Novel 2-Amino-1,4-dihydropyridine Calcium Antagonists. II.[1] Synthesis and Antihypertensive Effects of 2-Amino-1,4-dihydropyridine Derivatives Having *N,N*-Dialkylaminoalkoxycarbonyl Groups at 3- and/or 5-Position

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Novel 2-amino-1,4-dihydropyridine derivatives I, which contain *N,N*- dialkylaminoalkoxycarbonyl groups at the 3- and/or 5-position, were synthesized and their antihypertensive effects were evaluated in spontaneously hypertensive rats. Remarkably prolonged duration of antihypertensive action was observed when a tertiary amino group was introduced into either the 3- or 5-ester side-chain of the 1,4-dihydropyridine ring. In particular, the compounds containing cyclic amino moieties at the 3-position showed greater potency than those with acyclic amino moieties. Chemical modification studies indicated that the two ester side-chains of 1,4-dihydropyridine at the 3- and 5-position might function in a different manner in relation to the antihypertensive activities. 3-(1-Benzhydrylazetidin-3-yl) 5-isopropyl 2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylate, I-43 (CS-905), exhibited potent and long-lasting antihypertensive effects with gradual onset of action, and is a promising candidate as an antihypertensive drug.

Key words 1,4-dihydropyridine; calcium antagonist; antihypertensive effect; spontaneously hypertensive rat

1,4-Dihydropyridine (DHP) calcium antagonists such as nifedipine[2] and nicardipine[3] are clinically very effective antihypertensives. Their clinical usefulness, however, is limited not only because these drugs induce a rapid fall in blood pressure accompanied with a counteracting increase in heart rate, but also because frequent administration is required due to their relatively short duration of action. Therefore, new calcium antagonists possessing gradual onset and long-lasting antihypertensive activities would be desirable to improved patients' quality of life. Recently attempts have been made to solve these problems by replacing the methyl group at the 2-position on the DHP ring with a more hydrophilic substituent such as an aminoethoxymethyl group, a cyano group, or a carbamoyloxymethyl group.[4] We decided to introduce a simple amino group into the ring at the 2-position in order to increase the hydrophilicity.

Synthesis and antihypertensive effects of 2-amino-1,4-dihydropyridine derivatives having nitroxyalkoxycarbonyl groups at the 3- and/or 5-position were reported in our previous paper,[1] and some of them exhibited favorable profiles of antihypertensive action. In particular, a remarkably prolonged duration of action with gradual onset was observed when a tertiary amino group was introduced into either the 3- or 5-ester side chain of the DHP ring. These results encouraged us to examine the effects of various *N,N*-dialkylaminoalkyl groups introduced into ester side-chains on the antihypertensive activities.

In this paper, we describe the synthesis and antihypertensive effects of a series of 2-amino-1,4-dihydropyridine derivatives having *N,N*-dialkylaminoalkoxycarbonyl groups at the 3- and/or 5-position.

Chemistry

2-Amino-1,4-dihydropyridine derivatives I were synthesized by the modified Hantzsch reaction[5] with amidinoacetates II and benzylideneacetoacetates III, and 2,6-dimethyl-1,4-dihydropyridine derivatives I were also synthesized from aminocrotonates IV and compounds III as shown in Chart 1. The results are listed in Tables 1 and 2.

The synthesis of the amidinoacetates II was carried out by reaction of the imidates VII with ammonium chloride.[6] This reaction usually gives the product in very poor yield unless R^1 is a methyl or an ethyl group. Examination of the reaction conditions led us to the use of ammonium

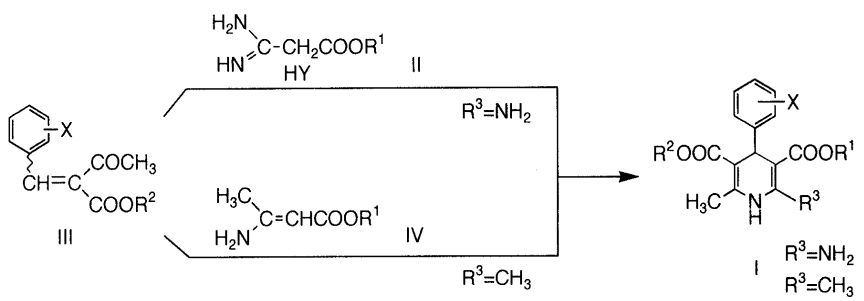

Chart 1

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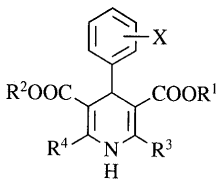
Table 1. Physical Properties and Antihypertensive Effects of 1,4-Dihydropyridines I



