acetonitrile by IR spectra comparison and by mixed melting point determination.

b) Reaction of 1,2-Diaminopyridinium Iodide (IX) with Benzoyl Chloride——To 330 mg. of Ⅸ was added 2 ml. of benzoyl chloride. The reaction mixture was refluxed for 1 hr. and added dropwise to water to hydrolyze excess of benzoyl chloride. The resulting solution was made alkaline with 2*N* KOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography on alumina with $CHCl_3$ to give 166 mg. of Ⅶ as colorless needles, m.p. 137~138°(recrystallized from benzene-petr. ether), yield: 61.2%.

Reaction of N-Methylaminopyridinium Chloride (XIII) with Cyanide Ion——In 1 ml. of H_2O was dissolved 340 mg. of XIII (hygroscopic colorless crystal) prepared by hydrolyzing N-methylacetamidopyridinium iodide[4] with HCl (1:1) in order to effect deacetylation and then treating with anion exchange resin (Amberilte IRA-400) treated with saturated NaCl solution. To this was added a solution of 1.5 g. of KCN in 3 ml. of H_2O at a time at room temperature (10~15°). The reaction mixture was allowed to stand overnight and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The resulting residue was separated by chromatography on alumina to give 28 mg. of Ⅲ as the first fraction eluted with ether, which was identified with the authentic sample prepared according to an alternative route by IR spectra comparison and by mixed melting point determination. Yield: 11.5%. In addition to Ⅲ, 10 mg. of hygroscopic yellow crystals (IR: 2200 cm^{-1}, UV $\lambda_{\max}^{\text{EtOH}}$ mμ: 238, 343; m.p. 189~191° (picrate)) and 9 mg. of reddish brown oily product (IR: 1695 cm^{-1}, UV $\lambda_{\max}^{\text{EtOH}}$: 265 mμ) were obtained as the fraction eluted with ether and $CHCl_3$, respectively. However, both of which were not proposed *s*-triazolo[1,5-*a*]pyridine derivatives.

Summary

N-Aminopyridinium salt (I) was reacted with cyanide ion in water at room temperature to give 2-(4-pyridyl)-*s*-triazolo[1,5-*a*]pyridine (Ⅳ). In alkaline medium I exists as an equilibrium mixture with the ylide type, N-iminopyridine (Ⅱ) which was reacted with several nitrile compounds to produce *s*-triazolo[1,5-*a*]pyridine derivatives by 1,3 dipolarcyclo addition. This novel triazole ring could also be synthesized by ring closure of 1,2-diaminopyridinium salt with a carboxylic acid, acid chloride or acid anhydride. Reaction of N-methylaminopyridinium salt (XIII) or N-acetamidopyridinium salt (XIV) with cyanide ion did not afford any 1,3-dipolar cycloaddition products. Explanation for the difference in reactivity among I, XIII and XIV was attempted from each pKa′ values.

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72. Toshihiko Okamoto, Masaaki Hirobe, and Tsuneyoshi Yamazaki:

Reaction of N-Aminopyridinium Derivatives. Ⅳ.[*1] Syntheses of N-Aminoquinolinium Salts and Their Reaction with Cyanide Ion.

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In the previous paper[1] of this series, syntheses of N-aminopyridinium salts and their reaction with cyanide ion were reported as an example of the nucleophilic sub-

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[*1] This paper constitutes Part Ⅷ of series entitled "Reaction Mechanism in Aromatic Heterocyclic Compounds" by T. Okamoto. Part Ⅶ: This Bulletin, **14**, 506 (1966).

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1) T. Okamoto, M. Hirobe *et al.*: Yakugaku Zasshi, **83**, 309 (1963); This Bulletin, **11**, 780 (1963).

stitutions. According to the report, the pyridine ring of N-methylacetamidopyridinium iodide showed reactivity at 2- and 4-positions, especially at 4-position. Thus, cyanation of N-methylacetamidopyridinium iodide mainly provided 4-cyanopyridine. The cyanation of N-alkoxypyridinium salts has also been reported,[2] but in this case, a mixture of 2- and 4-cyanopyridines was always obtained. The above fact shows that the pyridine ring in both types of pyridinium salts is reactive to nucleophilic reagents, but in the case of N-aminopyridinium salt, its 4-position is far more reactive than 2-position.

