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Studies on the Reaction of Quinazoline 3-Oxide with Ketone. The Transformation of Quinazoline 3-Oxide into Quinoline Derivatives

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The direct reaction of quinazoline 3-oxide (I) with ketones (III) without a base was carried and resulted in the transformation of I into quinoline derivatives (II), although the yields of II were very poor (small percentage) in some cases.

Thus, the reaction of I with acetophenone gave 2-phenylquinoline (II-3), quinazoline (IV) and 4,4′-biquinazoline (V), with propiophenone, 3-methyl-2-phenylquinoline (II-4) and V, with acetone, 2-methylquinoline (II-5), IV, V, and 2-aminobenzaldoxime (VI), with 3-pentanone, 2-ethyl-3-methylquinoline (II-6), IV and VI, with 2-butanone, 2,3-dimethylquinoline (II-7) and IV, with 2-pentanone, 3-ethyl-2-methylquinoline (II-8), IV and VI, with 3-methyl-2-butanone, 2-isopropylquinoline (II-9), IV and 4-methylquinazoline 3-oxide (VII), with 3,3-dimethyl-2-butanone, 2-*tert*-butylquinoline (II-10), IV, V, and VII, with 4-methyl-2-pentanone, 2-isobutylquinoline (II-11), IV and V, with cyclopentanone, 2,3-dihydro-1H-cyclopenta[*b*]quinoline (II-12), with cyclohexanone, 1,2,3,4-tetrahydroacridine (II-13), respectively.

We have recently shown that the reaction of quinazoline 3-oxide (I)[2] with active methylene compounds without a base resulted in the transformation of I into quinoline derivatives (II), although the yields of II were very poor (small percentage).[3] For example, the reaction of I with ethyl acetoacetate gave ethyl 2-methyl-3-quinolinecarboxylate (II-1) and 3-acetylcarbostyril (II-2).

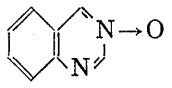
With the expectation that a similar transformation reaction might take place when I is treated with ketones in place of active methylene compounds, the investigation described in this paper was carried out and the desired transformation was found to occur, although the yields of II were also very poor in some cases shown in Table I.

Ketones (III) used in this paper were as follows: (a) aromatic ketones; acetophenone (III-1) and propiophenone (III-2); (b) symmetric aliphatic ketones; acetone (III-3) and 3-pentanone (III-4); (c) asymmetric aliphatic ketones; 2-butanone (III-5), 2-pentanone (III-6), 3-methyl-2-butanone (III-7), 3,3-dimethyl-2-butanone (III-8) and 4-methyl-2-pentanone (III-9); (d) cyclic ketones; cyclopentanone (III-10) and cyclohexanone (III-11). We chose suitable reaction temperature and time for each case as shown in Table I. Molar ratio of I to III of boiling point above 130° was set 1: 2, or weight ratio of I to III of boiling point below 130° was 1: 6.

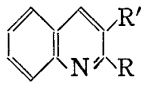
Thus, the reaction of I with III-1 gave 2-phenylquinoline (II-3),[4a] quinazoline (IV)[5] and 4,4′-biquinazoline (V),[6] with III-2, 3-methyl-2-phenylquinoline (II-4)[4b] and V, with

1) Location: *2–2–1, Oshika, Shizuoka-shi.*
2) K. Adachi, *Yakugaku Zasshi*, **77**, 507 (1957).
3) T. Higashino, Y. Nagano, and E. Hayashi. *Chem. Pharm. Bull.* (Tokyo), **21**, 1943 (1973).
4) *a*) O. Doebner and W. von Miller, *Ber.*, **16**, 1665 (1883); *b*) J. V. Braun and L. Brauns, *Ber.*, **60**, 1255 (1927); *c*) O. Doebner and W. von Miller, *Ber.*, **16**, 2465 (1883); *d*) *Idem*, *ibid.*, **17**, 1714 (1884); *e*) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 315 (1897); *f*) O. Doebner, *Ann.*, **242**, 279 (1887); *g*) R. Noyori, M. Kato, M. Kawanishi, and H. Nozaki, *Tetrahedron*, **25**, 1125 (1969); *h*) W. Borsche, *Ann.*, **377**, 121 (1910); *i*) *Idem*, *Ber.*, **41**, 2206 (1908).
5) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960).
6) T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1544 (1972).

