UDC 547.856.1

103. **Takeo Higashino**: Studies on Quinazoline 3-Oxide.

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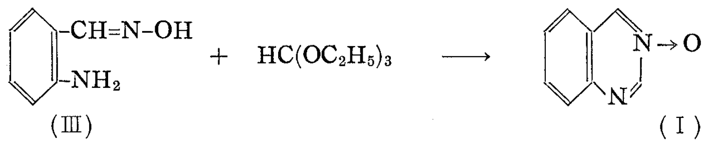
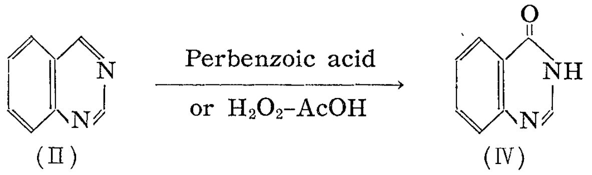
In a series of studies on the chemical properties of the pyrimidine portion in the quinazoline ring, the present author reported the reaction of anionoid reagents on quinazoline,[1] 4-alkoxyquinazoline 1-oxide,[2] and 4-cyanoquinazoline,[3] hydrolysis and alcoholysis of the cyano group in their 2-[4] and 4-positions,[5] and gained some interesting observations regarding the properties of the pyrimidine portion. As a part of these studies, chemical properties of quinazoline 3-oxide (I) were examined in the present series of work.

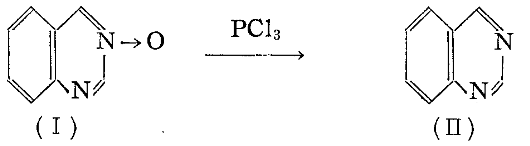
Quinazoline 3-oxide[6] (I) is obtained by condensation-cyclization of *o*-aminobenzaldehyde oxime (III) and ethyl orthoformate. The usual N-oxidation of (II) with organic peracid or with hydrogen peroxide in acetic acid results in the quantitative formation of 4(3*H*)-quinazolinone (IV) and not (I).[6]





Various reactions usually carried out on heterocyclic N-oxides were then carried out on (I) so obtained.

In general, deoxygenation of heterocyclic N-oxides is effected by application of phosphorus trichloride or tribromide,[7] or by catalytic reduction with Raney nickel.[8] The former reaction was found to proceed smoothly and (II) was obtained from (I).



The reaction was also found to proceed smoothly by catalytic reduction over Raney nickel, at ordinary temperature and pressure, resulting in absorption of 1 mole of hydrogen to form (II). If the reaction is allowed to proceed further, a total of 2 moles of hydrogen is absorbed to form 3,4-dihydroquinazoline (V). (II) so obtained was identified by admixture with an authentic specimen[1] prepared by another route from 4-chloroquinazoline (VI), and (V) was confirmed by its derivation to (II) by oxidation with alkaline ferricyanide.

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[1] T. Higashino: Yakugaku Zasshi, **80**, 245 (1960).

[2] *Idem*: *Ibid.*, **79**, 699 (1959).

[3] *Idem*: *Ibid.*, **80**, 1404 (1960).

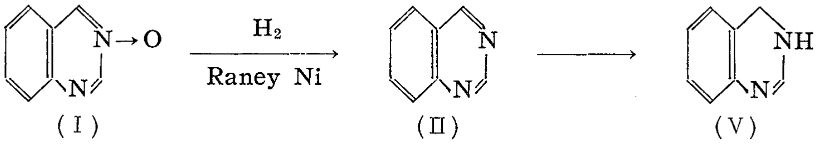
[4] *Idem*: *Ibid.*, **79**, 702 (1959).

[5] *Idem*: *Ibid.*, **80**, 842 (1960).

[6] K. Adachi: *Ibid.*, **77**, 507 (1957).

[7] M. Hamana: *Ibid.*, **75**, 123 (1955).

[8] E. Hayashi, H. Yamanaka, K. Shimizu: This Bulletin, **7**, 141 (1959).



