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Synthesis of β-Ketocarboxamide Derivatives Using 2,2-Dimethyl-2*H*,4*H*-1,3-dioxin-4-ones

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Thermal reaction of 2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-ones (**1**) with amines was studied. Acylketenes **2**, generated by heating of **1**, reacted with anilines and benzylamine to give the corresponding β-ketocarboxamides (**3**, **4**, and **5**) in good yields. The reaction of **1** with ammonia gave 3-amino-2-alkenamides (**7**), which were hydrolyzed to β-ketocarboxamides (**6**). The former products **7** were readily transformed to the 6-substituted 2-methyl-3*H*-pyrimidin-4-ones (**9**) *via* the 3-acetamido-2-alkenamides (**8**). Acylation of *O*-benzylhydroxylamine with **1** gave the β-ketohydroxamic acids **10**. Debenzylation of **10** followed by cyclization gave rise to 5-alkyl-3-hydroxyisoxazoles (**12**). The reaction of **1** with amides gave the corresponding *N*-acylated amides (**13**).

Keywords——2*H*,4*H*-1,3-dioxin-4-one; thermal fragmentation; acylketene; acylation; carboxamide; carboximide; hydroxamic acid; 3-hydroxyisoxazole; 3*H*-pyrimidin-4-one

In 1953, Carroll and Bader reported that 2,2,6-trimethyl-2*H*,4*H*-1,3-dioxin-4-one (**1a**), obtained from diketene and acetone, reacted with amines under heating to give acetoacetamides.[1] Recently, the reaction has been found to proceed through the intermediary acetylketene (**2a**: $R^1=H$, $R^2=Me$) which is thermally generated from **1a**.[2] Generation of acylketenes (**2**) from 1,3-dioxin-4-one derivatives seems to occur generally, since a variety of 2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-ones (**1**) reacted with 1,2- and 1,3-dipolar compounds under heating to give products which can be assumed to be cycloadducts of acylketenes (**2**) to the dipoles.[3] Since β-ketoamide derivatives are potentially useful for nitrogen heterocyclic synthesis, our attention was focused on the preparation of β-ketoamide derivatives by use of **1**.[4]

When aniline was heated with 2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-ones (**1b**, **1f**—**l**), the corresponding amides (**3**) were obtained in 49—78% yields. As reported previously,[3] the reaction of 5- or 6-monosubstituted dioxinones (**1b**, **1f**, and **1g**) proceeded at 120—140 °C while that of 5,6-disubstituted ones (**1h**—**k**) did so at higher temperatures (160—167 °C). The results are shown in Table I. Next, we examined the reaction of 2,2,5,6-tetramethyl-2*H*,4*H*-1,3-dioxin-4-one (**1h**) with aniline derivatives. As shown in Table II, weakly basic anilines such as nitroanilines and diphenylamine also gave the corresponding amides (**4**) in good yields. Therefore, the reaction is suggested to involve the formation of a methylacetylketene intermediate (**2h**: $R^1=R^2=Me$) as a strong electrophile.

Similarly, compound **1** reacted with benzylamine to give the amide **5**. The results are summarized in Table III.

When ammonia gas was passed into solutions of 6-substituted dioxinones (**1b**—**e**) at 115 °C, the corresponding enaminoamides (**7b**—**e**) were obtained in good yields. The initial product is the β-ketoamide **6**, which condenses with excess ammonia to give the product **7**. The same reaction of the 6-phenyldioxinone (**1f**) gave the ketoamide **6f** in a good yield.