The present paper relates to syntheses of N-aminoquinolinium salts and their reaction with cyanide ion which was performed in order to investigate the properties of N-aminoderivatives of quinoline.

N-aminoquinolinium iodide (I) was produced from quinoline and hydroxylamine-O-sulphonic acid by the procedure developed by Gösl and Meuwsen.[3] Acylation of I with an excess amount of acetic anhydride and successive treatment with sodium hydroxide provided ylide type compound, N-acetimidoquinoline (III). Alkaline treatment of I in dimethylformamide afforded N-iminoquinoline-dimer (II)[4] acylation of which with acetic anhydride and successive alkaline treatment also gave III. III showed a characteristic IR absorption band near 1565 cm^{-1} as was seen in the case of N-acetimidopyridine. The addition of hydroiodic acid to III provided N-acetamidoquinolinium iodide (IV) and the addition of methyl iodide afforded N-methylacetamidoquinolinium iodide (V).

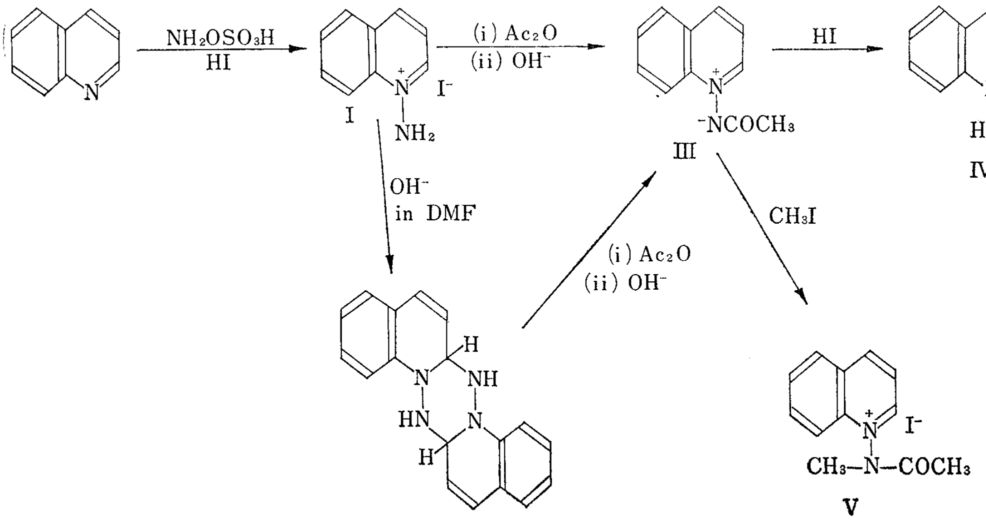

Chart 1.

I, IV, and V are also a kind of quaternary quinolinium salts as N-alkylquinolinium salts and N-alkoxyquinolinium salts and their ring hydrogen is expected to be easily substituted by nucleophilic reagents. In order to make sure of this point, the cyanation of I, IV, and V with potassium cyanide was performed.

Cyanation of I with an excess amount of potassium cyanide in water gave four crystalline products. One of them was a small amount of 4-cyanoquinoline which was identified with an authentic sample prepared according to the Kaufmann's

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2) T. Okamoto, H. Tani : This Bulletin, **7**, 925 (1959); **7**, 930 (1959).
3) R. Gösl, A. Meuwsen : Chem. Ber., **92**, 2521 (1959).
4) R. Huisgen : Angew. Chem., **75**, 604 (1963); Angew. Chem. inter. eddition, **2**, 565 (1963); Proc. Chem. Soc., **1961**, 357.

method.[5] Other three products had the following molecular formulas and UV absorptions:

VI $C_{11}H_5N_3$: m.p. 160~161°; UV $\lambda_{\max}^{EtOH}$ mμ (log ε) : 325 (3.77)
VII $C_{11}H_7ON_3$: m.p. 231°; UV $\lambda_{\max}^{EtOH}$ mμ (log ε) : 323 (3.82)
VIII $C_{20}H_{11}N_5$: m.p. 294°; UV $\lambda_{\max}^{EtOH}$ mμ (log ε) : 350 (4.17), 337 (4.09), and 324 (3.91)

When I was reacted with potassium cyanide in methanol, 4-cyanoquinoline (21%) and VII (7%) were isolated, but neither VI nor VIII was obtained.