Following are representative reactions by which a substituent is introduced into the 2- or 4-position by application of anionoid reagent to heterocyclic N-oxides :

(a) Introduction of cyano group by the Reissert reaction.[9]
(b) Introduction of a hydroxyl group by the use of tosyl chloride and alkali.[10]
(c) Introduction of acetyl group by the use of acetic anhydride (this acetyl group is easily hydrolyzed to hydroxyl group).[11]
(d) Introduction of chlorine by the use of sulfuryl chloride or phosphoryl chloride.[12]

Application of these reactions to 4-alkoxyquinazoline 1-oxide (VII) results in the introduction of the desired substituent in 2-position, as shown in Chart 1.[2]

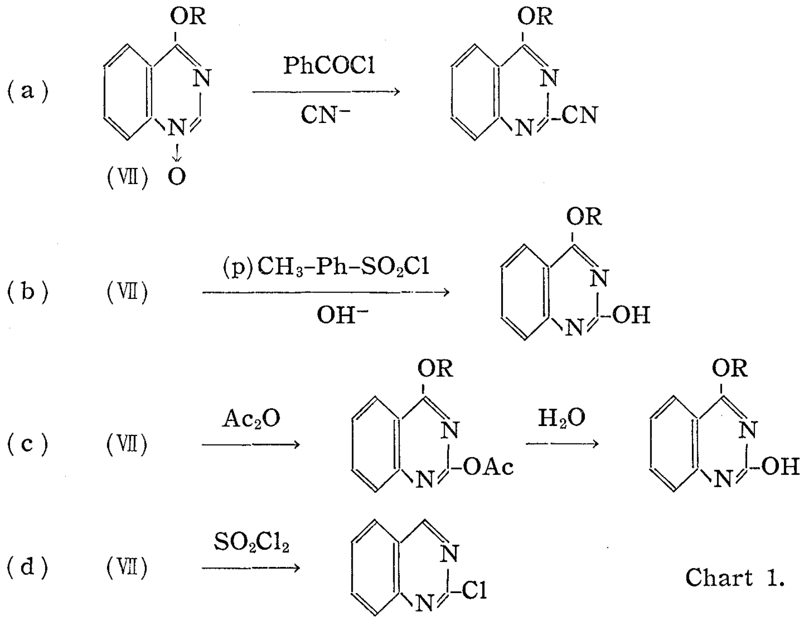
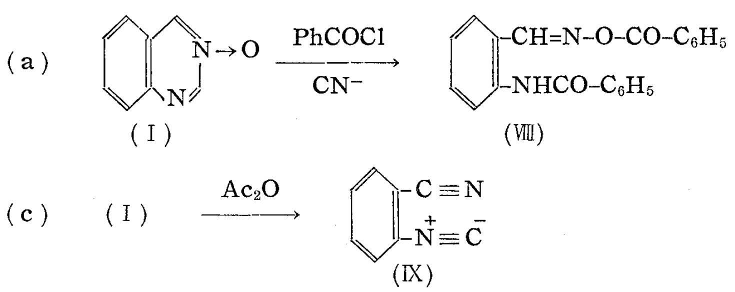


Chart 1.

On the other hand, these reactions on (I) failed to cause the desired reaction and a ring fission was found to occur at the position between 2 and 3, the reactions (a) and (c) with (I) producing 2′-(benzoyloxyiminomethyl)benzanilide[13] (VIII) and *o*-isocyanobenzonitrile (IX), respectively.



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9) O. Henze : Ber., **69**, 1566 (1936); E. Ochiai, I. Nakayama : Yakugaku Zasshi, **65**, 7 (1945).
10) E. Ochiai, T. Yokokawa : Yakugaku Zasshi, **75**, 213 (1955).
11) M. Katada : *Ibid.*, **67**, 15 (1947).
12) T. Itai : *Ibid.*, **65**, 70 (1945); J. Meisenheimer : Ber., **59**, 1848 (1926).

