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Convenient Syntheses of Cyclic Carboxamides from $\alpha,\beta,\gamma,\delta$ and ε-Halocarboxamides under Phase Transfer Conditions[1)]

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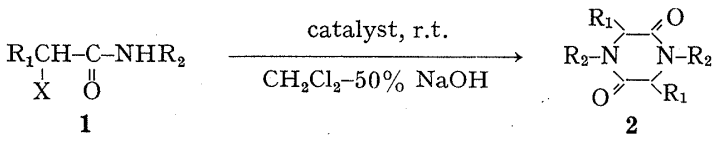
Piperazine-2,5-diones (**2**) were prepared by *N*-alkylation between two molecules of α-halocarboxamides (**1**) in the presence of a phase transfer catalyst in yields of 64—88%. β, γ, δ and ε-Lactams (**6**, **9** and **13**) were similarly synthesized by intramolecular *N*-alkylation of the corresponding halocarboxamides (**5**, **8** and **12**) under phase transfer conditions in 53—99% yields.

Keywords——piperazine-2,5-dione; β-lactam; γ, δ and ε-lactams; bis-β-lactam; phase transfer catalyst; intramolecular *N*-alkylation

N-Alkylation of carboxamides has hitherto required anhydrous conditions and the use of metallic amides and hydrides. Recently, phase transfer catalysts have been effectively applied to the *N*-alkylation of carboxamides.[2-5)] This method has the advantage of making the work-up easier. We therefore tried to use phase transfer catalysts in the cyclization of halocarboxamides by intramolecular *N*-alkylation. This paper deals with convenient syntheses of cyclic carboxamides from $\alpha,\beta,\gamma,\delta$ and ε-halocarboxamides under phase transfer conditions. A strongly basic ion exchange resin, Duolite A-109 Cl^- form(polystyrene quarternary type I, Diamond Shamrock, Co.) was used as the solid phase transfer catalyst, because soluble phase transfer catalysts often form emulsions and make the work-up difficult.

First, we hoped to synthesize piperazine-2,5-diones (**2**) by formal intermolecular *N*-alkylation of α-halocarboxamides (**1**). Piperazine-2,5-diones have recently attracted much attention because of their antitumor activity.[6)] These compounds have been obtained by the thermal dehydration of α-amino acids,[7)] in the preparation of α-amino acid esters as a by-product,[7)] in the cyclization of dipeptides,[8)] and from α-amino acid esters in the presence of a catalytic amount of rhodium trichloride.[9)] When compounds **1** were stirred for long periods in a mixture of dichloromethane and 50% aqueous sodium hydroxide solution in the presence of Duolite A-109 (Cl^- form) at room temperature, piperazine-2,5-diones (**2**) were obtained in yields of 64—88%.



R_1=H, CH_3 R_2=Ph, $PhCH_2$ X=Cl, Br

Chart 1

Soluble phase transfer catalysts, TBAI and BTEAC, were also examined and compared with the solid one. The reaction conditions and the yields are shown in Table I.

The product (**2**, R_1=H,R_2=$PhCH_2$) was also obtained in the absence of the catalyst, but the yield was extremely low. The soluble catalysts, BTEAC and TBAI, gave considerably lower yields of **2** than that obtained with Duolite A-109. When *N*-benzyl α-bromopropionate (**1**, R_1=CH_3, R_2=$PhCH_2$, X=Br) was treated with BTEAC, the ether (**3**) was unexpectedly obtained in the yield of 26% with no isolation of **2**. The compound **3** is assumed to be formed as shown in Chart 2.

Table I. Preparation of Piperazine-2,5-diones (2) from α-Halocarboxamides (1)

2	R_1	X	R_2	Catalyst	React. time (h)	Yield (%)
a	H	Cl	$PhCH_2$	none	24	14
b	H	Cl	$PhCH_2$	Duolite A-109	24	88
c	H	Cl	$PhCH_2$	TBAI	24	46
d	H	Cl	$PhCH_2$	BTEAC	24	51
e	H	Cl	Ph	Duolite A-109	18	64
f	CH_3	Br	$PhCH_2$	Duolite A-109	103	Trace
g	CH_3	Br	$PhCH_2$	BTEAC	103	Trace
h	CH_3	Br	Ph	Duolite A-109	24	64

Duolite A-109: a strongly basic ion exchange resin.
TBAI: tetrabutylammonium iodide.
BTEAC: benzyltriethylammonium chloride.

