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Synthesis and aldose reductase inhibitory activity of acetic acid derivatives of pyrrolo[1,2-*c*]imidazole

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Summary — Various acetic acid derivatives of pyrrolo[1,2-*c*]imidazole were prepared and evaluated for aldose reductase inhibitory activity. Most of the compounds inhibited aldose reductase isolated from rat lens *in vitro* and decreased sorbitol formation in sciatic nerves of diabetic rats *in vivo*. Of the test compounds, 2-carboxymethyl-6-ethyl-5,7-dimethyl-3-oxo-1(2*H*)-thioxo-1*H*-pyrrolo[1,2-*c*] imidazole **124** was found to be the most orally active aldose reductase inhibitor, with an inhibitory potency similar to that of AD-5467.

aldose reductase inhibitor / pyrrolo[1,2-*c*]imidazole derivatives / sorbitol accumulation inhibition

Introduction

A wide variety of compounds have been reported as aldose reductase inhibitors (ARIs) and are considered to offer therapeutic possibilities in the treatment of chronic complications in diabetes, such as retinopathy, neur-opathy, nephropathy and cataracts [1–3]. Active compounds of ARIs *in vivo* are limited, for the most part, to distinct structural classes, *ie*, acetic acid derivatives (*eg*, tolrestat, epalrestat, ponalrestat, AD-5467) and cyclic imide derivatives (*eg*, sorbinil, M-79175, CT-112).

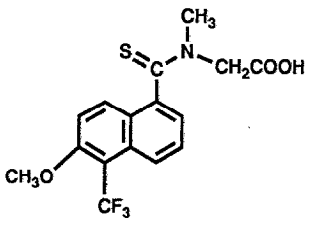
In order to search for new ARIs, we have focused on the synthesis and the biological activity of compounds with an acetic acid moiety because sorbinil with a cyclic imide moiety showed a low incidence of side effects due to hypersensitivity [4, 5]. We found that acetic acid derivatives of pyrrolo[1,2-*c*] imidazole showed inhibitory activity for AR.

In this article, we report on the synthesis and biological results of acetic acid derivatives of pyrrolo[1,2-*c*]imidazole. We found in this study that 2-carboxymethyl-6-ethyl-5,7-dimethyl-3-oxo-1(2*H*)-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole **124** represents a very potent orally active ARI. Its potency was similar to that of AD-5467, a carboxylic acid type ARI under clinical evaluation.

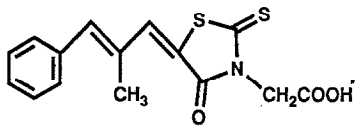
Chemistry

Derivatives of 2-carboxymethyl-1,3(2*H*)-dioxo-1*H*-pyrrolo[1,2-*c*]imidazole **7** were prepared as outlined in scheme 1. First, compounds **1** were treated with acyl halide in the presence of aluminium chloride according to the method of Murakami *et al* [6] to afford compounds **2**. The compounds **2** were treated with triethylsilane in trifluoroacetic acid according to the method of West et *al* [7] to give compounds **3**. Compounds **3** were hydrolyzed under alkaline conditions followed by amidation with glycine ethyl ester, diethyl cyanophosphonate and triethylamine according to the method of Yamada *et al* [8], to yield amide derivatives **5**. Finally, compounds **7** were prepared from esters **6**, obtained by cyclization of compounds **5** with 1,1'-carbonyldiimidazole, followed by acidic hydrolysis with concentrated HCl in acetic acid.

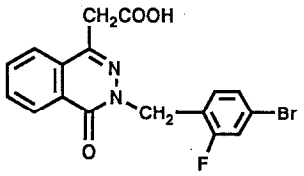
Derivatives of 2-carboxymethyl-3-oxo-1(2*H*)-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole **9** and derivatives of



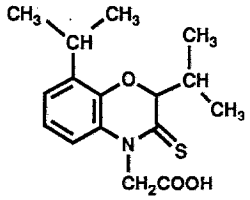
tolrestat



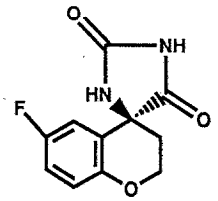
epalrestat



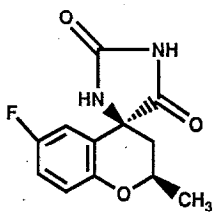
ponalrestat



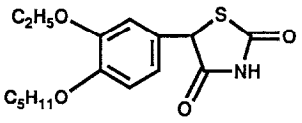
AD-5467



sorbinil



M-79175



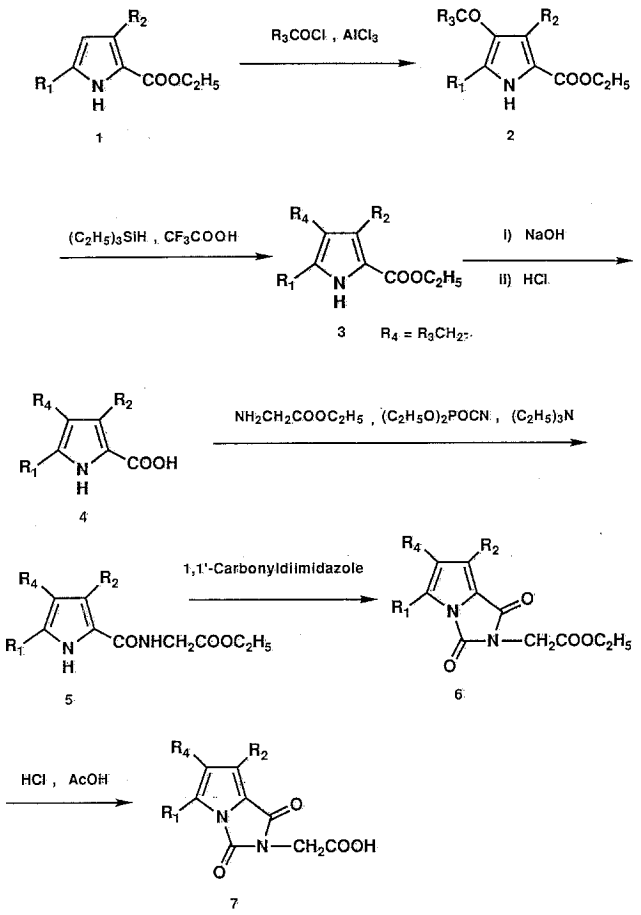
CT-112

2-carboxymethyl-1,3(2*H*)-dithioxo-1*H*-pyrrolo[1,2-*c*] imidazole **11** were obtained by following the procedure in scheme 2. Treatment of compounds **6** with phosphorus pentasulfide, according to the method of Papadopoulos [9], afforded compounds **8** and **10**. Acid hydrolysis of **8** and **10** gave compounds **9** and **11**, respectively. These compounds are listed in tables I and II.

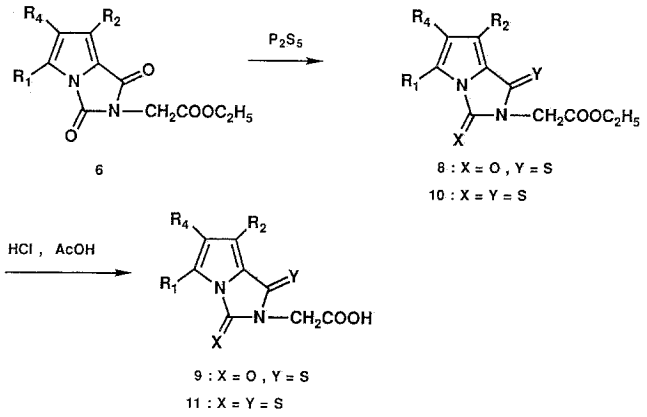
Results and discussion

The test compounds were evaluated for their *in vitro* inhibitory activity against aldose reductase iso-lated from rat lens and for their ability to inhibit sorbitol formation in the sciatic nerve of a streptozotocinized rat model after oral administration. These biological data are summarized in tables I and III.

Introduction of a lipophilic alkyl group to the 6-position of the 5,7-unsubstituted pyrroloimidazole ring enhanced *in vitro* activity (compare **78** with **79** – **81**; table I). Introduction of substituted benzyl groups to the 6-position enhanced *in vitro* activity, but the trifluoromethylbenzyl and *tert*-butylbenzyl groups showed slightly less activity than other benzyl groups (compare **78** with **82–87**). Monothiocarbonyl compounds with alkyl groups at the 6-position were more potent than corresponding dicarbonyl compounds (compare **78** with **112**, **79** with **113** and **80** with **114**; table I) and an increase in lipophilicity of the alkyl group at the 6-position enhanced activity (compare **112** with **113–115**; table I) as dicarbonyl, mono- and dithiocarbonyl 5,7-unsubstituted compounds. Although monothiocarbonyl compounds showed roughly the same activity as dithiocarbonyl compounds (compare **113** with **141** and **114** with **142**; table I), only compound **140** showed more activity than the corresponding monothiocarbonyl compound **112**. Changing the dicarbonyl compounds to the respective monothiocarbonyls (compare **83** with **117**; table III) and the monothiocarbonyls to their respective dithiocarbonyls (compare **114** with **142** and **120** with **148**; table III) increased activity at 100 x 2 (mg/kg/d), but the most active compound **148** among tested 5,7-unsubstituted compounds had significantly less activity *in vivo* at 50 x 2 (mg/kg/d) than at 100 x 2 (mg/kg/d) (**148**, table III).



Scheme 1.



Scheme 2.

In 5- and 7-methyl substituted compounds, introduction of a lipophilic alkyl group at the 6-position did not enhance *in vitro* activity (**89–92**; table I), but substituted benzyl groups at the 6-position showed an increase in *in vitro* activity (compare **88** with **93** and **94**). Change of a carbonyl group for the thiocarbonyl group showed enhancement in *in vitro* potency (compare **88** with **122**, **89** with **123**, **90** with **124**, **91** with **125**, **92** with **126** and **93** with **127**; table I). However, the high *in vitro* activities observed for 5,7-dimethyl compounds were not accompanied by equally high activities *in vivo* as 5,7-unsubstituted compounds. Among tested dimethyl compounds, 2-carboxymethyl-6-ethyl-5,7-dimethyl-3-oxo-1(2*H*)-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole (**124**; table III), with moderate *in vitro* activity (IC_{50} 2.3 x 10^{-7} M; table I), showed the most potent *in vivo* activity at 50 x 2 (mg/kg/d), which was almost the same as that of AD-5467 used as a reference compound. Change in the lipophilicity of the alkyl substituent, or replacement by the 4-fluorobenzyl or 4-bromo-2-fluorobenzyl group at the 6-position, did not improve *in vivo* activity (compare **124** with **123**, **125** and **126**, **124** with **127** and **128**; table III).

The above *in vitro* data demonstrate that introduction of a lipophilic alkyl group or a substituted benzyl group at the 6-position and/or changing from a dicarbonyl compound to the monothiocarbonyl or dithiocarbonyl compound increase *in vitro* activity, although in some cases the change in activity is relatively small.

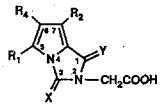
On the other hand, the high *in vitro* activities observed for 5,7-unsubstituted and 5,7-dimethyl compounds were not accompanied by equally high activities *in vivo*. Compound **124** having moderate *in vitro* activity among tested compounds showed the most potent activity *in vivo*. A possible explanation for this might be that the replacement by a methyl group at the 5- and 7-positions and introduction of a substituent possessing appropriate lipophilicity at the 6-position of the pyrroloimidazole ring may be effective in improving the intestinal absorption, metabolism and distribution to the target tissue, but data to this effect has not yet been collected.

This study has revealed that 2-carboxymethyl-6-ethyl-5,7-dimethyl-3-oxo-1(2*H*)-thioxo-1*H*-pyrrolo-[1,2-*c*]imidazole **124** is a very potent, orally active ARI and has activity similar to that of AD-5467, a carboxylic acid type ARI under clinical evaluation.

Experimental protocols

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were determined in the cited solvent on a JEOL JMN-FX100 (100 MHz) spectrometer with tetramethylsilane as internal

Table I. Physical and biological data for acetic acid derivatives of pyrrolo[1,2-*c*]imidazole.



