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Synthesis of Imidazo[4,5-*e*][1,4]diazepine and Imidazo[4,5-*e*][1,4]-oxazepine Derivatives Using Caffeidine, a Hydrolysis Product of Caffeine

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Synthesis of imidazo[4,5-*e*][1,4]diazepines using caffeidine (**1**) was studied. Caffeidine was condensed with various α,β-unsaturated carboxylic acid derivatives to give *N*-(α,β-unsaturated acyl)caffeidines (**4**). Intramolecular Michael addition of **4** having an electron-withdrawing group at the β-position of the α,β-unsaturated acyl group afforded imidazo[4,5-*e*][1,4]diazepines (**5**, **6**). Compounds of the same type (**14**) were also prepared by treatment of *N*-(α-halogenoacyl)caffeidines (**13**) with EtONa in abs. EtOH. On the other hand, heating of **13** in H_2O gave imidazo[4,5-*e*][1,4]oxazepines (**15**). Compounds **5d**, **15b**, and **15c** showed arterial relaxing activities.

Keywords——caffeidine; imidazo[4,5-*e*][1,4]diazepine; intramolecular Michael addition; imidazo[4,5-*e*][1,4]oxazepine; arterial relaxing activity

Many benzo[1,4]diazepines having physiological activities have been reported: benzodiazepine,[1] a psychotropic agent; anthramycin[2] having antitumor activity; and cyclopenin,[3] a metabolic product of fungi. Investigators have directed their efforts toward the synthesis of such compounds in the hope of finding new physiologically active compounds.[4] However, no studies on the imidazo[4,5-*e*][1,4]diazepine derivatives have been done except for the work by Edenhofer[5] and Bogatskii and Ivanov.[6] Since the pharmacological profiles of imidazo[4,5-*e*][1,4]diazepines remain to be studied, we have planned a synthetic program to obtain materials for examination of the physiological activities, which are anticipated because of the similarity of the heterocyclic ring system to that of benzo[1,4]diazepines. The present paper reports the synthesis of 1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepines (**5**, **6**) by Michael addition using caffeidine (**1**),[7,8] which is easily obtained by the hydrolysis of caffeine. 1,4-Dimethyl-5,8-dioxo-1,4,5,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]oxazepines (**15**) formed by a side reaction during the synthesis of imidazodiazepine derivatives (**14**) by Bogatskii and Ivanov's method are also discussed.

Bogatskii and Ivanov synthesized 1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine from *N*-chloroacetylcaffeidine (**13d**) (Chart 4). Initially, we tried the synthesis of an imidazodiazepine derivative from the caffeidine derivative (**3**) which had a hydroxy group in place of a halogen atom (Chart 1). Glycolic acid protected by a tetrahydropyranyl (THP) group reacted with **1** in the presence of propylphosphonic anhydride (PRPA),[9] to give **2**, whose THP group was eliminated in a usual manner to afford *N*-hydroxyacylcaffeidine (**3**). However, **3** did not undergo dehydration-cyclization in the presence of ethanolic hydrogen chloride as a catalyst, as employed in our previous work.[8]

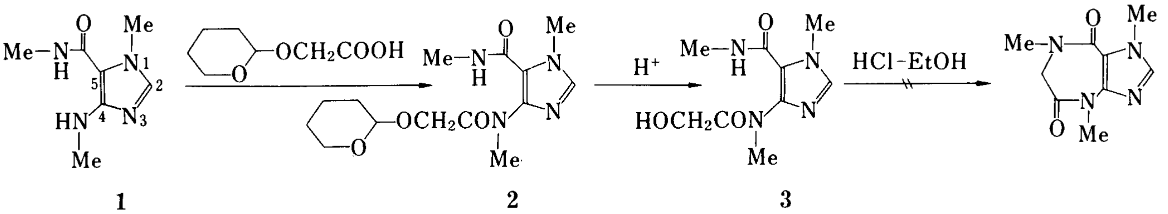
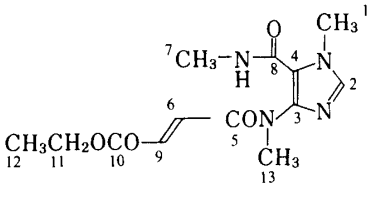


Chart 1

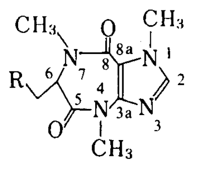
Table I. Reaction of **4a** to Give **5a**

Method	Solvent	Catalyst	Reaction time (refluxing time)	Yield (%)
a	EtOH	NaH (catalytic amount)	45 min	70
b	H_2O	—	2 h	90
c	EtOH	—	24 h	82
d	Pyridine	—	24 h	83
e	C_6H_6	—	8 h	0
f	AcOPr	—	8 h	0
g	EtOH.	AcOH (1.1 molar ratio against **4a**)	8 h	0

Table II. ^{13}C-NMR Spectral Data for **4a**, **5a** and **14a**



4a



R

5a: COOEt

14a: H

4a				**5a**				**14a**		
Position	δ	$^1J_{CH}$	$^{>1}J_{CH}$	Position	δ	$^1J_{CH}$	$^{>1}J_{CH}$	δ	$^1J_{CH}$	$^{>1}J_{CH}$
7	26.2 (dq)	139	4	N_7-CH_3	28.8 (q)	141		28.8 (q)	141	
13	35.2 (q)	143		N_4-CH_3	31.8 (q)	141		31.8 (q)	140	
1	36.5 (q)	142		N_1-CH_3	33.9 (q)	142		33.9 (q)	141	
9	131.8 (dd)	168	4	C_6-C	32.8 (td)	131	3	13.3 (dq)	128	4
6	133.3 (dd)	166	4	6	53.9 (d)	136		52.3 (td)	133	5
4	119.5 (s)			8a	114.1 (s)			114.2 (s)		
2	138.6 (qd)	211	4	2	139.4 (qd)	209	4	139.1 (qd)	209	4
3	141.1 (d)		12	3a	145.0 (d)		12	144.8 (d)		12
8	159.5 (m)			8	161.1 (m)			161.0 (m)		
5	165.2 (m)			5	166.3 (m)			167.4 (m)		
10	165.8 (m)			CO	169.8 (m)					
12	14.1 (tq)	128	3	CH_3	14.1 (tg)	127	3			
11	61.1 (qt)	147	5	OCH_2	61.2 (qt)	149	5			

Heindel and Lemke reported the synthesis, though in a low yield, of a benzo[1,4]diazepine derivative by intramolecular cyclization in the presence of MeONa between a carbamoyl group and an ester group of the adduct obtained by the reaction between 2-aminobenzamide and dimethylacetylene dicarboxylate (DMAD).[10] For the synthesis of imidazodiazepine derivatives, the reaction using caffeidine instead of the aminobenzamide did not give the desired compound, but a red–brown tarry mixture. This result suggested that **1** is highly reactive with dienophiles.

Since **1** was stabilized by acylation of the 4-amino group, it appeared that the desired compound might be produced from **1** which had been acylated at the 4-amino group by the

