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Cyclic Guanidines. X.[1] Synthesis of 2-(2,2-Disubstituted Ethenyl- and Ethyl)-2-imidazolines as Potent Hypoglycemics[2]

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2-(2,2-Disubstituted ethenyl- and ethyl)-2-imidazoline derivatives (**11**, **14**) were prepared by direct cyclization of active intermediates, 3,3-disubstituted acrylimidic ethyl esters (**9**, **10**), with ethylenediamine. The stereoisomers, (*Z*)- and (*E*)-3-phenyl-3-pyridylacrylic acid esters (**6c**—**e**), nitriles (**7c**—**e**) and amides (**8c**—**e**), as well as (*Z*)- and (*E*)-3-phenyl-3-pyridylacrylimidic acid esters (**10c**—**e**), and (*Z*)- and (*E*)-2-(2-pyridylethenyl)-2-imidazolines (**11c**—**e**), were isolated. Their structures are discussed. Compounds **11** and **14** showed potent hypoglycemic activity.

Keywords——2-(2,2-disubstituted ethenyl)-2-imidazoline; 2-(2,2-disubstituted ethyl)-2-imidazoline; Wittig-Horner reaction; stereoisomers of 3,3-disubstituted acrylic acid derivatives; hypoglycemic activity

We have reported that monocyclic guanidines and related compounds having a bulky group showed potent hypoglycemic activity.[4] 2-Imidazolines substituted with a bulky group at position 2, such as 2-(α-ethoxybenzyl)-,[5] 2-(α-hydroxybenzhydryl)-,[6] and 2-(2-phenylpropyl)-2-imidazoline,[7] are also potent hypoglycemics. The structure-activity relationships in the cyclic guanidines and 2-imidazoline derivatives suggested that a bulkyl group located at a distance of one or two carbon units from position 2 in the imidazoline ring is important for hypoglycemic activity. We also reported in the preceding paper[4g] that a tricyclic guanidine structure having a benzene ring in the bulky group coplaner with the imidazoline ring generally resulted in potent activity. This paper deals with the synthesis and biological activity of 2-(2,2-disubstituted ethenyl- and ethyl)-2-imidazoline derivatives.

A few 2-(2-monosubstituted ethenyl)-2-imidazoline derivatives have been synthesized by the reaction of 2-methyl-2-imidazoline with arylaldehydes[8] and by the cyclization of 2-thienylacrylimidic ester with ethylenediamine.[8]

3,3-Disubstituted acrylic acid derivatives, the ethyl esters (**6**), nitriles (**7**), and amides (**8**), were prepared from the phenyl ketone derivatives (**1**) with the diethyl phosphonoacetic acid derivatives (**2**, **3**, **4**), respectively, in the presence of sodium ethoxide in ethanol in good yield by Webb's modified Wittig-Horner reaction.[9] The pyridine-substituted compounds

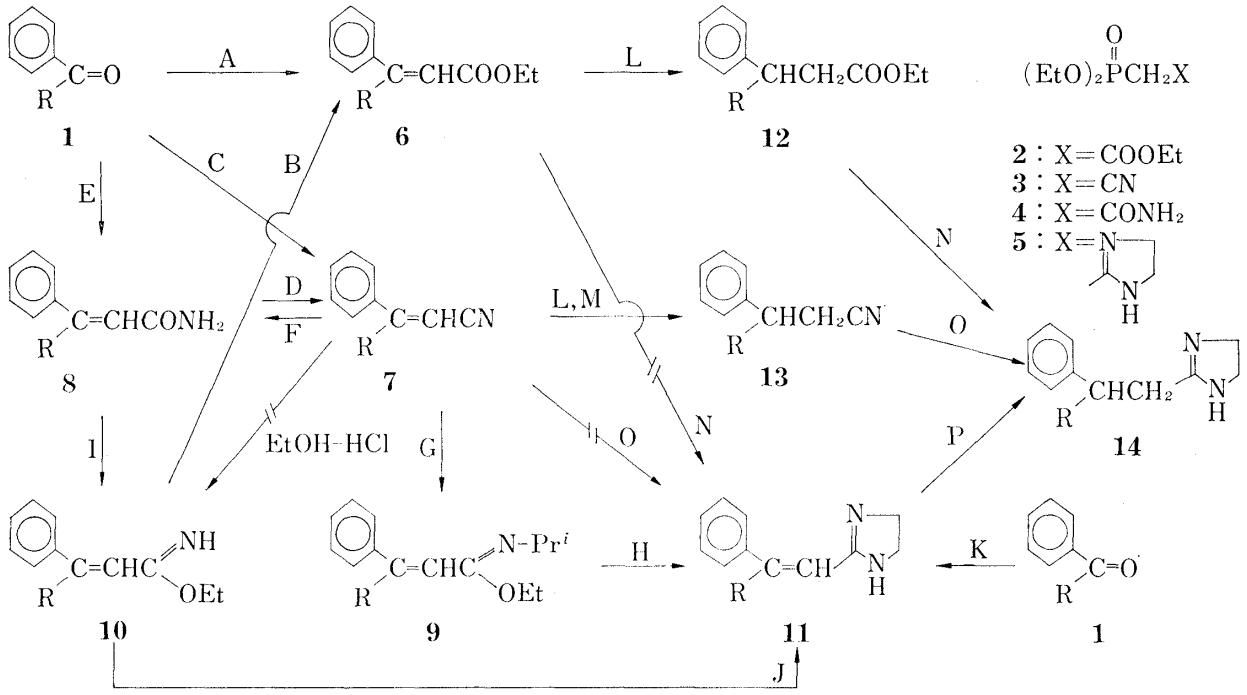
1) Part IX: F. Ishikawa, Y. Watanabe, and J. Saegusa, *Chem. Pharm. Bull.*, **28**, 1357 (1980); This paper is regarded as 10th report in our series on cyclic guanidines since the nature of the compounds described in this paper is analogous to that of the cyclic guanidines.
2) Presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August 1979.
3) Location: *1-16-13 Kitakasai, Edogawa-ku, Tokyo 132, Japan.*
4*a*) F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.*, **26**, 3658 (1978); *b*) F. Ishikawa, A. Kosasayama, and T. Konno, *ibid.*, **26**, 3666 (1978); *c*) A. Kosasayama, Y. Watanabe, K. Higashi, and F. Ishikawa, *ibid.*, **27**, 831 (1979); *d*) A. Kosasayama, T. Konno, K. Higashi, and F. Ishikawa, *ibid.*, **27**, 841 (1979); *e*) *Idem*, *ibid.*, **27**, 848 (1979); *f*) A. Kosasayama, K. Higashi, and F. Ishikawa, *ibid.*, **27**, 880 (1979); *g*) A. Kosasayama and F. Ishikawa, *ibid.*, **27**, 1596 (1979).
5) D.M. Bailey, C.G. Degrazia, D. Wood, and J. Siggins, *J. Med. Chem.*, **17**, 702 (1974).
6) A.C. White and R.M. Black, Ger. Offen. 2257784 (1973) [*Chem. Abstr.*, **79**, 78833 (1973)].
7) H. Roebke, Japan Kokai Tokkyo Koho 76143668 (1976).
8) L.H. Conover, J.M. Mcfarland, and W.C. Austin, U.S. Patent 3644624 (1972) [*Chem. Abstr.*, **77**, 5508 (1972)]; H.L. Wehlmeister, U.S. Patent 3812111 (1974) [*Chem. Abstr.*, **81**, 73546 (1974)].
9) G. Gallagher, Jr. and R.C. Webb, *Synthesis*, **1974**, 122.