Compd	R_4	mp (°C)	Recryst	Yield (%)	In vitro $IC_{50} \times 10^{-6}$ M
R_1=R_2=H ; X=Y=O					
78	H	161-163	A	42	>100
79	$(CH_3)_2CH$	155-156	A	62	75
80	$(CH_3)_2CHCH_2$	183.5-184	A	87	31
81	cyclohexylmethyl	182-184	A	86	9.8
82	4-CH_3-$C_6H_4CH_2$	166-167	A	85	6.8
83	4-Cl-$C_6H_4CH_2$	220-222	A	88	6.3
84	4-CF_3-$C_6H_4CH_2$	184-185	A	98	13
85	4-Br,2-F-$C_6H_3CH_2$	197.5-199	A	87	2.9
86	3,4-$(Cl)_2C_6H_3CH_2$	197-199	B	58	4.6
87	4-$(CH_3)_3C$-$C_6H_4CH_2$	179-180	A	86	12
R_1=R_2=CH_3 ; X=Y=O					
88	H	208-209	A	91	>100
89	CH_3	225-227	A	76	170
90	C_2H_5	190.5-192	C	86	170
91	$CH_3CH_2CH_2$	185-186	A	95	460
92	$(CH_3)_2CHCH_2$	170.5-171	A	90	170
R_1=R_2=CH_3 ; X=Y=O					
93	4-F-$C_6H_4CH_2$	210-210.5	A	92	50
94	4-Br,2-F-$C_6H_3CH_2$	205-207	A	97	6.3
R_1=R_2=H ; X=O , Y=S					
112	H	203-204	A	81	37
113	$(CH_3)_2CH$	176-178	A	97	15
114	$(CH_3)_2CHCH_2$	179-180	B	83	4.9
115	cyclohexylmethyl	157-158	B	78	3.7
116	4-CH_3-$C_6H_4CH_2$	200.5-201.5	B	72	2.4
117	4-Cl-$C_6H_4CH_2$	220-222	A	98	6.2
118	4-CF_3-$C_6H_4CH_2$	197-198	A	93	5.6
119	4-Br,2-F-$C_6H_3CH_2$	224-225	A	88	2.4
120	3,4-$(Cl)_2$-$C_6H_3CH_2$	165-167.5	A	92	3.3
121	4-$(CH_3)_3C$-$C_6H_4CH_2$	174-176	A	96	7.0
R_1=R_2=CH_3 ; X=O , Y=S					
122	H	226-227	A	65	100
123	CH_3	249-250	A	80	70
124	C_2H_5	213.5-214.5	A	83	23
125	$CH_3CH_2CH_2$	205-206	A	92	30
126	$(CH_3)_2CHCH_2$	187-189	A	90	21
127	4-F-$C_6H_4CH_2$	254-255	A	92	7.3
128	4-Br,2-F-$C_6H_3CH_2$	238-240	A	92	4.4
R_1=R_2=H; X=Y=S					
140	H	248-250	A	70	6.4
141	$(CH_3)_2CH$	163-165	A	83	7.0
142	$(CH_3)_2CHCH_2$	198-199.5	A	81	5.4
143	cyclohexylmethyl	186-188	E	79	4.1
144	4-CH_3-$C_6H_4CH_2$	230-233	A	78	3.8
145	4-Cl-$C_6H_4CH_2$	247-249	D	58	3.0
146	4-CF_3-$C_6H_4CH_2$	240-243	A	79	5.6
147	4-Br,2-F-$C_6H_3CH_2$	252-255	A	87	2.0
148	3,4-$(Cl)_2$-$C_6H_3CH_2$	203-205	A	93	4.4
149	4-$(CH_3)_3C$-$C_6H_4CH_2$	180-183	A	64	6.5
R_1=R_2=CH_3 ; X=Y=S					
150	C_2H_5	249-251	A	88	24

Recrystallization solvents. A: AcOH/H_2O; B: EtOH/H_2O; C: *iso*-Pr_2O/CH_2Cl_2/*n*-hexane; D: CH_2Cl_2/*n*-hexane/MeOH; E: MeOH/H_2O.

standard. The chemical shifts are given in ppm and the coupling constants in Hz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Electron ionization mass (EI-MS) spectra were recorded on a JEOL JMS DX-303 spectrometer. Elemental analyses (C, H, N) were performed on a Yanagimoto MT-2 CHN recorder. Analytical results for elements were within ± 0.4% of theoretical values.

Column chromatography and thin-layer chromatography were carried out on a Kieselgel 60 (70–230 mesh) and with a Kieselgel 60 F-254 (E Merck). Visualization was accomplished with UV light.

The starting acylchlorides were commercially available, and 4-bromo-2-fluorobenzoyl chloride was prepared from 4-bromo-2-fluorobenzoic acid [10] by treatment with thionyl chloride. AR inhibitor, AD-5467, was synthesized in our laboratory.

General procedure for the synthesis of ***12–21***

The following procedure for the synthesis of ethyl 4-isobutyryl-2-pyrrolecarboxylate **12** is representative. The other compounds, **13–21**, were obtained similarly. Physical data for these compounds are summarized in tables IV and V. Ethyl 3,5-dimethyl-2-pyrrolecarboxylate (**1**, $R_1 = R_2 = CH_3$) was commercially available and ethyl 2-pyrrolecarboxylate (**1**, $R_1 = R_2 = H$) was synthesized by the method of Bailey *et al* [11].

Ethyl 4-isobutyryl-2-pyrrolecarboxylate ***12***

(**2**, $R_1 = R_2 = H$, $R_3 = (CH_3)_2CH$)

A solution of ethyl 2-pyrrolecarboxylate (30.6 g, 220 mmol) in dichloroethane (100 ml) was added to a mixture of isobutyryl chloride (50.0 g, 469 mmol) and $AlCl_3$ (63.7 g, 478 mmol) in

Table II. Physical data for acetic acid derivatives of pyrrolo[1,2-*c*]imidazole.

Compd	Formula	Analysis	MS (M^+)	^{1}H-NMR (DMSO-d_6) δ ppm
78	$C_8H_6N_2O_4$	C, H, N	194	4.25 (s, 2H, CH_2COO), 6.60 (t, J=3 Hz, 1H, pyrrole H), 7.03 (d, J=3 Hz, 1H, pyrrole H), 7.68 (d, J=3 Hz, pyrrole H), 13.4 (br s, 1H, COOH)
79	$C_{11}H_{12}N_2O_4$	C, H, N	236	1.19 (d, J=7 Hz, 6H, $2CH_3$), 2.6-3.0 (m, 1H, CH), 4.23 (s, 2H, CH_2COO), 7.01 (s, 1H, pyrole H), 7.46 (s, 1H, pyrrole H), 13.5 (br s, 1H, COOH)
80	$C_{12}H_{14}N_2O_4$	C, H, N	250	0.88 (d, J=7 Hz, 6H, $2CH_3$), 1.6-2.0 (m, 1H,CH), 2.34 (d, J=7 Hz, 2H, CH_2), 4.22 (s, 2H, CH_2COO), 6.90(s, 1H, pyrrole H), 7.45 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
81	$C_{15}H_{18}N_2O_4$	C, H, N	290	0.6-2.0 (m, 11H, cyclohexane H), 2.34 (d, J=6 Hz, 2H, CH_2), 4.22 (s, 2H, CH_2COO),6.89 (s, 1H, pyrrole H), 7.43 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
82	$C_{16}H_{14}N_2O_4$	C, H, N	298	2.26 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 4.22 (s, 2H, CH_2COO), 6.86 (s, 1H, pyrrole H), 7.0-7.3 (m, 4H, ArH), 7.47 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
83	$C_{15}H_{11}ClN_2O_4$	C, H, N	318	3.82 (s, 2H, CH_2), 4.23 (s, 2H, CH_2COO), 6.90 (s, 1H, pyrrole H), 7.2-7.5 (m, 4H, ArH), 7.52 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
84	$C_{16}H_{11}F_3N_2O_4$	C, H, N	352	3.94 (s, 2H, CH_2), 4.22 (s, 2H, CH_2COO), 6.93 (s, 1H, pyrrole H), 7.50 (d, J=9 Hz, 2H, ArH), 7.57 (s, 1H, pyrrole H), 7.67 (d, J=9Hz, 2H, ArH), 13.3 (br s, 1H, COOH)
85	$C_{15}H_{10}BrFN_2O_4$	C, H, N	380	3.83 (s, 2H, CH_2), 4.22 (s, 2H, CH_2COO), 6.89 (s, 1H, pyrrole H), 7.15-7.6 (m, 3H, ArH), 7.49 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
86	$C_{15}H_{10}Cl_2N_2O_4$	C, H, N	352	3.84 (s, 2H, CH_2), 4.22 (s, 2H, CH_2COO), 6.95 (s, 1H, pyrrole H), 7.2-7.7 (m, 3H, ArH), 7.57 (s, 1H, pyrrole H)
87	$C_{19}H_{20}N_2O_4$	C, H, N	340	1.25 (s, 9H, $3CH_3$), 3.77 (s, 2H, CH_2), 4.21 (s, 2H, CH_2COO), 6.89 (s, 1H, pyrrole H), 7.18 (d, J=9 Hz, 2H, ArH), 7.32 (d, J=9 Hz, 2H, ArH), 7.50 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
88	$C_{10}H_{10}N_2O_4$	C, H, N	222	2.19 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.18 (s, 2H, CH_2COO), 6.16 (s, 1H, pyrrole H), 13.5 (br s, 1H, COOH)
89	$C_{11}H_{12}N_2O_4$ .H_2O	C, H, N	236	1.90 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.17 (s, 2H, CH_2COO), 13.6 (br s, 1H, COOH)
90	$C_{12}H_{14}N_2O_4$	C, H, N	250	1.03 (t, J=7 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.33 (t, J=7 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 4.17 (s, 2H, CH_2COO), 13.3 (br s, 1H, COOH)
91	$C_{13}H_{16}N_2O_4$	C, H, N	264	0.88 (t, J=7 Hz, 3H, CH_3), 1.2-1.7 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.35 (t, J=7 Hz, 2H, CH_2), 4.17 (s, 2H, CH_2COO), 13.5 (br s, 1H, COOH)