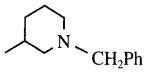
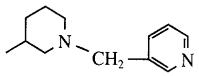
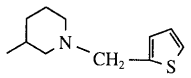
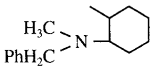
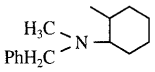
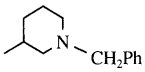
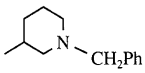
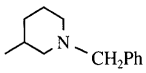
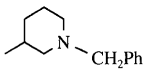
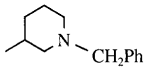
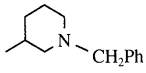
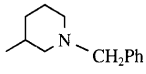
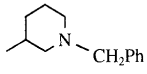
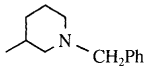
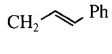
No.	X	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula[a]	Antihypertensive effects[b]					
									Dose (mg/kg)	*dBP* (%)	T_{max} (h)	$T_{1/2}$ (h)	12 h*A*[c] (mmHg·%)	24 h*A*[d]
1	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$	CH_3	NH_2	CH_3	57	41—46	$C_{25}H_{28}N_4O_6$	3	−18	2.0	6.1	−112	−92
2	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$	$CH(CH_3)_2$	NH_2	CH_3	87.7	105—108	$C_{27}H_{32}N_4O_6 \cdot 2HCl$	3	−18	8.0	12.0	−161	−181
3	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$		NH_2	CH_3	67.6	165—168	$C_{36}H_{41}N_5O_6 \cdot 3HCl$	3	−22	4.0	12.8	−215	−234
4	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$		NH_2	CH_3	63	59—62	$C_{35}H_{40}N_6O_6$	3	−20	5.0	8.3	−126	
5	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$		NH_2	CH_3	31	147—149	$C_{34}H_{39}N_5O_6S \cdot 4HCl$	3	−24	13.0	17.8	−219	−340
6	3-NO_2	$CH(CH_3)CH_2N(CH_3)CH_2Ph$	$CH(CH_3)_2$	NH_2	CH_3	9.6	113—116	$C_{28}H_{34}N_4O_6 \cdot 2HCl \cdot 2H_2O$	1	−12	22.0	>24		
7F1[e]	3-NO_2	$CH(CH_3)CH_2N(CH_3)CH_2Ph$	n-C_6H_{13}	NH_2	CH_3	17.6	89—92	$C_{31}H_{40}N_4O_6 \cdot 2HCl \cdot H_2O$	1	−5	12.0	17.0		
7F2[e]	3-NO_2	$CH(CH_3)CH_2N(CH_3)CH_2Ph$	n-C_6H_{13}	NH_2	CH_3	11.5	97—99	$C_{31}H_{40}N_4O_6 \cdot 2HCl$	1	−7	0.3	0.5		
8	3-NO_2	$CH_2CH(CH_3)N(CH_3)CH_2Ph$	$CH(CH_3)_2$	NH_2	CH_3	8.3	117—120	$C_{28}H_{34}N_4O_6 \cdot 2HCl \cdot 1/2H_2O$	1	−18	0.8	1.9		
9	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	45	81—85	$C_{31}H_{38}N_4O_6$	3	−10	7.0	11.6		
10	3-NO_2		n-C_6H_{13}	NH_2	CH_3	17.4	175—178	$C_{34}H_{44}N_4O_6$	1	−8	1.0	4.5		
11F1[e]	3-NO_2		CH_3	NH_2	CH_3	34	94	$C_{27}H_{30}N_4O_6$	3	−45	1.5	9.6	−338	−428
11F1[e]	3-NO_2		CH_3	NH_2	CH_3	35	93	$C_{27}H_{30}N_4O_6$	3	−14	5.0	6.4	−110	−141
12	3-NO_2		CH_2CH_3	NH_2	CH_3	69	74—77	$C_{28}H_{32}N_4O_6$	3	−35	2.0	11.2	−298	−359
13	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	82	84—87	$C_{29}H_{34}N_4O_6$	3	−35	4.0	15.3	−358	−537
14	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	65.0	157—160	$C_{29}H_{34}N_4O_6 \cdot 2HCl \cdot H_2O$	3	−24	0.8	12.2	−227	−275
15	3-NO_2			NH_2	CH_3	62.2	151—155	$C_{30}H_{34}N_4O_6 \cdot 2HCl$	3	−27	11.0	13.0	−214	−255
16	3-NO_2		n-C_6H_{13}	NH_2	CH_3	53.8	129—132	$C_{32}H_{40}N_4O_6 \cdot 2HCl$	3	−31	7.0	13.6	−282	−355
17	3-NO_2			NH_2	CH_3	58	168—172	$C_{32}H_{38}N_4O_6 \cdot 2HCl \cdot H_2O$	3	−30	11.0	18.0	−270	−430
18	3-NO_2			NH_2	CH_3	56.5	152—155	$C_{35}H_{36}N_4O_6 \cdot 2HCl$	3	−11	3.0	12.3	−100	