6c—e, **7c—e**, and **8c—e** were isolated as a mixture of the (*Z*)- and (*E*)-isomers. Among them the amides (**8c—e**), the 2-pyridyl-substituted ester (**6c**), and the nitrile (**7c**) could be separated into the (*Z*)- and (*E*)-isomers by silica gel chromatography or recrystallization. The *Z*: *E* formation ratios of the reaction products were determined by nuclear magnetic resonance (NMR) spectroscopy or high performance liquid chromatography (HPLC).

Heating the acrylic acid esters (**6**) or the nitriles (**7**) with ethylenediamine at 200° or higher temperatures did not give 2-ethylene-2-imidazolines (**11**). An attempt to prepare the active acrylimidic acid ester (**10**) from the nitrile (**7**) by treatment with ethanolic hydrogen chloride also failed.

Reaction of **7a, b** with feric chloride in isopropyl chloride followed by treatment with ethanol gave the corresponding ethyl N-isopropylacrylimidate (**9a, b**) in good yield by a modification of Jolivet's method[10] in which acrylonitrile was converted *via* the nitrilium salt to 2-propenyl amidines. Compound **9a** or **9b** readily reacted with ethylenediamine at 100—140° to give the desired 2-ethenyl-2-imidazoline derivative (**11a** or **11b**). However, the pyridine-substituted compounds **7c—e** did not yield the nitrilium salts because of the prior reaction of the pyridine base with ferric chloride.

Reaction of 3,3-diphenylacrylamide (**8b**) with the Meerwein reagent afforded the imidic ethyl ester (**10b**) as an oil in good yield. In the same way, although the free bases of pyridine-substituted derivatives (**8c—e**) did not yield the imidic ethyl esters (**10c—e**), the hydrocholides of (*Z*)- and (*E*)-**8c—e** (except for (*Z*)-**8c**) formed (*Z*)- and (*E*)-**10c—e** respectively. Compound



R: a=Me; b=  ; c=  ; d=  ; e=  .

A=**2**/NaOEt; B=HCl/aq-EtOH; C=**3**/NaOEt; D=$(CF_3CO)_2O/C_5H_5N$; E=**4**/NaOEt; F=H_2SO_4/AcOH; G=1. $FeCl_3$/i-PrCl, 2. EtOH; H=$H_2NCH_2CH_2NH_2/\Delta$; I=Et_3OBF_4; J=$H_2NCH_2CH_2NH_2/\Delta$; K=**5**/NaOEt; L=H_2/Pd-C; M=$NaBH_4$; N=$H_2NCH_2CH_2NH_2/\Delta$; O=$H_2NCH_2CH_2NH_2 \cdot TsOH/\Delta$; P=$H_2$/Pd-C.

Chart 1

10) *a*) Y. Jolivet and C. Lachevre, Ger. Offen. 2645128 (1977) [*Chem. Abstr.*, **87**, 55637 (1977)]; *b*) R.F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(*Z*)-**8c** reacted with the Meerwein reagent to give the reaction complex which decomposed to a resin on treatment with sodium bicarbonate solution for the isolation of (*Z*)-**10c**. Gentle heating of the imidic ethyl esters (**10**) with ethylenediamine readily gave the interesting 2-ethenyl-2-imidazoline derivatives (**11**).

The reaction of phenyl ketones (**1**) with 2-diethylphosphonomethyl-2-imidazoline (**5**) reported recently by Shiskin *et al.*[11] was attempted. Benzoyl pyridines (**10c—e**) readily gave mixtures of the (*Z*)- and (*E*)-isomers of **11c—e** on treatment with **5** at room temperature. However, separation of the isomers was difficult. On the other hand, reaction of the phenyl ketones (**1a, b**) with **5** did not proceed at room temperature and **11a, b** were obtained after prolonged heating in poor yield. It appears that compound **5** is rather unreactive in the Wittig-Horner reaction.

