

8. Eisaku Hayashi and Takeo Higashino : Studies on 4-Isopropylquinazoline 1-Oxide and 4-Isopropyl-2-quinazolinecarbonitrile.

(Shizuoka College of Pharmacy*¹)

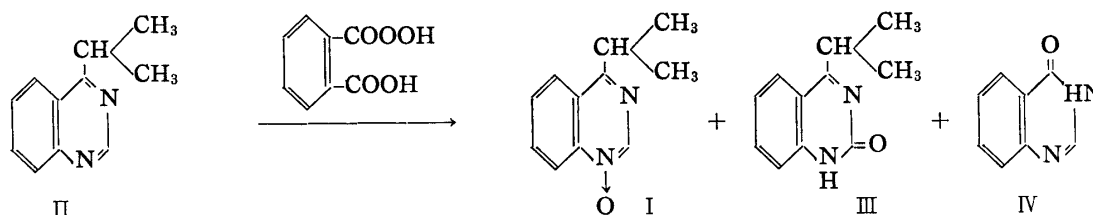
In a series of the studies on the chemical properties of pyrimidine portion in the quinazoline molecule, Higashino reported that the 2-position in 4-alkoxyquinazoline 1-oxide (A) was very reactive to the nucleophilic reagents.¹⁾

Now, considering the overlap some electronic effects of alkoxyl group in A and the nucleophilic activity of the 2-position, the reaction of 4-isopropylquinazoline 1-oxide (I), in which the electronic effects of isopropyl group are assumed to be smaller than those of alkoxyl group, with several kinds of nucleophilic reagents were made in order to compare with the reactivity of A.

1) N-Oxidation of 4-Isopropylquinazoline (II)

When 1.2~1.3 times the theoretical amount of monoperphthalic acid is made to react with II in ether, I, 4-isopropyl-2(1*H*)-quinazolinone (III) and a small amount of 4(3*H*)-quinazolinone (IV) are obtained.

In the case of 4-alkoxyquinazoline (B), Yamanaka reported that the reaction of B with monoperphthalic acid gave A and 4-alkoxy-2-quinazolinol 1-oxide (C).²⁾



I regenerates the original base (II) on reduction with phosphorus tribromide in chloroform or catalytic reduction in methanol over Raney nickel catalyst and the values of elemental analyses agreed with those for the corresponding mono-N-oxide, showing its nature of being the so-called aromatic heterocyclic amine N-oxide.

Thus, I must be either 4-isopropylquinazoline 1-oxide or 3-oxide, but it is surmised to be 1-oxide through the following data.

- i) The reaction of B with monoperphthalic acid gave the corresponding 1-oxide (A).²⁾
- ii) 2-Methyl-3-isopropylquinoxaline (V) gave 2-methyl-3-isopropylquinoxaline 1-oxide (VI) on N-oxidation, but in the case of 2,3-diisopropylquinoxaline (VII), the corresponding N-oxide was not obtained.³⁾ This may be understood that the isopropyl group of the α -position of the ring-nitrogen atom cause steric hindrance against N-oxidation.

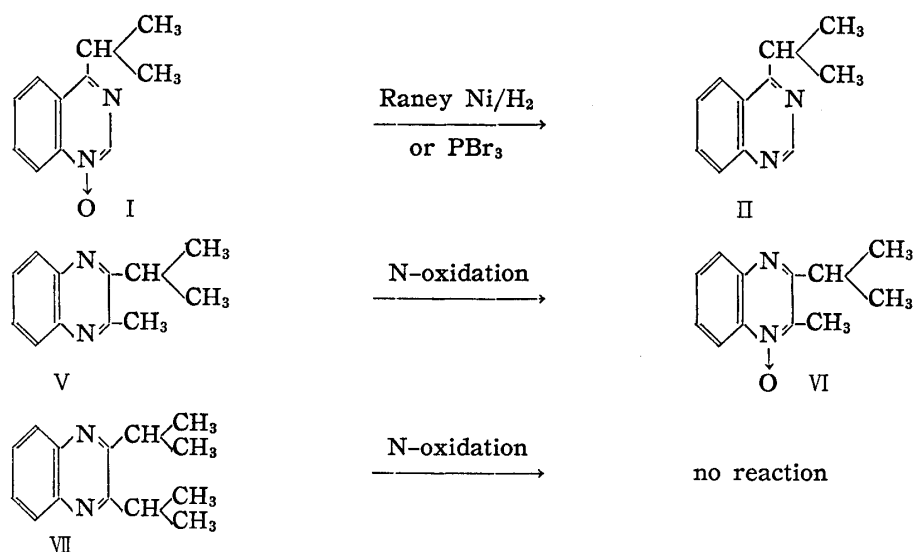
III appears to be an N-oxide of quinazoline since its analytical values agree with those of I. However, the structure of N-oxide is obviously contradictory with the postulation, since the reduction of III with phosphorus tribromide does not regenerate the original base, the decomposition point of III is fairly higher than the melting point of I, and the reaction of III with phosphoryl chloride gives 2-chloro-4-isopropylquinazoline (VIII). Those results show III to be 4-isopropyl-2(1*H*)-quinazolinone.

*¹ Oshika, Shizuoka (林 英作, 東野武郎).

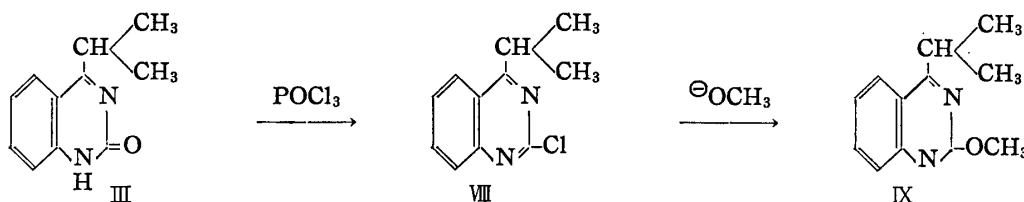
1) T. Higashino : Yakugaku Zasshi, **79**, 699 (1959).

2) H. Yamanaka : This Bulletin, **7**, 152 (1959).

3) J. K. Landquist, G. J. Stacy : J. Chem. Soc., **1953**, 2882.



In methanol, the reaction of VIII with methoxide ion gives 2-methoxy-4-isopropylquinazoline (IX). IX forms two picrates, m.p. 134° and 151°. Those picrates are assumed to be two isomers; 1-methyl and 2-methoxy derivatives. The infrared spectra of the free bases after hydrolysis of those picrates with sodium hydroxide solution are not consistent with the bands of $\text{N}(\text{CH}_3)=\text{O}$. As the results of above data, those picrates may be postulated to be polymorph each other.



The formation of III can be considered that the 2-position in II is attacked with nucleophilic oxidation, as shown in Chart 1.

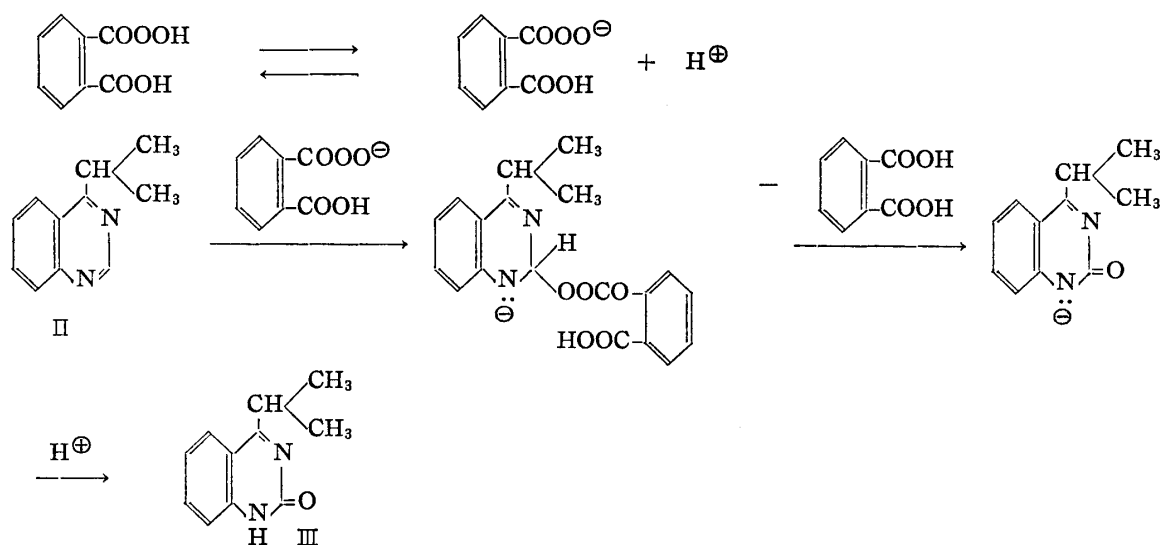
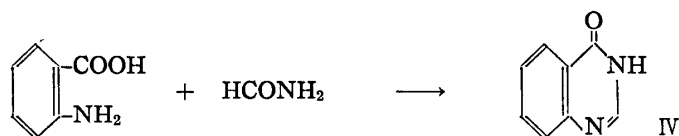


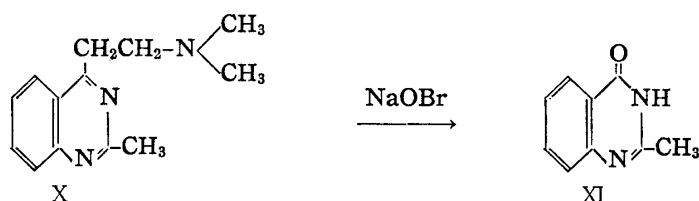
Chart 1.

IV hereby formed was identified by the mixed melting point with an authentic sample made by condensation-cyclization of anthranilic acid and formamide.⁴⁾



The formation of IV may be considered that the isopropyl group is eliminated by nucleophilic oxidation in spite of 4-substituted quinazoline. This shows that the 4-position in quinazoline is very reactive to nucleophilic reagents.

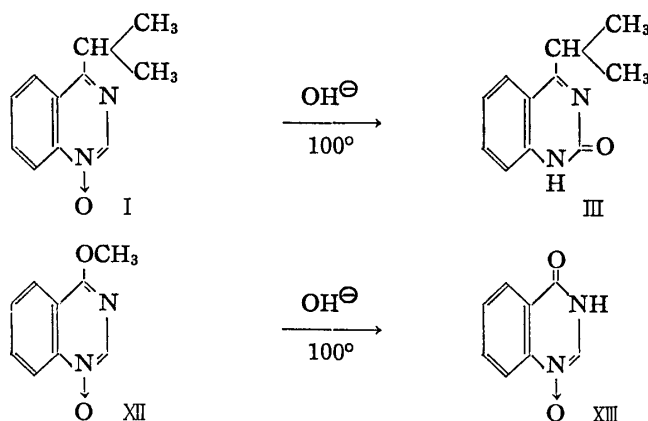
A similar example to the formation of oxidation product of the type (IV) has been found in the reaction of 2-methyl-4-(2-dimethylaminoethyl)quinazoline (X) with sodium hypobromite by Siegle, *et al.*⁵⁾



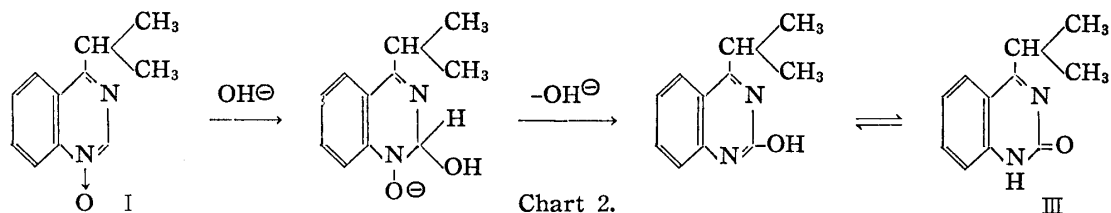
2) Reaction of I with Alkali

The reaction of I with 15% sodium hydroxide solution gives III at boiling point, but not at a room temperature.