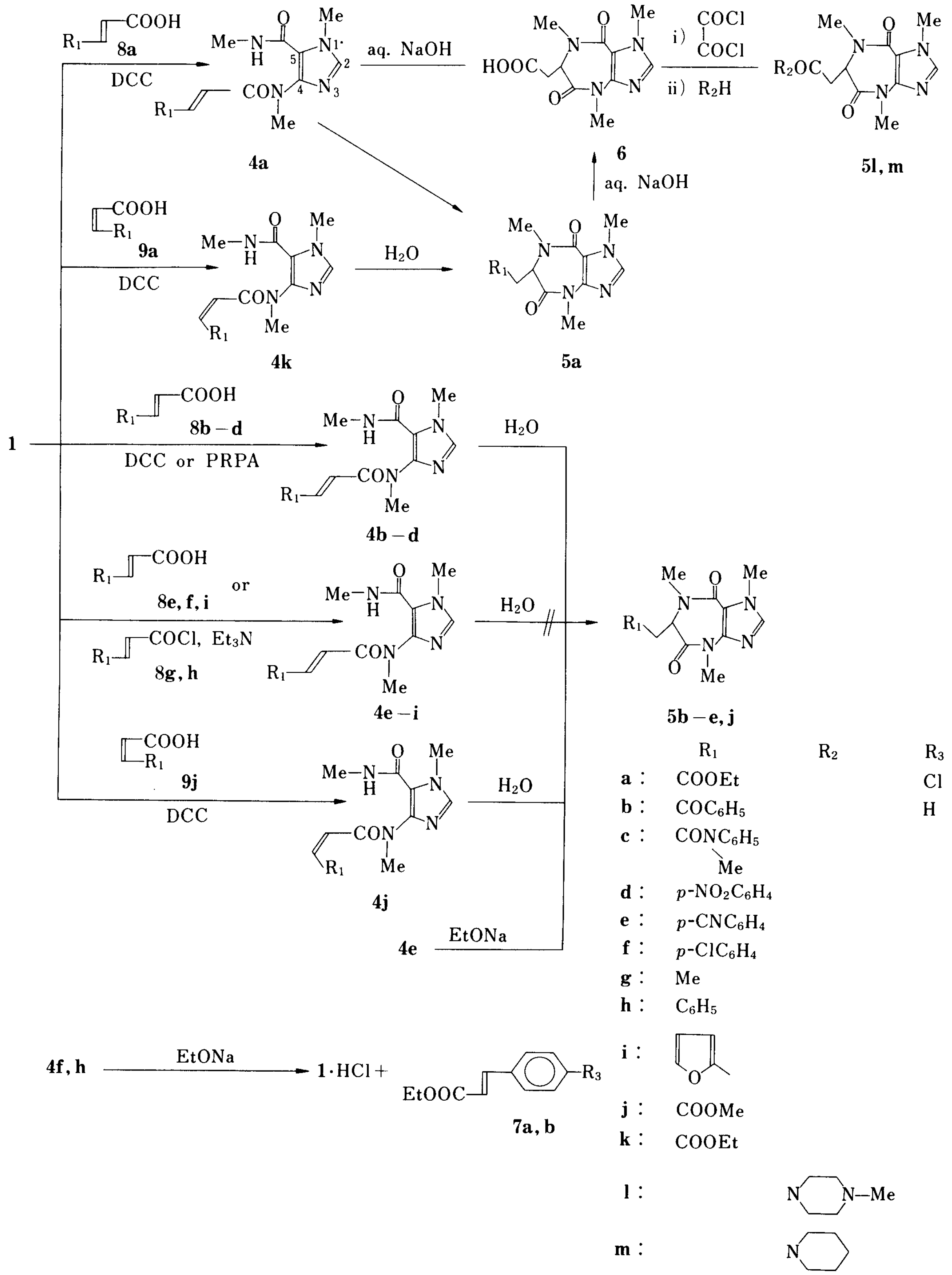


Chart 2

dienophile group rather than by the reaction between **1** and DMAD. Thus, fumaric acid monoethyl ester (**8a**) was condensed with **1** in the presence of dicyclohexylcarbodiimide (DCC) to introduce an ethyl fumaroyl group onto the 4-amino group of **1**, resulting in the formation of **4a** (Chart 2). Compound **4a** was refluxed in abs. EtOH for 45 min in the presence of a catalytic amount of EtONa to give **5a** as colorless needles (mp 109—110 °C) in 70% yield. From the elemental analysis and mass spectrum (MS), it was considered that **5a** had the same molecular formula as **4a**, $C_{13}H_{18}N_4O_4$. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5a**, signals due to an olefin proton (δ 6.83, 2H, s) and an amido proton (δ 6.24, 1H, br s) observed in **4a** had disappeared and new ABX-type signals appeared at δ 2.85 (1H, dd, $J=6$, 18 Hz), 3.07 (1H, dd, $J=9$, 18 Hz) and 4.62 (1H, dd, $J=6$, 9 Hz). In the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum, two signals due to olefin carbon atoms (δ 131.8 and 133.3) of **4a** had disappeared and two new signals due to aliphatic carbon atoms appeared at δ 32.8 and 53.9. In the infrared (IR) spectrum, an absorption band corresponding to the amido NH of **4a** was no longer seen, while that of an ester was shifted to a high-frequency region. Furthermore, the ^{1}H- and ^{13}C-NMR spectra of **14a**, described later (Chart 4), and those of **5a** were very similar to each other. These data indicated that the structure of **5a** was ethyl 1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine-6-acetate (Tables II, V and VI).

It was suggested that the intramolecular cyclization of **4a** to **5a** proceeded between the α-position of the 4-carbonylamino group and the carbamoyl group of **4a**. This type of reaction has not been reported so far to our knowledge and was of much interest to us. Some examinations of the effects of solvents and catalysts to elucidate the nature of this reaction revealed that the reaction proceeded in protic and basic solvents and that polar solvents and alkali promoted the reaction effectively (Table I). Reaction of an aq. solution of **4a** with an equivalent amount of NaOH at room temperature was completed within 2 h to give **6** as colorless prisms (mp 259—260 °C (dec.)) in 71% yield. Compound **6** was also obtained by the treatment of **5a** with alkaline aq. solution. As the ^{1}H-NMR spectrum of **6** showed a signal due to COOH at δ 12.5 (1H, br s) and as the signal pattern was remarkably similar to that of **5a**, it was suggested that **6** was the product of hydrolysis of the ester group of **5a**. Compound **6** was converted by treatment with oxalyl chloride into the acyl chloride, followed by the reaction with *N*-methylpiperazine and piperidine to provide the corresponding amido compounds, **5l** and **5m**, respectively.

To extend this diazepine-producing reaction, we tried intramolecular cyclization of 4-(*N*-α,β-unsaturated acyl)caffeidines, caffeidine derivatives having a dienophile group, which were prepared from **1** with various α,β-unsaturated carboxylic acid derivatives such as the *trans* forms of β-benzoylacrylic acid (**8b**), *N*-methyl-*N*-phenylfumaramic acid (**8c**), *p*-nitro- (**8d**), *p*-cyano- (**8e**), *p*-chloro- (**8f**) cinnamic acids, crotonoyl chloride (**8g**), cinamoyl chloride (**8h**) and β-furfurylacrylic acid (**8f**), and the *cis* forms of maleic monoethyl (**9a**) and methyl (**9j**) esters (Chart 2). Condensation of these carboxylic acids with **1** was carried out in the presence of

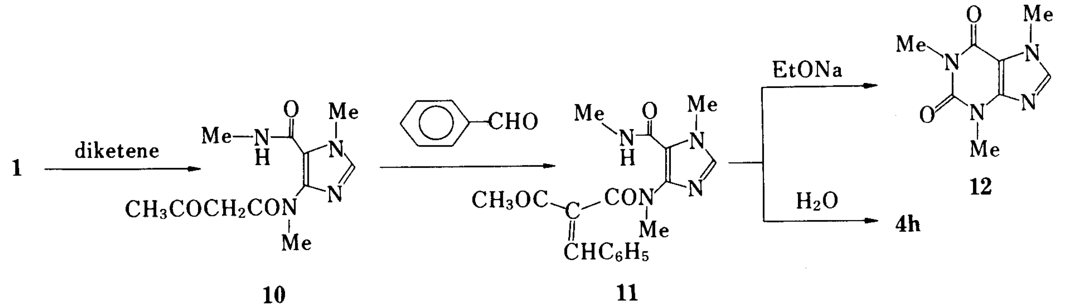
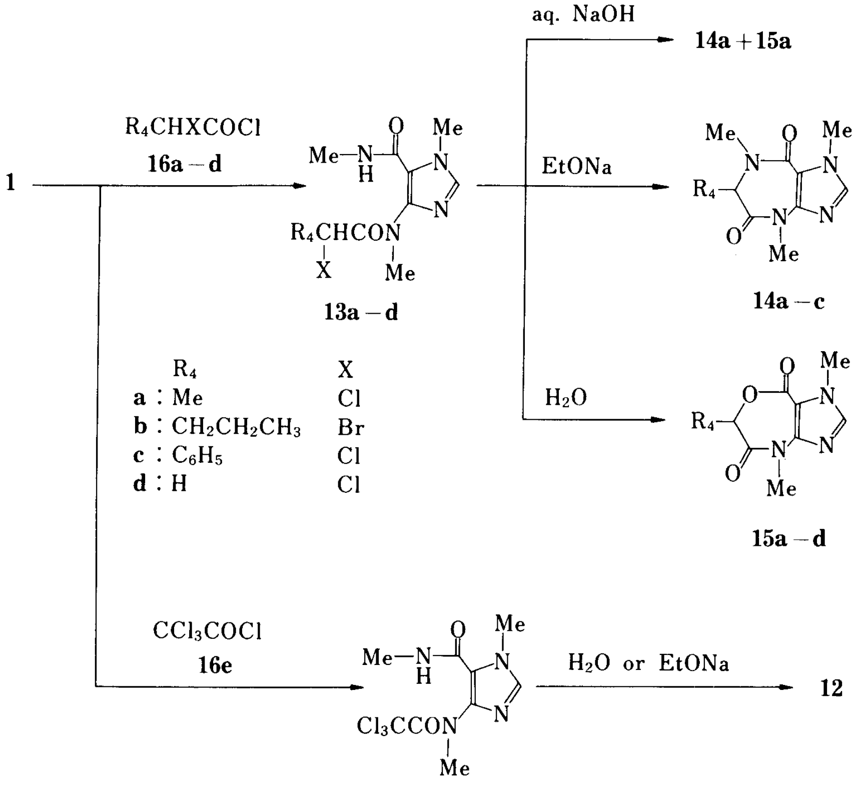