VI showed an IR absorption band near 2225 cm^{-1} corresponding to that of cyano-group. Alkaline hydrolysis of VI gave an amorphous acid (IX) (m.p. 242.5~244° (decomp.)), methylation of which with diazomethane gave dimethyl ester (X) (m.p. 131.5°, IR : $\nu_{C=O}$ 1740 cm^{-1}). Thus produced IX and X were proved to be identical with quinoline-2,4-dicarboxylic acid and its dimethyl ester, respectively, prepared by the alternative method.[6] Hence, VI was proved to be 2,4-dicyanoquinoline.

IR absorption spectrum of VII showed characteristic absorption bands near 2240 cm^{-1} ($\nu_{C\equiv N}$) 1710 cm^{-1} ($\nu_{C=O}$), and 3200 and 3500 cm^{-1} (ν_{NH_2}). Alkaline hydrolysis of VII provided quinoline-2,4-dicarboxylic acid, methylation of which gave its dimethyl ester. On the other hand, reaction of VII with sodium nitrite in acetic acid and sulfuric acid gave an acidic product (XI), which was decomposed to 4-cyanoquinoline when heated at a temperature of around 200°. Hence, VII was considered to be 2-carbamido-4-cyanoquinoline.

VIII showed also an IR absorption band at 2230 cm^{-1} corresponding to C≡N group. Alkaline hydrolysis of VIII gave yellow powder (XIII) which provided its methyl ester (XIV) (m.p. 210°) on methylation with diazomethane. VIII could also be prepared by dissolving VI and I in an aqueous acetone and stirring the resulting mixture for an hour in the presence of potassium bicarbonate and XIV could also be prepared by reacting I and methyl 2-cyanocinchoninate (XV)[6] (m.p. 133°) in dimethylformamide in the presence of potassium bicarbonate. From these facts, it is clear that VIII was 2-(4-cyano-2-quinolyl)-*s*-triazolo[1,5-*a*]quinoline and XIV was 2-(4-methoxy carbonyl-2-quinolyl)-*s*-triazolo[1,5-*a*]quinoline, respectively.

When I was reacted with methyl 4-cyanoquinaldate (XII) obtained by the methylation of XI with diazomethane, in the presence of potassium bicarbonate under analogous condition, only the starting material was recovered.

Reaction of IV with cyanide ion has also been attempted, but the starting material was always recovered as ylide form (III) in this case.

Reaction of V with potassium cyanide in water at room temperature gave colorless needles, whose IR absorption spectrum showed a band near 2220 cm^{-1}($\nu_{C\equiv N}$) and a band near 1665 cm^{-1} ($\nu_{C=O}$). This crystalline product was easily decomposed to give 2-cyanoquinoline and N-methylacetamide by recrystallization from an organic solvent. Therefore, the colorless crystalline product is considered to be an intermediate, 1-methylacetamido-2-cyano-1,2-dihydroquinoline (XVI).

In the reaction of I with cyanide ion, a cyano compound first produced is then reacted with N-iminoquinoline by means of 1,3-dipolar cycloaddition to form *s*-triazolo ring and in the reaction of V, comparatively stable dihydro-type intermediate could be separated. The reaction similar to the above has also been observed in the reaction of N-aminopyridinium salt with cyanide ion.[1,7] However, production of dicyano-compound is characteristic reaction of N-aminoquinolinium salt and its reaction mechanism is now under investigation.

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[5] A. Kaufmann : Ber., **42**, 776 (1909); **44**, 2058 (1911); **51**, 116 (1918).
[6] W. Pfitzinger : J. prakt. Chem., (2), **56**, 238 (1897); **66**, 263 (1902).
[7] T. Okamoto, M. Hirobe, *et al.* : This Bulletin, **14**, 506 (1966).

