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Studies on the Reaction of Quinazoline 3-Oxide with Active Methylene Compound. The Transformation of Quinazoline 3-Oxide into Quinoline Derivatives

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The reaction of quinazoline 3-oxide (I) with active methylene compound without a base catalyst was carried out and resulted in finding the transformation of I into quinoline derivatives even if the yields of quinoline derivatives were very poor (few percentage).

Thus, the reaction with malononitrile gave 2-amino-3-quinolinecarbonitrile (V), with phenylacetonitrile, 2-amino-3-phenylquinoline (VII), with ethyl cyanoacetate, ethyl 2-amino-3-quinolinecarboxylate (IX) and ethyl α-cyano-*o*-[N-(2-cyano-2-ethoxycarbonylvinyl)amino]cinnamate (XI), with 1,3-diphenyl-1,3-propanedione and 1-phenyl-1,3-butanedione, 2-phenylquinoline (XII), with 2,4-pentanedione, methyl 2-methyl-3-quinolyl ketone (XIV) and 4-acetonyl-8-quinolinecarbonitrile (XV), with ethyl acetoacetate, ethyl 2-methyl-3-quinolinecarboxylate (XVII) and 3-acetylcarbostyrile (XVIII), respectively. But in the case of the reaction with diethyl malonate, ethyl 4-quinazolineacetate (XX) was obtained.

The possible reaction process for this transformation was also proposed and discussed.

It has been reported that the polar effect of the N-oxide group in quinazoline 3-oxide (I), together with effect of ring nitrogen and the fused benzene ring, markedly increased the nucleophilic activity of 4-position in the quinazoline ring system, and the stability of the ring has been markedly decreased and facile ring fission occured between 2- and 3-position.[2,3] For example, I easily underwent ring fission at ordinary temperature to form 2′-(hydroxyiminomethyl)formanilide (II) by brief treatment with alkali hydroxide as a nucleophilic reagent, as observed by Higashino.[2]

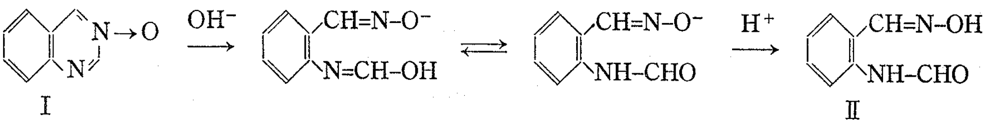

Chart 1

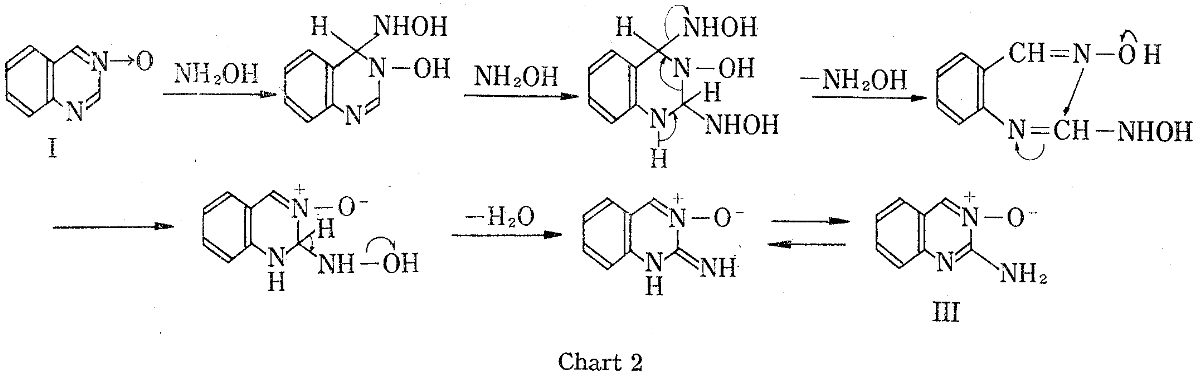

Chart 2

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1) Location: *2-2-1 Oshika, Shizuoka.*

2) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), 9, 635 (1961).

3) K. Adachi, *Yakugaku Zasshi*, 77, 510 (1957).

In the reaction of I with hydroxylamine, ring fission and ring closure in successive step resulted in the formation of 2-aminoquinazoline 3-oxide (III), as reported by Adachi.[3]

Moreover, it has been reported by Higashino and his co-workers that they succeeded in finding the transformation of quinazoline (IV) into 2-aminoquinoline derivatives in the reaction of IV with active methylene compound in which cyano group attached to active methylene group.[4] And they proposed the possible reaction process involving a route of ring fission between 2- and 3-position and successive ring closure accompanied with elimination of ammonia and cation A as shown in Chart 3.[4]

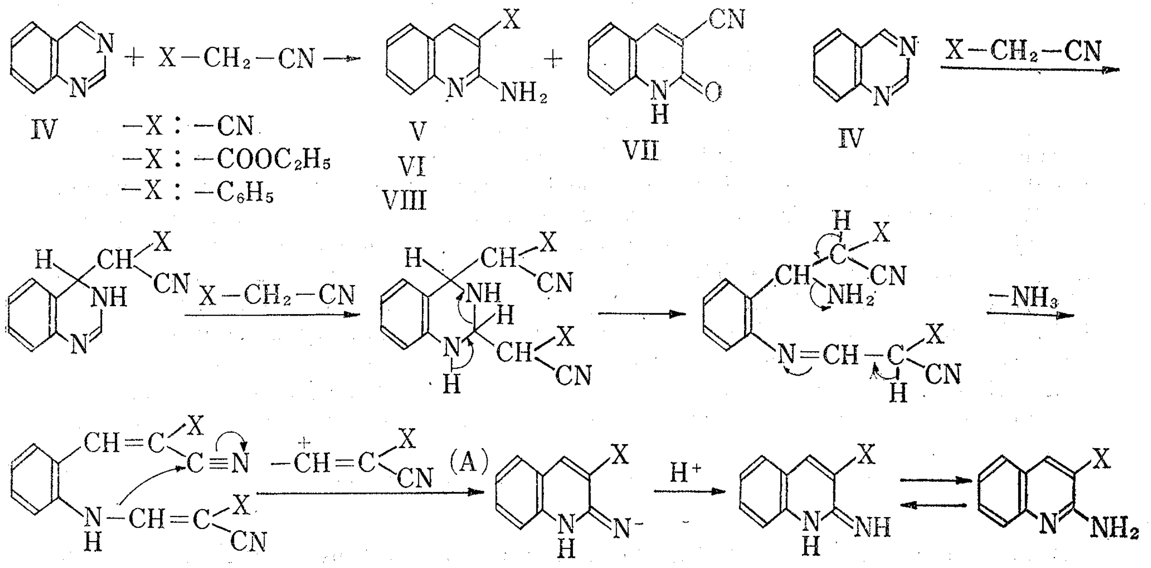

Chart 3

As it seemed to be expected that a similar transformation reaction might proceed in I by application of active methylene compound, the investigation described in this paper was carried out and resulted in finding the transformation of I into quinoline derivatives even if the yields of quinoline derivatives were very poor (few percentage).