Table 1. (continued)

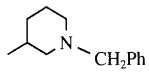
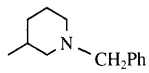
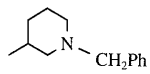
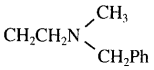
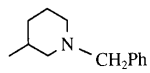
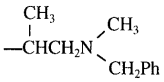
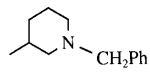
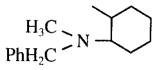
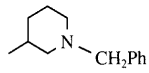
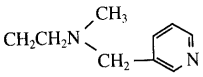
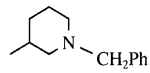
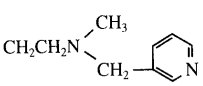
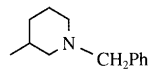
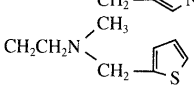
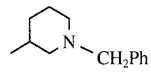
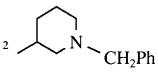
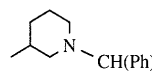
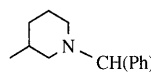
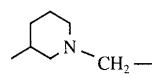
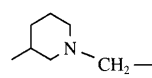
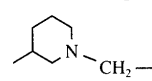
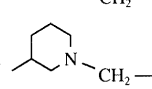
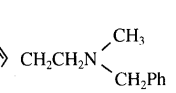
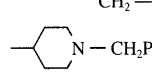
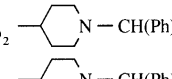
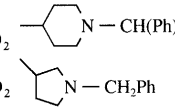
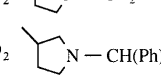
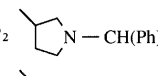
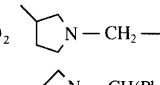
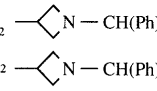
No.	X	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula[a]	Antihypertensive effects[b] Dose (mg/kg)	*dBP* (%)	T_{max} (h)	$T_{1/2}$ (h)	12 h*A*[c] (mmHg·%)	24 h*A*[d] (mmHg·%)
19	3-NO_2		$CH_2CH_2OCH_3$	NH_2	CH_3	79.6	143—146	$C_{29}H_{34}N_4O_7$ ·2HCl	3	−44	0.5	5.8	−242	−239
20	3-NO_2		$(CH_2)_6OH$	NH_2	CH_3	91.8	105—108	$C_{32}H_{40}N_4O_7$ ·2HCl	3	−24	5.0	13.2	−196	−268
21	3-NO_2			NH_2	CH_3	70	53—56	$C_{36}H_{41}N_5O_6$	3	−31	3.0	14.3	−281	−389
22	3-NO_2			NH_2	CH_3	69	162—164	$C_{37}H_{43}N_5O_6$ ·4HCl	3	−32	3.0	14.6	−280	−406
23	3-NO_2			NH_2	CH_3	50	162—164	$C_{40}H_{47}N_5O_6$ ·3HCl	3	−29	2.0	9.4	−242	−224
24F1[e]	3-NO_2			NH_2	CH_3	40	52—54	$C_{35}H_{40}N_6O_6$	3	−12	7	12.2		
24F2[e]	3-NO_2			NH_2	CH_3	33	98—101	$C_{35}H_{40}N_6O_6$	3	−15	21.0	>24.0	−89	−230
25	3-NO_2			NH_2	CH_3	72	51—53	$C_{34}H_{39}N_5O_6S$	3	−36	6.0	9.4	−209	−200
26	2-NO_2		CH_3	NH_2	CH_3	62	88—91	$C_{27}H_{30}N_4O_6$	3	−13	1.0	4.2	−27	
27	2,3-Cl_2		$CH(CH_3)_2$	NH_2	CH_3	86	84—88	$C_{29}H_{33}Cl_2N_3O_4$	3	−31	6.0	13.7	−284	−344
28	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	63.5	174—177	$C_{35}H_{38}N_4O_6$ ·2HCl·H_2O	1	−18	4.0	11.1	−142	−156
29	3-NO_2		n-C_6H_{13}	NH_2	CH_3	32.6	151—155	$C_{38}H_{44}N_4O_6$ ·2HCl·H_2O	1	−13	8.0	14.1	−109	−132
30	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	37	88—91	$C_{28}H_{33}N_5O_6$	3	−35	3.0	7.6	−257	−282
31	3-NO_2		n-C_6H_{13}	NH_2	CH_3	38.3	135—138	$C_{31}H_{39}N_5O_6$ ·3HCl	1	−16	1	9		
32	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	64	100—102	$C_{27}H_{32}N_4O_6S$	3	−51	1.0	9.2	−395	−377
33	3-NO_2			NH_2	CH_3	70	42—45	$C_{34}H_{39}N_5O_6S$	3	−27	5.0	14.6	−229	−250
34	3-NO_2		n-C_6H_{13}	NH_2	CH_3	24	137—139	$C_{32}H_{40}N_4O_6$	1	8	13.0	13.8		
35	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	82	109—111	$C_{35}H_{38}N_4O_6$	1	−13	0.5	2.6	−58	−85
36	3-NO_2		n-C_6H_{13}	NH_2	CH_3	25	160—163	$C_{38}H_{44}N_4O_6$	1	−10	1.0	1.5	−57	−58
37	3-NO_2		n-C_6H_{13}	NH_2	CH_3	34.3	97.5—99	$C_{31}H_{38}N_4O_6$ ·2HCl	1	−12	6.0	13.6		
38	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	68.5	166—169	$C_{34}H_{36}N_4O_6$ 2HCl	1	−23	4.0	10.8	−209	−247
39	3-NO_2		n-C_6H_{13}	NH_2	CH_3	35.9	104—108	$C_{37}H_{42}N_4O_6$ ·2HCl·H_2O	1	−18	5	10.5		
40	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	34.3	66—68	$C_{26}H_{30}N_4O_6S$	1	−21	7.0	16.2	−205	−284
41	3-NO_2		CH_3	NH_2	CH_3	66	88—92	$C_{31}H_{30}N_4O_6$	1	−10	6.0	10.9		
42F1[e]	3-NO_2		C_2H_5	NH_2	CH_3	12.5	107—109	$C_{32}H_{32}N_4O_6$ ·2HCl	3	−21	6.0	10.8	−181	−195

Table 1. (continued)

