Hydrogenolysis of the C-O Bond of the 1,2,4-Oxadiazine Ring. Adams Platinum Hydrogenation of 3-Aryl-5,6-dihydro-5-(substituted)-methylene-4*H*-1,2,4-oxadiazine Derivatives

Etsuko Kawashima, Toyozo Takada and Katsumi Tabei*

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

Tetsuzo Kato

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

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Adams platinum hydrogenation of *Z*-3-aryl-5,6-dihydro-5-(substituted)methylene-4*H*-1,2,4-oxadiazine (**1a-f**) proceeds very slowly through C-O bond fission to give *N*-(1-substitutedcarbonyl-2-propylidene)benzamide oxime derivative **2** as the main product. In the reaction of 5-(arylcarbamoyl)methylene analogues **1d-f**, 5-(arylcarbamoyl)methyl-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine (**4**) and *N*-aryl-3-hydroxybutanamide derivative **5** are also obtained as well as compound **2**.

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In the previous paper we reported that hydrogenation of *Z*-3-aryl-5,6-dihydro-5-(substituted)methylene-4*H*-1,2,4-oxadiazine **1** with Raney nickel catalyst leads to the ring-transformation *via* cleavage of N-O bond affording 6-hydroxymethyl-4-pyrimidinone derivatives and/or oxazole derivatives [2]. As a part of further studies on hydrogenation of our 1,2,4-oxadiazine derivatives, we attempted hydrogenolysis of **1** with Adams platinum catalyst and found that the ring-opening takes place at C-O bond to afford *N*-(1-substitutedcarbonyl-2-propylidene)benzamide oxime derivatives. We wish to describe the results in more detail.

In the presence of platinum oxide as a catalyst, *Z*-5-(ethoxycarbonyl)methylene-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine **1a** was reacted with hydrogen at atmospheric pressure in THF at room temperature for 72 hours to give a ring-opened product, *N*-(1-ethoxycarbonyl-2-propylidene)-benzamide oxime, **2a** and a ring-transformed product, 6-hydroxymethyl-2-phenyl-4-pyrimidinone, **3a** as crystalline products in 25% and 5.4% yields, respectively. An appreciable amount of the starting material was recovered (54%).

A similar hydrogenation of *p*-tolyl and *p*-methoxyphenyl homologues, **1b** and **1c**, yielded the corresponding *N*-(1-ethoxycarbonyl-2-propylidene)benzamide oxime derivatives **2b** and **2c** in 55% and 30% yields, respectively. 2-Aryl-6-hydroxymethyl-4-pyrimidinone derivatives **3b** and **3c** were also obtained as by-product.

Hydrogenation of 5,6-dihydro-3-phenyl-5-(phenylcarbamoyl)methylene-4*H*-1,2,4-oxadiazine **1d** in the presence of platinum oxide as a catalyst, on the other hand, afforded three kinds of crystalline products; *N*-(1-phenylcarbamoyl-2-propylidene)benzamide oxime **2d**, 5,6-dihydro-3-phenyl-5-(phenylcarbamoyl)methyl-4*H*-1,2,4-oxadiazine **4a**, and *N*-phenyl-3-hydroxybutanamide **5a** in 19%, 18%, and 26% yields, respectively. The starting material was recovered in 35% yield.