In the case of 4-methoxyquinazoline 1-oxide (XII), the reaction does not proceed at a room temperature but gives 4(3*H*)-quinazolinone 1-oxide (XIII)²⁾ at boiling point which is resulted from the hydrolysis of methoxyl group of the 4-position.



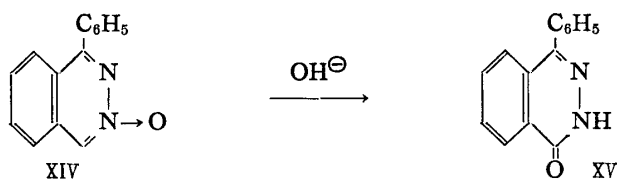
The formation of III may be considered to involve the reaction mechanism shown in Chart 2.



4) M.M. Endicott, E. Wick, M.L. Mercurry, M.L. Sherrill: J. Am. Chem. Soc., **68**, 1300 (1946).

5) J. Siegle, B.E. Christensen: *Ibid.*, **73**, 5777 (1951).

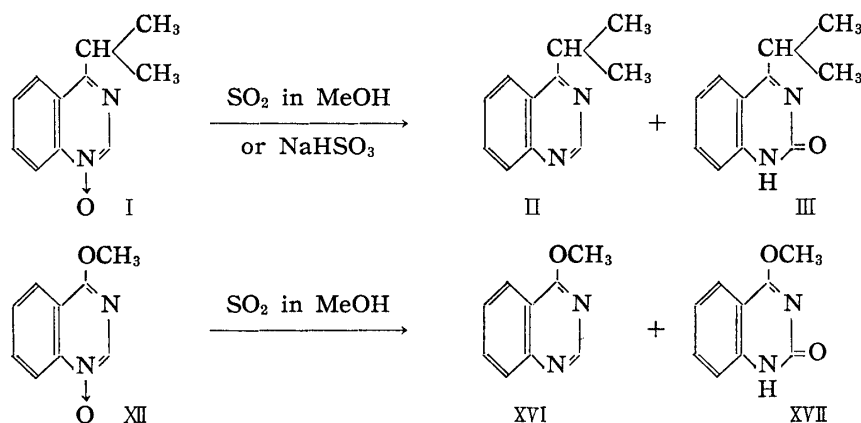
Similar fact had been only observed in 1-phenylphthazine 3-oxide (XIV)⁶⁾ but not been reported in other aromatic heterocyclic N-oxide.



3) Reaction of I with Sulfur Dioxide or Sodium Hydrogen Sulfite

The reaction of I with sulfur dioxide in methanol allowing to stand for a week at a room temperature, or with sodium hydrogen sulfite in diluted methanol under refluxing for 4 hours gives III and II, respectively.

Moreover, Yamanaka²⁾ reported that XII resisted the reduction by sulfur dioxide. However, the reaction of XII with sulfur dioxide according to his direction gives 4-methoxyquinazoline (XVI) and 4-methoxy-2(1*H*)-quinazoline (XVII).



The formation of II and XVI or III and XVII may be thought to involve a route as shown in Chart 3.

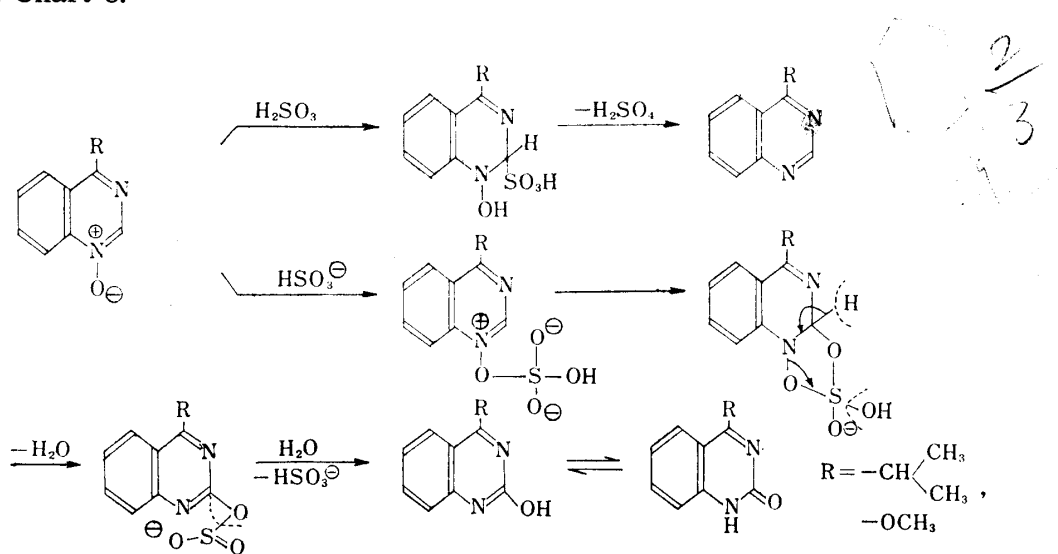
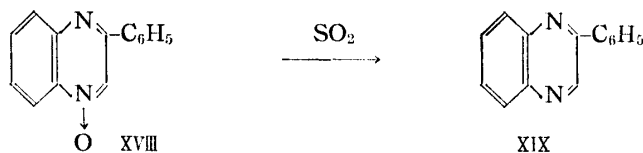


Chart 3.

6) E. Hayashi, E. Ōishi : Unpublished data.

The example of the reaction of aromatic heterocyclic amine N-oxide with sulfur dioxide to recover the original base as shown in this reaction, has been only reported in 2-phenylquinoxaline 4-oxide (XVIII).⁷⁾

The formation of the type of III or XVII have not been observed so far, thus this is the first example for this type of reaction.

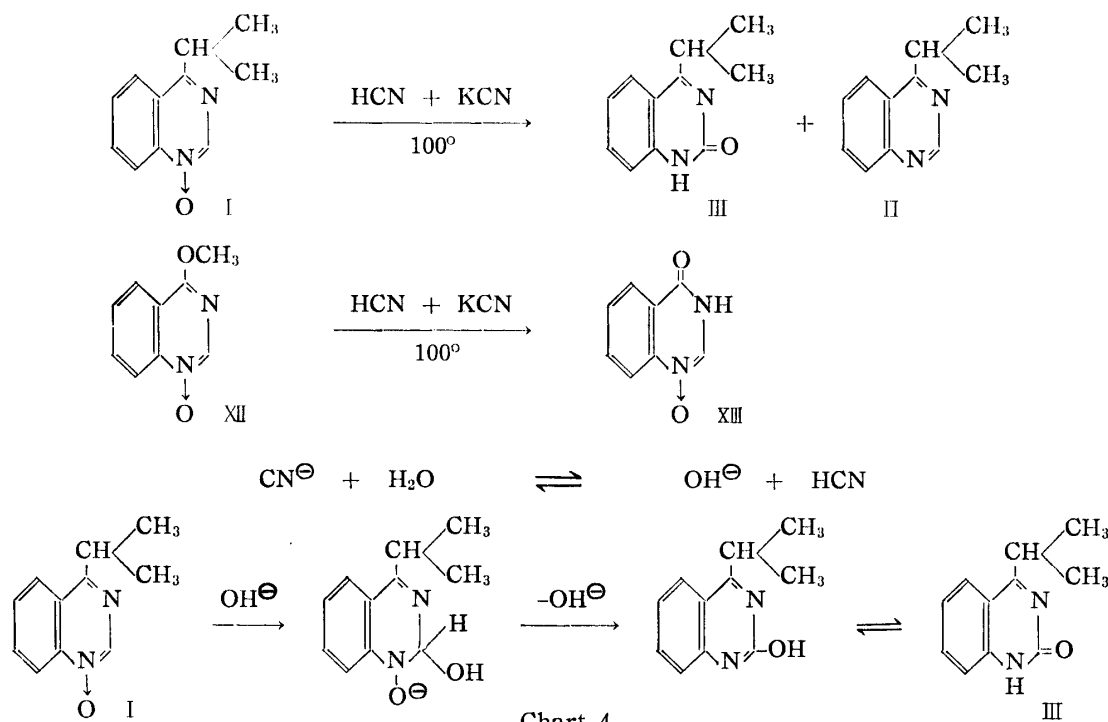


4) Reaction of I with Hydrogen Cyanide or Hydrogen Cyanide-Potassium Cyanide

The reaction of I with hydrogen cyanide in methanol at a room temperature or at 100° recovers the starting material, but with hydrogen cyanide-potassium cyanide at 100° gives III and II (extremely poor yield) and can not be found expected 4-isopropyl-2-quinazolinecarbonitrile (XX).

Also, XII does not react with hydrogen cyanide at 100°, but reacts with hydrogen cyanide-potassium cyanide at 100° to give 4(3*H*)-quinazolinone 1-oxide (XIII), that is, methoxyl group of the 4-position is hydrolyzed.

The process of the formation of II is unknown as yet and that of III may be considered to involve a route shown in Chart 4.



5) Reaction of I with Grignard Reagent

The addition product obtained by the reaction of I with phenylmagnesium bromide, according to general method in absolute ether, is hydrolyzed to 2-phenyl-4-isopropylquinazoline 1-oxide (XXI) with 2*N* hydrochloric acid.

XXI hereby obtained, gives 2-phenyl-4-isopropylquinazoline (XXII) on reduction with phosphorus tribromide in chloroform and its analytical values agree with C₁₇H₁₆ON₂.

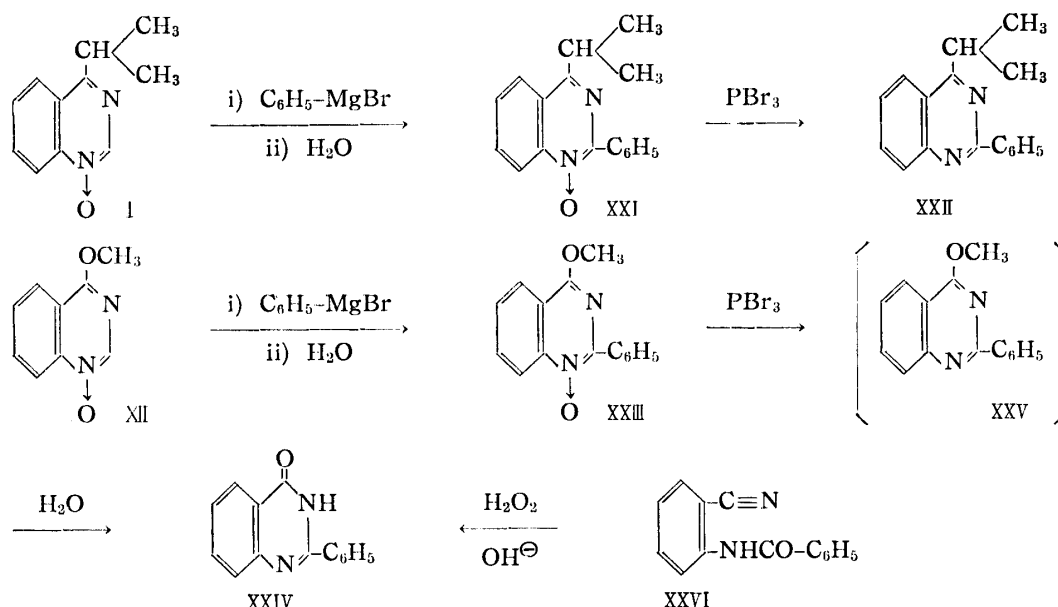
7) E. Hayashi, C. Iijima : Yakugaku Zasshi, 82, 1093 (1962).

The structure of XXI is eventually determined as 2-phenyl-4-isopropylquinazoline 1-oxide.

Similar reaction proceeds in the interaction between XII and phenylmagnesium bromide to give 2-phenyl-4-methoxyquinazoline 1-oxide (XXIII). Analytical values of XXIII agree with $C_{18}H_{12}O_2N_2$, and XXIII gives 2-phenyl-4(3*H*)-quinazolinone (XXIV) on reduction with phosphorus tribromide in chloroform.