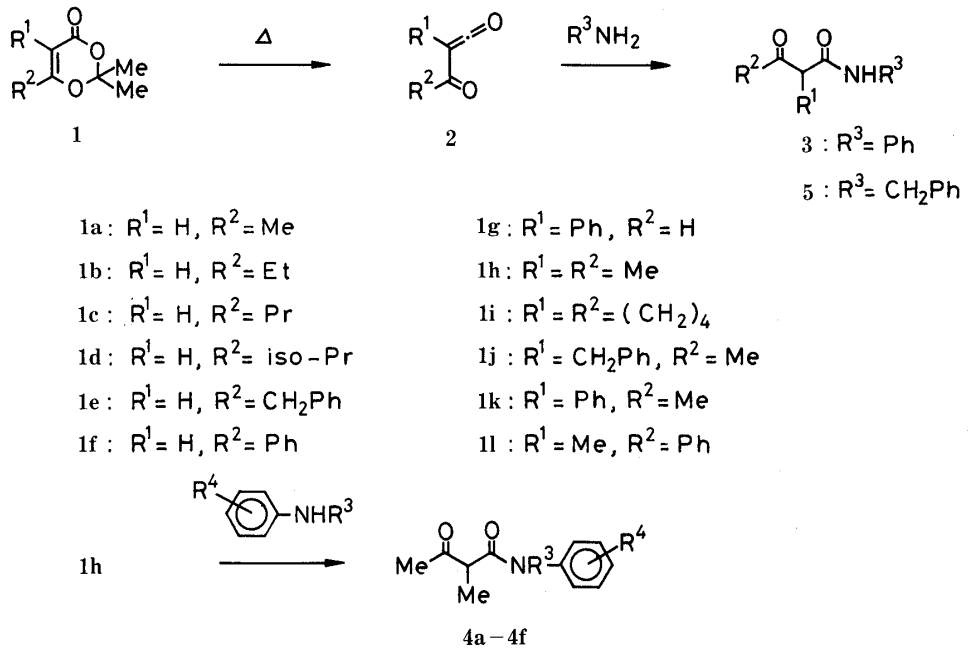

Chart 1

TABLE I. Reaction of 2,2-Dimethyl-2*H*,4*H*-1,3-dioxin-4-ones (**1**) with Aniline to Give **3**

Compd. No.	Substituent		Reaction conditions			Yield (%)	Recryst. solvent[b]	mp (lit. mp) (°C)
	R^1	R^2	Solvent[a]	Temp. (°C)	Time (min)			
3b	H	Et	A	140	45	78	C	83—85 (81—82)[c]
3f	H	Ph	A	140	45	70	C	105—107 (105—107)[d]
3g	Ph	H	A	140	20	46		Oil
3h	Me	Me	B	167	90	76	C	132—134 (135—139)[e]
3i	$-(CH_2)_4-$		B	160	60	49	D	103—106 (106—108)[f]
3j	CH_2Ph	Me	B	160	60	69	C	100—102
3k	Ph	Me	B	167	90	56	C	115—117
3l	Me	Ph	B	167	60	75	C	130—132 (137)[g]

a) A, xylene; B, mesitylene.
b) C, hexane–ethyl acetate; D, hexane–ether.
c) S. Nakano, *Yakugaku Zasshi*, **82**, 492 (1962).
d) Reference 17.
e) K. F. Hebenbrock, *Justus Liebigs Ann. Chem.*, **1978**, 320.
f) S. Hünig, K. Hübner, and E. Benzing, *Chem. Ber.*, **95**, 926 (1962).
g) L. Horner and E. Spietschka, *Chem. Ber.*, **85**, 225 (1952).

Compounds **7** were readily transformed to ketoamides **6b—e** in good yields by treatment with hydrochloric acid. Reaction of **1h** with ammonia in boiling mesitylene gave a complex reaction mixture, from which neither the ketoamide **6h** nor the enaminoamide **7h** was isolated.

We have previously found that β-aminocrotonamide (**7a**: R^1=H, R^2=Me) is a useful reagent in pyridine and pyrimidine syntheses.[5] Based on a previous method,[6] compounds **7b** and **7e** were acetylated with acetic anhydride to give the acetates **8b** and **8e**, respectively. Cyclization with sodium methoxide gave the corresponding 2-methyl-3*H*-pyrimidin-4-ones (**9b** and **9e**).

Previously, we reported that diketene reacted with *O*-benzylhydroxylamine to give the hydroxamic acid **10a** (R^2=Me), which, on debenzylation followed by cyclization, was

TABLE II. Reaction of 2,2,5,6-Tetramethyl-2*H*,4*H*-1,3-dioxin-4-one (**1h**) with Aniline Derivatives to Give **4**

Compd. No.	Substituent		Reaction time (min)	Yield (%)	Recryst. solvent[a]	mp (lit. mp) (°C)
	R^3	R^4				
4a	H	*o*-NO_2	60	76	A	76—78
4b	H	*m*-NO_2	60	78	B	66—68
4c	H	*p*-NO_2	60	74	B	152—154
4d	H	*o*-Cl	60	67	B	92—93 (94—94.5)[b]
4e	H	*o*-CO_2Me	90	72	C	49—51
4f	Ph	H	90	64	A	84—86

a) A, ether; B, ethyl acetate–hexane; C, hexane.
b) A. L. Searles and R. J. Kelly, *J. Am. Chem. Soc.*, **77**, 6075 (1955).

