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On the Reaction of Quinazoline with Active Methylene Compound

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The reaction of quinazoline (I) with active methylene compound in the presence of sodium amide were carried out and resulted in the formation of 4,4′-biquinazoline (III) and 4-substituted quinazoline. Thus reaction with phenylacetonitrile gave III and α-phenyl-4-quinazolineacetonitrile (IV), with ethyl cyanoacetate, III and methyl α-cyano-4-quinazolineacetate (V), with nitromethane, III and 4-(nitromethyl)quinazoline (VI), respectively. But in the case of the reaction with malononitrile, it gave III, 2-amino-3-quinolinecarbonitrile (VII) and 2-amino-6-methoxy-3,5-pyridinedicarbonitrile (VIII).

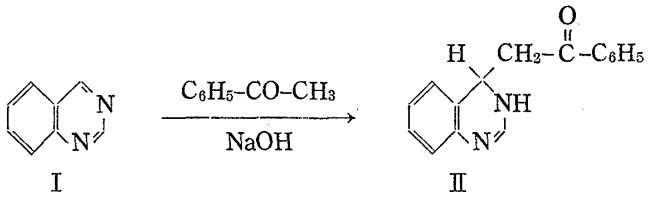
The reaction of I with active methylene compound without a base catalyst was also carried out and succeeded in finding the transformation of I into quinoline derivatives. Thus, the reaction with malononitrile gave VII, with ethyl cyanoacetate, ethyl 2-amino-3-quinolinecarboxylate (XV) and 2-hydroxy-3-quinolinecarbonitrile (XVI), with phenylacetonitrile, 2-amino-3-phenylquinoline, respectively. But in the case of the reaction with diethyl malonate, ethyl 4-quinazolineacetate (XVIII) was obtained.

1. The Reaction of Quinazoline (I) with Active Methylene Compound in the Presence of Methoxide Ion

Quinazoline (I) has been shown to add several nucleophilic reagents across 3,4-position of pyrimidine ring.[2] For example, the reaction of I with acetophenone in the presence of sodium hydroxide solution at room temperature gave 2-(3,4-dihydro-4-quinazolinyl)acetophenone (II).[2b] This reactivity has been explained due to overlapping of —M and —E effects of ring nitrogen atom and the effect of the fused benzene ring at 4-position.

As a similar reaction might be expected between 3,4-position of I, in this paper the reaction with several active methylene carbanions were carried out.

The reaction of I with active methylene compound in the presence of methoxide ion at room temperature afforded 4,4′-biquinazoline (III) and the corresponding 4-substituted quinazoline. For example, in the case of the reaction with phenylacetonitrile, III and α-phenyl-4-quinazolineacetonitrile (IV), with ethyl cyanoacetate, III and methyl α-cyano-4-quinazolineacetate (V), and with nitromethane, III and 4-(nitromethyl)quinazoline (VI)were given, respectively.



I II

Chart 1

But in the case of the reaction with malononitrile, it proceeded different way from them described above. It gave III, 2-amino-3-quinolinecarbonitrile (VII) and 2-amino-6-methoxy-3,5-pyridinedicarbonitrile (VIII) accompanied with elimination of ammonia.

The compound III was determined its structure to be 4,4′-biquinazoline by mixed melting point test with specimen[3] prepared from the reaction between I and sodium cyanide. The compound IV was also done its structure to be α-phenyl-4-quinazolineacetonitrile by mixed melting point test with specimen[4] prepared from the reaction between 4-chloroquin-

1) Location: *2-2-1 Oshika, Shizuoka-Shi.*
2) *a*) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960); *b*) E. Hayashi, and T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **12**, 1111 (1964).
3) W.L.F. Armarego, and R.E. Willette, *J. Chem. Soc.*, **1965**, 1258.
4) Y. Mizuno, K. Adachi, and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **2**, 225 (1954).