I. Reaction of I with Active Methylene Compound

(a) Reaction with Malononitrile——When a mixture of I and malononitrile is heated at 50—55° for 15 min, it gives 2-amino-3-quinolinecarbonitrile (V) which is identified its structure on admixture with the authentic specimen[5] prepared from reductive cyclization of 2-nitro-α-cyanocinnamonitrile (VI).

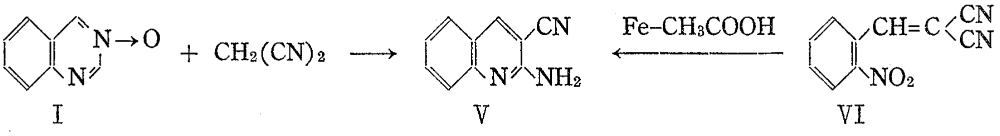

Chart 4

(b) Reaction with Phenylacetonitrile——When a mixture of I and phenylacetonitrile is heated at 160° for 5 hr, it gives II and 2-amino-3-phenylquinoline (VII) which is identified its structure on admixture with the authentic specimen[6] prepared from reductive cyclization of 2-nitro-α-phenylcinnamonitrile (VIII).

The possible reaction process for the formation of II may be considered to be as follows. During passing through a column of alumina in treatment of the reaction mixture, water

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[4] T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1544 (1972).
[5] E. Campaigene and G. Randau, *J. Heterocyclic Chem.*, **8**, 111 (1971).
[6] K.H. Bauer, *Ber.*, **71B**, 2226 (1938) [*C.A.*, **31**, 170 (1937)].

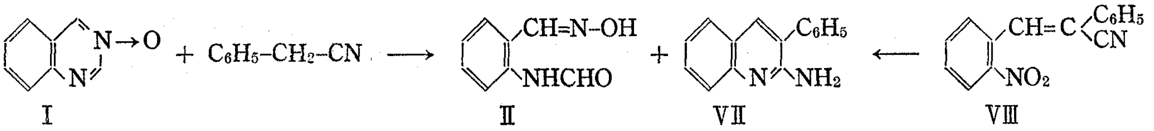

Chart 5

absorbed on alumina may add across 3- and 4-position in unchanged I by catalytic action of alumina to form B type of intermediate which leads to II through addition of another water across 2- and 1-position in B and successive ring fission accompanied with elimination of water, as shown in Chart 6. In fact, I easily undergoes ring fission to form II at ordinary temperature by passing through a column of alumina.

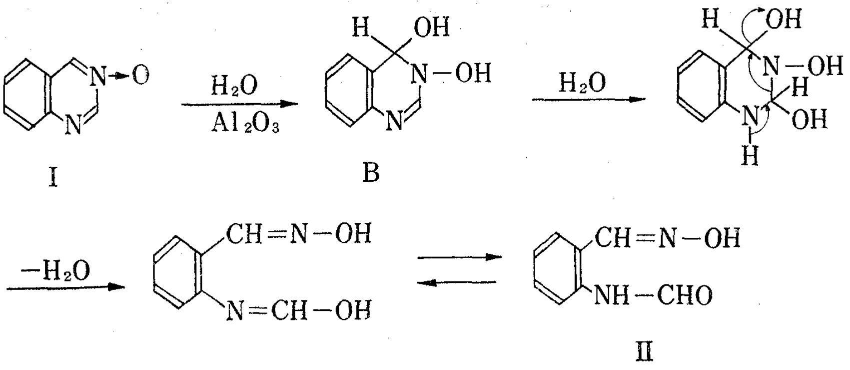

Chart 6

(c) **Reaction with Ethyl Cyanoacetate**——When a solution of I and ethyl cyanoacetate dissolved in benzene is heated at 80° for 2 hr, it gives II, ethyl 2-amino-3-quinolinecarboxylate (IX) and ethyl α-cyano-*o*-[N-(2-cyano-2-ethoxycarbonylvinyl)amino]cinnamate (XI). So obtained IX is identified its structure on admixture with the authentic specimen6) prepared from reductive cyclization of ethyl 2-nitro-α-cyanocinnamate (X). The structure of XI is presumed to be ethyl α-cyano-*o*-[N-(2-cyano-2-ethoxycarbonylvinyl)amino]cinnamate through the following data. Its infrared (IR) spectrum shows a peak at 2230 cm^{-1} due to cyano group and a peak at 1690 cm^{-1} due to a carbonyl group. The molecular ion (M^+) peak corresponding to $C_{18}H_{17}O_4N_3$ is recognized at *m/e* 339 in its mass spectrum.

