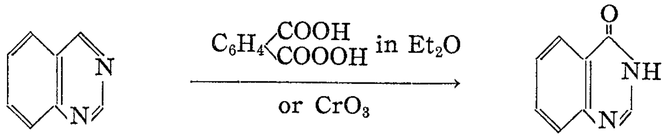
UDC 547.856.1

30. **Hiroshi Yamanaka**: Reaction of 4-Alkoxyquinazolines with Organic Peracid.

(*Shizuoka College of Pharmacy**)

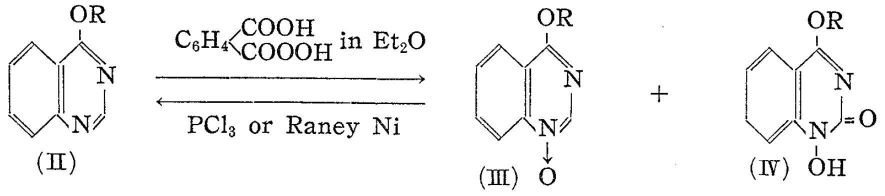
As reported earlier,[1] reaction of 4-alkoxy-6-methylpyrimidines (I) with hydrogen peroxide, warming at 60~65° in glacial acetic acid, or with perphthalic acid in ether at ordinary temperature results in the formation of a corresponding N-oxides in good yield, without the apparent formation of N,N-dioxide. On the other hand, there have been no examples of application of organic peracids to bicyclic compounds corresponding to pyrimidine, quinazoline and its derivatives. For comparison, reaction of 4-alkoxyquinazolines (II) with peracids was carried out and results somewhat different from the case of (I) were obtained. At the same time, the position of N-oxide group, undetermined in the case of (I), was confirmed by synthesis.

Adachi[2] reported that the application of monoperphthalic acid to quinazoline in ether, with the intention of obtaining its N-oxide, had afforded 4-quinazolinol in quantitative yield. Leonard[3] also obtained the same result by oxidation of quinazoline with chromium trioxide.



In order to prevent oxidation of 4-position and to correspond to (I) in structure, 4-alkoxyquinazoline (II) was taken up in the present series of experiment.

Treatment of (II) with hydrogen peroxide in glacial acetic acid, with warming, results in hydrolysis of the alkoxyl group in 4-position prior to N-oxidation and the N-oxide compound is not obtained. When the ether solution of monoperphthalic acid containing 1.3~1.5 times the calculated amount of active oxygen is reacted with (II) in ether, 4-alkoxyquinazoline N-oxide (III) is obtained, although in a lower yield than in the case of (I). In this case, 4-alkoxy-2-hydroxyquinazoline N-oxide (IV) is formed as a by-product in an average yield of 20%. Similarly as in the case of (I), there was no evidence for formation of an N,N-dioxide, but the two differed in the formation of a secondary oxidation product from (II).



(II)	(III)	(IV)
a: $R=CH_3$	a: $R=CH_3$	a: $R=CH_3$
b: C_2H_5	b: C_2H_5	b: C_2H_5
c: n-C_4H_9	c: n-C_4H_9	c: n-C_4H_9
d: C_6H_5	d: C_6H_5	d: C_6H_5
e: $C_6H_5CH_2$	e: $C_6H_5CH_2$	e: $C_6H_5CH_2$

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* Oshika, Shizuoka (山中 宏).

[1] H. Yamanaka: This Bulletin, **6**, 633(1958).

