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Reissert Reaction of Oxazole N-Oxides

Yoshinobu Goto and Motoyoshi Yamazaki

Faculty of Pharmaceutical Sciences, Fukuoka University[1]

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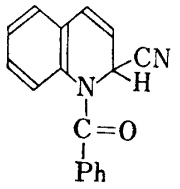
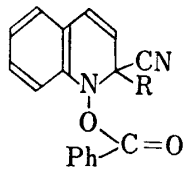
The preparations of the so-called Reissert compounds of oxazole N-oxides were reported. Reactions of 2,4,5-tri-substituted oxazole N-oxides with potassium cyanide in the presence of benzoyl chloride afforded the Reissert compounds, *i.e.* N-benzoyloxy-2-cyano-4,5-dimethyl-2-phenyl-(VII), 2-anisyl-N-benzoyloxy-2-cyano-4,5-dimethyl- (XII), N-benzoyloxy-2-cyano-4-methyl-2,5-diphenyl- (XIII) and 2-anisyl-N-benzoyloxy-2-cyano-5-methyl-4-phenyl-2,3-dihydro-oxazole (XIV) respectively. The structures of these four compounds were determined by their chemical behavior and spectral data. Mass spectral data of VII, XII, XIII and XIV were recorded and discussed on their fragmentations.

Since A. Reissert[2] was first to prepare N-benzoyl-1,2-dihydro-quinaldonitrile, Reissert compound (I), by the reaction of quinoline with potassium cyanide in the presence of benzoyl chloride in 1905, many reports have been published on the Reissert reaction of aromatic amine oxides.[3] However, there are no reports on the isolation of the Reissert compounds of N-oxides such as structure II.

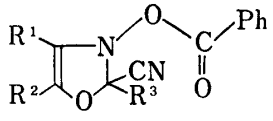
In the present paper we report to succeed in preparation of the so-called Reissert compounds (III) of oxazole N-oxides.



I



II



III

Generally, following tendency of substitution with the cyanide group is observed in the Reissert reaction. When the position α to the N-oxide group of quinoline derivatives is occupied, substitution with the cyanide group takes place in the γ-position. On the other hand, if both α- and γ-positions are occupied, instead of the introduction of the cyanide group, substitution with the benzoyloxyl group is occurred[4] as shown in Chart 1.

Quinoline N-oxide reacts also with alkali in the presence of benzoyl chloride to give carbostyril.[5] In this reaction, Hamana and Funakoshi succeeded to isolate a dihydro-intermediate (IV) of quinoline N-oxide similar to that of the Reissert reaction of quinoline. On the other hand, the Reissert reaction of quinaldine N-oxide, having the active methyl group on the position α, results in the formation of 2-benzoyloxymethylquinoline (V).[6]

1) Location: *Nanakuma, Fukuoka.*
2) A. Reissert, *Ber.*, **38**, 1603 (1905).
3) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co. Amsterdam, 1967, pp. 269—277.
4) M. Hamana and K. Shimizu, *Yakugaku Zasshi*, **86**, 59 (1966).
5) *a*) M. Henze, *Ber.*, **69**, 1566 (1936); *b*) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **80**, 1031 (1960).
6) *a*) M. Henze, *Ber.*, **69**, 534 (1936); *b*) I.J. Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953).

