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On N-Oxidation of 4-Alkyl-, 4-Phenyl-quinazoline and Reaction of 4-Methylquinazoline 1-Oxide

Takeo Higashino, Takashi Amano, Yatsuhiro Tamura, Nariyuki Katsumata, Youko Washizu, Takeshi Ono, and Eisaku Hayashi

Shizuoka College of Pharmacy[1]

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N-Oxidation of 4-alkylquinazoline (IX), [-R=-Me (IXa), -Et (IXb)], and 4-phenylquinazoline (X) with monoperphthalic acid were examined.

In the case of the reaction of IX, 4(3H)-quinazolinone (II) as a main product and the corresponding 1-oxide, [-R=-Me (XIa), -Et (XIb)] and 3-oxide [-R=-Me (XIIa), -Et (XIIb)] as byproducts were obtained. It may be concluded that in N-oxidation of IX monoperphthalic acid acts as nucleophilic reagent for 4-position's carbon atom rather than electrophilic one for ring nitrogen atom so that yields of the corresponding 1-oxide and 3-oxide are very poor. Accordingly it is unable to discuss steric effect of methyl and ethyl group at 4-position for N_3-oxidation. In that of X, 4-phenylquinazoline 1-oxide (XVI) and 2-aminobenzophenone (XVII) were obtained. It may be considered that formation of XVII has been originated from 4-phenylquinazoline 3-oxide (XVIII) as an intermediate.

Following representative reactions were also carried out on XIa. (a) Reissert reaction. (b) Reaction by use of Tosyl chloride and alkali. (c) Grignard reaction.

Reaction (a) and (b) afforded 4-methyl-2-quinazolinecarbonitrile (XX) and 2-chloro-4-methylquinazoline (XXI), respectively. Reaction (c) with methylmagnesium iodide and with ethylmagnesium bromide gave 2,4-dimethylquinazoline 1-oxide (XXVI) and 2-ethyl-4-methylquinazoline 1-oxide (XXVII), respectively. Reaction (c) with phenylmagnesium bromide gave 2-phenyl-4-methylquinazoline (XXVIII) and its 1-oxide (XXIX).

I. N-Oxidation of 4-Alkylquinazoline (IX) and 4-Phenylquinazoline (X)

It has been reported that usual N-oxidation of quinazoline (I) with organic peracid or with hydrogen peroxide in acetic acid resulted only in the quantitative formation of 4(3H)-quinazolinone (II) and failed to cause the desired N-oxidation.[2] This fact showed that organic peracid or hydrogen peroxide in acetic acid prefered to act as nucleophilic reagent rather than electrophilic reagent, owing to greater nucleophilicity of 4-position of I.

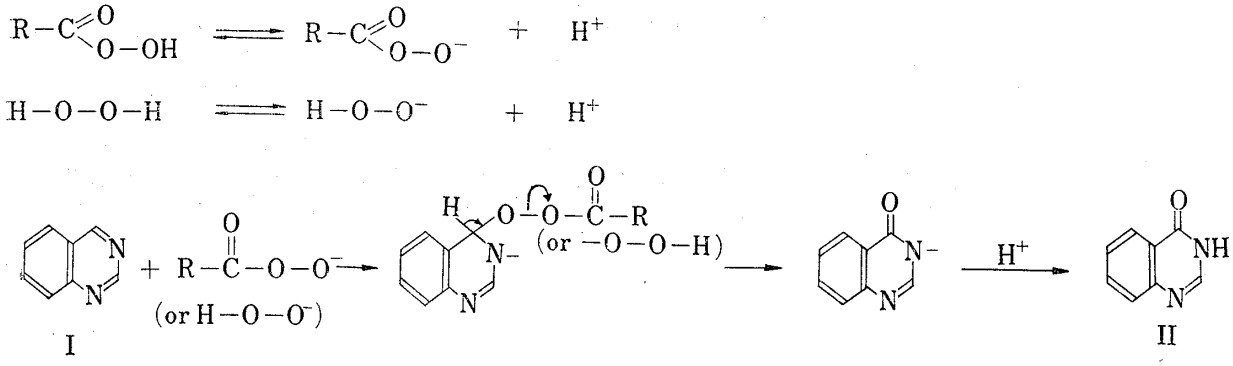


Chart 1

It has been also reported that, if 4-position was protected from nucleophilic attack by introducing substituent such as alkoxy or isopropyl group, usual N-oxidation of 4-alkoxy-

1) Location: *2-2-1, Oshika, Shizuoka-Shi.*
2) K. Adachi, *Yakugaku Zasshi*, 77, 507 (1957).

quinazoline (III) and 4-isopropylquinazoline (IV) with monoperphthalic acid resulted in the formation of the corresponding 1-oxide, V and VI as main product.[3] This may be understood that alkoxy and isopropyl group at 4-position of I causes steric hindrance against formation of 3-oxide.

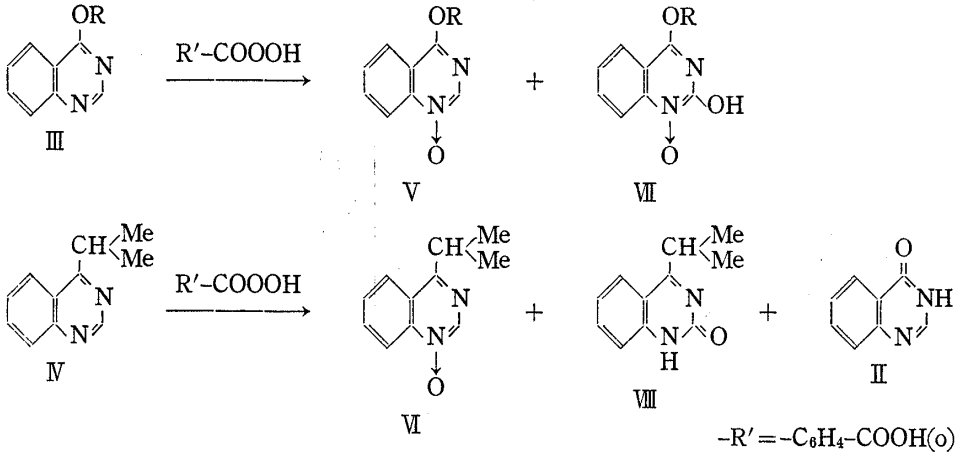


Chart 2

In order to elucidate steric effect of alkyl and phenyl group at 4-position of I against N_3-oxidation present work was carried out.

