[Chem. Pharm. Bull. 30(11)3987—3993(1982)]

Reaction of γ-Bromoacetoacetyl Compounds with Benzamide Oxime Derivatives: Synthesis of 4*H*-1,2,4-Oxadiazine Derivatives[1,2]

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(Received May 1, 1982)

Reaction of benzamide oxime derivatives (**1**) with ethyl γ-bromoacetoacetate in the presence of an acidic catalyst gave a mixture of geometrical isomers of 3-aryl-5-ethoxycarbonylmethylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives (**5**) in 60—75% yields. On separation of the mixtures by HPLC, the (*Z*)-ester (5-I) was obtained as the main product (60—70% yields) together with the (*E*)-ester (5-II) (3—5% yields). The structures of these isomers were determined by analysis of the IR and NMR spectra.

Methyl γ-bromoacetoacetate, *p*-methyl-γ-bromoacetoacetanilide and *p*-toluamide *O*-(γ-bromoacetoacetyl)oxime were also reacted with **1** to afford the corresponding 3-aryl-5-(substituted)methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives (8-I, 8-II, **9**, and **10**) in moderate yields.

Keywords——benzamide oxime; ethyl γ-bromoacetoacetate; 3-aryl-5-ethoxycarbonylmethylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives; geometrical isomer; γ-bromoacetoacetyl compounds; cyclization

In our synthetic studies of heterocyclic compounds using acetoacetyl compounds, we have previously reported the synthesis of 1,2-oxazine derivatives from *N*-phenylhydroxylamine and γ-bromoacetoacetyl bromide *via* *N*-γ-bromoacetoacetyl-*N*-phenylhydroxylamine,[3] and 1,2,4-oxadiazole derivatives from benzamide oxime and diketene *via* benzamide *O*-acetoacetyloxime.[4] In the present paper, we wish to describe the synthesis of 3-aryl-5-(substituted) methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives by the reaction of benzamide oxime derivatives with γ-bromoacetoacetyl compounds such as ethyl γ-bromoacetoacetate.

First, we investigated the reaction of benzamide oxime with γ-bromoacetoacetyl bromide. When benzamide oxime (**1a**, R=H) was allowed to react with γ-bromoacetoacetyl bromide in the presence of a basic catalyst or in refluxing solvent, a resinous substance was obtained. However, treatment of two mol equivalents of **1a** with γ-bromoacetoacetyl bromide at 0—5°C afforded benzamide *O*-(γ-bromoacetoacetyl)oxime (**2a**) and benzamide *O*-(3-phenyl-5,6-dihydro -4*H*-1,2,4-oxadiazin-5-ylideneacetyl)oxime (**3a**) in 72.7% and 3% yields, respectively.

On heating in boiling toluene, **2a** was converted to 5-(3-bromo-2-oxopropyl)-3-phenyl-1,2,4-oxadiazole (**4a**) in 23.6% yield. The structures of these products were determined on the basis of their infrared (IR), nuclear magnetic resonance (NMR), and mass spectral data and analyses as described in the experimental section. In regard to the formation of **2a** and **4a**, Sasaki and Yoshioka have reported a similar cyclization of benzamide *O*-acetoacetyloxime, which on heating afforded 5-acetonyl-3-phenyl-1,2,4-oxadiazole.[5]

The formation of the 1,2,4-oxadiazine skeleton probably involves the initial formation of an intermediate A, *O*-acetoacetonylamide oxime, from **2a** and **1a** with dehydrobromination. Then **3a** would be formed through dehydrative cyclization of the intermediate between the β-carbonyl carbon and amino nitrogen.