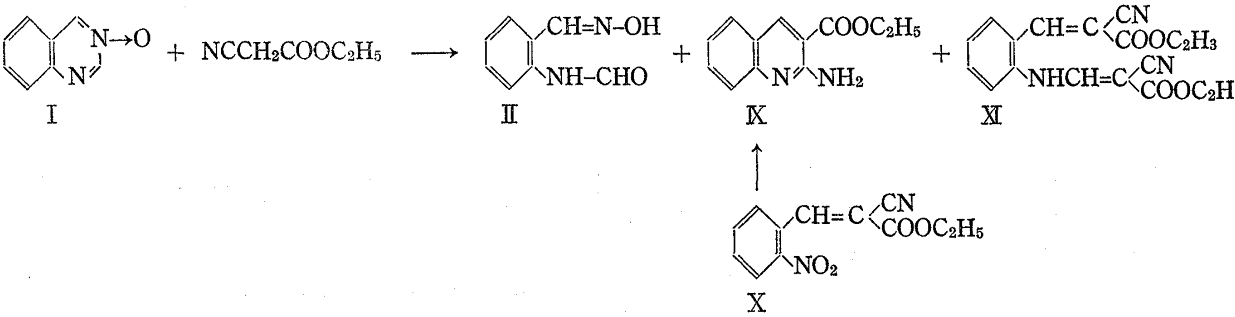

Chart 7

(d) **Reaction with 1,3-Diphenyl-1,3-propanedione**——When a mixture of I and 1,3-diphenyl-1,3-propanedione is heated at 130—140° for 4 hr, it gives II and 2-phenylquinoline (XII) which is identified its structure on admixture with the authentic specimen7) prepared from a reaction between 2-(methylsulfonyl)quinoline (XIII) and phenylmagnesium bromide. On the other hand, the application of this reaction to IV does not give the desired reaction products but also results in the recovery of starting material IV.

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7) E. Hayashi and T. Saito, *Yakugaku Zasshi*, **89**, 74 (1969).

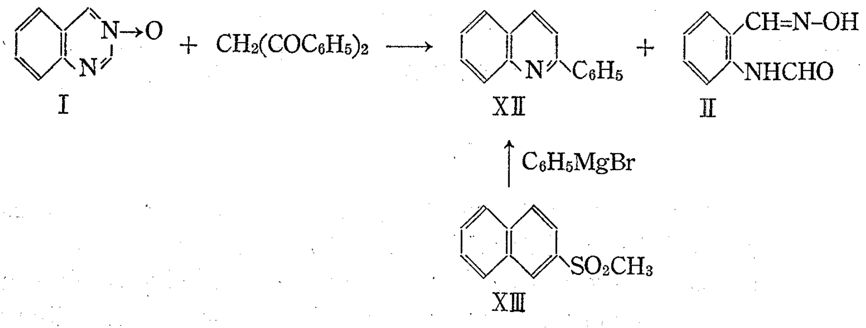

Chart 8

(e) **Reaction with 1-Phenyl-1,3-butanedione**——When a mixture of I and 1-phenyl-1,3-butanedione is heated at 120—130° for 4 hr, it gives II and XII. The application of this reaction to IV gives none of reaction products and results in the recovery of starting material IV.

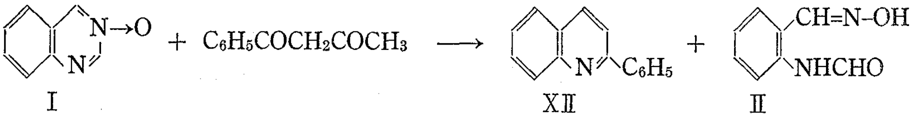

Chart 9

(f) **Reaction with 2,4-Pentanedione**——When a solution of I and 2,4-pentanedione dissolved in benzene is heated at 80° for 4 hr, it gives methyl 2-methyl-3-quinolyl ketone (XIV) and 4-acetonyl-8-quinolinecarbonitrile (XV). The application of this reaction to IV gives none of reaction products and results in the formation of starting material IV.

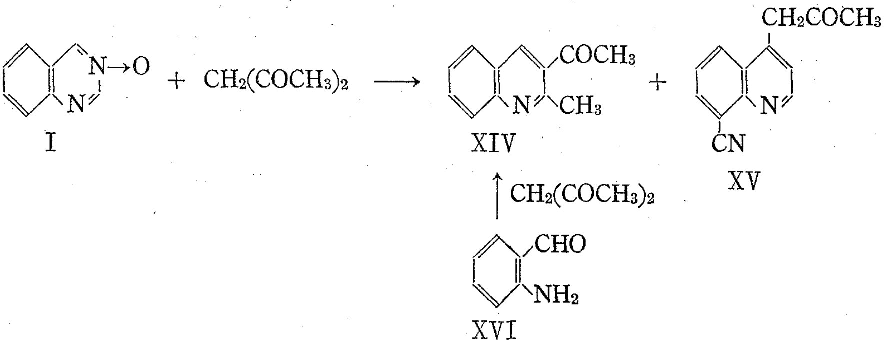

Chart 10

Identity of XIV is established to be methyl 2-methyl-3-quinolyl ketone on admixture with the authentic specimen[8] prepared from the Friedlaender synthesis with 2-aminobenzaldehyde (XVI) and 2,4-pentanedione.

The structure of XV is presumed to be 4-acetonyl-8-quinolinecarbonitrile through the following data. Its IR spectrum shows a peak at 2221 cm^{-1} due to cyano group and a peak at 1680 cm^{-1} due to carbonyl group. Fragmentation of XV under electron impact shown in Chart 11 is proceeded by one of dissociation pathway which is loss of methyl radical from M$^+$ and loss of carbon monoxide, in successive step, to form cyanobenzoazatropylium cation, *m/e* 167. Those data show that XV should have cyano and acetyl groups. In its nuclear magnetic resonance (NMR) spectrum, a singlet peak at 7.5 τ due to acetyl group is recognized and bands of Ha at 4.45 τ and of Hb at 4.85 τ shown in Chart 12 gives splitting in AM portion of AMX pattern in which Ha and Hb couples with each other (J_{a-b}=3.0 cps). Moreover

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8) Eliasberg and Friedlaender, *Ber.*, **25**, 1756 (*Beilstein*, **20**, 481).

Hb may couple with Hx in long range coupling ($J_{b-x}=1.2$ cps) which appears together with multiplet due to other 4 protons at range of 2.5—3.0 τ. And one proton in this multiplet is easily removed by D_2O exchange.

From foregoing spectrophotometric data it should be shown that XV may be existed to be as tautomeric isomer (XVb) of XV in $CDCl_3$ solution as shown in Chart 12.