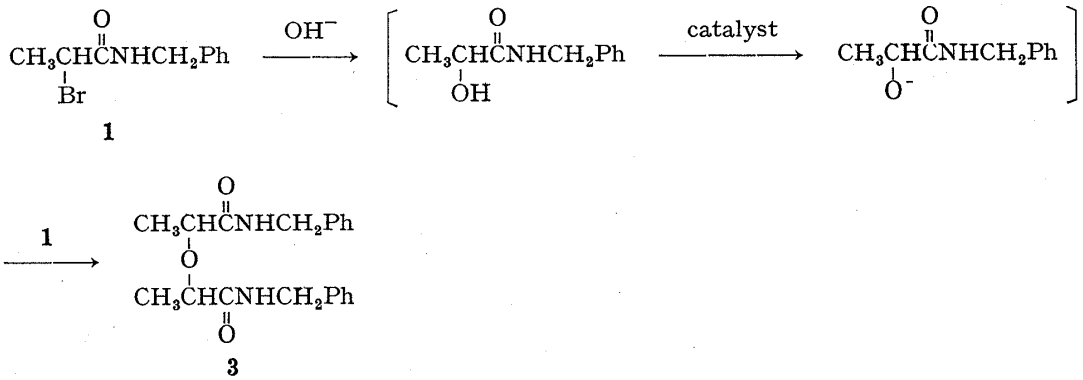
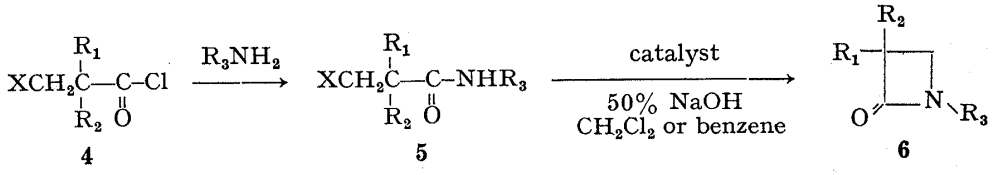


Chart 2

Hydrolysis of **2a** and **g** with 6 N HCl followed by hydrogenolysis over 10% palladium on charcoal gave the α-amino acids, which were identified by comparison with authentic samples.

Next, the conversion of β-halocarboxamides to β-lactams by intramolecular *N*-alkylation under phase transfer conditions was examined. The synthesis of β-lactams has been widely studied and reviewed.[10] Cyclization of β-halocarboxamides to β-lactams using soluble phase transfer catalysts has already been reported by Kay[11] and Yamazaki.[12] We succeeded in the cyclization of β-halocarboxamides under aqueous conditions using a solid phase transfer catalyst.

The reaction was performed by stirring β-halocarboxamides (**5**) in a mixture of aqueous 50% sodium hydroxide solution and dichloromethane or benzene in the presence of Duolite A-109 at room temperature. The compounds **5** were readily prepared by treating β-haloacyl halides (**4**) with amines.



X=Cl, Br R_1=H, CH_3 R_2=H, Br, CH_3 R_3=Ph, $PhCH_2$

Chart 3

The reaction conditions and the yields are summarized in Table II.

In the cases of *N*-phenyl and benzyl α,β-dibromo-α-methylpropionamides (**5**, X=R_1=Br, R_2=Ph and $PhCH_2$), the formation of β-lactams (**6**) by intramolecular *N*-alkylation occurred

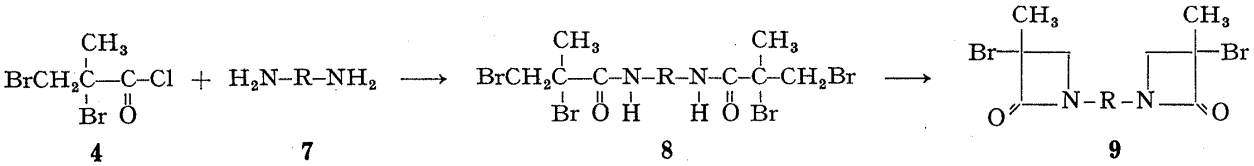
Table II. Preparation of β-Lactams (**6**) from β-Halocarboxamides (**5**)

