UDC 547.859.1.07

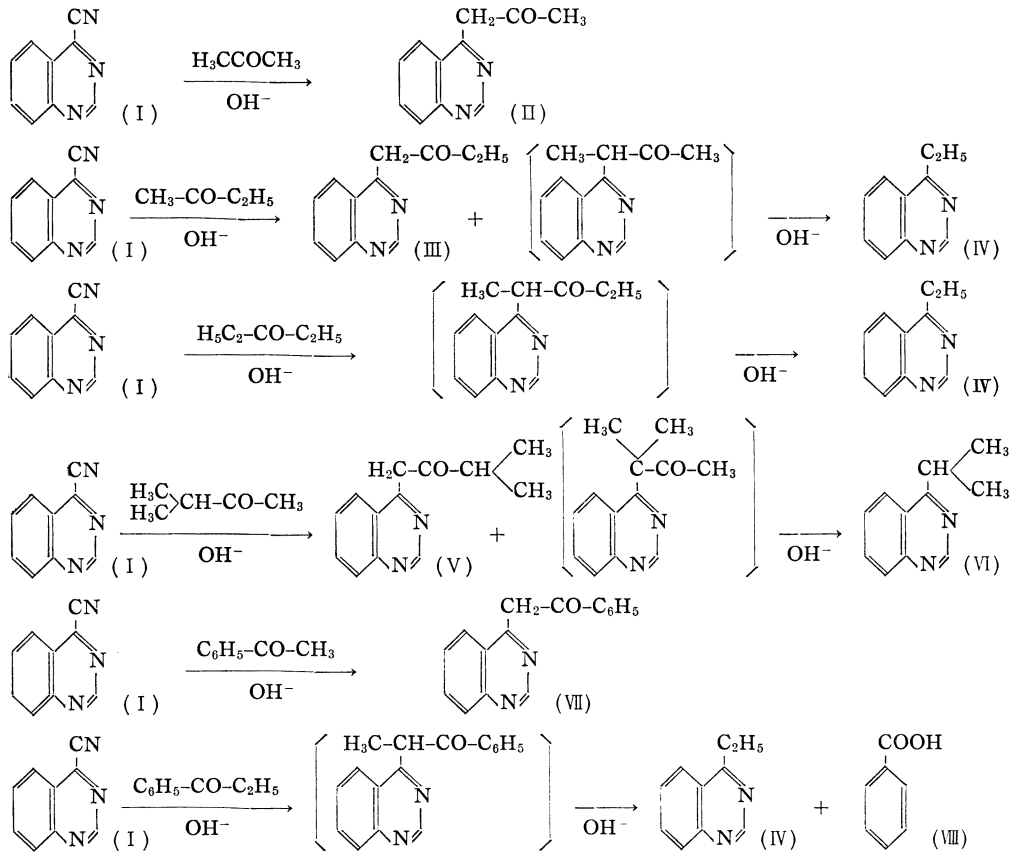
168. Takeo Higashino: On the Reaction of 4-Quinazolinecarbonitrile with Nucleophilic Reagents. III. Reaction of 4-Quinazolinecarbonitrile with Ketones.

(*Shizuoka College of Pharmacy*[*1])

In Part II[1] of this series, it was reported that the reaction of 4-quinazolinecarbonitrile (I) with Grignard reagents gave 4-alkylquinazolines, and the 4-position in (I) was very reactive to anionoid reagents.

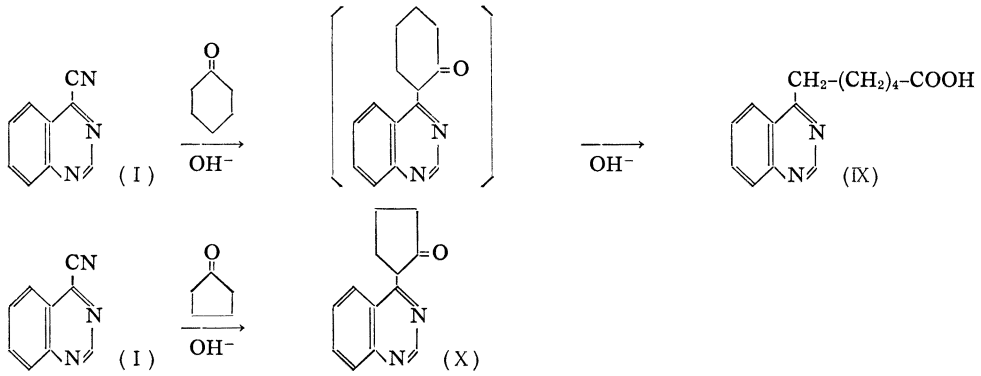
As Part III of this series, it seemed interesting to carry out reactions of (I) with ketones as anionoid reagents in order to elucidate the chemical properties of (I).