Chart 1

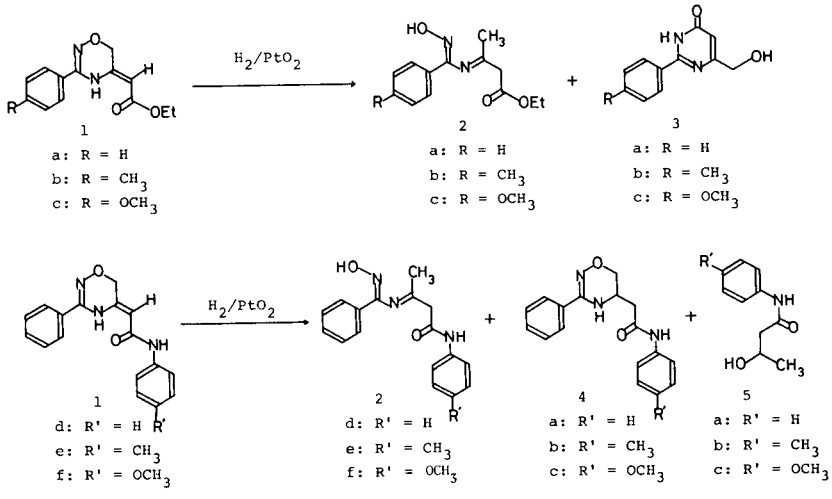


Table I

Adams Platinum Hydrogenation of 3-Aryl-5,6-dihydro-5-(substituted)methylene-4*H*-1,2,4-oxadiazine Derivatives **1a-f**

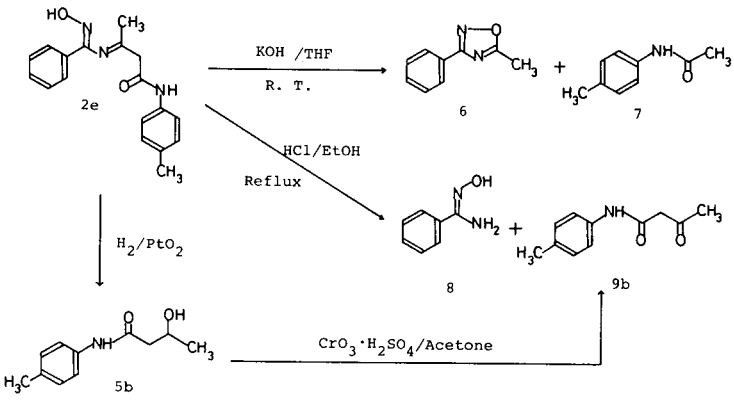
1	Material R or R'	Reaction Conditions Solvent	Time (hours)	Mp and Yield of Products Mp (°C)	Yield (%)		Recovery of **1** (%)
1a	R = H	THF	72	**2a** (89) [25]	**3a** (240) [5.4]		**1a** [54]
1b	R = CH_3	THF	72	**2b** (116) [55]	**3b** (254) [8.0]		**1b** [37]
1c	R = OCH_3	THF	72	**2c** (107) [30]	**3c** (250) [1.2]		**1c** [68]
1d	R = H	THF	48	**2d** (192) [19]	**4a** (225) [18]	**5a** (113) [26]	**1d** [35]
1e	R = CH_3	THF	48	**2e** (188) [16]	**4b** (203) [11]	**5b** (130) [5.8]	**1e** [61]
1f	R = OCH_3	THF	48	**2f** (170) [15]	**4c** (210) [23]	**5c** (135) [20]	**1f** [20]