Chart 3



	R$_4$	X
a	Me	Cl
b	CH$_2$CH$_2$CH$_3$	Br
c	C$_6$H$_5$	Cl
d	H	Cl

Chart 4

DCC, PRPA or Et$_3$N. PRPA was used for **8d**, **8e** and **8f** (which are scarcely soluble in the solvent used in the DCC method), Et$_3$N for acyl chlorides, **8g** and **8h**, and DCC for the others. Refluxing of **4b** or **4c** in water for 1 or 2 h afforded the expected imidazodiazepine derivatives, **5b** or **5c**, in yields of 90% and 76%, respectively. Compound **4d** required *ca.* 48 h for completion of the reaction and the yield of **5d** was excellent (80%). Compounds **4j** and **4k** both having a *cis*-type dienophile group required 2 h for completion of the reaction and gave **5j** and **5a**, respectively, though their yields were as low as *ca.* 50%. This low yield was due to the formation of a structurally unknown by-product which appeared near the starting point in thin layer chromatography (TLC) on a silica gel plate. Similar reactions were attempted on **4e**—**i**, but cyclization was unsuccessful. Thus, we examined the reactions of **4e**, **f**, **h** in the presence of a catalytic amount of EtONa under reflux in abs. EtOH. Of these compounds, only **4e** reacted, giving **5e** in 81% yield. On the other hand, **4f** and **4h** gave *p*-chlorocinnamic acid ethyl ester (**7a**) (50%) and **1** (65%), and cinnamic acid ethyl ester (**7b**) (85%) and **1** (79%), respectively.

Separately, **1** was reacted with diketone to obtain the acetoacetyl compound (**10**), which underwent Knoevenagel condensation with benzaldehyde to form **11**, having an acetyl group at the α-position to the 4-carbonylamino group. Then **11** was treated in the same manner as **4** (Chart 3). Refluxing of an aq. solution of **11** gave **4h** in a poor yield of 7% and the reaction with EtONa afforded caffeine (**12**) in a yield as high as 81%. However, these treatments did not lead to the formation of imidazodiazepines.

To establish the structure of the synthesized imidazodiazepine derivatives by spectral comparison, 1,4,6,7-tetramethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine (**14a**) was synthesized in a manner similar to that reported by Bogatskii and Ivanov$^{6)}$ (Chart 4). The reaction of **1** with α-chloropropionyl chloride (**16a**) in the presence of Et$_3$N furnished

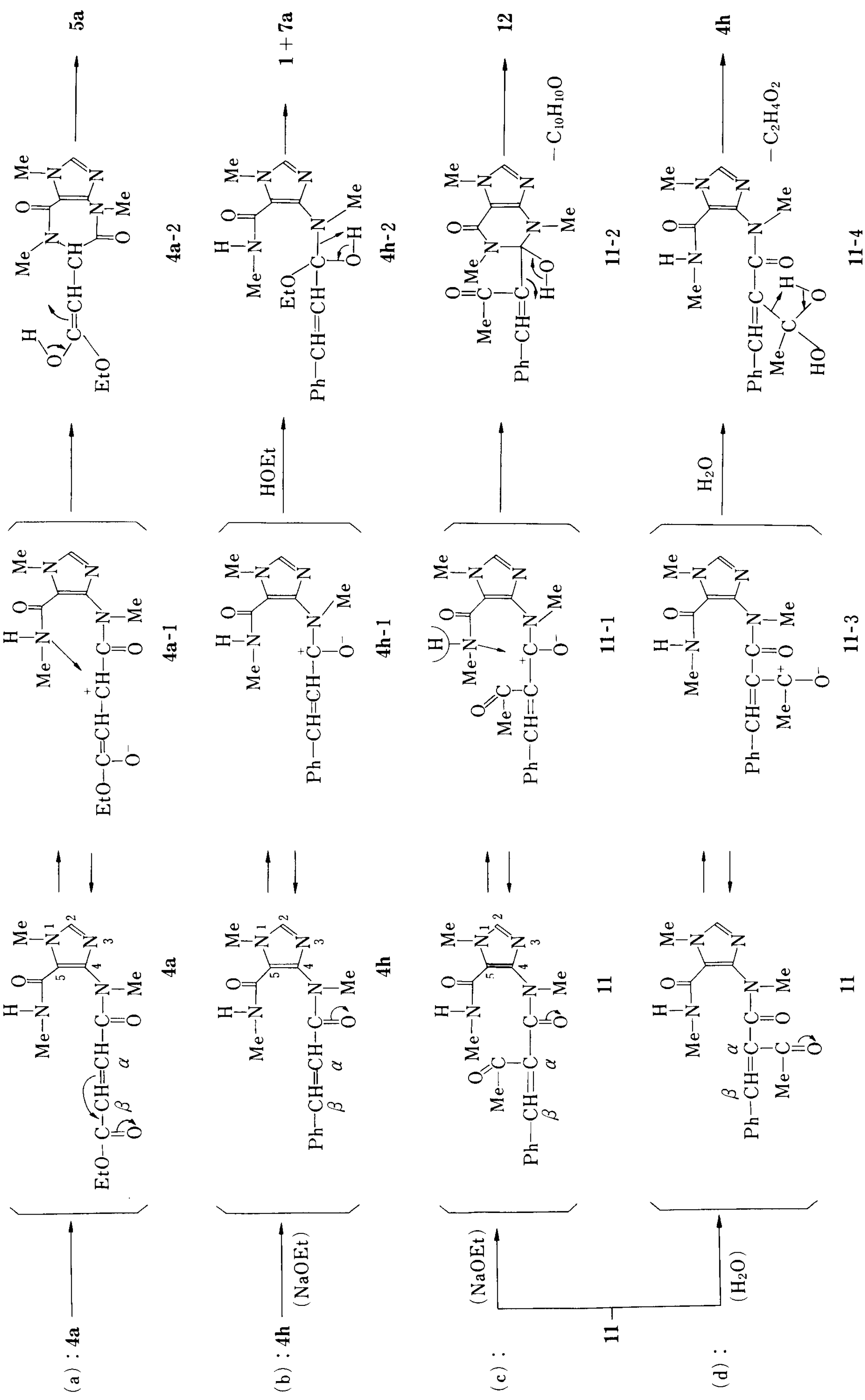

(a) : 4a
4a
4a-1
4a-2
5a
(b) : 4h
(NaOEt)
4h
4h-1
HOEt
4h-2
1 + 7a
(c) :
(NaOEt)
11
11-1
11-2
$-C_{10}H_{10}O$
12
(d) :
(H$_2$O)
11
11-3
H$_2$O
11-4
$-C_2H_4O_2$
4h

Chart 5

N-(α-chloropropionyl)caffeidine (**13a**). When an aq. solution of **13a** and an equivalent amount of NaOH was refluxed for 1.5 h, the desired compound (**14a**) and colorless needles (**15a**) with mp 204—208 °C were obtained in yields of 82% and 11%, respectively. Compound **15a** displayed no signal corresponding to CH_3NH of the carbamoyl group of **13a** in the ^1H-NMR spectrum, and a molecular ion (M^+) peak appeared at *m/z* 209 in MS. The IR spectrum of **15a** showed a strong absorption at $1210\,cm^{-1}$. These spectral data established the structure of **15a** as the novel compound, 1,4,6-trimethyl-5,8-dioxo-1,4,5,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]oxazepine (Tables X and XI). Compound **15a** was obtained by refluxing an aq. solution of **13a** (76% yield). Compound **15a** was presumed to be formed by the substitution of the hydroxy group of the carboxy moiety group with a chlorine atom which was produced by hydrolysis of the carbamoyl group of **13a**. This assumption was supported by the synthesis of 1-phenyl-4,1-benzoxazepine-2,5(1*H*,3*H*)-dione from *N*-chloroacetyl-*N*-phenylantranilic acid reported by Iacobelli *et al.*[11] and the fact that refluxing of **3** in H_2O resulted in recovery of **3** unchanged. Also, **13d** and **13b, c** obtained from **1** by treatment with α-halogenoacyl chloride (**16b**—**c**) under the same conditions as used for **13a** were refluxed in H_2O for 2—3 h to obtain the corresponding imidazo[4,5-*e*][1,4]oxazepine derivatives, **15b**—**d** in yields of 87% (**15b**), 38% (**15c**) and 79% (**15d**), respectively. The poor yield of **15c** was considered to be due to the low reactivity of Cl at the benzyl position. On the other hand, treatment of **13a**—**c** with EtONa in abs. EtOH afforded a single product in each case (**14a**—**c**). However, treatment of **13e** under the same conditions as used for **13a**—**d** led to the formation of caffeine (**12**) in high yield, presumably because of the facile elimination of the trichloromethyl group of **13e**.