Table II. *Continued.*

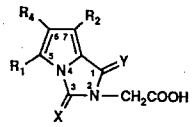
92	$C_{14}H_{18}N_2O_4$	C, H, N	278	0.88(d, J=6 Hz, 6H, $2CH_3$), 1.4-2.0 (m, 1H, CH), 2.15 (s, 3H, CH_3), 2.23 (d, J=7 Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 4.17 (s, 2H, CH_2COO)
93	$C_{17}H_{15}FN_2O_4$ .1/8H_2O	C, H, N	330	2.05 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 4.19 (s, 2H, CH_2COO), 6.9-7.3 (m, 4H, ArH), 13.4 (br s, 1H, COOH)
94	$C_{17}H_{14}BrFN_2O_4$	C, H, N	408	2.06 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.18 (s, 2H, CH_2COO), 7.0-7.6 (m, 3H, ArH)
112	$C_8H_6N_2O_3S$	C, H, N	210	4.54 (s, 2H, CH_2COO), 6.59 (t, J=3 Hz, 1H, pyrrole H), 7.14 (d, J=3 Hz, 1H, pyrrole H), 7.67 (d, J=3 Hz, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
113	$C_{11}H_{12}N_2O_3S$	C, H, N	252	1.19 (d, J=7 Hz, 6H, $2CH_3$), 2.6-3.0 (m, 1H, CH), 4.52 (s, 2H, CH_2COO), 7.13 (s, 1H, pyrrole H), 7.46 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
114	$C_{12}H_{14}N_2O_3S$	C, H, N	266	0.88 (d, J=7 Hz, 6H, $2CH_3$), 1.6-2.0 (m, 1H, CH), 2.33 (d, J=7 Hz, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 7.02 (s, 1H, pyrrole H), 7.45 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
115	$C_{15}H_{18}N_2O_3S$	C, H, N	306	0.6-2.0 (m, 11H, cyclohexane H), 2.34 (d, J=6 Hz, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 7.00 (s, 1H, pyrrole H), 7.43 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
116	$C_{16}H_{14}N_2O_3S$	C, H, N	314	2.26 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 6.95 (s, 1H, pyrrole H), 7.0-7.3 (m, 4H, ArH), 7.48 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
117	$C_{15}H_{11}ClN_2O_3S$	C, H, N	334	3.82 (s, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 7.0 (s, 1H, pyrrole H), 7.2-7.5 (m, 4H, ArH), 7.52 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
118	$C_{16}H_{11}F_3N_2O_3S$	C, H, N	368	3.93 (s, 2H, CH_2), 4.52 (s, 2H, CH_2COO), 7.04 (s, 1H, pyrrole H), 7.52 (d, J=9 Hz, 2H, ArH), 7.56 (s, 1H, pyrrole H), 7.68 (d, J=9 Hz, 2H, ArH), 13.4 (br s, 1H, COOH)
119	$C_{15}H_{10}BrFN_2O_3S$	C, H, N	396	3.83 (s, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 6.98 (s, 2H, pyrrole H), 7.2-7.6 (m, 3H, ArH), 7.49 (s, 1H, pyrrol H), 13.4 (br s, 1H, COOH)
120	$C_{15}H_{10}Cl_2N_2O_3S$	C, H, N	368	3.83 (s, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 7.05 (s, 1H, pyrrole H), 7.2-7.7 (m, 4H, ArH and pyrrole H), 13.4 (br s, 1H, COOH)
121	$C_{19}H_{20}N_2O_3S$	C, H, N	356	1.25 (s, 9H, $3CH_3$), 3.77 (s, 2H, CH_2), 4.51 (s, 2H, CH_2COO), 6.98 (s, 1H, pyrrole H), 7.19 (d, J=9 Hz, 2H, ArH), 7.33 (d, J=9 Hz, 2H, ArH), 7.50 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
122	$C_{10}H_{10}N_2O_3S$	C, H, N	238	2.28 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.49 (s, 2H, CH_2COO), 6.24 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
123	$C_{11}H_{12}N_2O_3S$	C, H, N	252	1.92 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.47 (s, 2H, CH_2COO), 13.3 (br s, 1H, COOH)

Table II. *Continued.*

124	$C_{12}H_{14}N_2O_3S$	C, H, N	266	1.04 (t, J=8 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.35 (t, J=7 Hz, 2H, CH_2), 4.48 (s, 2H, CH_2COO), 13.3 (br s, 1H, COOH)
125	$C_{13}H_{16}N_2O_3S$	C, H, N	280	0.89 (t, J=7Hz, 3H, CH_3), 1.1-1.7 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.34 (t, J=7 Hz, 2H, CH_2), 4.48 (s, 2H, CH_2COO), 13.4 (br s, 1H, COOH)
126	$C_{14}H_{18}N_2O_3S$	C, H, N	294	0.89 (d, J=6 Hz, 6H, $2CH_3$), 1.5-1.9 (m, 1H, CH), 2.26 (s, 3H, CH_3), 2.26 (d, J=7 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 4.48 (s, 2H, CH_2COO)
127	$C_{17}H_{15}FN_2O_3S$	C, H, N	346	2.16 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.49 (s, 2H, CH_2COO), 6.9-7.4 (m, 4H, ArH)
128	$C_{17}H_{14}BrFN_2O_3S$	C, H, N	424	2.17 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 4.49 (s, 2H, CH_2COO), 7.0-7.6 (m, 3H, ArH), 13.3 (br s, 1H, COOH)
140	$C_8H_6N_2O_2S_2$	C, H, N	226	4.83 (s, 2H, CH_2COO), 6.59 (t, J=3 Hz, 1H, pyrrole H), 7.20 (d, J=3 Hz, 1H, pyrrole H), 7.69 (d, J=3 Hz, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
141	$C_{11}H_{12}N_2O_2S_2$ .1/4CH_3COOH[a]	C, H, N	268	1.20(d, J=7 Hz, 6H, $2CH_3$), 2.6-3.0 (m, 1H, CH), 4.79 (s, 2H, CH_2COO), 7.21 (s, 1H, pyrrole H), 7.46 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
142	$C_{12}H_{14}N_2O_2S_2$	C, H, N	282	0.89 (d, J=6 Hz, 6H, $2CH_3$), 1.6-2.0 (m, 1H, CH), 2.34 (d, J=7 Hz, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.10 (s, 1H, pyrrole H), 7.47 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
143	$C_{15}H_{18}N_2O_2S_2$	C, H, N	322	0.6-2.0 (m, 11H, cyclohexane H), 2.35 (d, J=6 Hz, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.07 (s, 1H, pyrrole H), 7.45 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
144	$C_{16}H_{14}N_2O_2S_2$	C, H, N	330	2.26 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 4.78 (s, 2H, CH_2COO), 7.02 (s, 1H, pyrrole H), 7.0-7.3 (m, 4H, ArH), 7.48 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
145	$C_{15}H_{11}ClN_2O_2S_2$	C, H, N	350	3.83 (s, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.08 (s, 1H, pyrrole H), 7.2-7.5 (m, 4H, ArH), 7.54 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
146	$C_{16}H_{11}F_3N_2O_2S_2$	C, H, N	384	3.94 (s, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.11 (s, 1H, pyrrole H), 7.53 (d, J=9 Hz, 2H, ArH), 7.59 (s, 1H, pyrrole H), 7.68 (d, J=9 Hz, 2H, ArH), 13.4 (br s, 1H,COOH)
147	$C_{15}H_{10}BrFN_2O_2S_2$	C, H, N	412	3.84 (s, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.04 (s, 1H, pyrrole H), 7.2-7.65 (m, 3H, ArH), 7.51 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
148	$C_{15}H_{10}Cl_2N_2O_2S_2$	C, H, N	384	3.84 (s, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.13 (s, 1H, pyrrole H), 7.2-7.7 (m, 3H, ArH), 7.60 (s, 1H, pyrrole H), 13.4 (br s, 1H, COOH)
149	$C_{19}H_{20}N_2O_2S_2$ .3/4CH_3COOH[a]	C, H, N	372	1.26 (s, 9H, $3CH_3$), 3.78 (s, 2H, CH_2), 4.79 (s, 2H, CH_2COO), 7.06 (s, 1H, pyrrole H), 7.21 (d, J=9 Hz, 2H, ArH), 7.34 (d, J=9 Hz, 2H, ArH), 7.52 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH)
150	$C_{12}H_{14}N_2O_2S_2$	C, H, N	282	1.05 (t, J=8 Hz, 3H, CH_3), 2,28 (s, 3H, CH_3), 2.37 (q, J=8 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 4.80 (s, 2H, CH_2COO), 13.4 (br s, 1H, COOH)

[a]Determined by NMR analysis.

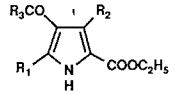
Table III. Inhibition of sorbitol accumulation in the sciatic nerves.



Compd	R_4	Inhibition of sorbitol accumulation % of control		
		100 x 2	50 x 2	25 x 2 (mg/kg/day)
R_1=R_2=H ; X=Y=O				
83	4-Cl-$C_6H_4CH_2$	3.1	NT	NT
85	4-Br,2-F-$C_6H_3CH_2$	NT	-1.8	NT
R_1=R_2=H ; X=O, Y=S				
114	$(CH_3)_2CHCH_2$	32.6*	NT	NT
115	cyclohexylmethyl	NT	-21.0	NT
117	4-Cl-$C_6H_4CH_2$	52.9***	NT	NT
119	4-Br,2-F-$C_6H_3CH_2$	NT	5.1	NT
120	3,4-$(Cl)_2$-$C_6H_3CH_2$	31.3*	NT	NT
R_1=R_2=CH_3 ; X=O, Y=S				
123	CH_3	NT	NT	0.4
124	C_2H_5	NT	46.9**	5.3
125	$CH_3CH_2CH_2$	NT	NT	-11.2
126	$(CH_3)_2CHCH_2$	NT	23.2	NT
127	4-F-$C_6H_4CH_2$	NT	20.4	NT
128	4-Br,2-F-$C_6H_3CH_2$	NT	3.1	NT
R1=R2=H ; X=Y=S				
140	H	NT	-16.3	NT
141	$(CH_3)_2CH$	NT	12.1	NT
142	$(CH_3)_2CHCH_2$	47.8***	NT	NT
143	cyclohexylmethyl	NT	4.5	NT
144	4-CH_3-$C_6H_4CH_2$	NT	1.1	NT
R1=R2=H ; X=Y=S				
145	4-Cl-$C_6H_4CH_2$	NT	13.4	NT
146	4-CF_3-$C_6H_4CH_2$	NT	19.1	NT
147	4-Br,2-F-$C_6H_3CH_2$	NT	16.6	NT
148	3,4-$(Cl)_2$-$C_6H_3CH_2$	64.4***	3.3	NT
149	4-$(CH_3)_3C$-$C_6H_4CH_2$	NT	-1.6	NT
R_1=R_2=CH_3 ; X=Y=S				
150	C_2H_5	NT	NT	1.9
AD-5467		NT	53.2***	NT

NT: not tested; Student's *t*-test; $*P < 0.01$; $**P < 0.05$; $***P < 0.001$.

Table IV. Physical data for ethyl acylpyrrolecarboxylate derivatives.



Compd	R_3	mp (°C)	Recryst	Yield (%)	Formula	Analysis
R_1=R_2=H						
12	$(CH_3)_2CH$	oil bp 150-152°C /0.02 mmHg		79	$C_{11}H_{15}NO_3$ .1/4H_2O	C, H, N
13	cyclohexyl	98-99.5	A	92	$C_{14}H_{19}NO_3$	C, H, N
14	4-CH_3-C_6H_4	105.5-106.5	B	64	$C_{15}H_{15}NO_3$	C, H, N
15	4-Cl-C_6H_4	124-125.5	C	98	$C_{14}H_{12}ClN_3O_3$	C, H, N
16	4-CF_3-C_6H_4	131-137	A	98	$C_{15}H_{12}F_3NO_3$ .2/3H_2O	C, H, N
17	4-Br,2-F-C_6H_3	108-109	D	98	$C_{14}H_{11}BrFNO_3$	C, H, N
18	3,4-$(Cl)_2$-C_6H_3	157.5-158.5	E	74	$C_{14}H_{11}Cl_2NO_3$	C, H, N
19	4-$(CH_3)_3C$-C_6H_4	150-152	B	31	$C_{18}H_{21}NO_3$	C, H, N
R_1=R_2=CH_3						
20	4-F-C_6H_4	153.5-155.5	F	95	$C_{15}H_{16}FNO_3$	C, H, N
21	4-Br,2-F-C_6H_3	169-171	F	95	$C_{15}H_{15}BrFNO_3$	C, H, N

Recrystallization solvents. A: *iso*-Pr_2O/*n*-hexane; B: *iso*-Pr_2O; C: $CHCl_3$/*n*-hexane; D: benzene/*n*-hexane; E: EtOH/H_2O; F: EtOH.

dichloroethane (100 ml) under ice cooling. The mixture was stirred at room temperature for 2 h, followed by heating under reflux for 2 h. The reaction mixture was poured into ice and extracted with chloroform. The organic layer was washed with water (H_2O), 1 N NaOH solution and saturated NaCl solution. After concentration, the residue was distilled under reduced pressure to give a pale brown oil (12, 36.1 g, 79%, bp: 150–152°C/0.02 mmHg). ^{1}H-NMR($CDCl_3$) δ: 1.21 (d, J = 7 Hz, 6H, $2CH_3$), 1.38 (t, J = 7 Hz, 3H, CH_3), 3.0–3.5 (m, 1H, CH), 4.36 (q, J = 7 Hz, 2H, CH_2), 7.2–7.4 (m, 1H, pyrrole H), 7.5–7.7 (m, 1H, pyrrole H), 10.2 (br s, 1H, NH). MS: 209 (M^+). Anal $C_{11}H_{15}NO_3 \cdot 1/4H_2O$ (C, H, N).

