Ring-transformation of 1,2,4-Oxadiazines. Raney Nickel Hydrogenation of *Z*-3-Aryl-5,6-dihydro-5-(substituted)methylene-4*H*-1,2,4-oxadiazine Derivatives [1]

Katsumi Tabei*, Etsuko Kawashima and Toyozo Takada

Department of Organic Chemistry, Tokyo College of Pharmacy, Horrinouchi 1432-1, Hachioji City, Tokyo 192-03, Japan

Tetsuzo Kato

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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Raney nickel hydrogenation of *Z*-3-aryl-5-(ethoxycarbonyl)methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine (**1a-c**) affords 2-aryl-6-hydroxymethyl-4-pyrimidinone (**2**) and ethyl (2-aryl-4-oxazolyl)acetate (**3**). A similar hydrogenation of *Z*-5-(arylcarbamoyl)methylene-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine (**1d-f**) gives *E*-4-(arylcarbamoyl)methylene-2-phenyl-2-oxazoline (**5**), 4-(arylcarbamoyl)methyl-2-phenyloxazole (**6**), and *Z*-4-(arylcarbamoyl)methylene-2-phenyl-2-oxazoline (**7**).

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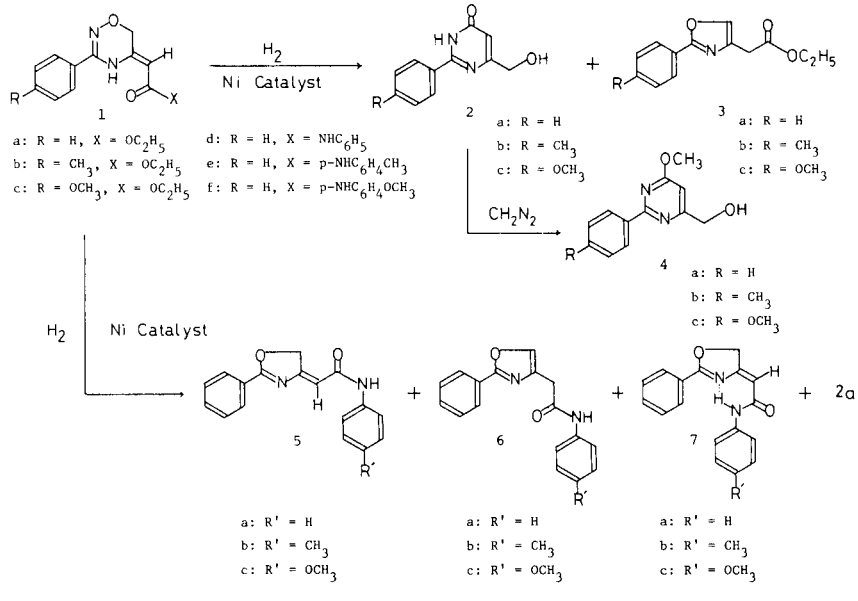
We have reported the synthesis of 3-aryl-5,6-dihydro-5-(substituted)methylene-4*H*-1,2,4-oxadiazine derivatives **1** from an aryl amide oxime and γ-haloacetoacetyl compound, such as ethyl γ-bromoacetoacetate or γ-bromoacetoacetanilide derivative [2]. In connection with the synthesis of 1,2,4-oxadiazine derivatives, Santilli and Scotese [3] have reported that methyl (3-aryl-4,5-dihydro-5-oxo-6*H*-1,2,4-oxadiazin-6-yliden)acetate was converted into 4-pyrimidinone derivative on heating with *N,N*-diethylethylenediamine. They have also mentioned the mechanism of the ring-transformation as proceeding through N-O bond fission by an attack of the amine at the 6-position of the oxadiazine ring. In the present paper, we wish to describe the ring-transformation of our 4*H*-1,2,4-oxadiazine derivatives.