When ether solution of monoperphthalic acid containing 1.2—1.3 times the calculated amount of active oxygen is made to react with 4-methylquinazoline (IXa) and 4-ethylquinazoline (IXb), two kinds of 4-alkylquinazoline N-oxide, XI and XII in poor yield and II are obtained. XI and XII regenerate the original base on reduction by catalytic hydrogenation in methanol over Raney nickel catalyst,[4] showing their nature of being the so-called aromatic heterocyclic amine N-oxide. And their values of elemental analyses and molecular ion peaks (M^+) in Mass spectra agreed with these for mono N-oxides. Therefore XI and XII must be either 4-alkylquinazoline 1-oxide or 3-oxide each other, and XII is found to be 3-oxide and XI to be 1-oxide through the following experiments.

Ultraviolet (UV) spectra of XII approximate to that of quinazoline 3-oxide (XIII)[2] prepared from condensation-cyclization of *o*-aminobenzaldehyde oxime (XIV) and ethyl orthoformate, on the other hand these of XI also do to those of 4-methoxyquinazoline 1-

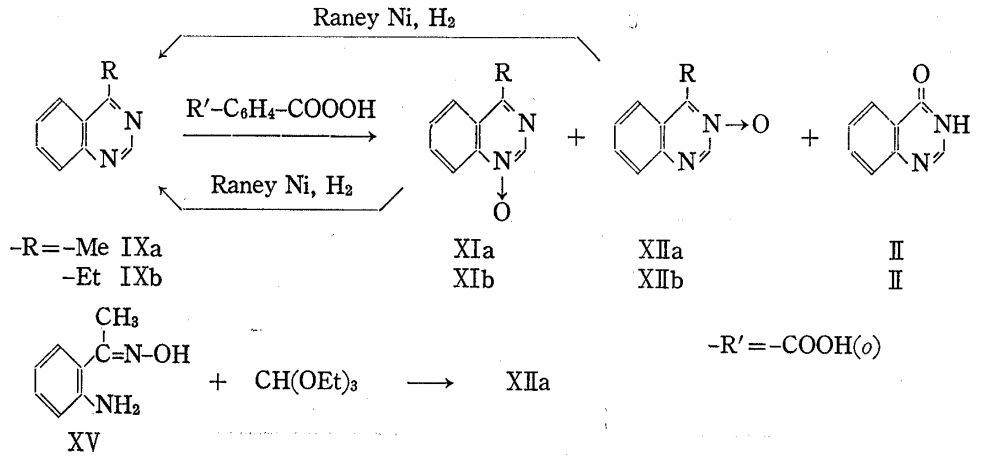


Chart 3

3) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **7**, 152 (1959); E. Hayashi and T. Higashino, *ibid.*, **12**, 43 (1964).
4) E. Hayashi, H. Yamanaka, and K. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **7**, 141 (1959).

oxide (Va) and VI. In fact the structure of XIIa is determined to be 4-methylquinazoline 3-oxide by mixed melting point test with authentic specimen prepared from condensation-cyclization of *o*-aminoacetophenone oxime (XV) and ethyl orthoformate.[2] This shows that compound (XIa) is to be 4-methylquinazoline 1-oxide and, in turn XIIb and XIb to be 4-ethylquinazoline 3-oxide and 4-ethylquinazoline 1-oxide respectively.

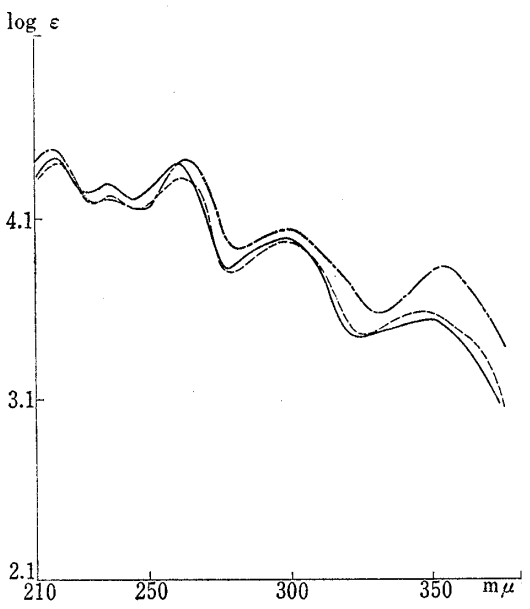


Fig. 1. UV Spectra of Quinazoline 3-Oxides

—: XIIa ----: XIIb •—•: XIII

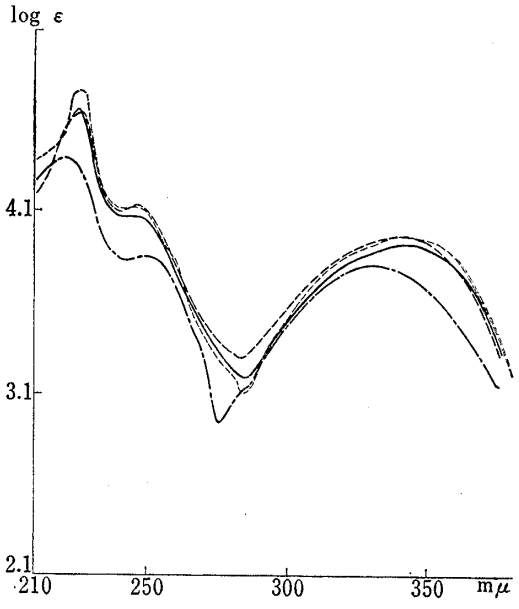


Fig. 2. UV Spectra of Quinazoline 1-Oxides

—: XIa ——: XIb •—•: Va ------: VI

In the case of the reaction of 4-phenylquinazoline (X) 4-phenylquinazoline mono N-oxide (XVI) and 2-aminobenzophenone (XVII) are obtained. So obtained XVI regenerates the original base X on reduction with phosphorous trichloride in chloroform solution,[5] showing its nature of being so-called aromatic heterocyclic amine N-oxide. Values of its elemental analysis and molecular ion peak of its mass spectrum agreed with these for mono-N-oxide. Therefore XVI must be 4-phenylquinazoline 1-oxide or 3-oxide and it is found to be 1-oxide through the following experiments.