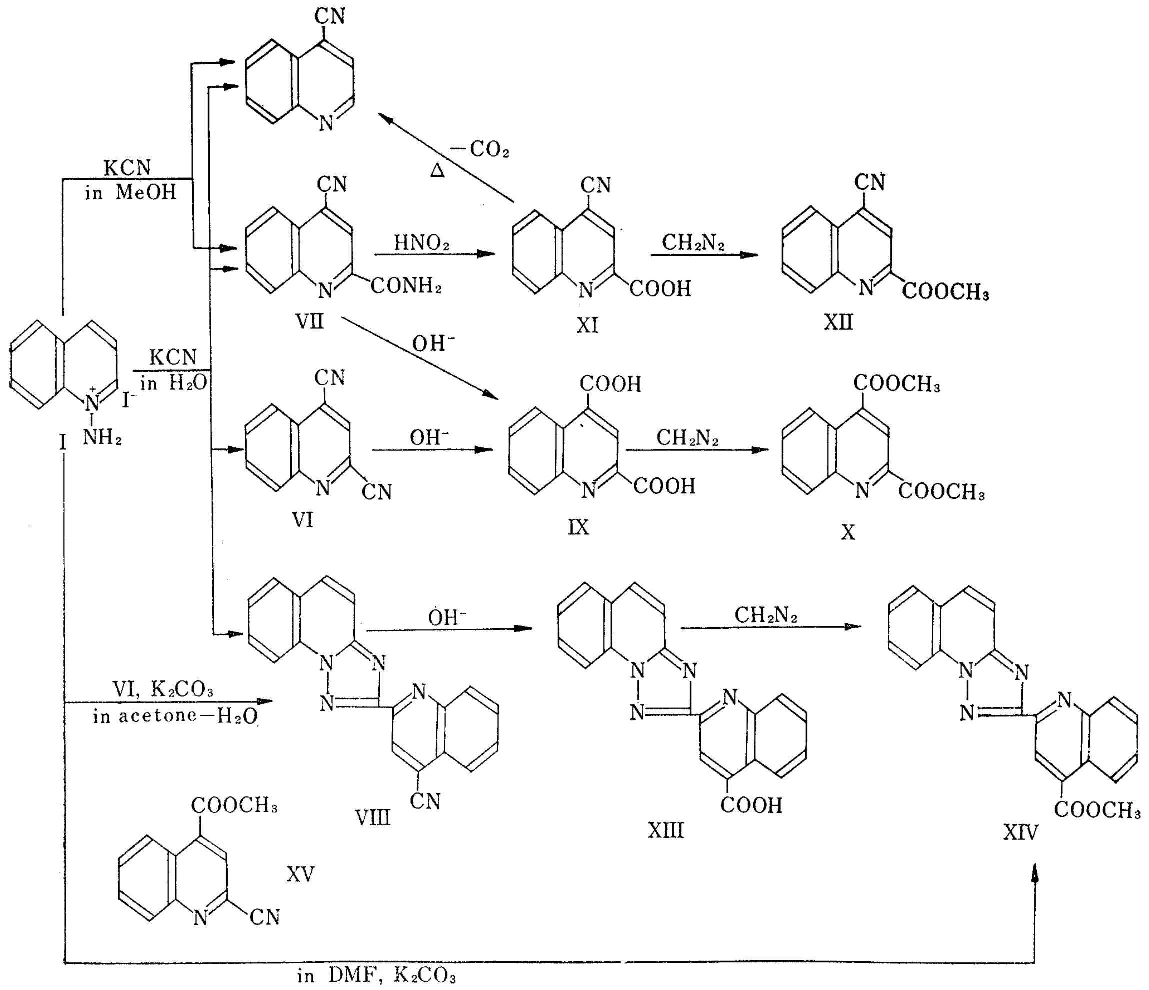

Chart 2.