Moreover, XXIV might be formed on hydrolysis of 2-phenyl-4-methoxyquinazoline (XXV), which appears probably to be produced on reduction of XXIII with phosphorus tri-bromide, during working up of the reaction mixture.

Also, XXIV is identified on admixture with an authentic specimen prepared by cyclization of 2-benzamidobenzonitrile (XXVI) with hydrogen peroxide in alkali.⁸⁾



The formation of XXI or XXIII is not obviously assumed, but may presumably be considered to involve a route shown in Chart 5.

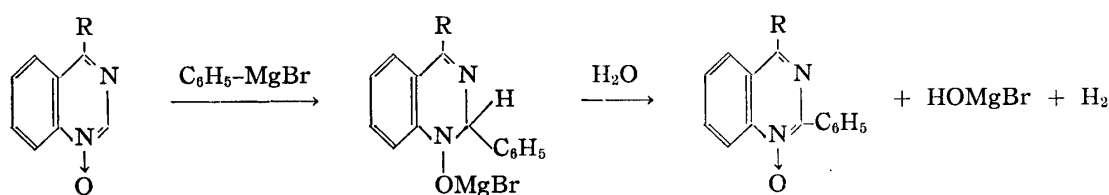
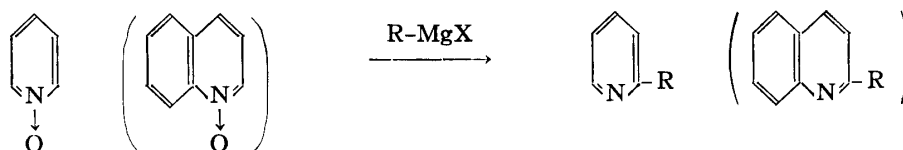


Chart 5.

In general, a reaction of aromatic heterocyclic amine N-oxide with Grignard reagent proceeds to form the corresponding 2-alkyl derivative, and to be accompanied with deoxygenation of N-oxide group, as found in that of pyridine N-oxide⁹⁾ or quinoline N-oxide.¹⁰⁾



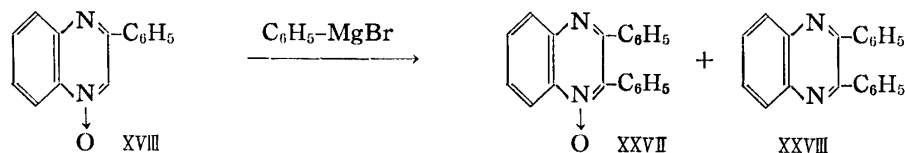
8) R. L. McKee, M. K. McKee, R. W. Bost : J. Am. Chem. Soc., **68**, 1902 (1946).

9) E. Ochiai, K. Arima : Yakugaku Zasshi, **69**, 51 (1949).

10) M. Colonna, A. Risalti : Gazz. chim. ital., **83**, 58 (1953).

Thus, these are two sorts of the reactions of aromatic heterocyclic amine N-oxide with grignard reagent; the first being to form the corresponding 2-alkyl derivative to be accompanied with deoxygenation of N-oxide group, the other being to form the corresponding 2-alkyl N-oxides.

Hayashi and his co-worker reported that both above described proceed concurrently in the reaction of XVIII with phenylmagnesium bromide.⁷⁾



6) Reaction of I with Phenyllithium

In the absolute ether, phenyllithium gives XXI to I similar to the reaction 5).

The formation of XXI in this reaction is also not clearly known, but may be thought to involve a route shown in Chart 6.

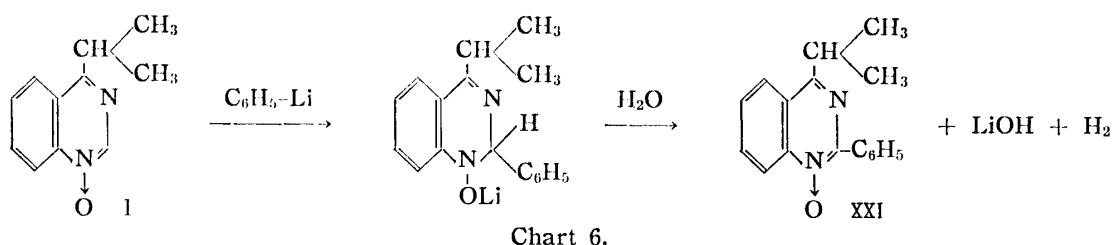
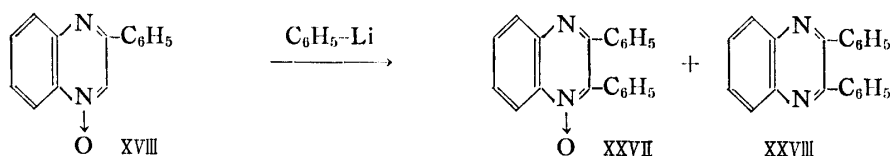


Chart 6.

The example of this reaction has also been observed as following.⁷⁾



7) Reissert Reaction

When calculated amount of benzoyl chloride is added to a solution of I and potassium cyanide in diluted methanol with shaken, an exothermic reaction takes place to give two reaction products. One of them shows m.p. 84° (XX) and the other m.p. 192° (decomp.) (XXIX).

Analytical values of XX so obtained agree with the corresponding nitrile, and XX undergoes very facile hydrolysis to the corresponding acid amide (XXX) on being treated with hydrogen peroxide and alkali carbonate in acetone. This fact reveals that XX has a cyano group.

Moreover, the reaction of XX with methoxide ion in methanol results in the introduction of methoxyl group into the 2-position from which the cyano group is liberated, and IX is finally obtained in a good yield. This fact gives a direct proof that a cyano group had been introduced into the 2-position by Reissert reaction. Thus, XX is 4-isopropyl-2-quinazolinecarbonitrile.

The structure of XXX is consistent with its elemental analytical values to $C_{12}H_{13}ON_3$ and the formation of XX by the reaction with phosphorus pentoxide.

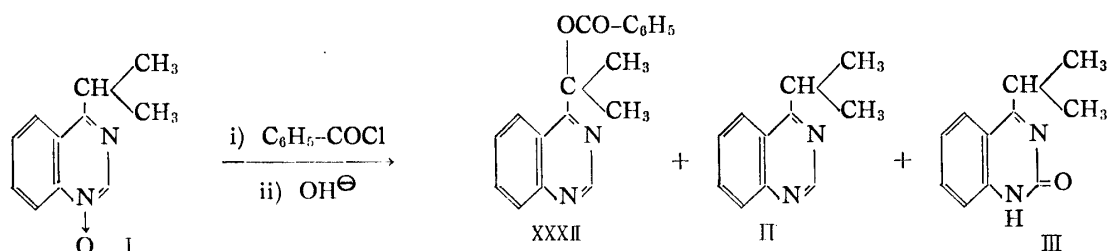
The analytical values of XXIX so obtained agree with those of XXX but the structure of XXIX is obviously different from that of XXX since the former shows clear decomposition point, the latter does melting point. XXIX is not regenerated to the corresponding

XX on treatment with phosphorus pentoxide, and shows the marked absorption bands at 1660~1695, 1600 cm^{-1} for acid amide in its infrared spectrum.

Consequently, it is assumed that α,α -dimethyl-4-quinazolineacetamide (XXIX) might be formed *via* a type of α,α -dimethyl-4-quinazolineacetonitrile (XXXI) by hydrolysis, as shown in Chart 7.

8) Reaction of I with Benzoyl Chloride

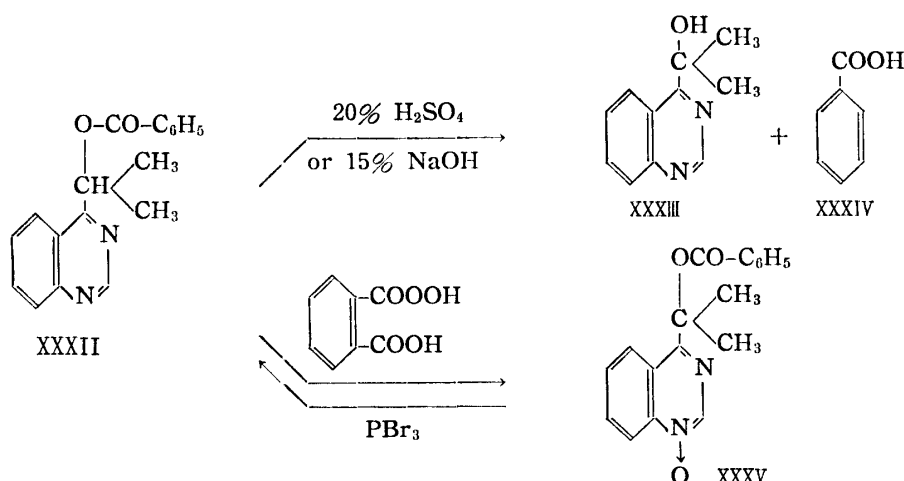
As a calculated amount of benzoyl chloride is added to a chloroform solution of I, an exothermic reaction takes place. The color of the reaction mixture changes from light brown to dark red, finally to reddish brown after cooling, and 4-(1-benzoyloxy-1-methylethyl)quinazoline (XXXII), II, and an extremely small amount of III after treatment of the reaction mixture with 2*N* potassium carbonate solution are obtained.



XXXII, which is well consistent with analytical values for $\text{C}_{18}\text{H}_{16}\text{O}_2\text{N}_2$ and with markedly absorption bands at 1696, 1270, and 1135 cm^{-1} for ester in its infrared spectrum, gives an alcohol (XXXIII) and benzoic acid (XXXIV) on hydrolysis in 20% sulfuric acid or 15% sodium hydroxide solution with refluxing for a few hours.

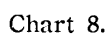
And XXXIII may be considered to α,α -dimethyl-4-quinazolinemethanol, because analytical values of its chloroplatinate agree with $\text{C}_{22}\text{H}_{24}\text{O}_2\text{N}_4\cdot\text{H}_2\text{PtCl}_6$ and the infrared spectrum of free base (XXXIII) exhibits hydroxyl group in the marked absorption in the neighbourhood 3440 cm^{-1} and it has neither phenolic nor enolic hydroxyl group, not forming its sodium salt in 2*N* sodium hydroxide solution.

Those experimentals may indicate XXXII to be 4-(1-benzoyloxy-1-methylethyl)quinazoline.



Moreover, the reaction of XXXII with monoperphthalic acid gives 4-(1-benzoyloxy-1-methylethyl)quinazoline 1-oxide (XXXV), and XXXV regenerates the original base (XXXII) on the reduction with phosphorus tribromide in chloroform.

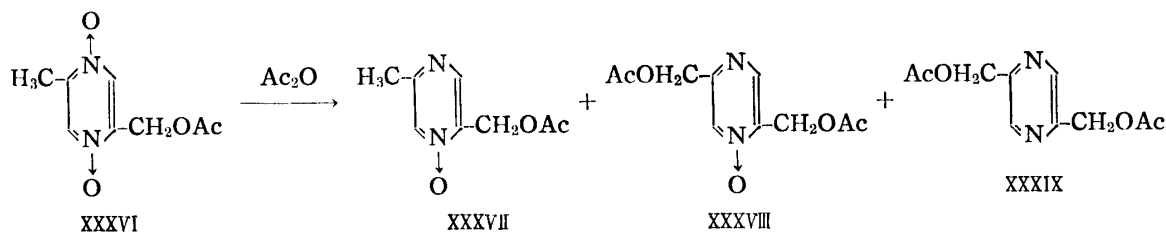
The formation of XXXII, II, and III in this reaction may be considered to involve a route shown in Chart 8.