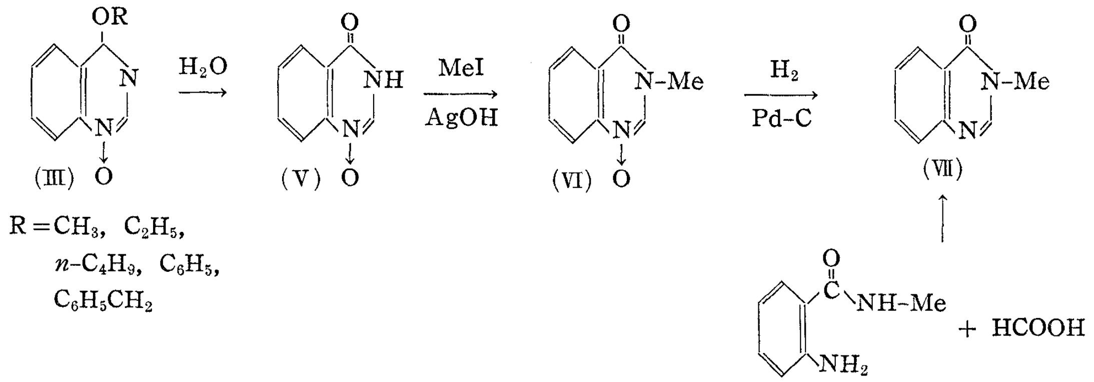
[2] K. Adachi: Yakugaku Zasshi, **77**, 507(1957).

[3] N. J. Leonard, W. V. Ruyle: J. Org. Chem., **13**, 903(1948).

On the Structure of 4-Alkoxyquinazoline N-Oxide (III)

(III) regenerates the original base on reduction with phosphorus trichloride in chloroform or by catalytic reduction in methanol over Raney nickel catalyst,[4] but resists reduction by sulfurous acid, showing its nature of being the so-called aromatic heterocyclic amine N-oxide. (III) does not color with ferric chloride. (III) was assumed to be a unity since any amount of purification failed to separate it into two or more substances, and the values of elemental analyses and molecular determination by the Rast method agreed with the value for N-monoxide. Therefore, (III) must be 4-alkoxyquinazoline 1-oxide or 3-oxide, and this was found to be 1-oxide through following experiments. The same assumption could also be made in the case of (I) but no decisive evidence was obtained with its N-oxide.

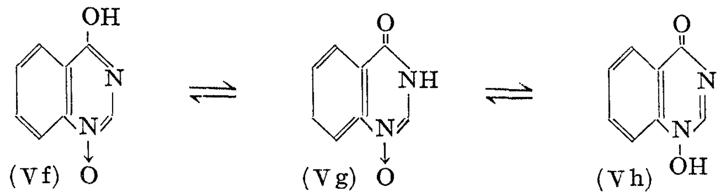
Irrespective of the alkyl group, compounds (IIIa) to (IIIe) undergo hydrolysis of the alkoxyl in 4-position when boiled in water over a long period or refluxed in dilute acetic acid for a short time, and one and the same 4-hydroxyquinazoline N-oxide (V), m.p. 225~230°(decomp.), is obtained from any of them. Methylation of (V) with a calculated amount of methyl iodide, in the presence of silver oxide, affords a viscous oil, assumed to be the monomethyl compound (VI). (VI) is an extremely hygroscopic substance and difficult to effect crystallization but catalytic reduction of this oily substance over palladium-carbon in methanol results in absorption of one mole of hydrogen and formation of a substance whose picrate melted at 209~211°. This picrate failed to show any depression of the melting point when fused with the picrate, m.p. 209~211°, of 3-methyl-4-quinazolone (VII), prepared from anthranilic acid N-methylamide and formic acid according to the method of Knape.[5] This has shown that the compound (VI) is 3-methyl-4-quinazolone 1-oxide and this, in turn, indicates that (III) is 4-alkoxyquinazoline 1-oxide.



(III) (V) (VI) (VII)

$R = CH_3$, C_2H_5, n-C_4H_9, C_6H_5, $C_6H_5CH_2$

The fact that neither 4-methoxyquinazoline 1-oxide nor 1-methoxy-4-quinazolone was obtained during methylation of (V) suggests the large contribution of the presumable tautomeric structure (Vg) to (V), together with the fact that (V) is easily reduced over palladium-carbon in methanol to 4-quinazolone.[4]



(Vf) (Vg) (Vh)

On the Structure of (IV)

(IV) appears to be an N,N-dioxide of quinazoline since its analytical values agree