In relation to the structure of *exo*-methylene-1,2,4-oxadiazine derivatives, Guzman *et al.*[6] have reported that the reaction of benzamide oxime with dimethyl acetylenedicarboxylate in methanol or in acetonitrile afforded an E-adduct and that the same reaction in bexzene gave, on the other hand, a *Z*-adduct. Accordingly, we reexamine the present unique cyclization

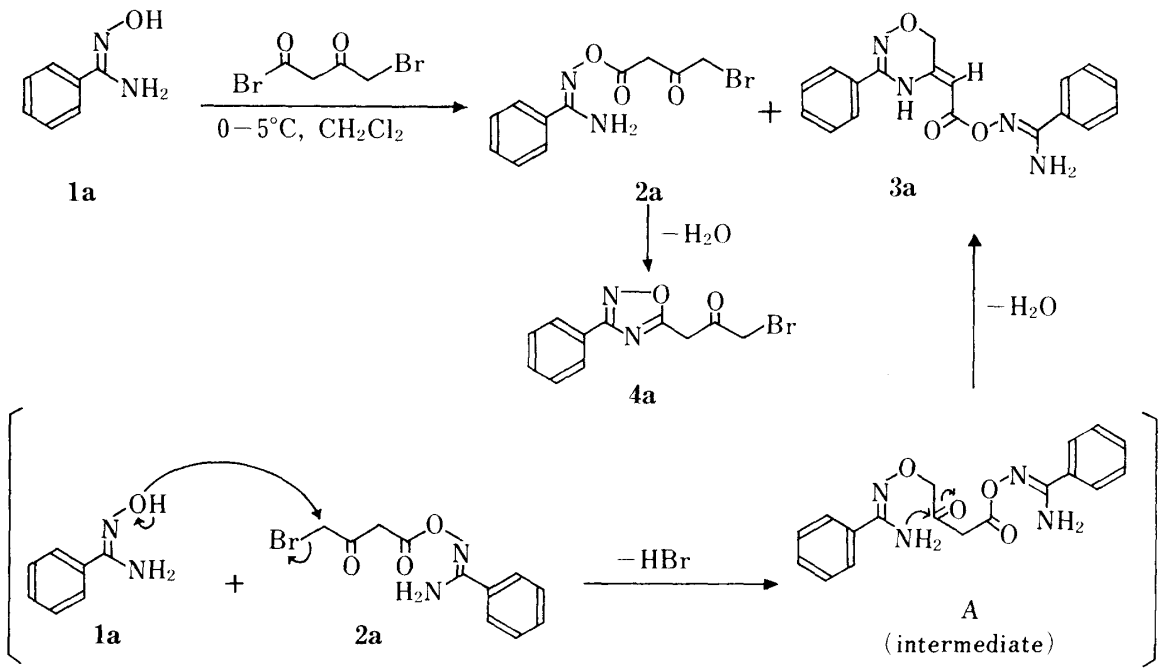


Chart 1

using ether γ-bromoacetoacetate in place of compound **2a**.

When benzamide oxime (**1a**) was allowed to react with ethyl γ-bromoacetoacetate in the presence of a basic catalyst such as triethylamine, no appreciable crystalline product formed, but a resinous substance was obtained. When an acid was used as a catalyst, on the other hand, the reaction of two mol equivalents of **1a** and one mol equivalent of ethyl γ-bromoacetoacetate afforded a mixture of geometrical isomers of 5-ethoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**5a**) in 18—77% yields. Under these reaction conditions, a half of **1a** was used as a trap for the eliminated hydrogen bromide.[7] The results are listed in Table I.

Table I. Reaction Conditions and Yield of **5a**

Catalyst	Solvent	Temperature	Time (h)	Yield (%)[a]
H_2SO_4	$CHCl_3$	R.T.	72	60.5
PPA	$CHCl_3$	R.T.	120	50.1
TsOH	CH_3Cl_2	R.T.	48	24.3
H_2SO_4	$CHCl_3$	Reflux	3	64.6
TsOH	CH_3CN	Reflux	3	76.8
CH_3COOH	$CHCl_3$	R.T.	24	25.6
$(COOH)_2$	$CHCl_3$	R.T.	24	17.8
C_6H_5COOH	THF	Reflux	3	75.6

a) Yields are calculated based on ethyl γ-bromoacetoacetate.

The mixture (**5a**) was then subjected to flash chromatography and subsequent high performance liquid chromatography (HPLC) on a silica gel column. Elution with *n*-hexane-ethyl acetate mixture gave colorless needles of mp 75°C (**5a**-I) as a main product (71.4%) and colorless needles of mp 126°C (**5a**-II) as a minor one (5.4%).