Pure (*Z*)- and (*E*)-isolmers of **8c—e** were treated with trifuluoroacetic anhydride in the presence of pyridine in dioxane at room temperature[12] to give the (*Z*)- and (*E*)-isomers of **7c—e**, respectively. Each isomer of **6c—e** was also prepared from the corresponding isomer of **10c—e** by heating in aqueous ethanol.

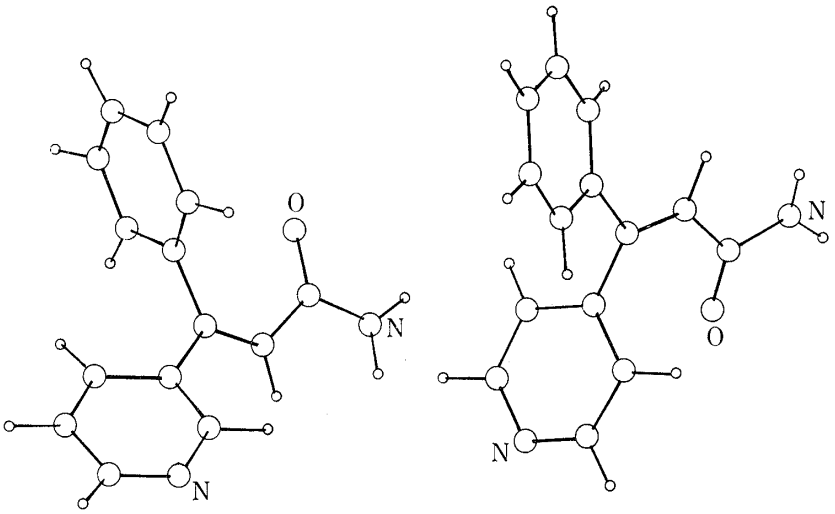
Table I. NMR Signals of Phenyl and Methine Protons in 2-Phenyl-2-pyridylacrylic Acid Derivatives (**6**, **7**, **8** and **10**) and 2-(2-Phenyl-2-pyridylethyl)-2-imidazoline (**11**)

Compd.	Solvent[a]	(*Z*)-Isomer		(*E*)-Isomer	
		Phenyl (*δ*)	Methine (*δ*)	Phenyl (*δ*)	Methine (*δ*)
6c	C	7.39(s)	6.47(s)	6.9—7.8(m)	7.18(s)
6d	C	7.39(s)	6.46(s)	7.1—7.7(m)	6.37(s)
6e	C	7.35(s)	6.46(s)	7.1—7.6(m)	6.49(s)
7c	C	7.2—7.5(m)	5.89(s)	7.50(s)	6.73(s)
7d	C	7.2—7.5(m)	5.89(s)	7.50(s)	5.83(s)
7e	C	7.2—7.5(m)	5.92(s)	7.50(s)	5.90(s)
8c	D	7.3—7.6(m)	6.67(s)	7.2—7.6(m)	7.23(s)
8d	D	7.0—7.7(m)	6.63(s)	7.0—7.8(m)	6.58(s)
8e	D	7.1—7.6(m)	6.61(s)	7.1—7.6(m)	6.68(s)
10c	C			6.9—7.7(m)	7.13(s)
10d	C	7.29(s)	6.39(s)	7.1—7.5(m)	6.33(s)
10e	C	7.29(s)	6.40(s)	7.1—7.5(m)	6.43(s)
11c	C	7.35(s)	6.82(s)	6.9—7.8(m)	7.28(s)
11d	C	7.32(s)	6.73(s)	7.1—7.7(m)	6.73(s)
11e	C	7.34(s)	6.76(s)	7.1—7.7(m)	6.90(s)

a) C: $CDCl_3$, D: DMSO-d_6.

The structures of the (*Z*)- and (*E*)-isomers of 2-pyridylsubstituted derivatives (**6c**, **7c**, **8c**) were confirmed on the basis of their NMR spectra. The chemical shift of the methine proton of the (*E*)-isomer is shifted 0.4—0.8 ppm to lower field in comparison with that of the (*Z*)-isomer, as shown in Table I, because of the anisotropy effect of the neighboring pyridine nitrogen atom. On the other hand, in the cases of the 3- and 4-pyridyl-substituted compounds no significant difference was observed in the chemical shift of the methine proton on the two isomers. Therefore, the structures were finally determined by X-ray analysis, as shown in Fig. 1.[13]

11) V.E. Shiskin, Y.L. Zotov, and B.I. No, *Zh. Obshch. Khim.*, **47**, 1270 (1977).
12) F. Campagna, A. Caretti, and G. Casini, *Tetrahedron Lett.*, **1977**, 1813.
13) K. Yamazaki, R. Moroi, and M. Sano: Details will be reported elsewhere.



(*E*)-8d (*Z*)-8e

Fig. 1. Stereoscopic Views of (*E*)-**8d** and (*Z*)-**8e**

NMR signal positions of the phenyl and methine protons of the (*Z*)- and (*E*)-isomers of **6c—e**, **7c—e**, **8c—e**, **10c—e**, and **11c—e** are listed in Table I. In the cases of the (*E*)-isomers of the esters (**6**), imidic acid esters (**10**), and imidazoline derivatives (**11**), the signals of phenyl protons are observed as multiplets because of the anisotropy effect of the carbonyl or imino group.[14] In the case of the (*Z*)-isomer, the phenyl protons are observed as a singlet. In the nitrile derivatives (**7**), the singlet signals of phenyl protons in the (*E*)-isomers are shifted to lower field as compared to the multiplet signals of the (*Z*)-isomers. The signals of the (*Z*)- and (*E*)-isomers of the amide derivatives (**8**) are observed as multiplets in hexadeuterodimethylsulfoxide.