III-3, 2-methylquinoline (II-5),[4c] IV, V and 2-aminobenzaldoxime (VI),[2] with III-4, 2-ethyl-3-methylquinoline (II-6),[4d] IV and VI, with III-5, 2,3-dimethylquinoline (II-7)[4e] and IV, with III-6, 3-ethyl-2-methylquinoline (II-8), IV and VI, with III-7, 2-isopropylquinoline (II-9),[4f] IV and 4-methylquinazoline 3-oxide (VII),[7] with III-8, 2-*tert*-butylquinoline (II-10),[4g] IV, V and VII, with III-9, 2-isobutylquinoline (II-11),[4f] IV and V, with III-10, 2,3-dihydro-1H-cyclopenta[*b*]quinoline (II-12),[4h] with III-11, 1,2,3,4-tetrahydroacridine (II-13),[4i] respectively.

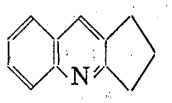


I

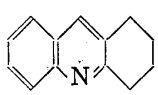


II

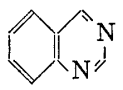
II-1 : R′=-$COOC_2H_5$, R=-CH_3
II-2 : R′=-$COCH_3$, R=-OH
II-3 : R′=-H, R=-C_6H_5
II-4 : R′=-CH_3, R=-C_6H_5
II-5 : R′=-H, R=-CH_3
II-6 : R′=-CH_3, R=-C_2H_5
II-6′ : R′=-H, R=-C_3H_7
II-7 : R′=-CH_3, R=-CH_3
II-8 : R′=-C_2H_5, R=-CH_3
II-9 : R′=-H, R=-$CH(CH_3)_2$
II-10 : R′=-H, R=-$C(CH_3)_3$
II-11 : R′=-H, R=-$CH_2CH(CH_3)_2$



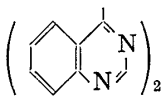
II-12



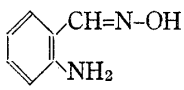
II-13



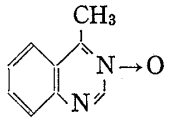
IV



V



VI



VII

Chart 1

TABLE I. Reaction of Quinazoline 3-Oxide (I) with Ketone (III)

Product Ketone	Reaction time (hr)	Reaction temp.(°C)	II (%)	mp of II (picrate, °C)[a]	IV (%)	V (%)	VI (%)	VII (%)
III-1	4	145—150	II-3 9	80—81[b]	trace	2	—	—
III-2	5	145—150	II-4 4	207—208	—	trace	—	—
III-3	12	160—170	II-5 3	192—193	1	1	17	—
III-4	8	145—150	II-6 4	193—194	2	—	11	—
III-5	9	140—150	II-7 17	234—235	8	—	—	—
III-6	8	150—160	II-8 3	226—227	trace	—	25	—
III-7	24	150—160	II-9 14	152—153	7	—	—	trace
III-8	24	145—150	II-10 6	172—173	4	24	—	trace
III-9	8	145—150	II-11 5	163—164	7	10	—	—
III-10	4	130—135	II-12 24	196—198	—	—	—	—
III-11	6	145—150	II-13 25	209—211	—	—	—	—

a) yellow needles b) mp of II-3 itself

7) T. Higashino, T. Amano, Y. Tamura, N. Katsumata, Y. Washizu, T. Ono, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1874 (1972).

Identities of II, IV, V, VI and VII except II-8 were respectively established by the mixed melting point tests with the corresponding authentic specimens prepared from other routes.[2,4,5,6,7] The values of elemental analyses of the picrate of II-8 corresponded to those of $C_{18}H_{16}O_7N_4$. Therefore II-8 must be either 3-ethyl-2-methylquinoline or 2-propylquinoline (II-6').[8] But the picrate of II-8 caused the depression of melting point on admixture with that of II-6' prepared from another route.[8] This fact showed that II-8 is 3-ethyl-2-methylquinoline.