General procedure for the synthesis of ***22–31***

The following procedure for the synthesis of ethyl 4-isobutyl-2-pyrrolecarboxylate 22 is representative. The other compounds, **23–31**, were obtained in a similar manner. Physical data for these compounds are summarized in tables VI and VII. Ethyl 3,5-dimethyl-4-propyl-2-pyrrolecarboxylate and ethyl 4-isobutyl-3,5-dimethyl-2-pyrrolecarboxylate were prepared by a previously described method [12, 13].

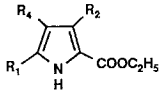
Ethyl 4-isobutyl-2-pyrrolecarboxylate ***22***
(**3**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)
Triethylsilane (45 ml, 282 mmol) was added to a solution of ethyl 4-isobutyryl-2-pyrrolecarboxylate (**12**, 14.6 g, 69.8 mmol) in trifluoroacetic acid (50 ml) and stirred for 3 h under ice cooling, followed by stirring at room temperature for 16 h.

Table V. Physical data for ethyl acylpyrrolecarboxylate derivatives.

Compd	Solvent	^{1}H-NMR δ ppm
12	C	1.21 (d, J=7 Hz, 6H, $2CH_3$), 1.38 (t, J=7 Hz, 3H, CH_3), 3.0-3.5 (m, 1H, CH), 4.36 (q, J=7 Hz, 2H, CH_2), 7.2-7.4 (m, 1H, pyrrole H), 7.5-7.7 (m, 1H, pyrrole H), 10.2 (br s, 1H, NH)
13	C	1.38 (t, J=7 Hz, 3H, CH_3), 1.0-2.1 (m, 10H, cyclohexane H), 2.7-3.1 (m, 1H, cyclohexane H), 4.36 (q, J=7 Hz, 2H, CH_2), 7.2-7.35 (m, 1H, pyrrole H), 7.5-7.65 (m, 1H, pyrrole H), 9.8 (br s, 1H, NH)
14	C	1.38 (t, J=7 Hz, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.36 (q, J=7 Hz, 2H, CH_2), 7.2-7.4 (m, 3H, ArH and pyrrole H), 7.5-7.6 (m, 1H, pyrrole H), 7.77 (d, J=8 Hz, 2H, ArH), 9.7 (br s, 1H, NH)
15	D	1.38 (t, J=7 Hz, 3H, CH_3), 4.37 (q, J=7 Hz, 2H, CH_2), 7.2-7.7 (m, 4H, ArH and pyrrole H), 7.7-8.0 (m, 2H, ArH), 10.1 (br s, 1H, NH)
16	D	1.30 (t, J=7 Hz, 3H, CH_3), 4.29 (q, J=7 Hz, 2H, CH_2), 7.15 (br s, 1H, pyrrole H), 7.64 (br s, 1H, pyrrole H), 7.8-8.2 (m, 4H, ArH), 12.8 (br s, 1H, NH)
17	D	1.29 (t, J=7 Hz, 3H, CH_3), 4.27 (q, J=7 Hz, 2H, CH_2), 7.07 (s, 1H, pyrrole H), 7.4-7.8 (m, 4H, ArH and pyrrole H), 12.8 (br s, 1H, NH)
18	D	1.31 (t, J=7 Hz, 3H, CH_3), 4.30 (q, J=7 Hz, 2H, CH_2), 7.16 (d, J=2 Hz, 1H, pyrrole H), 7.66 (d, J=2 Hz, 1H, pyrrole H), 7.7-8.0 (m, 3H, ArH), 12.8 (br s, 1H, NH)
19	D	1.30 (t, J=7 Hz, 3H, CH_3), 1.33 (s, 9H, $3CH_3$), 4.29 (q, J=7 Hz, 2H, CH_2), 7.15 (s, 1H, pyrrole H), 7.55 (d, J=9 Hz, 2H, ArH), 7.60 (s, 1H, pyrrole H), 7.76 (d, J=9 Hz, 2H, ArH), 12.7 (br s, 1H, NH)
20	D	1.31 (t, J=7 Hz, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 4.27 (q, J=7 Hz, 2H, CH_2), 7.2-7.8 (m, 4H, ArH), 11.9 (br s, 1H, NH)
21	D	1.29 (t, J=7 Hz, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.26 (q, J=7 Hz, 2H, CH_2), 7.3-7.8 (m, 3H, ArH), 12.1 (br s, 1H, NH)

Measurement solvents. C: $CDCl_3$; D: DMSO-d_6.

Table VI. Physical data for ethyl pyrrolecarboxylate derivatives.



Compd	R_4	mp (°C)	Recryst	Yield (%)	Formula	Analysis
R_1=R_2=H						
22	$(CH_3)_2CHCH_2$	oil	bp 108-112°C /0.04 mmHg	96	$C_{11}H_{17}NO_2$ .1/8H_2O	C, H, N
23	cyclohexylmethyl	oil	bp 141-143°C /0.05 mmHg	59	$C_{14}H_{21}NO_2$	C, H, N
24	4-CH_3-$C_6H_4CH_2$	67.5-68.5	A	76	$C_{15}H_{17}NO_2$	C, H, N
25	4-Cl-$C_6H_4CH_2$	76-77	A	81	$C_{14}H_{14}ClNO_2$	C, H, N
26	4-CF_3-$C_6H_4CH_2$	80-80.5	B	27	$C_{15}H_{14}F_3NO_2$ .1/16C_6H_{14}[a]	C, H, N
27	4-Br,2-F-$C_6H_3CH_2$	87-88	B	27	$C_{14}H_{13}BFNO_2$	C[b], H, N
28	3,4-$(Cl)_2$-$C_6H_3CH_2$	89-89.5	A	70	$C_{14}H_{13}Cl_2NO_2$	C, H, N
29	4-$(CH_3)_3C$-$C_6H_4CH_2$	66-66.5	B	70	$C_{18}H_{23}NO_2$	C, H, N
R_1=R_2=CH_3						
30	4-F-$C_6H_4CH_2$	128-129	B	28	$C_{16}H_{18}FNO_2$ .1/8H_2O	C, H, N
31	4-Br,2-F-$C_6H_3CH_2$	139-139.5	B	63	$C_{16}H_{17}BrFNO_2$	C, H, N

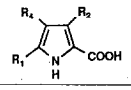
Recrystallization solvents. A: *iso*-Pr_2O/*n*-hexane; B: *n*-hexane; [a]determined by NMR analysis; C[b]: calcd, 51.55; found, 52.50.

Table VII. Physical data for ethyl pyrrolecarboxylate derivatives.

Compd	Solvent	^{1}H-NMR δ ppm
22	C	0.89 (d, J=6 Hz, 6H, $2CH_3$), 1.34 (t, J=7 Hz, 3H, CH_3), 1.5-2.0 (m, 1H, CH), 2.32 (d, J=7 Hz, 2H, CH_2), 4.31 (q, J=7 Hz, 2H, CH_2), 6.73 (br s, 2H, pyrrole H), 9.4 (br s, 1H, NH)
23	C	0.6-2.0 (m, 11H, cyclohexane H), 1.34 (t, J=7 Hz, 3H, CH_3), 2.32 (d, J=7 Hz, 2H, CH_2), 4.30 (q, J=7 Hz, 2H, CH_2), 6.72 (br s, 2H, pyrrole H), 7.10 (s, 4H, ArH), 9.25 (br s, 1H, NH)
24	C	1.32 (t, J=7 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 4.28 (q, J=7 Hz, 2H, CH_2), 6.6-6.8 (m, 2H, pyrrole H), 7.10 (s, 4H, ArH), 9.0 (br s, 1H, NH)
25	D	1.25 (t, J=7 Hz, 3H, CH_3), 3.73 (s, 2H, CH_2), 4.19 (q, J=7 Hz, 2H, CH_2), 6.57 (br s, 1H, pyrrole H), 6.84 (br s, 1H, pyrrole H), 7.1-7.4 (m, 4H, ArH), 11.7 (br s, 1H, NH)
26	D	1.25 (t, J= 7 Hz, 3H, CH_3), 3.84 (s, 2H, CH_2), 4.19 (q, J=7 Hz, 2H, CH_2), 6.60 (br s, 1H, pyrrole H), 6.89 (br s, 1H, pyrrole H), 7.43 (d, J=8 Hz, 2H, ArH), 7.46 (d, J=8 Hz, 2H, ArH), 11.7 (br s, 1H, NH)
27	D	1.25 (t, J=7 Hz, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.20 (q, J=7 Hz., 2H, CH_2), 6.59 (br s, 1H, pyrrole H), 6.85 (br s, 1H, pyrrole H), 7.1-7.6 (m, 3H, ArH), 11.7 (br s, 1H, NH)
28	D	1.25 (t, J=7 Hz, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.20 (q, J=7 Hz, 2H, CH_2), 6.61 (br s, 1H, pyrrole H), 6.88 (br s, 1H, pyrrole H), 7.1-7.6 (m, 3H, ArH), 11.7 (br s, 1H, NH)
29	D	1.25 (t, J=7 Hz, 3H, CH_3), 1.25 (s, 9H, $3CH_3$), 3.69 (s, 2H, CH_2), 4.19 (q, J=7 Hz, 2H, CH_2), 5.57 (br s, 1H, pyrrole H), 6.81 (br s, 1H, pyrrole H), 7.12 (d, J=9 Hz, 2H, ArH), 7.28 (d, J=9 Hz, 2H, ArH), 11.6 (br s, 1H, NH)
30	D	1.27 (t, J=7 Hz, 3H, CH_3), 2.12 (s, 6H, $2CH_3$), 3.67 (s, 2H, CH_2), 4.19 (q, J=7 Hz, 2H, CH_2), 7.03 (d, J=7 Hz, 4H, ArH), 11.5 (br s, 1H, NH)
31	D	1.26 (t, J=7 Hz, 3H, CH_3), 2.10 (s, 6H, $2CH_3$), 3.64 (s, 2H, CH_2), 4.19 (q, J=7 Hz, 2H, CH_2), 6.8-7.6 (m, 3H, ArH), 11.2 (br s, 1H, NH)

Measurement solvent. C: $CDCl_3$; D: DMSO–d_6.

Table VIII. Physical data for pyrrolecarboxylic acid derivatives.



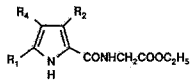
Compd	R_4	mp (°C)	Recryst	Yield (%)	Formula	Analysis
R_1=R_2=H						
32	$(CH_3)_2CHCH_2$	177-178.5	A	98	$C_9H_{13}NO_2$ .1/16H_2O	C, H, N
33	cyclohexylmethyl	153.5-154	B	98	$C_{12}H_{17}NO_2$ .1/8$C_6H_{14}O$[b]	C[a], H, N
34	4-CH_3-$C_6H_4CH_2$	199-200	A	98	$C_{13}H_{13}NO_2$	C, H, N
35	4-Cl-$C_6H_4CH_2$	192.5-193	C	98	$C_{12}H_{10}ClNO_2$	C, H, N
36	4-CF_3-$C_6H_4CH_2$	180-182	D	96	$C_{13}H_{10}F_3NO_2$	C, H, N
37	4-Br,2-F-$C_6H_3CH_2$	200-202	E	93	$C_{12}H_9BrFNO_2$	C, H, N
38	3,4-$(Cl)_2$-$C_6H_3CH_2$	184.5-185	A	98	$C_{12}H_9Cl_2NO_2$	C, H, N
39	4-$(CH_3)_3C$-$C_6H_4CH_2$	179-181	F	90	$C_{16}H_{19}NO_2$	C, H, N
R_1=R_2=CH_3						
40	$CH_3CH_2CH_2$	114.5-115.5	G	61	$C_{10}H_{15}NO_2$	C, H, N
41	$(CH_3)_2CHCH_2$	107.5-108.5	H	66	$C_{11}H_{17}NO_2$	C, H, N
42	4-F-$C_6H_4CH_2$	161.5-162.5	F	82	$C_{14}H_{14}FNO_2$	C, H, N
43	4-Br,2-F-$C_6H_3CH_2$	158-160	E	89	$C_{14}H_{13}BrFNO_2$ .3/4CH_3CN[b]	C, H, N

Recrystallization solvents. A: CH_2Cl_2/MeOH/*iso*-Pr_2O; B: CH_2Cl_2/*iso*-Pr_2O; C: $CHCl_3$/*iso*-Pr_2O; D: CH_3CN/$CHCl_3$; E: *iso*-Pr_2O/CH_3CN; F: *iso*-Pr_2O; G: *iso*-Pr_2O/*n*-hexane; H: *n*-hexane; C[a]: calcd, 69.60; found, 70.03; [b]determined by NMR analysis.