Catalytic hydrogenation with palladium-charcoal (Pd-C) of **6** gave the ethyl 3,3-disubstituted propionate (**12**) in good yield. Heating **12** with ethylenediamine at 200° or higher temperatures afforded 2-(2,2-disubstituted ethyl)-2-imidazolines (**14**) in moderate yield. The hydrogenation of nitriles (**7a,b**) also gave the propionitriles (**13a,b**) in good yield, while **7c—e**

Table II. Hypoglycemic Activities of 2-(2,2-Disubstituted Ethenyl- and Ethyl)-2-imidazolines (**11** and **14**) in Normal Rats

Compound	Blood glucose (% reduction)			
	1	2	3	5 hr
11b	8	19	15	12
(*E*)-**11c**	35	35	25	23
(*Z*)-**11d**	16	19	22	21
(*E*)-**11d**	23	20	26	25
(*Z*)-**11e**	34	41	32	29
(*E*)-**11e**	25	30	10	12
14a	6	10	13	19
14b	17	32	32	24
14c	17	34	46	30
14d	1	17	23	10
14e	16	16	14	19

Dose: 25 mg/kg, *p.o.*

14) P. Bass and H. Cerfontain, *Tetrahedron*, 33, 1509 (1977).

did not form the corresponding nitriles (**13c—e**) under the same conditions. However, heating **7c—e** with excess sodium borohydride in ethanol gave the nitriles (**13c—e**). Reaction of **13a,b** with ethylenediamine monotosylate at 140—160° yielded **14a,b**, while **13c—e** formed **14c—e** only at 220° or higher temperatures. Compounds **14a—e** were also easily obtained by catalytic hydrogenation of the 2-ethenyl-2-imidazoline derivatives (**11**).

Hypoglycemic activity was determined in normal fasted rats and the results are shown in Table II. Most of the compounds (**11** and **14**) were effective. The compounds having a bulkier groups, a phenyl or pyridyl rather than a methyl group, had more potent activity. The difference of activity among phenyl and 2-, 3-, and 4-pyridyl groups was small. Replacement of an ethyl group with ethenyl as a 2-substituent had little effect on the activity. 2-[2-Phenyl-2-(2-pyridyl)ethyl]-2-imidazoline (**14c**), which showed the highest hypoglycemic activity, the highest inhibitory effect against human blood platelet aggregation induced by epinephrine, and the lowest toxicity, was selected for further study from among the 2-substituted-2-imidazoline derivatives. Its pharmaceutical profile will be reported elsewhere.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer, and NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. HPLC were carried out on a Kyowa Seimitsu K-880-D machine. For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used.

Determination of the *Z*: *E* Ratio——After work-up in the manner described below, the NMR spectra of the crude reaction products were taken in $CHCl_3$ or DMSO-d_6. The methine regions were integrated three times and the average values were used to determine the Z: E ratio.

HPLC separation of **8c—e** was carried out on the K-880-D HPLC machine using a TSK-Gel LS-100 column, with 4% MeOH–$CHCl_3$ at a flow rate of 1.0 ml/min. Retension times were: **8c**; Z 295 sec, E 204 sec. **8d**; Z 458 sec, E 290 sec. **8e**; Z 497 sec, E 302 sec.

Reaction A. Ethyl 3-Phenyl-3-(2-pyridyl)acrylate (6c)——An ice-cold solution of 2.30 g (0.1 mmol) of Na metal in 75 ml of EtOH was treated with 22.4 g (0.1 mmol) of **2** and stirred at 5—10° for 10 min. Next, 16.5 g (0.09 mol) of **1c** was added. After stirring at room temperature for 1 hr, the mixture was refluxed for 2 hr and concentrated *in vacuo*. The mixture was treated with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled to give 21.2 g (93%) of a mixture of the (Z)- and (E)-isomers of **6c**. The mixture (5.0 g) could be separated by column chromatography on silica gel (200 g). The $CHCl_3$ eluate gave 2.36 g of the (Z)-isomer and 2.24 g of the (E)-isomer.

Compounds **6a, b, d, e** were obtained from **1a, b, d, e**, respectively, in a similar manner. The results are shown in Table III.

Reaction B. (*Z*)-Ethyl 3-Phenyl-3-(4-pyridyl)acrylate [(*Z*)-6e]——A mixture of 0.13 g (0.5 mmol) of (Z)-**10e** and 0.3 ml of conc. HCl in 2 ml of EtOH was heated at 50—55° for 2 hr, then concentrated *in vacuo*. The residue was mixed with 10 ml of satd. $NaHCO_3$ solution and extracted with Et_2O. The extract was concentrated *in vacuo* to give 0.12 g (92%) of (Z)-**6e**, mp 100—102°.

Other experimental results are shown in Table III.

Reaction C. 3-Phenyl-3-(2-pyridyl)acrylonitrile (7c)——An ice-cold solution of 2.3 g (0.1 mol) of Na metal in 75 ml of EtOH was treated with 17.7 g (0.1 mmol) of **3** and stirred at 5—10° for 10 min. Next, 16.5 g (0.09 mol) of **1c** was added. After stirring at room temperature for 1 hr, the reaction mixture was heated at 50—60° for 1 hr and then concentrated *in vacuo*. The residue was treated with H_2O and extracted with H_2O. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residual oil was distilled *in vacuo* to give 17.5 g (95%) of a mixture of the (Z)- and (E)-isomer of **7c**. The mixture (3.2 g) could be separated by column chromatography on silica gel (50 g). The $CHCl_3$ eluate gave 1.80 g of (E)-**7c** and 0.57 g of (Z)-**7c**.

Compounds **7a, b, d, e** were obtained from **1a, b, d, e**, respectively, in the same way. The results are shown in Table III.