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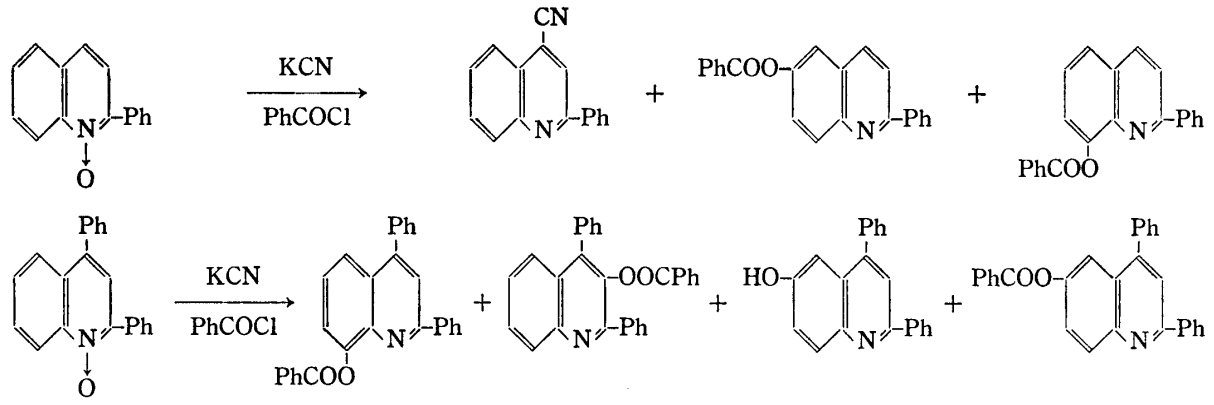


Chart 1

We reported that the reactions of 4-methyloxazole N-oxides, being occupied with substituents on both 2- and 5-positions, with phosphoryl chloride and acetic anhydride afforded smoothly 4-chloro- and 4-acetoxymethyloxazoles respectively.[7] Therefore, we expected that

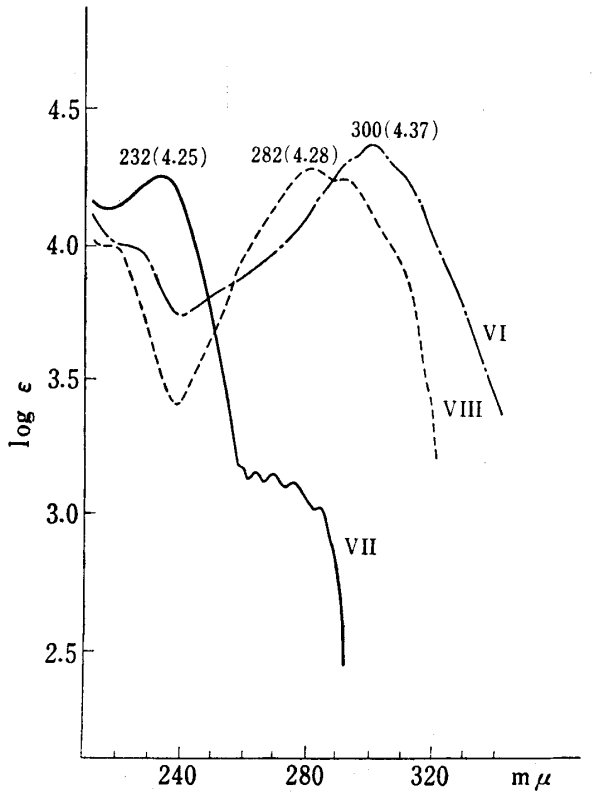
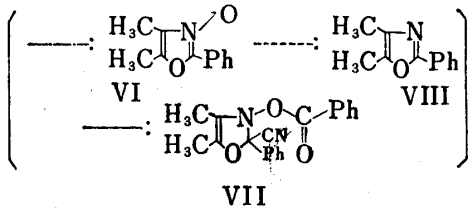
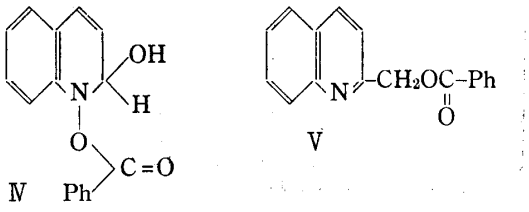


Fig. 1. UV Spectra of VI, VII and VIII in EtOH



VII



4-benzoyloxymethyloxazoles would be obtained by the Reissert reaction of the 4-methyloxazole N-oxides described above.

On the contrary, we succeeded in isolating the Reissert reaction intermediates, *i.e.*, N-benzoyloxy-2-cyano-2,3-dihydro-oxazoles (III).