The reaction mechanism from the caffeidine derivative having a dienophile group (**4**) to the imidazodiazepine derivatives (**5**, **6**) was deduced from the structures of **4** and their reaction conditions as shown in Chart 5(a): in **4a**—**e**, **j**, **k**, an electron-withdrawing group at the β-position of the 4-carbonylamino group polarized the α carbon to δ^+ as in the case of **4a**-1 and

TABLE III. Vascular Relaxing Responses to Imidazo[4,5-*e*][1,4]diazepines (**5**, **6**, **14**) and Imidazo[4,5-*e*][1,4]oxazepines (**15**) of Mesenteric Arterial Strips Isolated from Spontaneously Hypertensive Rats (SHR)

Compound[a]	% relaxation of strips[b]	
	10^{-5} M norepinephrine-contracted strips	30 mM K^+-contracted strips
5a	2.0	2.6
5d	19.3	12.6
5l	3.3	0.4
5m	2.9	4.0
6	1.6	0
14a	6.4	10.1
14c	10.0	5.6
15b	36.0	21.6
15c	19.1	11.2
15d	5.5	0.7
Prazosin (30 nM)	75.0 ± 4.2	0.4 ± 0.2
Phentolamine (1 μM)	78.3 ± 3.9	0.4 ± 0.2
Diltiazem (1 μM)	70.6 ± 3.8	96.2 ± 3.9
Verapamil (0.1 μM)	62.4 ± 3.1	84.9 ± 4.1

a) The concentration of compounds **5a** to **15d** was 100 μM, and the concentrations of other drugs were as shown in parentheses. *b*) Data are expressed as mean values of two strips for compounds **5a** to **15d** and mean ± S.E. of six strips for other drugs.

caused addition of the carbamoyl group to the α carbon (Michael addition) (**4a**-2) to form **5**. In this case, alkali might enhance the nucleophilicity of the carbamoyl group and the use of a polar solvent might facilitate the production of intermediates (**4a**-1). The proposed reaction mechanism for the formation of **1** and **7a**, **b** from **4f**—**h** is shown in Chart 5(b): in **4f**—**h** (having no electron-withdrawing group at the β-position of the 4-carbonylamino group), 1,2-addition of the solvent molecule *via* an ethoxide anion (**4h**-1) to a carbonyl group took place (**4h**-2) to form **1** and **7**. The 1,2-addition of the carbamoyl group or H_2O to a carbonyl group was also considered to occur in the reaction of **11** having an electron-withdrawing acetyl group at the α-position to the 4-carbonylamino group. Polarization of the α carbon did not occur in this case (Chart 5(c), 5(d)).

As mentioned above, the imidazo[4,5-*e*][1,4]diazepine derivative could be obtained from the *N*-(α,β-unsaturated acyl)caffeidine derivative having an electron-withdrawing group at the β-position by the intramolecular Michael addition of the carbamoyl group to the α,β-unsaturated acyl group. It is reasonable to presume that this synthetic method will be applicable for the formation of other condensed diazepine derivatives.

The newly synthesized imidazodiazepine derivatives reported here are cyclic homologues of caffeine which are ring-enlarged by one carbon unit between the 1- and 2-positions of caffeine. On the basis of this structural similarity to caffeine, the derivatives were investigated for vascular relaxing activity, one of the known physiological activities of xanthine derivatives, in mesenteric arterial strips of spontaneously hypertensive rats. In addition, imidazooxazepine derivatives were studied for the same activity. The results are summarized in Table III. Among the test compounds, **5d**, **15b**, and **15c** showed arterial relaxing activities, though the activities were low.

TABLE IV. Physicochemical Data for 1-Methyl-5-methylaminocarbonyl-4-[*N*-(α,β-unsaturated acyl)-*N*-methylamino]imidazole Derivatives (**4**)

Compd. No.	Formula	Analysis (%) Calcd (Found)			mp (°C)	Appearance	Yield (%)	Recryst. solvent
		C	H	N				
4a	$C_{13}H_{18}N_4O_4$	53.05 (52.99	6.16 6.15	19.04 19.19)	150—151	Colorless needles	79	Et_2O–EtOH
4b	$C_{17}H_{18}N_4O_3$	62.57 (62.60	5.56 5.62	17.17 17.00)	147—148	Colorless needles	48	Et_2O–AcOEt
4c	$C_{18}H_{21}N_5O_3$	60.83 (60.53	5.96 5.95	19.71 19.59)	207—208	Colorless needles	58	Et_2O–EtOH
4d	$C_{16}H_{17}N_5O_4$	55.97 (55.77	4.99 5.01	20.39 20.15)	220—222 (dec.)	Yellow needles	55	EtOH
4e	$C_{17}H_{17}N_5O_2$	63.15 (63.33	5.30 5.23	21.66 21.41)	195—196	Colorless needles	63	EtOH
4f	$C_{16}H_{17}ClN_4O_2$	57.75 (57.56	5.15 5.16	16.84 16.68)	206—207	Colorless needles	47	EtOH
4g	$C_{11}H_{16}N_4O_2$	55.92 (55.70	6.83 6.82	23.71 23.55)	145—146	Colorless needles	56	Et_2O–EtOH
4h	$C_{16}H_{18}N_4O_2$	64.41 (64.25	6.08 6.20	18.78 18.48)	147—148	Colorless needles	53	Et_2O–EtOH
4i	$C_{14}H_{16}N_4O_3$	58.32 (58.09	5.59 5.60	19.43 19.24)	172—173	Colorless needles	30	Et_2O–EtOH
4j	$C_{12}H_{16}N_4O_4$	51.42 (51.64	5.75 5.73	19.99 19.79)	118—119	Colorless needles	18	Et_2O–EtOH
4k	$C_{13}H_{18}N_4O_4$	53.05 (52.93	6.16 6.20	19.04 19.01)	110—111	Colorless needles	15	Et_2O–EtOH

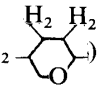
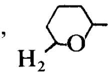
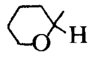
Table V. Spectral Data for 1-Methyl-5-methylaminocarbonyl-4-[*N*-(α,β-unsaturated acyl)-*N*-methylamino]imidazole Derivatives (**4**)