Since our 1,2,4-oxadiazines, *Z*-3-aryl-5,6-dihydro-5-(substituted)methylene-4*H*-1,2,4-oxadiazine derivatives do not have an activated exomethylene group at the 6-position of the ring, we attempted the hydrogenolysis of the N-O bond of the oxadiazines. That is to say, *Z*-5-(ethoxycarbonyl)-methylene-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine **1a** was reacted with hydrogen at atmospheric pressure with Raney nickel catalyst according to the method described by Shaw and Sugowdz [4] to afford 6-hydroxymethyl-2-phenyl-4-pyrimidinone **2a** in 55% yield with the recovery of a small amount of the starting material (9.5%). When

Scheme 1



the reaction was carried out at about 3 atmospheres pressure of hydrogen, the yield of **2a** increased to 76% and a small amount of ethyl (2-phenyl-4-oxazolyl)acetate **3a** was obtained as a viscous oil (5.6%) (Scheme 1).

The structure of the former product **2a** was determined by its analytical and spectral data and chemical transformation. In the ir spectrum, **2a** showed characteristic absorption bands due to NH, OH and an amide C=O group at 3350, 3100, and 1660 cm^{-1}, respectively. In the nmr spectrum, **2a** revealed characteristic signals due to OH, CH_2 of hydroxymethyl group, 4-OH, and H-5 of pyrimidine ring at 3.3 (1H, br), 4.41 (2H, s), 5.5 (1H, br), and 6.32 ppm (1H, s), respectively, thus confirming that **2a** exists in 4-hydroxypyrimidine structure in DMSO-d_6 solution. On treatment with diazomethane in ethanol, **2a** was converted to 6-hydroxymethyl-4-methoxy-2-phenylpyrimidine **4a** in 97% yield.

The structure of **3a** was also determined on the basis of its analytical and spectral data. The nmr spectrum of **3a** showed characteristic signal due to H-5 of oxazole skeleton at 7.71 ppm (1H, s). The structure of **3a** was finally determined by comparison of its ir spectrum with that of an authentic sample prepared by the method described in the literature [5].

A similar hydrogenation of *p*-tolyl and *p*-methoxyphenyl homologues, **1b** and **1c**, also yielded the corresponding 4-pyrimidinone derivatives **2b** and **2c** and ethyl (4-oxazolyl)acetate derivatives **3b** and **3c** in good yields as shown in Table I.

Table I

Ring-transformation of *Z*-3-Aryl-5-(ethoxycarbonyl)-methylene-5,6-dihydro-4*H*-1,2,4-oxadiazines **1a-c**

Material R =	Product	Mp (°C)	Yield (%) [1 atm H_2/-72 hours]	[Conditions] [3 atm H_2/-24 hours]
1a H	**2a**	240	55	76
	3a	Oil [a]	—	5.6
1b CH_3	**2b**	254	58	77
	3b	55	—	6.2
1c OCH_3	**2c**	250	74	42
	3c	50	1.5	22

[a] Boiling point: 160°/7 mm Hg.

Treatment of *Z*-5,6-dihydro-3-phenyl-5-(*p*-tolylcarbamoyl)methylene-4*H*-1,2,4-oxadiazine **1e** with hydrogen at atmospheric pressure under Raney nickel catalyst, on the other hand, gave a mixture of isomeric oxazole and oxazoline derivatives of the molecular formula of $C_{18}H_{16}N_2O_2$ which revealed very closely located spots on tlc.

Separation of the mixture was achieved by flash chromatography [6] and subsequently by hplc on a silica gel column using a mixture of *n*-hexane and ethyl acetate as the eluent to afford respective *E*-2-phenyl-4-(*p*-tolylcarbamoyl)methylene-2-oxazoline **5b**, 2-phenyl-4-(*p*-tolylcarbamoyl)methyloxazole **6b**, and *Z*-2-phenyl-4-(*p*-tolylcarbamoyl)methylene-2-oxazoline **7b** in this order in 22, 9.7, and