The reaction of I with excess acetic anhydride at 100° produces II and III. In the case of XIII the formation of XVII was already reported.¹⁾

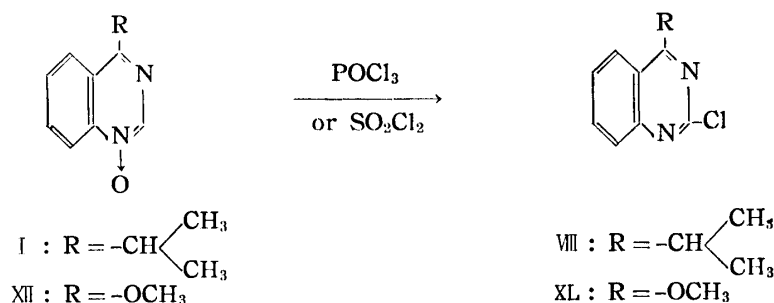
The formation mechanism of II in this reaction has not been known as yet.

The original base on the reaction of aromatic heterocyclic amine N-oxide with acetic anhydride has been recovered in the case of 2-acetoxymethyl-5-methylpyrazine 1,4-dioxide (XXXVI).¹¹⁾



10) Reaction of I with Phosphoryl Chloride (Sulfuryl Chloride)

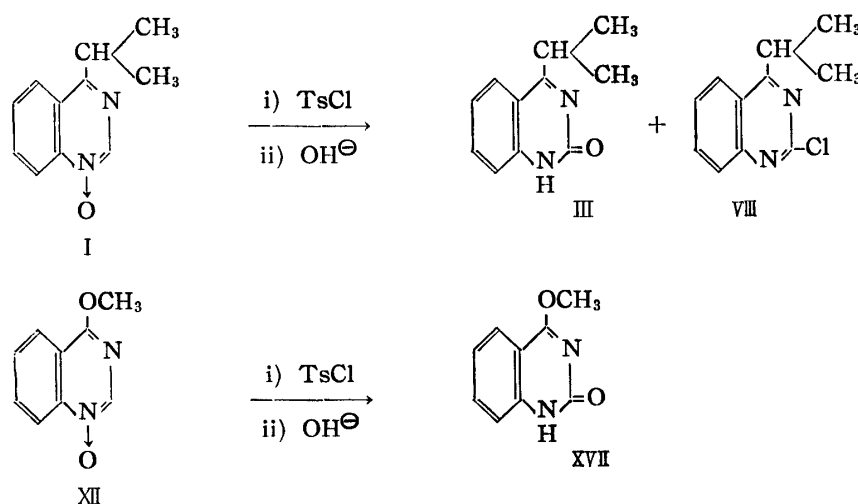
The reaction of I with excess phosphoryl chloride or sulfuryl chloride in the case similar to XII, has been reported,¹⁾ and yielded VIII.



11) Reaction of I with Tosyl Chloride

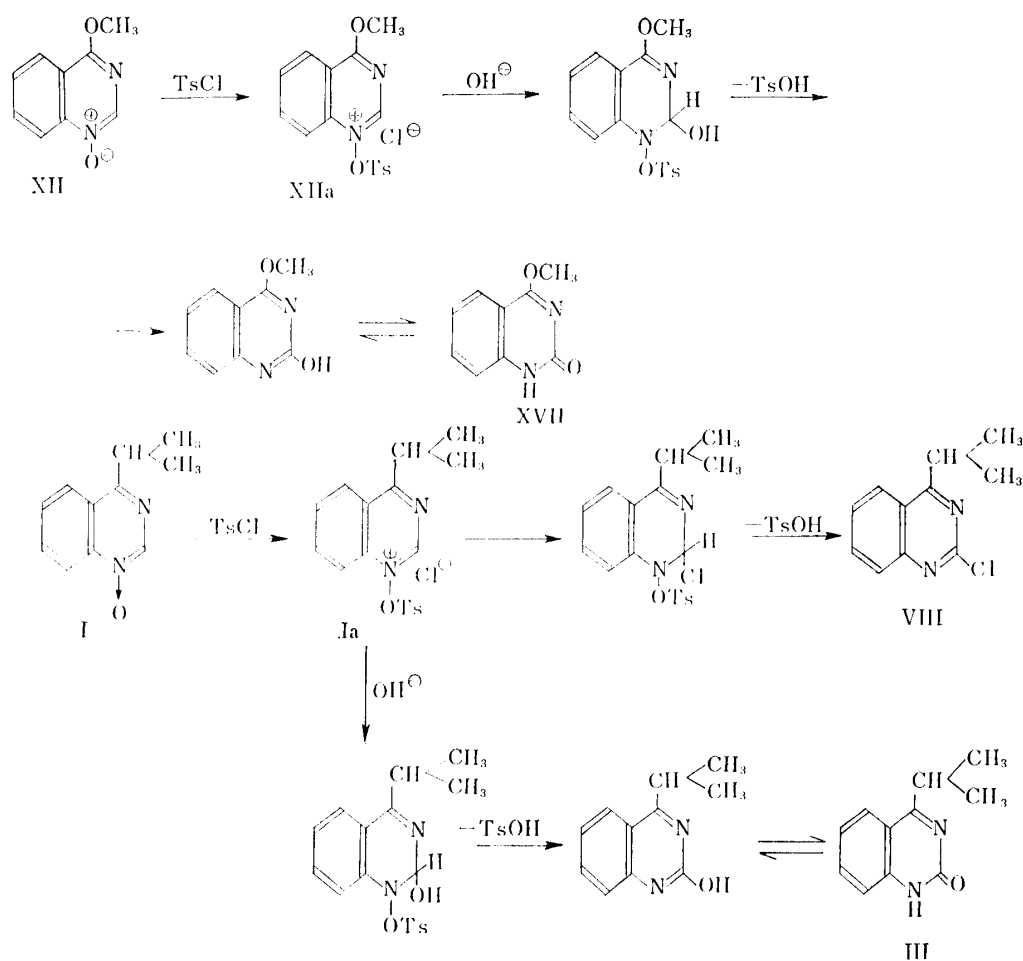
After the reaction of I with tosyl chloride in chloroform, the treatment of the reaction mixture with 2*N* potassium carbonate solution results in the formation of III and VIII.

It has been found that this reaction is applied to XII and introduced the desired substituent into the 2-position, as already reported.¹⁾



The formation mechanism of III and VIII in comparison with that of XVII may be considered to involve a route shown in Chart 9.

11) C. F. Koelsch, W. H. Gumprecht : J. Org. Chem., 23, 1603 (1956).



The nucleophilic activity of the 2-position in XIIa, may somewhat be decreased by overlapping with the electronic effect of methoxyl group in the 4-position, smaller than that of the 2-position in Ia, not decreased by overlapping with that of isopropyl group in the 4-position.

As a result, the selective attack of the 2-position in XIIa proceeds with hydroxyl ion, that is more reactive than chloro ion resulting in only the formation of XVII as the nucleophilic reagent.

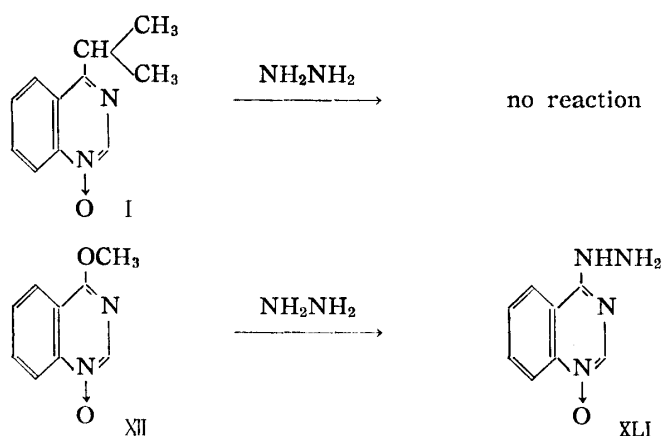
On the other hand, since the 2-position in Ia has a nucleophilic activity, and reacts with both hydroxyl and chloro ion, it reacts simultaneously with those ion to afford the corresponding products (III) and (VIII). As would be thought, those results can not clearly elucidate the differences of the reactivity between I and XII to the nucleophilic reagents, though a new additional conclusion is in hopes at this laboratory.

12) Other Reaction

In the methanol the reaction of I with excess hydrazine hydrate at a room or refluxing temperature does not proceed and recovers the starting material (I) in an excellent yield.

In the case of XII at a room temperature, the reaction resulted in the formation of 4-hydrazinoquinazoline 1-oxide (XLI) by the replacement of methoxyl group, as already reported.¹²⁾

12) T. Higashino: This Bulletin, 9, 635 (1961).



Though it will not be able to compare with both the nucleophilic activities of the 2-position in I and that in XII since the methoxyl group of the 4-position on the reactions of XII with several nucleophilic reagents is attacked first in general, as found in the reaction of 2, 4, and 12), it may be postulated that the definite difference between those reactivities will not be observed even from foregoing experimental.

However, the faint difference of those activities could be found in the reaction of 9 and 11).

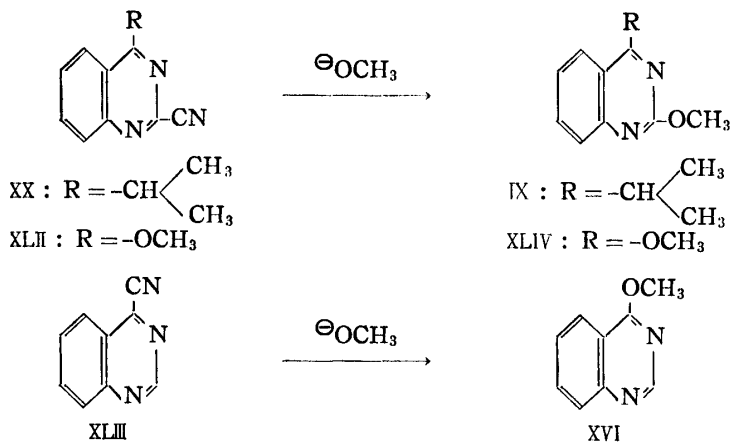
Moreover, though we might have not been expected, it is revealed that the tertiary carbon atom of isopropyl group in the 4-position of I is reactive as shown in the reaction of 7 and 8).

The reactions of XX, obtained in the reaction of 7), with several kinds of nucleophilic reagents are being described to compare with that of 4-methoxyl-2-quinazoline-carbonitrile (XLII)¹³ and 4-quinazolinecarbonitrile (XLIII),¹³⁻¹⁶ as shown in following reaction 13~17).

13) Reaction of XX with Methoxide Ion

The reaction of XX with methoxide ion in methanol gives IX as described on the reaction of 7).

In the case of XLII and XLIII, similar reactions were reported to give 2,4-dimethoxyquinazoline (XLIV)¹³ and XVI, respectively.



13) T. Higashino : Yakugaku Zasshi, **80**, 1403 (1960).

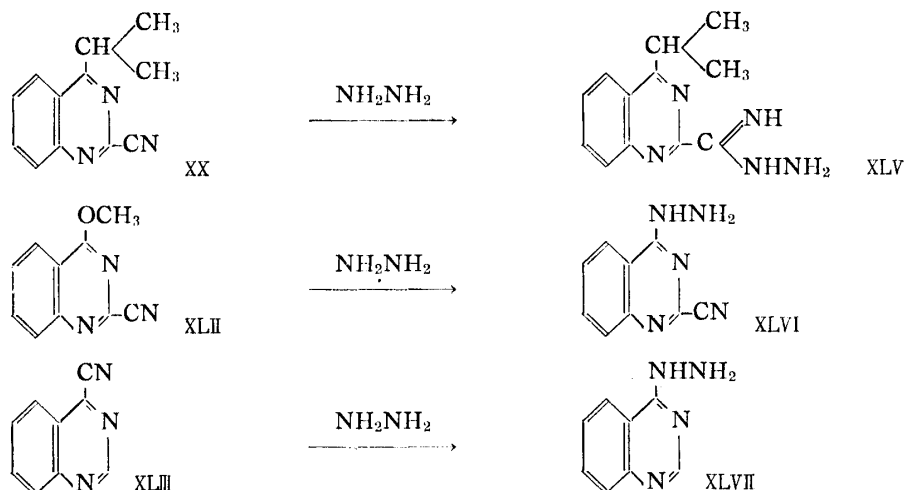
14) *Idem* : This Bulletin, **10**, 1043 (1962).