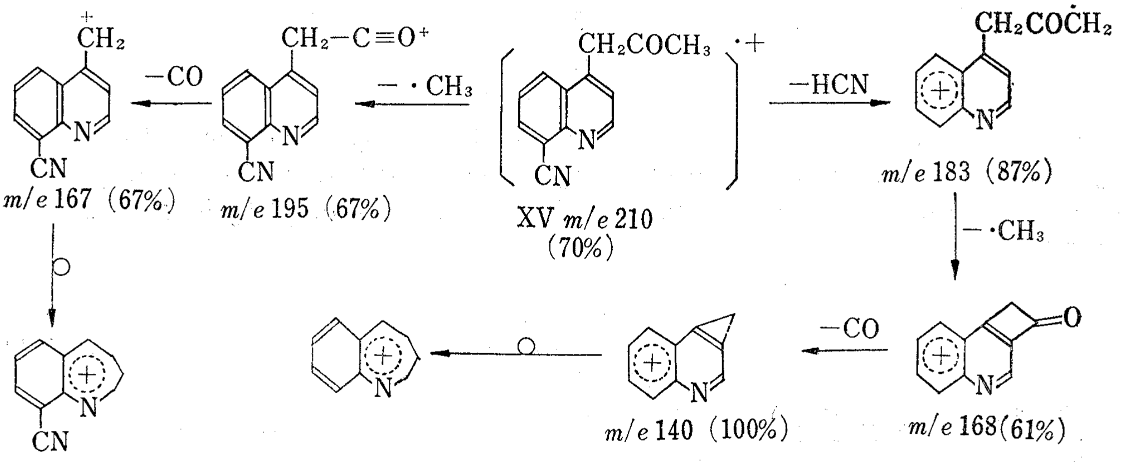

Chart 11. Fragmentation of XV under Electron Impact

(g) Reaction with Ethyl Acetoacetate——When a mixture of I and ethyl acetoacetate is heated at 160° for 1 hr, it gives ethyl 2-methyl-3-quinolinecarboxylate (XVII), 3-acetylcarbostyrile (XVIII) and XIX.

Identities of XVII and XVIII are established their structures on admixture with the corresponding authentic specimens[9] prepared from Friedlaender synthesis by means of XVI and ethyl acetoacetate. The compound XIX shows peaks due to cyano and carbonyl groups at 2221 and 1710 cm^{-1}, respectively, but its structure has not been determined as yet.

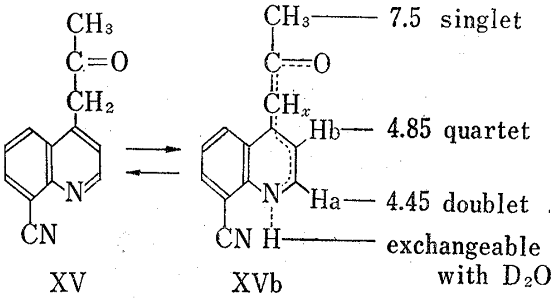

Chart 12

The application of this reaction to IV gives none of reaction products and results in the recovery of starting material IV.

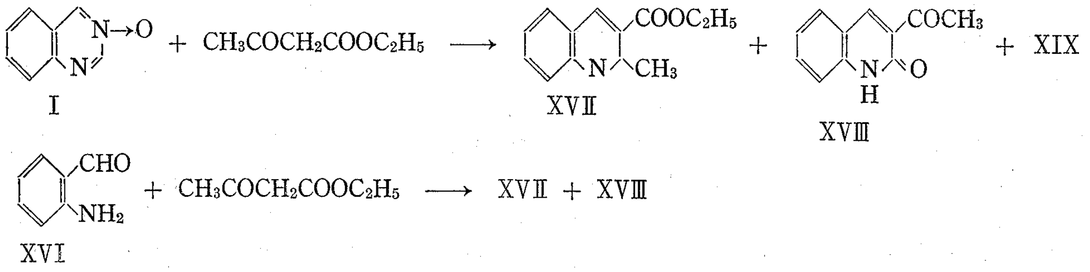

Chart 13

(h) Reaction with Diethyl Malonate——When a mixture of I and diethyl malonate is heated at 160° for 3 hr, a transformation reaction does not proceed to result only in the formation of ethyl 4-quinazolineacetate (XX) which is identified its structure on admixture

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9) Friedlaender and Gohing, *Ber.*, **16**, 1838 (*Beilstein*, **20**, 481).

with the authentic specimen[10] prepared from the reaction between 4-chloroquinazoline (XXI) and ethyl acetoacetate in the presence of sodium amide.

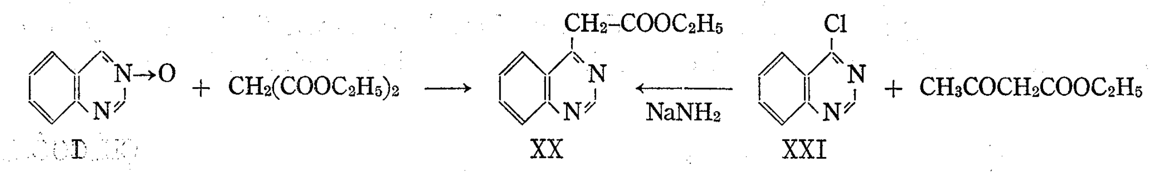

Chart 14

The possible reaction process for the formation of XX may be considered to be as follows. Diethyl malonate as a nucleophilic reagent may attack 4-position in I to form C type of intermediate which leads to XX accompanied with elimination of ethyl hydrogen carbonate, as shown in Chart 15.

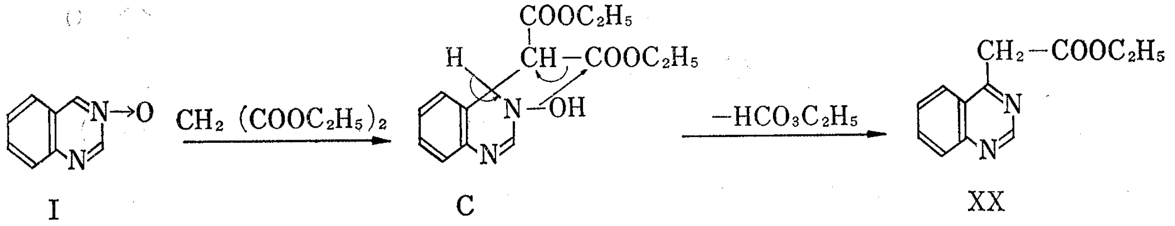

Chart 15

II. Discussion

Through reactions (a) to (g) described above it is found that the transformation of quinazoline 3-oxide (I) into quinoline derivatives occurs in the reaction between I and active methylene compounds without base catalyst. It has been found by Higashino ad his co-workers that similar transformation reaction occured in the reaction between IV and active methylene compound in which cyano group attached at the active methylene group and they proposed the possible reaction process involving a route shown in Chart 3.[4]