UV spectrum of XVI does not approximate to that of 4-phenylquinazoline 3-oxide (XVIII) prepared from condensation-cyclization of 2-aminobenzophenone oxime (XIX) and ethyl orthoformate. In fact XVI does not fail to show any depression of mixed melting

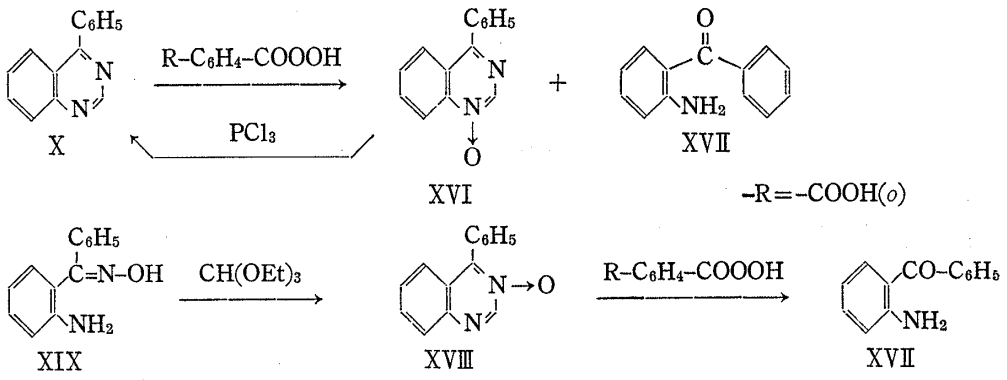


Chart 4

5) M. Hamana, *Yakugaku Zasshi*, **75**, 123 (1955).

point test with XVIII. This fact, in turn, indicates that the structure of XVI is to be 4-phenylquinazoline 1-oxide.

The structure of XVII is determined to be 2-aminobenzophenone by mixed melting point test with authentic specimen.[6]

It may be considered that formation of XVII has been originated from XVIII as an intermediate. This can be supported through reaction of XVIII with monoperphthalic acid gives XVII in 42.1% yield but that with XVI does none of XVII. From above experimental results possible mechanism for formation of XVII may be considered to involve a rout of nucleophilic oxidation as shown in Chart 5. Thus monoperphthalic acid as nucleophilic reagent may attack 2-position of XVIII to form A type of intermediate. Successive ring fission occurs between 2 and 3-position accompanied with loss of phthalic acid to give B type of intermediate. The second peracid may attack B to form C type of intermediate which then leads to XVII through loss of nitroso ester and hydrolysis, in successive step.