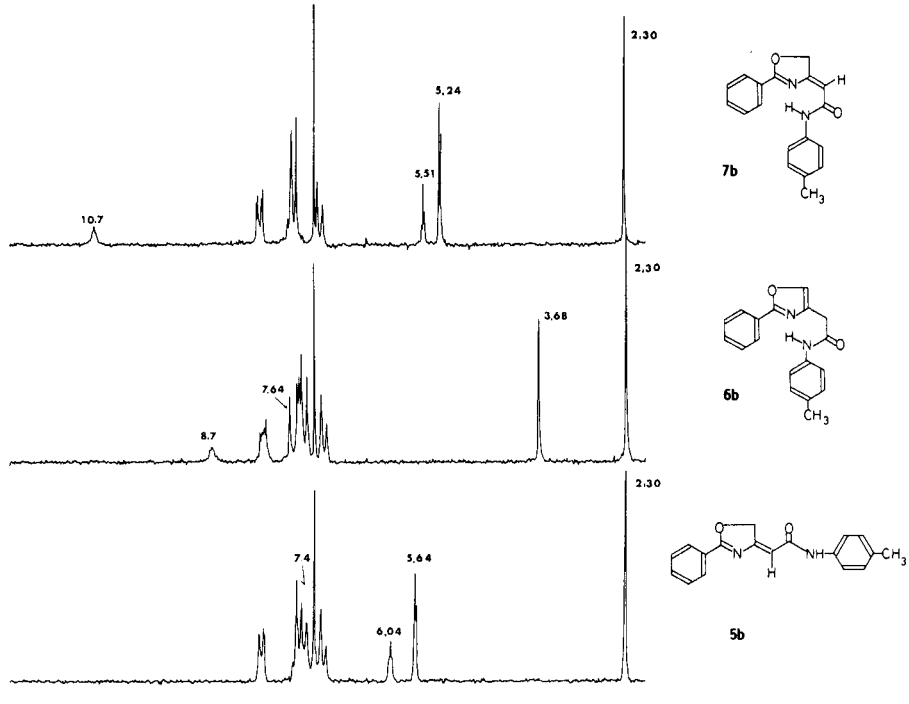


Figure 1. Pmr spectra of 5b, 6b, and 7b in deuteriochloroform solution.

46% yields. A similar result was obtained when the reaction was carried out at 3 atmospheres pressure of hydrogen. In the above case, 6-hydroxymethyl-2-phenyl-4-pyrimidinone **2a** was also obtained as a by-product in 5.0% yield.

The structures of these products were determined on the basis of their spectral data. It was revealed that **6b** has a different chromophor from those of **5b** and **7b**, since the uv spectrum of **6b** showed a single absorption peak at 258 nm (log ϵ = 4.41). On the other hand, the uv spectra of **5b** and **7b** showed two peaks at 258 nm (log ϵ = 4.18) and 337 nm (log ϵ = 4.39), and at 247 nm (log ϵ = 4.18) and 306 nm (log ϵ = 3.81), respectively. The ir spectrum of **6b** showed characteristic absorption band due to an amide C=O group at 1650 cm^{-1} whereas those of **5b** and **7b** showed characteristic C=C stretching band at 1635-1640 cm^{-1} region as well as an amide C=O band at 1660-1665 cm^{-1} region.

In the nmr spectrum of **6b**, characteristic signals due to CH_2 of carbamoylmethyl group and H-5 of oxazole ring appeared at 3.68 (2H, s) and 7.64 ppm (1H, s), respectively as shown in Figure 1.

The nmr spectra of **5b** and **7b** showed similar signal pattern at 5-6 ppm region. That is to say, the nmr spectrum of **5b** showed slightly coupled signals due to H-5 of 2-oxazoline ring and CH of exomethylene group at 5.64 (2H, d, J = 2 Hz) and 6.04 ppm (1H, br s), respectively. The corresponding signals of **7b** appeared at a little higher field, 5.24 (2H, d, J = 2 Hz) and 5.51 ppm (1H, br s), respectively. The NH proton signal of **7b** appeared at 10.7 ppm in deuteriochloroform solution, whereas, that of **5b** at 7.4 ppm region and was hidden by aromatic proton signals. The NH proton signal of **5b** was observed at 10.0 ppm in DMSO-d_6 solution.

From the above spectral data, the structure of **6b** was assigned to an oxazole derivative and those of **5b** and **7b** were also assigned to geometrical isomers of 4-exomethylen-2-oxazoline derivatives. In order to clarify the geometrical structure of **5b** and **7b**, the chemical shifts of NH proton signal were taken into account. Thus **7b** which showed NH signal at lower field (10.7 ppm), was assigned to the *Z*-isomer which may exist in a chelate structure stabilized by NH···N hydrogen bond.