The structure of the first eluted product (**5a**-I) was assumed to be an intramolecularly hydrogen-bonded structure, *Z*-form, on the basis of the following observations as shown in Table II; 1) relatively low value of capacity ratio in HPLC ($k'=2.75$), 2) relatively low frequency of carbonyl stretching band (1660 cm^{-1} in $CHCl_3$), and 3) relatively low-field chemical

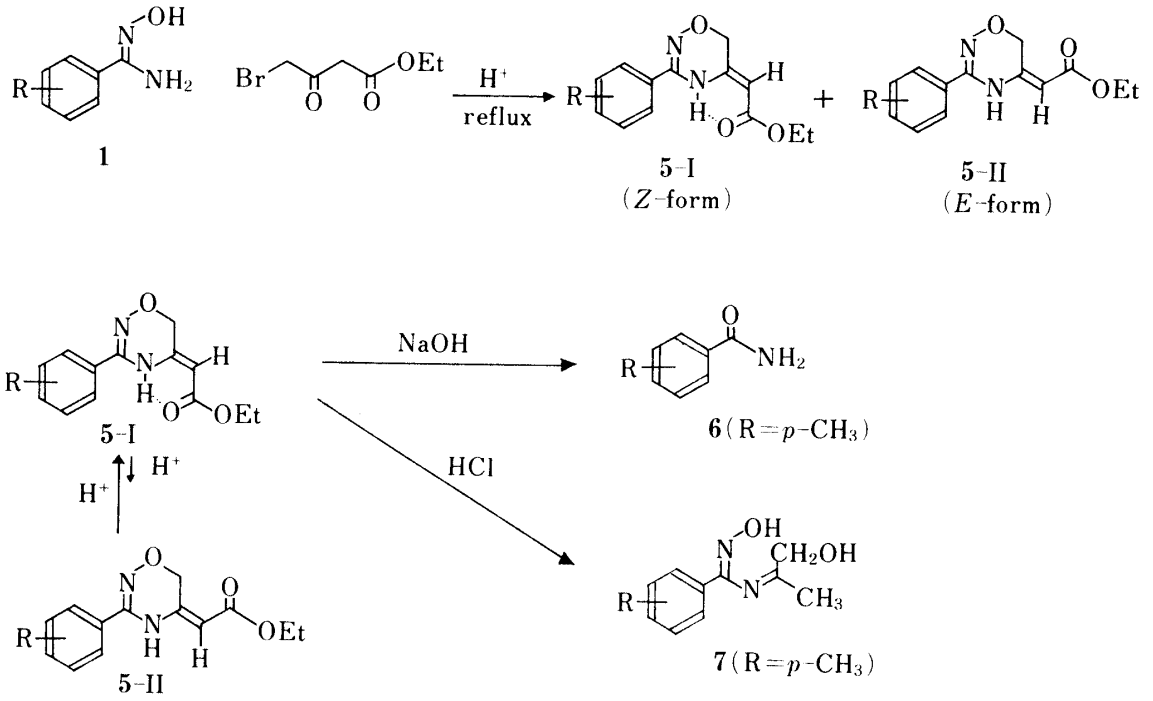


Chart 2

TABLE II. Comparison of Physical and Spectral Data of **5a**-I and -II

Data	5a-I	5a-II
Yield (%)[a]	71.4	5.4
Melting point (°C)	75	126
Capacity ratio in HPLC[b]	$k'=2.75$	$k'=6.98$
IR ν cm^{-1} ($CHCl_3$): $\nu_{C=O}$	1660	1698
NMR δ ($CDCl_3$) ppm: NH	—10.9	—7.6
6-CH_2	4.45	5.09
=CH–	4.90	5.25
UV λ_{Max}^{EtOH} nm (log ε):	256(4.21), 300(4.11)	254(4.18), 300(3.98)

a) Yields are calculated based on ethyl γ-bromoacetoacetate.
b) The k' value was measured on a Kusano KP-6H HPLC apparatus using a CIG column (SiO_2, 50 μ, 15ϕ × 300 mm) and UVILOG 254 detector. Eluent: *n*-hexane–EtOAc 6:1 mixture.

shift of the NH proton signal (—10.9 ppm). The structure of the minor product (**5a**-II) was assumed to be *E*-form.