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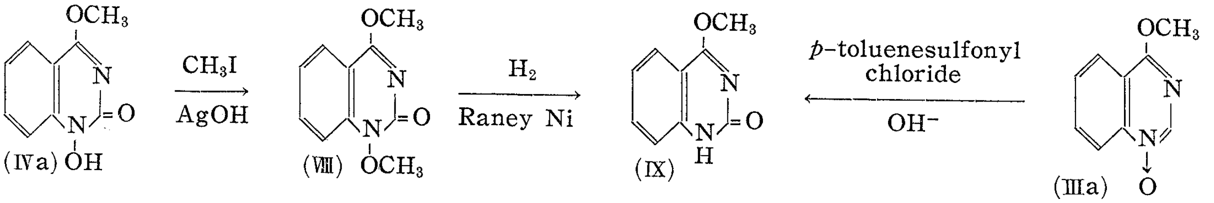
[4] T. Higashino: Paper presented at the Kanto Local Meeting of the Pharmaceutical Society of Japan, June 26, 1958.

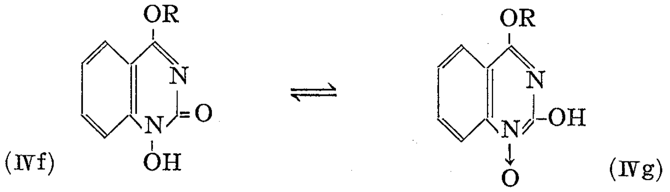
[5] W. Knape: J. prakt. Chem., (2), **43**, 222(1889) (Beilstein's, **24**, 144).

with those of a dioxide and further treatment of (III) with peracid affords (IV) in a good yield. However, structure of a dioxide is contradictory since reduction of (IV) with phosphorus trichloride does not regenerate (II), (IV) forms a pale yellow potassium salt, sparingly soluble in water, when it is added to 10% potassium carbonate solution, and the melting point of (IV) is rather high. As a result of various experiments, (IV) was determined as 4-alkoxy-2-hydroxyquinazoline 1-oxide.

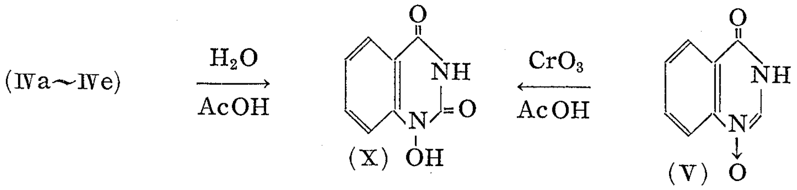
Methylation of 4-methoxy-2-hydroxyquinazoline N-oxide (IVa) with methyl iodide, in the presence of silver oxide, affords a monomethyl compound (VIII), m.p. 110°, whose reduction with a large amount of Raney nickel in methanol results in absorption of one mole of hydrogen to form 4-methoxy-2-quinazolone (IX). (IX) is identical with a sample prepared by the method of Ochiai and Yokokawa⁶⁾ from (IIIa) and *p*-toluenesulfonyl chloride. This indicates that (VIII), obtained by methylation of (IVa), is 1,4-dimethoxy-2-quinazolone and proves that (IV) is a product obtained by further oxidation of 2-position in (III).



In this reaction, there seemed to be no formation of a derivative in which a methoxyl had been introduced into 2-position and this signifies a fairly large contribution of the structure (IVf) among the possible tautomeric formulae in (IV).



Hydrolysis of (IVa) to (IVe) by refluxing with dilute acetic acid results in the formation of the same 2,4-dihydroxyquinazoline 1-oxide (X) from any of them and (X) was found to be identical with a product obtained by oxidation of (V) with chromium trioxide. This result also supports the structure of (IV) and this explains the deep red coloration of (IVa) to (IVe) to ferric chloride solution, like benzohydroxamic acid and 2-hydroxyquinoline 1-oxide.