Table II

Physical, Analytical and Spectral Data for Compounds **2**, **4** and **5**

Compound	Mp (°C)	Formula	Analysis (%) Calcd./(Found) C	H	N	IR ν cm^{-1} (potassium bromide)	NMR δ ppm (Deuteriochloroform)
2a	89	$C_{13}H_{16}N_2O_3$	62.89 (62.99)	6.50 (6.43)	11.28 (11.00)	3250, 1720	1.28 and 4.20 (3H and 2H, t and q, J = 9 Hz, CH_3CH_2O), 1.70 (3H, s, CH_3), 2.88 (2H, AB_q, J = 17 Hz, $COCH_2C$=N), 5.75 (1H, br s, O*H*), 7.4-7.7 (5H, m, phenyl)
2b	116	$C_{14}H_{18}N_2O_3$	64.10 (64.12)	6.92 (6.77)	10.68 (10.51)	3200, 1725	1.30 and 4.25 (3H and 2H, t and q, J = 10 Hz, CH_3CH_2O), 1.70 (3H, s, CH_3), 2.40 (3H, s, tolyl-CH_3), 2.85 (2H, AB_q, J = 16 Hz, $COCH_2C$=N), 5.70 (1H, br s, O*H*), 7.25 and 7.61 (2H and 2H, AB_q, J = 9 Hz, aromatic)
2c	107	$C_{14}H_{18}N_2O_4$	60.42 (60.21)	6.52 (6.36)	10.07 (9.97)	3200, 1738	1.75 and 4.18 (3H and 2H, t and q, J = 10 Hz, CH_3CH_2O), 1.68 (3H, s, CH_3), 2.82 (2H, AB_q, J = 18 Hz, $COCH_2C$=N), 3.80 (3H, s, OCH_3), 5.60 (1H, br s, O*H*), 6.91 and 7.59 (2H and 2H, AB_q, J = 10 Hz, aromatic)
2d	192	$C_{17}H_{17}N_3O_2$	69.13 (68.91)	5.80 (5.77)	14.23 (14.00)	3260, 3200 1680	1.75 (3H, s, CH_3), 2.89 (2H, AB_q, J = 19 Hz, $COCH_2C$=N), 5.85 (1H, br s, O*H*), 7.3-7.7 (10H, m, aromatic), 7.95 (1H, br, N*H*)
2e	188	$C_{18}H_{19}N_3O_2$	69.88 (69.77)	6.19 (6.12)	13.58 (13.55)	3300, 3180 1670	1.70 (3H, s, CH_3), 2.30 (3H, s, tolyl-CH_3), 2.90 2H, AB_q, J = 17 Hz, $COCH_2C$=N), 6.0 (1H, br s, O*H*), 7.0-7.7 (9H, m, aromatic), 8.14 (1H, br, N*H*)
2f	170	$C_{18}H_{19}N_3O_3$	66.44 (66.15)	5.89 (5.85)	12.92 (12.78)	3300, 3200 1670	1.70 (3H, s, CH_3), 2.82 (2H, AB_q, J = 17 Hz, $COCH_2C$=N), 3.75 (3H, s, OCH_3), 5.7 (1H, br, O*H*), 6.8-7.7 (9H, m, aromatic), 7.9 (1H, br, N*H*)
4a	225	$C_{17}H_{17}N_3O_2$	69.13 (69.11)	5.80 (5.75)	14.23 (14.18)	3300, 1660	2.56-3.01 (2H, m, 6-CH_2), 3.95-3.98 (2H, br s, CH_2CO), 4.18 (1H, m, 5-C*H*), 5.73 (1H, b, 4-N*H*), 7.2-7.6 (10H, m, aromatic), 7.8 (1H, br, amide-N*H*)
4b	203	$C_{18}H_{19}N_3O_2$	69.88 (69.87)	6.19 (6.16)	13.58 (13.52)	3300, 1680	2.31 (3H, s, tolyl-CH_3), 2.47-2.9 (2H, m, 6-CH_2), 3.92 (2H, br, CH_2CO), 4.17 (1H, m, 5-C*H*), 5.77 (1H, br s, 4-N*H*), 7.06-7.63 (9H, m, aromatic), 7.98 (1H, br s, amide-N*H*)
4c	210	$C_{18}H_{19}N_3O_3$	66.44 (66.73)	5.89 (5.84)	12.92 (12.82)	3300, 1650	2.42-2.95 (2H, m, 6-CH_2), 3.78 (3H, s, OCH_3), 3.95 (2H, br s, $COCH_2$), 4.25 (1H, br s, 5-C*H*), 5.22 (1H, br, 4-N*H*), 6.8-7.6(9H, m, aromatic), 7.70 (1H, br s, amide-N*H*)
5a	113	$C_{10}H_{13}NO_2$	67.07 (67.05)	7.31 (7.24)	7.82 (8.10)	3300, 1670 1660	1.24 (3H, d, J = 8 Hz, -CH_3), 2.45 (2H, d, J = 8 Hz, $COCH_2$), 2.80 (1H, br, O*H*), 4.30 (1H, m, -C*H*), 7.2-7.5 (5H, m, phenyl), 7.90 (1H, br, N*H*)
5b	130	$C_{11}H_{15}NO_2$	68.37 (68.33)	7.82 (7.81)	7.25 (7.19)	3300, 1680 1660	1.25 (3H, d, J = 9 Hz, -CH_3), 2.30 (3H, s, tolyl-CH_3), 2.48 (2H, d, J = 9 Hz, $COCH_2$), 4.30 (1H, m, -C*H*), 3.0 (1H, br, O*H*), 7.18 and 7.45 (2H and 2H, AB_q, J = 12 Hz, aromatic), 7.85 (1H, br, amide-N*H*)
5c	135	$C_{11}H_{15}NO_3$	63.14 (62.99)	7.23 (7.14)	6.69 (6.98)	3300, 1675 1650	1.25 (3H, d, J = 9 Hz, -CH_3), 2.42 (2H, d, J = 9 Hz, $COCH_2$), 3.50 (1H, br s, O*H*), 4.30 (1H, m, -C*H*), 6.85 and 7.41 (2H and 2H, AB_q, J = 12 Hz, aromatic), 7.85 (1H, br, amide-N*H*)