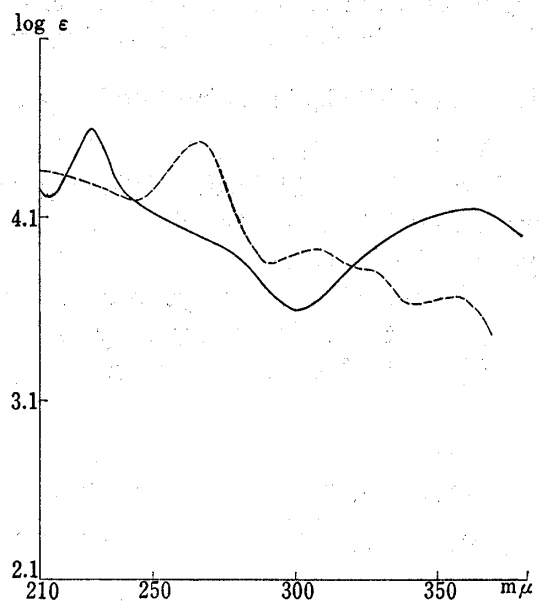


Fig. 3. UV Spectra of XVI and XVIII
—: XVI ----: XVIII

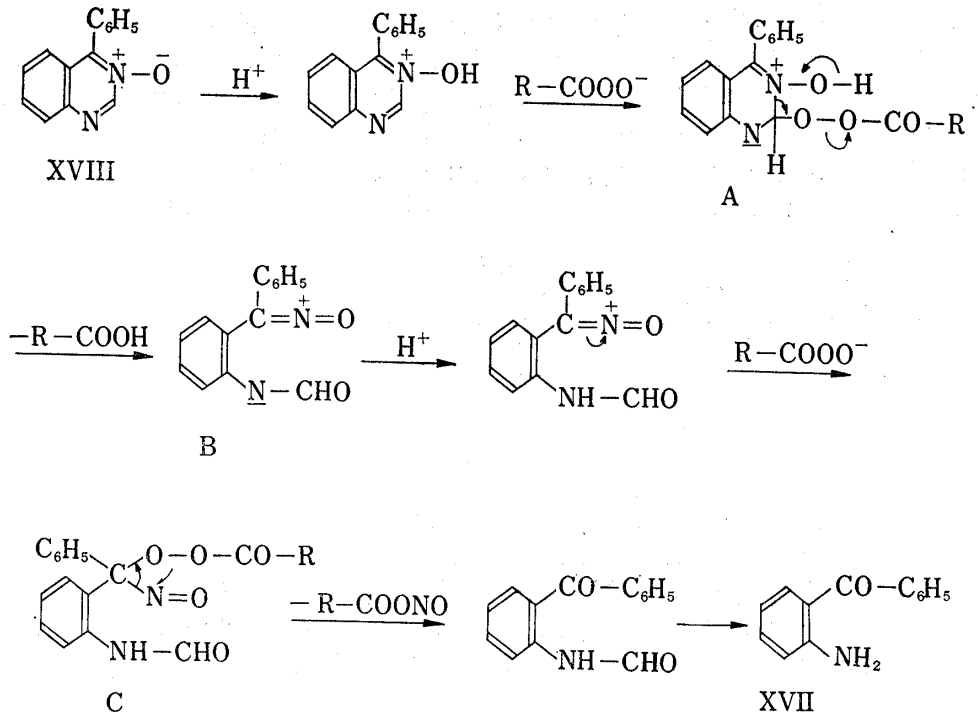


Chart 5

Through the foregoing experimental results it may be concluded that in N-oxidation of IX monoperphthalic acid acts as nucleophilic reagent for 4-position's carbon atom rather than electrophilic one for ring nitrogen atom so that yields of the corresponding 1-oxide and 3-oxide are very poor. Accordingly it is unable to discuss steric effect of methyl and ethyl group at 4-position for N_3-oxidation. If it is supposed that formation of XVII has been

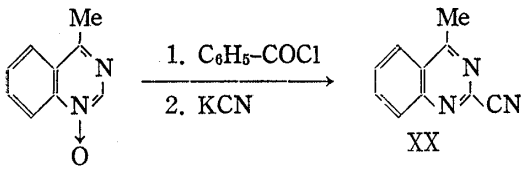
6) Hollman, *Rec. Trav. Chim.*, 13 432 [*Beilstein*, 7, 416].

originated from XVIII, it may be considered that phenyl group at 4-position does not cause absolute steric hindrance for N_3-oxidation.

II. On 4-Methylquinazoline 1-Oxide (XIa)

Various reaction usually carried out on aromatic heterocyclic amine N-oxide are then made on XIa so obtained. Following are representative reaction by which a substituent is introduced into 2- or 4-position by application of nucleophilic reagent to aromatic heterocyclic amine N-oxide.

(a) Introduction of cyano group by Reissert reaction.[7]
(b) Introduction of hydroxy or chloro group by use of Tosyl chloride and alkali.[8]
(c) Introduction of alkyl or phenyl group by Grignard reaction.[9]



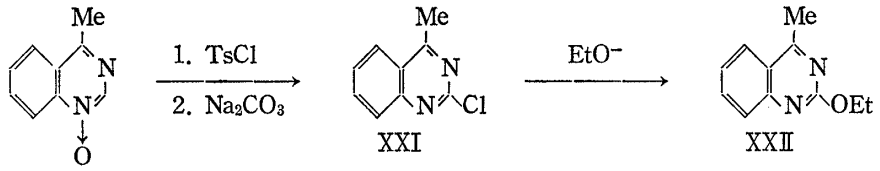
XIa XX

Chart 6

Application of reaction (a) to XIa results in the formation of 4-methyl-2-quinazolinecarbonitrile (XX). Compound XX shows the corresponding M^+ ion peak in its mass spectrum, absorption peak for cyano group at 2220 cm^{-1} in its infrared (IR) spectrum and disappearance of peak (τ: 0.85, singlet) due to proton at 2-position in its nuclear magnetic resonance (NMR) spectrum. From these spectrophotometric data the structure of XX is established to be 4-methyl-2-quinazolinecarbonitrile.

Application of reaction (b) to XIa results in the formation of 2-chloro-4-methylquinazoline (XXI) in 31% yield. The structure of XXI is determined to be 2-chloro-4-methylquinazoline through following reaction. It shows the corresponding M^+ ion peak in its mass spectrum and gives 2-ethoxy-4-methylquinazoline (XXII) by reaction with ethoxide ion.

Identity of XXII is established to be 2-ethoxy-4-methylquinazoline through the following data. Its M^+ ion peak corresponds to $C_{11}H_{12}N_2O$. Presence of marked bands due to ethoxy (τ: 8.47, t, 5.42, q), to methyl group (τ: 7.07, s) and disappearance of peak due to proton at 2-position (τ: 0.85, s) are recongnized in its NMR spectrum.



XIa Ts=Tosyl XXI XXII

Chart 7

It has been well known that reaction of aromatic heterocyclic amine N-oxide with Grignard reagent resulted in the formation of the corresponding 2-substituted aromatic heterocyclic amine (XXIV) and its N-oxide (XXV) as found in that of quinoline 1-oxide.[9]

Application of reaction (c) (methylmagnesium iodide and ethylmagnesium bromide) to XIa give 2,4-dimethylquinazoline 1-oxide (XXVI) and 2-ethyl-4-methylquinazoline 1-oxide (XXVII) respectively.

In the case of reaction with phenylmagnesium bromide both 2-phenyl-4-methylquinazoline (XXVIII) and its 1-oxide (XXIX) are obtained. The compound XXIX gives XXVIII on reduction with phosphorous tribromide in chloroform solution.

7) O. Henze, *Ber.*, **69**, 1566 (1936); E. Ochiai and I. Nakayama, *Yakugaku Zasshi*, **65**, 7 (1945).
8) E. Ochiai and T. Yokoyama, *Yakugaku Zasshi*, **75**, 213 (1955); E. Hayashi and T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **12**, 43 (1964).
9) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **82**, 1093 (1962); T. Kato, H. Yamanaka, and M. Hikichi, *ibid.*, **85**, 331 (1965).