Six kinds of substituted benzamide oxime derivatives (**1b**—**g**) were also subjected to similar cyclization with ethyl γ-bromoacetoacetate in the presence of *p*-toluenesulfonic acid (TsOH) to afford the corresponding (*Z*)-esters (**5b**—**g**-I) as main products and (*E*)-esters (**5b**—**g**-II)as minor ones, as shown in Table III. In the case of *p*-nitrobenzamide oxime (**1g**, R=*p*-NO_2), only the (*Z*)-ester (**5g**-I) was obtained and no (*E*)-ester could be isolated. The geometrical structures of these products were also determined on the basis of their characteristic NH proton signal and carbonyl stretching band.

In an acidic medium, (*E*)-esters (**5**-II) were converted to (*Z*)-esters (**5**-I). On alkaline hydrolysis, compound **5b**-I gave *p*-toluamide (**6**) in 36% yield. Heating of **5b**-I with dilute hydrochloric acid caused fission of the N–O bond with elimination of carbon dioxide to afford colorless needles of *N*-(1-hydroxy-2-propylidene)-*p*-toluamide oxime (**7**).

Finally, as we had intended, other 1,2,4-oxadiazine derivatives were successfully synthesized using several γ-bromoacetoacetyl compounds. Reaction of **1a** with methyl γ-bromo-

acetoacetate in the manner described above afforded *Z*- and *E*-5-methoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine, (**8**-I) and (**8**-II), in 57.2% and 2.6% yields, respectively. When *p*-methyl-γ-bromoacetoacetanilide was allowed to react with **1a** under the above conditions, *Z*-5-(*p*-methylphenylcarbamoyl)methylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**9**) was obtained in 77.8% yield. *p*-Toluamide oxime (**1b**) was also allowed to react with *p*-toluamide *O*-(γ-bromoacetoacetyl)oxime (**2b**) in the presence of TsOH in boiling methylene chloride to give *Z*-3-(*p*-methylphenyl)-5-[3-(*p*-methylphenyl)-1,2,4-oxadiazol-5-yl]methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine (**10**) in 26% yield.[8] The structures of these products were identified by consideration of their spectral and analytical data, as described in the experimental section.

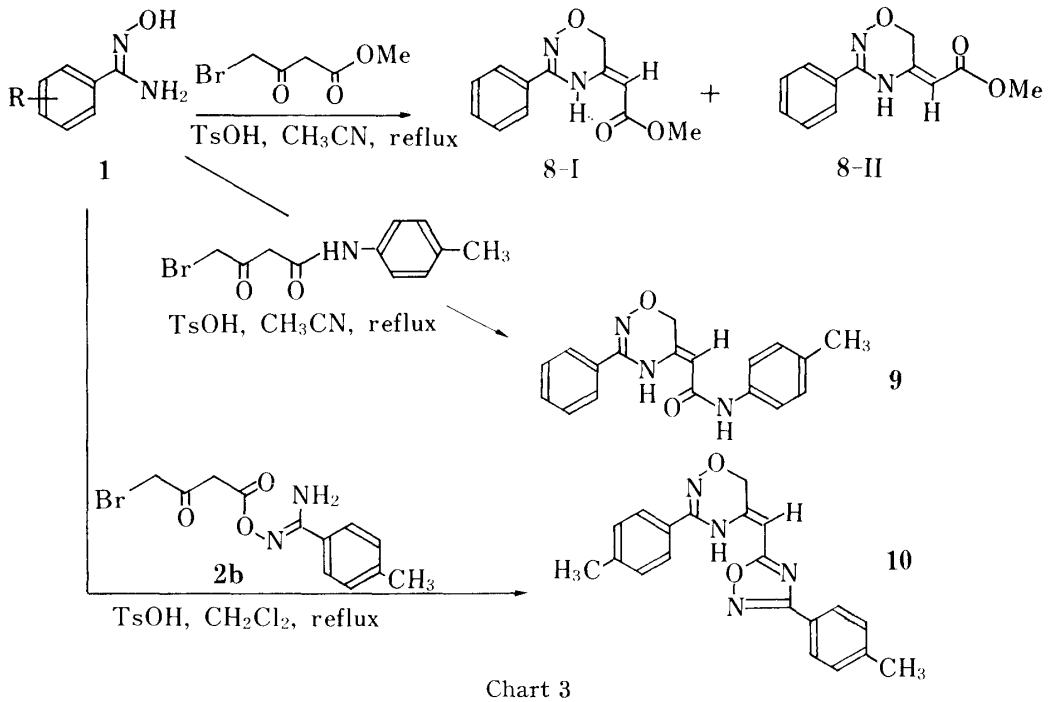


Chart 3

In conclusion, we believe that the reaction of benzamide oxime derivatives with γ-bromoacetoacetyl compounds in the presence of an acid as a catalyst provides a general method for the synthesis of 3-aryl-5-(substituted)methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives. It is also clear that the main products of the present cyclization are the (*Z*)-isomers. Further extension of this cyclization is presently under investigation.