6	X	R_1	R_2	R_3	Solvent	Catalyst	React. time (h)	Yield (%)
a	Cl	H	H	Ph	CH_2Cl_2	Duolite A-109	70	5[a]
b	Cl	H	H	$PhCH_2$	CH_2Cl_2	Duolite A-109	100	Trace
c	Cl	CH_3	CH_3	Ph	Benzene	Duolite A-109	9	96
d	Cl	CH_3	CH_3	Ph	Benzene	BTEAC	9	96
e	Cl	CH_3	CH_3	$PhCH_2$	Benzene	Duolite A-109	80	91
f	Br	CH_3	Br	Ph	Benzene	Duolite A-109	4	95
g	Br	CH_3	Br	$PhCH_2$	Benzene	Duolite A-109	100	91
h	Br	CH_3	Br	$PhCH_2$	Benzene	BTEAC	100	93
i	Br	CH_3	Br	$PhCH_2$	Benzene	none	100	26

a) Identical with a sample prepared by Wasserman's method.[13]

predominantly, and another possible cyclization to piperazine-2,5-diones by intermolecular *N*-alkylation was not observed. The compounds **5** having two substituents(methyl and bromo) on the α-carbon were successfully converted to β-lactams (**6c**—**h**) quantitatively, while the yield of **6** was 26% in the absence of the catalyst. On the other hand, when a hydrogen atom was present on the α-carbon of **5**, β-elimination predominantly occurred to afford the acrylamide, accompanied by a small amount of β-lactam. No difference between the results with BTEAC and Duolite A-109 was observed.

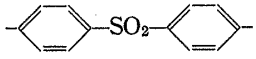
Bis-β-lactams (**9**) were also prepared from bis-β-halocarboxamides (**8**) under the same conditions in quantitative yield. The compounds **8** were easily prepared by the reaction of α,β-dibromo-α-methylpropionyl chloride (**4**, $R_1=CH_3$, $R_2=X=Br$) with diamines (**7**). The reaction conditions and the yields are shown in Table III.



4 **7** **8** **9**

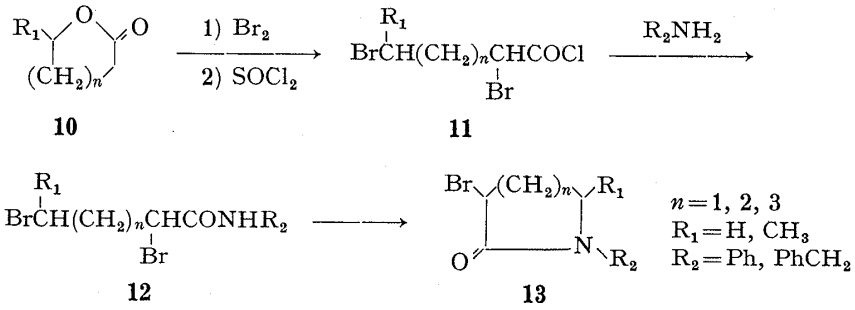
Chart 4

Table III. Praparation of Bis-β-lactams (**9**)

R	React.time (h)	Temp.	mp (°C)	Yield (%)
$-CH_2CH_2-$	3	r.t.	119—120	97
	3	r.t.	178—179	95
	1	r.t.	152—153	98
	1	r.t.	264—265	96
	1	r.t.	224—225	89

A variety of synthetic methods for γ,δ and ε-lactams are known: the reaction of lactone with amine at high temperature,[14] the addition of amine to unsaturated carboxylic acid followed by thermal ring closure,[15] the cyclization by thermal dehydration of γ and δ-amino acid derivatives,[16] Beckman rearrangement of cyclic ketoxime,[17] Schmidt rearrangement of cyclic ketone,[18] the intramolecular *N*-alkylation of halocarboxamide using metallic amide.[19] These methods are not mild or facile, and often provide low yields owing to side reactions.

When γ,δ and ε-halocarboxamides (**12**) were treated with a small amount of phase transfer catalyst in a mixture of aqueous 50% sodium hydroxide solution and dichloromethane at room temperature, the corresponding γ,δ and ε-lactams (**13**) were obtained in 53—96% yields. The compounds **12** were easily prepared from the γ,δ and ε-lactones (**10**) through three steps, bromination, chlorination and amination. The results are shown in Table IV.