Table IX. Physical data for pyrrolecarboxylic acid derivatives.

Compd	^{1}H-NMR (DMSO-d_6) δ ppm
32	0.85 (d, J=7 Hz, 6H, $2CH_3$), 1.4-2.0 (m, 1H, CH), 2.25 (d, J=7 Hz, 2H, CH_2), 6.53 (br s, 1H, pyrrole H), 6.72 (br s, 1H, pyrrole H), 11.4 (br s, 1H, NH), 12.05 (br s, 1H, COOH)
33	0.6-2.0 (m, 11H, cyclohexane H), 2.25 (d, J=7 Hz, 2H, CH_2), 6.51 (br s, 1H, pyrrole H), 6.70 (br s, 1H, pyrrole H), 11.35 (br s, 1H, NH), 12.05 (br s, 1H, COOH)
34	2.25 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 6.50 (br s, 1H, pyrrole H), 6.73 (br s, 1H, pyrrole H), 7.08 (s, 4H, ArH), 11.4 (br s, 1H, NH), 12.1 (br s, 1H, COOH)
35	3.73 (s, 2H, CH_2), 6.53 (br s, 1H, pyrrole H), 6.78 (br s, 1H, pyrrole H), 7.1-7.45 (m, 4H, ArH), 11.5 (br s, 1H, NH), 12.1 (br s, 1H, COOH)
36	3.85 (s, 2H, CH_2), 6.57 (br s, 1H, pyrrole H), 6.84 (br s, 1H, pyrrole H), 7.44 (d, J=8 Hz, 2H, ArH), 7.64 (d, J=8 Hz, 2H, ArH), 11.6 (br s, 1H, NH), 12.2 (br s, 1H, COOH)
37	3.73 (s, 2H, CH_2), 6.52 (br s, 1H, pyrrole H), 7.78 (br s, 1H, pyrrole H), 7.1-7.6 (m, 3H, ArH), 11.5 (br s, 1H, NH), 12.2 (br s, 1H, COOH)
38	3.76 (s, 2H, CH_2), 6.58 (br s, 1H, pyrrole H), 6.85 (br s, 1H, pyrrole H), 7.1-7.6 (m, 3H, ArH), 11.6 (br s, 1H, NH), 12.2 (br s, 1H, COOH)
39	1.25 (s, 9H, $3CH_3$), 3.68 (s, 2H, CH_2), 6.51 (br s, 1H, pyrrole H), 6.76 (br s, 1H, pyrrole H), 7.11 (d, J=9 Hz, 2H, ArH), 7.29 (d, J=9 Hz, 2H, ArH), 11.5 (br s, 1H, NH), 12.1 (br s, 1H, COOH)
40	0.85 (t, J=7 Hz, 3H, CH_3), 1.1-1.6 (m, 2H, CH_2), 1.21(s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.26 (t, J=7 Hz, 2H, CH_2), 11.4 (br s, 1H, NH), 12.0 (br s, 1H, COOH)
41	0.83 (d, J=6 Hz, 6H, $2CH_3$), 1.6-1.8 (m, 1H, CH), 2.09 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.16 (d, J=6 Hz, 2H, CH_2), 10.9 (br s, 1H, NH), 11.7 (br s, 1H, COOH)
42	2.10 (s, 6H, $2CH_3$), 2.65 (s, 2H, CH_2), 7.07 (d, J=7 Hz, 4H, ArH), 11.1 (br s, 1H, NH), 11.8 (br s, 1H, COOH)
43	2.08 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 6.8-7.6 (m, 3H, ArH), 11.1 (br s, 1H, NH), 11.9 (br s, 1H, COOH)

Table X. Physical data for ethyl pyrrolecarbonylaminoacetate derivatives.



Compd	R_4	mp (°C)	Recryst	Yield (%)	Formula	Analysis
R_1=R_2=H						
44	H	112-113	A	65	$C_6H_{12}N_2O_3$ .1/3H_2O	C, H, N
45	$(CH_3)_2CH$	102-104	A	88	$C_{12}H_{18}N_2O_3$	C, H, N
46	$(CH_3)_2CHCH_2$	136.5-138	B	98	$C_{13}H_{20}N_2O_3$	C, H, N
47	cyclohexylmethyl	123-124	B	98	$C_{16}H_{24}N_2O_3$	C, N, N
48	4-CH_3-$C_6H_4CH_2$	104-106.5	B	98	$C_{17}H_{20}N_2O_3$ .1/2H_2O	C, H, N
49	4-Cl-$C_6H_4CH_2$	124.5-125.5	B	80	$C_{16}H_{17}ClN_2O_3$	C, H, N
50	4-CF_3-$C_6H_4CH_2$	96-99	C	90	$C_{17}H_{17}F_3N_2O_3$ .1/8$C_6H_{14}O$[a]	C, H, N
51	4-Br,2-F-$C_6H_3CH_2$	133-134	D	84	$C_{16}H_{16}BrFN_2O_3$ .1/8$C_6H_{14}O$[a]	C, H, N
52	3,4-$(Cl)_2$-$C_6H_3CH_2$	97.5-98.5	B	71	$C_{16}H_{16}Cl_2N_2O_3$	C, H, N
53	4-$(CH_3)_3C$-$C_6H_4CH_2$	101-101.5	E	88	$C_{20}H_{26}N_2O_3$	C, H, N
R_1=R_2=CH_3						
54	H	135-137	F	79	$C_{11}H_{16}N_2O_3$ .1/8H_2O	C, H, N
55	CH_3	155-156.5	F	98	$C_{12}H_{18}N_2O_3$	C, H, N
R_1=R_2=CH_3						
56	C_2H_5	127-128	B	84	$C_{13}H_{20}N_2O_3$	C, H, N
57	$CH_3CH_2CH_2$	103-104.5	F	83	$C_{14}H_{22}N_2O_3$	C, H, N
58	$(CH_3)_2CHCH_2$	144.5-145.5	F	79	$C_{15}H_{24}N_2O_3$	C, H, N
59	4-F-$C_6H_4CH_2$	144.5-145.5	F	89	$C_{18}H_{21}FN_2O_3$	C, H, N
60	4-Br,2-F-$C_6H_3CH_2$	166-167	F	98	$C_{18}H_{20}BrFN_2O_3$	C, H, N

Recrystallization solvents. A: only washed with H_2O; B: CH_2Cl_2/*iso*-Pr_2O; C: *iso*-Pr_2O/*n*-hexane; D: CH_3CN/*iso*-Pr_2O; E: *iso*-Pr_2O; F: EtOH; [a]determined by NMR analysis.

Table XI. Physical data for ethyl pyrrolecarbonylaminoacetate derivatives.

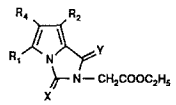
Compd	Solvent	^{1}H-NMR δ ppm
44	D	1.20 (t, J=7 Hz, 3H, CH_3), 3.94 (d, J=6Hz, 2H, CH_2COO), 4.11 (q, J=7 Hz, 2H, CH_2), 6.0-6.2 (m, 1H, pyrrole H), 6.7-8.0 (m, 2H, pyrrole H), 8.44 (t, J=6 Hz, 1H, CONH), 11.5 (br s, 1H, NH)
45	D	1.17 (d, J=7 Hz, 6H, $2CH_3$), 1.21 (t, J=7 Hz, 3H, CH_3), 2.6-3.0 (m, 1H, CH), 3.93 (d, J=6 Hz, 2H, CH_2COO), 4.12 (q, J=7 Hz, 2H, CH_2), 6.68 (s, 1H, pyrrole H), 6.70 (s, 1H, pyrrole H), 8.36 (t, J=6 Hz, 1H, CONH), 11.2 (br s, 1H,NH)
46	D	0.87 (d, J=7 Hz, 6H, $2CH_3$), 1.20 (t, J=7 Hz, 3H, CH_3), 1.4-2.0 (m, 1H, CH), 2.26 (d, J=7 Hz, 2H, CH_2), 3.91 (d, J=6 Hz, 2H, CH_2COO), 4.11 (q, J=7 Hz, 2H, CH_2), 6.62 (br s, 2H, pyrrole H), 8.31 (t, J=6 Hz, 1H, CONH), 11.2 (br s, 1H, NH)
47	D	0.6-1.8 (m, 11H, cyclohexane H), 1.20 (t, J=7 Hz, 3H, CH_3), 2.26 (d, J=6 Hz, 2H, CH_2), 3.91 (d, J=6 Hz, 2H, CH_2COO), 4.11 (q, J=7 Hz, 2H, CH_2), 6.60 (s, 1H, pyrrole H), 6.62 (s, 1H, pyrrole H), 8.31 (t, J=6 Hz, 1H, CONH), 11.2 (br s, 1H, NH)
48	D	1.18 (t, J=7 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 3.89 (d, J=6 Hz, 2H, CH_2COO), 4.09 (q, J=7 Hz, 2H, CH_2), 6.57 (br s, 1H, pyrrole H), 6.68 (br s, 1H, pyrrole H), 7.08 (s, 4H, ArH), 8.34 (t, J=6 Hz, 1H, CONH), 11.3 (br s, 1H, NH)
49	D	1.18 (t, J=7 Hz, 3H, CH_3), 3.74 (s, 2H, CH_2), 3.89 (d, J=6 Hz, 2H, CH_2COO), 4.09 (q, J=7 Hz, 2H, CH_2), 6.58 (br s, 1H, pyrrole H), 6.71 (br s, 1H, pyrrole H), 7.1-7.45 (m, 4H, ArH), 8.33 (t, J=6 Hz, 1H, CONH), 11.3 (br s, 1H,NH)
50	D	1.19 (t, J=7 Hz, 3H, CH_3), 3.85 (s, 2H, CH_2), 3.89 (d, J=6 Hz, 2H, CH_2COO), 4.09 (q, J=7 Hz, 2H, CH_2), 6.59 (br s, 1H, pyrrole H), 6.77 (br s, 1H, pyrrole H), 7.43 (d, J=8 Hz, 2H, ArH), 7.64 (d, J=8 Hz, 2H, ArH), 8.34 (t, J=5 Hz, 1H, CONH), 11.3 (br s, 1H, NH)
51	D	1.19 (t, J=7 Hz, 3H, CH_3), 3.74 (s, 2H, CH_2), 3.89 (d, J=6 Hz, 2H, CH_2COO), 4.09 (q, J=7 Hz, 2H, CH_2), 6.58 (br s, 1H, pyrrole H), 6.72 (br s, 1H, pyrrole H), 7.1-7.6 (m, 3H, ArH), 8.35 (t, J=6 Hz, 1H, CONH), 11.3 (br s, 1H, NH)
52	C	1.28 (t, J=7 Hz, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.16 (d, J=5 Hz, 2H, CH_2COO), 4.23 (q, J=7 Hz, 2H, CH_2), 6.41 (br s, 1H, pyrrole H), 6.55 (t, J=5 Hz, 1H, CONH), 6.70 (br s, 1H, pyrrole H), 6.9-7.4 (m, 3H, ArH), 10.95 (br s, 1H, NH)
53	D	1.18 (t, J=7 Hz, 3H, CH_3), 3.69 (s, 2H, CH_2), 3.89 (d, J=6 Hz, 2H, CH_2COO), 4.09 (q, J=7 Hz, 2H, CH_2), 6.59 (br s, 1H, pyrrole H), 6.70 (br s, 1H, pyrrole H), 7.12 (d, J=9 Hz, 2H, ArH), 7.29 (d, J=9 Hz, 2H,ArH), 8.3 (t, J=6 Hz, 1H, CONH), 11.2 (br s, 1H, NH)
54	D	1.22 (t, J=7 Hz, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.98 (d, J=6 Hz, 2H, CH_2COO), 4.13 (q, J=7 Hz, 2H, CH_2), 5.68 (s, 1H, pyrrole H), 7.48 (t, J=6 Hz, 1H, CONH), 10.9 (br s, 1H, NH)
55	D	1.20 (t, J=7 Hz, 3H, CH_3), 1.83 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.95 (d, J=6 Hz, 2H, CH_2COO), 4.10 (q, J=7 Hz, 2H, CH_2), 7.48 (t, J=6 Hz, 1H, CONH), 10.7 (br s, 1H, NH)