Experimental

Melting points were determined with a hot-stage microscope and are uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer. NMR spectra were recorded with a JEOL PS-100 spectrometer at 100 MHz with TMS as an internal standard. MS were recorded on a Hitachi RMU-7 mass spectrometer.

The starting materials, benzamide oxime derivatives (**1**), were prepared from the corresponding benzonitrile derivatives and hydroxylamine following the method described in the literature.[9] Ethyl γ-bromoacetoacetate, methyl γ-bromoacetoacetate, and γ-bromoacetoacetotoluidide were derived from γ-bromoacetoacetyl bromide with the corresponding alcohol and amine in the usual manner.[10]

Reaction of Benzamide Oxime (1a) with γ-Bromoacetoacetyl Bromide——A solution of γ-bromoacetoacetyl bromide [prepared from diketene (0.42 g, 5 mmol) and one mol eq of bromine] in carbon tetrachloride (10 ml) was added in small portions to a solution of benzamide oxime (**1a**) (1.36 g, 10 mmol) in dichloromethane (*50 ml*) at 0—5°C under vigorous stirring. After being stirred for 3 h at that temperature, the reaction mixture was diluted with EtOAc (150 ml) and washed with water. The organic layer was dried over Na_2SO_4,

and concentrated *in vacuo*. The resulting residue was subjected to flash chromatography on a silica gel column.[11] Elution with *n*-hexane–$CHCl_3$ (1: 1) mixture gave colorless needles of benzamide *O*-(γ-bromoacetoacetyl)oxime (**2a**), mp 97.5°C (from EtOH), in 72.7% yield (1.09 g) together with benzamide *O*-(3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazin-5-ylideneacetyl)oxime (**3a**) as a viscous oil in 3% yield (21 mg). (**2a**): *Anal.* Calcd for $C_{11}H_{11}BrN_2O_3$: C, 44.16; H, 3.71; N, 9.37. Found: C, 44.12; H, 3.60; N, 9.49. IR ν_{max}^{KBr} cm^{-1}: 3430, 3320 (NH), 1745 (ester C=O), 1720 (keto C=O), 1640 (C=N). NMR δ ($CDCl_3$) ppm: 3.90 (2H, s, α-CH_2), 4.08 (2H, s, γ-CH_2), —5.3 (2H, b, disappeared on addition of D_2O, NH_2), 7.4—7.6 (5H, m, aromatic). MS *m/e*: 280 (M^+). (**3a**): High MS: $C_{18}H_{16}N_4O_3$. IR ν_{max}^{oil} cm^{-1}: 3450, 3330 (NH), 1695 (conjugated ester C=O), 1645 (C=N). NMR δ ($CDCl_3$) ppm: 4.40 (2H, s, 6-CH_2), 5.12 (1H, s, =CH–), —5.1 (2H, b, disappeared on addition of D_2O, NH_2), 7.1—7.6 (10H, m, aromatic), —10.9 (1H, br s, very slowly disappeared on addition of D_2O, NH). MS *m/e*: 336 (M^+).