10 **11** **12** **13**

Chart 5

TABLE IV. Preparation of γ, δ and ε-Lactams (**13**)

13	n	R_1	R_2	Catalyst	React. time (h)	Yield (%)
a	1	H	$PhCH_2$	None	27	65
b	1	H	$PhCH_2$	Duolite A-109	27	96[20]
c	1	H	$PhCH_2$	BTEAC	27	91
d	1	H	Ph	Duolite A-109	2.5	94
e	1	CH_3	$PhCH_2$	Duolite A-109	45	53
f	1	CH_3	Ph	Duolite A-109	4.5	72
g	2	H	$PhCH_2$	Duolite A-109	34	89
h	2	H	Ph	Duolite A-109	5.5	92
i	3	H	$PhCH_2$	Duolite A-109	150	—
j	3	H	$PhCH_2$	BTEAC	150	—
k	3	H	Ph	Duolite A-109	95	63

In this cyclization, **12** having an *N*-phenyl substituent exhibited higher reactivity more than the compound posessing the benzyl group because of the enhanced acidity of the NH group owing to the phenyl substituent. In the case of $n=3$, it should be noted that *N*-benzyl derivatives (**12i** and **i**) did not show any reactivity. In these reactions, no appreciable difference was observed in catalytic effects between solid Duolite A-109 and soluble BTEAC.

Further applications to other cyclic carboxamides are being investigated.

Experimental

All the melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-I grating infrared spectrometer. Nuclear magnetic resonance (^{1}H-NMR) spectra were determined with a JEOL-60H high resolution NMR instrument. Mass spectra (MS) were measured with a JEOL-01SG mass spectrometer.

General Procedure for Preparation of N-Benzyl and Phenyl α-Halocarboxamides (**1**)——An α-haloacyl chloride (0.05 mol) was gradually added to a solution of benzylamine (0.11 mol) or aniline (0.11 mol) in benzene (70 ml) under cooling with ice and water. After the addition was over, the reaction mixture was stirred for 5 h at room temperature. The solution was washed with 0.1 N HCl (20 ml), 1% $NaHCO_3$ (20 ml), and H_2O (20 ml × 2), and dried over anhydrous Na_2SO_4. After removal of benzene, the residue was recrystallized from $CHCl_3$. The melting points, yields, IR spectral data, and elemental analyses are listed in Table V.

General Procedure for Preparation of Piperazine-2,5-diones (**2**)——A mixture of an α-halocarboxamide (10 mmol), CH_2Cl_2 (10 ml), 50% NaOH (10 ml), and catalyst (0.5—1.0 mmol) was stirred for 18—103 h at room temperature. Ice and water were poured into the reaction mixture (after the catalyst had been filtered off in the case of Duolite A-109), then the aqueous layer was extracted with CH_2Cl_2 (10 ml × 2). The CH_2Cl_2

Table V. α-Halocarboxamides (1)

X	R_1	R_2	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	Analysis (%) Calcd (Found) C	H	N
Cl	H	$PhCH_2$	89—90	95	3260 (NH) 1650 (C=O)	59.02 (59.36	5.46 5.60	7.65 7.27)
Cl	H	Ph	138—140	97	3260 (NH) 1650 (C=O)	56.65 (56.55	4.75 4.77	8.26 8.33)
Br	CH_3	$PhCH_2$	79—80	91	3250 (NH) 1650 (C=O)	49.61 (49.74	5.00 4.96	5.79 5.67)
Br	CH_3	Ph	98	93	3260 (NH) 1660 (C=O)	47.39 (47.54	4.42 4.27	6.14 6.28)

Table VI. Piperazine-2,5-diones (2)

R_1	R_2	mp (°C)	IR ν_{max}^{KBr} cm^{-1} (C=O)	NMR (δ) in $CDCl_3$	*m/e* (M^+)	Analysis (%) Calcd (Found) C	H	N
H	$PhCH_2$	174—175	1650	3.88 (s, $CH_2\times2$, 4H), 4.55 (s, $PhCH_2\times2$, 4H) 7.26 (s, arom×2, 10H)	294	73.45 (73.58	6.16 6.27	9.52 9.45)
H	Ph	266—268	1650	a)	266	72.16 (72.34	5.30 5.42	10.52 10.71)
CH_3	Ph	155	1670	1.68 (d, $CH_3\times2$, 6H) 4.48 (q, CH×2, 2H)	294	73.45 (73.65	6.16 5.91	9.52 9.46)

a) No suitable solvent for NMR spectroscopy could be found.

layer and the extract were combined, washed with H_2O (20 ml×2), and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from $CHCl_3$. The melting points, IR, NMR, and mass spectral data, and elemental analyses are summarized in Table VI.