Formation of this kind of a secondary oxidation product during N-oxidation had been thought possible in the past. Ochiai and Hayashi⁷⁾ had reported that, during preparation of N-oxides of thiazole derivatives, the yield of N-oxide of 4-methylthiazole was very poor and that a decomposition product, ammonium sulfate, had been obtained in a fairly large amount. Similar fact had been observed in pyrimidine derivatives. In monocyclic compounds, N-oxidation is accompanied by cleavage of the ring and compounds corresponding to (IV) had not been obtained but in bicyclic and higher condensed-ring compounds, there have been few examples of a formation of oxidation

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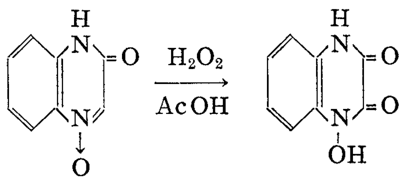
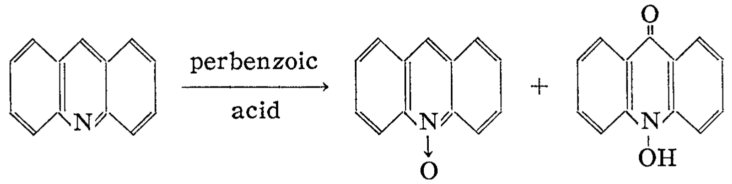
6) E. Ochiai, T. Yokokawa: Yakugaku Zasshi, **75**, 213(1955).
7) E. Ochiai, E. Hayashi: *Ibid.*, **67**, 34(1947).

products of the type of (IV), such as the quinoxaline[8] and acridine.[9]





Formation of (IV) is also one of such few examples and in this case, the fact that N-oxidation precedes oxidation of 2-position is clear from the evidences that oxidation of (III) to (IV) progresses smoothly but not that of (IX) to (IV).

The author expresses his deep gratitude to Prof. E. Ochiai of the University of Tokyo, to Dr. T. Ukai, Dean of this College, and to Prof. E. Hayashi of this Colloge for their kind and unfailing guidance throughout the course of this work. The author is indebted to Mr. T. Higashino for technical assistance, and to Misses Y. Saito and N. Kamoto for elemental analyses.

Experimental

4-Benzyloxyquinazoline (IIe)—To a solution of 3.4 g. of metallic Na dissolved in 140 cc. of benzyl alcohol, 15.5 g. of purified 4-chloroquinazoline was added in small portions with stirring and the mixture was warmed on a boiling water bath for 30 mins. During this time, separation of NaCl was observed. Benzyl alcohol was evaporated under a reduced pressure, water was added to the oily residue, and the mixture was extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, $CHCl_3$ was evaporated and the residue was submitted to low-pressure distillation, collecting a fraction of b.p$_1$ 170~180°. Yield, 14.5 g.(68%).
Picrate: m.p. 159~161° (from MeOH). *Anal.* Calcd. for $C_{15}H_{12}ON_2 \cdot C_6H_3O_7N_3$ (4-Benzyloxyquinazoline picrate): C, 54.20; H, 3.25; N, 15.05. Found: C, 54.13; H, 3.47; N, 14.39.

Reaction of 4-Alkoxyquinazolines (II) and Monoperphthalic Acid—i) Reaction of 4-Methoxyquinazoline (IIa) and Monoperphthalic Acid: To a solution of 8.8 g. of (IIa) dissolved in 30 cc. of Et_2O, 100 cc. of Et_2O solution of monoperphthalic acid containing 0.0095 g./cc. of active oxygen was added and the mixture was allowed to stand for 3 days at room temperature. Et_2O was evaporated under a reduced pressure, 40 cc. of water was added to the crystalline residue, and the phthalate was decomposed with addition of K_2CO_3. After adjusting the solution to strong alkalinity, this was extracted with 100~150 cc. of $CHCl_3$. The yellow crystals that separated out at this stage were removed by filtration. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, passed through a column of activated alumina to remove colored material, and $CHCl_3$ was evaporated from the effluent. The colorless crystalline residue so obtained was recrystallized from a mixture of benzene and petr. ether (b.p. 60~80°), and 4.5 g.(46%) of (IIIa) was obtained. Mol. wt., Calcd.: 176.17. Found: 171.