Table XI. *Continued.*

56	C	1.04 (t, J=7 Hz, 3H, CH_3), 1.31 (t, J=7 Hz, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.38 (q, J=7 Hz, 2H, CH_2), 4.21 (d, J=5 Hz, 2H, CH_2COO), 4.25 (q, J=7 Hz, 2H, CH_2), 6.22 (t, J=5 Hz, 1H, CONH), 9.05 (br s, 1H, NH)
57	D	0.85 (t, J=7 Hz, 3H, CH_3), 1.20 (t, J=7 Hz, 3H, CH_3), 1.1-1.6 (m, 2H, CH_2), 2.11 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.26 (t, J=7 Hz, 2H, CH_2), 3.95 (d, J=6 Hz, 2H, CH_2COO), 4.10 (q, J=7 Hz, 2H, CH_2), 7.48 (t, J=6 Hz, 1H, CONH), 10.7 (br s, 1H, NH)
58	D	0.84 (d, J=6 Hz, 6H, $2CH_3$), 1.20 (t, J=7 Hz, 2H, CH_2), 1.3-1.7 (m, 1H, CH), 2.10 (s, 3H, CH_3), 2.14 (d, J=6 Hz, 2H, CH_2), 2.15 (s, 3H, CH_3), 3.95 (d, J=6 Hz, 2H, CH_2COO), 4.11 (q, J=7 Hz, 2H, CH_2), 10.7 (br s, 1H, NH)
59	D	1.20 (t, J=7 Hz, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 3.95 (d, J=6 Hz, 2H, CH_2COO), 4.10 (q, J=7 Hz, 2H, CH_2), 6.9-7.2 (m, 4H, ArH), 7.53 (t, J=6 Hz, 1H, CONH), 10.9 (br s, 1H, NH)
60	D	1.20 (t, J=7 Hz, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.64 (s, 2H, CH_2), 3.95 (d, J=6 Hz, 2H, CH_2COO), 4.11 (q, J=7 Hz, 2H, CH_2), 6.8-7.6 (m, 3H, ArH), 11.9 (br s, 1H, NH)

Measurement solvents. C: $CDCl_3$; D: DMSO–d_6.

Table XII. Physical data for ethyl acetate derivatives of pyrrolo[1,2-*c*]imidazole.



Compd	R_4	mp (°C)	Recryst	Yield (%)	Formula	Analysis
R_1=R_2=H ; X=Y=O						
61	H	126-127	A	82	$C_{10}H_{10}N_2O_4$ .1/8H_2O	C, H, N
62	$(CH_3)_2CH$	96-97	B	52	$C_{13}H_{16}N_2O_4$	C, H, N
63	$(CH_3)_2CHCH_2$	99-100	C	73	$C_{14}H_{18}N_2O_4$	C, H, N
64	cyclohexylmethyl	66.5-67.5	D	78	$C_{17}H_{22}N_2O_4$	C, H, N
65	4-CH_3-$C_6H_4CH_2$	83-84	C	65	$C_{18}H_{18}N_2O_4$	C, H, N
66	4-Cl-$C_6H_4CH_2$	104-105	E	79	$C_{17}H_{15}ClN_2O_4$	C, H, N
67	4-CF_3-$C_6H_4CH_2$	138.5-140	E	59	$C_{18}H_{15}F_3N_2O_4$	C, H, N
68	4-Br,2-F-$C_6H_3CH_2$	134-135	E	79	$C_{17}H_{14}BrFN_2O_4$	C, H, N
69	3,4-$(Cl)_2$-$C_6H_3CH_2$	160.5-161.5	E	75	$C_{17}H_{14}Cl_2N_2O_4$	C, H, N
70	4-$(CH_3)_3C$-$C_6H_4CH_2$	70.5-71	E	79	$C_{21}H_{24}N_2O_4$	C, H, N
R_1=R_2=CH_3 ; X=Y=O						
71	H	90-92	E	25	$C_{12}H_{14}N_2O_4$ .1/4H_2O	C, H, N
72	CH_3	100-101	E	29	$C_{13}H_{16}N_2O_4$	C, H, N
73	C_2H_5	104-105	C	10	$C_{14}H_{18}N_2O_4$	C, H, N
74	$CH_3CH_2CH_2$	102-105	E	26	$C_{15}H_{20}N_2O_4$	C, H, N
R_1=R_2=CH_3 ; X=Y=O						
75	$(CH_3)_2CHCH_2$	94-95	E	23	$C_{16}H_{22}N_2O_4$	C, H, N
76	4-F-$C_6H_4CH_2$	148-149	E	23	$C_{19}H_{19}FN_2O_4$	C, H, N
77	4-Br,2-F-$C_6H_3CH_2$	132-134	E	18	$C_{19}H_{18}BrFN_2O_4$	C, H, N
R_1=R_2=H ; X=O, Y=S						
95	H	oil	B	65	$C_{10}H_{10}N_2O_3S$	
96	$(CH_3)_2CH$	70-71	B	76	$C_{13}H_{16}N_2O_3S$	C, H, N
97	$(CH_3)_2CHCH_2$	116.5-117	D	78	$C_{14}H_{18}N_2O_3S$	C, H, N
98	cyclohexylmethyl	92-93	D	56	$C_{17}H_{22}N_2O_3S$ .1/16C_6H_{14}[a]	C, H, N
99	4-CH_3-$C_6H_4CH_2$	77-78	D	48	$C_{18}H_{18}N_2O_3S$	C, H, N
100	4-Cl-$C_6H_4CH_2$	95.5-96.5	F	82	$C_{17}H_{15}ClN_2O_3S$	C, H, N
101	4-CF_3-$C_6H_4CH_2$	141-143	G	37	$C_{18}H_{15}F_3N_2O_3S$	C, H, N
102	4-Br,2-F-$C_6H_3CH_2$	126.5-127.5	G	40	$C_{17}H_{14}BrFN_2O_3S$	C, H, N,
103	3,4-$(Cl)_2$-$C_6H_3CH_2$	153.5-154.5	H	57	$C_{17}H_{14}Cl_2N_2O_3S$	C, H, N,
104	4-$(CH_3)_3C$-$C_6H_4CH_2$	103-104	G	54	$C_{21}H_{24}N_2O_3S$	C, H, N
R_1=R_2=CH_3 ; X=O, Y=S						
105	H	115-116	G	66	$C_{12}H_{14}N_2O_3S$	C, H, N
106	CH_3	118-120	G	50	$C_{13}H_{16}N_2O_3S$	C, H, N
107	C_2H_5	119-120	B	70	$C_{14}H_{18}N_2O_3S$	C, H, N,
108	$CH_3CH_2CH_2$	103-104	G	63	$C_{15}H_{20}N_2O_3S$	C, H, N
109	$(CH_3)_2CHCH_2$	98-100	G	56	$C_{16}H_{22}N_2O_3S$	C, H, N
110	4-F-$C_6H_4CH_2$	154.5-156	G	69	$C_{19}H_{19}FN_2O_3S$ .1/4H_2O	C, H, N
111	4-Br,2-F-$C_6H_3CH_2$	146-148.5	I	45	$C_{19}H_{18}BrFN_2O_3S$	C, H, N
R_1=R_2=H ; X=Y=S						
129	H	50-52	B	40	$C_{10}H_{10}N_2O_2S_2$	C, H, N
130	$(CH_3)_2CH$	oil	B	36	$C_{13}H_{16}N_2O_2S_2$	
131	$(CH_3)_2CHCH_2$	102-103	D	50	$C_{14}H_{18}N_2O_2S_2$	C, H, N
132	cyclohexylmethyl	98-100	B	41	$C_{17}H_{22}N_2O_2S_2$	C, H, N
133	4-CH_3-$C_6H_4CH_2$	oil	B	46	$C_{18}H_{18}N_2O_2S_2$	C, H, N
134	4-Cl-$C_6H_4CH_2$	69-73	B	49	$C_{17}H_{15}ClN_2O_2S_2$ .1/4H_2O	C, H, N
135	4-CF_3-$C_6H_4CH_2$	86-87	F	24	$C_{18}H_{15}F_3N_2O_2S_2$	C, H, N
136	4-Br,2-F-$C_6H_3CH_2$	96-98	G	49	$C_{17}H_{14}BrFN_2O_2S_2$	C, H, N
137	3,4-$(Cl)_2$-$C_6H_3CH_2$	117.5-118.5	F	48	$C_{17}H_{14}Cl_2N_2O_2S_2$	C, H, N
138	4-$(CH_3)_3C$-$C_6H_4CH_2$	67-70	D	5	$C_{21}H_{24}N_2O_2S_2$	C, H, N
R_1=R_2=CH_3 ; X=Y=S						
139	C_2H_5	142-144	B	51	$C_{14}H_{18}N_2O_2S_2$ .1/16$CHCl_3$[a]	C, H, N

Recrystallization solvents. A: washed with *n*-hexane; B: purified by column chromatography on silica gel; C: EtOH/H_2O; D: *n*-hexane; E: EtOH; F: *iso*-Pr_2O/*n*-hexane; G: *iso*-Pr_2O; H: CH_2Cl_2/*iso*-Pr_2O; I: *iso*-Pr_2O/$CHCl_3$; [a]determined by NMR analysis.

Table XIII. Physical data for ethyl acetate derivatives of pyrrolo[1,2-*c*]imidazole.