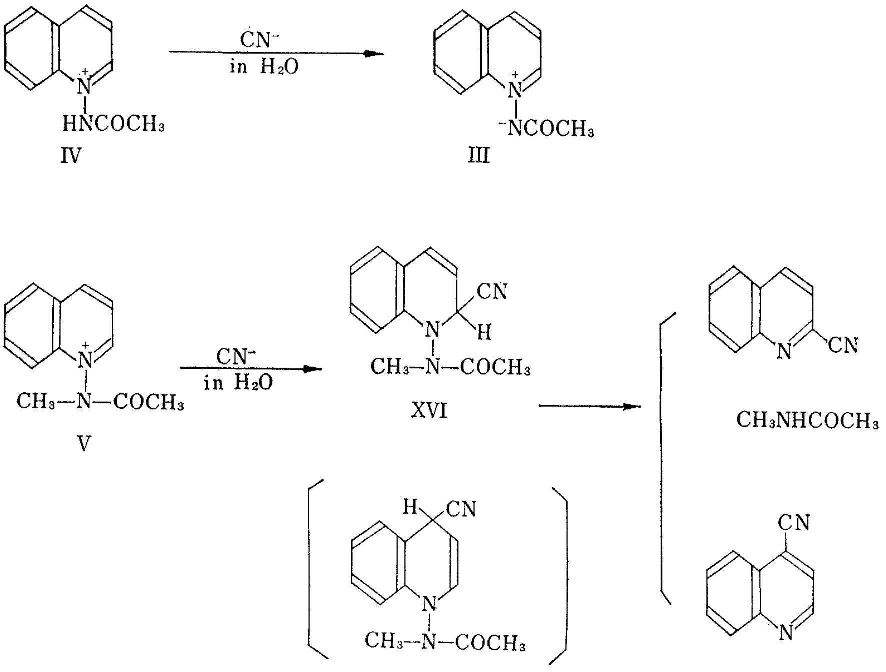

Chart 3.

Experimental

N-Aminoquinolinium Iodide (I)——A solution of 40 g. (0.35 mole) of NH_2OSO_3H in 80 ml. of H_2O was neutralized with an aqueous solution of 19.6 g. (0.35 mole) of KOH. This solution was added dropwise to 90 g. (0.7 mole) of quinoline warmed on a water bath at 70~80° during the course of 15 min. The reaction mixture was further stirred for 35 min. at 70~80°. After cooling, 24 g. of K_2CO_3 dissolved in 80 ml. of H_2O was added to the reaction mixture, which was then washed with ether to remove unreacted quinoline and concentrated to 100 ml. at a temperature below 40° under a reduced pressure. To the concentrated mixture, 400 ml. of EtOH was added and the precipitated inorganic salt was filtered off. To the filtrate was added 50 ml. of 57% HI and the solution was cooled with acetone-dry ice. The precipitated crude crystalline product was filtered and recrystallized from EtOH to give 17.9 g. of I as yellowish red plates, yield: 20%, m.p. 178~179° (decomp.): picrate, 169° (decomp.). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 318 (3.86). *Anal.* Calcd. for $C_9H_9N_2I$: C, 39.73; H, 3.33; N, 10.30. Found: C, 39.47; H, 3.70; N, 10.19.

N-Iminoquinoline Dimer (II)——To a solution of 3.62 g. of I dissolved in 40 ml. of dimethylformamide, 2 g. of K_2CO_3 was added and the reaction mixture was stirred at room temperature for 2 hr. To this was slowly added 60 ml. of H_2O. The precipitated crystalline product was filtered and washed with MeOH. Thus, 1.54 g. of II was obtained, m.p. 155~156° (decomp.): picrate, 182~183.5° (decomp.). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 318 (3.82). *Anal.* Calcd. for $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43. Found: C, 74.74; H, 5.72; N, 19.34. *Anal.* Calcd. for $C_{18}H_{16}N_4 \cdot C_{12}H_6O_{14}N_6$ (di-picrate): C, 48.26; H, 2.97; N, 18.76. Found: C, 48.02; H, 3.22; N, 18.97.

N-Acetimidoquinoline (III)——A solution of 960 mg. of II dissolved in 20 ml. of acetic anhydride was allowed to stand overnight at room temperature, poured into 20 ml. of H_2O, made alkaline with NaOH and extracted with $CHCl_3$ for several times. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and evaporated to dryness under a reduced pressure to give 695 mg. of III as hygroscopic pale yellow needles, yield: 57%, m.p. 89~90°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 322 (3.82), picrate; m.p. 198° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_8N_5$ (picrate): C, 49.16; H, 3.16; N, 16.86. Found: C, 49.54; H, 3.17; N, 17.00.

N-Acetamidoquinolinium Iodide (IV)——To a solution of 710 mg. of III in 10 ml. of EtOH, 2 ml. of 57% HI was added. The mixture was cooled with ice and separated crystals were filtered to give 498 mg. of IV, (recrystallized from EtOH), m.p. 202° (decomp.): picrate, 198° (decomp.). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 318 (3.85). *Anal.* Calcd. for $C_{11}H_{11}ON_2I$: C, 42.08; H, 3.50; N, 8.92. Found: C, 42.07; H, 3.42; N, 8.94.

N-Methylacetamidoquinolinium Iodide (V)——A suspension of 291 mg. of III in 25 ml. of CH_3I was allowed to stand overnight at room temperature. Excess of CH_3I was evaporated under a reduced pressure and the residue was recrystallized from EtOH to give 362 mg. of V as yellow plates, m.p. 172~174° (decomp.), yield: 71%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 318 (3.91). *Anal.* Calcd. for $C_{12}H_{13}ON_2I$: C, 43.92; H, 3.99; N, 8.57. Found: C, 43.91; H, 3.84; N, 7.88.