15) *Idem* : *Ibid.*, **10**, 1048 (1962).

16) *Idem* : *Ibid.*, **10**, 1052 (1962).

14) Reaction of XX with Hydrazine

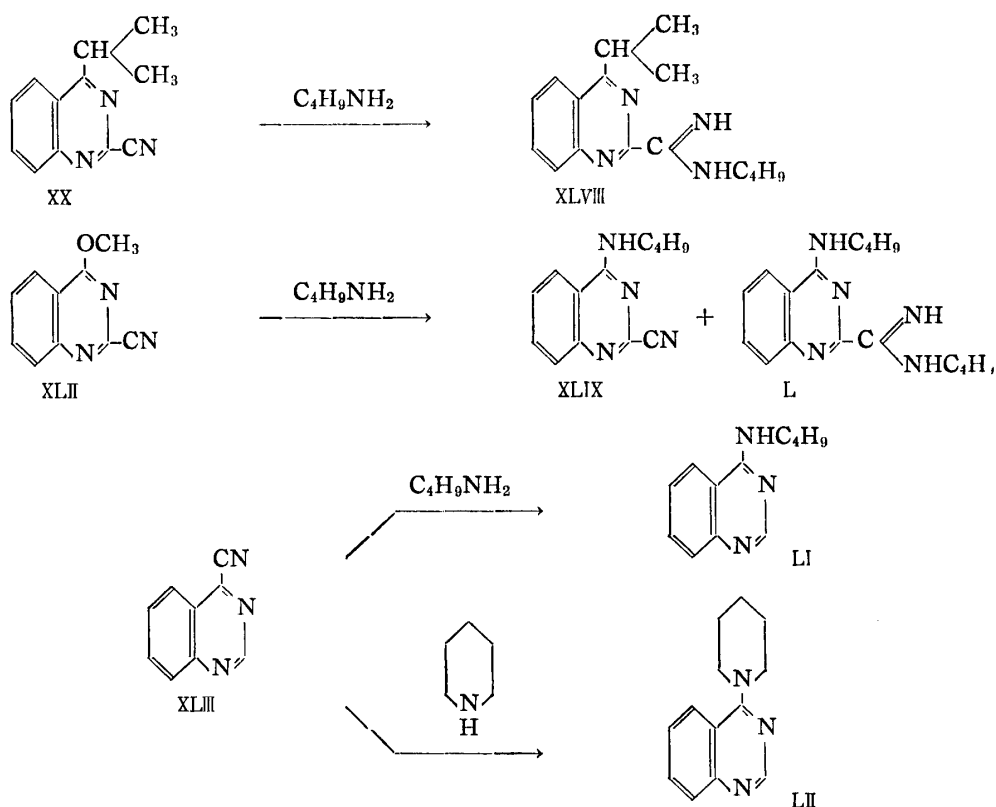
The reaction of XX, XLII, or XLIII with excess 80% hydrazine hydrate in methanol at a room temperature gives 4-isopropyl-2-quinazolinecarboximidic acid hydrazide (XLV), 4-hydrazino-2-quinazolinecarbonitrile (XLVI), or 4-hydrazinoquinazoline (XLVII)¹³⁾ respectively.



In the case of the second, 80% hydrazine hydrate is assumed to attack the aromatic carbon atom of the 4-position in XLII rather than the triple bond between carbon and nitrogen in the cyano group of the 2-position; the reaction product (XLVI) being exempted from the reaction medium as a crystal.

15) Reaction of XX with Amine

The reaction of XX with butylamine does not proceed at a room temperature but at 100° gives N-butyl-4-isopropyl-2-quinazolinecarboxamidine (XLVIII).



Under the same conditions XLII is observed to form 4-butylamino-2-quinazolinecarbo-nitrile (XLIX) and N-butyl 4-butylamino-2-quinazolinecarboxamide (L).

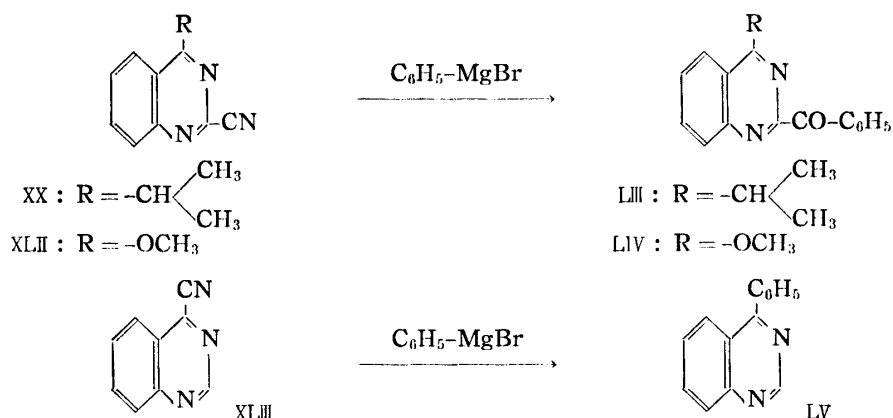
And the reaction of XX or XLII with piperidine at 100° gives a resinous substance from which expected reaction product can not be separated.

Moreover, the reaction of XLIII with butylamine or piperidine at a room temperature gives 4-butylaminoquinazoline (LI) and 4-piperidinoquinazoline (LII), respectively, as already reported.¹³⁾

16) Reaction of XX with Phenylmagnesium Bromide

When XX or XLII is made to react with phenylmagnesium bromide in absolute ether according to the usual method, the reagent attacks the triple bond between carbon and nitrogen in the cyano group and results in the formation of 2-benzoyl-4-isopropylquina-zoline (LIII) and 2-benzoyl-4-methoxyquinazoline (LIV) respectively.

On the other hand, in the case of XLIII the formation of 4-phenylquinazoline (LV) from which the cyano group was liberated.¹⁴⁾



17) Other Reaction

The nitrile in the 4-position in quinazoline is characteristically classified in its substitution with ketone in the presence of 50% sodium hydroxide at a room temperature. For example, the reaction of XLIII with acetone results in the substitution of acetyl group in the 4-position from which the cyano group was liberated; 4-acetylquinazoline (LVI) being obtained in a good yield.¹⁵⁾

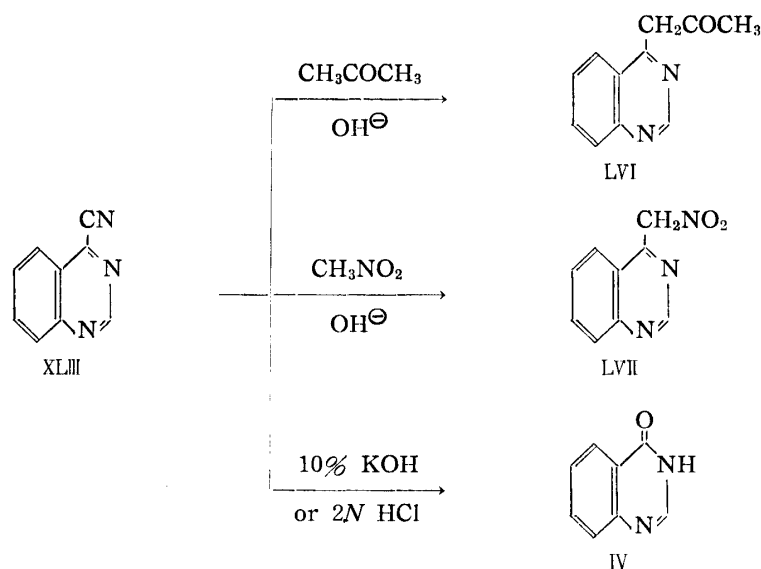
And similar reaction proceeds in the reaction of XLIII with nitromethane as active methylene compounds to afford 4-nitromethylquinazoline (LVII).¹⁶⁾

And then the reaction of XLIII with 10% potassium hydroxide solution or 2*N* hydrochloric acid at a room temperature gives 4(3*H*)-quinazolinone (IV) in an excellent yield, as recently reported.¹³⁾

Application of those reactions described above, to XX or XLII fails to cause the substitution at the 2-position and results in the recovery of the starting materials.

Judging the results through the reactions of 13) to that of 17), the reactivity between XX and XLIII to the nucleophilic reagents might be concluded as following; it appears that the 2-position in XX and the 4-position in XLIII is reactive to the nucleophilic reagent as shown in the reaction of 13). This nucleophilic activity may be due to the overlapping of -M, -E effects of the two nitrogen atoms of the molecule, -E effects of the fused benzene ring, and -I effect of the cyano group.

If the overlapping of those effects on the 2-position in XX and that on the 4-position in XLIII is not significantly differed each other, the nucleophilic activity of the former will be identical with that of the latter, and the reaction of XX with the nucleophilic reagents will similarly proceed to that of XLIII.



However, in the case of XLIII, the reactions result in the formation of the corresponding 4-substituted quinazoline accompanying the elimination of the cyano group as found in the reactions of 14~17), on the other hand, in the case of XX, the reagents attack the triple bond between carbon and nitrogen in the cyano group rather than the ring-carbon atom of the 2-position, and the ordinary behaviour of the cyano group to the nucleophilic reagents are also observed as in the reaction of 14~16).

Thus, it may be eventually demonstrated that the nucleophilic activity of XX is different from that of XLIII, and these effects described above overlap the 4-position in XLIII more than the 2-position in XX, in another word the nucleophilic activity of the former is larger than that of the latter.

Moreover, in comparison with the nucleophilic activity between the 2-position in XX and that in XLIII, it may be concluded that the significant differences of these activities can not be found in the reaction of 13~17).

Experimental

N-Oxidation of 4-Isopropylquinazoline (II) with Monoperphthalic Acid—To a solution of 10 g. of II dissolved in an equal amount of Et_2O , 100 ml. of monoperphthalic acid ether solution (1 ml. contains 0.010 g. of active oxygen), prepared in accordance with formula of Bome,¹⁷⁾ was added and the mixture was allowed to stand in a cool, dark place. After 1~3 days, oily substance began to separate out and the oily substance was crystallized after around one week. The Et_2O layer was decanted, the crystals were decomposed with 20% K_2CO_3 solution, and salted out with excess anhyd. K_2CO_3 . The alkaline mixture was extracted several times with CHCl_3 , the extract was dried over anhyd. Na_2SO_4 , and CHCl_3 was evaporated. The residual oil underwent crystallization on being cooled and the crystals were recrystallized from benzene. 4-Isopropyl-2(1H)-quinazolinone (III), m.p. 231~232°, yield 2.5 g. (23%). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{12}\text{ON}_2$ [4-isopropyl-2(1H)-quinazolinone]: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.05; H, 6.43; N, 14.99.

The filtrate was passed through a column of alumina to separate 4-isopropylquinazoline 1-oxide (I) and 4(3H)-quinazolinone (IV).

I was recrystallized from petroleum, m.p. 97~98°, yield 4.3 g. (40%). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{12}\text{ON}_2$ (4-isopropylquinazoline 1-oxide): C, 70.18; H, 6.43; N, 14.88. Found: C, 70.15; H, 6.50; N, 14.94.