Reactions of (I) with acetone in the presence of 50% sodium hydroxide at ordinary temperature afforded 1-(4-quinazolinyl)-2-propanone (II), with 2-butanone, produced 1-(4-quinazolinyl)-2-butanone (III) and 4-ethylquinazoline (IV), with 3-pentanone, gave (IV), with 3-methyl-2-butanone, 1-(4-quinazolinyl)-3-methyl-2-butanone (V) and 4-isopropylquinazoline (VI), with acetophenone, 2-(4-quinazolinyl)acetophenone (VII), with propiophenone, (IV) and benzoic acid (VIII), with cyclohexanone, (4-quinazoline)hexanoic acid (IX), and with cyclopentanone, 2-(4-quinazolinyl)cyclopentanone (X).



*1 Oshika, Shizuoka (東野武郎).

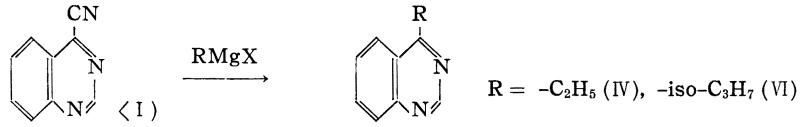
1) T. Higashino: This Bulletin, **10**, 1043(1962).



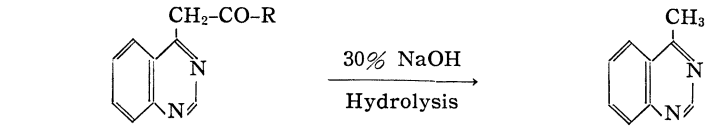
The above experimental results showed that when (I) combined with the primary carbon atom in the α-position of the carbonyl group, the reaction product underwent no hydrolysis, when (I) combined with the secondary or the the tertiary carbon atom at the α-position of the carbonyl group, the intermediate product was hydrolyzed to 4-alkylquinazoline.

However, in case of the reaction of (I) with cyclopentanone possessing the secondary carbon atom at the α-position of the carbonyl group, the substituted reaction product was obtained without undergoing hydrolysis.

The picrates of (IV) and (VI), so obtained, were identified on admixture with authentic samples prepared by another route.[1]



(II), (III), (V), and (VII) were hydrolyzed to 4-methylquinazoline (XI)[1] by heating with 30% sodium hydroxide on a boiling water bath for 4 hours.

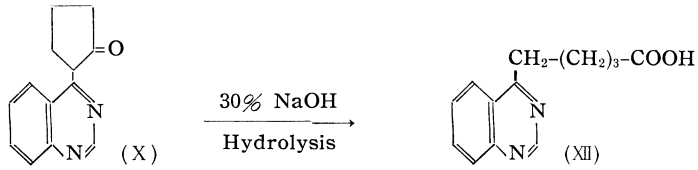


From these results, it is clear that a quinazoline ring combined with a methyl group of ketones, and the elemental analyses of (II), (III), (V), and (VII) correspond to $C_{11}H_{10}ON_2$, $C_{12}H_{12}ON_2$, $C_{13}H_{14}ON_2$, and $C_{16}H_{12}ON_2$, respectively.

The structure of (IX) was deduced from the fact that it gave the analytical values corresponding to $C_{14}H_{16}ON_2$, formed a potassium salt in potassium carbonate solution, and exhibited absorptions at 1680, 1290, and 1390 cm^{-1} for carboxyl group in its infrared spectrum.

The structure of (X) was established by correspondence of its elemental analytical values to $C_{13}H_{12}ON_2$ and by the formation of 4-quinazolinevaleric acid (XII) by hydrolysis with 30% sodium hydroxide on a boiling water bath for 30 minutes.

The structure of (XII) was identified by the fact that it has an empirical formula $C_{13}H_{14}O_2N_2$, formed a potassium salt in potassium carbonate solution and showed absorptions at 1680, 1300, and 1400 cm^{-1} for carboxyl group in its infrared spectrum.