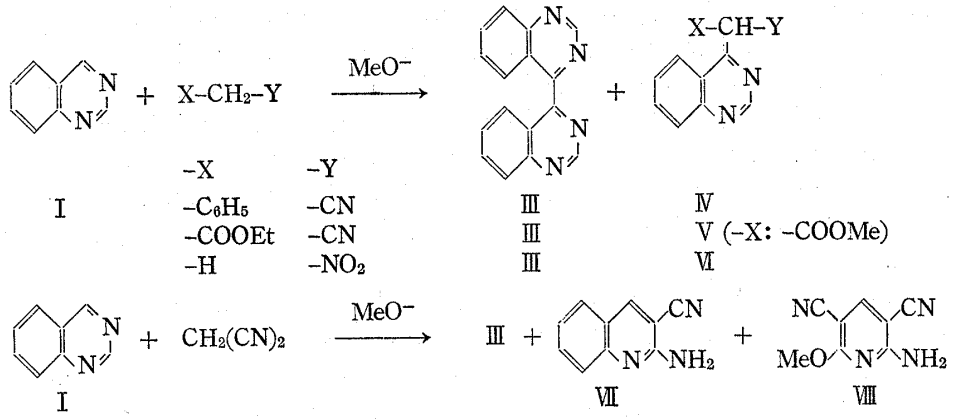


Chart 2

azoline (IX) and phenylacetonitrile in the presence of sodium amide. The compound V was also done its structure to be methyl α-cyano-4-quinazolineacetate by the correspondence of its photometric data with those of specimen prepared from the reaction between ethyl α-cyano-4-quinazolineacetate (X)[4] and methoxide ion. The compound VI was also done its structure to be 4-(nitromethyl)quinazoline by the correspondence its photometric data with those of specimen[5] prepared from the reaction between 4-quinazolinecarbonitrile (XI) and nitromethane in the presence of potassium carbonate. The compound VII was also done its structure to be 2-amino-3-quinolinecarbonitrile by mixed melting point test with specimen[6] prepared from the reductive cyclization of 2-nitro-α-cyanocinnamonitrile (XII). The compound VIII was also done its structure to be 2-amino-6-methoxy-3,5-pyridinedicarbonitrile by mixed melting point test with specimen[7] prepared from the reaction of malononitrile with haloform in the presence of methoxide ion.

In order to elucidate the reaction process for the formation of III and 4-substituted quinazoline, IV, V, and VI, we took the reaction with phenylacetonitrile as a sample and carried out following experiments.

As there was a possibility that III was formed by attacking methoxide ion to I, the reaction of I with methoxide ion was made. But none of III was obtained in this reaction. And when the reaction of I with phenylacetonitrile in the presence of methoxide ion was carried out in nitrogen stream, dark place, yields of III and IV did not show any change.

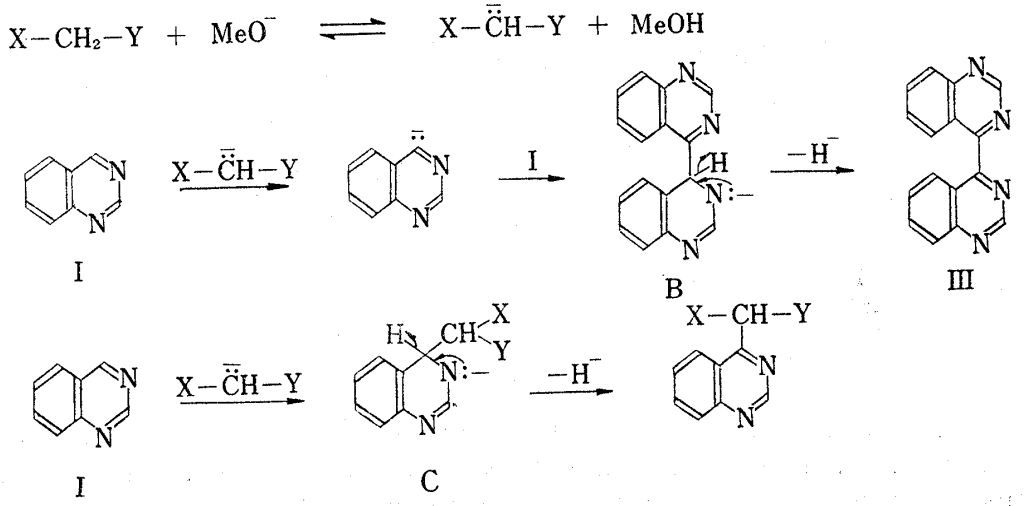


Chart 3

5) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **10**, 1052 (1962).
6) H. Junek, *Monatsh*, **94**, (5), 890 (1963).
7) A.P. Krapcho and P.S. Huyffer, *J. Org. Chem.*, **28** (9), 2461 (1963).