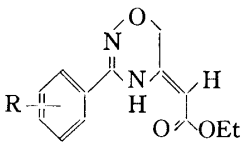
Cyclization of 2a——A solution of **2a** (300 mg, 1 mmol) in toluene (50 ml) was refluxed for 30 min. After removal of the solvent, the residue was subjected to flash chromatography on a silica gel column. Elution with *n*-hexane–CH_2Cl_2 (1: 1) mixture gave colorless needles of 5-(3-bromo-2-oxopropyl)-3-phenyl-1,2,4-oxadiazole (**4a**), mp 86°C, in 23.6% yield (67.5 mg). *Anal.* Calcd for $C_{11}H_9BrN_2O_2$: C, 47.01; H, 3.23; N, 9.97. Found: C, 47.07; H, 3.36; N, 10.07. IR ν_{max}^{KBr} cm^{-1}: 3100 (OH), 1658, 1640 (each C=N). NMR δ ($CDCl_3$) ppm: 4.01 and 4.05 (1.2H and 0.8H, each s, Br–CH_2–), 4.32 and 5.09 (0.6H and 0.4H, each s, each –CH=), —7.4 (1H, b, disappeared on addition of D_2O, enol OH), 7.4—7.5 (5H, m, aromatic). MS *m/e*: 280 (M^+).

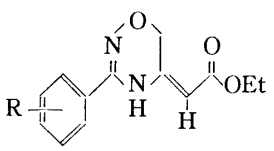
Reaction of Benzamide Oxime with Ethyl γ-Bromoacetoacetate (General Procedure)——A mixture of **1a** (1.36 g, 10 mmol), ethyl γ-bromoacetoacetate (1.05 g, 5 mmol) and TsOH (10 mg) in CH_3CN (50 ml) was refluxed for 3 h until the spot of ethyl γ-bromoacetoacetate had disappeared on TLC. After evaporation of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$ and subjected to flash chromatography and subsequently to HPLC on a silica gel column. Elution with *n*-hexane–EtOAc (6: 1 to 4: 1) mixture gave colorless needles of (*Z*)-5-ethoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**5a**-I), mp 75°C, in 71.4% yield (878 mg) and (*E*)-5-ethoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**5a**-II), mp 126°C, in 5.4% yield (67 mg).

Six kinds of benzamide oxime derivatives (**1b**—**g**) were treated with ethyl γ-bromoacetoacetate in the manner described above to afford the corresponding (*Z*)-esters as main products (**5**-I) and (*E*)-esters as minor ones (**5**-II). Mps, yields, IR and NMR spectral data are listed in Table III.

Alkaline Hydrolysis of 5b-I——A mixture of **5b**-I (520 mg, 2 mmol) and 5% NaOH (50 ml) was stirred for 30 min at 85—90°C. The mixture was neutralized and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue

Table III. 3-Aryl-5-ethoxycarbonylmethylene-5, 6-dihydro-4*H*-1, 2, 4-oxadiazines (**5**)[a]





5	R	**5**-I: (*Z*)-form mp (°C)	Yield[b] (%)	IR $\nu_{c=o}$[c] (cm^{-1})	NMR δ(ppm)[d] NH	6-CH_2	=CH–	**5**-II: (*E*)-form mp (°C)	Yield[b] (%)	IR $\nu_{c=o}$[c] (cm^{-1})	NMR δ (ppm)[d] NH	6-CH_2	=CH–
a	H	75	71.4	1660	10.9	4.45	4.90	126	5.4	1698	7.6	5.09	5.25
b	*p*-CH_3	60	71.1	1660	10.5	4.42	4.85	147	4.3	1700	7.7	5.05	5.22
c	*m*-CH_3	56	62.5	1680	10.5	4.43	4.89	135	4.5	1695	7.5	5.10	5.15
d	*o*-CH_3	Oil	68.8	1668	10.4	4.47	4.85	133	7.6	1680	7.7	4.95	5.07
e	*p*-OCH_3	98	62.4	1680	10.4	4.40	4.90	134	4.1	1690	7.5	5.07	5.24
f	*p*-Cl	112	65.4	1670	10.6	4.45	4.90	142	4.3	1695	7.1	5.15	5.21
g	*p*-NO_2	213	60.4	1660	10.7	4.48	4.96	—	—	—	—	—	—