If it is supposed that the reaction process for the transformation of I into 2-aminoquinoline derivatives in the reactions (a) to (c) may be similar to that of IV,[4] the possible reaction process may be considered to be as follows. Active methylene compound may attack 4-position of I to form an intermediate such as 3,4-dihydro-compound (D). Then excess of active methylene compound attacks 2-position of D to form an intermediate (E). Successive ring fission between 2- and 3-positions and elimination of hydroxylamine may give G type of intermediate *via* F. Consequently, 2-aminoquinoline derivatives may be formed *via* intermediates G and H through ring closure accompanied with elimination of cation A.[4] In fact, as the compound XI obtained in the reaction (c) may be considered to be G type of intermediate, it can be understood that this possible reaction process is well reasoned.

The possible reaction process for the transformation of I into XII in the reaction with active methylene compound having benzoyl group such as 1,3-diphenyl-1,3-propanedione and 1-phenyl-1,3-butanedione in reaction (d) and (e) may be considered to be as follows. The formation of K type of intermediate may proceed through the same way as that of F type of intermediate shown in Chart 16. Elimination of hydroxamic acid from K forms L type of intermediate which leads to XII through ring closure accompanied with elimination of cation N and successive loss of hydroxide ion, as shown in Chart 17.

The possible reaction process for the transformation of I into 2-methylquinoline derivatives (XIV and XVII) and XVIII in reaction with active methylene compound having acetyl group

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[10] Y. Mizuno, K. Adachi, and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **2**, 225 (1945).

such as 2,4-pentanedione and ethyl acetoacetate described in reaction (f) and (g) may be considered to be as follows. A process for the formation of R type of intermediate may be as same as that of G type of intermediate involving a route of ring fission between 2- and 3-position and of successive elimination of hydroxylamine shown in Chart 16. If ring closure in R occurs between nitrogen and carbonyl carbon of acetyl group accompanied with elimina-