Reaction D. (*Z*)-3-Phenyl-3-(2-pyridyl)acrylonitrile [(*Z*)-7c]——A mixture of 1.12 g (5 mmol) of (Z)-**8c** and 0.79 g (10 mmol) of pyridine in 30 ml of dioxane was treated with 1.16 g (5.5 mmol) of $(CF_3CO)_2O$ at 10—15° with stirring. The mixture was stirred at room temperature for 2 hr and then concentrated *in vacuo*. The residue was mixed with 10% Na_2CO_3 solution and extracted with Et_2O. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was purified by silica gel (10 g) chromatography to give 0.67 g (68%) of (Z)-**7c**.

TABLE III. 3-Phenyl-3-substituted Acrylic Acid Derivatives (**6**, **7**, **8**, and **10**) and 2-(2-Phenyl-2-substituted Ethenyl)-2-imidazolines (**11**)

Compound	Start. material	Reaction	Yield[a] (%)	mp (Solv.) bp (mmHg) (°C)	(Z):(E) Ratio[b]	(Z)-Isomer Yield[c] (%)	(Z)-Isomer mp (Solv.) (°C)	(Z)-Isomer IR (cm^{-1})	(Z)-Isomer Analysis[d] (%) Found	(E)-Isomer Yield[c] (%)	(E)-Isomer mp (Solv.) (°C)	(E)-Isomer IR (cm^{-1})	(E)-Isomer Analysis[d] (%) Found
6a[15]	**1a**	A	92	114—116[f] (4)				1705 1620					
6b[15]	**1b**	A	87	154—156[f] (2)				1725 1620					
6c[16]	**1c**	A	93	167—169[f] (1)	1 : 1	37	Oil	1720 1630 1590 1160	C 75.52 H 5.45 N 5.37	45	Oil	1720 1630 1585 1170	C 75.47 H 5.83 N 5.29
	(*E*)-**10c**	B				89							
6d	**1d**	A	82	178—181 (3)	2 : 1		Oil	1720 1615 1170	C 75.62 H 6.10 N 5.72		Oil	1725 1620 1170	C 75.51 H 6.21 N 5.70
	(*Z*)-**10d**	B				88							
	(*E*)-**10d**	B								90			
6e[16]	**1e**	A	92	165—167[f] (2)	3 : 2	52	101—103 (Et_2O)	1715 1630 1170	C 76.12 H 6.04 N 5.58	35	Oil	1725 1625 1170	C 76.15 H 5.97 N 5.61
	(*Z*)-**10e**	B				92							
	(*E*)-**10e**	B								90			
7a[17]	**1a**	C	96	115—117[f] (5)									
7b[17]	**1b**	C	95	160—165[f] (1)									
7c	**1c**	C	95	160—162 (2)	1 : 2	17	73—75 (Et_2O–p-ether)	2200 1580 1560	C 81.17 H 4.49 N 13.45	53	55—56 (Et_2O–p-ether)	2200 1575	C 81.54 H 5.02 N 13.28
	(*Z*)-**8c**	D				65				78			
	(*E*)-**8c**	D											
7d	**1d**	C	92	182—184 (4)	3 : 1		Oil	2210 1595 1585	C 81.21 H 5.00 N 13.30		Oil	2210 1595 1580	C 81.35 H 5.09 N 13.43
	(*Z*)-**8d**	D				69				78			
	(*E*)-**8d**	D											
7e	**1e**	C	93	75—85	4 : 1		106—107 (Et_2O–Me_2CO)	2210 1600 1585	C 81.72 H 5.01 N 13.43		118—120 (Me_2CO)	2220 1590	C 81.35 H 4.98 N 13.31
	(*Z*)-**8e**	D				87							
	(*E*)-**8e**	D								88			
8b[18]	**1b**	E	62	150—151[f] (MeOH)				1650 1605					
8c	**1c**	E	78		2 : 1	40	200—202 (MeOH)	1660 1600	C 74.74 H 5.46 N 12.74	20	155—157 (MeOH)	1660 1605	C 75.10 H 5.53 N 12.13
	(*Z*)-**7c**	F				0				70			
	(*E*)-**7c**	F											
8d	**1d**	E	75		2 : 1	42	176—177 (MeOH)	1665	C 75.20 H 5.44 N 12.45	25	152—153 (MeOH)	1670	C 75.30 H 5.52 N 12.39
	7d	F	76										
8e	**1e**	E	75		3 : 1	58	225—228 (MeOH)	1690 1630 1595	C 74.63 H 5.52 N 12.29	22	168—169 (MeOH)	1670 1600	C 75.13 H 5.49 N 12.36
	7e	F	67										
10b	**8b**	I	96	Oil				1625 1070					
10c	(*Z*)-**8c**	I				0					Oil	1620	
	(*E*)-**8c**	I								62		1580 1080	
10d	(*Z*)-**8d**	I				53	Oil	1625 1090			Oil	1630 1080	
	(*E*)-**8d**	I								52			
10e	(*Z*)-**8e**	I				65	78—80 (Et_2O–p-ether)	3250 1635 1600 1115	C 76.17 H 6.40 N 11.01		Oil	1635 1595 1090	
	(*E*)-**8e**	I								50			
11a	**1a**	K	43	64—66 (Et_2O)				1640 1595	C 77.05 H 7.05 N 14.98				
	9a	H	32										
11b	**1b**	K	40	103—104 (Et_2O)				1625 1620 1580	C 81.67 H 6.43 N 11.02				
	9b	H	55										
	10b	J	88										
11c	**1c**	K	70	Oil	1 : 1						90—92	1580	C 77.04
	(*E*)-**10c**	J								70	(Me_2CO–Et_2O)	1560	H 6.06 N 16.80
11d	**1d**	K	77	Oil			196—198[e]	1635 1625 1570	C 59.38 H 5.34 N 12.95	20	124—125 (Me_2CO–Et_2O)	1625 1570 1550	C 77.09 H 6.08 N 16.80
	(*Z*)-**10d**	J				68				68			
	(*E*)-**10d**	J											
11e	**1e**	K	79	Oil	1 : 1	5	144—145 (Me_2CO)	1600 1490 1410	C 76.98 H 6.07 N 16.85	3	96—97 (Et_2O)	1585 1485 1405	C 77.01 H 6.12 N 16.71
	(*Z*)-**10e**	J				64				81			