TABLE III. Reaction of **1** with Benzylamine to Give **5**

Compd. No.	Substituent		Reaction solvent[a]	Method A			Method B Yield (%)	Recryst. solvent[c]	mp (lit. mp) (°C)
	R^1	R^2		Temp.[b] (°C)	Time (min)	Yield (%)			
5b	H	Et	A	140	45	42	69	C	81—83
5f	H	Ph	A	140	90	77	78	C	82—83 (91—92)[d]
5h	Me	Me	B	167	90	63	62	C	82—85 (85—86)[e]
5i	$-(CH_2)_4-$		B	162	60	55	18	D	84—88 (89—90)[e]
5j	CH_2Ph	Me	B	167	60	51	68	C	104—105
5k	Ph	Me	B	167	80	43	51	D	95—97
5l	Me	Ph	B	167	60	69	69	C	112—114

a) A, xylene; B, mesitylene.
b) Bath temperature.
c) C, ethyl acetate–hexane; D, ether–hexane.
d) G. Cordella, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 10 (1958) [*Chem. Abstr.*, **53**, 9679*i* (1959)].
e) Reference 13*d*.

transformed to 3-hydroxy-5-methylisoxazole **12a** (R^2 = Me).[7] This is a convenient method for preparing **12a**, which is a well-known soil fungicide, Tachigaren. Dioxinones served as a tool for preparing analogous isoxazoles. When 6-ethyl and 6-benzyl dioxinones (**1b** and **1e**) were heated with *O*-benzylhydroxylamine, the corresponding *O*-benzylhydroxamic acids (**10b** and **10e**) were obtained. Compounds **10b** and **10e** were debenzylated by catalytic hydrogenation to give the β-ketohydroxamic acids **11b** and **11e**, respectively. They were readily cyclized to the corresponding 5-substituted 3-hydroxyisoxazoles **12b** and **12e** on treatment with hydrogen chloride in acetic acid.

Masked acetylketene (**1a**) is an excellent reagent for the acetoacetylation of weak nucleophiles such as amides and urethane,[2b] and *N*-acetoacetyl derivatives of amides and urethane are potentially useful as intermediates for 1,3-oxazin-4-one[8] and 1,3-thiazin-4-one derivatives.[9] Thus, reactions of the 6-phenyl and 5,6-dimethyl dioxinones (**1f** and **1h**) with acetamide, benzamide, and urethane were carried out. The corresponding *N*-acylacetyl derivatives (**13**, **14**, and **15f**) were obtained in good yields as shown in Table V. The reaction of **1h** with urethane did not give the acylated compound (**15h**). This compound was cyclized to 5,6-dimethyl-2*H*,4*H*-1,3-oxazine-2,4-dione (**16**) during the thermal reaction. Recently, Yamamoto *et al.* have reported that acyl Meldrum's acids react with amides to give *N*-

TABLE IV. Analytical and IR Spectral Data for **3**, **4**, and **5**

Compd. No.	Formula	Analysis (%) Calcd (Found)			IR ($CHCl_3$) cm^{-1}	
		C	H	N	NH	C=O
3g	$C_{15}H_{13}NO_2$[a]	75.30 (76.11	5.48 5.75	5.85 5.31)	3400	1720, 1670, 1640
3j	$C_{17}H_{17}NO_2$	76.38 (76.17	6.41 6.40	5.24 5.30)	3300	1695, 1672
3k	$C_{16}H_{15}NO_2$	75.87 (75.79	5.97 5.94	5.53 5.31)	3300	1700, 1668
4a	$C_{11}H_{12}N_2O_4$	55.93 (55.74	5.12 4.95	11.86 11.79)	3350	1720, 1695
4b	$C_{11}H_{12}N_2O_4$	55.93 (55.67	5.12 4.92	11.86 11.65)	3310	1700, 1685
4c	$C_{11}H_{12}N_2O_4$	55.93 (55.69	5.12 5.09	11.86 11.78)	3290	1700
4e	$C_{13}H_{15}NO_4$	62.64 (62.45	6.07 6.05	5.62 5.57)	3300, 3270	1720, 1685
4f	$C_{17}H_{17}NO_2$	76.38 (76.32	6.41 6.45	5.24 5.18)	—	1715, 1665
5b	$C_{12}H_{15}NO_2$	70.22 (70.11	7.37 7.37	6.82 6.81)	3310	1700, 1652
5j	$C_{18}H_{19}NO_2$	76.84 (76.57	6.81 6.78	4.98 5.25)	3360	1690, 1660
5k	$C_{17}H_{17}NO_2$	76.38 (76.05	6.41 6.44	5.24 5.43)	3360	1710, 1660
5l	$C_{17}H_{17}NO_2$	76.38 (76.54	6.41 6.48	5.24 5.41)	3360	1690, 1660

a) Determined by mass spectrometry. Found: 239.0947; Calcd for M^+: 239.0946.