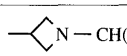
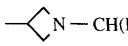
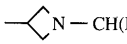
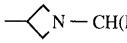
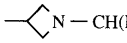
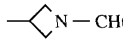
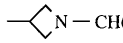
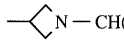
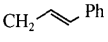
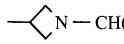
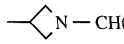
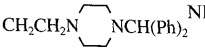
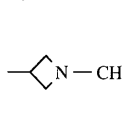
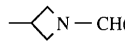
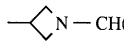
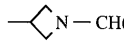
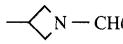
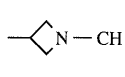
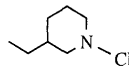
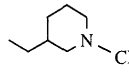
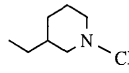
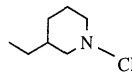
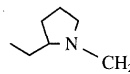
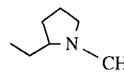
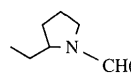
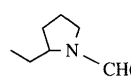
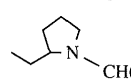
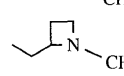
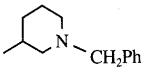
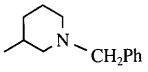
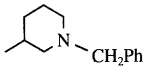
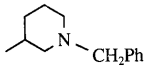
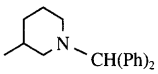
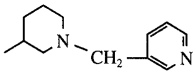
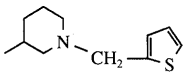
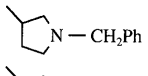
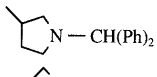
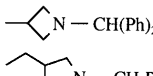
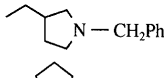
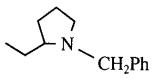
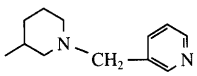
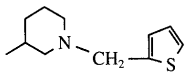
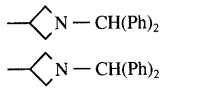
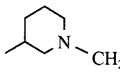
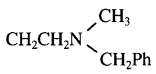
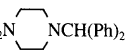
No.	X	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula[a]	Antihypertensive effects[b] Dose (mg/kg)	*dBP* (%)	T_{max} (h)	$T_{1/2}$ (h)	12 h*A*[c] (mmHg·%)	24 h*A*[d] (mmHg·%)
42F2[e]	3-NO_2		C_2H_5	NH_2	CH_3	23.0	134—136	$C_{32}H_{32}N_4O_6$	1	−17	8.0	14.6	−141	−187
42F2[e]	3-NO_2		C_2H_5	NH_2	CH_3	13.0	113—114.5	$C_{32}H_{32}N_4O_6$ ·2HCl	3	−24	8.0	13.6	−232	−281
43 CS-605	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	74	95—98	$C_{33}H_{34}N_4O_6$	3 1	−47 −22	5.0 6.0	16.0 12.9	−480 −213	−698 −252