Chart 2



A similar hydrogenation of 5-*p*-tolylcarbamoyl and 5-*p*-methoxyphenylcarbamoyl homologues **1e** and **1f** yielded the corresponding *N*-(1-arylcarbamoyl-2-propylidene)benzamide oxime derivatives **2e** and **2f**, 5-(arylcarbamoyl)-methyl-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine derivatives **4b** and **4c**, and *N*-aryl-3-hydroxybutanamide derivatives **5b** and **5c** in moderate yields. The melting points and yields are listed in Table I.

The structure of compound **2** was established by analytical and spectral data (Table II). The ir spectrum of **2** showed characteristic OH stretching band at about 3200 cm^{-1} region. In the nmr spectrum of **2**, the signals due to methyl, methylene, and hydroxyl group appeared at about 1.7 ppm (3H, singlet), at 2.8-2.9 ppm (2H, AB-quartet), and at 5.6-5.7 ppm (1H, broad singlet), respectively.

The structure of **2** was also confirmed by the following chemical derivations (Chart 2). That is to say, **2e** was treated with potassium hydroxide in THF at room temperature for 24 hours to afford 5-methyl-3-phenyl-1,2,4-oxadiazole **6** and *p*-acetotoluidide **7b**. On refluxing with a mixture of hydrochloric acid and ethanol, **2e** gave benzamide oxime **8** and *p*-acetoactotoluidide **9b** as crystalline products. Hydrogenation of **2e** with platinum oxide as a catalyst afforded *N*-(*p*-tolyl)-3-hydroxybutanamide **5b** which on treatment with chromium trioxide and sulfuric acid in acetone was converted into **9b**.

The structure of compound **4** was established by analytical and spectral data. The ir spectrum of **4** showed characteristic absorption bands due to NH and amide C=O group at about 3300 cm^{-1} region and at 1660-1680 cm^{-1}, respectively. In the nmr spectrum of **4**, characteristic signals due to 6-methylene of 1,2,4-oxadiazine ring appeared at 2.4-3.1 ppm region as multiplet (2H). The signals due to carbamoylmethylene group and 5-methine group of the ring appeared at 3.7-4.0 ppm region (2H, broad singlet) and at 4.1-4.3 ppm region (1H, multiplet), respectively (Table II).

The structure of compounds **3, 5, 6, 7, 8** and **9** were determined by mixed-melting point determination or by the comparison of their ir spectra with those of authentic specimen [3].

From the above results, it was revealed that Adams platinum hydrogenation of **1** proceeds very slowly through the fission of C-O bond of 1,2,4-oxadiazine ring to give propylidenebenzamide oxime derivatives. In the case of 5-ethoxycarbonylmethylene derivatives **1a-c**, the fission of the N-O bond of the ring also proceeded as in Raney nickel hydrogenation previously reported and yielded 4-pyrimidinone derivatives **3a-c** were obtained but in low yields. In the reaction of 5-(arylcarbamoyl)methylene homologues **1d-f**, the fission of N-O bond was not observed but normal hydrogenation of the exo-methylene group proceeded to give 5-carbamoylmethyl derivatives **4** in comparable yield. 3-Hydroxybutanamide derivatives **5** may probably be derived by hydrolysis of compound **2**. As far as we are aware, the present hydrogenolysis of **1** with Adams platinum catalyst is the first instance of the cleavage of C-O bond of 1,2,4-oxadiazine ring.