The formation of (VIII) and (IX) is considered to involve a route shown in Chart 2. (VIII) hereby formed was identified by its synthesis by application of 2 moles of benzoyl chloride to (III) in pyridine.[13] Identity of (IX) was established by correspondence of its elemental analytical values to $C_8H_4N_2$ and the presence of marked absorptions at 2243 and 2140 cm^{-1} for aromatic $C\equiv N$ and $-\overset{+}{N}\equiv\overset{-}{C}$ groups, respectively, in its infrared spectrum.

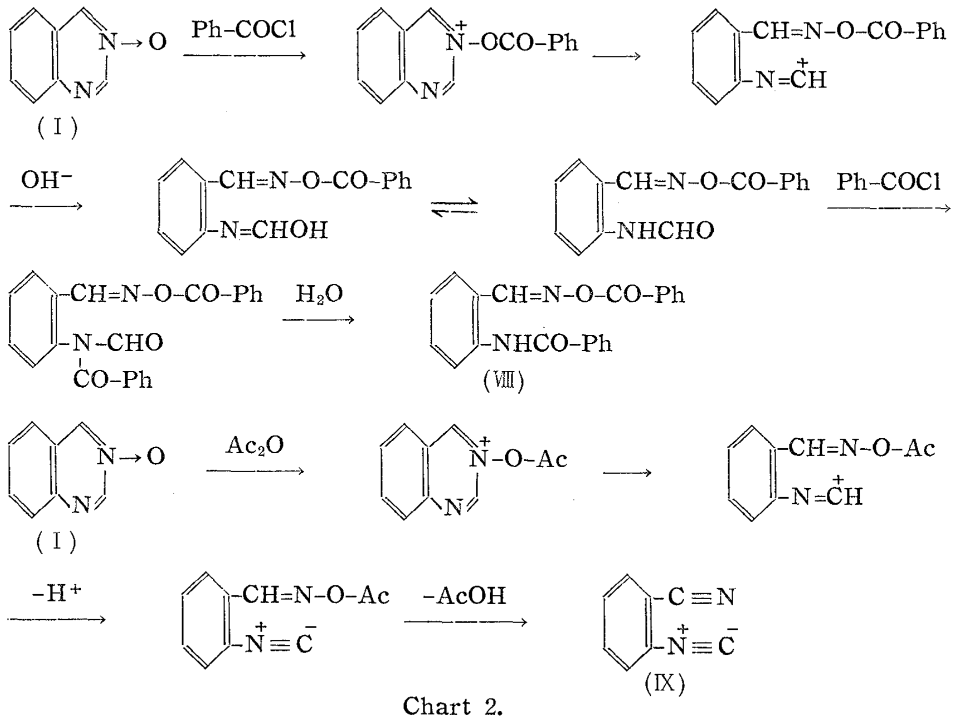
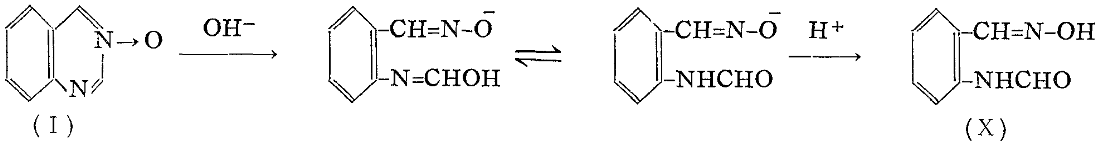


Chart 2.

Reactions (b) and (c) on (I) respectively afforded a crystalline and liquid products but their structure has not been determined as yet. It is certain, however, that introduction of the desired substituent into 4-position to form (IV) and (VI) was not effected and it is assumed that a ring opening had taken place, as in the reactions (a) and (c).