44	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	96.7	118—120	$C_{33}H_{34}N_4O_6$ 2HCl	3 1	−23 −15	4.0 7	17.5 15.2	−228	−336
45	3-NO_2			NH_2	CH_3	66.2	156—160	$C_{34}H_{34}N_4O_6$	1	−13	8.0	11.6	−73	−73
46	3-NO_2		n-C_6H_{13}	NH_2	CH_3	55	106—108	$C_{36}H_{40}N_4O_6$ ·2HCl	3	−32	9.0	13.2	−280	−355
47	3-NO_2			NH_2	CH_3	34.5	113—114.5	$C_{30}H_{38}N_4O_6$ ·2HCl·1/2H_2O	1	−15	4.0	11.5	−133	−156
48	3-NO_2			NH_2	CH_3	60.3	114—117	$C_{39}H_{36}N_4O_6$ ·H_2O	1	−14	4.0	15.6	−139	−189
49	3-NO_2		$CH_2CH_2OCH_3$	NH_2	CH_3	86.5	83—85	$C_{33}H_{34}N_4O_7$	1	−10	9	16.9		
50	3-NO_2			NH_2	CH_3	23.9	122—125	$C_{49}H_{50}N_6O_6$ ·1/2H_2O						
51	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	60.4	116—118	$C_{34}H_{36}N_4O_6$	1	−13	6.0	10.3	−112	−118
52	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	26	118—120	$C_{33}H_{32}F_2N_4O_6$	1	−23	7.0	11.8	−218	−247
53	2-Cl		$CH(CH_3)_2$	NH_2	CH_3	48	85—86	$C_{33}H_{34}ClN_3O_4$	1	−10	6.0	10.0	−56	−61
54	2,3-Cl_2		$CH(CH_3)_2$	NH_2	CH_3	74.6	100—102	$C_{33}H_{33}Cl_2N_3O_4$	1	−22	6.0	12.0	−203	−226
55	3-CF_3		$CH(CH_3)_2$	NH_2	CH_3	93	96—98	$C_{34}H_{34}F_3N_3O_4$	1	−10	6.0	6.7	−35	−45
56	3-CN		$CH(CH_3)_2$	NH_2	CH_3	43	95—97	$C_{34}H_{34}N_4O_4$	1	−12	6.0	13.6		
57	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	19.2	93.5—95	$C_{28}H_{32}N_4O_6$						
58	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	65.1	70—73	$C_{30}H_{36}N_4O_6$ ·H_2O	1	−17	0.8	2.6		
59	3-NO_2		n-C_6H_{13}	NH_2	CH_3	43.6	121—124	$C_{33}H_{42}N_4O_6$ ·2HCl	1	−14	0.8	6.8		
60	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	12.8	89—93	$C_{36}H_{40}N_4O_6$	1	−10	13.0	13.5	−28	−23
61	3-NO_2		n-C_6H_{13}	NH_2	CH_3	6.8	111—114	$C_{31}H_{40}N_4O_6S$ ·2HCl	1	−17	0.8	2.4	−121	−133
62	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	62	119—121	$C_{29}H_{34}N_4O_6$ ·2HCl	3	−48	0.8	7.2	−292	−272
63	3-NO_2		n-C_6H_{13}	NH_2	CH_3	47	90—94	$C_{32}H_{40}N_4O_6$ ·2HCl	1	−12	2	4.2		
64	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	50.3	84—88	$C_{34}H_{36}N_4O_6$	1	−11	8.0	12.2	−72	−96
65	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	55	116—119	$C_{27}H_{32}N_4O_6S$ ·2HCl	1	6	22.0	>24.0	−10	18
66	3-NO_2		n-C_6H_{13}	NH_2	CH_3	27	89—92	$C_{30}H_{38}N_4O_6S$ ·2HCl	—	—				
67	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	67	88—91	$C_{33}H_{34}N_4O_6$	—	—				