The yellow crystals obtained above were found to be K salt which was decomposed with 5% AcOH and the white precipitate so formed was collected, washed with water, dried, and recrystallized from MeOH, affording 2.3 g.(22%) of (IVa).

ii) Reaction of (IIb), (IIc), and (IIe): In accordance with the procedure for (IIa), Et_2O solution of monoperphthalic acid containing 1.5 times the calculated amount of active oxygen was added to Et_2O solution of (IIb), (IIc), or (IIe), and treated exactly as for (IIa).

iii) Reaction of 4-Phenoxyquinazoline (IId): Et_2O solution of monoperphthalic acid containing 1.5 times the calculated amount of oxygen was added to a solution of 7.6 g. of (IId) dissolved in 70 cc. of Et_2O and the mixture was treated as for (IIa). The $CHCl_3$ extract was dried over anhyd. Na_2SO_4, the solvent evaporated under a reduced pressure, and the residue was dissolved in benzene. This benzene solution was passed through a column of 60 cc. of alumina and the column was eluted with benzene from which 0.4 g. of white needles, m.p. 78~79°, was obtained, This was identified with the starting compound (IId). Further elution of the column with $CHCl_3$ afforded 0.9 g. (10%) of pale yellow needles (IIId). The treatment of sparingly soluble K salt followed that for (IIa).

The properties, yield, and analytical values of the products obtained by above experiments are summarized in Table I.

Reduction of 4-Ethoxyquinazoline 1-Oxide (IIIb) with PCl_3—A solution of 0.3 cc. of PCl_3 dissolved in 1.5 cc. of $CHCl_3$ was added dropwise into a solution of 0.3 g. of (IIIb) dissolved in 2 cc. of $CHCl_3$ and the mixture was allowed to stand at room temperature for 30 mins. after completion of this addition. The mixture was then refluxed on a boiling water bath for 1 hr., cooled, and poured

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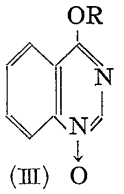
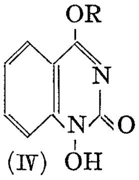
[8] R. C. Elderfield: 'Heterocyclic Compound,' Vol. VI, 474(1957). John Wiley & Sons, New York.
[9] K. Lehmstedt, H. Klee: Ber., **69**, 1514(1936).

Table I.



Compd. No.	R	m.p. (°C)*	Yield (%)	Appearance	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
(Ⅲa)	CH_3	80～81	46	White needles	$C_9H_8O_2N_2$	61.36	4.58	15.90	60.66	4.87	15.77
(Ⅲb)	C_2H_5	75～76	37	〃	$C_{10}H_{10}O_2N_2$	—	—	14.73	—	—	14.77
(Ⅲc)	n-C_4H_9	95～96	36	Pale yellow needles	$C_{12}H_{14}O_2N_2$	66.03	6.47	12.84	66.16	6.57	13.00
(Ⅲd)	C_6H_5	152～153	10	〃	$C_{14}H_{10}O_2N_2$	70.58	4.23	11.76	70.61	4.15	11.76
(Ⅲe)	$C_6H_5CH_2$	126～127	54	〃	$C_{15}H_{12}O_2N_2$	71.41	4.80	11.11	71.41	5.24	11.23



Compd. No.	R	m.p. (°C)*	Yield (%)	Appearance	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
(Ⅳa)	CH_3	229～231	22	White needles	$C_9H_8O_3N_2$	56.29	4.20	14.58	56.35	4.29	14.86
(Ⅳb)	C_2H_5	208～210	26	〃	$C_{10}H_{10}O_3N_2$	58.52	4.89	13.58	58.34	4.96	13.78
(Ⅳc)	n-C_4H_9	152～154	21	Pale yellow needles	$C_{12}H_{14}O_3N_2$	61.52	6.02	11.96	61.32	5.85	12.03
(Ⅳd)	C_6H_5	246～247	21	White needles	$C_{14}H_{10}O_3N_2$	66.13	3.96	11.02	66.16	4.03	11.42
(Ⅳe)	$C_6H_5CH_2$	206～207	22	〃	$C_{15}H_{12}O_3N_2$	67.15	4.51	10.44	67.10	4.60	10.59

into a large amount of ice water. $CHCl_3$ layer was removed, aqueous layer was neutralized with K_2CO_3, and extracted with Et_2O. After drying over anhyd. K_2CO_3, Et_2O was evaporated and the residue was distilled under a reduced pressure. The distillate solidified into 0.1 g. (37%) of crystals melting at 46～48°, undepressed on admixture with (Ⅱb).