Those fact showed that the formations of III and IV were independent of oxygen in air or photochemical reaction and should need phenylacetonitrile carbanion.

So the reaction process for the formation of III might be considered as a following manner. The active methylene carbanion which was formed by equilibrium between active methylene compound and methoxide ion attacked the proton of 4-position of I to resulted in the formation of quinazoline carbanion (A). This carbanion reacted to ring carbon atom of 4-position of excess of I to give B type of intermediate, followed by elimination of hydride ion to form III.

The corresponding 4-substituted quinazoline, IV, V, and VI might be also formed through the following route. The active methylene carbanion described above attacked 4-position's ring carbon atom of I to give C type of intermediate which eliminated hydride ion to resulted in the formation of the corresponding 4-substituted quinazoline.

Although I might be considered to be hydride ion acceptor in this reaction, it could not be isolated reduction products such as 3,4-dihydroquinazoline (XIII) which was easily oxidized to form I. Consequently it could not clear the substance to be hydride ion acceptor.

The reaction process for the formations of VII and VIII would be described in Section 2.

2. The Reaction of I with Active Methylene Compound without Base Catalyst (The Transformation of I into Quinoline Derivatives)

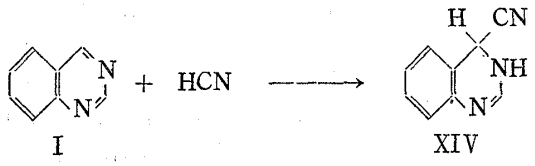


Chart 4

It has been well known that the reactions of I with several ketones[2b,8] should be carried out in the presence of base catalyst such as methoxide ion. No study has been published on the reactions between I and several carbanions without base catalyst except that of I with hydrogen cyanide affording 3,4-dihydro-4-quinazolinecarbonitrile (XIV).[2a]

In this section we carried out the reactions of I with several active methylene compounds without a base catalyst and succeeded in finding the transformation of I into quinoline derivatives.

Thus the reactions of I with malononitrile, ethyl cyanoacetate and phenylacetonitrile gave VII, ethyl 2-amino-3-quinolinecarboxylate (XV), 2-hydroxy-3-quinolinecarbonitrile (XVI) and 2-amino-3-phenylquinoline (XVII), respectively, as shown in Chart 5. But in the case of diethyl malonate, ethyl 4-quinazolineacetate (XVIII) was obtained.

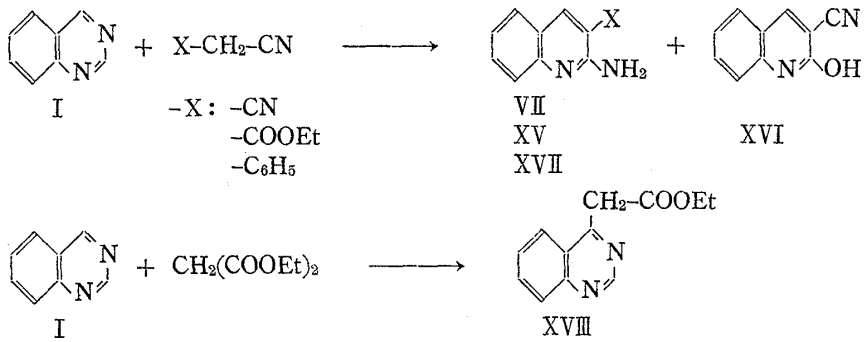


Chart 5

The compound XV was determined its structure to be ethyl 2-amino-3-quinolinecarboxylate by mixed melting point test with specimen[9] prepared from H. Pupe *et al.* method. The compound XVI was also done its structure to be 2-hydroxy-3-quinolinecarbonitrile by mixed melting point test with specimen[6] prepared from the reaction of VII with nitrous

