standing at $30\sim 40^\circ$ for 7 hr., the crystals were filtered and recrystallized from MeOH to give 2.1 g. (88%) of ethyl α -cyano-2-quinolineacetate (II), yellow scales, m.p. $166\sim 167^\circ$, alone and on admixture with a specimen prepared as described in 2). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{N}_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.99; H, 5.01; N, 11.62. The filtrate from II was made alkaline with K_2CO_3 solution and extracted with CHCl_3 . The extract was shaken with 10% HCl and the acidic layer was separated; from the latter 0.1 g. of I was recovered.

(b) To a solution of I (1.5 g.) in dioxane (5 ml.) was successively added BzCl (1.7 g.) and ethyl cyanoacetate (1.3 g.), and the whole was warmed at $30\sim 40^\circ$ under shaking at times for 10 hr. The reaction mixture was steam-distilled, and the residue was made alkaline with K_2CO_3 and extracted with CHCl_3 . The CHCl_3 solution was extracted with 10% HCl, from which 0.85 g. of I was recovered. Evaporation of the solvent from the CHCl_3 extract gave 0.5 g. of II.

2) Ethyl α -Cyano-2-quinolineacetate (II)—A mixture of 2-quinolineacetonitrile¹⁾ (III) (1 g.) and powdered NaNH_2 (0.5 g.) in anhyd. Et_2O (20 ml.) was refluxed on a water-bath for ca. 10 min. To this mixture was added dropwise diethyl carbonate (20 ml.) at room temperature and the whole was refluxed under stirring for 2 hr. After cooling, the reaction mixture was treated with H_2O to decompose excess NaNH_2 and extracted with Et_2O . The solvent was evaporated and the residual crystals were recrystallized from MeOH to 0.8 g. of II, yellow scales, m.p. $164\sim 166^\circ$. *Anal.* Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{N}_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.15; H, 5.34; N, 11.38.

3) Reaction of Lepidine 1-Oxide (I') with Cyanoacetate—When I' (0.8 g.) was treated with ethyl cyanoacetate (0.7 g.) and Ac_2O (0.7 ml.) in the same way as described in 1), 0.5 g. of ethyl α -cyano-4-methyl-2-quinolineacetate (II') was obtained and 0.3 g. of I' was recovered. II' formed yellow needles of m.p. $176\sim 177^\circ$ after recrystallization from MeOH. The melting point was not depressed on admixture with a specimen prepared by the procedure described in 6). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_2\text{N}_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.64; H, 5.72; N, 10.76.

4) 2-Chloromethyllepidine—(a) To a stirring solution of 2,4-dimethylquinoline 1-oxide (1.7 g.) in CHCl_3 (10 ml.) was added TsCl (2.1 g.) in small portions, and stirring was continued further 5 hr. After shaking with K_2CO_3 solution, the CHCl_3 layer was separated and extracted with 10% HCl. The HCl solution was made again alkaline with K_2CO_3 and extracted with Et_2O . The extract was passed through alumina column and the effluent was crystallized from petr. benzin to afford 0.85 g. of colorless needles, m.p. $59\sim 60^\circ$, of 2-chloromethyllepidine, identical with a sample prepared by the procedure (b). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{10}\text{NCl}$: C, 68.93; H, 5.22; N, 7.31. Found: C, 69.01; H, 5.29; N, 7.36. Picrate: m.p. $186\sim 187^\circ$ (MeOH). *Anal.* Calcd. for: $\text{C}_{11}\text{H}_{10}\text{NCl}\cdot\text{C}_6\text{H}_5\text{O}_7\text{N}_3$: C, 48.51; H, 3.09; N, 13.32. Found: C, 48.81; H, 3.25; N, 13.48.

(b) A solution of 4-methyl-2-quinolinemethanol⁴⁾ (0.5 g.) and POCl_3 (1 g.) in AcOEt (30 ml.) was refluxed on a water bath for 1 hr. and then kept at room temperature for 4 hr. The solvent was removed at aspirator pressure, and the residue was made alkaline with K_2CO_3 solution and extracted with Et_2O . Similar treatment of the extract as in (a) gave 0.55 g. of 2-chloromethyllepidine, colorless needles, m.p. $59\sim 60^\circ$. Picrate: m.p. $186\sim 187^\circ$.