a) *Anal.* Calcd (Found): (**5a**–I) $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38 (C, 63.26; H, 5.70; N, 11.70). (**5a**–II) $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38 (C, 63.38; H, 5.66; N, 11.41). (**5b**–I) $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76 (C, 64.30; H, 6.23; N, 10.71). (**5b**–II) $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76 (C, 64.41; H, 6.22; N, 10.69). (**5c**–I) $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76 (C, 64.52; H, 6.20; N, 10.83). (**5c**–II) $C_{14}N_{16}N_2O_3$: C,64.60; H,6.20; N, 10.76 (C, 64.71; H, 6.28; N, 10.85). (**5d**–II) $C_{14}H_{16}N_2O_3$:C, 64.60; H, 6.20; H,10.76 (C, 64.59; H, 6.19; N, 10.82). (**5e**–I) $C_{14}H_{16}N_2O_{3\ 4}$: C, 60.86; H, 5.84; N, 10.14 (C,60.63; H, 5.89; N, 10.00). (**5e**–II) $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14 (C, 60.77; H, 5.89; N, 10.08). (**5f**–I) $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98 (C, 55.36; H, 4.64; N, 10.10). (**5f**–II) $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N,9.98 (C, 55.71; H, 4.65;N, 10.00). (**5g**–I) $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43 (C, 53.65; H, 4.68 ; N, 14.56).

b) Yields are calculated basd on ethyl γ-bromoacetoacetate.

c) Measured in KBr disk.

d) Measured in $CDCl_3$ solution.

was subjected to flash chromatography on a silica gel column using $CHCl_3$ as an eluent to give 97 mg (35.8%) of *p*-toluamide (**6**) as colorless needles, mp 155°C, undepressed on admixture of the product with an authentic sample.

Acidic Hydrolysis of 5b-I——A mixture of **5b**-I (520 mg, 2 mmol) and 5% HCl (50 ml) was refluxed for 30 min. The mixture was neutralized with $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to flash chromatography on a silica gel column. Elution with $CHCl_3$ gave colorless needles of *N*-(1-hydroxy-2-propylidene)-*p*-toluamide oxime (**7**), mp 114°C (from EtOH), in 46.9% yield (193 mg). *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.56. Found: C, 63.91; H, 6.91; N, 13.61. IR ν_{max}^{KBr} cm^{-1}: 3300—3000 (OH), 1625 (C=N). NMR δ ($CDCl_3$) ppm: 1.15 (3H, s, CH_3), 2.34 (3H, s, tolyl-CH_3), 2.9 (1H, br, disappeared on addition of D_2O, OH), 3.55 and 4.01 (2H, AB_q, $J=12$ Hz, =C–CH_2–OH), 5.5 (1H, br, disappeared on addition of D_2O, OH), 7.23 and 7.50 (each 2H, AB_q, $J=8$ Hz, aromatic). MS *m/e*: 206 (M^+).

Reaction of Benzamide Oxime with Methyl γ-Bromoacetoacetate——Following a procedure similar to that given for **5**, a mixture of **1a** (1.36 g, 10 mmol), methyl γ-bromoacetoacetate (980 mg, 5 mmol) and TsOH (10 mg) in CH_3CN (50 ml) was refluxed for 2.5 h. After evaporation of the solvent, the residue was subjected to flash chromatography and subsequent HPLC on a silica gel column using *n*-hexane–EtOAc (6: 1) mixture as an eluent to give colorless needles of (*Z*)-5-methoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**8**-I), mp 94.5°C, in 57.2% yield (664 mg) and colorless needles of (*E*)-5-methoxycarbonylmethylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**8**-II), mp 143°C, in 2.6% yield (30 mg).

(**8**-I): *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.89; H, 5.13; N, 11.97. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1660 (C=O), 1638 (C=N). NMR δ ($CDCl_3$) ppm: 3.70 (3H, s, CH_3), 4.41 (2H, s, 6-CH_2), 4.88 (1H, s, =CH–), 7.3—7.7 (5H, m, aromatic), —10.4 (1H, br, very slowly disappeared on addition of D_2O, NH). MS *m/e*: 232 (M^+).

(**8**-II): *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.21; H, 5.11; N, 11.99. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1700 (C=O), 1650 (C=N). NMR δ ($CDCl_3$) ppm: 3.70 (3H, s, CH_3), 5.13 (2H, s, 6-CH_2), 5.30 (1H, s, =CH–), —7.4 (1H, br, slowly disappeared on addition of D_2O, NH), 7.5—7.7 (5H, m, aromatic). MS *m/e*: 232 (M^+).