The foregoing experimental results have shown that quinazoline 3-oxide differs markedly from 1-oxide in its behavior to anionoid reagents. Whereas the desired substitution reaction takes place with the 1-oxide compound, ring fission occurs in the 3-oxide compound and this even occurs in the use of merely alkali hydroxide as a reagent with which (VII) remains unchanged, while (I) easily undergoes ring fission at ordinary temperature to form 2′-(hydroxyiminomethyl)formanilide (X). If the reaction is carried out with warming, the product is hydrolyzed to result in deformylation and formation of (III), as observed by Adachi.[14]



Reaction of (I) with hydrogen cyanide, sodium hydrogensulfite, and hydrazine was then examined. These are less reactive as anionoid reagents than those mentioned above and do not react with 2-position of quinazoline 1-oxides with the exception of hydrazine which reacts with the methoxyl group in 4-methoxyquinazoline 1-oxide (VIIa) to form 4-hydra-

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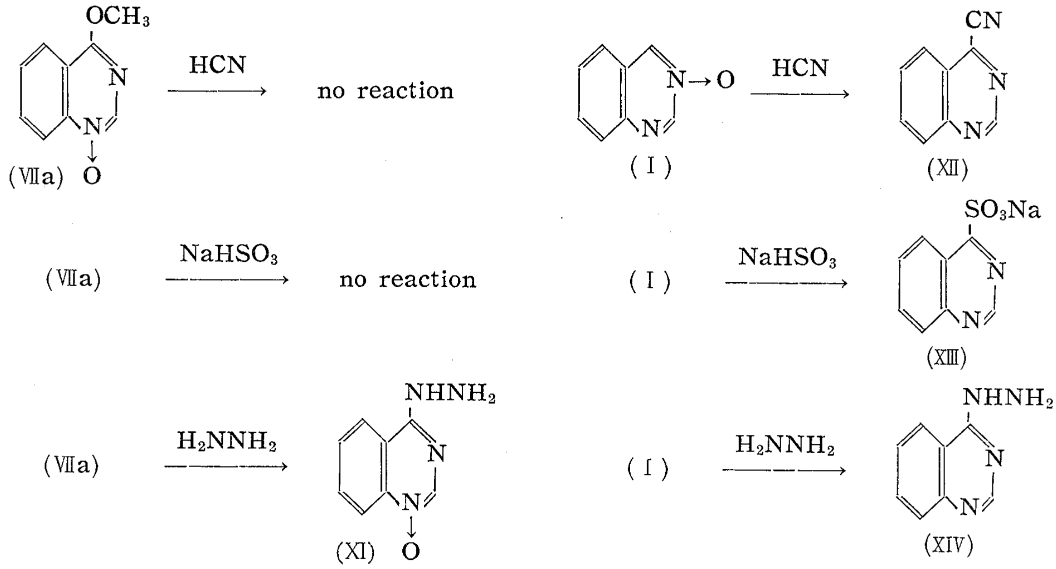
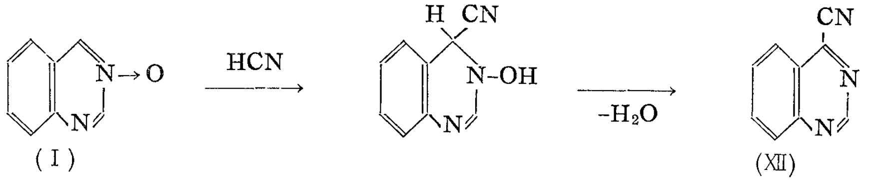
[13] K. von Auwers, E. Frese : Ann., **450**, 290 (1926).
[14] K. Adachi : This Bulletin, **7**, 479 (1959).