5) 4-Methyl-2-quinolineacetonitrile (III')—A mixture of 2-chloromethyllepidine (3 g.), KCN (1.3 g.), EtOH (50 ml.) and H_2O (5 ml.) was heated under reflux for 2 hr., cooled and the deposited inorganic salts were filtered off. The filtrate was concentrated, made alkaline with K_2CO_3 and extracted with

CHCl_3 . After removal of CHCl_3 , the residue was distilled *in vacuo* and the fraction of b.p._{0.1} 160~180° was collected and crystallized from petr. benzin-Et₂O to 1.7 g. of faintly yellow, short needles of m.p. 45~46°. Picrate: yellow feathers, m.p. 192~194° (MeOH). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2 \cdot \text{C}_6\text{H}_5\text{O}_7\text{N}_3$: C, 52.56; H, 3.19; N, 17.03. Found: C, 52.57; H, 3.28; N, 17.31.

6) **Ethyl α -Cyano-4-methyl-2-quinolineacetate (II')**—III' (0.5 g.) was allowed to react in Et₂O (10 ml.) with NaNH_2 (0.3 g.) and diethyl carbonate (10 ml.) in the same way as described in 2). On similar treatment of the reaction mixture, 0.55 g. (82 %) of II' was obtained as yellow needles of m.p. 176~178° (MeOH).

7) **Reaction of Quinoline 1-Oxide (I) with 1,3-Indandione**—To a mixture of I (1.5 g.) in Ac₂O (1.3 g.) was added dropwise a solution of 1,3-indandione (1.7 g.) in CHCl_3 (10 ml.) with shaking and ice-cooling. After shaking at room temperature for 5 hr. and standing overnight, the precipitated crystals were collected and recrystallized from EtOH to give 1.7 g. of yellow feathers, m.p. 238~239°, of quinophthalone (IV). Additional 0.3 g. of IV was obtained by the concentration of the mother liquor. The total yield was 2 g. (73 %). It did not depress the melting point of the authentic sample.⁵⁾ *Anal.* Calcd. for $\text{C}_{18}\text{H}_{11}\text{O}_2\text{N}$: C, 79.11; H, 4.06; N, 5.13. Found: C, 79.25; H, 4.27; N, 4.78.

8) **Reaction of Lepidine 1-Oxide (I') with 1,3-Indandione**—By the same procedure as described in 7), 2-(4-methyl-2-quinolyl)-1,3-indandione (IV') was obtained in 55 % yield from I'. After recrystallization from EtOH, IV' forms yellow needles, m.p. 240~241°, alone and on admixture with an authentic sample⁵⁾. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{13}\text{O}_2\text{N}$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.46; H, 4.76; N, 4.62.

9) **Reaction of Quinoline 1-Oxide with Diethyl Malonate**—To I (1.5 g.) dissolved in Ac₂O (1.3 g.) was added diethyl malonate (1.9 g.), and the mixture was warmed at 30~40° on a water bath for 20 hr. The precipitated crystals were collected and recrystallized from MeOH to give 0.7 g. (34 %) of colorless scales, m.p. 174~175°, of diethyl di-2-quinolinemalonate (VII). *Anal.* Calcd. for $\text{C}_{25}\text{H}_{22}\text{O}_4\text{N}_2$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.50; H, 5.42; N, 6.75. IR: $\nu_{\text{C=O}}$ 1754 cm^{-1} (Nujol).

After decomposing excess Ac₂O by adding MeOH, the filtrate from VII was concentrated at aspiratory pressure, made alkaline with Na_2CO_3 solution and extracted with CHCl_3 . The extract was evaporated, steam-distilled and the residual solution was again made alkaline with Na_2CO_3 solution and extracted with CHCl_3 . The CHCl_3 solution was washed with 10% HCl to separate unaltered I, evaporated, and the residue was purified by passing its Et₂O solution through alumina column and recrystallized from petr. benzin-Et₂O to 0.1 g. (7 %) of yellow pillars, m.p. 73~74°, of diethyl 2-quinolinemalonate (VI). It did not depress the melting point of an authentic sample prepared as described in 10). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_4\text{N}$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.08; H, 5.98; N, 4.79.