When a chloroform solution of 4,5-dimethyl-2-phenyloxazole N-oxide (VI) was shaken with aqueous potassium cyanide in the presence of benzoyl chloride at room temperature, a crystalline substance $C_{19}H_{16}O_3N_2$ (VII) (III: $R^1=R^2=CH_3$, R^3=phenyl) was found to be a major product accompanied with benzamide as a minor product. This molecular formula ($C_{19}H_{16}O_3N_2$) suggested the crystalline being an adduct between VI and benzoyl cyanide.

On hydrogenation of VII with Raney Ni at atmospheric pressure, 4,5-dimethyl-2-phenyloxazole (VIII) and ammonium benzoate were obtained. The isolation of VIII showed that no skeletal transformation of VI occurred.

7) Y. Goto, M. Yamazaki, and M. Hamana, Abstracts of Papers, 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968, p. 122.

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We tried to convert the cyanide group of VII into the amide group, but VII was not changed by the reaction with 15% hydrogen peroxide in the presence of potassium carbonate. The reaction of VII with 30% hydrogen peroxide in the presence of potassium carbonate gave only the ring-opening products *i.e.*, benzamide and benzoic acid along with recovery of small amount of the starting material VII.

On the basis of these chemical behavior and the spectral data as will be discussed later, we assigned the only reasonable structure for the crystalline VII is N-benzoyloxy-2-cyano-4,5-dimethyl-2-phenyl-2,3-dihydro-oxazole.

As shown in Figure 1, no absorption due to a phenyloxazole ring in the ultraviolet (UV) spectrum of VII shows that VII seems to be a structure having a dihydro-oxazole ring.

In the infrared (IR) spectrum of VII (Fig. 2), no absorption of a cyanide group is observed. This is agreeable for VII, because both the so-called Reissert compound I and acyl derivatives of cyanohydrine, of which partial structures are very similar to that of VII, have also no ab sorption in the range 2200—2400 cm^{-1} due to a cyano group.[8]

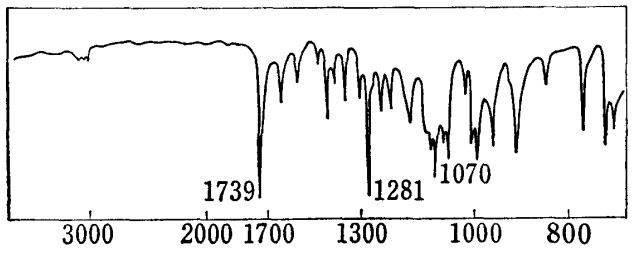

Fig. 2. IR spectrum of VII (KBr Disc)

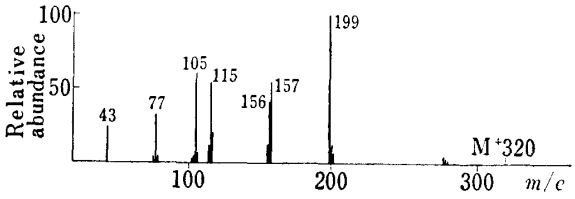

Fig. 3. Mass Spectrum of VII

The nuclear magnetie resonance (NMR) spectrum of VII (Table 1) exhibited two methyl protons at 8.2 and 7.74 τ as a singlet, therefore, it is obvious that neither benzoyloxyl nor cyanide group was introduced into the methyl groups of VI.

As shown in Figure 3, the mass spectrum of VII showed peaks at the following positions, *m/e* 320 (parent peak), 199, 157, 156, 115, 105, 77 and 43. The important fragmentation in the mass spectrum of VII (Fig. 3) is shown in Chart 2.