The mechanism for these reactions may be suggested as follows.

For example, the carbanion as an anionoid reagent, which may be formed by treatment of acetone with sodium hydroxide solution, attacks the 4-position of (I) which is susceptible to anionoid reagents.[2]

Consequently, the substituted compound (II) is formed via an intermediate complex of (IIa) type, as shown in Chart 1.

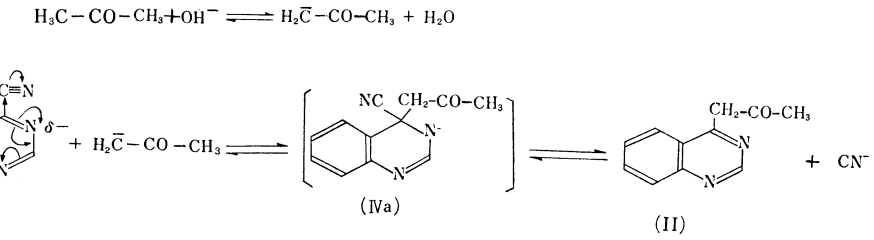
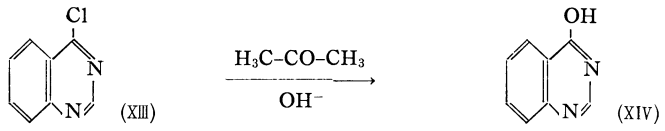


Chart 1.

It is pertinent to note that the reactions of ketones as anionoid reagents with the cyano group in other aromatic heterocyclic compounds have not been reported so far, and this is the first example for this type of reactions.

The application of acetone to 4-chloroquinazoline (XIII) resulted in the formation of 4-quinazolinol (XIV) instead of (II).



This indicated that the chemical properties of (I) differed markedly from those of (XIII) in its behavior toward ketones as anionoid reagents.

The foregoing experiments also showed that the 4-position in (I) was very reactive to anionoid reagents, as demonstrated in Part I[2] and II[1] of this series.

Experimental

Reaction of 4-Quinazolinecarbonitrile (I) with Acetone——A mixture of 0.5 g. of (I), 10 cc. of Me_2CO, and 50% NaOH (0.5 g. of NaOH dissolved in 0.5 cc. of H_2O) was shaken vigorously for 2 hr. at room temperature.

After neutralization with 10 cc. of 20% AcOH, Me_2CO was removed under reduced pressure from the reaction mixture, and the deposited crystals were extracted with benzene, and the benzene solution was dried over anhyd. Na_2SO_4. By evaporation of benzene, 0.4 g. (66%) of 1-(4-quinazolinyl)-2-propanone (II) was obtained as pale yellow needles, m.p. 121~122°, from petroleum (b.p. 60~80°). *Anal.* Calcd. for $C_{11}H_{10}ON_2$ (1-(4-quinazolinyl)-2-propanone): C, 70.95; H, 5.41; N, 15.05. Found: C, 70.51; H, 5.72; N, 14.90.

Reaction of (I) with Acetophenone——Treatment of 0.5 g. of (I) with 5 cc. of acetophenone and 0.5 cc. of 50% NaOH and crystallization of the product from a petroleum (b.p. 60~80°)-benzene mixture afforded 0.4 g. (50%) of 2-(4-quinazolinyl)acetophenone (VII)as pale green needles, m.p. 160~161°. *Anal.*

2) T. Higashino: Yakugaku Zasshi, **80**, 1404 (1960).

Calcd. for $C_{16}H_{12}ON_2$ (2-(4-quinazolinyl)acetophenone) : C, 77.40; H, 4.87; N, 11.28. Found : C, 77.38; H, 4.79; N, 11.23.

Reaction of (I) with Cyclopentanone——Treatment of 0.4 g. of (I), 7 cc. of cyclopentanone and 0.5 cc. of 50% NaOH by the above described method and crystallization from a petroleum (b.p. 60~80°)-benzene mixture afforded 2-(4-quinazolinyl)cyclopentanone (X) as orange needles, m.p. 154~155°. Yield, 0.43 g. (78%). *Anal.* Calcd. for $C_{13}H_{12}ON_2$ (2-(4-quinazolinyl)cyclopentanone) : C, 73.56; H, 5.70; N, 13.20. Found : C, 73.53; H, 5.53; N, 13.20.