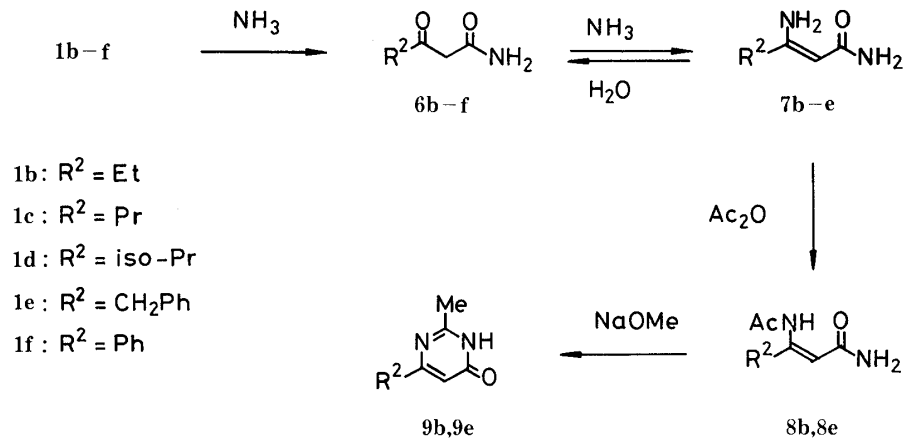

Chart 2

(acylacetyl)amides (**13** and **14**, $R^1=H$).[10] Use of **1** provides a facile method for preparing such compounds having a substituent (R^1) at the α-position.

It is well recognized that diketene is useful in the synthesis of nitrogen heterocycles.[11] The results of the present paper and our previous papers[3] show that 2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-ones (**1**) serve as chemical equivalents to the mixed diketenes **17**, which are not easily accessible.[12] Previous methods[13] for the synthesis of β-ketocarboxamides have not proved to