***N,N'*-Dibenzyl-α,α'-oxydipropionamide** (3)——The residue mentioned above was dissolved in Et_2O (10 ml), and the insoluble part was recrystallized from benzene to give *N,N'*-dibenzyl α,α'-oxydipropionamide (3) (0.49 g, 28%): mp 123—125°C. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1650 (C=O). NMR (δ) ($CDCl_3$): 1.38 (d, $CH_3\times2$, 6H), 3.97 (q, CH×2, 2H), 4.43 (d, $CH_2\times2$, 4H), 6.68 (br, NH×2, 2H), 7.27 (s, arom 2, 10H). MS *m/e*: 340 (M^+). *Anal.* Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.29; H, 7.04; N, 8.29.

β-Chloro-α,α-dimethylpropionyl Chloride (4, $R_1=R_2=CH_3$, X=Cl)——This compound was obtained by refluxing β-chloropivalic acid (24.6 g, 0.18 mol) with $SOCl_2$ (32.1 g, 0.27 mol). bp 110—112°C. Yield 14.5 g (52%).

α,β-Dibromo-α-methylpropionic Acid——This compound was prepared according to Rhinesmith's method[21] from 2-methylpropenoic acid (43 g, 0.5 mol) and bromine (80 g, 0.5 mol). Yield 95 g (77%), bp 106—109°C/3 mmHg. mp 43—46°C. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd for $C_4H_6Br_2O_2$: C, 19.54; H, 2.46. Found: C, 19.63; H, 2.41.

α,β-Dibromo-α-methylpropionyl Chloride (4, $R_1=CH_3$, $R_2=X=Br$)——This compound was prepared from α,β-dibromo-α-methylpropionic acid (73.5 g, 0.3 mol) and $SOCl_2$ (53.6 g, 0.45 mol). Yield 38.0 g (48%). bp 83—85°C/25 mmHg.

***N*-Phenyl and Benzyl β-Chloropropionamides** (5a and b)——These compounds were prepared from β-chloropropionyl chloride (4, 6.4 g, 0.05 mol) and aniline (10.2 g, 0.11 mol) or benzylamine (11.8 g, 0.11 mol) according to the method described for the preparation of 1. The melting points, yields, IR spectra and elemental analyses are listed in Table VII.

***N*-Phenyl and Benzyl β-Chloro-α,α-dimethylpropionamides** (5c and d)——These compounds were prepared by the reaction of 4 with aniline or benzylamine by the method described above, and recrystallized from *n*-hexane–benzene. The melting points, yields, IR and NMR spectra, and elemental analyses are listed in Table VII.

***N*-Phenyl and Benzyl α,β-Dibromo-α-methylpropionamides** (5e and f)——These amides were prepared by the reaction of 4 with aniline or benzylamine by the method described above, and recrystallized from $CHCl_3$. The melting points, yields, IR and NMR spectra, and elemental analyses are listed in Table VII.

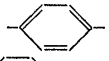
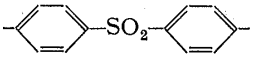
Table VII. β-Halocarboxamides (5)

5	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (δ) in $CDCl_3$	Analysis (%) Calcd (Found) C	H	N
a	115—117	3270 (NH) 1655 (C=O)		58.87 (58.66	5.49 5.56	7.63 7.77)
b	92	3270 (NH) 1640 (C=O)		60.76 (60.61	6.12 5.90	7.09 6.79)
c	84—87	3300 (NH) 1650 (C=O)	1.40 (s, $CH_3\times2$, 6H), 3.69 (s, CH_2, 2H), 7.35 (m, arom and NH, 6H)	62.41 (62.49	6.67 6.70	6.62 6.54)
d	46	3290 (NH) 1655 (C=O)	1.28 (s, $CH_3\times2$, 6H), 3.62 (s, CH_2, 2H), 4.33 (d, Ph$\underline{CH}_2$, 2H), 6.15 (br, NH, 1H), 7.28 (s, arom, 5H)	63.85 (63.79	7.16 7.22	6.21 6.08)
e	65—66	3300 (NH) 1660 (C=O)	2.10 (s, CH_3, 3H), 3.96 (s, CH_2, 2H), 7.32 (m, arom, 5H), 8.26 (br, NH, 1H)	37.40 (36.92	3.45 3.33	4.36 4.28)
f	68—71	3280 (NH) 1650 (C=O)	2.08 (s, CH_3, 3H), 3.94 (s, CH_2, 2H), 4.44 (d, Ph$C\underline{H}_2$, 2H), 6.94 (br, NH, 1H), 7.30 (s, arom, 5H)	39.91 (39.75	3.91 4.02	4.18 4.12)