a) Yield of a mixture of the (*Z*)- and (*E*)-isomers.
b) Determined by NMR spectroscopy or HPLC.
c) Yield of separated prepure (*Z*)- and (*E*)-isomer, as indicated.
d) Formula (Calcd): **6c**—**e**=$C_{16}H_{15}NO_2$ (C, 75.87; H, 5.97; N, 5.53), **7c**—**e**=$C_{14}H_{16}N_2$ (C, 81.53; H, 4.89; N, 13.58), **8c**—**e**=$C_{16}H_{12}N_2O$ (C, 74.98; H, 5.39; N, 12.49), **10c**—**e**=$C_{16}H_{16}N_2O$ (C, 76.16; H, 6.39; N, 11.01), **11a**=$C_{12}H_{14}N_2$ (C, 77.38; H, 7.58; N, 14.98), **11b**=$C_{17}H_{16}N_2$ (C, 82.26; H, 6.45; N, 11.29), **11c**—**e**=$C_{16}H_{16}N_2$ (C, 77.08; H, 6.06; N, 16.86), (*Z*)-**11d**=$C_{16}H_{17}Cl_2N_3$ (C, 59.63; H, 5.32; N, 13.04).
e) Hydrochloride salt.
f) Boiling and melting points reported in the literature are as follows: **6a**=bp 140—141° (4 mmHg), **6b**=bp 186—189° (15 mmHg), **6c**=mp 48—48.5°, **6e**=mp 104—105°, **7a**=bp 91—93° (3 mmHg), **7b**=bp 160—200° (1.5 mmHg), **8b**=mp 153—154°.

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Table IV. 3-Phenyl-3-substituted Propionic Acid Derivatives (**12** and **13**) and 2-(2-Phenyl-2-substituted Ethyl)-2-imidazolines (**14**)

Compound	Start. material	Reaction	Yield (%)	mp (Solv.) bp (mmHg) (°C)	IR (cm^{-1})	Analysis[a] (%) Found	NMR[b] (δ)
12a[19]	**6a**	L	92	93—95[c] (5)	1730		
12b[20]	**6b**	L	95	153—154[c] (3)	1735		
12c[21]	**6c**	L	97	158—162[c] (2)	1730 1590	C 75.12 H 6.51 N 5.69	8.55 (1H, m, 2-Pyr. –H) 7.27 (5H, s, C_6H_5) 4.63 (1H, t, CH) 2.7—3.7 (2H, m(ABX), CH_2)
12d[22]	**6d**	L	91	52—53[c] (Et_2O–p-ether)	1710	C 74.99 H 6.68 N 5.64	8.42 (2H, m, 2-Pyr. –H) 7.22 (5H, s, C_6H_5) 4.53 (1H, t, CH) 3.02 (2H, d, CH_2)
12e	**6e**	L	93	179—181 (1)	1715 1630	C 75.44 H 6.76 N 5.43	8.50 (2H, m, 2-Pyr. –H) 7.24 (5H, s, C_6H_5) 4.53 (1H, t, CH) 3.04 (2H, d, CH_2)
13a[23]	**7a**	L	89	93—94[c] (3)	2240 1490		
13b[23]	**7b**	L	89	87—90 (Et_2O–p-ether)	2240 1590 1440		
13c	**7c** **7c**	L M	0 65	166—169 (2)	2240 1590 1430	C 80.53 H 5.94 N 13.58	8.67 (1H, m, 2-Pyr. –H) 7.36 (1H, s, C_6H_5) 4.45 (1H, t, CH) 2.7—3.7 (2H, m(ABX), CH_2)
13d	**7d** **7d**	L M	0 61	180—182 (2)	2240 1425	C 80.61 H 6.08 N 13.53	8.57 (2H, m, 2-Pyr. –H) 7.36 (5H, s, C_6H_5) 4.45 (1H, t, CH) 3.07 (2H, d, CH_2)
13e	**7e** **7e**	L M	0 67	178—179 (1)	2240 1595	C 80.06 H 6.11 N 13.53	8.60 (2H, m, 2-Pyr. –H) 7.1—7.5 (7H, m, Ar. –H) 4.46 (1H, t, CH) 3.07 (2H, d, CH_2)
14a[7]	**12a**	N	72	59—61[c] (Et_2O–hexane)	1605	C 76.62 H 8.42 N 14.71	7.30 (5H, s, C_6H_5) 2.9—3.6 (1H, m, CH) 3.48 (4H, s, CH_2CH_2) 2.50 (2H, d, CH_2) 1.32 (3H, d, CH_3)
14b[24]	**11b** **13b**	P O	95 56	98—101[c] (Et_2O–hexane)	1605	C 81.42 H 7.32 N 11.11	7.26 (10H, s, C_6H_5) 4.47 (1H., t, CH) 3.42 (4H, s, CH_2CH_2) 3.02 (2H, d, CH_2)
14c[21]	**11c** **12c** **13c**	P N O	96 60 66	119—120[c] (Me_2CO)	1615 1585	C 76.21 H 6.85 N 16.42	8.50 (1H, m, 2-Pyr. –H) 6.85—7.6 (8H, m, Ar. –H) 4.55 (1H, t, CH) 3.38 (4H, s, CH_2CH_2) 2.65—3.5 (2H, m(ABX), CH_2)
14d	**11d** **12d** **13d**	P N O	92 61 58	104—105 (Me_2CO)	1605 1490	C 76.19 H 6.85 N 16.35	8.51, 8.37 (2H, m, 2-Pyr. –H) 7.23 (5H, s, C_6H_5) 4.53 (1H, t, CH) 3.43 (4H, s, CH_2CH_2) 2.95 (2H, d, CH_2)