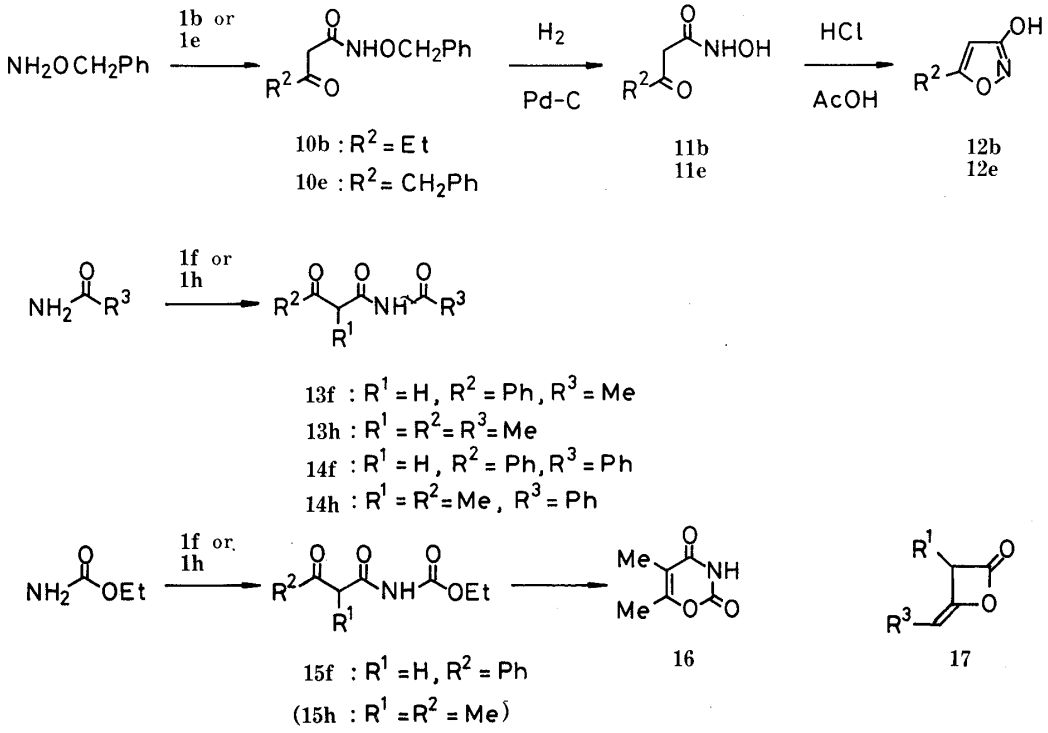

Chart 3

TABLE V. Reaction of **1h** and **1f** with Amides

Compd. No.	Substituent			Yield (%)	Recryst. solvent[a]	mp (°C) (lit. mp)	IR ($CHCl_3$) cm^{-1}		Formula	Analysis (%) Calcd (Found)		
	R^1	R^2	R^3				NH	C=O		C	H	N
13f	H	Ph	Me	67	A	104—106 (104—105)[b]	3260	1730 1705				
13h	Me	Me	Me	59		Oil	3280 3200	1720 1700	$C_7H_{11}NO_3$	53.49 (53.25	7.05 7.26	8.91 8.76)
14f	H	Ph	Ph	73	B	174—175 (168—169)[b] (178—179)[c]	3300	1705 1690				
14h	Me	Me	Ph	69	A	110—112	3290	1720 1690	$C_{12}H_{13}NO_3$	65.74 (65.77	5.98 5.95	6.39 6.65)
15f	H	Ph	OEt	66	C	94—96	3200	1755 1705	$C_{12}H_{13}NO_4$	61.27 (60.99	5.77 5.34	5.96 5.84)

a) A, ethyl acetate–hexane; B, ethyl acetate; C, ether–hexane.
b) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Am. Chem. Soc.*, **86**, 872 (1964).
c) Reference 10.

be consistently practical. The reaction of the masked acylketenes (**1**) with amino compounds appears to provide a new and general method for the preparation of β-ketocarboxamides.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a JEOL JNM-PMX 60 spectrometer and are reported as δ values (ppm) relative to

tetramethylsilane as an internal standard. 2,2-Dimethyl-2*H*,4*H*-1,3-dioxin-4-ones (**1e**,[3a] **1f**—**l**[14]) were prepared by the reported procedures.

General Procedure for Preparation of 6-Alkyl-2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-one (1b—d)——The reported procedure[15] was modified; a mixture of acyl Meldrum's acid[16] (0.1 mol), dry acetone (2.9 g, 0.05 mol) and dry toluene (100 ml) was refluxed for 1 h, then the reaction mixture was concentrated *in vacuo*, and the resulting oil was distilled under reduced pressure.

6-Ethyl-2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-one (**1b**): Oil of bp 65—67 °C (0.2 mmHg) [lit.[15] bp 65—67 °C (0.2 mmHg)]. Yield, 84%.

2,2-Dimethyl-6-propyl-2*H*,4*H*-1,3-dioxin-4-one (**1c**): Oil of bp 55—56 °C (0.08 mmHg). Yield, 85%. IR ($CHCl_3$): 1720 (C=O), 1625 (C=C) cm^{-1}. ^{1}H-NMR (CCl_4) δ: 0.96 (3H, t, J=7 Hz, $\underline{Me}CH_2$), 1.30—1.85 (2H, m, $MeC\underline{H}_2$), 1.63 (6H, s, C_2–Me_2), 2.16 (2H, t, J=7 Hz, $EtC\underline{H}_2$), 5.06 (1H, s, C_5–H). MS *m/e*: 170 (M^+), 112 (M^+ − acetone). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 62.88; H, 8.19.

6-Isopropyl-2,2-dimethyl-2*H*,4*H*-1,3-dioxin-4-one (**1d**): Oil of bp 57—58 °C (0.05 mmHg). Yield, 80%. IR ($CHCl_3$): 1720 (C=O), 1625 (C=C) cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.15 (6H, d, J=7 Hz, $\underline{Me}_2CH$), 1.65 (6H, s, C_2–Me_2), 2.40 (1H, m, $Me_2C\underline{H}$), 5.10 (1H, s, C_5–H). MS *m/e*: 170 (M^+), 112 (M^+ − acetone). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.21; H, 8.46.

General Procedure for Reaction of 1 with Aniline to Give the Amides 3——A solution of **1** (10 mmol) and aniline (10 mmol) in xylene or mesitylene (20 ml) was heated on an oil bath. The solvent was evaporated off *in vacuo* and the residue was crystallized from hexane. Crystals were collected by suction and purified by recrystallization. Compound **3g** was purified by silica gel column chromatography with a mixture of hexane–ethyl acetate (20 : 1, v/v). Reaction conditions, recrystallization solvents, melting points, and yields are shown in Table I. Analytical and spectral data for new compounds are listed in Table IV.

General Procedure for Reaction of 2,2,5,6-Tetramethyl-2*H*,4*H*-1,3-dioxin-4-one (1h) with Aniline Derivatives to Give Amides 4——A solution of **1h** (10 mmol) and an aniline derivative in mesitylene (10 ml) was heated at 165 °C (bath temperature). Work-up as described above yielded the product **4**. Reaction periods, recrystallization solvents, yields, and melting points are shown in Table II. Analytical and spectral data for new compounds are listed in Table IV.

General Procedure for Reaction of 1 with Benzylamine to Give the Amides 5——Method A: The above general procedure for the reaction of **1** with aniline was employed.