Compd. No.	MS (m/z) M^+	IR (cm^{-1})			^{1}H-NMR (δ)						
		NH	CO	Others	N_1-CH_3 (s)	C_2-H (s)	C_5-Substituent		C_4-Substituent		
							N-CH_3 (d)	NH (br s)	N-CH_3 (s)	Olefin-H	Others
4a	294	3420	1720 1660 1640	1310 (COC)	3.97	7.42	2.92 (J=6 Hz)	6.24	3.31	6.83 (2H, s)	1.27 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 4.19 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$)
4b	326	3410	1650		3.96	7.41	2.92 (J=5 Hz)	6.18	3.48	6.90 (1H, d, J=15 Hz) 7.97 (1H, d, J=15 Hz)	7.32—7.70 (3H, m, Ph-H_3, H_4, H_5), 7.93—8.01 (2H, m, Ph-H_2, H_6)
4c	355	3390	1650		3.96	7.36	2.84 (J=5 Hz)	6.13	3.32	6.82 (2H, s)	3.22 (3H, s, CH_3N), 7.04—7.52 (5H, m, Ph)
4d	343	3380	1650	1510 1340 (NO_2)	3.99	7.46	2.91 (J=5 Hz)	6.08	3.38	6.50 (1H, d, J=16 Hz) 7.76 (1H, d, J=16 Hz)	7.51 (2H, d, J=9 Hz, Ph-H_2, H_6), 8.17 (2H, d, J=9 Hz, Ph-H_3, H_5)
4e[a)]	323	3380	1650	2220 (CN)	3.77	7.71	2.67 (J=5 Hz)	—	3.20	6.59 (1H, d, J=16 Hz) 7.53 (1H, d, J=16 Hz)	7.65 (2H, d, J=8 Hz, Ph-H_2, H_6), 7.82 (2H, d, J=8 Hz, Ph-H_3, H_5)
4f	332	3400	1660, 1650		3.98	7.45	2.90 (J=5 Hz)	6.24	3.36	6.32 (1H, d, J=15 Hz) 7.69 (1H, d, J=15 Hz)	7.30 (4H, s, Ph-H_2, H_3, H_5, H_6)
4g	236	3400	1660, 1640		3.96	7.42	2.90 (J=5 Hz)	6.20	3.27	5.10; 5.80[b)] (1H, d, J=15 Hz), 7.00 (1H, qd, J=7, 15 Hz)	1.81 (3H, d, J=7 Hz, CH_3)
4h	298	3350	1660		3.98	7.45	2.90 (J=5 Hz)	6.28	3.36	6.36 (1H, d, J=16 Hz) 7.75 (1H, d, J=16 Hz)	7.34 (5H, s, Ph)
4i	288	3360	1660		3.97	7.41	2.90 (J=5 Hz)	6.35	3.34	6.26 (1H, d, J=13 Hz) 7.50 (1H, d, J=13 Hz)	6.41 (1H, dd, J=2, 3 Hz, furan-H_4) 6.55 (1H, d, J=2 Hz, furan-H_3) 7.42 (1H, d, J=3 Hz, furan-H_5)
4j	280	3390	1710, 1660	1230, 1160 (COC)	3.88	7.30	2.95 (J=5 Hz)	7.37	3.27 3.30[b)]	5.79, 6.15[b)] (1H, d, J=12 Hz), 6.72 (1H, d, J=12 Hz)	3.73, 3.80[b)] (3H, s, CH_3O)
4k	294	3400	1710, 1660, 1650	1220, 1160 (COC)	3.88 3.91[b)]	7.30	2.94 (J=5 Hz)	7.39	3.27 3.30[b)]	5.78, 6.15[b)] (1H, d, J=12 Hz) 6.71 (1H, d, J=12 Hz)	1.27, 1.32[b)] (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 4.17, 4.25[b)] (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$)

a) ^{1}H-NMR spectrum was measured in DMSO-d_6. *b*) These signals are twin peaks arising from restricted internal rotation of the type observed elsewhere for carbonyl-nitrogen bonds.

Experimental

All melting points are uncorrected. IR spectrophotometry and MS were performed with a Hitachi 285 spectrophotometer and JEOL JMS-DX300 spectrometer, respectively. ^{1}H- and ^{13}C-NMR spectra (^{1}H-NMR at 89.55 MHz and ^{13}C-NMR at 22.50 MHz) were recorded with a JEOL JMN-FX90Q spectrometer using tetramethylsilane as the internal standard. Unless otherwise stated, $CDCl_3$ was used as the solvent. Chemical shifts are given in δ values (ppm) and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Column chromatography was done on silica gel (Wakogel C-200) unless otherwise stated. All organic extracts were dried over anhydrous Na_2SO_4.

1-Methyl-5-methylaminocarbonyl-4-[*N*-(2-tetrahydropyranyloxyacetyl)-*N*-methylamino]imidazole (2)——A mixture of glycolic acid (0.2 g), 3,4-dihydro-2*H*-pyran (0.28 g) and 1 drop of EtOH–HCl was stirred at room temperature for 2 h. Dry CH_2Cl_2 (15 ml), Et_3N (1 ml) and **1** (0.5 g) were added to the mixture and 25% (w/v) PRPA (3 g) was added dropwise with stirring at −5—0 °C. Subsequently the reaction mixture was stirred at room temperature for *ca.* 16 h, washed with water, and evaporated *in vacuo* to afford a residue, which was purified by chromatography using $CHCl_3$–EtOH (20 : 1) as the eluent to give 0.44 g (48%) of **2** as colorless needles (from Et_2O), mp 153—154 °C. *Anal.* Calcd for $C_{14}H_{22}N_4O_4$: C, 54.18; H, 7.14; N, 18.05. Found: C, 54.14; H, 7.20; N, 17.76. IR ν_{max}^{KBr} cm^{-1}: 3380 (NHCO), 1690, 1650 (CON), 1130 (COC). ^{1}H-NMR δ: 1.2—2.0 (6H, m, H_2 ), 2.92 (3H, d, J=5 Hz, C$\underline{H}_3$NHCO), 3.20 (3H, s, CH_3N), 3.3—3.8 (2H, m, ), 3.91 (3H, s, N_1-CH_3), 4.13 (2H, s, OCH_2CO), 4.52 (1H, m, ), 6.75 (1H, br s, $CH_3N\underline{H}CO$), 7.37 (1H, s, C_2-H). MS *m*/*z*: 310 (M^+).

4-(*N*-Hydroxyacetyl-*N*-methylamino)-1-methyl-5-methylaminocarbonylimidazole (3)——A solution of **2** (0.3 g)

Table VI. Physicochemical Data for 1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine Derivatives (**5**, **6**, **14**)

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C)	Appearance	Yield (%)	Recryst. solvent
5a	$C_{13}H_{18}N_4O_4$	53.05 (52.96	6.16 6.15	19.04 19.07)	109—110	Colorless needles	90$^{a)}$	Et_2O–petr. ether
5b	$C_{17}H_{18}N_4O_3$	62.57 (62.42	5.56 5.56	17.17 16.95)	238—239	Colorless needles	90	Et_2O–$CHCl_3$
5c	$C_{18}H_{21}N_5O_3$	60.83 (60.67	5.96 5.95	19.71 19.68)	187—188	Colorless needles	76	Et_2O–EtOH
5d	$C_{16}H_{17}N_5O_4$	55.97 (55.88	4.99 5.04	20.39 20.22)	177—178	Yellow needles	80	EtOH
5e	$C_{17}H_{17}N_5O_2$	63.15 (63.37	5.30 5.23	21.66 21.55)	184—185	Colorless needles	81	EtOH
5j	$C_{12}H_{16}N_4O_4$	51.42 (51.44	5.75 5.74	19.99 20.17)	135—136	Colorless needles	50	Et_2O–petr. ether
5l	$C_{16}H_{24}N_6O_3$		348.1909$^{b)}$ (348.1926)		183—184	Colorless needles	58	Et_2O–EtOH
5m	$C_{16}H_{23}N_5O_3$		333.1799$^{b)}$ (333.1826)		178—179	Colorless needles	56	EtOH
6	$C_{11}H_{14}N_4O_4$	49.62 (49.68	5.30 5.27	21.04 21.03)	259—260 (dec.)	Colorless needles	71	H_2O
14a	$C_{10}H_{14}N_4O_2$	54.04 (53.92	6.35 6.42	25.21 25.23)	116—117	Colorless prisms	84	Et_2O
14b	$C_{12}H_{18}N_4O_2$		250.1429$^{b)}$ (250.1440)			Colorless oil	71	
14c	$C_{15}H_{16}N_4O_2$	63.36 (63.23	5.67 5.62	19.71 19.69)	174—175	Colorless prisms	70	Et_2O–$CHCl_3$

a) See Table I. *b*) Determined by high-resolution mass spectrometry. Upper figure, Calcd for M^+; lower figure found.