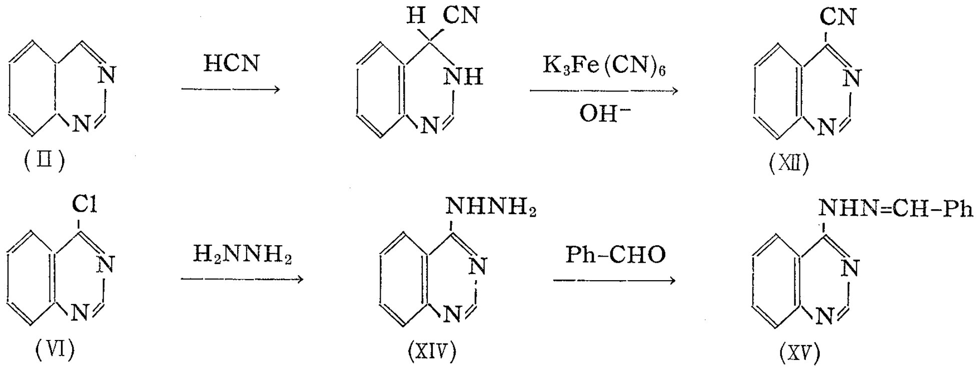
zinoquinazoline 1-oxide (XI). In the case of (I), however, all these reagents reacted smoothly, in the cold or at ordinary temperature, and respectively produced 4-quinazolinecarbonitrile (XII), sodium 4-quinazolinesulfonate (XIII), and 4-hydrazinoquinazoline (XIV). It is thereby recognized that the nucleophilic activity of 4-position in (I) is greater than that of 2-position in (VII).



These reactions are considered to proceed in the following manner, taking that of hydrogen cyanide as an example :

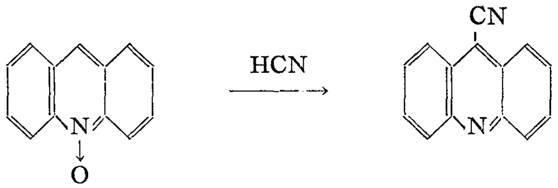


The compound (XIV) hereby obtained was identified with the authentic specimen prepared by a different route,[1] together with (XII), by its condensation with benzaldehyde to form 4-benzylidenehydrazinoquinazoline (XV).



The structure of (XIII) was presumed through the correspondence of its analytical values to $C_8H_5N_2NaS \cdot H_2O$ and by comparison of the reaction of (I) with hydrogen cyanide and hydrazine.

Example of a reaction of these anionoid reagents with other cyclic N-oxide compounds



is found only in the reaction of acridine 10-oxide and hydrogen cyanide.[15]

It is also known that the application of hydrogen cyanide, sodium hydrogensulfite, or hydrazine to phenanthridine 5-oxide and 2-phenylquinoxaline 4-oxide does not result in the same reaction as in (I).[16]

It may be concluded from the foregoing experimental results that the polar effect of the N-oxide group, together with the effect of ring-nitrogen, as well as that of the fused benzene ring, markedly increases the nucleophilic activity of the 4-position in quinazoline N-oxides. On the other hand, the N-oxide group markedly tends to reduce the stability of the ring, resulting in the facile fission of the ring between 2- and 3-positions.

Experimental

Catalytic Reduction of Quinazoline 3-Oxide (I) with Raney Nickel——i) Raney Ni prepared from 2.0 g. of Ni-Al alloy was added to 1.3 g. of (I) in 20 cc. of MeOH and the mixture was shaken in H_2 stream. The reaction was stopped when 1 mole of H_2 had been absorbed. The catalyst was filtered off, the filtrate was evaporated, and 1.1 g. of oily residue was distilled to collect the fraction of b.p. 240～243°. The fraction solidified to give 0.8 g. of crystals melting at 48～49°, undepressed on admixture with quinazoline (Ⅱ) obtained through 4-chloroquinazoline.

ii) Raney Ni prepared from 2.0 g. of Ni-Al alloy was added to 0.75 g. of (I) in 30 cc. of MeOH and the mixture was shaken in H_2 stream. The reaction stopped after absorption of 2 moles of H_2. The catalyst was filtered off, MeOH was evaporated from the filtrate, and 0.3 g. of 3,4-dihydroquinazoline (Ⅴ) was obtained.

Oxidation of (V) with Potassium Ferricyanide——To a mixture of 5 g. of (Ⅴ) in 100 cc. of benzene and 6 g. of NaOH in 20 cc. of H_2O, 26.5 g. of $K_3Fe(CN)_6$ dissolved in 150 cc. of H_2O was added in small portions with shaking during 30 min. The reaction mixture was filtered and the benzene layer was separated from the filtrate. After drying over anhyd. Na_2SO_4, benzene was evaporated and 2.0 g. of (Ⅱ), b.p$_{15\sim16}$ 115～118°, m.p. 48°, was obtained. This was undepressed on admixture with (Ⅱ), obtained through 4-chloroquinazoline.