Table VIII. β-Lactams (6)

6	mp (°C)	IR $\nu_{max}^{KBr\ (film)}$ cm^{-1} (C=O)	^{1}H-NMR (δ) in $CDCl_3$	m/e (M^+)	Analysis (%) Calcd (Found) C	H	N
a	78—79	1740	3.05 (t, CH_2, 2H), 3.57 (t, CH_2, 2H), 7.22 (m, arom, 5H)	147	73.45 (73.43	6.16 6.22	9.52 9.46)
c—d	oil	1740	1.38 (s, $CH_3\times2$, 6H), 3.40 (s, CH_2, 2H), 7.30 (m, arom, 5H)	175	75.40 (75.51	7.48 7.43	7.99 7.79)
e	oil	1740	1.28 (s, $CH_3\times2$, 6H), 2.92 (s, CH_2, 2H), 4.33 (s, Ph$\underline{CH}_2$, 2H), 7.36 (s, arom, 5H)	189	76.16 (76.27	7.99 7.79	7.40 7.22)
f	73	1750	2.00 (s. CH_3, 3H), 3.95 (q, CH_2, 2H), 7.31 (m, arom, 5H)	241 239	50.02 (50.42	4.20 4.16	5.83 5.84)
g—i	oil	1760	1.85 (s, CH_3, 3H), 3.45 (q, CH_2, 2H), 4.35 (s, Ph$C\underline{H}_2$, 2H), 7.25 (s, arom, 5H)	255 253	51.99 (52.34	4.76 4.89	5.51 5.59)

Table IX. Bis-(α,β-dibromo-α-methylpropionamides) (8)

R	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	Analysis (%) Calcd (Found) C	H	N
$-CH_2CH_2-$	146—147	93	3310 (NH) 1660 (C=O)	23.28 (23.66	3.13 3.19	5.43 5.49)
	159—160	94	3270 (NH) 1680 (C=O)	29.82 (30.39	2.86 2.90	4.97 5.07)
	101—102	96	3300 (NH) 1665 (C=O)	29.82 (30.00	2.86 2.82	4.97 4.83)
	213—215	95	3330 (NH) 1660 (C=O)	29.82 (29.72	2.86 2.75	4.97 4.86)
	132—133	96	3300 (NH) 1675 (C=O) 1310, 1150 (SO_2)	34.12 (34.23	2.86 2.90	3.98 3.60)

General Procedure for Preparation of β-Lactams (6)——The compounds **6** were prepared by stirring a mixture of the appropriate compound **5** (10 mmol), CH_2Cl_2 (20 ml), 50% NaOH (10 ml), and a catalyst (0.5—1.0 mmol) at room temperature by the method described for piperazine-2,5-diones (**2**). The products were purified by recrystallization from *n*-hexane–benzene or by silica-gel column chromatography (2.5×20.0 cm) (benzene: AcOEt=9: 1). The melting points, yields, IR, NMR, and mass spectra, and elemental analyses are listed in Table VIII.

***N*-Phenyl Acrylamide**——The residue from the preparation of **5a** was subjected to silica-gel column chromatography (benzene: AcOEt=4: 1), and recrystallized from *n*-hexane–benzene to give *N*-phenyl acrylamide (0.85 g, 58%). mp 101—103°C. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1655 (C=O), 1635 (C=C). NMR

Table X. Bis-β-lactams (**9**)

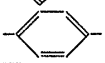
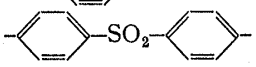
R	IR ν_{max}^{KBr} cm^{-1} (C=O)	^{1}H-NMR(δ) in $CDCl_3$	*m/e* (M^+)	Analysis (%) Calcd (Found) C	H	N
$-CH_2CH_2-$	1760	1.88 and 1.93 (s, $CH_3\times2$, 6H), 3.21 (m, $CH_2\times2$, 4H), 3.70 (m, $CH_2\times2$, 4H)	355 353	33.92 (34.17	3.99 3.91	7.91 8.07)
	1760	2.07 (s, $CH_3\times2$, 6H), 4.10 (q, $CH_3\times2$, 4H), 7.23 (s, arom, 4H)	403 401	41.82 (41.93	3.51 3.41	6.97 7.04)
	1750	2.03 (s, $CH_3\times2$, 6H), 4.00 (q, $CH_2\times2$, 4H), 7.27 (m, arom, 4H)	403 401	41.82 (41.74	3.51 3.51	6.97 6.91)
	1740	2.01 (s, $CH_3\times2$, 6H), 3.96 (q, $CH_2\times2$, 4H), 7.32 (s, arom, 4H)	403 401	41.82 (41.53	3.51 3.45	6.97 6.97)
	1760	2.02 (s, $CH_3\times2$, 6H), 4.01 (q, $CH_2\times2$, 4H), 7.65 (m, arom×2, 8H)	543 541	44.30 (44.76	3.35 3.30	5.17 5.02)