8) E. Hayashi and T. Higashino, *Chem. Pharm. Bull.* (Tokyo), 13, 291 (1965).
9) H. Pupe and A. Hechendorn, *Helv. Chem. Acta.*, 9, 983 (1926).

acid. The compound XVII was also done its structure to be 2-amino-3-phenylquinoline[10] by mixed melting point test with specimen prepared by Pschorr's method. The compound XVIII was also done its structure to be ethyl 4-quinazolineacetate by mixed melting point test with specimen[4] prepared from the reaction of IX with ethyl acetoacetate in the presence of sodium amide.

In order to elucidate the reaction process of this transformation, we took the reaction with malononitrile as a sample and carried out the following experiment.

The relationship between yield of VII and molar ratio of malononitrile against I changing 1, 1.5, 2.0, and 3.0 showed that the transformation should need more than two moles of malononitrile against one mole of I as shown in Table I.

Table I. Rerationship between Yield of VII and Molar Ratio of $CH_2(CN)_2$/I

Yield of VII (%)	Molar ratio of $CH_2(CN)_2$/I	Yield of VII (%)	Molar ratio of $CH_2(CN)_2$/I
39.1	1.0	81.0	2.0
66.8	1.5	78.9	3.0

Moreover, it has been reported by K. Adachi[11] and E. Hayashi[12] that ring of I was cleavaged between 2 and 3 position to afford N-(hydroxyiminomethyl)anthraniloaldehyde oxime (XIX) accompanied with elimination of ammonia by application with hydroxylamine.

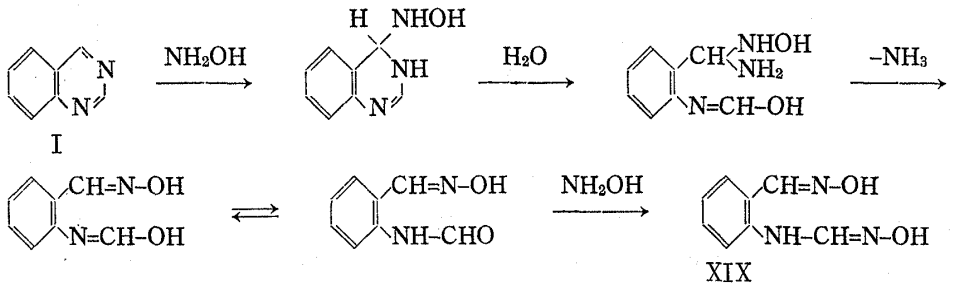


Chart 6

Considering the facts described above, the possible reaction process might be proposed to involve a route shown in Chart 7.

Thus active methylene group may attack 4-position of I which is susceptible to nucleophilic reagent to form an intermediate such as 3,4-dihydro-compound (D), followed by the reaction with excess of active methylene compound to give an intermediate (E) accompanied with ring cleavage between 2 and 3 position. Consequently, quinoline ring may be formed *via* intermediates E and F through elimination of ammonia and successive ring closure accompanied with elimination of cation (G).

The formation of cation G might be shown by following data. In section I, it was shown that the reaction of I with malononitrile in the presence of methoxide ion gave III, VII, and VIII. VII obtained in this reaction might be formed as following manner as shown in Chart 8. Thus the reaction between cation G and malononitrile carbanion gave 1-propene-1,1,3,3-tetracarbonitrile (XX) which formed the pyridine ring by ring closure by applying methoxide ion. It agreed with the result of the reaction of XX with methoxide ion affording VIII reported by A.P. Krapcko, *et al.*[7] Consequently, it was able to stand to reason that cation G was formed during the transformation into quinoline ring.

10) Pschoorr, *Chem. Ber.*, **31**, 1293 (1898).
11) K. Adachi, *Chem. Pharm. Bull.* (Tokyo), **7**, 479 (1959).
12) E. Hayashi, *Collection of Papers, 10th Anniversary of Shizuoka College of Pharmacy*, **1963**, 31.