Reaction of (I) with 2-Butanone——A mixture of 1.5 g. of (I), 15 cc. of 2-butanone and 1.0 cc. of 50% NaOH was shaken vigorously for 2 hr. at room temperature. After removal of 2-butanone under reduced pressure, the reaction mixture was neutralized with 20% AcOH, and extracted with benzene. The benzene solution was dried over anhyd. Na_2SO_4 and passed through a column of alumina (200 mesh. 20 cc.), yielding 0.5 g. (32%) of 4-ethylquinazoline (IV) (oily substance) and 0.6 g. (31%) of 1-(4-quinazolinyl)-2-butanone (III) (crystals).

(IV) was converted to its picrate (IVa), yellow needles, m.p. 170~171° (from MeOH), which was undepressed on admixture with 4-ethylquinazoline picrate prepared in Part II[1] of this series.

Recrystallization of (III) from petroleum (b.p. 60~80°) afforded pale yellow needles, m.p. 111~112°. *Anal.* Calcd. for $C_{12}H_{12}ON_2$ (1-(4-quinazolinyl)-2-butanone) : C, 71.98; H, 6.04; N, 13.99. Found : C, 72.18; H, 5.87; N, 13.86.

Reaction of (I) with 3-Methyl-2-butanone——Treatment of 1.0 g. of (I), 10 cc. of 3-methyl-2-butanone and 0.5 cc. of 50% NaOH by the same way as above afforded 0.2 g. (18%) of 4-isopropylquinazoline (VI) (liquid) and 0.38 g. (27%) of 1-(4-quinazolinyl)-3-methyl-2-butanone (V) (crystals).

(VI) was transformed into its picrate (VIa), yellow needles, m.p. 161~162°, from MeOH, which was undepressed on admixture with 4-isopropylquinazoline picrate reported in Part II[1] of this series.

Recrystallization of (V) from petroleum (b.p. 60~80°) gave pale yellow needles, m.p. 111~112°. *Anal.* Calcd. for $C_{13}H_{14}ON_2$ (1-(4-quinazolinyl)-3-methyl-2-butanone) : C, 72.87; H, 6.59; N, 13.08. Found : C, 72.70; H, 6.66; N, 13.01.

Reaction of (I) with 3-Pentanone——Treatment of 0.5 g. of (I), 7 cc. of 3-pentanone and 0.5 cc. of 50% NaOH by the same method as in reaction of (I) with Me_2CO afforded 0.36 g. (70%) of 4-ethylquinazoline (IV); its picrate (IVa), yellow needles, m.p. 170~171°, from MeOH. (IVa) was identified on admixture with 4-ethylquinazoline prepared by another route.[1]

Reactinn of (I) with Propiophenone——A mixture of 0.5 g. of (I), 5 cc. of propiophenone and 0.5 cc. of 50% NaOH was shaken vigorously for 3 hr. at room temperature. 10 cc. of benzene was added, and the reaction mixture was extracted several times with 2*N* HCl, and then with 2*N* NaOH.

The HCl layer was neutralized with K_2CO_3, and extracted with benzene. The benzene solution was dried over anhyd. Na_2SO_4 and removal of benzene afforded 0.4 g. (76%) of 4-ethylquinazoline (IV). (IV) was converted to its picrate (IVa), m.p. 170~171°, from MeOH, which (IVa) was undepressed on admixture with 4-ethylquinazoline picrate obtained from another route.[1]

The NaOH layer was neutralized with 2*N* HCl to give 0.3 g. (61%) of benzoic acid (VIII), m.p. 121°.

Reaction of (I) with Cyclohexanone——A mixture of 0.3 g. of (I), 5 cc. of cyclohexanone and 0.5 cc. of 50% NaOH was shaken vigorously for 3 hr. at room temperature. The reaction mixture was neutralized with 5 cc. of 20% AcOH, and extracted with benzene. The benzene solution was extracted with 2*N* HCl and the HCl layer was neutralized and basified with an excess of K_2CO_3.

By neutralization of the K_2CO_3 layer with AcOH, the crystals began to separate out, which upon recrystallization from a petroleum (b.p. 60~80°)-benzene mixture afforded 0.2 g. (44%) of 4-quinazolinehexanoic acid (IX) as white needles, m.p. 100~101°. *Anal.* Calcd. for $C_{14}H_{16}O_2N_2$ (4-quinazolinehexanoic acid) : C, 68.83; H, 6.60; N, 11.47. Found : C, 69.17; H, 6.59; N, 11.27. IR ν_{max}^{Nujol} cm^{-1} : 1680, 1290, 1390 (-COOH).