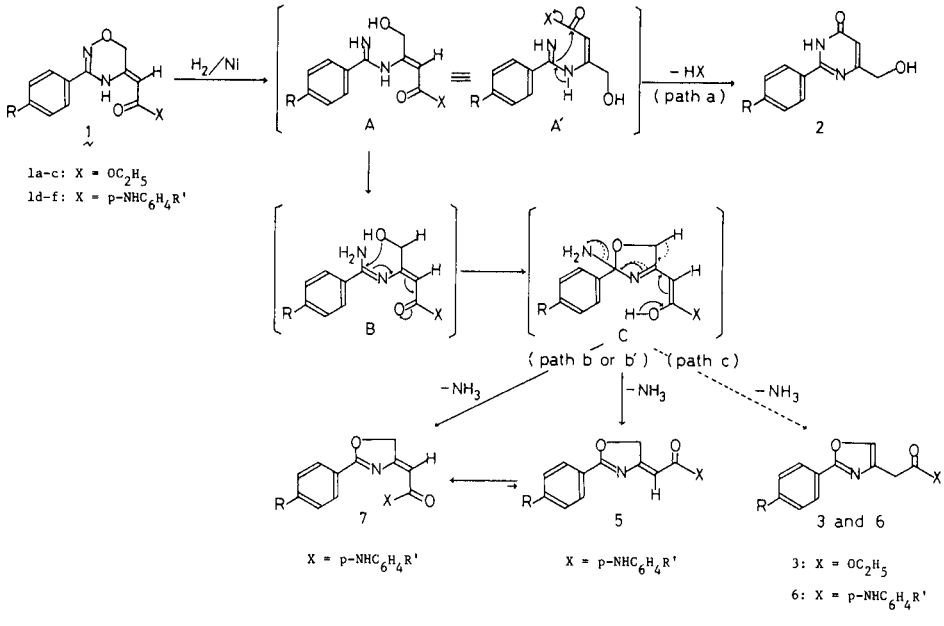
A similar hydrogenolysis of phenylcarbamoyl and *p*-methoxyphenylcarbamoyl homologues **1d** and **1f** using a nickel catalyst at atmospheric pressure of hydrogen and at 3 atmospheres pressure of hydrogen yielded the corresponding *E*-4-(arylcarbamoyl)methylene-2-phenyl-2-oxazoline derivatives **5a,c**, 4-(arylcarbamoyl)methyl-2-phenylox-

Table II

Ring-transformation of *Z*-5-(Arylcarbamoyl)methylene-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine Derivatives **1d-f**

Material R =	Product	Mp (°C)	Yield (%) [1 atm H_2/- 72 hours]	[Conditions] [3 atm H_2/- 24 hours]
1d H	**5a**	177	21	14
	6a	154	4.3	6.2
	7a	160	54	62
	2a	240	1.4	3.5
1e CH_3	**5b**	205	22	20
	6b	137	9.7	4.2
	7b	169	46	56
	2a	240	—	5.0
1f OCH_3	**5c**	190	18	21
	6c	151	12	13
	7c	183	49	47
	2a	240	—	3.0

Figure 2



azole derivatives **6a,c**, and *Z*-4-(arylcarbamoyl)methylene-2-phenyl-2-oxazoline derivatives **7a,c** in totally good yields (Table II). In the above cases, **2a** was also obtained as a by-product.

Mechanistically, the present ring-transformation could be explained as shown in Figure 2, by assuming that the reaction begins by hydrogenolysis of the N-O bond of 1,2,4-oxadiazine ring, generating an intermediate **A**. When the substituent X is ethoxyl group (**1a-c**), the reaction may undergo preferentially through cyclization of an intermediate **A'**, and concomittantly elimination of ethanol to form 4-pyrimidinone derivative **2** (path a). However, when the substituent X is an arylamino group (**1d-f**), the reaction may proceed preferentially through elimination of ammonia from the terminal intermediate **C** *via* the intermediate **B**.

Oxazoline derivatives **5** and **7** can be formed by elimination of ammonia from **C** through path b or b' (a solid line). Whereas, oxazole derivatives **3** and **6** can be formed from **C** through the aromatization of 3-oxazoline skeleton of **C** and subsequently elimination of ammonia through path c (a dotted line).

Interconversion between *E*- and *Z*-isomers **5** and **7** was observed by tlc studies on **5b** and **7b**. Thus, **5b** transformed into **7b** in about 50% yield on standing in THF solution at room temperature for 24 hours, on the other hand, **7b** changed very slowly to **5b** in the identical reaction conditions. The interconversion of **6b** into **5b** or **7b** was not observed and *vice versa*. In the reaction of **1a-c**, oxazole derivative **3** was solely obtained as a five-membered product but in low yield.