Reaction of N-aminoquinolinium Iodide (I) with Cyanide Ion——A) To a solution of 15 g. of I in 250 ml. of H_2O was added 15 g. of KCN dissolved in 100 ml. of H_2O. The reaction mixture was allowed to stand at room temperature for 20 min. and the precipitated solid was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 10% HCl and evaporated to dryness. The residue (3.54 g.) was chromatographed on Al_2O_3 to give 0.62 g. of VI (eluted with ether), 0.82 g. of VIII (eluted with ether-$CHCl_3$ (1:1) to $CHCl_3$) and 1.46 g. of VII (eluted with $CHCl_3$ containing 0.5% of MeOH). The HCl layer was made alkaline with aqueous NaOH solution and extracted with $CHCl_3$. The residue (3.69 g.) obtained on evaporation of the solvent was chromatographed on Al_2O_3 to give 0.26 g. of 4-cyanoquinoline from the fraction eluted with ether. *Anal.* Calcd. for $C_{11}H_5N_3$ (VI): C, 73.73; H, 2.81; N, 23.45. Found: C, 73.68; H, 2.85; N, 23.53. *Anal.* Calcd. for $C_{11}H_7ON_3$ (VII): C, 67.00; H, 3.58; N, 21.31. Found: C, 66.94; H, 3.60; N, 21.42. *Anal.* Calcd. for $C_{20}H_{11}N_5$ (VIII): C, 74.74; H, 3.44; N, 21.81. Found: C, 74.87; H, 3.40; N, 21.43.

B) To a solution of 1 g. of I in 50 ml. of MeOH was added a solution of 1 g. of KCN in 50 ml. of MeOH. The reaction mixture was allowed to stand overnight at room temperature, evaporated to dryness and extracted with H_2O. The remaining residue was separated by alumina chromatography to give 26 mg. of 4-cyanoquinoline (eluted with benzene). On the other hand, the aqueous solution was further extracted with ether and the extract was separated by alumina chromatography to give 119 mg. of 4-cyanoquinoline (eluted with hexane-$CHCl_3$ (1:2)) and 61 mg. of VII (eluted with $CHCl_3$ containing 1% of MeOH). Total yield: 4-cyanoquinoline, 25.6%; VII, 8.4% (calculated from I).

Hydrolysis of 2,4-Dicyanoquinoline (VI)——To a solution of NaOH in 6 ml. of EtOH-H_2O (1:1), 84 mg. of VI was added. The resulting solution was refluxed on a water bath for 12 hr. After cooling, the reaction mixture was acidified with conc. HCl. The precipitated amorphous solid was filtered and washed with H_2O to give 80 mg. of IX, m.p. 242.5~244° (decomp.).

Reaction of 4-Cyanoquinaldamide (VII) with Sodium Nitrite——To a solution of 150 mg. of VII in 20 ml. of acetic acid was added 2 ml. of 10% (w/v) solution of $NaNO_2$ in H_2SO_4. The reaction mixture was allowed to stand at room temperature for 2 hr. and then concentrated to half its volume under reduced pressure. To the concentrated mixture was added 10 ml. of H_2O and then gradually 20% NaOH solution. Under pH 1, 110 mg. of XI was obtained as crystals, m.p. 214° (decomp.).

Pyrolysis of 4-Cyanoquinaldic Acid (XI)——In a glass tube (one side of which was sealed) 28 mg. of XI was placed and heated on an oil bath. Pyrolysis was started at temperatures around 190～200°. The glass tube was further heated to 220°. After cooling, the bottom of the glass tube was crushed and the contents were washed out with ether and purified by chromatography on alumina to give 8 mg. of 4-cyanoquinoline.

2-(4-Cyano-2-quinolyl)-*s*-triazolo[1,5-*a*]quinoline (VIII)——To a solution of 64 mg. of I and 108 mg. of VI dissolved in 7 ml. of acetone-H_2O (6:1), 84 mg. of K_2CO_3 was added. The reaction mixture was stirred at room temperature for 1 hr. The precipitated white crystalline product was filtered and recrystallized from benzene to give 42 mg. of VIII, m.p. 294°. The filtrate of the reaction mixture was concentrated and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was chromatographed on Al_2O_3 to give 24 mg. of VIII and 52 mg. of the starting material (VI).