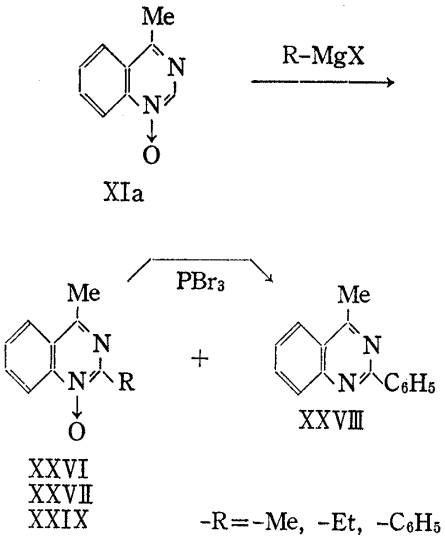


Chart 8

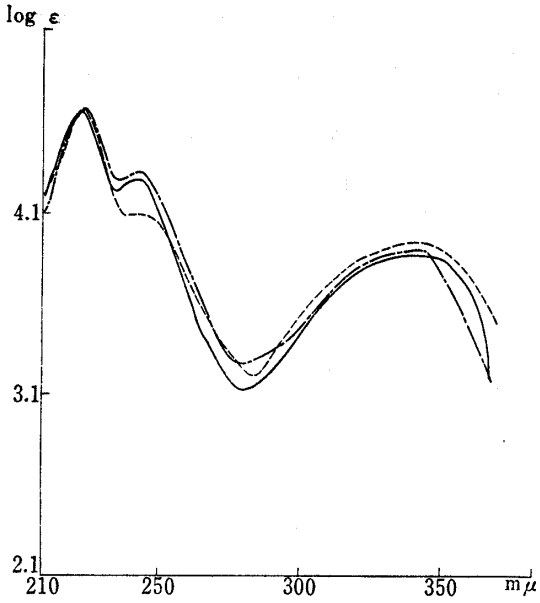


Fig. 4. UV Spectra of XXVI, XIa, and XXVII

—: XXVI ----: XIa ·—·: XXVII

The structure of XXVI is determined to be 2,4-dimethylquinazoline 1-oxide through following data. i) Absorption peaks approximate to those of XIa in its UV spectrum. ii) A peak due to two magnetic equivalent methyl groups (τ: 7.08, s) and disappearance of a peak due to proton at 2-position (τ: 0.85, s) are reconginzed in its NMR spectrum. iii) Fragmentation of XXVI under electron impact shown in Chart 9 shows two dissociation pathway through loss of oxygen from M^+ ion[10] and one step elimination of hydroxyl radical involving the so-called *ortho* effect[11] as found in that of 2-alkylpyridine 1-oxide (XXX).

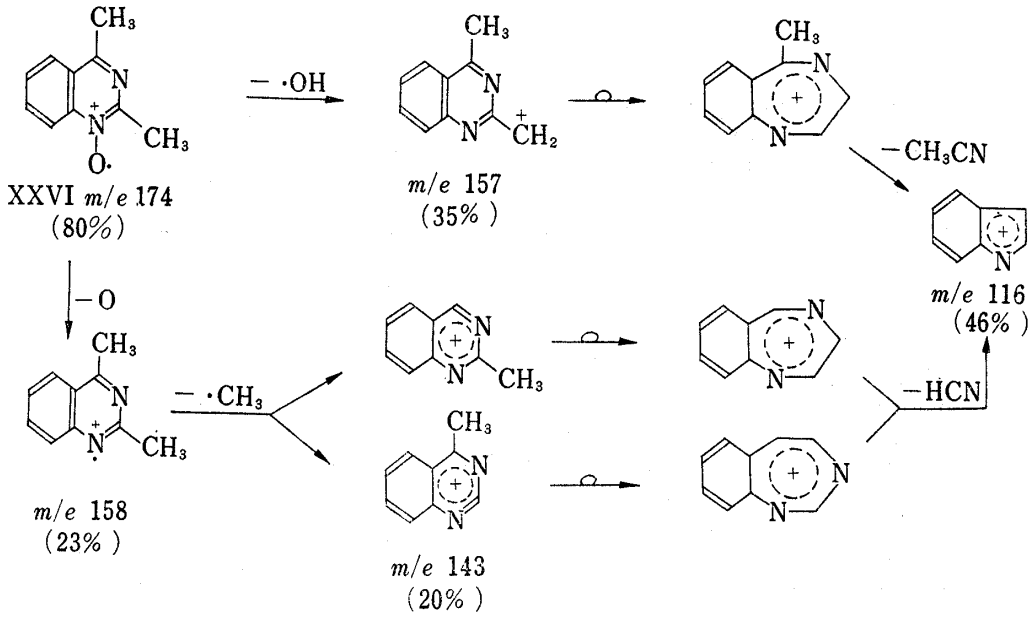


Chart 9. Fragmentation of XXVI under Electron Impact

base peak: *m/e* 28

10) T.A. Bryce and J.R. Maxwell, *Chem. Comm.*, 206 (1965).
11) R. Grigg, B.G. Odell, *J. Chem. Soc.* (*B*), 218 (1966).