Compd	Solvent	^{1}H-NMR δ ppm
61	D	1.21 (t, J=7 Hz, 3H, CH_3), 4.18 (q, J=7 Hz, 2H, CH_2), 4.37 (s, 2H, CH_2COO), 6.61 (t, J=3 Hz, pyrrole H), 7.05 (d, J=3 Hz, 1H, pyrrole H), 7.69 (d, J=3 Hz, 1H, pyrrole H)
62	D	1.19 (d, J=7 Hz, 6H, $2CH_3$), 1.21 (t, J=7 Hz, 3H, CH_3), 2.6-3.0 (m, 1H, CH), 4.17 (q, J=7 Hz, 2H, CH_2), 4.34 (s, 2H, CH_2COO), 7.02 (s, 1H, pyrrole H), 7.47 (s, 1H, pyrrole H)
63	C	0.93 (d, J=7 Hz, 6H, $2CH_3$), 1.29 (t, J=7 Hz, 3H, CH_3), 1.6-2.0 (m, 1H, CH), 2.36 (d, J=7 Hz, 2H, CH_2), 4.24 (q, J=7 Hz, 2H, CH_2), 4.32 (s, 2H, CH_2COO), 6.66 (s, 1H, pyrrole H), 7.04 (s, 1H, pyrrole H)
64	D	0.6-2.0 (m, 11H, cyclohexane H), 1.21 (t, J=7 Hz, 3H, CH_3), 2.34 (d, J=6 Hz, 2H, CH_2), 4.17 (q, J=7 Hz, 2H, CH_2), 4.33 (s, 2H, CH_2COO), 6.90 (s, 1H, pyrrole H), 7.44 (s, 1H, pyrrole H)
65	C	1.28 (t, J=7 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.23 (q, J=7 Hz, 2H, CH_2), 4.30 (s, 2H, CH_2COO), 6.66 (s, 1H, pyrrole H), 7.01 (s, 1H, pyrrole H), 7.11 (s, 4H, ArH)
66	D	1.20 (t, J=7 Hz, 3H, CH_3), 3.82 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.33 (s, 2H, CH_2COO), 6.91 (s, 1H, pyrrole H), 7.1-7.45 (m, 4H, ArH), 7.52 (s, 1H, pyrrole H)
67	D	1.20 (t, J=7 Hz, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.33 (s, 2H, CH_2COO), 7.50 (d, J=8 Hz, 2H, ArH), 7.58 (s, 1H, pyrrole H), 7.67 (d, J=8 Hz, 2H, ArH)
68	D	1.20 (t, J=7 Hz, 3H, CH_3), 3.83 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.33 (s, 2H, CH_2COO), 6.90 (s, 1H, pyrrole H), 7.50 (s, 1H, pyrrole H), 7.15-7.6 (m, 3H, ArH)
69	C	1.29 (t, J=7 Hz, 3H, CH_3), 3.80 (s, 2H, CH_2), 4.24 (q, J=7 Hz, 2H, CH_2), 4.32 (s, 2H, CH_2COO), 6.63 (s, 1H, pyrrole H), 6.9-7.5 (m, 3H, ArH), 7.05 (s, 1H, pyrrole H)
70	D	1.20 (t, J=7 Hz, 3H, CH_3), 1.25 (s, 9H, $3CH_3$), 3.77 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.33 (s, 2H, CH_2), 6.91 (s, 1H, pyrrole H), 7.18 (d, J=8 Hz, 2H, ArH), 7.32 (d, J=8 Hz, 2H, ArH), 7.51 (s, 1H, pyrrole H)
71	D	1.21(t, J=7 Hz, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.17 (q, J=7 Hz, 2H, CH_2), 4.29 (s, 2H, CH_2COO), 6.17 (s, 1H, pyrrole H)
72	D	1.21 (t, J=7 Hz, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.16 (q, J=7 Hz, 2H, CH_2), 4.28 (s, 2H, CH_2COO)
73	D	1.03 (t, J=7 Hz, 3H, CH_3), 1.21 (t, J=7 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.34 (q, J=7 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 4.16 (q, J=7 Hz, 2H, CH_2), 4.28 (s, 2H, CH_2COO)
74	D	0.87 (t, J=7 Hz, 3H, CH_3), 1.20 (t, J=7 Hz, 3H, CH_3), 1.2-1.7 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.79 (t, J=7 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 4.16 (q, J=7 Hz, 2H, CH_2), 4.27 (s, 2H, CH_2COO)
75	D	0.88 (d, J=7 Hz, 6H, $2CH_3$), 1.21 (t, J=7 Hz, 3H, CH_3), 1.5-1.9 (m, 1H, CH), 2.16 (s, 3H, CH_3), 2.23 (d, J=7 Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 4.17 (q, J=7 Hz, 2H,CH_2), 4.28 (s, 2H, CH_2COO)
76	D	1.22 (t, J=7 Hz, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 4.17 (q, J=7 Hz, 2H, CH_2), 4.30 (s, 2H, CH_2COO), 6.9- 7.35 (m, 4H, ArH)

Table XIII. *Continued.*

77	D	1.23 (t, J=7 Hz, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 4.18 (q, J=7 Hz, 2H, CH_2), 4.31 (s, 2H, CH_2COO), 7.0-7.6 (m, 3H, ArH)
95	D	1.20 (t, J=7 Hz, 3H, CH_3), 4.17 (q, J=7 Hz, 2H, CH_2), 4.65 (s, 2H, CH_2COO), 6.59 (t, J=3 Hz, 1H, pyrrole H), 7.15 (d, J=3 Hz, 1H, pyrrole H), 7.68 (d, J=3 Hz, 1H, pyrrole H)
96	D	1.19 (d, J=7 Hz, 6H, $2CH_3$), 1.20 (t, J=7 Hz, 3H, CH_3), 2.6-3.0 (m, 1H, CH), 4.16 (q, J=7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2COO), 7.15 (s, 1H, pyrrole H), 7.48 (s, 1H, pyrrole H)
97	C	0.93 (d, J=7 Hz, 6H, $2CH_3$), 1.29 (t, J=7 Hz, 3H, CH_3), 1.6-2.0 (m, 1H, CH), 2.35 (d, J=7 Hz, 2H, CH_2), 4.24 (q, J=7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2COO), 6.80 (s, 1H, pyrrole H), 6.94 (s, 1H, pyrrole H)
98	C	0.6-2.0 (m, 11H, cyclohexane H), 1.28 (t, J=7 Hz, 3H, CH_3), 2.35 (d, J=6 Hz, 2H, CH_2), 4.23 (q, J=7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2COO), 6.80 (s, 1H, pyrrole H), 6.94 (s, 1H, pyrrole H)
99	C	1.27 (t, J=7 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 4.22 (q, J=7 Hz, 2H, CH_2), 4.60 (s, 2H, CH_2COO), 6.79 (s, 1H, pyrrole H), 6.93 (s, 1H, pyrrole H), 7.11 (s, 4H, ArH)
100	D	1.19 (t, J=7 Hz, 3H, CH_3), 3.82 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2COO), 7.02 (s, 1H, pyrrole H), 7.3-7.5 (m, 4H, ArH), 7.53 (s, 1H, pyrrole H)
101	D	1.19 (t, J=7 Hz, 3H, CH_3), 3.93 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2COO), 7.06 (s, 1H, pyrrole H), 7.53 (d, J=8 Hz, 2H, ArH), 7.57 (s, 1H, pyrrole H), 7.68 (d, J=8 Hz, 2H, ArH)
102	D	1.19 (t, J=7 Hz, 3H, CH_3), 3.83 (s, 2H, CH_2), 4.15 (q, J=7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2COO), 6.99 (s, 1H, pyrrole H), 7.15-7.6 (m, 3H, ArH), 7.51 (s, 1H, pyrrole H)
103	C	1.28 (t, J=7 Hz, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.23 (q, J=7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2COO), 6.76 (s, 1H, pyrrole H), 6.97 (s, 1H, pyrrole H), 6.9-7.5 (m, 3H, ArH)
104	D	1.19 (t, J=7 Hz, 3H, CH_3), 1.25 (s, 9H, $3CH_3$), 3.77 (s, 2H, CH_2), 4.15 (q, J=7 Hz, 2H, CH_2), 4.61 (s, 2H, CH_2COO), 7.00 (s, 1H, pyrrole H), 7.19 (d, J=9 Hz, 2H, ArH), 7.33 (d, J=9 Hz, 2H, ArH), 7.51 (s, 1H, pyrrole H)
105	D	1.20 (t, J=7 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.16 (q, J=7 Hz, 2H, CH_2), 4.59 (s, 2H, CH_2COO), 6.24 (s, 1H, pyrrole H)
106	D	1.20 (t, J=7 Hz, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.16 (q, J=7 Hz, 2H, CH_2), 4.57 (s, 2H, CH_2COO)
107	D	1.04 (t, J=7 Hz, 3H, CH_3), 1.20 (t, J=7 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.35 (t, J=7 Hz, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.58 (s, 2H, CH_2COO)
108	D	0.89 (t, J=7 Hz, 3H, CH_3), 1.20 (t, J=7 Hz, 3H, CH_3), 1.2-1.7 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.34 (t, J=7 Hz, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.57 (s, 2H, CH_2COO)
109	D	0.89 (d, J=7 Hz, 6H, $2CH_3$), 1.20 (t, J=7 Hz, 3H, CH_3), 1.5-1.9 (m, 1H, CH), 2.26 (s, 3H, CH_3), 2.26 (d, J=7 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 4.16 (q, J=7 Hz, 2H, CH_2), 4.58 (s, 2H, CH_2COO)
110	D	1.20 (t, J=7 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.58 (s, 2H, CH_2COO), 6.9-7.35 (m, 4H, ArH)

Table XIII. *Continued.*

111	D	1.20 (t, J=7 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.59 (s, 2H, CH_2COO), 7.0-7.6 (m, 3H, ArH)
129	D	1.20 (t, J=7 Hz, 3H, CH_3), 4.17 (q, J=7 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2COO), 6.59 (t, J=3 Hz, 1H, pyrrole H), 7.21 (d, J=3 Hz, 1H, pyrrole H), 7.69 (d, J=3 Hz, 1H, pyrrole H)
130	D	1.19 (d, J=7 Hz, 6H, $2CH_3$), 1.20 (t, J=7 Hz, 3H, CH_3), 2.6-3.0 (m, 1H, CH), 4.16 (q, J=7 Hz, 2H, CH_2), 4.88 (s, 2H, CH_2COO), 7.20 (s, 1H, pyrrole H), 7.44 (s, 1H, pyrrole H)
131	C	0.94 (d, J=7 Hz, 6H, $2CH_3$), 1.28 (t, J=7 Hz, 3H, CH_3), 1.6-2.0 (m, 1H, CH), 2.34 (d, J=7 Hz, 2H, CH_2), 4.24 (q, J=7 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2COO), 6.79 (s, 1H, pyrrole H), 7.08 (s, 1H, pyrrole H)
132	C	0.6-2.0 (m, 11H, cyclohexane H), 1.28 (t, J=7 Hz, 3H, CH_3), 2.34 (d, J=6 Hz, 2H, CH_2), 4.23 (q, J=7 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2COO), 6.78 (s, 1H, pyrrole H), 7.06 (s, 1H, pyrrole H)
133	C	1.27 (t, J=7 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 4.22 (q, J=7 Hz, 2H, CH_2), 4.90 (s, 2H, CH_2COO), 6.76 (s, 1H, pyrrole H), 6.9-7.2 (m, 4H, ArH), 7.06 (s, 1H, pyrrole H)
134	C	1.28 (t, J=7 Hz, 3H, CH_3), 3.80 (s, 2H, CH_2), 4.23 (q, J=7 Hz, 2H, CH_2), 4.91 (s, 2H, CH_2COO), 6.74 (s, 1H, pyrrole H), 7.06 (s, 1H, pyrrole H), 7.0-7.4 (m, 4H, ArH)
135	D	1.19 (t, J=7 Hz, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.16 (q, J=7 Hz, 2H, CH_2), 4.89 (s, 2H, CH_2COO), 7.13 (s, 1H, pyrrole H), 7.54 (d, J=8 Hz, 2H, ArH), 7.61 (s, 1H, pyrrole H), 7.68 (d, J=8 Hz, 2H, ArH)
136	D	1.18 (t, J=7 Hz, 3H, CH_3), 3.85 (s, 2H, CH_2), 4.89 (s, 2H, CH_2COO), 7.06 (s, 1H, pyrrole H), 7.2-7.65 (m, 3H, ArH), 7.52 (s, 1H, pyrrole H)
137	C	1.28 (t, J=7 Hz, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.23 (q, J=7 Hz, 2H, CH_2), 4.92 (s, 2H, CH_2COO), 6.74 (s, 1H, pyrrole H), 6.9-7.5 (m, 3H, ArH)
138	D	1.18 (t, J=7 Hz, 3H, CH_3), 1.26 (s, 9H, $3CH_3$), 3.78 (s, 2H, CH_2), 4.15 (q, J=7 Hz, 2H, CH_2), 4.89 (s, 2H, CH_2COO), 7.08 (s, 1H, pyrrole H), 7.21 (d, J=9 Hz, 2H, ArH), 7.34 (d, J=9 Hz, 2H, ArH), 7.53 (s, 1H, pyrrole H)
139	D	1.07 (t, J=8 Hz, 3H, CH_3), 1.28 (t, J=7 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.40 (q, J=8 Hz, 2H, CH_2), 2.48 (s, 3H, CH_3), 4.17 (q, J=7 Hz, 2H, CH_2), 4.91 (s, 2H, CH_2COO)

Measurement solvents. C: $CDCl_3$; D: DMSO–d_6.

After concentration, the residue was dissolved in ethyl ether (150 ml), washed with 1 N NaOH solution and saturated NaCl solution, dried over Na_2SO_4 and concentrated. The residue was distilled under reduced pressure to give a yellow oil (22, 13.0 g, 96%, bp: 108–112°C/0.04 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (d, J = 6 Hz, 6H, $2CH_3$), 1.34 (t, J = 7 Hz, 3H, CH_3), 1.5–2.0 (m, 1H, CH), 2.32 (d, J = 7 Hz, 2H, CH_2), 4.31 (q, J = 7 Hz, 2H, CH_2), 6.73 (br s, 2H, pyrrole H), 9.4 (br s, 1H, NH). MS: 195 (M^+). Anal $C_{11}H_{17}NO_2 \cdot 1/8H_2O$ (C, H, N).