Hydrolysis of 2-(4-Cyano-2-quinolyl)-*s*-triazolo[1,5-*a*]quinoline (VIII)——In 20 ml. of 5% NaOH solution in aqueous alcohol (H_2O-EtOH=1:1) was heated 70 mg. of VIII for 8 hr. After cooling, the separated white needles were filtered (yield : 55 mg.), and dissolved in 20 ml. of H_2O. To this solution was added 3 drops of conc. HCl, to provide 19 mg. of XIII as pale yellow powder, m.p. above 300°. XIII was methylated with diazomethane to give the methylester (m.p. 210～212°) which was confirmed to be identical with 2-(4-methoxycarboxyl-2-quinolyl)-*s*-triazolo[1,5-*a*]quinoline (XV), prepared by reacting I and XIV, by IR and mixed melting point determination.

2-(4-Methoxycarbonyl-2-quinolyl)-*s*-triazolo[1,5-*a*]quinoline (XIV)——To a solution of 570 mg. of I and 232 mg. of XV in 10 ml. of dimethylformamide, 500 mg. of K_2CO_3 was added and the reaction mixture was allowed to stand at room temperature for 2 days. The precipitated crystalline product was filtered and dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with a small amount of 2*N* HCl, dried over anhyd. Na_2SO_4, and evaporated to dryness. The residue was recrystallized from benzene to give 190 mg. of XV. Yield : 51% (calculated from XIV), m.p. 212°. UV λ_{max}^{EtOH} mμ (log ε) : 338 (4.07). *Anal.* Calcd. for $C_{21}H_{14}O_2N_4$: C, 71.18; H, 3.98; N, 15.81. Found : C, 71.01; H, 4.01; N, 15.90.

Reaction of N-Acetamidoquinolinium Iodide (IV) with Cyanide Ion——To a solution of 144 mg. of IV in 3 ml. of H_2O, was added 110 mg. of KCN dissolved in 2 ml. of H_2O. The reaction mixture was allowed to stand for 30 min. and extracted with $CHCl_3$. Thus, 71 mg. of III "ylide" form of IV, was recovered as needles, m.p. 88.5～90°.

Reaction of N-Methylacetamidoquinolinium Iodide (V) with Cyanide Ion——To a solution of 436 mg. of V in 5 ml. of H_2O, 454 mg. of KCN dissolved in 4 ml. of H_2O was added. The reaction mixture was allowed to stand at 0° for 30 min. The precipitated crystalline product was filtered, and recrystallized from hexane to give 118 mg. of 2-cyanoquinoline (m.p. 95.5～96°). The filtrate of the reaction mixture was extracted with ether and the combined extract and hexane filtrate was evaporated to dryness. The residue was chromatographed on Al_2O_3 to give 29 mg. of 2-cyanoquinoline, a small amount of 4-cyanoquinoline (6 mg. as the picrate) from the fraction eluted with hexane-$CHCl_3$ (4:1 to 2:1) and 22 mg. of N-methylacetamide from the fraction eluted with $CHCl_3$. Total Yield : 2-cyanoquinoline, 72%; 4-cyanoquinoline, 1.2%; N-methylacetamide, 23%.

Summary

N-Aminoquinolinium iodide (I) was treated with alkali in dimethylformamide to afford N-iminoquinoline dimer (II) which was further converted into N-acetimidoquinoline (III) by the reaction with acetic anhydride and successive alkaline treatment. The addition of hydroiodic acid or methyl iodide to III provided N-acetamidoquinolinium iodide (IV) or N-methylacetamidoquinolinium iodide (V) respectively.

Reaction of I, IV, and V with cyanide ion was investigated. In water, I provided four products; 4-cyanoquinoline, 2,4-dicyanoquinoline (VI), 4-cyanoquinaldamide (VII) and 2-(4-cyano-2-quinolyl) -*s*-triazolo[1,5-*a*]quinoline (VIII), but in methanol two products; 4-cyanoquinoline and VII. V was also reacted in water to give a reaction intermediate, 1-methylacetamido-2-cyano-1,2-dihydroquinoline (XVI) which was easily decomposed to 2-cyanoquinoline and N-methylacetamide quantitatively. But IV did not afford any products as above and was recovered as its ylide compound (III).

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