Table XI. γ, δ and ε-Halocarboxamides (**12**)

12	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (δ) in $CDCl_3$	Analysis (%) Calcd (Found) C	H	N
a—c	80—82	3250 (NH) 1640 (C=O)	2.50 (q, CH_2, 2H), 3.48 (t, CH_2, 2H), 4.46 (q, CH and Ph<u>CH_2</u>, 3H), 7.20 (s, arom, 5H), 7.75 (broad, NH, 1H)	39.43 (39.84	3.91 3.93	4.18 4.19)
d	96—97	3280 (NH) 1660 (C=O)	2.60 (m, CH_2, 2H), 3.56 (t, CH_2, 2H), 4.65 (q, CH, 1H), 7.37 (m, arom, 5H), 8.00 (br, NH, 1H)	37.41 (37.69	3.45 3.34	4.36 4.30)
e	101—102	3240 (NH) 1655 (C=O)	1.82 (m, CH_3, 3H), 2.49 (m, CH_2, 2H), 4.35 (m, CH_2 and Ph<u>CH_2</u>, 4H), 6.49 (br, NH, 1H), 7.28 (s, arom, 5H)	41.29 (41.59	4.33 4.31	4.01 3.58)
f	147	3230 (NH) 1660 (C=O)	1.79 (d, CH_3, 3H), 2.44 (m, CH_2, 2H), 4.54 (m, CH×2, 2H), 7.44 (m, arom, 5H), 9.88 (br, NH, 1H)	39.43 (40.09	3.91 4.00	4.18 4.12)
g	66—67	3260 (NH) 1640 (C=O)	2.10 (m, $CH_2\times2$, 4H), 3.40 (t, CH_2, 2H), 4.35 (m, CH and $PhCH_2$, 3H), 6.75 (br, NH, 1H), 7.28 (s, arom, 5H)	41.29 (41.63	4.33 4.31	4.01 3.99)
h	93—95	3210 (NH) 1660 (C=O)	2.30 (m, $CH_2\times2$, 4H), 3.41 (t, CH_2, 2H), 4.45 (t, CH, 1H), 7.33 (m, arom, 5H), 8.05 (br, NH, 1H)	39.43 (39.59	3.91 3.90	4.18 4.22)
i—j	79	3260 (NH) 1650 (C=O)	1.85 (m, $CH_2\times3$, 6H), 3.40 (m, CH_2, 2H), 4.45 (m, CH and Ph<u>CH_2</u>, 3H), 6.65 (br, NH, 1H), 7.25 (s, arom, 5H)	43.00 (42.88	4.72 4.57	3.86 3.71)
k	69—70	3280 (NH) 1660 (C=O)	1.90 (m, $CH_2\times3$, 6H), 3.40 (m, CH_2, 2H), 4.45 (t, CH, 1H), 7.40 (m, arom, 5H), 8.15 (br, NH, 1H)	41.29 (41.45	4.33 4.46	4.01 3.93)

(δ) ($CDCl_3$): 5.64 (m, CH, 1H), 6.29 (m, CH_2, 2H), 7.28 (m, arom, 5H), 7.98 (br, NH, 1H). *Anal.* Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.86; H, 6.20; N, 9.47.

Bis-(α,β-Dibromo-α-methylpropionamides (**8**)——These compounds (**8**) were prepared from **4** and the diamines (**7**), and purified by recrystallization from benzene. The melting points, yields, IR spectra, and elemental analyses are listed in Table IX.

Bis-β-Lactams (**9**)——These compounds (**9**) were prepared from **8** (5 mmol) by the method described for the preparation of **2**, and purified by recrystallization from $CHCl_3$ or benzene. The spectral data are given in Table X.