TABLE VII. Spectral Data for 1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine Derivatives (**5**, **6**, **14**)

Compd.	MS (m/z)	IR (cm^{-1})		^{1}H-NMR (δ)					
No.	M$^+$	CO	Others	N_1-CH_3 (s)	C_2-H (s)	N_4-CH_3 (s)	C_6-H	N_7-CH_3 (s)	C_6-Substituent
5a	294	1740, 1690, 1650	1240 (COC)	3.92	7.44	3.46	4.62 (dd, $J=6$, 9 Hz)	2.99	1.26 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 2.84 (1H, dd, $J=6$, 18 Hz, C_6-CH), 3.07 (1H, dd, $J=9$, 18 Hz, C_6-CH), 4.16 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$)
5b	326	1660, 1640		3.93	7.45	3.48	4.96 (dd, $J=5$, 9 Hz)	3.04	3.45 (1H, dd, $J=5$, 21 Hz, C_6-CH), 4.06 (1H, dd, $J=9$, 21 Hz, C_6-CH), 7.3—7.7 (3H, m, Ph-H_3, H_4, H_5), 7.9—8.1 (2H, m, Ph-H_2, H_6)
5c	355	1680, 1650		3.89	7.35	3.44	4.80 (dd, $J=6$, 9 Hz)	2.78	2.50 (1H, dd, $J=6$, 16 Hz, C_6-CH), 3.16 (1H, dd, $J=9$, 16 Hz, C_6-CH), 3.26 (3H, s, CH_3), 7.2—7.6 (5H, m, Ph)
5d$^{a)}$	343	1680, 1640	1510, 1340 (NO_2)	3.83	7.67	3.31	4.55 (t, $J=9$ Hz)	2.89	3.16 (1H, d, $J=9$ Hz, C_6-CH), 3.18 (1H, d, $J=9$ Hz, C_6-CH), 7.42 (2H, td, $J=2$, 8 Hz, Ph-H_2, H_6), 8.05 (2H, td, $J=2$, 8 Hz, Ph-H_3, H_5)
5e$^{b)}$	323	1640	2220 (CN)	3.83	7.70	3.30	4.53 (t, $J=8$ Hz)	2.87	3.19 (1H, d, $J=8$ Hz, C_6-CH), 3.22 (1H, d, $J=8$ Hz, C_6-CH), 7.37 (2H, d, $J=8$ Hz, Ph-H_2, H_6), 7.65 (2H, d, $J=8$ Hz, Ph-H_3, H_5)
5j	280	1750, 1690, 1630	1240 (COC)	3.91	7.44	3.46	4.63 (dd, $J=5$, 9 Hz)	2.99	2.86 (1H, dd, $J=7$, 18 Hz, C_6-$C\underline{H}_2$), 3.10 (1H, dd, $J=9$, 18 Hz, C_6-$C\underline{H}_2$), 3.71 (3H, s, OCH_3)
5l	348	1680, 1630		3.90	7.42	3.46	4.81 (dd, $J=5$, 9 Hz)	3.10	2.31 (3H, s, CH_3), 2.42 (4H, m, piperazine-H_3, H_5), 2.76 (1H, dd, $J=5$, 18 Hz, C_6-CH), 3.39 (1H, dd, $J=9$, 18 Hz, C_6-CH), 3.62 (4H, m, piperazine-H_2, H_6)
5m	333	1680, 1650, 1630		3.90	7.42	3.46	4.81 (dd, $J=5$, 9 Hz)	2.99	1.4—1.9 (6H, m, piperidine-H_3, H_4, H_5), 2.75 (1H, dd, $J=5$, 16 Hz, C_6-CH), 3.42 (1H, dd, $J=9$, 16 Hz, C_6-CH), 3.58 (4H, m, piperadine-H_2, H_6)
6$^{b)}$	266	1730, 1680, 1610	3250— 2700 (COOH)	3.81	7.85	3.31	4.47 (dd, $J=6$, 10 Hz)	2.84	2.89 (1H, d, $J=6$ Hz, C_6-CH), 3.07 (1H, d, $J=10$ Hz, C_6-CH), 12.49 (1H, br s, COOH)
14a	222	1670, 1640		3.92	7.43	3.46	4.24 (q, $J=7$ Hz)	3.02	1.54 (3H, d, $J=7$ Hz, C_6-CH_3)
14b$^{c)}$	250	1680, 1630		3.81	7.67	3.32	4.08 (t, $J=7$ Hz)	2.93	0.86 (3H, t, $J=7$ Hz, CH_3), 1.08—1.48 (2H, m, CH_2), 1.60—1.88 (2H, m, C_6-CH_2)
14c	284	1670, 1640		3.68	7.23	3.54	5.46 (s)	3.12	6.90—7.24 (5H, m, Ph)

a) ^{1}H-NMR spectrum was measured in DMSO-d_6 at 150 °C. *b*) ^{1}H-NMR spectra were measured in DMSO-d_6 at 120 °C. *c*) IR spectrum was measured in $CHCl_3$.

and 1 drop of conc. HCl in H_2O–EtOH (3:1) (10 ml) was stirred at 60 °C for 1 h, then neutralized with aq. $NaHCO_3$. The mixture was evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH (20:3) as the eluent to give 0.18 g (82%) of **3** as colorless needles (from Et_2O–EtOH), mp 185—187 °C. *Anal.* Calcd for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.76. Found: C, 47.52; H, 6.30; N, 24.53. IR ν_{max}^{KBr} cm^{-1}: 3360 (NHCO), 3200 (OH), 1700, 1640 (CON), 1070 (COH). ^{1}H-NMR (DMSO-d_6) δ: 2.74 (3H, d, J = 8 Hz, $C\underline{H}_3NHCO$), 3.06 (3H, s, CH_3N), 3.73 (3H, s, N_1-CH_3), 3.78 (2H, d, J = 6 Hz, $C\underline{H}_2OH$), 4.63 (1H, t, J = 6 Hz, $CH_2O\underline{H}$), 7.68 (1H, s, C_2-H). MS *m/z*: 226 (M^+).

1-Methyl-5-methylaminocarbonyl-4-[*N*-(α,β-unsaturated acyl)-*N*-methylamino]imidazoles (4)——i) A solution of DCC (3 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of a carboxylic acid derivative (**8a**—**c**, **i**, **9a**, **j**) (3.3 mmol) in CH_2Cl_2 (15 ml) with stirring at −5—0 °C. Fifteen minutes later, a solution of **1** (3 mmol) in CH_2Cl_2 (6 ml) was added dropwise, and subsequently the mixture was stirred at room temperature for 2 h. Insoluble material was removed by filtration. The filtrate was evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH as the eluent to afford 4-[*N*-[(*E*)-3-ethoxycarbonylpropenoyl]-*N*-methylamino]-(**4a**), 4-[*N*-[(*E*)-3-benzoylpropenoyl]-*N*-methylamino]-(**4b**), 4-[*N*-[(*E*)-3-(*N*-methylanilinocarbonyl)propenoyl]-*N*-methylamino]-(**4c**), 4-[*N*-[(*E*)-3-(2-furyl)propenoyl]-*N*-methylamino]-(**4i**), 4-[*N*-[(*Z*)-3-ethoxycarbonylpropenoyl]-*N*-methylamino]-(**4k**), and 4-[*N*-[(*Z*)-3-methoxycarbonylpropenoyl]-*N*-methylamino]-(**4j**) 1-methyl-5-methylaminocarbonylimidazoles.

ii) A CH_2Cl_2 solution (5 g) of 25% (w/v) PRPA was added dropwise to a solution of a carboxylic acid derivative (**8d**—**f**) (3.3 mmol), **1** (3 mmol) and Et_3N (1 ml) in dry CH_2Cl_2 (15 ml) with stirring at −5—0 °C and the mixture was subsequently stirred at room temperature for 16—18 h. The reaction mixture was washed with aq. $NaHCO_3$ and H_2O and evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH as the eluent to afford 4-[*N*-(4-nitrocinnamoyl)-*N*-methylamino]- (**4d**), 4-[*N*-(4-cyanocinnamoyl)-*N*-methylamino]- (**4e**) and 4-[*N*-(4-chlorocinnamoyl)-*N*-methylamino]- (**4f**) 1-methyl-5-methylaminocarbonylimidazoles.

iii) A dry $CHCl_3$ solution (4 ml) of an acyl chloride (**8g**—**h**) (3.3 mmol) was added dropwise to a solution of **1** (3 mmol) and Et_3N (3.6 mmol) in dry $CHCl_3$ (20 ml) with stirring at −10—0 °C, and the mixture was subsequently stirred at room temperature for 1 h. The reaction mixture was washed with aq. $NaHCO_3$ and H_2O and evaporated *in vacuo* to afford a residue, which was purified by chromatography using $CHCl_3$–EtOH as the eluent to afford 4-(*N*-crotonoyl-*N*-methylamino)-(**4g**) and 4-(*N*-cinnamoyl-*N*-methylamino)-(**4h**) 1-methyl-5-methylaminocarbonylimidazoles.

Ethyl 1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine-6-acetate (5a)——Method a: A solution of NaH (catalytic amount) and **4a** (0.3 g) in abs. EtOH (10 ml) was refluxed for 45 min and evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH (25:1) as the eluent to afford 0.21 g of **5a**.