EXPERIMENTAL

All melting points were determined by a Yanagimoto hot-stage melting point apparatus and are uncorrected. The ir spectra were recorded on a Hitachi 215 spectrometer. The nmr spectra were recorded on a Varian EM-390 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 described method [4].

Adams Platinum Hydrogenation of **1a-c**. General Procedure.

A suspension of *Z*-3-aryl-5,6-dihydro-5-(ethoxycarbonyl)methylene-4*H*-1,2,4-oxadiazine derivatives **1a-c** (1 mmole) and 50 mg of platinum oxide in 25 ml of THF was stirred for 72 hours under a stream of hydrogen at atmospheric pressure at room temperature. To the reaction mixture, 30 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 thus obtained was mixed with 20-30 ml of ethyl

acetate and the mixture was filtered to get an insoluble product. The crude solid thus obtained was recrystallized from ethanol to give 2-aryl-6-hydroxymethyl-4-pyrimidinone derivatives **3a-c**. The above filtrate was concentrated under reduced pressure to dryness. The residue was subjected to flash chromatography [5] on silica gel column using a mixture of *n*-hexane and ethyl acetate (2:1) as the eluent to give *N*-(1-ethoxycarbonyl-2-propylidene)benzamide oxime derivatives **2a-c** and the starting materials **1a-c** in this order. The melting points and yields are listed in Table I. The physical, analytical and spectral data for **2** are listed in Table II.

Adams Platinum 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 50 mg of platinum oxide in 25 ml of THF was stirred for 48 hours under a stream of hydrogen at atmospheric pressure at room temperature. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (1:1) as the eluent to afford subsequently the starting materials **1d-f**, *N*-(1-arylcarbamoyl-2-propylidene)benzamide oxime derivatives **2d-f**, *N*-aryl-3-hydroxybutanamide derivatives **5a-c**, and 5-(arylcarbamoyl)methyl-5,6-dihydro-3-phenyl-4*H*-1,2,4-oxadiazine derivatives **4a-c**. The melting points and yields are listed in Table I. The physical, analytical and spectral data for compounds **2d-f**, **4a-c** and **5a-c** are also listed in Table II.

Reaction of **2e** with Potassium Hydroxide.

A solution of *N*-(1-*p*-tolylcarbamoyl-2-propylidene)benzamide oxime **2e** (7.6 mg, 0.025 mmole) and 10 mg of potassium hydroxide in 10 ml of THF was stirred for 24 hours at room temperature. After evaporation of the solvent under reduced pressure, the residue was subjected to flash chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (2:1) as the eluent to give 5-methyl-3-phenyl-1,2,4-oxadiazole **6** (mp 41°, 3.9 mg, 76%) and *p*-acetotoluidide **7b** (mp 153°, 3.7 mg, 83%).

Hydrolysis of **2e** with Hydrochloric Acid.

A mixture of **2e** (15 mg, 0.05 mmole) and 5 ml of 10% hydrochloric acid in 20 ml of ethanol was refluxed for 2 hours. The reaction mixture was neutralized by sodium hydrogencarbonate and extracted with 50 ml of ethyl acetate and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced presssure, the residue thus obtained was subjected to flash chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (1:1) as the eluent to afford *p*-acetoacetotoluidide **9b** (mp 95°, 2 mg, 21%) and benzamide oxime **8** (mp 80°, 1.7 mg, 26%) in this order.

Hydrogenation of **2e** with Adams Platinum Catalyst.

A suspension of **2e** (58 mg, 0.19 mmole) and 10 mg of platinum oxide in 20 ml of THF was stirred for 20 hours under a stream of hydrogen at atmospheric pressure at room temperature. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure into dryness. The residue was subjected to flash chromatography on a silica gel column using a mixture of *n*-hexane and ethyl acetate (1:1) as the eluent to give the starting material **2e** (44 mg, 76%) and *N*-*p*-tolyl-3-hydroxybutanamide **5b** (mp 130°, 8.5 mg, 23%) in this order.

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