IV was recrystallized from MeOH, m.p. 215~216°, yield 1.1 g. (10%), and identified by the mixed melting point with the authentic sample prepared by M. M. Endicott, *et al.*⁴⁾

Reduction of 4-Isopropylquinazoline 1-Oxide (I) with Raney Nickel—Raney Ni prepared from 0.5 g. of Ni-Al alloy was added to a solution of 0.3 g. of I dissolved in 10 ml. of MeOH and the mixture was shaken in H_2 stream. The reaction was stopped when 1 mol. of H_2 had been absorbed. The

17) Org. Syntheses, 20, 70 (1940).

catalyst was filtered off, the filtrate was evaporated, and 0.24 g. (73%) of oily substance was obtained. Its picrate, m.p. 161–162° (from MeOH), was undepressed on admixture with 4-isopropylquinazoline picrate, m.p. 161–162°, prepared by another route.¹⁴⁾

Reaction of I with Phosphorus Tribromide—A solution of 0.2 g. of I and 0.4 g. of PBr₃ dissolved in 3 ml. of CHCl₃ was refluxed for 30 min. and the reaction mixture was poured into a large amount of H₂O, and neutralized with 15% K₂CO₃ solution. CHCl₃ layer was dried with anhyd. K₂CO₃ and CHCl₃ was evaporated to afford 0.12 g. (66%) of the oily substance. Its picrate, m.p. 161–162°, undepressed on admixture with 4-isopropylquinazoline picrate, m.p. 161–162°, prepared by another route.¹⁴⁾

Preparation of 2-Chloro-4-isopropylquinazoline (VIII)—A mixture of 0.2 g. of III and 6 ml. of POCl₃ was refluxed for 3 hr. After cooling POCl₃ was removed under a reduced pressure, and the residue was dissolved in 10 ml. of CHCl₃. CHCl₃ solution was washed with 40 ml. of 2% NaOH solution and then H₂O. The CHCl₃ solution was dried over anhyd. Na₂SO₄ and removing CHCl₃ afforded the oily substance. The oily substance was dissolved in 1 ml. of benzene and the benzene solution was passed through a column of alumina to remove impurities. VIII was obtained in 83% (0.18 g.) yield.

Preparation of 2-Methoxy-4-isopropylquinazoline (IX)—To a solution of 0.07 g. of metallic Na dissolved in 2 ml. of MeOH, 0.1 g. of VIII in 1 ml. of MeOH was added and the mixture was refluxed on a water bath for 1 hr. MeOH was evaporated from the reaction mixture, and 10 ml. of H₂O was added to the residue, and the residue was extracted with benzene. After drying over with anhyd. K₂CO₃, benzene was removed and 0.08 g. (81%) of IX was obtained as the oily substance.

IX was derivated to the two picrates; m.p. 134° and m.p. 151° (from MeOH). *Anal.* Calcd. for C₁₈H₁₇O₈N₅ (4-isopropyl-2-methoxyquinazoline picrate, m.p. 134°): C, 50.12; H, 3.97; N, 16.24. Found: C, 50.09; H, 4.09; N, 16.17. Calcd. for C₁₈H₁₇O₈N₅ (2-methoxy-4-isopropylquinazoline picrate, m.p. 151°): C, 50.12; H, 3.97; N, 16.24. Found: C, 50.13; H, 4.09; N, 16.24. IR $\nu_{\text{max}}^{\text{liquid}}$ cm⁻¹: 1650–1750 (lactam) were not recognized for the free bases (IX) after hydrolysis of those picrates with 10% NaOH solution and gave the same chart each other.

Reaction of I with Alkali—A solution of 0.1 g. of I and 6 drops of 15% NaOH solution in 3 ml. of MeOH was refluxed for 4 hr. After cooling MeOH was removed under a reduced pressure and 2 ml. of H₂O was added to the residue and extracted with benzene. The H₂O layer was neutralized with dil. AcOH. The crystals separated out from the H₂O layer, were collected by suction and recrystallized from benzene to afford 0.03 g. (30%) of white needles, m.p. 231–232°, undepressed on admixture with an authentic sample (III).

Reaction of 4-Methoxyquinazoline 1-oxide (XII) with Alkali—A solution of 0.3 g. of III and 10 drops of 15% NaOH solution in 3 ml. of MeOH was refluxed for 3 hr. After cooling MeOH was removed under a reduced pressure and 2 ml. of H₂O was added to the residue, and the mixture was neutralized with dil. AcOH. The crystals separated out from H₂O solution were collected by suction and recrystallized from MeOH to afford 0.2 g. of 4(3H)-quinazolinone 1-oxide (XIII) (74%), m.p. 228° (decomp.). *Anal.* Calcd. for C₈H₆O₂N₂ [4(3H)-quinazolinone 1-oxide]: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.14; H, 3.68; N, 17.19.

Catalytic Reduction of XIII with Raney Nickel—Raney Ni prepared from 0.3 g. of Ni-Al alloy was added to a solution of 0.3 g. of XIII dissolved in 30 ml. of MeOH and the mixture was shaken in H₂ stream. The reaction was stopped after absorption of 1 mol. of H₂. The catalyst was filtered off. The filtrate was evaporated, and crystalline residue was recrystallized from MeOH to give 0.2 g. (72%) of white needles, m.p. 215–216° (from MeOH), undepressed on admixture with 4(3H)-quinazolinone (IV) prepared by another route.⁴⁾

Reaction of I and XII with Sulfur Dioxide—SO₂ gas was introduced into a solution of 0.3 g. of I dissolved in 5 ml. of MeOH, until saturation at a room temperature and the reaction solution was allowed to stand for a week at a room temperature, and MeOH was removed under a reduced pressure. 4 ml. of H₂O was added to the residue, and neutralized and then saturated with K₂CO₃. The H₂O solution was extracted with CHCl₃. After drying with anhyd. K₂CO₃, CHCl₃ was removed to obtain the oily substances. The oily substances were partially crystallized with addition of benzene, and the crystals were collected by suction and recrystallized from benzene to give 0.08 g. (27%) of white needles, m.p. 231–232°, undepressed on admixture with 4-isopropyl-2(1H)-quinazolinone (III) obtained by N-oxidation of II.

The filtrate was passed through a column of alumina to separate 0.05 g. (15%) of the oily substance, picrate, m.p. 161–162°, and 0.1 g. (33%) of the starting material (I).

The picrate, m.p. 161–162°, was undepressed on admixture with 4-isopropylquinazoline picrate, m.p. 161–162°, prepared by another route.¹⁴⁾

Treatment of 0.3 g. of XII by the same way as above gave 0.05 g. (18%) of 4-methoxyquinazoline (XVI) and 0.09 g. (30%) of 4-methoxy-2(1H)-quinazolinone (XVII), m.p. 218–219° (from MeOH).

XVI was undepressed on admixture with 4-methoxyquinazoline, m.p. 36°, prepared by another route,¹³⁾ and XVII was also undepressed on admixture with 4-methoxy-2(1H)-quinazolinone prepared by reaction of XII with Ac₂O.¹⁾

Reaction of I with Sodium Hydrogen Sulfite—A solution of 0.3 g. of I and 0.2 g. of NaHSO_3 dissolved in 6 ml. of 50% MeOH was refluxed for 4 hr. on the water bath. After removing of MeOH, the reaction mixture was extracted with CHCl_3 and CHCl_3 layer was dried over anhyd. K_2CO_3 . Evaporation of CHCl_3 afforded 0.24 g. of the residue. The residue was dissolved in 1 ml. of benzene to separate the benzene soluble part and the insoluble part. The benzene soluble part was passed through a column of alumina to remove the impurities. 0.11 g. (40%) of II was obtained, picrate, m.p. 161~162°, undepressed on admixture with 4-isopropylquinazoline picrate.¹⁴⁾

Recrystallization of the benzene insoluble part from H_2O afforded 0.1 g. (33%) of white needles, m.p. 231~232°, undepressed on admixture with 4-isopropyl-2(1*H*)-quinazolinone obtained by the N-oxidation of II.

Reaction of I with Hydrogen Cyanide or Hydrogen Cyanide-Potassium Cyanide—i) A solution of 0.3 g. of I and 0.3 g. of HCN in 5 ml. of MeOH was refluxed for 4 hr. in a sealed tube. After cooling MeOH was removed under a reduced pressure, and the residue was recrystallized from petr. ether to recover 0.24 g. (80%) of the starting material (I), m.p. 97~98°.

ii) A solution of 0.3 g. of I, 0.1 g. of KCN, and 0.3 g. of HCN dissolved in 5 ml. of MeOH was refluxed for 3 hr. in a sealed tube. After cooling the reaction mixture was filtered off and MeOH was removed from the filtrate under a reduced pressure. The residue was separated to the benzene soluble part and insoluble part by addition of 3 ml. of benzene.

The benzene soluble part was passed through a column of alumina to separate 0.1 g. (33%) of the starting material (I) and 0.07 g. (26%) of II. Picrate of II, m.p. 161~162° (from MeOH), was undepressed on admixture with 4-isopropylquinazoline picrate.¹⁴⁾

The benzene insoluble part was dissolved in a small amount of MeOH and passed through a column of alumina to remove impurities. Recrystallization from H_2O afforded 0.05 g. (17%) of white needles, m.p. 231~232°, undepressed on admixture with 4-isopropyl-2(1*H*)-quinazolinone obtained by N-oxidation of II.

Reaction of XII with Hydrogen Cyanide or Hydrogen Cyanide-Potassium Cyanide—i) Treatment of 0.3 g. of XII and 0.3 g. of HCN in 5 ml. of MeOH by the same way as reaction of I with HCN recovered the starting material (XII) in an excellent yield.

ii) A solution of 0.3 g. of I, 0.1 g. of KCN, and 0.3 g. of HCN in 5 ml. of MeOH was refluxed for 3 hr. in a sealed tube. After cooling the reaction mixture was filtered off and MeOH was removed from the filtrate under a reduced pressure to give a white crystalline. Recrystallization from MeOH afforded 0.21 g. (81%) of white needles, m.p. 228° (decomp.). *Anal.* Calcd. for $\text{C}_8\text{H}_6\text{O}_2\text{N}_2$ [4(3*H*)-quinazolinone 1-oxide]: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.18; H, 3.86; N, 17.36.

Reaction of I with Phenylmagnesium Bromide—Phenylmagnesium bromide was prepared by use of 0.3 g. of bromobenzene and 0.07 g. of Mg in 5 ml. of abs. Et_2O .

This solution was added to a solution of 0.3 g. of I dissolved in 10 ml. of abs. Et_2O dropwise with shaking. The reaction mixture was refluxed for 2 hr. on a water bath and was decomposed with 2*N* HCl. The HCl layer was neutralized with 15% NaOH solution and extracted with benzene. The benzene solution was dried over anhyd. K_2CO_3 , and evaporation of benzene afforded 0.24 g. (57%) of the crystals. The recrystallization from petr. ether (b.p. 60~80°) gave 2-phenyl-4-isopropylquinazoline 1-oxide (XXI), m.p. 115~116°, as a pale yellow needles. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{ON}_2$ (4-isopropyl-2-phenylquinazoline 1-oxide): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.21; H, 6.10; N, 10.70.

Reaction of XII with Phenylmagnesium Bromide—Phenylmagnesium bromide was prepared by use of 0.3 g. of bromobenzene and 0.07 g. of Mg in 5 ml. of abs. Et_2O . This solution was added to a solution of 0.3 g. of XII dissolved in 5 ml. of benzene and 5 ml. of abs. Et_2O in a small portions with shaking. After refluxing for 1 hr. on a water bath, reaction mixture was treated similarly as described in the reaction of I with phenylmagnesium bromide to give 0.18 g. (40%) of 2-phenyl-4-methoxyquinazoline 1-oxide (XXIII), m.p. 134° (from petr. ether). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{N}_2$ (2-phenyl-4-methoxyquinazoline 1-oxide): C, 71.41; H, 4.80; N, 11.11. Found: C, 71.92; H, 4.80; N, 11.46.

Reaction of XXI with Phosphorus Tribromide—A solution of 0.17 g. of PBr_3 in 1 ml. of CHCl_3 was added to a solution of 0.13 g. of XXI dissolved in 2 ml. of CHCl_3 and the reaction mixture was refluxed for 1 hr. on a water bath. After cooling the reaction mixture was poured into a large amount of 2% NaOH solution, and extracted with CHCl_3 . CHCl_3 solution was dried over anhyd. K_2CO_3 , and CHCl_3 was evaporated to afford 0.1 g. (83%) of 4-isopropyl-2-phenylquinazoline (XXII), m.p. 66~67° (from petr. ether). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2$ (2-phenyl-4-isopropylquinazoline): C, 82.22; H, 6.50; N, 11.28. Found: C, 81.93; H, 6.45; N, 11.02.