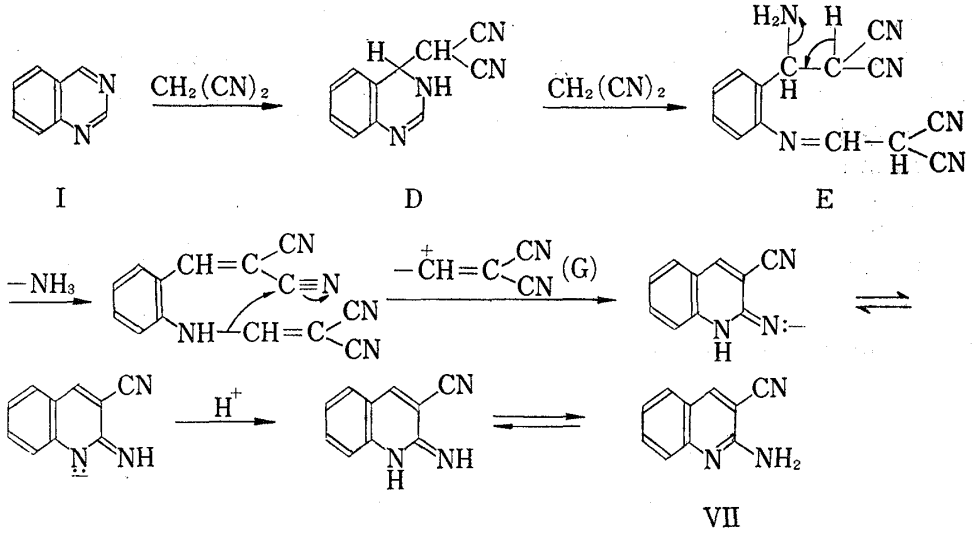


Chart 7

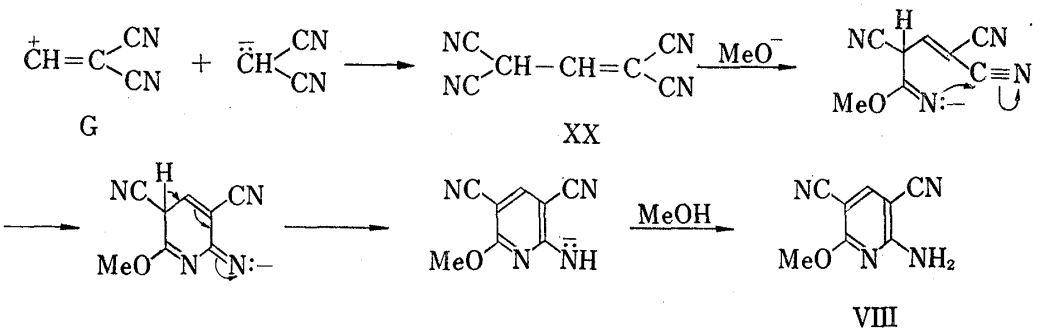


Chart 8

And it might be saying that this transformation could be proceeded by application of the following type of active methylene compound in which cyano group attached to active methylene group.

$X\text{–}CH_2\text{–}CN$ –X: ellectron attracting group

Chart 9

Considering the reagent attacks 4-position of I in the first step of the reaction process, it may be concluded that this transformation reaction may be caused by greater nucleophilicity of 4-position's carbon atom of I due to smaller aromaticity of pyrimidine portion.

Experimental

Ultraviolet spectra (UV spectra) were measured in 99.5% EtOH on a Hitachi Spectrophotometer Model ESP-2U.

Infrared spectra (IR spectra) were recorded with a Jasco Grating Infrared Spectrophotometer Model IRA-1.

Nuclear magnetic resonance (NMR) were measured at 60 Mc and 23° on a Japan Electron Optics Lab. Spectrophotometer Model JNM-C-60H. Tetramethylsilane was used as internal standard.

Mass spectra were recorded on a Hitachi RMS-4 single focusing mass spectrometer. The ionisation energy normally used was 80 eV. Samples were vaporised in all glass inlet system for compounds having melting point below 150° and direct inlet system for the above 150°.