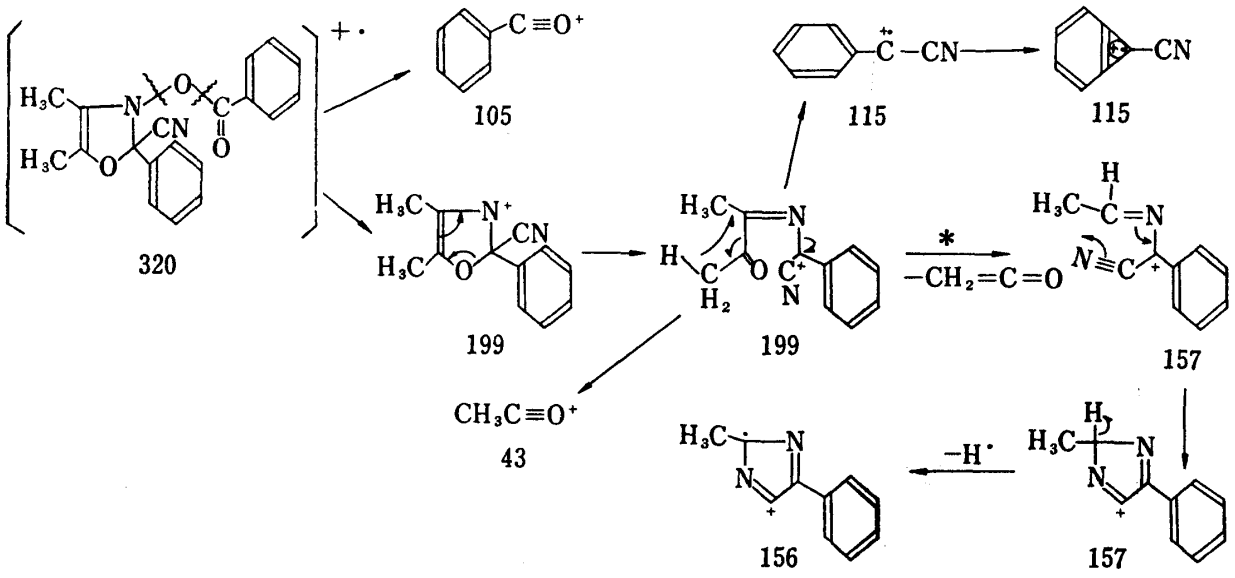

Chart 2

8) W.E. McEwen and R.L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

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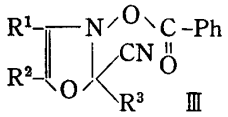
An *m/e* 199 ion was produced from the parent peak by the elimination of benzoyloxyl group. Furthermore, an *m/e* 157 fragment should come from the *m/e* 199 ion from which ketene eliminated. A peak at *m/e* 124 can be considered as a metastable ion transited from *m/e* 199 to *m/e* 157 ion by the loss of ketene (Calcd. for 199→157; 123.9). An *m/e* 115 ion can be regarded as the fragment being produced from the *m/e* 199 ion by the cleavage of the phenyl group attached to the 2-position of oxazole ring together with the cyanide group. The occurrence of the *m/e* 115 fragment shows obviously that the cyanide group entered the 2-position of the oxazole ring being already occupied with the phenyl group. The results of these spectral data described above support undoubtedly the structure VII.

The Reissert compounds of 2-anisyl-4,5-dimethyl- (IX), 4-methyl-2,5-diphenyl- (X) and 2-anisyl-5-methyl-4-phenyl-oxazole N-oxide (XI) were also obtained in the same way as described above. As shown in Table I and II, the spectral data of these three compounds are quite similar to those of VII.