10) **Diethyl 2-Quinolinemalonate (VI)**—Ethyl 2-quinolineacetate¹⁾ (1 g.) was allowed to react in Et₂O (20 ml.) with NaNH_2 (0.5 g.) and diethyl carbonate (20 ml.) in the same way as described in 2). The crude product was purified by passing its Et₂O solution through alumina column and recrystallized from petr. benzin to give 0.8 g. (60 %) of VI as yellow pillars of m.p. 73~74°. *Anal.* Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_4\text{N}$: C, 66.88; H, 5.96; N, 4.88. Found: C, 67.11; H, 6.11; N, 5.14.

11) **Hydrolysis of Diethyl Di-2-quinolylmalonate (VII) with Hydrochloric Acid**—A suspension of VII (1 g.) in 20% HCl (40 ml.) was heated under reflux for 2 hr., VII solving gradually to a clear, red-brown solution. After removal of HCl at aspiratory pressure, the residue was made alkaline with Na_2CO_3 solution and extracted with CHCl_3 . CHCl_3 was evaporated and the residue was recrystallized from petr. ether-Et₂O to give 0.5 g. of 2,2'-methylenediquinoline (VIII) as light brown needles of m.p. 107°, alone and on admixture with an authentic sample.⁷⁾

12) **KMnO₄-Oxidation of 2,2'-Methylenediquinoline (VIII)**—To a solution of VIII (0.5 g.) in Me₂CO (100 ml.) was added finely pulverized KMnO_4 (0.5 g.) and the mixture was allowed to stand at room temperature for 48 hr. Decomposition the excess KMnO_4 with oxalic acid, followed by filtration of precipitates and evaporation of solvent left solide, which was recrystallized from benzene to give 0.3 g. of di(2-quinolyl) ketone as light brown prisms, m.p. 165~166°, alone and on admixture with an authentic sample. IR: $\nu_{\text{C=O}}$ 1681 cm^{-1} (Nujol).

13) **Reaction of Quinoline 1-Oxide (I) with Diethyl 2-Quinolinemalonate**—To I (0.1 g.) dissolved in Ac₂O (0.1 g.) was added diethyl 2-quinolinemalonate (VI) (0.15 g.), and the mixture was warmed at 30~40° for 12 hr. After addition of a small amount of H₂O, the deposited crystals were collected and recrystallized from MeOH to give 0.15 g. (69 %) of colorless scales, m.p. 174~176°, undepressed on admixture with a sample of VII obtained in 10).

14) **Reaction of Quinoline 1-Oxide with Diethyl Nitromalonate**—To quinoline 1-oxide (I) (3.0 g.) dissolved in Ac₂O (2.6 g.) was added diethyl nitromalonate (4.6 g.), and the mixture was warmed at 30~40° for 24 hr. After adding MeOH, the solvent was evaporated and the residue was neutralized with NaHCO_3 solution and extracted with CHCl_3 . The CHCl_3 extract was shaken with 10% HCl to separate unaltered I and purified by passing it through alumina column and eluting with CHCl_3 to give 4.26 g. (63 %) of diethyl α -nitro-2-quinolinemalonate (X) as the first fraction and 0.25 g. of ethyl α -nitro-2-quinolineacetate (XI) as the second. On recrystallization from petr. benzin, X forms colorless prisms,

m.p. 53~54°. *Anal.* Calcd. for $C_{16}H_{16}O_6N_2$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.97; H, 5.05; N, 8.33. IR: $\nu_{C=O}$ 1779, 1761 cm^{-1} , $\nu_{as\ N-O}$ 1580 cm^{-1} , $\nu_{s\ N-O}$ 1302 cm^{-1} (Nujol).

XI was recrystallized from MeOH to give yellow needles, m.p. 124~125°, which showed no depression on admixture with a specimen prepared as described in 16). *Anal.* Calcd. for $C_{13}H_{12}O_4N_2$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.25; H, 4.97; N, 10.61. IR: $\nu_{C=O}$ 1724 cm^{-1} ; $\nu_{as\ N-O}$ 1527 cm^{-1} ; $\nu_{s\ N-O}$ 1314 cm^{-1} (Nujol).