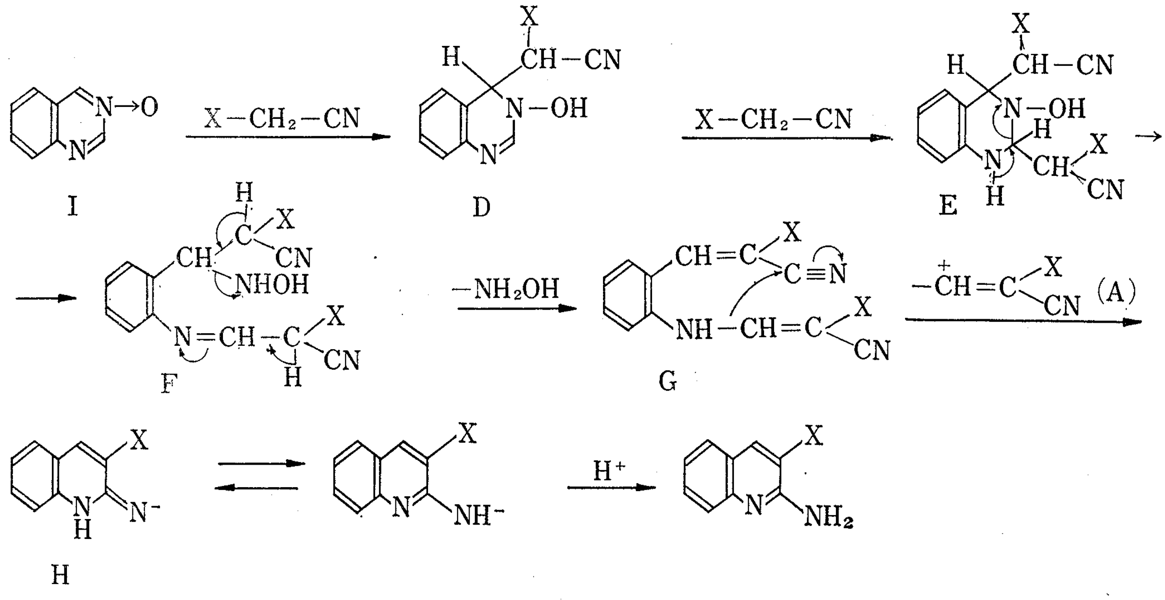

Chart 16

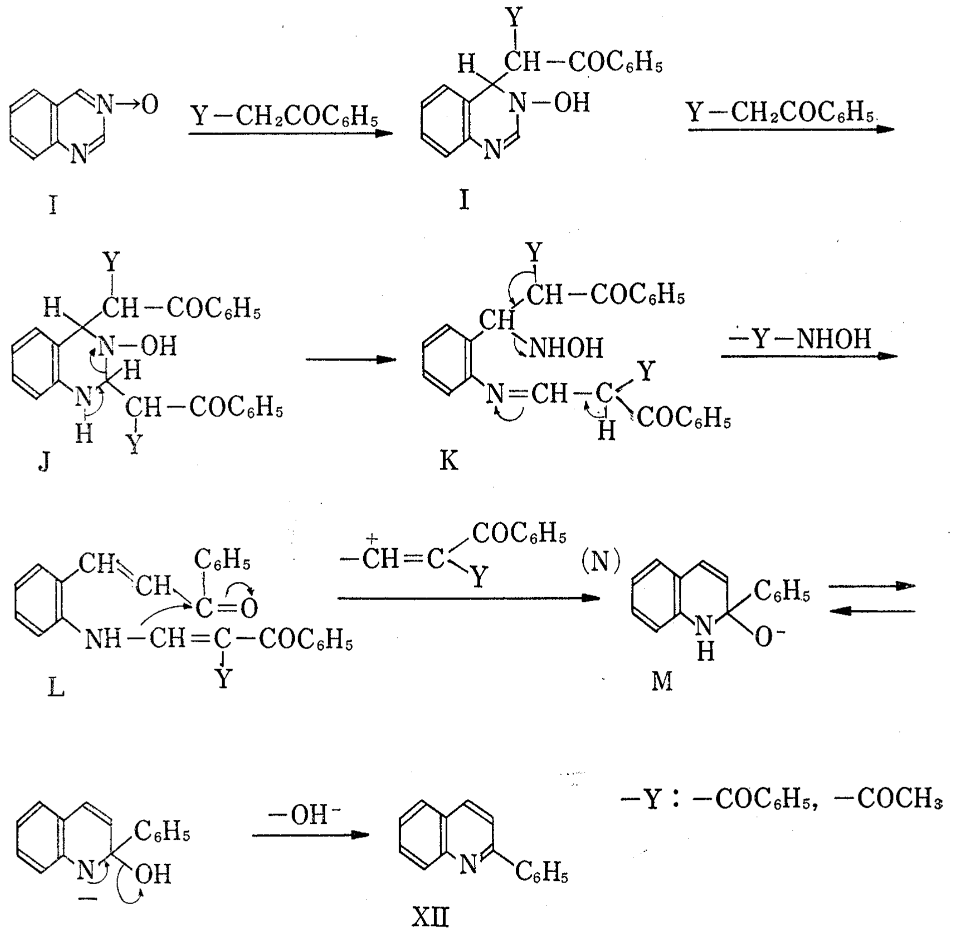

Chart 17

tion of cation A′, it results in the formation of 2-methyl quinoline derivatives through loss of hydroxide ion from S type of intermediate. On the other hand, if ring closure in R′ occurs between nitrogen and carbonyl carbon of ethoxycarbonyl group accompanied with elimination of cation A″, it results in the formation of XVIII through loss of ethoxide ion from S′ type of intermediate.