Reaction of I with Phenylacetonitrile in the Presedce of Sodium Methoxide——i) A solution of 1.000 g of I and 0.900 g of phenylacetonitrile dissolved in sodium methoxide solution (0.300 g of Na dissolved in 8.0 ml of MeOH) was allowed to stand at room temperature for 3 days. Separated crystals were collected by suction and washed with H_2O. Recrystallization from MeOH gave III as colourless needles, mp 244—246° in 44.8% yield (0.440 g). *Anal.* Calcd. for $C_{16}H_{10}N_4$ (4,4′-biquinazoline): C, 74.40; H, 3.90; N, 21.70. Found: C, 74.33; H, 3.99; N, 22.33. UV λ_{max}^{EtOH} mμ (log ε): 214 (4.76), 320 (3.87). Mass Spectrum *m/e*: 258 (M^+).

The filtrate was neutralized with dil. AcOH and concentrated under reduced pressure. The residue was dissolved in 2N HCl and HCl layer was extracted with benzene to remove impurities. The HCl layer was neutralized, salted out with anhyd. K_2CO_3 to separate oily substances which were extracted with benzene and dried over anhyd. Na_2SO_4.

The elution from a column of alumina with benzene gave I in 27.0% yield (0.270 g). The elution with $CHCl_3$ gave IV, mp 101—110° as orange granular crystals from mixture of benzene and petr. ether in 1.3% yield (0.024 g). UV λ_{max}^{EtOH} mμ (log ε): 247 (3.82), 283 (3.97), 374 (4.17). IR ν_{max}^{KBr} cm^{-1}: 2180 (-C≡N). Mass Spectrum *m/e*: 245 (M^+).

ii) The reaction used 2.000 g of I, 1.800 g of phenylacetonitrile in sodium methoxide solution (0.600 g of Na dissolved in 16 ml of MeOH) in N_2 stream, dark place was treated as same as described above to give III in 46.6% yield (0.924 g) and IV in 0.7% yield (0.026 g).

Reaction of I with Ethyl Cyanoacetate in the Presence of Sodium Methoxide——A solution of 1.000 g of I, 1.000 g of ethyl cyanoacetate dissolved in sodium methoxide solution (0.400 g of Na dissolved in 10 ml of MeOH) was allowed to stand at room temperature for 15 days. Separated crystals were filtered off, washed with 2N NaOH. Recrystallization from MeOH gave III in 2.0% yield (0.200 g).

The filtrate was neutralized with AcOH to separate crystals which were collected by suction. Recrystallization from MeOH gave V as white needles, mp 230° (decomp.) in 2.9% yield (0.051 g). *Anal.* Calcd. for $C_{12}H_9O_2N_3$ (methyl α-cyano-4-quinazolineacetate): C, 63.43; H, 3.99; N, 18.94. Found: C, 63.23; H, 4.01; N, 18.49. UV λ_{max}^{EtOH} mμ (log ε): 235 (3.85), 240 (3.85), 285 (3.96), 348 (4.15), 364 (4.35), 382 (4.30). IR ν_{max}^{KBr} cm^{-1}: 2191 (-C≡N), 1650 (=C=O). Mass Spectrum *m/e*: 227 (M^+).

The filtrate removed from V recovered I in 21% yield (0.210 g).

Reaction of X with Methoxide Ion——A solution of 0.300 g of X dissolved in sodium methoxide solution (0.300 g of Na dissolved in 3.0 ml of MeOH) was allowed to stand for 1 day at room temperature. MeOH was removed under reduced pressure and H_2O was added to a residue which was neutralized with dil. AcOH to separate crystals. Recrystallization gave V as white needles, mp 230° (decomp.) in 23.4% yield (0.066 g).

Reaction of I with Nitromethane in the Presence of Sodium Methoxide——To a solution of 3.000 g of I dissolved in sodium methoxide solution (0.900 g of Na dissolved in 20 ml of MeOH), a solution of 1.400 g of nitromethane dissolved in 2 ml of MeOH was dropwise added with stirring. The reaction mixture was allowed to stand at room temperature for 4 days. The separated crystals were filtered off and washed with 2N NaOH. Recrystallization from MeOH gave III in 5.0% yield (0.150 g).