Method B: A solution of **1** (5 mmol) and benzylamine (5 mmol) in xylene or mesitylene (25 ml) was added dropwise to the boiling solvent (50 ml) over 15 min, during which time about 20 ml of the solvent was distilled off through a condenser. Heating was continued for an additional 45 min to distill another 60 ml of the solvent. The reaction mixture was worked up as described for method A.

The results of methods A and B are shown in Table III. Analytical and spectral data for new compounds are shown in Table IV.

General Procedure for Reaction of 1b—e with Ammonia to Give Enaminoamides 7——Ammonia gas was passed into a solution of **1** (20 mmol) in xylene (50 ml) at 115 °C (bath temperature) for 2 h. Chloroform (30 ml) was added to the reaction mixture and the whole was dried over anhydrous potassium carbonate. Evaporation of the solvent *in vacuo* yielded crude products **7b—d** as yellowish oils or **7e** as crystals. Compounds **7b**, **7c**, and **7d** were characterized by the ^{1}H-NMR spectroscopy, and were used directly for further reactions. Compound **7e** was purified by recrystallization from chloroform.

3-Amino-2-pentenamide (**7b**): Yield, 86%. IR ($CHCl_3$): 3500, 3410, 3310 (NH), 1640 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz, Me), 2.13 (2H, q, J=7 Hz, CH_2), 4.50 (1H, s, =CH–), 5.20 (2H, br, NH_2), 6.52 (2H, br, $CONH_2$).

3-Amino-2-hexenamide (**7c**): Yield, 89%. IR ($CHCl_3$): 3500, 3410, 3300 (NH), 1638 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7 Hz, Me), 1.33—1.96 (2H, m, $MeC\underline{H}_2$), 1.96—2.40 (2H, m, $EtC\underline{H}_2$), 4.47 (1H, s, =CH–), 5.20 (2H, br, NH_2), 6.54 (2H, br, $CONH_2$).

3-Amino-4-methyl-2-pentenamide (**7d**): Yield, 86%. IR ($CHCl_3$): 3500, 3410, 3300 (NH), 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (6H, d, J=7 Hz, Me), 2.03—2.59 (1H, m, $Me_2C\underline{H}$), 4.50 (1H, s, =CH–), 5.23 (2H, br, NH_2), 6.54 (2H, br, $CONH_2$).

3-Amino-4-phenyl-2-butenamide (**7e**): Yield, 72%. mp 107—110 °C. IR ($CHCl_3$): 3480, 3410, 3300 (NH), 1640 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, s, $PhC\underline{H}_2$), 4.53 (1H, s, =CH–), 5.33 (2H, br, NH_2), 6.45 (2H, br, $CONH_2$), 7.30 (5H, s, Ph). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.89; H, 6.78; N, 15.82.

Benzoylacetamide (6f)——2,2-Dimethyl-6-phenyl-2*H*,4*H*-1,3-dioxin-4-one (**1f**) (2.04 g, 10 mmol) was allowed to react with ammonia in the manner used for the reaction of **1** with ammonia. Evaporation of the solvent gave a crystalline substance. Recrystallization from chloroform gave the product **6f** as needles of mp 112—113 °C (lit.[13b] mp 112—113 °C). Yield, 1.30 g (80%).

General Procedure for Hydrolysis of 7 to Give β-Ketoamides 6b—e——A mixture of crude **7** (10 mmol), conc. hydrochloric acid (1 g) and chloroform (50 ml) was stirred at room temperature for 10 min. The organic layer was

separated, washed with brine, and then dried over anhydrous magnesium sulfate. Evaporation of chloroform left **6** as a crystalline substance.

3-Oxopentanamide (**6b**): Leaves of mp 71—73 °C (recrystallized from ether). Yield, 0.7 g (61%). IR ($CHCl_3$): 3490, 3410, 3350 (NH), 1713, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, t, J=7 Hz, $\underline{Me}CH_2$), 2.60 (2H, q, J=7 Hz, $MeC\underline{H}_2$), 3.45 (2H, s, $COCH_2CO$), *ca.* 6.6 and 7.1 (each 1H, br, NH_2). *Anal.* Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 51.88; H, 7.72; N, 12.17.

3-Oxohexanamide (**6c**): Prisms of mp 79—81 °C (recrystallized from ether) (lit.[17] mp 79 °C). Yield, 1.24 g (96%). IR ($CHCl_3$): 3490, 3350 (NH), 1710 (shoulder), 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7 Hz, Me), 1.22 (2H, m, $MeC\underline{H}_2$), 2.44 (2H, t, J=7 Hz, $CH_2C\underline{H}_2CO$), 3.33 (2H, s, $COCH_2CO$), *ca.* 6.2 and 7.0 (each 1H, br, NH_2).