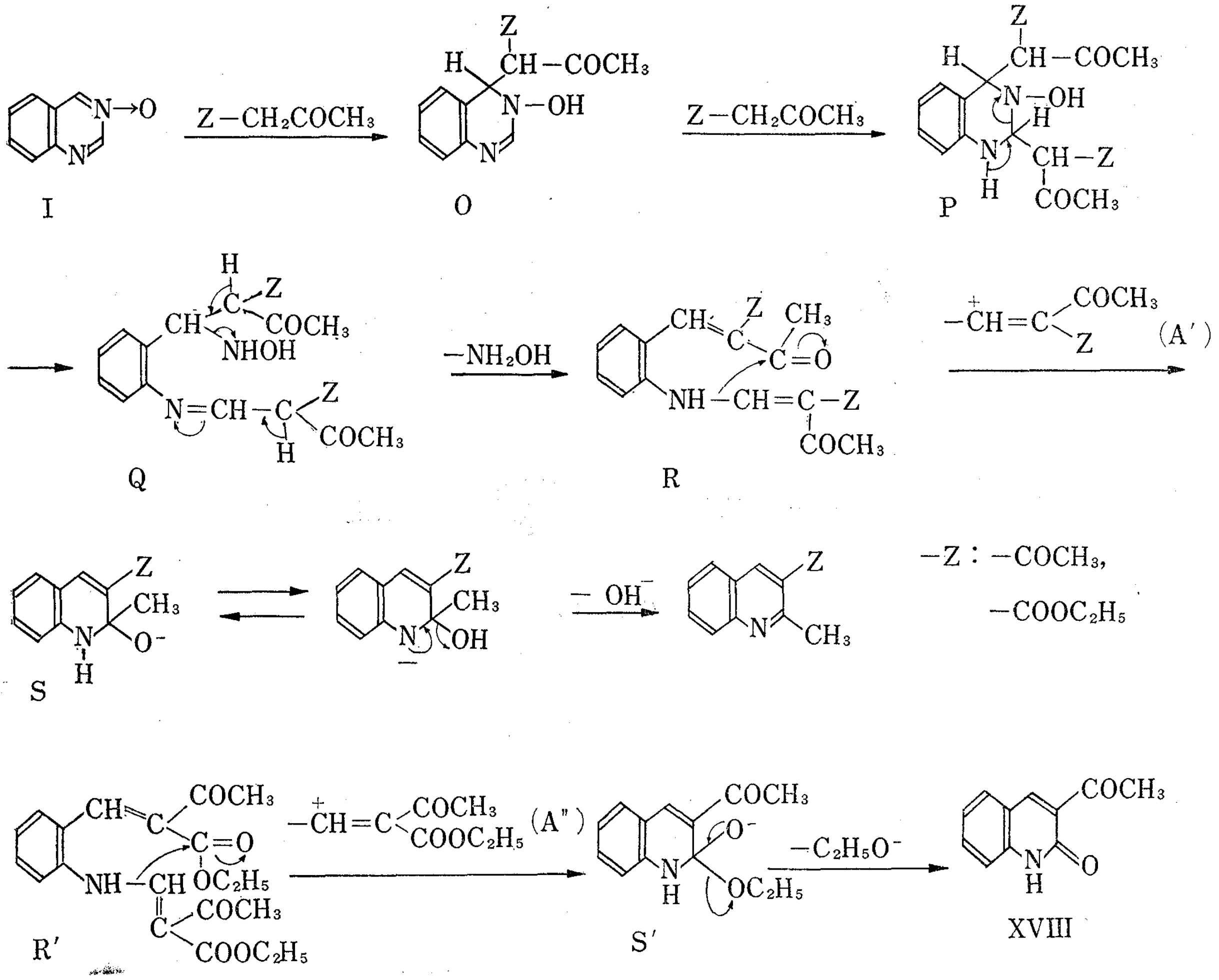

Chart 18

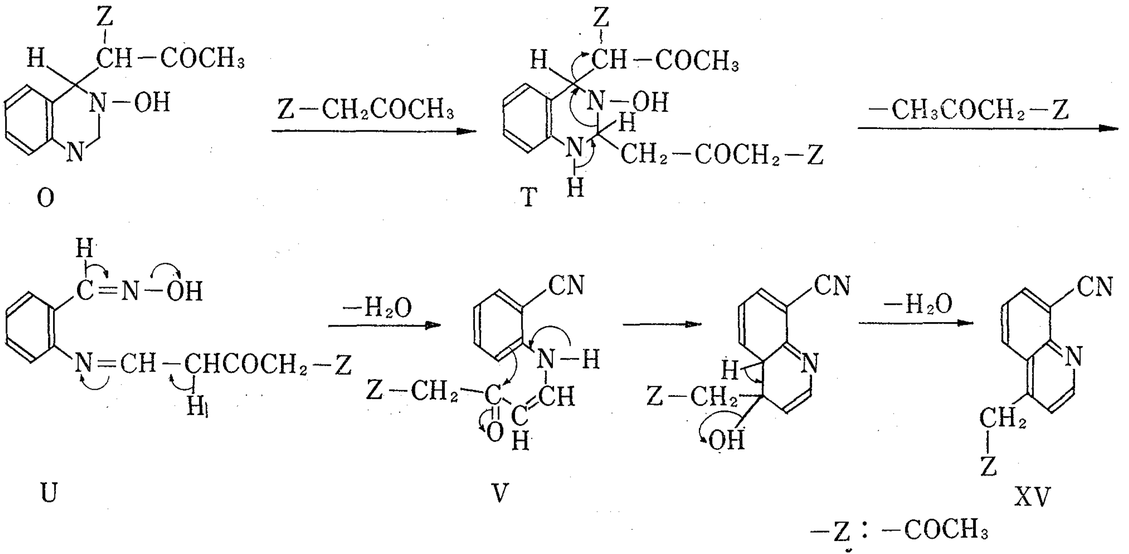

Chart 19

And the possible reaction process for the formation of XV in reaction (f) may be considered to be as follows. Methyl group in 2,4-pentanedione may attack 2-position in 0 to form 1,2,3,4-tetrahydro-compound (T) which leads to U type of intermediate through ring fission between 2- and 3-position accompanied with loss of 2,4-pentanedione. And then loss of water from U and ring closure of V, in successive step, lead to XV as shown in Chart 19.

The transformation of IV into quinoline derivatives as reported in previous paper[4] could proceed by application of the following type of active methylene compound in which cyano group attached to active methylene group. In this paper available active methylene compound for the transformation of quinazoline 3-oxide into quinoline derivatives are expanded to following type of compound having cyano, benzoyl and acetyl groups.

$Y{-}CH_2{-}Z$ $-Y$: $-CN$ $-Z$: $-CN$, $-C_6H_5$, $-COOC_2H_5$
$-Y$: $-COC_6H_5$ $-Z$: $-COC_6H_5$, $-COCH_3$
$-Y$: $-COCH_3$ $-Z$: $-COCH_3$, $-COOC_2H_5$

Considering that the reagent attacks 4-position in I in the first step of the reaction process, it may be concluded that this transformation reaction may be caused by greater nucleophilic activity of 4-position due to smaller aromaticity of pyrimidine portion of quinazoline 3-oxide.

Experimental[11]

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

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

NMR spectra 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 ionization 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 those above 150°.

Reaction of I with Malononitrile——When a mixture of 500 mg of I and 700 mg of malononitrile was heated at 50—55° for 15 min, the reaction mixture changed its color from pale yellow to black. Malononitrile was removed from the reaction mixture by treating with 10 ml of 2N NaOH. Separate crystals were treated with charcoal in MeOH. So obtained crystals were recrystallized from MeOH to give V, yellow prisms, mp 223—225°, in 6.6% yield (38 mg). *Anal.* Calcd. for $C_{10}H_7N_3$ (2-amino-3-quinolinecarbonitrile): C, 70.99; H, 4.17; N, 28.84. Found: C, 70.96; H, 4.37; N, 23.51. IR ν_{max}^{KBr} cm^{-1}: 3393, 3304 (NH_2), 2227 (CN). UV λ_{max}^{EtOH} mμ (log ε): 217 (4.56), 248 (4.64), 289 (3.37), 374 (4.06).

This compound was undepressed on admixture with 2-amino-3-quinolinecarbonitrile[5] prepared another route.

Reaction of I with Phenylacetonitrile——A mixture of 500 mg of I and 1 ml of phenylacetonitrile was heated at 160° for 5 hr. The reaction mixture was passed through a column of alumina.

The elution with benzene gave phenylacetonitrile. The elution with $CHCl_3$ gave VII, mp 149—150°, colourless needles from petr. ether, in 0.7% yield (5 mg), which was undepressed on admixture with 2-amino-3-phenylquinoline[6] prepared from another route. The elution with MeOH gave II, mp 151—152°, white crystals from benzene, in 5.0% yield (28 mg), which was undepressed on admixture with 2′-(hydroxyiminomethyl)formanilide[2] prepared from another route. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3190 (NH), 1660 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 235 (4.45), 272 (4.05).

Reaction of I with Ethyl Cyanoacetate——A solution of 500 mg of I and 1 ml of ethyl cyanoacetate dissolved in 1 ml of benzene was heated at 80° for 2 hr. The reaction mixture was passed through a column of alumina by changing eluate as follows: benzene, benzene–$CHCl_3$ mixture (1: 1), $CHCl_3$ and MeOH.

The elution with benzene gave XI, mp 198—200°, white needles from MeOH, in 0.3% yield (3 mg). *Anal.* Calcd. for $C_{18}H_{17}O_4N_3$ (ethyl α-cyano-*o*-[N-(2-cyano-2-ethoxycarbonylvinyl)amino]cinnamate): C, 63.71; H, 5.05; N, 12.38. Found: C, 63.28; H, 5.13; N, 12.24. Mass Spectrum *m*/*e*: 339 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3190 (NH), 2230 (CN), 1690 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 212 (4.37), 234 (4.42), 307 (4.47), 329 (4.44).

The elution with benzene–$CHCl_3$ mixture (1: 1) gave IX, mp 128—130°, yellow needles from petr. ether, in 3.2% yield (24 mg), which was undepressed on admixture with ethyl 2-amino-3-quinolinecarboxylate[6] prepared from another route.

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[11] All melting points were not corrected.

The elution with $CHCl_3$ gave starting material I in 2.4% yield (12 mg) and the elution with MeOH gave II, mp 151—152° in 2.3% yield (13 mg).

Reaction of I with 1,3-Diphenyl-1,3-propanedione——A mixture of 500 mg of I and 1600 mg of 1,3-diphenyl-1,3-propanedione was heated at 130—140° for 4 hr. The reaction mixture was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH.