Reissert Reaction of (I). 4′-(Benzoyloxyiminomethyl)benzanilide (VIII)——To a solution of 0.5 g. of (I) dissolved in 10 cc. of H_2O, 0.23 g. of KCN was added and dissolved to form a solution, and 0.5 g. of BzCl was added to it in small portions, with shaking. Exothermic reaction took place and orange oily substance separated out. After allowing the mixture to stand over night, the oily substance was extracted with Et_2O, and the Et_2O solution was washed thoroughly with 10% NaOH. After drying over anhyd. Na_2SO_4, Et_2O was evaporated, the orange oily residue was dissolved in a small amount of benzene, and passed through a column of alumina to remove impurities. Recrystallization from petr. ether (b.p. 60～80°) afforded 0.12 g. of (Ⅷ), m.p. 147～148. This was undepressed on admixture with (Ⅷ) obtained by reaction of *o*-aminobenzaldehyde oxime with BzCl in pyridine. *Anal.* Calcd. for $C_{21}H_{16}O_3N_2$(Ⅷ) : C, 73.24; H, 4.68; N, 8.14. Found : C, 73.42; H, 4.89; N, 8.37.

Reaction of (I) with Tosyl Chloride——To a solution of 0.5 g. of (I) in 15 cc. of $CHCl_3$ in an ice bath, 0.6 g. of tosyl chloride dissolved in 2 cc. of $CHCl_3$ was added with shaking. Exothermic reaction took place and 0.4 g. of white crystals separated out. The structure of this substance has not been determined yet.

Reaction of (I) with Acetic Anhydride; 2-Isocyanobenzonitrile (IX)——A solution of 0.5 g. of (I) dissolved in 6 cc. of Ac_2O was heated at 90° for 4 hr. on a water bath. After cool, Ac_2O was removed in a reduced pressure, the residue was basified with excess of 15% K_2CO_3, and the mixture was extracted several times with benzene. After drying over anhyd. Na_2SO_4, the benzene layer was passed through a column of alumina to remove impurities. Recrystallization from petr. ether (b.p. 60～80°) afforded 0.08 g. of (Ⅸ), m.p. 109～110°. *Anal.* Calcd. for $C_8H_4N_2$(Ⅸ) : C, 74.99; H, 3.15; N, 21.87. Found : C, 75.22; H, 3.39; N, 21.63. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 2243(-CN), 2140(-NC).

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[15] K. Lehmstedt, H. Klee : Ber., **69**, 1157 (1936).

[16] H. Hayashi, T. Iijima : Unpublished data.

Reaction of (I) with Sulfuryl Chloride——A solution of 0.5 g. of (I) and 10 cc. of SO_2Cl_2 was refluxed on a water bath for 1 hr. After cool, SO_2Cl_2 was evaporated in a reduced pressure, the residue was poured on cracked ice, and neutralized with 15% K_2CO_3. This was extracted with $CHCl_3$, $CHCl_3$ solution was dried over anhyd. Na_2SO_4, $CHCl_3$ was evaporated, and 0.1 g. of an oily substance was obtained. The structure of this oily substance has not been determined yet.

Reaction of (I) with NaOH; 2′-(Hydroxyiminomethyl)formanilide (X)——A solution of 0.3 g. of (I) dissolved in 3 cc. of 2*N* NaOH was allowed to stand over night at room temperature. After the reaction mixture was neutralized with AcOH, water was evaporated in a reduced pressure, the residue was collected by suction, and washed several times with benzene. Recrystallization from benzene afforded 0.21 g. of (X), m.p. 154~155°. *Anal.* Calcd. for $C_8H_8O_2N_2$ (X): C, 58.53; H, 4.91; N, 17.07. Found: C, 58.12; H, 4.70; N, 16.82.