The possible reaction mechanism of the transformation described in this paper is considered to be analogous to that of the formation of II in the reaction[3] between I and active methylene compounds reported previously and may be written as shown in Chart 2. The first step is the formation of a 3,4-dihydroquinazoline derivative (**a**) by attack of III at the most reactive 4-position of I. Then another molecule of III adds to **a** to form a tetrahydroquinazoline intermediate (**b**). Subsequent ring fission of **b** between the 2- and 3-positions followed by elimination of a hydroxylamine molecule give **d** *via* **c**. Finally, II is formed from **d** through **e** and **f**; that is to say, ring closure of **d** accompanied by elimination of a carbonium ion (**g**) give **e**, and loss of hydroxide anion from **e** or its tautomer **f** leads to II.

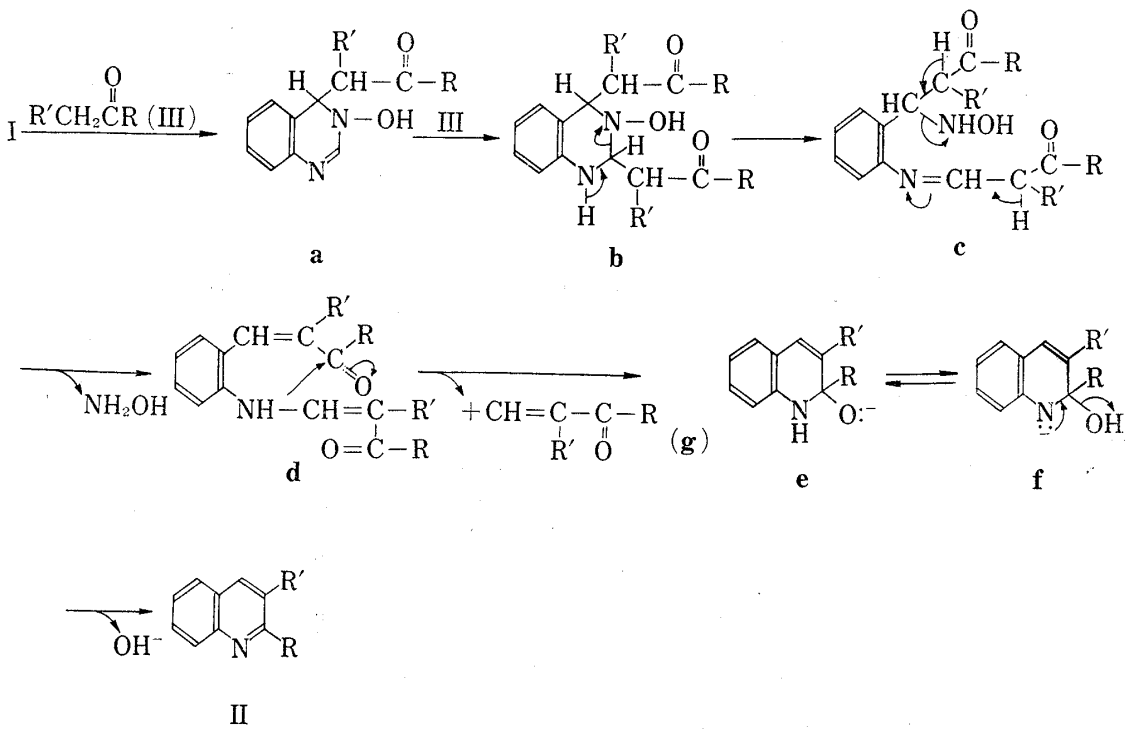


Chart 2

The formation of IV and V is considered to be as follows. The thermal deoxygenation of the N-oxide group of I produces IV and the oxygen atom this liberated removes the hydrogen at the 4-position of IV by radical course to form quinazolinyl radical (**h**). The radical **h**, in turn, couples to each other to form V, as shown in Chart 3. In fact, when I was heated at 140° for 10 hr in a sealed tube, V was formed in 11% yield.

The formation of VII in the cases of III-7 and III-8 may involve the reaction mechanism leading to the loss of aldehyde molecule from **a** by heating, as shown in Chart 3.

The formation of VI may be considered to be as follows. During the separation process of the reaction mixture by passing through a column of alumina, the addition of water absorbed

8) J. Meisenheimer and M. Schutze, *Ber.*, **56**, 1353 (1923).

on alumina to unchanged I and successive ring fission result in 2'-(hydroxyiminomethyl)-formanilide (VIII)[2,9] to form VI through hydrolysis, as shown in Chart 3.