In conclusion, the course of cyclization may be determined by the difference of activity of the substituent X, ethoxyl, NH_2, and aryl-NH group, as leaving group. The reaction of these 1,2,4-oxadiazine derivatives with platinum catalyst will be reported elsewhere.

Table III

Physical, Analytical, and Spectral Data of Compounds **2**, **3**, and **4**

Compound	Mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν cm^{-1} (potassium bromide)	NMR δ ppm (Solvent) [a]
2a	240	$C_{11}H_{10}N_2O_2$	65.33 (65.14)	4.98 (4.93)	13.86 (13.89)	3350, 1660, 1640	3.3 (1H, br, O*H*), 4.41 (2H, s, CH_2OH), 5.5 (1H, br, O*H*), 6.32 (1H, s, H-5 of pyrimidine), 7.5-8.15 (5H, m, phenyl) (D)
2b	254	$C_{12}H_{12}N_2O_2$	66.65 (66.40)	5.59 (5.58)	12.96 (12.84)	3300, 1660, 1640	2.38 (3H, s, tolyl-CH_3), 3.3 (1H, br, O*H*), 4.36 (2H, s, CH_2OH), 5.5 (1H, br, O*H*), 6.30 (1H, s, H-5 of pyrimidine), 7.31 and 8.06 (2H and 2H, ABq, J = 8 Hz, aromatic) (D)
2c	250	$C_{12}H_{12}N_2O_3$	62.06 (61.81)	5.21 (5.17)	12.06 (12.02)	3400, 1670	3.3 (1H, br, O*H*), 3.80 (3H, s, OCH_3), 4.31 (2H, s, CH_2OH), 5.45 (1H, br, O*H*), 6.25 (1H, s, H-5 of pyrimidine), 7.00 and 8.15 (2H and 2H, ABq, J = 9 Hz, aromatic) (D)
3a	Oil [b]	$C_{13}H_{13}NO_3$	67.52 (67.27)	5.67 (5.67)	6.06 (5.94)	1735	1.30 and 4.25 (3H and 2H, t and q, J = 10 Hz, CH_3CH_2O), 3.61 (2H, s, CH_2COO), 7.45-8.05 (5H, m, phenyl), 7.71 (1H, s, H-5 of oxazole) (C)
3b	55	$C_{14}H_{15}NO_3$	68.55 (68.61)	6.16 (6.18)	5.71 (5.68)	1738	1.30 and 4.25 (3H and 2H, t and q, J = 9 Hz, CH_3CH_2O), 2.38 (3H, s, tolyl-CH_3), 3.65 (2H, s, CH_2COO), 7.20 and 7.88 (2H and 2H, ABq, J = 9 Hz, aromatic), 7.65 (1H, s, H-5 of oxazole) (C)
3c	50	$C_{14}H_{15}NO_4$	64.36 (64.28)	5.79 (5.70)	5.36 (5.44)	1735	1.30 and 4.25 (3H and 2H, t and q, J = 7 Hz, CH_3CH_2O), 3.65 (2H, s, CH_2COO), 3.88 (3H, s, OCH_3), 6.95 and 7.99 (2H and 2H, ABq, J = 9 Hz, aromatic), 7.65 (1H, s, H-5 of oxazole) (C)
4a	110	$C_{12}H_{12}N_2O_2$	66.65 (66.45)	5.59 (5.59)	12.96 (12.93)	3250	3.5 (1H, br, O*H*), 4.06 (3H, s, OCH_3), 4.68 (2H, s, CH_2OH), 6.60 (1H, s, H-5 of pyrimidine), 7.50-8.45 (5H, m, phenyl) (C)
4b	75	$C_{13}H_{14}N_2O_2$	67.81 (67.52)	6.31 (6.07)	12.17 (12.08)	3200	2.20 (3H, s, tolyl-CH_3), 3.60 (1H, br, O*H*), 4.06 (3H, s, OCH_3), 4.68 (2H, s, CH_2OH), 6.54 (1H, s, H-5 of pyrimidine), 7.28 and 8.35 (2H and 2H, ABq, J = 9 Hz, aromatic) (C)
4c	93	$C_{13}H_{14}N_2O_3$	63.40 (63.44)	5.73 (5.74)	11.38 (11.29)	3250	3.55 (1H, br, O*H*), 3.85 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.71 (2H, s, CH_2OH), 6.55 (1H, s, H-5 of pyrimidine), 6.95 and 8.41 (2H and 2H, ABq, J = 9 Hz, aromatic) (C)

[a] (C): Deuteriochloroform, (D): DMSO-d_6. [b] Boiling point 160°/7 mm Hg.