Method b: A solution of **4a** (0.2 g) in H_2O (10 ml) was refluxed for 2 h and evaporated *in vacuo* to give a residue. The residue was recrystallized from Et_2O–petr. ether to afford 0.18 g of **5a**.

Method c: A solution of **4a** (0.5 g) in abs. EtOH (15 ml) was refluxed for 24 h and evaporated *in vacuo* to give a residue. The residue was treated in the same manner as in method a to give 0.41 g of **5a** and 0.07 g (14%) of **4a**.

Method d: A solution of **4a** (0.3 g) in dry pyridine (5 ml) was refluxed for 24 h and evaporated *in vacuo* to give a residue. Treatment of the residue in the same manner as in method a afforded 0.25 g of **5a** and 0.02 g (7%) of **4a**.

1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine-6-acetic Acid (6)——i) A solution of **4a** (1.11 g) and 1 N NaOH (4 ml) in H_2O (10 ml) was stirred at room temperature for 2 h, adjusted to pH 1.6 with 1 N HCl, and concentrated *in vacuo*. The precipitate was collected by filtration and recrystallized from H_2O to give 0.71 g of **6**.

ii) A solution of **5a** (0.18 g) in 0.1 N NaOH (10 ml) was stirred at room temperature for 2 h and 0.1 N HCl (11 ml) was added. Then, the mixture was treated in the same manner as in i) to give 0.11 g (68%) of **6**.

1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine Derivatives (5a—d)——A solution of one of **4b**—**d**, **j**, **k** (2.5 mmol) in H_2O was refluxed for 1—48 h (**4b**, 1 h; **4c**, **j**, **k**, 2 h; **4d**, 48 h) and evaporated *in vacuo*. The residue insoluble in $CHCl_3$–EtOH (25:1) from **4j** and **4k** afforded structurally unknown compounds (13% and 20%, respectively). The residues soluble in $CHCl_3$–EtOH (25:1) were purified by chromatography using $CHCl_3$–EtOH as the eluent to afford 6-(2-oxo-2-phenylethyl)-1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo-[4,5-*e*][1,4]diazepine (**5b**), 1,4,7-trimethyl-(*N*-methyl-*N*-phenyl)-5,8-diozo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]-diazepine-6-acetamide (**5c**), 6-(4-nitrobenzyl)-1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]-diazepine (**5d**), methyl 1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine-6-acetate (**5j**), and **5a**.

6-(4-Cyanobenzyl)-1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine (5e)——A solution of NaH (catalytic amount) and **4e** (0.7 g) in abs. EtOH (30 ml) was refluxed for 4 h and concentrated *in vacuo*. The precipitate was collected by filtration and recrystallized from EtOH to give 0.57 g of **5e**.

1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine-6-acetamide Derivatives (5l, m)——Oxalyl chloride (0.4 ml) was added to a suspension of **6** (0.3 g) in dry $CHCl_3$ (10 ml), and the mixture was refluxed for 30 min. The reaction mixture was evaporated *in vacuo* to give a residue, which was dissolved in dry $CHCl_3$ (*ca.*

TABLE VIII. Physicochemical Data for 4-[*N*-(α-Halogenoacyl)-*N*-methylamino]-1-methyl-5-methylaminocarbonylimidazole Derivatives (**13**)

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	N	mp (°C)	Appearance	Yield (%)	Recryst. solvent
13a	$C_{10}H_{15}ClN_4O_2$	46.43 (46.47	5.84 5.86	21.66 21.80)	112—113	Colorless prisms	77	$CHCl_3$–Et_2O
13b	$C_{12}H_{19}BrN_4O_2$	43.52 (43.81	5.78 5.81	16.92 16.81)	157—159	Colorless needles	64	Petr. ether–Et_2O
13c	$C_{15}H_{17}ClN_4O_2$	56.17 (56.16	5.34 5.19	17.47 17.63)	97—98	Colorless needles	75	$CHCl_3$–Et_2O
13e	$C_9H_{11}Cl_3N_4O_2$	34.47 (34.52	3.54 3.50	17.87 17.90)	137—138 (dec.)	Colorless cubes	72	Et_2O–petr. ether

TABLE IX. Spectral Data for 4-[*N*-(α-Halogenoacyl)-*N*-methylamino]-1-methyl-5-methylaminocarbonylimidazole Derivatives (**13**)

Compd. No.	MS (*m/z*) M^+	IR (cm^{-1}) NH	CON	^{1}H-NMR (δ) N_1-CH_3 (s)	C_2-H (s)	C_5-Substituent N-CH_3 (d)	NH (br s)	C_4-Substituent N-CH_3 (s)	Others
13a	258	3430	1680, 1650	3.96	7.41	2.94 (J=5 Hz)	6.26	3.28	1.64 (3H, d, J=7 Hz, CH_3), 4.60 (1H, q, J=7 Hz, CHCl)
13b	330	3260	1660	3.96	7.42	2.95 (J=5 Hz)	6.36	3.23	0.91 (3H, t, J=7 Hz, CH_3), 1.10—1.64 (2H, m, CH_2), 1.78—2.28 (2H, m, CH_2), 4.44 (1H, t, J=7 Hz, CHBr)
13c	320	3440	1700, 1660	3.92	7.46	2.66 (J=5 Hz)	5.43	3.22	5.65 (1H, s, CHCl), 7.30 (5H, s, Ph)
13e[a]	313 (MH^+)	3250	1700, 1660	3.88	7.41	2.92 (J=5 Hz)	6.38	3.51	

[a] MS was measured by fast atom bombardment-MS.

5 ml). The $CHCl_3$ solution was added dropwise to a solution of *N*-methylpiperazine (0.5 ml) in $CHCl_3$ (10 ml) with stirring at −10—0 °C, and the mixture was subsequently stirred at room temperature for 1 h. The reaction mixture was washed with aq. $NaHCO_3$ and evaporated *in vacuo* to give a residue, which was recrystallized from EtOH–Et_2O to afford 0.25 g of 1,4,7-trimethyl-6-(*N*-methyl)piperazinocarbonylmethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo-[4,5-*e*][1,4]diazepine (**5l**).

After reaction of **6** with piperidine in the same manner as for **5l**, the reaction mixture was purified by chromatography using $CHCl_3$–EtOH (25 : 1) as the eluent to give 0.21 g of 1,4,7-trimethyl-6-piperidinocarbonylmethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine (**5m**).

Reaction of 4f, h with EtONa——A solution of NaH (catalytic amount) and **4f** (0.6 g) in abs. EtOH (15 ml) was refluxed for 2.5 h and evaporated *in vacuo* to give a residue, which was purified by chromatography using 25 : 1 and 10 : 3 mixtures of $CHCl_3$–EtOH as the eluent. The former eluate (25 : 1 mixture) gave 0.19 g (50%) of oily ethyl *p*-chlorocinnamate (**7a**) and the latter eluate (10 : 3 mixture) gave **1**, which was converted by EtOH–HCl treatment into 0.24 g (65%) of **1**·HCl. The ^{1}H-NMR spectrum of **7a** and the IR spectrum of **1**·HCl were consistent with those of authentic samples.

A similar treatment of **4h** (0.5 g) gave 0.25 g (85%) of ethylcinnamate (**7b**) and 0.27 g (79%) of **1**·HCl.

4-[*N*-(3-Oxobutanoyl)-*N*-methylamino]-1-methyl-5-methylaminocarbonylimidazole (10)——A mixture of **1** (1 g), diketene (1 ml) and Et_3N (1 drop) in $CHCl_3$ (20 ml) was refluxed for 1 h and evaporated *in vacuo* to give a residue,

Table X. Physicochemical Data for 5,8-Dioxo-1,4,5,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]oxazepine Derivatives (**15**)

Compd. No.	Formula	Analysis (%) Calcd (Found)			mp (°C)	Appearance	Yield (%)	Recryst. solvent
		C	H	N				
15a	$C_9H_{11}N_3O_3$	51.67 (51.55	5.30 5.28	20.09 20.13)	204—205	Colorless needles	76	H_2O
15b	$C_{11}H_{15}N_3O_3$	55.69 (55.49	6.37 6.39	17.71 17.72)	116—117	Colorless needles	87	Petr. ether–Et_2O
15c	$C_{14}H_{13}N_3O_3$	61.99 (61.97	4.83 4.84	15.49 15.61)	203—204	Colorless needles	38	H_2O–EtOH
15d	$C_8H_9N_3O_3$	49.23 (49.08	4.65 4.65	21.53 21.53)	191—192	Colorless needles	79	EtOH