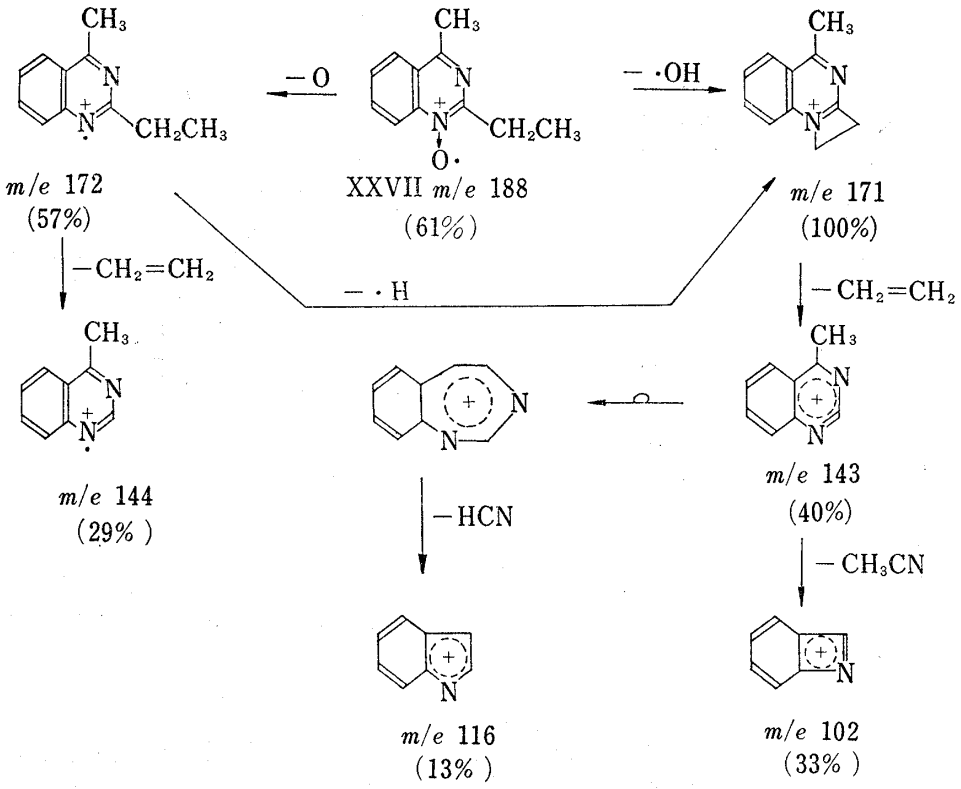


Chart 10. Fragmentation of XXVII under Electron Impact

The structure of XXVII is also determined to be 2-ethyl-4-methylquinazoline 1-oxide through spectrophotometric data by the same way used in the case of XXVI.

The compound XXVIII shows the corresponding M^+ ion peak in its mass spectrum and a singlet peak due to methyl protons at τ: 6.98 and disappearance of a peak (τ: 0.85, s) due to proton at 2-position in its NMR spectrum. From these data the structure of XXVIII is established to be 2-phenyl-4-methylquinazoline.

Experimental[12]

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

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

NMR spectra were measured in $CDCl_3$ solution at 60 Mc and 23° on a Japan Electron Optics Lab. Spectrophotometer Model JNM-C-60H. Tetramethylsilane was used as internal standard.

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

N-Oxidation of 4-Methylquinazoline (IXa) with Monoperphthalic Acid——To a solution of 2.00 g of IXa dissolved in 10 ml of ether, 30 ml of monoperphthalic acid ether solution (1 ml contains 0.009 g of active oxygen) was gradually added under cooling and the mixture was allowed to stand in a cool, dark place. After 5 hr solvent was decanted, separated oily substance was decomposed with 20% K_2CO_3. The alkaline mixture was extracted with $CHCl_3$. After dring over anhyd. Na_2SO_4, the extract was passed through a column of alumina to separate the first and another fractions.

The mixture obtained from the first fraction was treated with 4 ml of 15% NaOH and extracted with $CHCl_3$. After dried over anhyd. Na_2SO_4, $CHCl_3$ was removed and residue was recrystallized from mixture of petr. ether and benzene to give 4-methylquinazoline 1-oxide (XIa), mp 158—161° as a pale yellow needle in 6.3% yield (0.14 g). *Anal.* Calcd. for $C_9H_8ON_2$ (4-methylquinazoline 1-oxide): C, 67.48; H, 5.03; N, 17.49. Found: C, 67.37; H, 5.11; N, 17.33. NMR (in $CDCl_3$) τ: 0.85 (1H, singlet, H-2), 1.32 (1H, quartet, H-8), 1.8—2.4 (3H, multiplet, H-5,6,7), 7.10 (3H, singlet, $-CH_3$). Mass Spectrum *m/e*: 160 (M^+).

The sodium hydroxide solution was carefully neutralized with dil. AcOH and extracted with $CHCl_3$. After dried over anhyd. Na_2SO_4, $CHCl_3$ was removed to afford 4-methylquinazoline 3-oxide (XIIa), mp 166—168° as orange yellow needles from mixture of petr. ether and benzene in 5.4% yield (0.12 g). *Anal.*

12) All melting points were not corrected.

Calcd. for $C_9H_8ON_2$ (4-methylquinazoline 3-oxide): C, 67.48; H, 5.03; N, 17.49. Found: C, 67.21; H, 5.31; N, 17.33. NMR (in $CDCl_3$) τ: 0.72 (1H, singlet, H-2), 1.6—2.3 (4H, multiplet, H-5,6,7,8), 7.02 (3H, singlet $-CH_3$). Mass Spectrum *m/e*: 160 (M^+).

From another fraction 4(3H)-quinazolinone (II) was obtained in 18.6% yield (0.51 g), mp 212—213° as white needeles.

N-Oxidation of 4-Ethylquinazoline (IXb) with Monoperphthalic Acid——To a solution of 12.60 g of IXb dissolved in 30 ml of ether, 140 ml of monoperphthalic acid ether solution (1 ml contains 0.011 g of active oxygen) was gradually added under cooling and the mixture was allowed to stand in a cool, dark place for over night. After removing ether the reaction mixture was decomposed and salted out with anhyd. K_2CO_3. The alkaline mixture was extracted with $CHCl_3$ and dried over anhyd. Na_2SO_4. The extract was passed through a column of alumina to separate the first, the second and another fractions.

From the first fraction 4-ethylquinazoline 3-oxide (XIIb) was obtained as orang yellow needles, mp 106.5° from petr. ether in 1.9% yield (0.27 g). *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (4-ethylquinazoline 3-oxide): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.87; H, 5.90; N, 15.95. Mass Spectrum *m/e*: 174 (M^+).

From the second fraction 4-ethylquinazoline 1-oxide (XIb) was obtained as yellow needles, mp 101° from petr. ether in 2.1% yield (0.29 g). *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (4-ethylquinazoline 1-oxide): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.90; H, 5.93; N, 15.98. Mass Spectrum *m/e*: 174 (M^+).

From another fraction II was obtained in 15.0% yield (1.75 g).