General procedure for the synthesis of ***32–43***

The following procedure for the synthesis of 4-isobutyl-2-pyrrolecarboxylic acid **32** is representative. The other compounds, **33–43**, were obtained similarly. Physical data for these compounds are summarized in tables VIII and IX. 2-Pyrrolecarboxylic acid was commercially available. 4-Isopropyl-2-pyrrolecarboxylic acid, 3,5-dimethyl-2-pyrrolecarboxylic acid, 3,4,5-trimethyl-2-pyrrolecarboxylic acid and 4-ethyl-3,5-dimethyl-2-pyrrolecarboxylic acid were synthesized by a previously described method [14–17].

4-Isobutyl-2-pyrrolecarboxylic acid ***32***

(**4**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)

A solution of ethyl 4-isobutyl-2-pyrrolecarboxylate (**22**, 3.50 g, 17.9 mmol) and 2 N NaOH (17.9 ml, 35.8 mmol) in EtOH (20 ml) were heated under reflux for 2 h. After concentration, H_2O (30 ml) was added to the residue and acidified with

concentrated HCl. The solid was collected on a filter, washed with H_2O and recrystallized from dichloromethane (CH_2Cl_2)/MeOH/isopropyl ether(*iso*-Pr_2O) to give colorless needles (32, 2.94 g, 98%, mp: 177–178.5°C with decomp). ^{1}H-NMR (DMSO–d_6) δ: 0.85 (d, J = 7 Hz, 6H, $2CH_3$), 1.4–2.0 (m, 1H, CH), 2.25 (d, J = 7 Hz, 2H, CH_2), 6.53 (br s, 1H, pyrrole H), 6.72 (br s, 1H, pyrrole H), 11.4 (br s, 1H, NH), 12.05 (br s, 1H, COOH). MS: 167 (M^+). Anal $C_9H_{13}NO_2 \cdot 1/16H_2O$ (C, H N).

General procedure for the synthesis of ***44–60***

The following procedure for the synthesis of ethyl 4-isobutyl-2-pyrrolecarbonylaminoacetate **46** is representative. The other compounds, **44**, **45**, **47–60**, were obtained similarly. Physical data for these compounds are summarized in tables X and XI.

Ethyl 4-isobutyl-2-pyrrolecarbonylaminoacetate ***46***
(**5**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)
Diethyl phosphorocyanidate (4.39 g, 24.2 mmol) was added to 4-isobutyl-2-pyrrolecarboxylic acid (**32**, 2.70 g, 16.1 mmol) and glycine ethyl ester (4.99 g, 48.4 mmol) in dimethyl formamide (10 ml) under ice cooling, followed by the addition of triethylamine (2.45 g, 24.2 mmol). The mixture was stirred at room temperature (rt) for 24 h. After concentration, H_2O (50 ml) was added to the residue, which was then stirred at rt for 30 min. A white solid was collected on a filter, washed with H_2O and recrystallized from CH_2Cl_2/*iso*-Pr_2O to give colorless needles (46, 3.98 g, 98%, mp: 136.5–138°C). ^{1}H-NMR (DMSO–d_6) : δ 0.87 (d, J = 7 Hz, 6H, $2CH_3$), 1.20 (t, J = 7 Hz, 3H, CH_3), 1.4–2.0 (m, 1H, CH), 2.26 (d, J = 7 Hz, 2H, CH_2), 3.91 (d, J = 6 Hz, 2H, CH_2COO), 4.11 (q, J = 7 Hz, 2H, CH_2), 6.62 (br s, 2H, pyrrole H), 8.31 (t, J = 6 Hz, 1H, CONH), 11.2 (br s, 1H, NH). MS: 252 (M^+). Anal $C_{13}H_{20}N_2O_3$ (C, H, N).

General procedure for the synthesis of ***61–77***

The following procedure for the synthesis of 2-ethoxycarbonylmethyl-6-isobutyl-1,3(2*H*)-dioxo-1*H*-pyrrolo[1,2-*c*]imidazole **63** is representative. The other compounds, **61**, **62**, **64–77**, were obtained in a similar manner. Physical data for these compounds are summarized in tables XII and XIII.

2-Ethoxycarbonylmethyl-6-isobutyl-1,3(2H)-dioxo-1H-pyrrolo[1 ,2-c]imidazole ***63***
(**6**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)
A mixture of 1,1'-carbonyldiimidazole (4.63 g, 28.5 mmol) and ethyl 4-isobutyl-2-pyrrolecarbonylaminoacetate (**46**, 3.60 g, 14.3 mmol) was heated at 150°C for 40 min. After cooling, EtOH (30 ml) and H_2O (30 ml) were added to the reaction mixture and kept at 4°C for 4 h. The solid was collected on a filter, washed with 50% EtOH and recrystallized from 60% EtOH to give colorless needles (63, 2.89 g, 73%, mp: 99–100°C). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (d, J =7 Hz, 6H, $2CH_3$), 1.29 (t, J = 7 Hz, 3H, CH_3), 1.6–2.0 (m, 1H, CH), 2.36 (d, J = 7 Hz, 2H, CH_2), 4.24 (q, J = 7 Hz, 2H, CH_2), 4.32 (s, 2H, CH_2COO), 6.66 (s, 1H, pyrrole H), 7.04 (s, 1H, pyrrole H).MS: 278 (M^+). Anal $C_{14}H_{18}N_2O_4$ (C, H, N).

General procedure for the synthesis of ***78–94***, ***112–128***, ***140–150***

The following procedure for the synthesis of 2-carboxymethyl-6-isobutyl-1,3(2*H*)-dioxo-1*H*-pyrrolo[1,2-*c*]imidazole **80** is representative. The other compounds, **78**, **79**, **81–94**, **112–128**, **140–150**, were obtained in a similar manner. Physical data for these compounds are summarized in tables I and II.

2-Carboxymethyl-6-isobutyl-1,3(2H)-dioxo-1H-pyrrolo[1,2-c]imidazole ***80***
(**7**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)
A mixture of 2-ethoxycarbonylmethyl-6-isobutyl-1,3(2*H*)-dioxo-1*H*-pyrrolo[1,2-*c*]imidazole (**63**, 0.70 g, 2.52 mmol) and concentrated HCl (5 ml) in acetic acid (AcOH)(15 ml) was heated under reflux for 3 h. After addition of concentrated HCl (3 ml), heating of the mixture was continued under reflux for 2 h. Water (20 ml) was added to the reaction mixture and the insoluble material was collected on a filter to give colorless needles (80, 0.548 g, 87%, mp: 183.5–184°C). ^{1}H-NMR (DMSO–d_6) δ: 0.88 (d, J = 7 Hz, 6H, $2CH_3$), 1.6–2.0 (m, 1H, CH), 2.34 (d, J = 7 Hz, 2H, CH_2), 4.22 (s, 2H, CH_2COO), 6.90 (s, 1H, pyrrole H), 7.45 (s, 1H, pyrrole H), 13.3 (br s, 1H, COOH). MS: 250 (M^+). Anal $C_{12}H_{14}N_2O_4$ (C, H, N).

General procedure for the synthesis of ***95–111***

The following procedure for the synthesis of 2-ethoxycarbonylmethyl-6-isobutyl-3-oxo-1(2*H*)-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole **97** is representative. The other compounds, **95**, **96**, **98–111**, were obtained in a similar manner. Physical data for these compounds are summarized in tables XII and XIII.

2-Ethoxycarbonylmethyl-6-isobutyl-3-oxo-1(2H)-thioxo-1H-pyrrolo[1,2-c]imidazole ***97***
(**8**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)
A mixture of 2-ethoxycarbonylmethyl-6-isobutyl-1,3(2*H*)-dioxo-1*H*-pyrrolo[1,2-*c*]imidazole (**63**, 2.00 g, 7.19 mmol) and phosphorus pentasulfide (3.99 g, 18.0 mmol) in dioxane (40 ml) were heated under reflux for 8 h. After cooling, the supernatant was separated by decantation and concentrated. The residue was chromatographed on a silica gel column (150 g, eluent, $CHCl_3$/hexane = 2.5:1). The eluate was recrystallized from *n*-hexane to give yellow needles (97, 1.65 g, 78%, mp: 116.5–117°C). ^{1}H-NMR ($CDCl_3$) δ : 0.93 (d, J = 7 Hz, 6H, $2CH_3$), 1.29 (t, J = 7 Hz, 3H, CH_3), 1.6–2.0 (m, 1H, CH), 2.35 (d, J = 7 Hz, 2H, CH_2), 4.24 (q, J = 7 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2COO), 6.80 (s, 1H, pyrrole H), 6.94 (s, 1H, pyrrole H). Anal $C_{14}H_{18}N_2O_3S$ (C, H, N).

General procedure for the synthesis of ***129–139***

The following procedure for the synthesis of 2-ethoxycarbonylmethyl-6-isobutyl-1,3(2*H*)-dithioxo-1*H*-pyrrolo[1,2-*c*]imidazole **131** is representative. The other compounds, **129**, **130**, **132–139**, were obtained similarly. Physical data of these compounds are summarized in tables XII and XIII.

2-Ethoxycarbonylmethyl-6-isobutyl-1,3(2H)-dithioxo-1H-pyrrolo[1,2-c]imidazole ***131***
(**10**, $R_1 = R_2 = H$, $R_4 = (CH_3)_2CHCH_2$)
A mixture of 2-ethoxycarbonylmethyl-6-isobutyl-1,3(2*H*)-dioxo-1*H*-pyrrolo[1,2-*c*]imidazole (**63**, 2.00 g, 7.19 mmol) and phosphorus pentasulfide (8.00 g, 36.0 mmol) in xylene (50 ml) was heated under reflux for 24 h. The supernatant was separated by decantation and concentrated. The residue was chromatographed on a silica gel column (150 g, eluent, $CHCl_3$/hexane = 1.5:1). The eluate was recrystallized from *n*-hexane to give a reddish-orange powder (131, 1.11 g, 50%, mp: 102-103°C). ^{1}H-NMR ($CDCl_3$) δ : 0.94 (d, J = 7 Hz, 6H, $2CH_3$), 1.28 (t, J =7 Hz, 3H, CH_3), 1.6–2.0 (m, 1H, CH), 2.34 (d, J =7 Hz, 2H, CH_2), 4.24 (q, J = 7 Hz, 2H, CH_2), 4.92 (s,

2H, CH_2COO), 6.79 (s, 1H, pyrrole H), 7.08 (s, 1H, pyrrole H). MS: 310 (M^+). Anal $C_{14}H_{18}N_2O_2S_2$ (C, H, N).

Pharmacology

Inhibition of aldose reductase in vitro

The preparation of aldose reductase from rat lens and determination of its activity were essentially conducted according to the method of Hayman *et al* [18]. AR activity was assayed by determining spectrophotometrically at 340 nm oxidation of reduced nicotine amide adenine dinucleotid phosphate (NADPH) to NADP using DL-glyceraldehyde as the substrate. The reaction mixture contained 0.1 M phosphate buffer (pH 6.2), 0.25 mM NADPH, 1.5 mM DL-glyceraldehyde and the enzyme in a total volume of 1.00 ml. The effects of inhibitors on enzyme activity were determined by adding them to the reaction mixture in the desired concentration. The % inhibition for each inhibitor was calculated by comparing the reaction rate of the solutions containing the inhibitor with that of control. IC_{50} values were obtained by estimating graphically from the log concentration–response curves.

Inhibition of sorbitol accumulation in vivo

Six-wk-old male Wistar rats were rendered diabetic by an intravenous injection of streptozotocin (70 mg/kg body weight). After 1 wk of induction of diabetes, rats with plasma glucose levels > 400 mg/dl were grouped and given a test compound as a suspension in 0.5 % methyl cellulose orally twice a day for 1 d. The rats were kept in identical cages and had free access to laboratory chow and water. Eighteen h after final administration of the compound, the rats were anesthesized with ether and the sciatic nerves were removed. Sorbitol was extracted from the sciatic nerve by the method of Peterson *et al* [19] and measured enzymatically by the method of Clements *et al* [20]. The sorbitol contents were compared with that obtained for the control group given a vehicle only.

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