Reduction of 4-Ethoxyquinazoline 1-Oxide (IIIb) with SO_2—SO_2 gas was introduced into a solution of 0.3 g. of (Ⅲb) dissolved in 10 cc. of water, until saturation at room temperature and the mixture was allowed to stand over night. SO_2 gas was again saturated and the mixture allowed to stand over night. The mixture was then basified with K_2CO_3, extracted with $CHCl_3$, and the solvent was evaporated from the extract after drying over anhyd. Na_2SO_4, affording 0.25 g. of crystals. Recrystallization from benzene-petr. ether afforded 0.2 g. of needles, m.p. 75～76°, undepressed on admixture with (Ⅲb).

Hydrolysis of 4-Alkoxyquinazoline 1-Oxide (**III**)—i) 4-Methoxyquinazoline 1-Oxide (Ⅲa): A mixture of 8.4 g. of (Ⅲa) and 85 cc. of water was refluxed for 4 hrs., water was evaporated under a reduced pressure, and the crystalline residue was recrystallized from MeOH to 4.1 g. (53%) of white needles, m.p. 225～232°(decomp.). *Anal.* Calcd. for $C_8H_6O_2N_2$ (4-Hydroxyquinazoline 1-oxide): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.29; H, 3.81; N, 17.34.

Entirely the same result was obtained by hydrolysis with 50% AcOH solution, the reaction being completed in 2 hrs.

ii) 4-Ethoxyquinazoline 1-Oxide (Ⅲb): The reaction progressed in entirely the same manner and afforded the same compound (Ⅴ), m.p. 225～236°(decomp.), in 58% yield.

iii) 4-Butoxyquinazoline 1-Oxide (Ⅲc): The same reaction afforded the same compound (Ⅴ) in 48% yield.

iv) 4-Phenoxyquinazoline 1-Oxide (Ⅲd): The same reaction afforded the same compound (Ⅴ) in 60% yield.

v) 4-Benzyloxyquinazoline 1-Oxide (Ⅲe): The same reaction afforded the same compound (Ⅴ) in 63% yield.

Methylation of 4-Hydroxyquinazoline 1-Oxide (Ⅴ)—A mixture of 1.0 g. of (Ⅴ), 1.8 g. of MeI, and Ag_2O prepared from 2.2 g. of $AgNO_3$ was sealed in a tube with 5 cc. of MeOH and the mixture was heated in a water bath at 100° for 4 hrs. with occasional shaking. The yellowish orange solution was filtered by suction, evaporated under a reduced pressure, and 0.8 g. of oily residue so ob-

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* All melting points are not corrected.

tained was dissolved in Me_2CO. This solution was passed through a column of 30 cc. of alumina, but neither the residue obtained from the effluent nor its picrate crystallized. This oily substance was used for the next step without analysis.

Catalytic Reduction of the Oily Substance (3-Methyl-4-quinazolone 1-Oxide) (VI)—A solution of 0.65 g. of the above oily substance dissolved in 10 cc. of MeOH, added with a catalyst prepared from 15 cc. of 1% $PdCl_2$ and 0.7 g. of activated carbon, was shaken in H_2 stream. After absorbing 85 cc. of H_2, the reduction stopped. The catalyst was filtered off, MeOH was evaporated from the filtrate under a reduced pressure, and 0.3 g. of the oily residue so obtained was derived to a picrate by the usual method. The picrate, m.p. 209∼211°, as recrystallized from EtOH showed no depression of m.p. on admixture with the picrate, m.p. 209∼211°, of 3-methyl-4-quinazolone (VII) prepared by the method of Knape.⁵⁾

Methylation of 2-Hydroxy-4-methoxyquinazoline 1-Oxide (IVa)—A mixture of 1.0 g. of (IVa), 0.8 g. of MeI, Ag_2O prepared from 1.0 g. of $AgNO_3$ by the usual method, and MeOH was sealed in a tube and heated at 100° for 4 hrs. with occasional shaking. The mixture was filtered with suction and the filtrate was evaporated to dryness under suction. The reddish orange, crystalline residue was recrystallized from petr. ether to 0.8 g.(75%) of white needles, m.p. 110°. *Anal.* Calcd. for $C_{10}H_{10}O_3N_2$ (1,4-Dimethoxy-2-quinazolone): C, 58.52; H, 4.86; N, 13.58. Found: C, 58.68; H, 4.86; N, 13.48.