Reaction of XXIII with Phosphorus Tribromide—A solution of 0.1 g. of XXIII and 0.3 g. of PBr_3 in 4 ml. of CHCl_3 was refluxed for 30 min. on a water bath. After cooling, the reaction mixture was poured into a large amount of H_2O and then neutralized with 5% NaOH solution. CHCl_3 layer was dried over anhyd. Na_2SO_4 , and evaporation of CHCl_3 gave 0.07 g. (77%) of colorless needles, m.p. 235~236° (from MeOH), undepressed on admixture with 2-phenyl-4(3*H*)-quinazolinone (XXIV) prepared by cyclization of *o*-benzamidobenzonitrile (XXVI). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{10}\text{ON}_2$ [2-phenyl-4(3*H*)-quinazolinone]: C, 78.03; H, 4.09; N, 11.38. Found: C, 77.94; H, 4.15; N, 11.42.

Preparation of 2-Phenyl-4(3*H*)-quinazolinone (XXIV)—To a solution of 2.0 g. of *o*-benzoylamino-benzonitrile (XXVI) in 40 ml. of MeOH and 8 g. of NaOH in 40 ml. of H₂O, 24 ml. of 33% H₂O₂ was added in a small portions and the reaction mixture was refluxed for 1 hr. on the water bath. And then 10 ml. of 33% H₂O₂ was added to a reaction mixture, and refluxed for 30 min. After cooling, the reaction mixture was neutralized with 15 g. of AcOH, and separated crystals were recrystallized from MeOH. XXIV was obtained in 80% (1.6 g.) yield, m.p. 235~236°. *Anal.* Calcd. for C₁₄H₁₀ON₂ (2-phenyl-4(3*H*)-quinazolinone): C, 78.03; H, 4.09; N, 11.38. Found: C, 78.12; H, 3.96; N, 11.43.

Reaction of I with Phenyllithium—To a solution of 0.3 g. of I dissolved in 10 ml. of abs. Et₂O, a solution of 0.003 g. of Li and 0.3 g. of bromobenzene dissolved in 5 ml. of abs. Et₂O was added in a small portions under cooling and refluxed for 3 hr. on the water bath. After cooling the reaction mixture was poured into a large amount of ice H₂O. Et₂O layer was extracted with 2*N* HCl and HCl layer was neutralized with K₂CO₃ to separate an oily substance. The oily substance was extracted with benzene, and the benzene solution dried over anhyd. K₂CO₃, and passed through a column of alumina to remove impurities. Recrystallization from petr. ether afforded 0.2 g. of pale yellow needles, m.p. 115~116°, undepressed on admixture with 2-phenyl-4-isopropylquinazoline 1-oxide (XXI).

Reissert Reaction of I—To a solution of 0.3 g. of I dissolved in 20 ml. of dil. MeOH-H₂O (1:3), 0.17 g. of KCN was added and dissolved to make a uniform solution, and 0.3 g. of BzCl was added to it in small portions with shaking. Exothermic reaction took place and an orange oily substance separated out at first, which gradually solidified as reaction progressed. After allowing the mixture to stand over night, the crystals were extracted with benzene. The benzene solution was washed thoroughly with 2*N* NaOH solution.

After drying over anhyd. Na₂SO₄, benzene was evaporated and an orange yellow residue crystallized on being stimulated. Recrystallization from petr. ether (b.p. 60~80°) afforded 0.1 g. (33%) of 4-isopropyl-2-quinazolinecarbonitrile (XX), m.p. 84° as a white prisms. *Anal.* Calcd. for C₁₂H₁₁N₃ (4-isopropyl-2-quinazolinecarbonitrile): C, 73.07; H, 5.62; N, 21.31. Found: C, 73.14; H, 5.52; N, 21.21.

The benzene insoluble crystals were collected by suction, and recrystallization from MeOH afforded 0.12 g. (35%) of white needles, m.p. 192° (decomp.). *Anal.* Calcd. for C₁₂H₁₃ON₃ (α,α -dimethyl-4-quinazolineacetamide (XXIX)): C, 66.95; H, 6.09; N, 19.52. Found: C, 67.45; H, 6.32; N, 19.36. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1660~1695, 1600 (-CONH₂).

Preparation of 4-Isopropyl-2-quinazolinecarboxamide (XXX)—To a mixture of 0.2 g. of XX in 1.5 ml. of 30% K₂CO₃ solution, Me₂CO was dropped in until XX went into uniform solution and 0.5 ml. of 30% H₂O₂ was added dropwise, by which the reaction occurred with effervescence an evolution of heat. The mixture was allowed to stand for 1 day, Me₂CO was distilled off under a reduced pressure. The crystals separated out were collected by suction and recrystallization from benzene to give 0.18 g. of white needles, m.p. 171°. *Anal.* Calcd. for C₁₂H₁₃ON₃ (4-isopropyl-2-quinazolinecarboxamide): C, 66.95; H, 6.09; N, 19.52. Found: C, 66.92; H, 6.43; N, 19.76.

Reaction of XX with Methoxide Ion—To a solution of 0.1 g. of Na dissolved in 2 ml. of MeOH, 0.2 g. of XX was added, and the reaction mixture was refluxed on a water bath for 4 hr. After cooling MeOH was evaporated from the reaction mixture, and 10 ml. of H₂O was added to the residue, and extracted with benzene. After drying over anhyd. K₂CO₃, benzene was removed and 0.17 g. (82%) of IX was obtained. Picrates of IX, m.p. 134° and m.p. 151°, were undepressed on admixture with authentic samples, respectively.

Reaction of XXX with Phosphorus Pentoxide—A mixture of 0.1 g. of XXX and 0.1 g. of P₂O₅ was heated at 205~210° on an oil bath for 2.5 hr. After cooling sublimated crystals were collected and recrystallized from petr. ether (b.p. 60~80°) to give 0.05 g. (61%) of white prisms, m.p. 84°, undepressed on admixture with 4-isopropyl-2-quinazolinecarbonitrile (XX).

Treatment of 0.3 g. of XXIX and 0.3 g. of P₂O₅ in a manner similar to that described above, only afforded a resinous substance and could not obtained the desired reaction product.

Reaction of I with Benzoyl Chloride—To a solution of 0.3 g. of I dissolved in 2 ml. of CHCl₃, 0.3 g. of BzCl was added and exothermic reaction took place and the color of the reaction mixture changed from light brown to dark red. The reaction mixture was refluxed for 30 min. on a water bath. After cooling CHCl₃ solution was washed through with 2*N* K₂CO₃ solution and then H₂O and the color of CHCl₃ layer changed from dark red to reddish brown. After drying over anhyd. K₂CO₃, evaporation of CHCl₃ afforded the oily substances. The oily substances were divided into the benzene soluble part and insoluble part by addition of 1 ml. of benzene.

The benzene soluble part was passed through a column of alumina to separate 0.06 g. (28%) of II and 0.11 g. (24%) of 4-(1-benzoyloxy-1-methylethyl)quinazoline (XXXII), m.p. 118° (from petr. ether). *Anal.* Calcd. for C₁₈H₁₆O₂N₂ (4-(1-benzoyloxy-1-methylethyl)quinazoline): C, 73.95; H, 5.52; N, 9.58. Found: C, 74.09; H, 5.47; N, 9.57. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1696, 1270, 1135 (ester).

The benzene insoluble part was recrystallized from MeOH to give 0.02 g. (7%) of III, m.p. 231~232°, undepressed on admixture with 4-isopropyl-2(1*H*)-quinazolinone prepared by another route.

Hydrolysis of XXXII—i) A mixture of 0.3 g. of XXXII in 10 ml. of 20% H₂SO₄ solution was refluxed for 4 hr. After cooling separated 0.1 g. (83%) of benzoic acid (XXXIV) was collected by suction, and the

filtrate was neutralized with 2*N* NaOH solution to separate the oily substances. The mixture was extracted with 1 ml. of benzene. After drying over anhyd. K_2CO_3 , the benzene solution was passed through a column of alumina to remove impurities. α,α -Dimethyl-4-quinazolinemethanol (XXXIII) was obtained in 52% (0.1 g.) yield. IR: $\nu_{\text{liquid}}^{\text{max}}$ 3440 cm^{-1} (—OH). Its chloroplatinate, m.p. 208~209° (decomp.) (from MeOH). *Anal.* Calcd. for $C_{22}H_{24}O_2N_4 \cdot H_2PtCl_6$ (α,α -dimethyl-4-quinazolinemethanol chloroplatinate): C, 33.59; H, 3.40; N, 7.11. Found: C, 33.83; H, 3.71; N, 6.94.

XXXIII did not form its sodium salt by application of 2*N* NaOH solution.

ii) A mixture of 0.3 g. of XXXII and 10 ml. of 15% NaOH was refluxed for 4 hr. After cooling the reaction mixture was extracted with benzene. After drying over anhyd. K_2CO_3 , the benzene solution was passed through a column of alumina to remove impurities. 0.1 g. (52%) of XXXIII was obtained.

From the H_2O layer, 0.09 g. (80%) of XXXIV was obtained by the neutralization with dil. AcOH.

Preparation of 4-(1-Benzoyloxy-1-methylethyl)quinazoline 1-Oxide (XXXV)—To a solution of 1.06 g. of XXXII dissolved in 10 ml. of Et_2O , 4.3 ml. of Et_2O solution of monoperphthalic acid (1 ml. contains 0.0156 g. of active oxygen) was added and the mixture was allowed to stand for 2 days at a room temperature. Et_2O was evaporated under a reduced pressure, 20 ml. of 20% K_2CO_3 solution was added to the crystalline residue in order to decompose the phthalate. The mixture was extracted with $CHCl_3$ and dried over anhyd. K_2CO_3 , passed through a column of alumina to remove impurities. XXXV was obtained in 72% (0.79 g.) yield, m.p. 178° (from benzene). *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$ (4-(1-benzoyloxy-1-methylethyl)quinazoline 1-oxide): C, 70.11; H, 5.24; N, 9.09. Found: C, 70.83; H, 4.83; N, 9.37.

Reaction of XXXV with Phosphorus Tribromide—To a solution of 0.1 g. of XXXV dissolved in 2 ml. of $CHCl_3$, a solution of 0.3 g. of PBr_3 dissolved in 2 ml. of $CHCl_3$ was added dropwise and the mixture was refluxed for 4 hr. on the water bath, cooled, and poured into a large amount of ice H_2O . $CHCl_3$ layer was removed, aqueous layer was neutralized with K_2CO_3 and extracted with benzene. After drying over anhyd. K_2CO_3 , the benzene solution was passed through a column of alumina to remove impurities. XXXII was obtained in 42% (0.04 g.) yield, m.p. 118° (from petr. ether), undepressed on admixture with 4-(1-benzoyloxy-1-methylethyl)quinazoline.

Reaction of I with Acetic Anhydride—A solution of 0.3 g. of I dissolved in 5 ml. of Ac_2O , was heated at 100° for 2 hr. on the water bath. Ac_2O was removed under a reduced pressure and 10 ml. of 20% K_2CO_3 solution was added to the mixture and extracted with $CHCl_3$. $CHCl_3$ solution was dried over anhyd. K_2CO_3 and $CHCl_3$ was removed to obtain the oily residue. The oily residue was divided to the benzene soluble part and insoluble part by addition of 1 ml. of benzene.

The benzene insoluble part (white crystals) was washed with benzene and recrystallized from benzene to afford 0.08 g. (27%) of white needles, m.p. 231~232°, undepressed on admixture of 4-isopropyl-2(1*H*)-quinazolinone (III).

The benzene soluble part was passed through a column of alumina to remove impurities. 0.14 g. (51%) of the oily substance was obtained. Its picrate showed m.p. 161° (from MeOH), undepressed on admixture with 4-isopropylquinazoline picrate, m.p. 161~162°, prepared by another route.¹⁴⁾

Reaction of I with Phosphoryl Chloride or Sulfuryl Chloride—i) A solution of 0.3 g. of I and 0.3 g. of $POCl_3$ dissolved in 3 ml. of $CHCl_3$, was refluxed for 3 hr. After cooling the reaction mixture was poured into 50 ml. of ice H_2O and neutralized with 15% NaOH solution. $CHCl_3$ layer was dried over anhyd. Na_2SO_4 , and removing $CHCl_3$ afforded the crude VIII. The crude VIII was dissolved in 1 ml. of benzene and passed through a column of alumina to remove impurities. VIII was obtained in 63% (0.21 g.) yield.