Table XI. Spectral Data for 5,8-Dioxo-1,4,5,8-tetrahydro-6*H*-imidazo[4,5-*e*]-[1,4]oxazepine Derivatives (**15**)

Compd. No.	MS (*m*/*z*) M^+	IR (cm^{-1}) CO	IR (cm^{-1}) COC	^{1}H-NMR (δ) N_1-CH_3 (s)	C_2-H (s)	N_4-CH_3 (s)	C_6-H	C_6-Substituent
15a	209	1720, 1670	1210	3.92	7.52	3.50	4.87 (1H, q, $J=7$ Hz)	1.65 (3H, d, $J=7$ Hz, C_6-CH_3)
15b	237	1730, 1670	1220	3.93	7.53	3.50	4.64 (1H, t, $J=7$ Hz)	0.98 (3H, t, $J=7$ Hz, CH_3), 1.32—1.80 (2H, m, CH_2), 2.04 (2H, q, $J=7$ Hz, C_6-CH_2)
15c	271	1700, 1680	1220	3.89	7.52	3.55	5.81 (1H, s)	7.39 (5H, s, C_6-Ph)
15d	195	1720, 1680	1220, 1090	3.92	7.52	3.49	4.76 (2H, s)	

which was purified by chromatography using $CHCl_3$–EtOH (25 : 1) as the eluent to afford 1.18 g (79%) of **10** as colorless needles (from Et_2O), mp 102—103 °C. *Anal.* Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21. Found: C, 52.07; H, 6.38; N, 21.96. IR ν_{max}^{KBr} cm^{-1}: 3400 (NHCO), 1730 (CO), 1650 (CON). ^{1}H-NMR δ: 2.12 (3H, s, CH_3CO), 3.00 (3H, d, $J=5$ Hz, $C\underline{H}_3NHCO$), 3.19 (3H, s, CH_3N), 3.77 (2H, s, $CH_3COC\underline{H}_2$), 3.88 (3H, s, N_1-CH_3), 7.35 (1H, s, C_2-H, 1H, br s, $CH_3N\underline{H}CO$). MS *m*/*z*: 252 (M^+).

4-[*N*-(2-Acetyl-3-phenylpropenoyl)-*N*-methylamino]-1-methyl-5-methylaminocarbonylimidazole (11)——A mixture of **10** (1.0 g), benzaldehyde (1 ml) and catalytic amounts of piperidine and benzoic acid in C_6H_6 (30 ml) was refluxed for 2 h, with removal of water by use of a water separator, and evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH (20 : 1) as the eluent to afford 1.02 g (75%) of **11** as colorless needles (from Et_2O–EtOH), mp 167—168 °C. *Anal.* Calcd for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.30; H, 5.99; N, 16.36. IR ν_{max}^{KBr} cm^{-1}: 3340 (NHCO), 1670, 1640 (CO, CON). ^{1}H-NMR δ: 2.35, 2.56 (3H, s, CH_3CO), 2.86, 3.05 (3H, d, $J=5$ Hz, $C\underline{H}_3NHCO$), 3.12, 3.31 (3H, s, CH_3N), 3.79, 3.93 (3H, s, N_1-CH_3), 7.00, 7.10, 7.36—7.80 (br s, s, m, 8H, $CH_3N\underline{H}CO$, CH=C, C_2-H, phenyl). MS *m*/*z*: 340 (M^+).

Reaction of 11 with EtONa——A solution of NaH (catalytic amount) and **11** (0.5 g) in abs. EtOH (15 ml) was refluxed for 1.5 h and concentrated *in vacuo*. The precipitate was collected by filtration and recrystallized from EtOH to give 0.23 g (81%) of caffeine (**12**). The IR spectrum of **12** coincided with that of an authentic sample.

Reaction of 11 in H_2O——A solution of **11** (0.68 g) in H_2O (20 ml) was refluxed for 5 h and evaporated *in vacuo* to give a residue, which was purified by chromatography on a column of silanized silica gel (Merck) using 25 : 1 and 10 : 3 mixtures of $CHCl_3$–EtOH as the eluent. The eluate with the former (25 : 1 mixture) gave 0.04 g (7%) of **4h** and that with the latter (10 : 3 mixture) gave a structurally unknown hygroscopic material (0.17 g, 25%). The IR spectrum of **4h** coincided with that of a synthetic sample.

4-[*N*-(α-Halogenoacyl)-*N*-methylamino]-1-methyl-5-methylaminocarbonylimidazoles (13)——An α-halogenoacyl chloride (**16a**—**c**, **e**) (3.3 mmol) and **1** (3 mmol) were treated as described for the synthesis of **4g**, **h** to give

4-[*N*-(2-chloropropionyl)-*N*-methylamino]-(**13a**), 4-[*N*-(2-bromopentanoyl)-*N*-methylamino]-(**13b**), 4-[*N*-(2-chloro-2-phenylacetyl)-*N*-methylamino]-(**13c**) and 4-(*N*-trichloroacetyl-*N*-methylamino)-(**13e**) 1-methyl-5-methylaminocarbonylimidazoles.

Reaction of 13a in aq. NaOH Solution——A solution of **13a** (0.58 g) and 1 N NaOH (2.2 ml) in H_2O (10 ml) was refluxed for 1.5 h then evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH (50 : 1) as the eluent to afford 0.05 g (11%) of 1,4,6-trimethyl-5,8-dioxo-1,4,5,8-tetrahydro-6*H*-imidazo-[4,5-*e*][1,4]oxazepine (**15a**) and subsequently 0.41 g (81%) of 1,4,6,7-tetramethyl-5,8-dioxo-1,4,5,6,7,8-hexahydro-imidazo[4,5-*e*][1,4]diazepine (**14a**).

Procedure for Preparation of 1,4,7-Trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepine Derivatives (14) from 13——A solution of NaH (3.3 mmol) and one of **13a**—**c** (3 mmol) in abs. EtOH (15 ml) was stirred at 60—70 °C for 1 h, cooled, and filtered to remove insoluble materials. The filtrate was evaporated *in vacuo* to give a residue, which was purified by chromatography using $CHCl_3$–EtOH (25 : 1) as the eluent to afford **14a**, 6-propyl- (**14b**) and 6-phenyl- (**14c**) 1,4,7-trimethyl-5,8-dioxo-1,4,5,6,7,8-hexahydroimidazo[4,5-*e*][1,4]diazepines.

1,4-Dimethyl-5,8-dioxo-1,4,5,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]oxazepine Derivatives (15a—d)——An aq. solution of one of **13a**—**d** was refluxed for 2—3 h (**13a**, **b**, **d**, 2 h; **13d**, 3 h) and then evaporated *in vacuo* to afford a residue, which was purified by recrystallization or chromatography using $CHCl_3$–EtOH as the eluent to give **15a**, 6-propyl- (**15b**), 6-phenyl- (**15c**), and 6-unsubstituted- (**15d**) 1,4-dimethyl-5,8-dioxo-1,4,5,8-tetrahydro-6*H*-imidazo-[4,5-*e*][1,4]oxazepines.

Reaction of 13e——i) A solution of NaH (0.09 g) and **13e** (1.13 g) in abs. EtOH (20 ml) was refluxed for 2 h and evaporated *in vacuo* to afford a residue, which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and evaporated *in vacuo* to give a residue, which was recrystallized from EtOH to give 0.46 g (66%) of **12**.

ii) A solution of **13e** (0.64 g) in H_2O (15 ml) was refluxed for 1 h and evaporated *in vacuo* to afford a residue, which was recrystallized from EtOH to give 0.32 g (0.81%) of **12**.

Vascular Relaxing Effects——Helical strips (0.8 mm in width and 7 mm in length) of mesenteric arteries (0.6—0.8 mm in outside diameter) isolated from 13-week-old spontaneously hypertensive rats (SHR) were used according to the method described by Asano *et al.*[12] The strips were mounted for isometric recording of tension in a 20-ml water-jacketed tissue bath (37 ± 0.5 °C) containing oxygenated Krebs' bicarbonate solution. Relaxing responses of the strips to **5a**, **d**, **l**, **m**, **6**, **14a**, **b**, **c**, and **15b**, **c**, **d** were evaluated by the procedures described by Asano and Hidaka.[13] Briefly, the strips were contracted by exposure to either 10^{-5} M norepinephrine or 30 mM KCl. After the contraction had reached a plateau, one of the test compounds at a concentration of 100 μM was added. The relaxation induced by the compound was expressed as a percentage of the contraction developed by each agonist.

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