Table I. UV and NMR Spectra of Reissert Compounds of Oxazole N-Oxides



III

Compound No.	R^1 R^2 R^3	UV λ_{max}^{EtOH} mμ (log ε)	NMR τ in $CDCl_3$, 60 Mc
VII	Me Me Ph	232(4.25), 258(3.18), 263(3.15), 269(3.15), 276(3.12), 284(3.01)	8.2(3H, s, Me), 7.74(3H, s, Me) 2.45—2.85(8H,m, Ph-H), 2.2—2.35(2H,m, Ph-H)
XII	Me Me Anis	234(4.49), 274(3.43), 280(3.35)	8.15(3H,s,Me), 7.71(3H,s,Me), 6.17(3H, s, OMe), 3.05(2H,d,J=9 cps, anis-3,5H), 2.42(2H, d,J=9 cps, anis-2,6H), 2.3—2.75(3H,m, Ph—3,4,5H), 1.82—2.2(2H,m, Ph-H)
XIII	Me Ph Ph	234(4.36), 263(3.27), 269.5(3.24), 276(3.13), 284(3.01)	7.85(3H,s,Me), 2.3—2.9(13H,m,Ph-H), 1.92—2.1 (2H,m,Ph-H)
XIV	Ph Me Anis	236(4.48), 258(4.34), 283(3.81)	8.05(3H,s,Me), 6.20(3H,s,OMe), 3.12(2H, d, J=9 cps, anis-3,5H), 2.42(2H,d, J=9 cps, anis-2,6 H), 2.5—2.9(6H,m,Ph-H), 1.95—2.2(4H,m,Ph-H)

Me=methyl, Ph=phenyl, Anis=anisyl

Table II. Mass Spectra of Reissert Compounds of Oxazole N-Oxides

Compound No.		M	(A)-$C_6H_5CO_2$	(B)-CH_2CO	(C)-H	X-⟨⟩-CN [a)]	C_6H_5CO	C_6H_5	CH_3CO
		(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)
VII	*m/e*	320	199	157	156	115	105	77	43
	Rel. Ab.[b)]	<0.5	100	52	38	52	61	33	25
XII	*m/e*	350	229	187	186	145	105	77	43
	Rel. Ab.	10	61	20	23	46	100	19	13
XIII[c)]	*m/e*	382	261	—	156	115	105	77	—
	Rel. Ab.	2	26	—	50	29	100	31	—
XIV	*m/e*	412	291	249	248	145	105	77	43
	Rel. Ab.	6	46	21	43	68	100	43	21

a) X=H or OMe *b*) Rel.Ab.=relative abundance,
c) Mass spectrum of this compound shows the peaks of *m/e* (Rel. Ab.) 220 (9), 192 (6) and 165 (3) besides the peaks in this table (*cf.* Chart 3).