The elution with petr. ether gave XII, mp 81—82°, white crystals from petr. ether, in 4.8% yield (30 mg). *Anal.* Calcd. for $C_{15}H_{11}N$ (2-phenylquinoline): C, 87.77; H, 5.40; N, 6.82. Found: C, 87.79; H, 5.53; N, 7.01. IR ν_{max}^{KBr} cm^{-1}: 1602, 1496, 841, 775, 685. UV λ_{max}^{EtOH} mμ (log ε): 256 (4.60). This compound was undepressed on admixture with 2-phenylquinoline[7] prepared from another route.

The elution with MeOH gave II, mp 151—152° in 2.0% yield (11 mg).

Reaction of IV with 1,3-Diphenyl-1,3-propanedione——A mixture of 500 mg of IV and 1500 mg of 1,3-diphenyl-1,3-propanedione was heated ay 150° for 5 hr. The reaction mixture was treated by the same manner as that described in reaction of I with 1,3-diphenyl-1,3-propanedione and resulted only recovery of IV from the elution with benzene in 61% yield (305 mg).

Reaction of I with 1-Phenyl-1,3-butanedione——A mixture of 500 mg of I and 1400 mg of 1-phenyl-1,3-butanedione was heated at 120—130° for 4 hr. The reaction mixture was passed through a column of alumina by changing eluate as follow: petr. ether, benzene, $CHCl_3$ and MeOH.

The elution with petr. ether gave XII, mp 81—82° in 3.9% yield (27 mg). The elution with MeOH gave II in 1.6% yield (9 mg).

Reaction of IV with 1-Phenyl-1,3-butanedione——A mixture of 500 mg of IV and 1400 mg of 1-phenyl-1,3-butanedione was heated at 150° for 5 hr. Treatment of reaction mixture as same manner as that described in reaction of I with 1-phenyl-1,3-butanedione gave none of reaction products and resulted in the recovery of IV from the elution with benzene in 59% yield (293 mg).

Reaction of I with 2,4-Pentanedione——A solution of 500 mg of I and 1 ml of 2,4-pentanedione dissolved in 1 ml of benzene was heated at 80° for 4 hr. The reaction mixture was dissolved in benzene, extracted with 2N NaOH and 2N HCl. The benzene layer was dried over anhyd. Na_2SO_4 and passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. The elution with petr. ether gave XV, mp 111—113°, reddish brown crystals from petr. ether, in 1.4% yield (10 mg). *Anal.* Calcd. for $C_{13}H_{10}ON_2$ (4-acetonyl-8-quinolinecarbonitrile): C, 74.27; H, 4.79; N, 13.33. Found: C, 74.32; H, 4.92; N, 13.16. UV λ_{max}^{EtOH} mμ (log ε): 251 (4.48), 307 (3.35), 400 (2.44).

The hydrochloric acid solution was neutralized with K_2CO_3 and extracted with benzene. After drying over anhyd. Na_2SO_4, benzene was evaporated to dryness. So obtained oily substance was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. The elution with petr. ether gave XIV, mp 75—76°, white needles from petr. ether, in 3.2% yield (20 mg). *Anal.* Calcd. for $C_{12}H_{11}ON$ (methyl 2-methyl-3-quinolyl ketone): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.57; H, 5.91; N, 7.82. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 241 (4.60), 283 (3.83). This compound was undepressed on admixture with methyl 2-methyl-3-quinolyl ketone[8] prepared from another route.

Reaction of IV with 2,4-Pentanedione——A mixture of 500 mg of IV and 1 ml of 2,4-pentanedione was heated at 160° for 5 hr. The reaction mixture was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. None of reaction products were obtained and resulted only in the recovery of IV from the elution with benzene on 63% yield (317 mg).

Reaction of I with Ethyl Acetoacetate——A mixture of 500 mg of I and 1 ml of ethyl acetoacetate was heated at 160° for 1 hr. The reaction mixture was dissolved in benzene, extracted with 2N HCl and 2N NaOH. The benzene layer was washed with H_2O and dried over anhyd. Na_2SO_4. After removing benzene, the residue was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. The elution with petr. ether gave 8 mg of XIX, yellow oil, which could not been determined its structure as yet.

The hydrochloric acid solution was neutralized with Na_2CO_3, extracted with benzene and dried over anhyd. Na_2SO_4. After removing benzene, the extract was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. The elution with petr. ether gave XVII, mp 66—67°, white crystals, in 2.3% yield (17 mg), which was undepressed on admixture with ethyl 2-methyl-3-quinolinecarboxylate[9] prepared from another route. IR ν_{max}^{KBr} cm^{-1}: 1714 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 238 (4.66), 282(3.75). The elution with MeOH gave XVIII, mp 237°, white crystals, in 0.9% yield (6 mg), which was undepressed on admixture with 3-acetylcarbostyril[9] prepared from another route . Mass Spectrum *m/e*: 187 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1684, 1656 (C=O). UV ν_{max}^{EtOH} mμ (log ε): 337 (4.59), 292 (4.07), 370 (3.88).

Reaction of IV with Ethyl Acetoacetate——A mixture of 500 mg of IV and 1 ml of ethyl acetoacetate was heated at 160° for 3 hr. The reaction mixture was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. None of reaction products were obtained and resulted in the recovery of IV from the elution with benzene in 61% yield (307 mg).

Reaction of I with Diethyl Malonate——A mixture of 500 mg of I and 1 ml of diethyl malonate was heated at 160° for 3 hr. The reaction mixture was dissolved in benzene and extracted with 2N HCl. The hydrochloric acid solution was neutralized with Na_2CO_3 and extracted with benzene. The benzene solution was dried over anhyd. Na_2SO_4. After removing benzene, the residue was passed through a column of alumina by changing eluate as follows: petr. ether, benzene, $CHCl_3$ and MeOH. The elution with $CHCl_3$ gave XX, mp 105°, white needles from MeOH, in 4.3% yield (32 mg), which was undepressed on admixture with ethyl 4-quinazolineacetate[10]) prepared from another route.

2′-(Hydroxyiminomethyl)formanilide——A solution of 100 mg of I dissolved in 20 ml of $CHCl_3$ was passed through a column of alumina by changing eluate as follows: $CHCl_3$ and MeOH. The elution with MeOH gave II, mp 151—152°, in 11% yield (12 mg).

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