Catalytic Reduction of 1,4-Dimethoxy-2-quinazolone (VIII)—Raney Ni catalyst prepared from 5 g. of Ni-Al (1:1) alloy was added to a solution of 0.5 g. of (VIII) dissolved in 10 cc. of MeOH and the mixture was shaken in H_2 stream at atmospheric pressure. The absorption of H_2 became sluggish when 55 cc. of H_2 was absorbed and the reaction was stopped at this stage. The catalyst was filtered off, the filtrate was evaporated to dryness under a reduced pressure, and the residue was washed with a small amount of benzene. Recrystallization from benzene afforded 0.3 g.(58%) of white needles, m.p. 218∼221°, undepressed on admixture with 4-methoxy-2-quinazolone (IX), m.p. 218∼221°, prepared by another route.¹⁰⁾

Hydrolysis of 4-Alkoxy-2-hydroxyquinazoline 1-Oxide (IV)—i) 2-Hydroxy-4-methoxyquinazoline 1-Oxide (IVa): A mixture of 0.6 g. of (IVa) and 50% AcOH solution was refluxed for 2 hrs., by which the crystals dissolved gradually and the reaction mixture acquired a pink tint. The mixture was allowed to cool at room temperature, and the crystals that separated out were collected and recrystallized from MeOH to 0.46 g.(83%) of (VI) as white needles, m.p. 287∼289°(decomp.). *Anal.* Calcd. for $C_8H_6O_3N_2$ (2,4-Dihydroxyquinazoline 1-oxide): C, 53.94; H, 3.40; N, 15.73. Found: C, 54.10; H, 3.62; N, 15.36.

ii) 2-Hydroxy-4-ethoxyquinazoline 1-Oxide (IVb): The same reaction afforded (X) in 86% yield.

iii) 2-Hydroxy-4-butoxyquinazoline 1-Oxide (IVc): The same reaction afforded (X) in 89% yield.

iv) 2-Hydroxy-4-phenoxyquinazoline 1-Oxide (IVd): The same reaction afforded (X) in 95% yield.

v) 2-Hydroxy-4-benzyloxyquinazoline 1-Oxide (IVe): The same reaction afforded (X) in 97% yield.

Oxidation of 4-Hydroxyquinazoline 1-Oxide (V) with CrO_3—A mixture of 1.3 g. of (V), 0.7 g. of CrO_3, and 10 cc. of glacial AcOH was heated in a boiling water bath for 3 hrs., cooled, and poured into a large amount of ice water. The crystals that separated out after standing the mixture over night were collected by filtration, washed with water, and recrystallized from EtOH to 0.7 g.(50%) of white needles, m.p. 287∼288°(decomp.). This substance possessed the same elemental analytical values and the same decomposition point as those of (X), obtained by hydrolysis of (IV), and the two were thought to be identical. *Anal.* Calcd. for $C_8H_6O_3N_2$ (2,4-Dihydroxyquinazoline 1-oxide): C, 51.94; H, 23.40; N, 15.73. Found: C, 53.88; H, 3.43; N, 15.71.

Reaction of 4-Methoxyquinazoline 1-Oxide (IIIa) and Monoperphthalic Acid—To a solution of 2.0 g. of (IIIa) dissolved in 20 cc. of 1:1 mixture of Et_2O and benzene, 25 cc. of Et_2O solution of monoperphthalic acid containing 0.016 g./cc. of active oxygen was added and the mixture was allowed to stand in a cool, dark place for a few days. The crystals that precipitated out were collected, washed with water, and recrystallized from MeOH to 1.2 g.(57%) of pale yellow needles, m.p. 229∼231°, undepressed on admixture with 2-hydroxy-4-methoxyquinazoline 1-oxide (IVa), m.p. 229∼231°, formed as a by-product during preparation of (IIIa).