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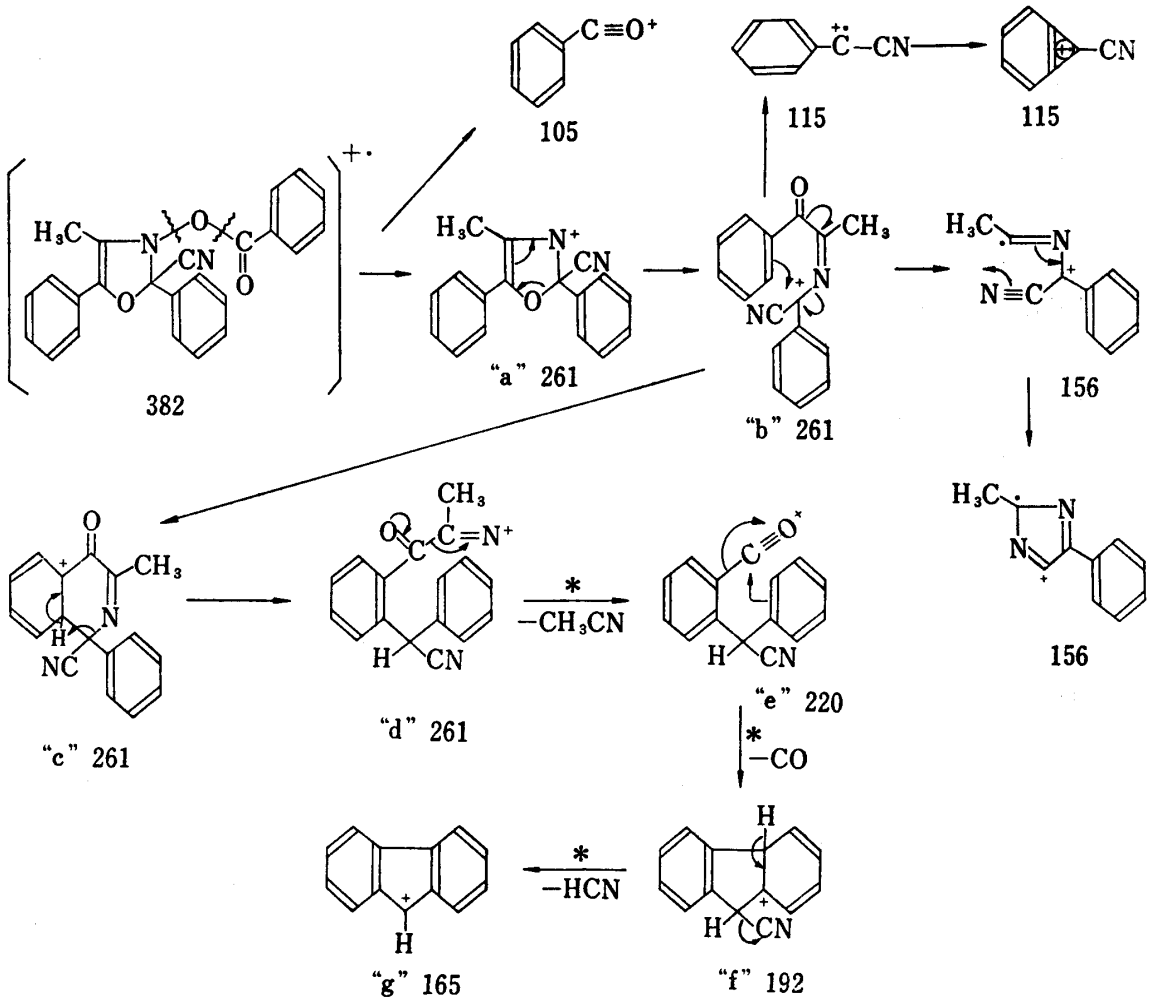

Chart 3

Fragmentation of the mass spectrum of N-benzoyloxy-2-cyano-4-methyl-2,5-diphenyl-2,3-dihydro-oxazole (XIII) is also shown in Chart 3. As in the previous fragmentation of VII, the first transition of the molecular ion of XIII is the loss of a benzoyloxyl group to form an *m/e* 261 ion. In this spectrum also, an *m/e* 115 ion is observed, which is identical with that of the fragmentation of VII. The ring-opening of ion "a" gives ion "b". The resulting ion "b" may then ring-close to form ion "c", which cleaves *via* 1,2-hydrogen shift and ion "d" is produced. Acetonitrile is eliminated from ion "d" owing to a sequence of electron shifts to give ion "e" and the ring-closure occurs by the elimination of carbon monoxide to form ion "f". Ion "f" then ejects hydrogen cyanide to give the fluorenyl ion "g".[9] The appearance of metastable ion at *m/e* 185.5, 167.6 and 141.8 supports the above route described in Chart 3 (ion "d"→ion "e"→ion "f"→ion "g").

On the other hand, the Reissert reaction of 4,5-dimethyl-2-phenyloxazole (VIII) did not proceed under the same condition as described above and only unchanged material was recovered.

The reaction of 2-anisyl-4,5-dimethyloxazole N-oxide (IX) with potassium cyanide in the presence of tosyl chloride instead of benzoyl chloride gave rise to 2-anisyl-4-chloromethyl-5-methyloxazole (XV) and anisamide, whereas the reaction of IX with alkali in the presence of benzoyl chloride gave only the ring-opening product, anisamide, by the attacking of hydroxide ion on the 2-position of the oxazole N-oxide.

9) W.D. Crow, J.H. Hodgkin and J.S. Shannon, *Australian J. Chem.*, **18**, 1433 (1965).

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As described above, although the position α to the N-oxide group of the oxazole N-oxides, used in this study, were occupied with substituents, the so-called Reissert compounds of oxazole N-oxides could be obtained as a relatively stable form. These above results indicate obviously that the 2-position of oxazoles is more easily attacked than that of quinoline derivatives by anionoid agents.