4-Methyl-3-oxopentanamide (**6d**): Needles of mp 46—49 °C (recrystallized from ether) (lit.[18] mp 42 °C). Yield, 1.12 g (87%). IR ($CHCl_3$): 3490, 3400, 3350 (NH), 1710 (shoulder), 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.64 (6H, d, J=7 Hz, 2×Me), 2.8 (1H, m, $Me_2C\underline{H}$), 3.59 (2H, s, $COCH_2CO$), *ca.* 6.5 and 7.1 (each 1H, br, NH_2).

3-Oxo-4-phenylbutanamide (**6e**): Prisms of mp 104—106 °C (recrystallized from benzene). Yield, 1.68 g (96%). IR ($CHCl_3$): 3490, 3410, 3350 (NH), 1710, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (2H, s, $PhC\underline{H}_2$), 3.42 (2H, s, $COCH_2CO$), *ca.* 6.2 and 6.9 (each 1H, br, NH_2). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.53; H, 6.11; N, 7.83.

3-Acetamido-2-pentenamide (8b)——Acetic anhydride (1.02 g, 10 mmol) was added to a solution of **7b** (0.57 g, 5 mmol) in chloroform (3 ml) under ice-cooling. The mixture was then heated under reflux for 2 h. The mixture was concentrated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate to give **8b** as prisms of mp 166—167 °C. Yield, 0.44 g (56%). IR ($CHCl_3$): 3520, 3420, 3330 (NH), 1705 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7.5 Hz, $\underline{Me}CH_2$), 2.05 (3H, s, Me), 2.74 (2H, q, J=7.5 Hz, $MeC\underline{H}_2$), 4.78 (1H, s, =CH–), 5.57 (2H, br, NH_2), 11.91 (1H, br, NH). *Anal.* Calcd for $C_7H_{12}N_2O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.64; H, 7.20; N, 20.21.

3-Acetamido-4-phenyl-2-butenamide (8e)——Following the procedure given for **8b**, compound **7e** (0.88 g, 5 mmol) was acetylated to give **8e** as prisms of mp 167—170 °C. Yield, 0.62 g (56%). IR ($CHCl_3$): 3530, 3420, 3320 (NH), 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, Me), 4.08 (2H, s, CH_2), 4.58 (1H, s, =CH–), 5.56 (2H, br, NH_2), 7.20 (5H, s, Ph), 11.93 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.87; H, 6.53; N, 12.65.

6-Ethyl-2-methyl-3*H*-pyrimidine-4-one (9b)——Compound **8b** (0.28 g, 1.8 mmol) was added to a sodium methoxide solution in methanol [prepared from sodium metal (0.041 g, 1.8 mmol) and absolute methanol (5 ml)]. After being refluxed for 1.5 h, the reaction mixture was neutralized with dil. hydrochloric acid and concentrated to dryness *in vacuo*. The residue was boiled with chloroform (30 ml) and then filtered. Concentration of the filtrate gave a crystalline substance. Recrystallization from acetone gave **9b** as needles of mp 121—123 °C (lit.[19] mp 122—123 °C). Yield, 0.24 g (86%).

6-Benzyl-2-methyl-3*H*-pyrimidin-4-one (9e)——Following the procedure given for **9b**, compound **8e** (0.436 g, 2 mmol) was treated with sodium methoxide to give **9e** as needles of mp 222—224 °C. Yield, 0.335 g (84%). IR ($CHCl_3$): 3150—2600 (NH), 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s, Me), 3.81 (2H, s, CH_2), 5.98 (1H, s, =CH–), 7.22 (5H, s, Ph), 13.4 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.95; H, 6.11; N, 13.98.

***N*-Benzyloxy-3-oxopentanamide (10b)**——Following method B given for **5**, compound **1b** (3.12 g, 20 mmol) was allowed to react with *O*-benzylhydroxylamine (2.46 g, 20 mmol) in xylene. The solvent was evaporated off *in vacuo* and the oily residue was crystallized from hexane under ice-cooling. Crystals were collected by suction and recrystallized from ether to give **10b** as needles of mp 72—75 °C. Yield, 2.67 g (61%). IR ($CHCl_3$): 3300 (NH), 1705, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7 Hz, Me), 2.49 (2H, q, J=7 Hz, $MeC\underline{H}_2$), 3.28 (2H, s, $COCH_2CO$), 9.65 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; H, 6.33. Found: C, 64.93; H, 6.84; N, 6.36.