Reaction of (I) with HCN; 4-Quinazolinecarbonitrile (XII)——A solution of 0.3 g. of (I) and 0.3 g. of HCN dissolved in 30 cc. of MeOH was allowed to stand over night at room temperature. On removing MeOH in a reduced pressure, the crystals were obtained. Recrystallization from petr. ether (b.p. 60~80°) afforded 0.15 g. of (XII), m.p. 118~119°, which was undepressed on admixture with (XII) derived from 3,4-dihydro-4-quinazolinecarbonitrile by oxidation.

Reaction of 4-methoxyquinazoline 1-oxide (VIIa) with HCN, using 0.3 g. of (VIIa) and treated in a similar way as (I), resulted in the recovery of 0.2 g. of the starting material.

Reaction of (I) with $NaHSO_3$; Sodium 4-Quinazolinesulfonate (XIII)——To a solution of 1 cc. of 20% $NaHSO_3$, 0.3 g. of (I) was added and an exothermic reaction took place. When cooled, the crystals separated out suddenly. The crystals were collected by filtration and recrystallization from H_2O afforded 0.25 g. of (XIII), m.p. above 360°. *Anal.* Calcd. for $C_8H_5O_3N_2SNa \cdot H_2O$(XIII): C, 38.40; H, 2.82; N, 11.20. Found: C, 38.45; H, 2.68; N, 11.31.

The reaction of (VIIa) with $NaHSO_3$, using 0.3 g. of (VIIa) and treated by a similar way as (I), gave 0.18 g. of the recovered starting material.

Reaction of (I) with NH_2NH_2; 4-Hydrazinoquinazoline (XIV)——To a solution of 0.3 g. of (I) dissolved in 2 cc. of MeOH, 0.13 g. of 80% $NH_2NH_2 \cdot H_2O$ was added and dissolved to form a solution. Exothermic reaction took place and on cooling, the crystals separated out gradually. After allowing the mixture to stand over night, the crystals were collected by filtration and recrystallization from MeOH afforded 0.16 g. of (XIV), m.p. 188~189° (decomp.). *Anal.* Calcd. for $C_8H_8N_4$(XIV): C, 59.98; H, 5.03; N, 34.98. Found: C, 59.93; H, 4.98; N, 34.91.

4-Benzylidenehydrazinoquinazoline (XV)——To a solution of 0.35 g. of (XIV) dissolved in 25 cc. of MeOH, 0.3 g. of benzaldehyde was added to make a uniform solution and the solution was refluxed for 3 hr. on a water bath. After cool, MeOH was evaporated in a reduced pressure and 0.2 g. of crystals (XV), m.p. 171~172°, so obtained were recrystallized from benzene. (XV) was undepressed on admixture with 4-benzylidenehydrazinoquinazoline.

Reaction of (VIIa) with NH_2NH_2; 4-Hydrazinoquinazoline 1-Oxide (XI)——To a solution of 0.3 g. of (VIIa) in 1 cc. of MeOH, 0.2 g. of 80% $NH_2NH_2 \cdot H_2O$ in 2 cc. of MeOH was added in small portions. The crystals that separated out were collected by filtration and washed with MeOH to 0.2 g. of (XI), m.p. 167~168° (decomp.). *Anal.* Calcd. for $C_8H_8ON_4$ (XI): C, 54.54; H, 4.58; N, 31.80. Found: C, 54.44; H, 4.67.

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Summary

Catalytic reduction of quinazoline 3-oxide (I) using Raney nickel catalyst results in formation of quinazoline (II) by absorption of one mole of hydrogen and 3,4-dihydroquinazoline (V) by absorption of two moles of hydrogen. Deoxygenation of (I) with phosphoryl chloride also gives (II).

Reaction of (I) with anionoid reagents was examined. The Reissert reaction and the reaction with acetic anhydride failed to form the anticipated 4-substituted compound and a ring fission of the pyrimidine portion occurred, affording 2′-(benzoyloxyiminomethyl)-benzanilide (VIII) and *o*-isocyanobenzonitrile (IX). Formation of these compounds was presum-