Experimental[10]

Reissert Reaction of Oxazole N-Oxidies

General Procedure——Into a mixture of oxazole N-oxide (0.01 mole) in $CHCl_3$ (5 ml) and KCN (0.02 mole) in H_2O (10 ml), benzoyl chloride (0.011 mole) was added dropwise with shaking under cooling with ice. The resulting mixture was further shaken for 1 hr at room temperature. The $CHCl_3$ layer was separated and the aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ layer and extract were combined, washed with aqueous K_2CO_3, dried over anhyd. Na_2SO_4 and the solvent removed. The residue was recrystallized from ether or benzene to give Reissert compound. The mother liquor was chromatographed over alumina to yield the small amounts of the additional Reissert compound and amide.

Reissert Reaction of VI——N-Benzoyloxy-2-cyano-4,5-dimethyl-2-phenyl-2,3-dihydro-oxazole (VII): Colorless prisms (from ether), mp 141—142°, 38% yield. *Anal.* Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.27; H, 4.81; N, 8.62. Mass spectrum Calcd. for $C_{19}H_{16}O_3N_2$ (M^+): 320.116, Obsd.: 320.117. IR ν_{max}^{KBr} cm^{-1}: 1739, 1281, 1070. A very small amount of benzamide was eluted with ether by alumina chromatography.

Reissert Reaction of IX——2-Anisyl-N-benzoyloxy-2-cyano-4,5-dimethyl-2,3-dihydro-oxazole (XII): White needles (from ether), mp 104°, 32% yield. *Anal.* Calcd. for $C_{20}H_{18}O_4N_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.11; H, 4.77; N, 8.20. Mass spectrum Calcd. for $C_{20}H_{18}O_4N_2$ (M^+): 350.127, Obsd.: 350.131. IR ν_{max}^{KBr} cm^{-1}: 1738, 1279, 1269, 1067, 1036.

Reissert Reaction of X——N-Benzoyloxy-2-cyano-4-methyl-2,5-diphenyl-2,3-dihydro-oxazole (XIII): White prisms (from ether), mp 145—146°, 11% yield. *Anal.* Calcd. for $C_{24}H_{18}O_3N_2$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.13; H, 4.61; N, 7.13. Mass spectrum Calcd. for $C_{24}H_{18}O_3N_2$ (M^+): 382.132, Obsd.: 382.134. IR ν_{max}^{KBr} cm^{-1}: 1735, 1274, 1051. Benzamide (8%) was obtained by alumina chromatography.

Reissert Reaction of XI——2-Anisyl-N-benzoyloxy-2-cyano-5-methyl-4-phenyl-2,3-dihydro-oxazole (XIV): White fine columns (from benzene), mp 178—179°, 27% yield. *Anal.* Calcd. for $C_{25}H_{20}O_4N_2$: C, 72.80; H, 4.89; N, 6.79. Found: C, 73.15; H, 4.58; N, 6.82. Mass spectrum Calcd. for $C_{25}H_{20}O_4N_2$ (M^+): 412.142, Obsd.: 412.144. IR ν_{max}^{KBr} cm^{-1}: 1734, 1282, 1263, 1033, 1017. A very small amount of anisamide was eluted with $CHCl_3$ by alumina chromatography.

Reduction of VII——A solution of VII (1.07 g) in MeOH (60 ml) was shaken with Raney Ni (from 1 g of Ni–Al alloy) in H_2 stream at atmospheric pressure. Reduction stopped when 230 ml of H_2 had been absorbed. The catalyst was removed by filtration. The solvent was evaporated to dryness *in vacuo*, and the reddish brown oil was taken up in ether. After the ether extract was dried over anhyd. Na_2SO_4, ether was removed and the residue was chromatographed over alumina with petr. ether–ether (2:1, v/v) to give 4,5-dimethyl-2-phenyloxazole (VIII) (0.02 g, 4% yield) and a small amount of unknown oil. The ether-insoluble material was ammonium benzoate (0.12 g, 26% yield), identical with IR spectrum of an authentic sample.