***N*-Benzyloxy-3-oxo-4-phenylbutanamide (10e)**——Compound **1e** (4.36 g, 20 mmol) was allowed to react with *O*-benzylhydroxylamine (2.46 g, 20 mmol) according to the procedure given for **10b**. Recrystallization of the product from a mixture of hexane and ether gave **10e** as needles of mp 86—89 °C. Yield, 3.23 g (57%). IR ($CHCl_3$): 3320 (NH), 1710, 1685 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.35 (2H, s, $COCH_2CO$), 4.83 (2H, s, $PhC\underline{H}_2$), 7.02—7.49 (5H, m, Ph), 9.46 (1H, br, NH). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.76; H, 6.15; N, 4.94.

***N*-Hydroxy-3-oxopentanamide (11b)**——A mixture of **10b** (0.77 g, 3.5 mmol), 20% Pd–C (0.25 g) and absolute ethanol (15 ml) was shaken in a hydrogen atmosphere (1 atm) at room temperature for 3.5 h, during which time 80 ml of hydrogen was absorbed. The catalyst was filtered off and the filtrate was concentrated to dryness *in vacuo*. Recrystallization of the residue from ethyl acetate gave **11b** as needles of mp 66—69 °C. Yield, 0.33 g (72%). IR (Nujol): 3300, 3200, 3000—2650 (NH, OH), 1710, 1680, 1650 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=7 Hz, Me), 2.65 (2H, q, J=7 Hz, $MeC\underline{H}_2$), 3.32 (2H, s, $COCH_2CO$), 8.6—10.6 (2H, br, NHOH). *Anal.* Calcd for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.76; H, 6.88; N, 10.52.

***N*-Hydroxy-3-oxo-4-phenylbutanamide (11e)**——Employing the procedure given for **11b**, compound **10e** (0.99 g, 3.5 mmol) was debenzylated to give **11e**. Recrystallization from ethyl acetate gave leaves of mp 120—121 °C. Yield,

0.45 g (66%). IR (Nujol): 3250, 3000—2700 (NH, OH), 1720, 1640 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.35 (2H, s, $COCH_2CO$), 3.92 (2H, s, Ph–$C\underline{H}_2$), 9.02 and 10.67 (each 1H, br, NHOH). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.04; H, 5.75; N, 7.26.

5-Ethyl-3-hydroxyisoxazole (12b) and 5-Benzyl-3-hydroxyisoxazole (12e)——Compound **11b** (0.228 g, 1.74 mmol) was dissolved in acetic acid (2 ml) saturated with dry hydrogen chloride. The solution was left standing at room temperature overnight, then concentrated to dryness *in vacuo*. The residue was recrystallized from hexane to give **12b** as needles of mp 45—46 °C (lit.[20] mp 45—46 °C). Yield, 0.107 g (54%). Similarly, compound **11e** (0.324 g, 1.7 mmol) was treated with a mixture of acetic acid and hydrogen chloride to give **12e** as needles of mp 94—95 °C. Yield, 0.223 g (76%). IR ($CHCl_3$): 3150—2400 (OH), 1620 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.00 (2H, s, CH_2), 5.68 (1H, s, C_4–H), 7.34 (5H, s, Ph), 11.49 (1H, s, OH). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.69; H, 5.18; N, 8.00.

General Procedure for Reaction of 1f with Acetamide, Benzamide, and Urethane——A mixture of **1f** (2.04 g, 10 mmol), acetamide (0.59 g, 10 mmol), and dry toluene (20 ml) was refluxed for 1 h. The solvent was evaporated off *in vacuo* and the residue was purified by recrystallization to give *N*-acetylbenzoylacetamide (**13f**). Compounds **14f** and **15f** were prepared in the same manner. Yields, melting points, and recrystallization solvents are shown in Table V.

General Procedure for Reaction of 1h with Acetamide, Benzamide, and Urethane——A mixture of **1h** (1.56 g, 10 mmol), benzamide (1.21 g, 10 mmol), and dry mesitylene (10 ml) was heated at 165 °C (bath temperature) for 1 h. The solvent was evaporated off *in vacuo* and the residue was recrystallized to give **14h**. Similar treatment of **1h** with acetamide or urethane gave an oily residue. Purification by silica gel column chromatography with a mixture of hexane and ethyl acetate (1 : 1, v/v) yielded compound **13h** or **16**. Yields, physical data, and analytical data are given in Table V.

3,4-Dihydro-5,6-dimethyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**16**): Needles of mp 168—170 °C from ether. Yield, 21%. IR ($CHCl_3$): 3400 (NH), 1760, 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, C_5–Me), 2.23 (3H, s, C_6–Me), 9.8 (1H, br, NH). *Anal.* Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.19; H, 4.85; N, 10.32.

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