Dibromoacyl Chlorides (**11**)——Dibromocarboxylic acids were prepared from the corresponding lactones (0.5 mol) and bromine (80.0 g, 0.5 mol) according to Phillips' method.[22] The resulting crude acids were converted to the products **11** by refluxing with $SOCl_2$ (89.3 g, 0.75 mol). $n=1$, $R_1=H$, bp 84—87°C/8 mmHg, yield 71.3 g (58%). $n=1$, $R_1=CH_3$, bp 115—135°C/21 mmHg, yield 79.2 g (57%). $n=2$, $R_1=H$, bp 146—151°C/51 mmHg, yield 86.7 g (63%). $n=3$, $R_1=H$, bp 100—101°C/4 mmHg, yield 85.3 g (58%).

***N*-Phenyl and Benzyl Dibromocarboxamides** (**12**)——These compounds (**12**) were prepared by the reaction of **11** (0.05 mol) with aniline (0.11 mol) or benzylamine (0.11 mol), and purified by recrystallization from *n*-hexane–benzene or $CHCl_3$. The yields were almost quantitative. The melting points, IR and NMR spectra, and elemental analyses are listed in Table XI.

General Procedure for the Preparation of γ, δ and ε-Lactams (**13**)——By the same method as described for the preparation of **2**, compounds **12** (10 mmol) were converted to compounds **13**, which were purified by recrystallization from *n*-hexane–benzene or by silica-gel column chromatography (2.5×20.0 cm (benzene: AcOEt=4:1 or 9:1). The melting points and spectral data are listed in Table XII.

Table XII. γ, δ and ε-Lactams (**13**)

13	mp (°C)	IR $\nu_{max}^{KBr(film)}$ cm^{-1} (C=O)	^{1}H-NMR (δ) in $CDCl_3$	*m/e* (M^+)	Analysis (%) Calcd (Found) C	H	N
a—**c**	oil	1710	2.80 (m, CH_2×2, 4H), 4.49 (q, CH,1 H), 4.45 (s, Ph<u>CH_2</u>, 2H), 7.21 (s, arom, 5H)	255 253	51.99 (50.94	4.76 4.53	5.51 5.32)
d	99	1700	2.55 (m, CH_2, 2H), 3.90 (m, CH_2, 2H), 4.55 (q, CH, 1H), 7.45 (m, arom, 5H)	241 239	50.02 (50.44	4.20 4.16	5.83 5.84)
e	oil	1710	1.29 (m, CH_3, 3H), 2.08 (m, CH_2, 2H), 4.12 (m, CH_2 and $PhCH_2$, 4H), 7.25 (s, arom, 5H)	269 267	53.75 (53.90	5.26 5.19	5.22 5.24)
f	103—104	1700	1.28 (m, CH_3, 3H), 2.24 and 3.01 (m, CH×2, 2H), 4.48 (m, CH, 1H), 7.34 (m, arom, 5H)	255 253	51.99 (52.16	4.76 4.84	5.51 5.47)
g	oil	1650	1.95 (m, CH_2×2, 4H), 3.28 (m, CH_2, 2H), 4.25 (m, CH and Ph<u>CH_2</u>, 3H), 7.25 (s, arom, 5H)	269 267	53.75 (52.82	5.26 5.01	5.22 5.09)
h	84—85	1650	2.15 (m, CH_2×2, 4H), 3.70 (m, CH_2, 2H), 4.56 (t, CH, 1H), 7.28 (s, arom, 5H)	255 253	51.99 (51.93	4.76 4.83	5.51 5.47)
k	211—213	1660	1.80 (m, CH_2×3, 6H), 3.30 (m, CH_2, 2H), 4.70 (m, CH, 1H), 7.40 (s, arom, 5H)	269 267	53.75 (53.34	5.26 5.13	5.22 5.02)

References and Notes

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20) The reaction with L-valine benzyl ester as the amino component was carried out under the same conditions to afford **13** (R_1=H, R_2=L-$(CH_3)_2$ÇHCOOCH$_2$Ph) in the yield of 56%, and this product was purified by silica-gel column chromatography ($CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1725 (C=O), 1708 (C=O). NMR (δ) ($CDCl_3$): 1.97 (d, $CH_3\times2$, 6H), 2.33 (m, CH_2 and CH, 3H), 3.57 (t, CH_2, 2H), 4.43 (m, $CH\times2$, 2H), 5.15 (d, PhC$\underline{H}_2$, 2H), 7.33 (s, arom, 5H). MS *m/e*: 354 (M^+). *Anal.* Calcd for $C_{16}H_{20}BrNO_3$: C, 54.25; H, 5.69; N, 3.95. Found: C, 53.84; H, 5.39; N, 3.87.
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