Table IV

Physical, Analytical, and Spectral Data of Compounds **5**, **6**, and **7**

Compound	Mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν cm^{-1} (potassium bromide)	NMR δ ppm (Solvent) [a]
5a	177	$C_{17}H_{14}N_2O_2$	73.36 (73.32)	5.07 (5.18)	10.07 (9.86)	1665, 1640	5.58 (2H, d, J = 3 Hz, H-5 of 2-oxazoline), 6.12 (1H, t, J = 3 Hz, =C*H*-CO), 7.0-8.15 (10H, m, phenyl), 7.4 (1H, br, hidden by aromatic protons, N*H*) (D) [b]
5b	205	$C_{18}H_{16}N_2O_2$	73.95 (73.97)	5.52 (5.52)	9.58 (9.62)	1660, 1638	2.30 (3H, s, tolyl-CH_3), 5.64 (2H, d, J = 2 Hz, H-5 of 2-oxazoline), 6.04 (1H, br s, =C*H*-CO), 7.1-8.17 (9H, m, aromatic), 7.4 (1H, br, hidden by aromatic protons, N*H*) (D) [c]
5c	190	$C_{18}H_{16}N_2O_3$	70.11 (69.96)	5.23 (5.29)	9.09 (9.00)	1665, 1642	3.76 (3H, s, OCH_3), 5.59 (2H, d, J = 3 Hz, H-5 of 2-oxazoline), 6.16 (1H, t, J = 3 Hz, =C*H*-CO), 6.87 and 8.12 (2H and 2H, ABq, J = 9 Hz, aromatic), 7.63 (5H, m, phenyl), 9.19 (1H, br, N*H*) (A)
6a	154	$C_{17}H_{14}N_2O_2$	73.36 (73.11)	5.07 (5.00)	10.07 (10.32)	1662	3.78 (2H, s, CH_2CO), 7.2-8.15 (10H, m, phenyl), 7.63 (1H, s, H-5 of oxazole), 9.05 (1H, br, N*H*) (C)
6b	137	$C_{18}H_{16}N_2O_2$	73.95 (74.09)	5.52 (5.55)	9.58 (9.60)	1650	2.30 (3H, s, tolyl-CH_3), 3.68 (2H, s, CH_2CO), 6.95-8.15 (9H, m, aromatic), 7.64 (1H, s, H-5 of oxazole), 8.76 (1H, br, N*H*) (C)
6c	151	$C_{18}H_{16}N_2O_3$	70.11 (70.03)	5.23 (5.23)	9.09 (8.92)	1665	3.66 (2H, s, CH_2CO), 3.75 (3H, s, OCH_3), 6.8-8.1 (9H, m, aromatic), 7.60 (1H, s, H-5 of oxazole), 8.50 (1H, br, N*H*) (C)
7a	160	$C_{17}H_{14}N_2O_2$	73.36 (73.36)	5.07 (5.10)	10.07 (9.98)	1665, 1640	5.22 (2H, d, J = 2 Hz, H-5 of 2-oxazoline), 5.50 (1H, t, J = 2 Hz, =C*H*-CO), 7.05-8.22 (10H, m, aromatic), 10.8 (1H, br, N*H*) (C)
7b	169	$C_{18}H_{16}N_2O_2$	73.95 (74.15)	5.52 (5.52)	9.58 (9.58)	1663, 1640	2.30 (3H, s, tolyl-CH_3), 5.24 (2H, d, J = 2 Hz, H-5 of 2-oxazoline), 5.51 (1H, br s, =C*H*-CO), 7.1-8.15 (9H, m, aromatic), 10.7 (1H, br, N*H*) (C)
7c	183	$C_{18}H_{16}N_2O_3$	70.11 (69.94)	5.23 (5.24)	9.09 (8.97)	1665, 1630	3.81 (3H, s, OCH_3), 5.22 (2H, d, J = 2 Hz, H-5 of 2-oxazoline), 5.52 (1H, br s, =C*H*-CO), 6.90-8.20 (9H, m, aromatic), 10.7 (1H, br, N*H*) (C)

[a] (A): Perdeuterioacetone, (C): deuteriochloroform, (D): DMSO-d_6. [d] Appeared at 10.1 ppm in DMSO-d_6 solution. [c] Appeared at 10.0 ppm in DMSO-d_6 solution.