The filtrate was neutralized with dil. AcOH to separate crystals which were recrystallized from MeOH to afford VI, mp 225—227° (decomp.) as yellow needles in 2.6% yield (0.114 g). *Anal.* Calcd. for $C_9H_7O_2N_3$ [4-(nitromethyl)quinazoline]: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.12; H, 3.83; N, 22.00. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.27), 251 (3.70), 260 (3.66), 298 (3.86), 393 (4.45), 413 (4.53). Mass Spectra *m/e*: 189 (M^+).

Reaction of I with Methoxide Ion——A solution of 1.000 g of I dissolved in sodium methoxide solution (0.300 g of Na dissolved in 8 ml of MeOH) was allowed to stand at room temperature for 20 days. The reaction mixture was neutralized with AcOH and concentrated to dryness. After adding of 10 ml of 2N HCl to a residue, impurities were removed by extraction with 10 ml of benzene. The HCl solution was neutralized, salted out with anhyd. K_2CO_3. The separated oily substance was extracted with benzene, dried over anhyd. Na_2SO_4. Evaporation of benzene recovered I, mp 48° in 92.4% yield (0.924 g). I did not show any depression on admixture with quinazoline[2] prepared from another route.

Reaction of I with Malononitrile in the Presence of Sodium Methoxide——A solution of 1.000 g of I, 0.600 g of malononitrile dissolved in sodium methoxide solution (0.300 g of Na dissolved in 8 ml of MeOH) was allowed to stand at room temperature for 4 hr. The crystals separated out from the solution accompanied with elimination of NH_3 were filtered off and recrystallized from MeOH to give III in 2.6% yield (0.026 g).

The filtrate was neutralized with AcOH, concentrated to dryness under reduced pressure. The residue was passed through a column of alumina. The elution with benzene gave I in 24.0% yield (0.240 g).

The first fraction from the elution with $CHCl_3$ gave VII as yellow prisms, mp 223—225° from MeOH in 2.0% yield (0.026 g). *Anal.* Calcd. for $C_{10}H_7N_3$ (2-amino-3-quinolinecarbonitrile): C, 70.99; H, 4.17; N, 24.84. Found: C, 70.96; H, 4.37; N, 23.51. UV λ_{max}^{EtOH} mμ (log ε): 217 (4.56), 248 (4.64), 289 (3.78), 374 (4.06). IR ν_{max}^{KBr} cm^{-1}: 3393, 3304 (-NH_2), 2227 (-C≡N). Mass Spectrum *m/e*: 169 (M^+).

The second fraction from the elution with $CHCl_3$ gave VIII, mp 244—245° as white needles from MeOH in 1.4% yield (0.019 g). *Anal.* Calcd. for $C_8H_6ON_4$ (2-amino-6-methoxy-3,5-pyridinedicarbonitrile): C, 55.17; H, 3.47; N, 32.17. Found: C, 55.45; H, 3.69; N, 31.84. UV λ_{max}^{EtOH} mμ (log ε): 274 (4.27), 320 (4.06). IR ν_{max}^{KBr} cm^{-1}: 3406, 3311 (-NH_2), 2204 (-C≡N). NMR (in DMSO) τ: 5.95 (3H, singlet, -OCH_3), 1.52 (2H, broad singlet, -NH_2), 1.15 (1H, singlet, H-4). Mass Spectrum *m/e*: 174 (M^+).

Reaction of I with Malononitrile——A solution of 1.000 g of I dissolved in desired amount of malononitrile described in Table I was heated at 75—80° for 15 min. The separated crystals were collected by suction, washed with MeOH and recrystallized from MeOH to give VII as yellow prisms, mp 223—225°. Yields for VII were shown in Table I.