Reaction of VII with 30% H_2O_2–K_2CO_3——To a solution of VII (0.32 g) in MeOH (40 ml) and 5% aqueous K_2CO_3 (1 ml), 30% H_2O_2 (2 ml) was added dropwise at room temperature. After the reaction mixture was allowed to stand for 6 hr at room temperature, the solvent was evaporated to dryness under diminished pressure at 50°. A small amount of H_2O was added to the residue and the aqueous solution was extracted with $CHCl_3$. After the $CHCl_3$ extract was dried over anhyd. Na_2SO_4, $CHCl_3$ was evaporated, and the residue was chromatographed over alumina. The starting material VII (0.03 g, 10% yield) was eluted with ether, and further elution with $CHCl_3$ afforded 0.01 g (8% yield) of benzamide. When the aqueous solution was made acidic with hydrochloric acid, benzoic acid was obtained in the yield of 0.16 g (66%).

Reaction of IX with KCN–TsCl——a) Reaction under Ice–Cooling: To a solution of IX in $CHCl_3$ (10 ml) and 1.30 g (0.02 mole) of KCN in H_2O (10 ml), 1.90 g (0.01 mole) of tosyl chloride in $CHCl_3$ (5 ml) was added dropwise with stirring under ice-cooling. After stirring was further continued for 2 hr while being cooled with ice, the $CHCl_3$ layer was separated, washed with 10% aqueous K_2CO_3, dried over anhyd. Na_2SO_4, and the solvent removed. The residue was taken up in ether. The ether–insoluble material was recrystallized

10) All melting points are uncorrected. UV spectra were measured on a Shimadzu SV-50A Spectrophotometer, IR spectra on a Nihon–Bunko DS-301 Spectrophotometer, NMR spectra on a Japan Electron Optics JNM C-60-H Spectrometer at 60 Mc with tetramethylsilane as an internal standard, Mass spectra on a Japan Electron Optics Model JMS-01SG Mass spectrometer.

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from benzene to give 0.19 g (13% yield) of anisamide. The ether soluble fraction was chromatographed over alumina with petr. ether–ether (2:1, v/v) to afford 0.55 g (23% yield) of 2-anisyl-4-chloromethyl-5-methyloxazole (XV), undepressed by admixture with an authentic sample.[7]

b) Reaction at Room Temperature: After the mixture of IX, KCN and tosyl chloride was shaken for 1 hr at room temperature, the reaction mixture was treated just as described above. Chloromethyl compound XV and anisamide were obtained in the yield of 6% and 10% respectively.

Reaction of IX with KOH-BzCl——To a solution of 2.19 g (0.01 mole) of IX in $CHCl_3$ (10 ml) and 1.12 g (0.02 mole) of KOH in H_2O (10 ml), 1.55 g (0.011 mole) of benzoyl chloride was added dropwise under ice-cooling. The resulting solution was shaken for 1 hr at room temperature, and then anisamide precipitated in a crystallized condition from the reaction mixture, was removed by filtration (0.41 g). The $CHCl_3$ layer was separated, washed with H_2O, dried over anhyd. Na_2SO_4, purified by alumina chromatography to give 0.1 g of anisamide (total 0.51 g, 33% yield) accompanied with a small amount of unknown oil.

Acknowledgement The authors are grateful to Professor M. Hamana, Kyushu University, for valuable discussions and encouragement. Thanks are also due the members of the Analytical Center of the Faculty of Pharmaceutical Sciences, Kyushu University, for elemental analyses and IR-spectral measurements, the Research Laboratory of Yoshitomi Pharmaceutical Co., Ltd. and Japan Electron Optics Lab. Ltd. for mass spectral measurements and the Research Laboratory of Hisamitsu Pharmaceutical Co., Ltd. for a part of UV spectral measurements.

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