Hydrolysis of (II), (III), (V), and (VII)——A mixture of 0.1 g. of (III) and 5 cc. of 30% NaOH was heated on the water bath for 4 hr. After cooling, the reaction mixture was extracted with benzene, and the benzene solution was dried over anhyd. Na_2SO_4, and benzene was removed to give 0.05 g. of 4-methylquinazoline (XI) as its picrate, yellow needles, m.p. 182~183°, from MeOH. This was identified on admixture with an authentic sample reported in Part II[1] of this series.

Hydrolysis of (II), (V), or (VII) by the same method as above afforded (XI) in 50~60% yield.

Hydrolysis of (X)——A mixture of 0.6 g. of (X) and 7 cc. of 30% NaOH was heated for 30 min. After cooling and neutralization with 20% AcOH, 4-quinazolinevaleric acid (XII) began to separate out. Recrystallization from H_2O afforded white needles, m.p. 136°. Yield, 0.4 g. (61%). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$ (4-quinazolinevaleric acid) : C, 67.81; H, 6.13; N, 12.17. Found : C, 67.83; H, 6.06; N, 11.99. IR ν_{max}^{Nujol} cm^{-1} : 1680, 1300, 1400 (-COOH).

The K-salt of (XII) was formed by dissolving (XII) in 3% K_2CO_3 solution.

Reaction of 4-Chloroquinazoline (XIII) with Acetone——A mixture of 0.5 g. of (XIII), 10 cc. of Me_2CO and 0.5 cc. of 50% NaOH was shaken vigorously for 2 hr. at room temperature. After Me_2CO was removed under reduced pressure from the reaction mixture, the residue was neutralized with 20%

AcOH. The crystals began to separate out from dil. AcOH solution. Recrystallization from MeOH afforded 0.4 g. (85%) of 4-quinazolinol (XIV), m.p. 216~218°. (XIV) was identified on admixture with an authentic sample prepared by another method.[2]

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Summary

Reactions of 4-quinazolinecarbonitrile (I) with ketones in the presence of 50% sodium hydroxide were carried out in order to elucidate the chemical properties of (I).

With acetone afforded 1-(4-quinazolinyl)-2-propanone (II), with 2-butanone, 1-(4-quinazolinyl)-2-butanone (III) and 4-ethylquinazoline (IV), with 3-pentanone (IV), with 3-methyl-2-butanone, 1-(4-quinazolinyl)-3-methyl-2-butanone (V) and 4-isopropylquinazoline (VI), with acetophenone, 2-(4-quinazolinyl)acetophenone (VII), with propiophenone, (IV) and benzoic acid (VIII), with cyclohexanone, 4-quinazolinehexanoic acid (IX), and with cyclopentanone, 2-(4-quinazolinyl)cyclopentanone (X).

The foregoing experiments showed that the 4-position in (I) was very reactive to anionoid reagents, as already demonstrated in Part I[2] and II[1] of this series.

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169. Takeo Higashino: On the Reaction of 4-Quinazolinecabonitrile with Nucleophilic Reagents. IV. Reaction of 4-Quinazolinecarbonitrile with Active Methylene Compounds.

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In the previous papers,[1~3] it was reported that the 4-position in 4-quinazolinecarbonitrile (I) was very reactive to anionoid reagents.

In this paper, the reaction of (I) with active methylene compounds was studied in order to elucidate the chemical properties of (I).

In benzene, reaction of (I) with ethyl acetoacetate or diethyl malonate in the presence of sodium amide gave ethyl 4-quinazolineacetate (II).

(II) was identified by admixture with an authentic sample prepared by Y. Mizuno, *et al.*[4] by reaction of 4-chloroquinazoline with acetoacetate.

Treatment of (I) with ethyl cyanoacetate in place of ethyl acetoacetate gave ethyl α-cyano-4-quinazolineacetate (III).

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1) Part I. T. Higashino: Yakugaku Zasshi, **80**, 1404 (1960).
2) Part II. *Idem*: This Bulletin, **10**, 1043 (1962).
3) Part III. *Idem*: *Ibid.*, **10**, 1048 (1962).
4) Y. Mizuno, K. Adachi, K. Ikeda: *Ibid.*, **2**, 225 (1954).