Catalytic Reduction of XI and XII——i) Raney Ni prepared from 0.5 g of Ni-Al alloy added to 0.002 moles of XIa in 5 ml of MeOH and the mixture was shaken in H_2 stream. The reaction was stopped when 0.002 moles of H_2 (45 ml) had been absorbed. The catalyst was filtered off, the filtrate was evaporated to afford IXa, picrate mp 183° as yellow needles, in 43% yield (0.12 g). This picrate was identified on admixture with 4-methylquinazoline picrate,[13] mp 183° prepared from another route.

ii) Reduction of 0.002 moles of XIIa over Raney Ni catalyst by the same method described above afforded IXa in 39% yield (0.11 g).

iii) Reduction of 0.002 moles of XIb over Raney Ni catalyst by the same method described above afforded IXb in 33% yield (0.10 g), picrate mp 170—171°. This picrate was identified on admixture with 4-ethylquinazoline picrate, mp 170—171° prepared from another route.[13]

iv) Reduction of 0.002 moles of XIIb over Raney Ni catalyst by the same method described above afforded IXb in 36% yield (0.11 g).

N-Oxidation of 4-Phenylquinazoline (X) with Monoperphthalic Acid——To a solution of 1.00 g of X dissolved in 25 ml of ether, 7 ml of monoperphthalic acid-ether solution (1 ml contains 0.013 g of active oxygen) was gradually added and the reaction mixture was allowed to stand overnight in a cool, dark place. After removing ether the reaction mixture was decomposed with 10% K_2CO_3. The alkaline mixture was extracted with $CHCl_3$, dried over anhyd. Na_2SO_4. The extract was dissolved in $CHCl_3$ and passed through a column of alumina to afford 4-phenylquinazoline 1-oxide (XVI), mp 166—167° as yellow needles from benzene in 7.9% yield (0.085 g). *Anal.* Calcd. for $C_{14}H_{10}ON_2$ (4-phenylquinazoline 1-oxide): C, 75.65; H, 4.54; N, 12.61. Found: C, 75.46; H, 4.68; N, 12.37. Mass Spectrum *m/e*: 222 (M^+). NMR (in $CDCl_3$) τ: 0.66 (1H, singlet, H-2), 1.0—2.7 (9H, multiplet, H-aromatic).

After XVI was completely run out from alumina column, treatment with MeOH gave 2-aminobenzophenone (XVII), mp 110—112° as white plates from benzene in 1.2% yield (0.11 g).

Reaction of XVI with PCl_3——To a solution 0.053 g of XVI dissolved in 2 ml of $CHCl_3$, 0.50 g of PCl_3 was gradually added with shaking under cooling and reaction mixture was refluxed for 15 min. The reaction mixture was poured into a large amount of NH_4OH-ice mixture and extracted with $CHCl_3$. The chloroform layer was dried over anhyd. Na_2SO_4 and passed through a column of alumina to remove impurities. The compound X, mp 96—97° as pale yellow plates from benzene was obtained in 46.8% yield (0.023 g). This was identified on admixture with 4-phenylquinazoline prepared from another route.[13]

4-Phenylquinazoline 3-Oxide (XVIII)——A mixture of 0.500 g of 2-aminobenzophenone oxime and 6 ml of ethyl orthoformate was refluxed for 1 hr and excess of orthoformate was removed under reduced pressure. Separated crystals was recrystallized from benzene to give XVIII as white needles, mp 170—171° in 43.9% yield (0.230 g). *Anal.* Calcd. for $C_{14}H_{10}ON_2$ (4-phenylquinazoline 3-oxide): C, 75.65; H, 4.54; N, 12.61. Found: C, 76.08; H, 4.67; N, 12.31. Mass Spectrum *m/e*: 222 (M^+). NMR (in $CDCl_3$) τ: 0.87 (1H, singlet, H-2), 1.5—2.90 (4H, multiplet, H-5,6,7,8), 2.35 (5H, singlet, $-C_6H_5$).

Reaction of XVIII with PCl_3——Reaction used 0.051 g of XVIII by the same method described in reaction of XVI with PCl_3 gave X, mp 96—97° in 40.0% yield (0.019 g).

Reaction of XVIII with Monoperphtalic Acid——To a solution of 0.020 g of XVIII dissolved in 2 ml of $CHCl_3$, 5 ml of monoprephthalic acid-ether solution (1 ml contains 0.010 g of active oxygen) was added and the reaction mixture was allowed to stand for 24 hr. After removing solvent the reaction mixture was decomposed with 15% K_2CO_3 and extracted with $CHCl_3$. After dring over anhyd. Na_2SO_4 the extract was passed through a column of alumina to remove XVIII. After XVIII was completely run out, the column was treated with MeOH to afford XVII, mp 110—111° from benzene in 42.1% yield (0.007 g).

13) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **10**, 1043 (1962).

Reissert Reaction of XIa (Reaction (a))——To a solution of 0.300 g of XIa dissolved in small amount of dil. MeOH–H_2O (1:5), 0.170 g of KCN was added and dissolved in make a uniform solution, and 0.300 g of BzCl was added to it in small portions with shaking. The reaction mixture was allowed to stand over night. Separated crystals were extracted with benzene and the extract was washed with 2N NaOH. After dring over anhyd. Na_2SO_4, the extract was passed through a column of silica gel to remove impurities. Recrystallization from mixture of petr. ether and benzene gave 4-methyl-2-quinazolinecarbonitrile, mp 145—147° as colourless neddles in 12.3% yield (0.039 g). *Anal.* Calcd. for $C_{10}H_7N_3$ (4-methyl-2-quinazolinecarbonitrile): C, 70.99; H, 4.17; N, 24.84. Found: C, 70.93; H, 4.19; N, 25.01. IR ν_{max}^{KBr} cm^{-1}: 2220 (-CN). NMR (in $CDCl_3$) τ: 1.50—2.6 (4H, multiplet, H-aromatic), 6.94 (3H, singlet, $-CH_3$). Mass Spectrum *m/e*: 169 (M^+). UV λ_{max}^{EtOH} mμ (log ε): 239 (4.65), 289 (3.62), 306 (3.49, shoulder), 318 (3.26).