15) Hydrogenation of Diethyl α -Nitro-2-quinolinemalonate (X)—A solution of X (0.5 g.) in MeOH (20 ml.) was hydrogenated at ordinary temperature and pressure over 20% Pd-C. After absorption of 3 moles of H_2 , the catalyst was filtered and the solution was evaporated, a yellow solid being obtained. It forms yellow pillars, m.p. 74~76°, from petr. benzin and was shown to be identical with diethyl 2-quinolinemalonate (VI) obtained in 10) by a mixed melting point determination.

16) Reaction of Quinoline 1-Oxide (I) with Ethyl Nitroacetate—To a solution of I (1.5 g.) in Ac_2O (3 g.) was added dropwise ethyl nitroacetate (1.4 g.) under agitating and ice-cooling, and the mixture was warmed at 40° for 2 hr. After standing at room temperature for 12 hr., the deposited crystals were filtered and recrystallized from MeOH to give 1.4 g. of ethyl α -nitro-2-quinolineacetate (XI), yellow needles, m.p. 124~125°. The filtrate from the above crystals was evaporated after addition of MeOH, the residue was dissolved in $CHCl_3$ and washed with 10% NaOH. The NaOH solution was weakly acidified with dil. HCl and extracted with $CHCl_3$, from which an additional 0.1 g. of XI was obtained. Total yield was 1.5 g. (58%).

17) Reaction of Pyridine 1-Oxide with Ethyl Cyanoacetate—To a solution of pyridine 1-oxide (1.9 g.) in Ac_2O (2.6 g.) was added ethyl cyanoacetate (2.6 g.), and the mixture was allowed to stand at room temperature for 3 days. After adding MeOH to destroy excess Ac_2O , the reaction mixture was evaporated, the residue was made alkaline with $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was shaken with 10% NaOH, the NaOH solution was neutralized with dil. AcOH and extracted with Et_2O . The Et_2O solution was washed successively with $NaHCO_3$ solution and H_2O , and purified by passing through alumina column. The effluent was recrystallized from petr. benzin- Et_2O to afford 1 g. (26%) of slightly yellow scales of ethyl α -cyano-2-pyridineacetate (XII), m.p. 107~108°, which did not depress the melting point of an authentic specimen prepared as described in 18). *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.83; H, 5.34; N, 14.43.

18) Ethyl α -Cyano-2-pyridineacetate (XII)—A mixture of α -cyano-2-pyridineacetonitrile (1 g.) and finely pulverized $NaNH_2$ (0.5 g.) in anhyd. Et_2O (20 ml.) was refluxed for 10 min. on a water bath and then cooled. To this mixture was added diethyl carbonate (20 ml.) and another portion of Et_2O (20 ml.) under ice-cooling, and the mixture was refluxed for 2 hr. After decomposing excess $NaNH_2$ by adding H_2O , aqueous layer was separated, neutralized with AcOH and extracted with $CHCl_3$. The extract was washed with K_2CO_3 solution, dried and passed through alumina column. The effluent was recrystallized from petr. benzin- Et_2O to 1.7 g. of slightly yellow scales of XII, m.p. 107~108°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.33; H, 5.33; N, 15.19.

19) Reaction of 2-Picoline 1-Oxide with Ethyl Cyanoacetate—To a solution of 2-picoline 1-oxide (3.3 g.) in Ac_2O (3.7 g.) was added ethyl cyanoacetate (4.1 g.), and the mixture was warmed at 30~40° for 12 hr. The deposited crystals of XIII (0.6 g.) were filtered and washed with MeOH. The combined filtrate and washings were evaporated at aspiratory pressure, and the residue was made alkaline with K_2CO_3 solution and extracted with $CHCl_3$. The extract was washed with 5% HCl, dried over K_2CO_3 and passed through alumina column. From the effluent an additional 0.45 g. of XIII was obtained. The total yield was 1.05 g. (17%). It forms yellow needles, m.p. 154~155°, from MeOH, and did not depress the melting point of a sample prepared as described in 20). *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 65.18; H, 6.09; N, 13.67.

20) Ethyl α -Cyano-methyl-2-pyridineacetate (XIII)—As described for the preparation of XII, 6-methyl-2-pyridineacetonitrile (1 g.) was allowed to react with $NaNH_2$ (0.5 g.) and diethyl carbonate (20 ml.) in Et_2O . On similar treatment, 0.55 g. of XIII, yellow needles of m.p. 154~155°, was obtained. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.62; H, 5.94; N, 13.62.