Reaction of I with Ethyl Cyanoacetate——A solution of 1.000 g of I dissolved in 1.000 g of ethyl cyanoacetate was allowed to stand at room temperature for 11 days. The separated crystals were removed by filteration, washed with MeOH and recrystallized from MeOH to give XVI as pale yellow needles, mp 308—310° in 2.8% yield (0.037 g). *Anal.* Calcd. for $C_{10}H_6ON_2$ (2-hydroxy-3-quinolinecarbonitrile): C, 70.58; H, 3.55; N, 16.46. Found: C, 70.30; H, 3.60; N, 16.33. UV λ_{max}^{EtOH} mμ (log ε): 235 (4.50), 289 (4.07), 360 (3.80). IR ν_{max}^{KBr} cm^{-1}: 1664 (=C=O), 2246 (-C≡N). Mass Spectrum *m/e*: 170 (M^+).

After removing MeOH, the filtrate was passed through a column of alumina. From the elution with benzene I was obtained in 68.0% yield (0.680 g). From the elution with $CHCl_3$, XV was obtained as yellow needles, mp 130—131° from petr. ether in 0.7% yield (0.011 g). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (ethyl 2-amino-3-quinolinecarboxylate): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.89; H, 5.61; N, 13.34. UV λ_{max}^{EtOH} mμ (log ε): 220 (4.54), 250 (4.63), 290 (3.81), 298 (3.80), 379 (3.64). IR ν_{max}^{KBr} cm^{-1}: 3411, 3261 (-NH_2), 1691 (=C=O). NMR (in $CDCl_3$) τ: 8.58 (3H, triplet, -CH_3), 5.61 (2H, quartet, -CH_2-Me), 3.12 (2H, broad, -NH_2), 2.2—3.0 (4H, multiplet, H-aromatic). Mass Spectrum *m/e*: 216 (M^+).

Reaction of I with Phenylacetonitrile——A solution of 1.000 g of I dissolved in 1.0 ml of phenylacetonitrile was heated at 195—200° for 2.5 hr. To the reaction mixture, 15.0 ml of 2N HCl was added and extracted with 15.0 ml of benzene to remove excess of phenylacetonitrile. The HCl layer was neutralized with anhyd. K_2CO_3 and the separated oily substance was extracted with benzene. After dring over anhyd. Na_2SO_4, the extract was passed through a column of alumina. The elution with benzene gave I in 75.0% yield (0.750 g). The elution with $CHCl_3$ gave XVII as white needles, mp 149—151° from petr. ether in 3.3% yield (0.056 g). *Anal.* Calcd. for $C_{15}H_{12}N_2$ (2-amino-3-phenylquinoline): C, 81.79; H, 5.49; N, 12.72. Found: C, 81.59; H, 5.53; N, 12.92. UV λ_{max}^{EtOH} mμ (log ε): 238 (4.56), 344 (3.83). IR ν_{max}^{KBr} cm^{-1}: 3432, 3292 (-NH_2). NMR (in $CDCl_3$) τ: 4.75 (2H, broad, -NH_2), 2.26—3.00 (9H, multiplet, H-aromatic), 2.25 (1H, singlet, H-4). Mass Spectrum *m/e*: 220 (M^+).

Reaction of I with Diethyl Malonate——A solution of 2.000 g of I dissolved in 2.0 ml of diethyl malonate was heated at 180—185° for 3 hr. The reaction mixture was treated as same as the reaction of I with phenylacetonitrile. The elution from a column of alumina with benzene gave I in 66% yield (1.320 g). The elution with $CHCl_3$ gave XVIII as white needles, mp 105° from MeOH in 0.7% yield (0.023 g). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (ethyl 4-quinazolineacetate): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.63; H, 5.75; N, 12.74. UV λ_{max}^{EtOH} mμ (log ε): 211 (4.44), 239 (3.70), 246 (3.75), 272 (4.19), 280 (4.27), 345 (4.18), 359 (4.24), 379 (3.98). IR ν_{max}^{KBr} cm^{-1}: 1644 (=C=O). NMR (in $CDCl_3$) τ: 8.70 (3H, triplet, -CH_3), 5.81 (2H, quartet, -CH_2-Me), 4.53 (1H, singlet, Ar-CH=C(-O)-R), 1.9—3.0 (5H, multiplet, H-aromatic), −4.1 (1H, broad, H-chelating). Mass Spectrum *m/e*: 220 (M^+).

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