From the foregoing experimental results together with the results on the previous paper,[3] it is concluded that the transformation of I into II takes place in both reactions with active methylene compounds and with III.

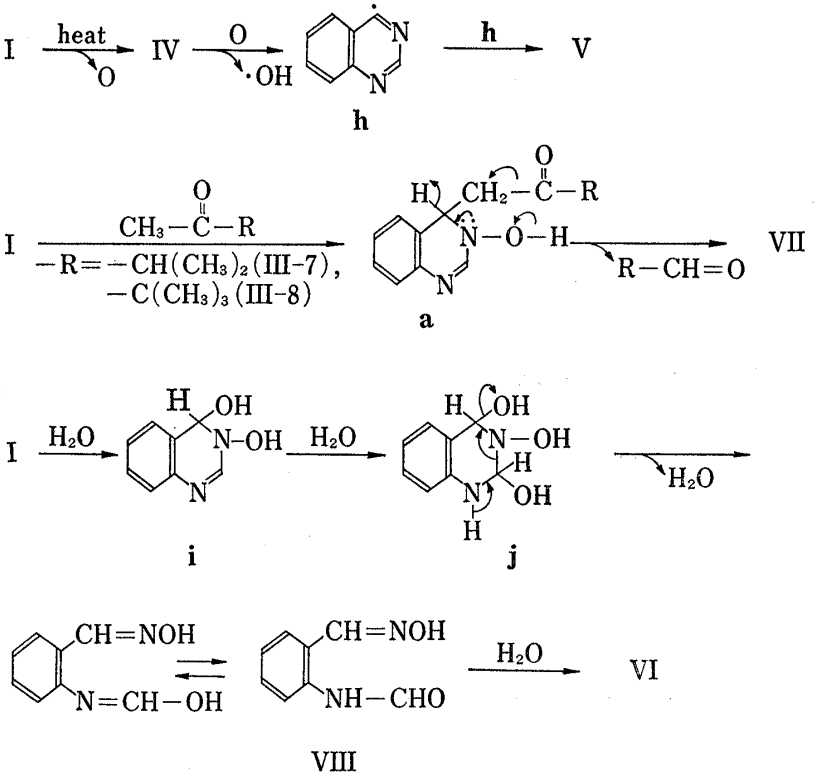


Chart 3

Experimental[10]

Reaction of I with III——i) Case of the Reaction with III of Boiling Point below 130°: A mixture of 500 mg of I and 3.0 g of III in a sealed tube was heated under the conditions described in Table I. After III was removed under reduced pressure, the residue was passed through a column of alumina by changing eluate as follows; benzene, benzene–$CHCl_3$ mixture (1: 1) and $CHCl_3$. The elution with benzene gave II. Picrate of II was recrystallized from MeOH. The elution with benzene–$CHCl_3$ mixture gave IV, mp 48° (from petr. ether). The first elution with $CHCl_3$ gave V, mp 244—246° (colourless needles from MeOH). The second elution with $CHCl_3$ gave VI, mp 134—135° (slightly yellow needles from benzene–petr. ether mixture). The third elution with $CHCl_3$ gave VII, mp 166—168° (orange yellow needles from benzene–petr. ether mixture).

Anal. Calcd. for $C_{18}H_{16}O_7N_4$ (3-ethyl-2-methylquinoline picrate): C, 54.00; H, 4.03; N, 14.00. Found: C, 54.15; H, 4.26; N, 13.96.

ii) Case of the Reaction with III of Boiling Point above 130°: A mixture of 0.0034 mole (500 mg) of I and 0.0070 mole of III was heated under the reaction conditions described in Table I. The reaction mixture was extracted with 10 ml of 2N HCl. The extract was neutralized with K_2CO_3 and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, $CHCl_3$ was removed. So obtained residue was passed through a column of alumina, according to the same manner described in i), to separate II, IV, and V.

Yields of reaction products were listed in Table I.

4,4'-Biquinazoline (V)——In a sealed tube 300 mg of I was heated at 140—150° for 10 hr. So obtained dark brown solid was dissolved in hot MeOH and treated with charcoal. After removing MeOH brown solid

9) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **9**, 635 (1961).
10) All melting points were not corrected.

was dissolved in $CHCl_3$ and passed through a column of alumina to remove impurities. Recrystallization from MeOH afforded V in 11% yield (33 mg).

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