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Summary

Quinoline 1-oxides were found to react smoothly with compounds containing reactive hydrogens in the presence of acetic anhydride, producing the corresponding 2-substituted

quinolines. The yields were generally good to excellent in the reactions of ethyl cyanoacetate, 1,3-indandione, diethyl malonate, diethyl nitromalonate, ethyl nitroacetate (e.g. ethyl α -cyano-2-quinolineacetate in 88% yield), but acetone, acetophenone or phenylacetonitrile could not enter into the reaction. The reaction of quinoline 1-oxide using benzoyl chloride instead of acetic anhydride and those of pyridine 1-oxides in the presence of acetic anhydride proceeded similarly but in much lower yields.

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75. Hisao Tsukamoto, Hidetoshi Yoshimura, and Kiyoshi Tatsumi: Metabolism of Drugs. XXXV.*¹ Metabolic Fate of Meprobamate. (3).*² A New Metabolic Pathway of Carbamate Group—The Formation of Meprobamate N-Glucuronide in Animal Body.

(*Institute of Pharmaceutical Sciences, Medical Faculty, Kyushu University**³)

Glucuronic acid conjugation appears to be a common metabolic pathway of drugs which possess hydroxyl, carboxyl, and amino groups. The amino group conjugate, called N-glucuronide, has been extensively investigated in recent years,¹⁾ however no other group has yet been found to form N-glucuronide.

Early in 1961, B. J. Ludwig, *et al.*²⁾ identified the hydroxylated metabolite of meprobamate (2-methyl-2-propyl-1,3-propanediol dicarbamate) in human urine and also commented on the formation of glucuronide of meprobamate, although they failed to obtain it in pure form. Therefore, its chemical structure was not delineated. Later, the authors*² independently isolated meprobamate N-glucuronide with five other metabolites from urine of the rabbit which was administered meprobamate, however the purification and structure elucidation of this particular glucuronide have not been accomplished sufficiently.

We now wish to report that this metabolite has been further purified and that its structure was established to be meprobamate-N-mono- β -D-glucopyranosiduronic acid (I) by means of chemical synthesis.

Methods and Results

Paper Chromatography—In all cases, the development was performed by ascending method using Toyo Roshi No. 50 and the solvent systems of I : BuOH-AcOH-H₂O (4:1:5) and II : BuOH saturated with 3% NH₄OH. The spots on the paper chromatogram were revealed with (a) Ehrlich's reagent (5% *p*-dimethylaminobenzaldehyde solution in MeOH and 1/3 volume of conc. HCl) followed by hot air or (b) NaIO₄ reagent (6.42 g. of NaIO₄ in 750 cc. of H₂O and 250 cc. of *t*-BuOH) followed by benzidine reagent (a mixture of 5.52 g. of benzidine in 500 cc. of *t*-BuOH and 48 g. of NH₄NO₃ in 500 cc. of H₂O). The results are shown in Table I.

*¹ Part XXXIV. K. Kato, K. Yoshida, H. Tsukamoto : This Bulletin, **10**, 1242 (1962).

*² Part (2). A. Yamamoto, H. Yoshimura, H. Tsukamoto : *Ibid.*, **10**, 540 (1962); Part (I). *Idem* : *Ibid.*, **10**, 522 (1962).

*³ Katakasu, Fukuoka (塚元久雄, 吉村英敏, 辰己 淳).

1) J. N. Smith, R. T. Williams : *Biochem. J.*, **44**, 242 (1949); **44**, 250 (1949); E. Boyland, D. Manson, S. F. D. Orr. : *Ibid.*, **60**, 11 (1955); **65**, 417 (1957); S. R. M. Bushby, A. J. Woiwod : *Ibid.*, **63**, 406 (1956); S. Ôgiya, H. Kataoka : *Yakugaku Zasshi*, **79**, 947 (1959); Ôgiya : *Ibid.*, **79**, 953 (1959).

2) B. J. Ludwig, *et al.* : *J. Med. Pharm. Chem.*, **3**, 53 (1961).