Reaction of Benzamide Oxime with *p*-Methyl-γ-bromoacetoacetanilide——A mixture of **1a** (1.36 g, 10 mmol), *p*-methyl-γ-bromoacetoacetanilide (1.35 g, 5 mmol) and TsOH (10 mg) in CH_3CN (100 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in EtOAc (250 ml). The organic layer was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give a residual solid which was recrystallized from EtOH to give colorless needles of (*Z*)-5-(*p*-methylphenylcarbamoyl)methylene-3-phenyl-5,6-dihydro-4*H*-1,2,4-oxadiazine (**9**), mp 196.5°C, in 77.8% yield (795 mg). From the mother liquor, *p*-methyl-γ-bromoacetoacetanilide was recovered (154 mg). *Anal.* Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.24; H, 5.53; N, 13.61. IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1660 (C=O), 1635 (C=N). NMR δ (DMSO-d_6) ppm: 2.30 (3H, s, tolyl-CH_3), 4.52 (2H, s, 6-CH_2), 5.18 (1H, s, =CH–), 7.16 (2H, d, a part of AB_q of *p*-tolyl protons, $J=9$ Hz), 7.5—7.8 (7H, m, aromatic), —10.0 (1H, br, very slowly disappeared on addition of D_2O, NH of 1,2,4-oxadiazine moiety), —11.5 (1H, br s, disappeared on addition of D_2O, NH). MS *m/e*: 307 (M^+).

Reaction of *p*-Toluamide Oxime with *p*-Toluamide *O*-(γ-Bromoacetoacetyl)oxime——A mixture of **1b** (600 mg, 4 mmol), **2b** (626 mg, 2 mmol) and TsOH (10 mg) in CH_2Cl_2 (50 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in EtOAc (150 ml). The EtOAc solution was washed with water, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The residual solid was subjected to flash chromatography on a silica gel column using *n*-hexane–EtOAc (4: 1) mixture as an eluent to afford colorless needles of *Z*-3-(*p*-methylphenyl)-5-[3-(*p*-methylphenyl)-1,2,4-oxadiazol-5-yl]methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine (**10**), mp 182°C (from EtOAc), in 26% yield (189 mg). *Anal.* Calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.55; H, 5.31; N, 16.09. IR ν_{max}^{KBr} cm^{-1}: 3460 (NH), 1675 (C=N). NMR δ (DMSO-d_6) ppm: 2.34 and 2.40 (each 3H, each s, each *p*-tolyl-CH_3), 4.52 (2H, s, 6-CH_2), 5.25 (1H, s, =CH–), 7.4—7.8 (8H, m, aromatic), —10.8 (1H, br, very slowly disappeared on addition of D_2O, NH). MS *m/e*: 346 (M^+).

Acknowledgement The authors are indebted to Mr. S. Yukawa and Miss M. Sanada for supplying materials. Thanks are also due to Mr. Y. Shida for measurement of MS, to Mr. S. Suzuki for elemental analysis, and to Mrs. C. Sakuma for measurement of NMR spectra.

References and Notes

1) This work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan (April 1982, Osaka).
2) This paper forms Part V of "Reaction of γ-Bromoacetoacetyl Bromide with *N*-Phenylhydroxylamine Derivatives." Part IV: Ref. 4.
3) K. Tabei, E. Kawashima, and T. Kato, *Chem. Pharm. Bull.*, **27**, 1842 (1979).

4) K. Tabei, E. Kawashima, T. Takada, and T. Kato, *Chem. Pharm. Bull.*, **30**, 336 (1982).
5) T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.*, **42**, 3008 (1969).
6) A. Guzmán, S. Romero, E.M. Guadalupe Urquiza, and J.M. Muchowski, *J. Heterocyclic Chem.*, **17**, 1101 (1980).
7) Under the optimized conditions (TsOH, CH_3CN, reflux for 3 h), **1a** was recovered as the hydrobromide in 69% yield.
8) Since the reaction was carried out in refluxing solvent, the intermediate corresponding to compound **3** could not be detected.
9) D. Krug, *Chem. Ber.*, **18**, 1053 (1885).
10) F. Chick and N.T.M. Wilsmore, *J. Chem. Soc.*, **97**, 1978 (1910).
11) Flash chromatography was carried out on a Kimura Kagaku flash chromatography apparatus with Kieselgel 60 (Merck, 230—400 mesh) under the elution conditions described in the literature: W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).