The reaction of VIII with methoxide ion, using 0.21 g. of VIII and 0.05 g. of Na in 3 ml. of MeOH, in a same way of the preparation of IX as described above gave IX in 80% (0.16 g.) yield. Picrates of IX, m.p. 134° and 151°, were undepressed on admixture with authentic samples, respectively.

Reaction of I with Tosyl Chloride—To a solution of 0.3 g. of I dissolved in 3 ml. of $CHCl_3$, a solution of 0.45 g. of $TsCl$ dissolved in 3 ml. of $CHCl_3$ was added and refluxed for 15 min. on the water bath. After cooling the reaction mixture was neutralized with 15 ml. of 2*N* K_2CO_3 solution and then shaken vigorously. $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated from the mixture. The oily residue was divided to the benzene soluble part and insoluble part by addition of 1 ml. of benzene.

The benzene insoluble part was recrystallized from benzene to afford 0.07 g. (23%) of white needles, m.p. 231~232°, undepressed on admixture with 4-isopropyl-2(1*H*)-quinazolinone (III).

The benzene soluble part was passed through a column of alumina to remove impurities. 0.12 g. (36%) of VIII was obtained. VIII was also identified with 2-chloro-4-isopropylquinazoline from which was derived to IX in a same way in the preparation of IX as described above.

Reaction of I with Hydrazine—A solution of 0.3 g. of I and 0.25 g. of 80% $NH_2NH_2 \cdot H_2O$ dissolved in 3 ml. of MeOH was refluxed for 2 hr. on the water bath. After cooling MeOH was removed and the residue was solidified gradually. The crystals were collected and recrystallized from petr. ether (b.p. 60~80°) recovered 0.24 g. (80%) of I, m.p. 97~98°, undepressed on admixture with 4-isopropylquinazoline 1-oxide.

Reaction of 4-Isopropyl-2-quinazolinecarbonitrile (XX) with Hydrazine—A solution of 0.2 g. of XX and 0.2 g. of 80% $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ dissolved in 4 ml. of MeOH was allowed to stand over night at a room temperature. MeOH was removed from the reaction mixture under a reduced pressure to obtained the oily residue. The residue was solidified gradually by stimulation. Recrystallization of the crystals gave 0.12 g. of orange yellow prisms (51%), m.p. 156° (decomp.). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_5$ (4-isopropyl-2-quinazolinecarboximidic acid hydrazide): C, 62.86; H, 6.60; N, 30.55. Found: C, 63.23; H, 7.18; N, 30.39.

Reaction of 4-Methoxy-2-quinazolinecarbonitrile (XLII) with Hydrazine—A solution of 0.2 g. of XLII and 0.2 g. of 80% $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ dissolved in 2 ml. of MeOH was allowed to stand for 4 hr. at a room temperature. The crystals separated out from the reaction medium and collected by suction and recrystallized from MeOH to give 0.16 g. (80%) of the orange yellow crystals, m.p. above 250° . *Anal.* Calcd. for $\text{C}_9\text{H}_7\text{N}_5$ (4-hydrazino-2-quinazolinecarbonitrile): C, 58.37; H, 3.81; N, 37.82. Found: C, 58.11; H, 3.57; N, 38.38.

Reaction of XX with Butylamine—A mixture of 0.3 g. of XX and 0.5 g. of butylamine was heated at 100° for 4 hr. 3 ml. of H_2O was added to the reaction mixture and extracted with CHCl_3 . CHCl_3 solution was dried over anhyd. K_2CO_3 and evaporation of CHCl_3 afforded the oily substances. The oily substances were dissolved in 1 ml. of benzene and passed through a column of alumina to remove impurities. N-Butyl-4-isopropyl-2-quinazolinecarboxamidine (XLVIII) obtained in 56% (0.23 g.) yield, its picrate, m.p. 197° (from MeOH). *Anal.* Calcd. for $\text{C}_{22}\text{H}_{25}\text{O}_7\text{N}_7$ (N-Butyl-4-isopropyl-2-quinazolinecarboxamidine picrate): C, 52.90; H, 5.04; N, 19.63. Found: C, 53.13; H, 5.01; N, 20.13.

This reaction did not proceed at a room temperature.

Reaction of XLII with Butylamine—A mixture of 0.3 g. of XLII and 0.2 g. of butylamine was heated 30 min. at 100° . After cooling the crystals separated out from the reaction mixture and 3 ml. of benzene was added to the reaction mixture. The benzene insoluble crystals were collected by suction and recrystallized from benzene, m.p. $186\sim 187^\circ$, yield 0.1 g. (21%). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{25}\text{N}_5$ (N-butyl-4-butylamino-2-quinazolinecarboxamidine): C, 68.19; H, 8.42; Found: C, 68.28; H, 8.40.

The filtrate was passed through a column of alumina to remove impurities. 4-Butylamino-2-quinazolinecarbonitrile (XLIX) was obtained in 22% (0.08 g.) yield, m.p. $109\sim 110^\circ$ (from petr. ether). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_4$ (4-butylamino-2-quinazolinecarbonitrile): C, 69.00; H, 6.24; N, 24.76. Found: C, 69.20; H, 6.35; N, 24.51.

Reaction of XX or XLII with Piperidine—A mixture of 0.3 g. of XX and 0.5 g. of piperidine or that of 0.3 g. of XLII and 0.5 g. of piperidine was heated at 100° for 4 hr. After cooling treatment of the reaction mixture in a manner similar to reaction of XX with butylamine described above gave a resinous substance from which expected reaction product could not be separated respectively.

Reaction of XX with Phenylmagnesium Bromide—Phenylmagnesium bromide was prepared by use of 0.5 g. of bromobenzene and 0.11 g. of Mg in 5 ml. of abs. Et_2O .

This solution was added to a solution of 0.5 g. of XX dissolved in 5 ml. of abs. Et_2O , in a small portions with shaking. The reaction mixture was refluxed for 1.5 hr. on the water bath. After cooling the reaction mixture was decomposed with 5 ml. of 2N HCl solution. HCl layer was neutralized with 5 ml. of 15% of NaOH solution, and extracted with benzene. The benzene solution was dried over anhyd. K_2CO_3 , and evaporation of benzene afforded 0.56 g. (80%) of white crystals, m.p. $107\sim 108^\circ$ (from petr. ether). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{16}\text{ON}_2$ (2-benzoyl-4-isopropylquinazoline): C, 78.23; H, 5.84; N, 10.14. Found: C, 79.01; H, 6.09; N, 10.25.

Reaction of XLII with Phenylmagnesium Bromide—Phenylmagnesium bromide was prepared by use of 0.3 g. of bromobenzene and 0.07 g. of Mg in 10 ml. of abs. Et_2O .

This solution was added to a solution of 0.3 g. of XLII dissolved in 5 ml. of abs. Et_2O dropwise with shaking. The reaction mixture was refluxed for 2 hr. on the water bath. After cooling the reaction mixture was treated in the same way the reaction of XX with phenylmagnesium bromide described above to give 0.3 g. (71%) of 2-benzoyl-4-methoxyquinazoline (LIV), m.p. 124° (from petr. ether). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{N}_2$ (2-benzoyl-4-methoxyquinazoline): C, 72.71; H, 4.58; N, 10.60. Found: C, 72.47; H, 4.84; N, 10.44.

Reaction of XX or XLII with Acetone—i) A mixture of 0.5 g. of XX, 10 ml. of Me_2CO and 50% NaOH solution (0.5 g. of NaOH dissolved in 0.5 ml. of H_2O) was shaken vigorously for 2 hr. at a room temperature. Treatment of the mixture in the same manner as for the reaction of 4-quinazolinecarbonitrile (XLIII) with Me_2CO ¹⁵⁾ recovered 0.4 g. (80%) of the starting material (XX).

ii) Treatment of 0.5 g. of XLII, 10 ml. of Me_2CO and 50% NaOH solution (0.5 g. of NaOH dissolved in 0.5 ml. of H_2O) by the same method as in i) described above also recovered 0.36 g. (72%) of the starting material (XLII).

Reaction of XX or XLII with Nitromethane—i) A mixture of 0.5 g. of XX, 0.5 g. of nitromethane, and 0.5 g. anhyd. K_2CO_3 in 10 ml. of benzene was refluxed for 12 hr. After cooling, treatment of the reaction mixture by the same method as described in the reaction of XLIII with nitromethane¹⁶⁾ recovered 0.43 g. (86%) of the starting material (XX).

ii) Treatment of 0.5 g. of XLII, 0.5 g. of nitromethane by the same method as described above also recovered 0.39 g. (78%) of the starting material (XLII).

Reaction of XX or XLII with Alkali—i) A mixture of 0.5 g. of XX and 3 ml. of 10% KOH solution was vigorously shaken for 15 min. at a room temperature. The reaction did not proceed and recovered XX in an excellent yield.

ii) Treatment of 0.5 g. of XLII and 3 ml. of 10% KOH solution by the same method as above also recovered (XLII) in an excellent yield.

Reaction of XX or XLII with 2N Hydrogen Chloride—i) A mixture of 0.2 g. of XX dissolved in 5 ml. of 2N HCl solution was vigorously shaken to make a uniform solution for 15 min. at a room temperature. The solution was carefully neutralized with 15% K_2CO_3 solution, and separated the crystals were collected by suction and recrystallized from petr. ether to give the starting material (XX) in an excellent yield, m.p. 84° , undepressed on admixture with 4-isopropyl-2-quinazolinecarbonitrile.

ii) Treatment of 0.2 g. of XLII and 5 ml. of 2N HCl solution by the same method as above also recovered XLII in an excellent yield.

Reaction of I with Phosphoryl Chloride or Sulfuryl Chloride—ii) A solution of 0.3 g. of I and 3 ml. of SO_2Cl_2 was refluxed for 1 hr. on the water bath. After cooling SO_2Cl_2 was removed under a reduced pressure from the reaction mixture to obtained oily residue and decomposed with 15% K_2CO_3 solution and extracted with $CHCl_3$. $CHCl_3$ layer was dried over anhyd. Na_2SO_4 , and removing $CHCl_3$ afforded the crude VIII. The crude VIII was dissolved in 1 ml. of benzene and passed through a column of alumina to remove impurities. VIII was obtained in 58% (0.19 g.) yield.

The authors express their deep gratitude to Prof. Emeritus E. Ochiai of Tokyo University and to Dr. T. Ukai, Dean of this College for their unfailing guidances and encouragement throughout the course of this work.

The authors are also indebted to Mr. K. Narita of this College for microanalytical data. Part of the expenses for this work was defrayed by a Grant-in-Aid of Scientific Research for 1962 from the Ministry of Education, which is gratefully acknowledged.

Summary

On the study of the 4-isopropylquinazoline 1-oxide, various following reactions were examined in detail. Those results and considerations are given with the reaction formula in the text.

1) N-oxidation of 4-isopropylquinazoline. 2) Reaction with alkali. 3) Reaction with sulfur dioxide or sodium hydrogensulfite. 4) Reaction with hydrogen cyanide or hydrogen cyanide-potassium cyanide. 5) Reaction with Grignard reagent. 6) Reaction with phenyllithium. 7) Reissert reaction. 8) Reaction with benzoyl chloride. 9) Reaction with acetic anhydride. 10) Reaction with phosphorus oxychloride (sulfuryl chloride). 11) Reaction with tosyl chloride. 12) Other reactions.

As well as on 4-isopropyl-2-quinazolinecarbonitrile prepared by the reaction 7), various following reaction are examined in detail. The results are also given.

13) Reaction with methoxide ion. 14) Reaction with hydrazine. 15) Reaction with amine. 16) Reaction with phenylmagnesium bormide. 17) Another reaction.

(Received July 20, 1963)