EXPERIMENTAL

All melting points were determined by a Yanagimoto hot-stage micro melting point apparatus and are uncorrected. The ir spectra were recorded on a Hitachi 215 spectrometer. The nmr spectra were recorded on a JEOL PS-100 spectrometer with TMS as an internal standard. Mass spectra were recorded on a Hitachi RMU-7 mass spectrometer.

The starting materials **1a-f** were prepared from the corresponding aryl amide oxime and ethyl γ-bromoacetoacetate or γ-bromoacetoacetanilide derivatives by previously reported method [2].

Raney Nickel Hydrogenation of **1a-c**. General Procedure.

A suspension of *Z*-3-aryl-5-(ethoxycarbonyl)methylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives **1a-c** (1 mmole) and 0.5 g of Raney nickel catalyst [7] in 25 ml of THF was stirred for 72 hours under a stream of hydrogen at atmospheric pressure or for 24 hours at 3 atmospheres pressure at room temperature. To the reaction mixture, 50 ml of THF was added to dissolve a precipitated product. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to dryness. The residue was washed with 25-30 ml of ethyl acetate and the crude product thus obtained was collected and recrystallized from ethanol to give the corresponding 2-aryl-6-hydroxymethyl-4-pyrimidinone derivatives **2a-c**. The washing solution was concentrated under reduced pressure to dryness. The residue was subjected to flash chromatography on a silica gel column to give the corresponding ethyl (2-aryl-4-oxazolyl)acetate derivatives **3a-c** as a by-product. The melting points and yields are listed in Table I.

Reaction of **2a-c** with Diazomethane.

A solution of 2-aryl-6-hydroxymethyl-4-pyrimidinone derivatives **2a-c** (0.1 mmole) in 20 ml of ethanol was treated with an ethereal solution of diazomethane prepared from *p*-toluenesulfonylmethylnitrosoamide [8]. After evaporation of the solvent, the residue was subjected to hplc on a silica gel column [9]. The first eluent with a mixture of *n*-hexane and ethyl acetate (2:1) gave the corresponding 2-aryl-6-hydroxymethyl-4-methoxypyrimidine derivatives **4a-c**. The yields of **4a,b,c** were 97, 83, and 86%, respectively.

The physical, analytical, and spectral data of **2**, **3**, and **4** are listed in Table III.

Raney Nickel Hydrogenation of **1d-f**. General Procedure.

A suspension of *Z*-5-(arylcarbamoyl)methylene-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine derivatives **1d-f** (1 mmole) and 0.5 g of nickel catalyst in 25 ml of THF was stirred for 24 hours under a stream of hydrogen at atmospheric pressure or for 3 hours at 3 atmospheres pressure at room temperature. The catalyst was filtered off and the filtrate was concentrated under reduced pressure into dryness. The residue thus obtained was subjected to flash chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (2:1) as the eluent. The first eluent was concentrated and then subjected to hplc on a silica gel column with a mixture of *n*-hexane and ethyl acetate (2:1) as the eluent to give the corresponding *E*-4-(arylcarbamoyl)methylene-2-phenyl-2-oxazoline derivatives **5a-c**, 4-(arylcarbamoyl)methyl-2-phenyloxazole derivatives **6a-c**, and *Z*-4-(arylcarbamoyl)methylene-2-phenyl-2-oxazoline derivatives **7a-c** in this

order. These products were recrystallized from a mixture of *n*-hexane and ethyl acetate. From the second eluent on flash chromatography, **2a** was obtained as a by-product. The melting points and yields are listed in Table II.

The physical, analytical, and spectral data for **5**, **6**, and **7** are listed in Table IV.

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[9] The hplc was carried out on a Kusano Kagaku KP-6H apparatus using a CIG column (silica, 50μ, 15ϕ × 300 mm) and UVILOG 254 detector.