Summary

Reaction of 4-alkoxyquinazolines (II) with perphthalic acid afforded, besides the objective 4-alkoxyquinazoline 1-oxides (III), 2-hydroxy-4-alkoxyquinazoline 1-oxides (IV) as a by-product, formed by oxidation of 2-position. (III) was hydrolyzed to 4-hydroxyquinazoline 1-oxide (V), methylated, and catalytically reduced to 3-methyl-4-quinazolone

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[10] T. Higashino: Paper presented at the 78th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April, 1958.

(VII), whose identification by admixture with an authentic specimen proved the original compounds to be the 1-oxide. The structure of (IV) was also proved by its methylation followed by catalytic reduction to form 4-alkoxy-2-quinazolone (IX).

(Received June 13, 1958)

UDC 547.854.1-568

31. **Hiroshi Yamanaka**: Catalytic Reduction of 4-Benzyloxy-6-methylpyrimidine and Related Compounds.

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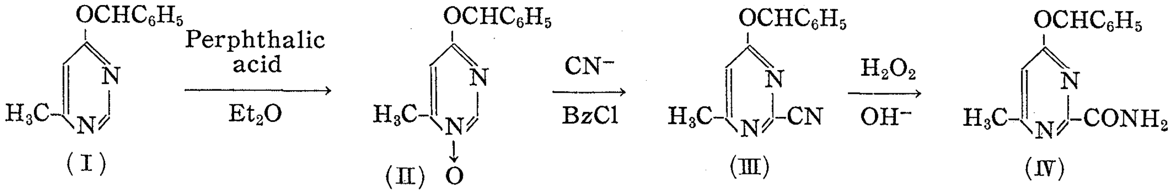
4-Benzyloxy-6-methylpyrimidine (I) easily affords its 1-oxide (II) when treated with perphthalic acid in ether or with 30% hydrogen peroxide in glacial acetic acid. Reissert reaction of (II) gives (III) which undergoes hydrolysis to form 4-benzyloxy-6-methylpyrimidine-2-carbonamide (IV).[1]



Catalytic reduction was carried out on (II) and (IV) of this series and on a few of the related compounds in the present series of experiments.

Some time ago, Ochiai and Teshigawara[2] carried out catalytic reduction of 4-benzyloxypyridine 1-oxide over palladium-carbon catalyst in methanol at ordinary temperature and pressure, and found that the absorption of hydrogen stopped after absorption of one mole to afford 4-hydroxypyridine 1-oxide. In order to prepare 4-hydroxy compound of pyrimidine derivatives of this type by the same reaction, (II) was submitted to catalytic reduction in methanol over palladium-carbon but unexpectedly, the compound absorbed two moles of hydrogen, forming 6-methyl-4-pyrimidinol (V) alone, and the desired 4-hydroxy-6-methylpyrimidine 1-oxide (VI) was not obtained at all. The hydrogen absorption curve in this case is shown in Fig. 1 and it will be seen that the rate of hydrogen absorption differs markedly in the initial and latter stages.

For the sake of comparison, (IV), possessing only the benzyloxyl group that could be reduced, was submitted to catalytic reduction under the same conditions and one mole of hydrogen was absorbed to form 4-hydroxy-6-methylpyrimidine-2-carbonamide (VII), m.p. 285~286°(decomp.), in quantitative yield. The hydrogen absorption curve in this case was similar to that of (II) during the first half period of reduction.

It follows, therefore, that the benzyloxyl group in 4-position of (II) is first reduced and that of the N-oxide then follows, and it was assumed that stopping of the reduction after absorption of one mole of hydrogen would afford the desired (VI). This was found to be true and (VI), m.p. 198°(decomp.), was finally obtained, though in a somewhat unsatisfactory yield. Catalytic reduction of (VI) resulted in absorption of one mole of hydrogen to form (V). The same was found to be true of 2,6-dimethyl-4-benzyloxypyrimidine 1-oxide (II′).

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[1] H. Yamanaka: This Bulletin, **6**, 633(1958).

[2] E. Ochiai, T. Teshigawara: Yakugaku Zasshi, **65A**, 1(1945).