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Compound	Start. material	Reaction	Yield (%)	mp (Solv.) bp (mmHg) (°C)	IR (cm^{-1})	Analysis[a] (%) Found	NMR[b] (δ)
14e	**11e**	P	94	107—108	1610	C 76.72	8.45 (2H, m, 2-Pyr. -H)
	12e	N	65	(C_6H_5)	1590	H 6.87	7.27 (5H, s, C_6H_5)
	13e	O	54			N 16.54	4.49 (1H, t, CH)
							3.43 (4H, s, CH_2CH_2)
							2.93 (2H, d, CH_2)

a) Formula (Calcd): **12c—e**=$C_{16}H_{17}NO_2$ (C, 75.25; H, 6.71; N, 5.69), **13c—e**=$C_{14}H_{12}N_2$ (80.36; H, 5.92; N, 13.72), **14a**=$C_{12}H_{16}N_2$ (C, 76.55; H, 8.57; N., 14.88), **14b**=$C_{17}H_{18}N_2$ (C, 81.59; H, 7.25; N, 11.20), **14c—e**=$C_{16}H_{17}N_3$ (C, 76.43; H, 6.81; N, 16.42).
b) Solvent: $CDCl_3$.
c) Boiling and melting points reported in the literature are as follows: **12a**=bp 118° (9 mmHg), **12b**=bp 190—193° (12 mmHg), **12c**=bp not described, **12d**=mp 59—60°, **13a**=bp not described, **13b**=mp 88—90°, **14a**=mp 92.5—9·45° (maleate), **14b**=mp 101°, **14c**=mp 122—123°.

Other experimental results are shown in Table III.

Reaction E. 3-Phenyl-3-(4-pyridyl)acrylamide (8e)——An ice-cold solution of 2.30 g (0.1 mmol) of Na metal in 75 ml of EtOH was treated with 20 g (0.1 mmol) of **4** and stirred at 5—10° for 10 min. Next, 16.5 g (0.09 mol) of **1e** was added. After stirring at room temperature for 1 hr, the mixture was heated at 50—60° for 1 hr and concentrated *in vacuo*. The resulting crystalline material was filtered and washed with H_2O to give 16.8 g (83%) of crude **8e** as a mixture of the (*Z*)- and (*E*)-isomers. The mixture could be separated by column chromatography on silica gel (400 g). Elution with MeOH–$CHCl_3$ (1: 100) gave 11.5 g (58%) of (*Z*)-**8e** and 4.4 g (22%) of (*E*)-**8e**.

Compounds **8a—d** were obtained from **1a—d**, respectively, in the same way. The mixtures of (*Z*)- and (*E*)-isomers of **8c, d** could also be separated by column chromatography on silica gel. The results are shown in Table III.

Reaction F. (*E*)-3-Phenyl-3-(2-pyridyl)acrylamide [(*E*)-8c]——A mixture of 0.50 g (2.4 mmol) of (*E*)-**7c** and 1.5 g of conc. H_2SO_4 in 1.5 g of AcOH was heated at 100° for 4 hr then poured into ice-water. The mixture was made basic with 10% NaOH solution and insoluble material was collected to give 0.38 g (70%) of (*E*)-**8c**.

Other experimental results are shown in Table III.

Reaction G. Ethyl N-Isopropyl-3-phenyl-2-butenoimidate (9a)——A mixture of 4.85 g (30 mmol) of $FeCl_3$ in 20 ml of 2-chloropropane was treated with 4.30 g (30 mmol) of **7a** at 0° with stirring. The mixture was refluxed with stirring for 4 hr and cooled to 0° in an ice-bath. Next, 4.5 ml of EtOH was added below 5° with stirring, and the mixture was poured into 100 ml of 10% Na_2CO_3 solution. The organic layer was separated and the water layer was extracted with Et_2O. The combined organic layer was washed with H_2O, dried and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 6.7 g (87%) of **9a**, bp 182—184° (9 mmHg). IR ν_{max}^{KBr} cm^{-1}: 2960, 1665. NMR δ ($CDCl_3$): 7.5 (5H, m, C_6H_5), 6.30 (1H, s, =CH), 4.25 (2H, q, O–CH_2), 3.72 (1H, m, N–CH), 2.20 (3H, s, CH_3), 1.33 (3H, t, CH_3), 1.10 (6H, d, CH_3). *Anal.* Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.84; H, 9.05; N, 6.01.

Following a procedure similar to that used for the synthesis of **9a**, 2.05 g (10 mmol) of **7b** was treated with 1.60 g $FeCl_3$ in 20 ml of 2-chloropropane and then with 1.5 ml of EtOH to give 2.6 g (89%) of **9b**, bp 113—115° (2 mmHg). IR ν_{max}^{KBr} cm^{-1}: 2960, 1660. NMR δ ($CDCl_3$): 7.35 (5H, s, C_6H_5), 7.3—8.0 (5H, m, C_6H_5), 6.41 (1H, s, =CH), 3.95 (2H, q, O–CH_2), 3.72 (1H, m, N–CH), 0.96 (6H, d, CH_3), 0.90 (3H, t, CH_3). *Anal.* Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.50; H, 7.98; N, 4.77.