Reaction of XIa with TsCl (Reaction (b))——A solution of 0.300 g of XIa and 0.450 g of TsCl dissolved in 30 ml of $CHCl_3$ was refluxed for 20 min. 15 ml of 2N Na_2CO_3 was added and the reaction mixture was vigorously shaken for 15 min. The chloroform layer was dried over anhyd. Na_2SO_4 and passed through a column of alumina to remove impurities. 2-Chloro-4-methylquinazoline (XXI), mp 74—76° as colourless needles from petr. ether was obtained in 5.0% yield (0.010 g). *Anal.* Calcd. for $C_9H_7N_2Cl$ (2-chloro-4-methylquinazoline): C, 60.52; H, 7.06; N, 15.68. Found: C, 60.59; H, 7.13; N, 15.26. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.57), 276 (3.52), 311 (3.62). Mass Spectrum *m/e*: 180 (M^+), 178 (M^+).

2-Ethoxy-4-methylquinazoline (XXII)——To a solution of 0.020 g of Na dissolved in 2 ml of EtOH, 0.030 g of XXI was added and the reaction mixture was refluxed for 30 min. The solvent was evaporated from the reaction mixture and 1 ml of H_2O was added to the residue. Separated oily substance was extracted with benzene. After dring over anhyd. Na_2SO_4, benzene was removed to afford XXII, mp 45—46° as colourless needles from petr. ether in 31.6% yield (0.010 g). *Anal.* Calcd. for $C_{11}H_{12}ON_2$ (2-ethoxy-4-methylquinazoline): C, 70.18; H, 6.43; N, 14.88. Found: C, 70.26; H, 6.33; N, 15.04. Mass Spectrum *m/e*: 188 (M^+). UV λ_{max}^{EtOH} mμ (log ε): 229 (4.44), 235 (4.40, shoulder), 256 (3.55), 266 (3.45), 325 (3.56), 338 (3.44).

Grignard Reaction of XIa (Reaction (c))——i) 2,4-Dimethylquinazoline 1-Oxide (XXVI): Methylmagnesium iodide was prepared by the usual method from 0.300 g of MeI and 0.070 g of Mg in 5 ml of anhyd. ether. To a mixture of 0.300 g of XIa and 10 ml of anhyd. ether, a proper quantity of anhyd. benzene was added until to become a uniform solution. Methylmagnesium iodide solution was gradually added to this uniform solution and the reaction mixture was refluxed for 2 hr. After cooling 15 ml of 2N HCl was added, the HCl layer was neutralized with 15% NaOH and extracted with benzene. The extract was dried over anhyd. K_2CO_3 and passed through a column of alumina to remove impurities. Recrystallization from mixture of petr. ether and benzene gave colourless needles in 15.3% yield (0.050 g), mp 76—78°. *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (2,4-dimethylquinazoline 1-oxide): C, 68.95; H, 5.79; N, 16.08. Found: C, 69.08; H, 5.45; N, 16.12. UV λ_{max}^{EtOH} mμ (log ε): 224.5 (4.54), 243.5 (4.16), 345 (3.73).

ii) 2-Ethyl-4-methylquinazoline 1-Oxide (XXVII): Reaction used 0.300 g of XIa, 0.300 g of EtBr and 0.07 g of Mg by the same method described in XXVI gave XXVII, mp 92—94° as colourless needles in 12.8% yield (0.045 g). *Anal.* Calcd. for $C_{11}H_{12}ON_2$ (2-ethyl-4-methylquinazoline 1-oxide): C, 70.18; H, 6.43; N, 14.88. Found: C, 70.21; H, 6.55; N, 14.57. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.56), 244 (4.20), 343 (3.78). NMR (in $CDCl_3$) τ: 1.1—2.6 (4H, multiplet, H-aromatic), 6.66 (2H, quartet, J=7 cps, Ar-CH_2-Me), 7.10 (3H, singlet, $-CH_3$), 8.55 (3H, triplet, J=7 cps, $-CH_3$).

iii) 2-Phenyl-4-methylquinazoline (XXVIII) and Its 1-Oxide (XXIX): Reaction used 0.300 g of XIa, 0.300 g of PhBr and 0.07 g of Mg was treated by the same method described in XXVI. Spearation of XXVIII and XXIX was as follow.

The elution from a column of alumina with benzene gave XVIII, mp 85—87° as colourless needles from mixture of petr. ether and benzene in 6.0% yield (0.025 g). *Anal.* Calcd. for $C_{15}H_{12}N_2$ (2-phenyl-4-methylquinazoline): C, 81.79; H, 5.49; N, 12.72. Found: C, 81.75; H, 5.63; N, 12.57. Mass Spectrum *m/e*: 220 (M^+). UV λ_{max}^{EtOH} mμ (log ε): 261.5 (4.60), 287 (4.45), 299.5 (4.01, shoulder), 321 (3.73), 335 (3.60).

The elution with $CHCl_3$ gave XXIX, mp 112—114° as colourless needles from mixture of petr. ether and benzene in 9.0% yield (0.040 g). *Anal.* Calcd. for $C_{15}H_{12}ON_2$ (2-phenyl-4-methylquinazoline 1-oxide): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.18; H, 5.35; N, 11.59. Mass Spectrum *m/e*: 236 (M^+). NMR (in $CDCl_3$) τ: 1.00—2.60 (4H, multiplet, H-aromatic), 7.06 (3H, singlet, $-CH_3$). UV λ_{max}^{EtOH} mμ (log ε): 216.5 (4.25, shoulder), 226.5 (4.30), 280.5 (4.47), 345 (3.81).

Reaction of XXIX with PBr_3——A solution of 0.100 g of XXIX and 0.150 g of PBr_3 in 2 ml of $CHCl_3$ was refluxed for 1 hr. After cooling the reaction mixture was poured into a large excess of 2% NaOH solution, and extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3 and $CHCl_3$ was evaporated to afford XXVIII, mp 85—87° in 34.4% yield (0.032 g).

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