Reaction H. 2-(2-Phenyl-1-propenyl)-2-imidazoline (11a)——A mixture of 2.31 g (10 mmol) of **9a** and 0.90 g (15 mmol) of ethylenediamine was heated at 110—120° for 1 hr. After cooling, the reaction mixture was dissolved in Et_2O and the solution was washed with satd. NaCl solution, dried, and concentrated to give 0.56 g (32%) of **11a**.

Compound **11b** was obtained in a similar way. The results are shown in Table III.

Reaction I. (*E*)-Ethyl 3-Phenyl-3-(2-pyridyl)acrylimidate [(*E*)-10c]——The hydrochloride of (*E*)-**8c** (2.60 g, 10 mmol) was added to a solution of Meerwein salt, prepared from 5.80 g (40 mmol) of BF_3–Et_2O and 2.90 g (40 mmol) of epichlorohydrin, in 40 ml of CH_2Cl_2. The mixture was heated under reflux with stirring overnight and then poured into cold satd. Na_2CO_3 solution. The organic layer was separated and the water layer was extracted with $CHCl_3$. The combined organic layer was washed with H_2O, dried, and concentrated *in vacuo*. The residue was mixed with a large amount of petr. ether and insoluble material was filtered off. The filtrate was concentrated *in vacuo* to give 1.55 g (62%) of (*E*)-**10c** as a crude oil which was used for the subsequent reaction without further purification.

Other experimental results are shown in Table III.

Reaction J. (*E*)-2-[2-phenyl-2-(2-pyridyl)ethenyl]-2-imdazoline [(*E*)-11c]——A solution of 1.55 g (6.2 mmol) of crude (*E*)-**8c** and 0.73 g (12 mmol) of ethylenediamine in 15 ml of EtOH was refluxed for 2 hr.

The mixture was concentrated *in vacuo* and the residue was dissolved in Et_2O. The solution was washed with satd. NaCl solution, dried, and concentrated *in vacuo* to give 1.08 g (70%) of (*E*)-**11c**.

Compounds **11b**, **d**, **e** were similarly obtained from **8b**, **d**, **e**, respectively, by the method described above. The results are shown in Table III.

Reaction K. 2-[2-Phenyl-2-(2-pyridyl)ethenyl]-2-imidazoline (11c)——An ice-cold solution of 0.46 g (20 mmol) of Na metal in 15 ml of EtOH was treated with 4.44 g (20 mmol) of **3** and stirred at 5—10° for 10 min. Next, 2.76 g (15 mmol) of **1c** was added. The mixture was stirred at room temperature for 8—10 hr then concentrated *in vacuo*. The residue was mixed with H_2O and neutralized to pH 6—7 adding conc. HCl. After washing the mixture with Et_2O to remove the unchanged ketone (**1c**), the mixture was made basic with conc. NaOH solution and extracted with $CHCl_3$. The extract was washed with satd. NaCl solution, dried, and concentrated *in vacuo* to give 2.52 g (70%) of oily **11c** as a mixture of the (*Z*)- and (*E*)-isomers.

Compounds **11a**, **b**, **d**, **e** were similarly obtained from **1a**, **b**, **d**, **e**, respectively, in the manner described above, except in the cases of **1a**, **b**, which were refluxed for 10—20 hr. The results are shown in Table III.

Reaction L. Ethyl 3-phenyl-3-(4-pyridyl)propionate (12e)——Compound **6e** (4.00 g, 16 mmol) in 20 ml of EtOH was hydrogenated over 2.5 g of 5% Pd-C catalyst at room temperature under atmospheric pressure. When H_2 absorption ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was distilled *in vacuo* to give 3.70 g (93%) of **12e**.

Compounds **12a—d**, **13a**, **b** were obtained similarly from **6a—d**, **7a**, **b**, respectively, in the manner described above. The results are shown in Table IV.

Reaction M. 3-Phenyl-3-(2-pyridyl)propionitrile (13c)——A mixture of 2.06 g (10 mmol) of **7c** and 2.00 g of $NaBH_4$ in 50 ml of EtOH was refluxed for 8 hr then concentrated *in vacuo*. The residue was mixed with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The remaining oil was distilled *in vacuo* to give 1.36 g (65%) of **13c**, bp 166—169° (2 mmHg).

Compounds **13d**, **e** were obtained from **7d**, **e**, respectively, in the manner described above. The results are shown in Table IV.

Reaction N. 2-(2-Phenylpropyl)-2-imidazoline (14a)[6]——A mixture of 13.4 g (70 mmol) of **12a** and 42.0 g (0.7 mol) of ethylenediamine was refluxed for 20 hr. Excess ethylenediamine was evaporated off at atmospheric pressure. Next, 1.50 g of Mg metal was added and the mixture was heated at 230—240° for 2 hr under an N_2 atmosphere. The reaction residue was distilled *in vacuo* to give 9.40 g (72%) of **14a**.

Compounds **14b—e** were obtained from **12b—e**, respectively, in a similar manner. The results are shown in Table IV.

Reaction O. 2-(2,2-Diphenylethyl)-2-imidazoline (14b)——A mixture of 2.07 g (10 mmol) of **13b** and 2.78 g (12 mmol) of ethylenediamine monotosylate was heated at 200—220° for 3 hr. After cooling, the residue was treated with 10% NaOH solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give 1.40 g (56%) of **14b**.

Compounds **14c—e** were similarly prepared from **13c—e**, respectively. The results are shown in Table IV.

Reaction P. 2-(2,2-Diphenylethyl)-2-imidazoline (14b)——Compound **11b** (3.70 g, 13 mmol) in 10 ml of EtOH was hydrogenated over 0.30 g of 5% Pd-C and worked up in the usual way to give 2.70 g (83%) of **14b**.

Compounds **14a**, **c—e** were obtained from **11a**, **c—e**, respectively, in a similar manner. The results are shown in Table IV.

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