Table 1. (continued)

No.	X	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula[a]	Antihypertensive effects[b] Dose (mg/kg)	*dBP* (%)	T_{max} (h)	$T_{1/2}$ (h)	12 h*A*[c] (mmHg·%)	24 h*A*[d] (mmHg·%)
68F2[e]	3-NO_2	CH_3		NH_2	CH_3	24	82—85	$C_{27}H_{30}N_4O_6$	3	−43	1.5	7.5	−305	−396
69	3-NO_2	CH_2CH_3		NH_2	CH_3	63.8	72—75	$C_{28}H_{32}N_4O_6$	3	−25	6.0	12.2	−234	−267
70	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	15	71—74	$C_{29}H_{34}N_4O_6$	3	−31	3.0	10.5	−263	−287
71	2,3-Cl_2	$CH(CH_3)_2$		NH_2	CH_3	88	84—87	$C_{29}H_{33}Cl_2N_3O_4$	3	−22	5.0	13.6	−198	−233
72	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	62.3	112—116	$C_{35}H_{38}N_4O_6$	1	−13	6.0	9.9	−98	−102
73	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	86	106—109	$C_{28}H_{33}N_5O_6$	3	−26	5.0	9.4	−208	−184
74	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	84	96—99	$C_{27}H_{32}N_4O_6S$	3	−30	2.0	16.2	−271	−427
75	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	53.9	102—105	$C_{28}H_{32}N_4O_6$	3	−14	4.0	7.2	−86	−74
76	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	37.0	107—110	$C_{34}H_{36}N_4O_6$	1	−11	2.0	8.0	−88	−97
77	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	56	104—107	$C_{33}H_{34}N_4O_6$	1	−17	6.0	12.1	−146	−172
78	2,3-Cl_2	$CH(CH_3)_2$		NH_2	CH_3	62.8	88—92	$C_{29}H_{33}Cl_2N_3O_4$	3	−17	3.0	7.8	−115	−130
79	3-NO_2	$CH(CH_3)_2$		NH_2	CH_3	71.2	132—134	$C_{29}H_{34}N_4O_6$ ·2HCl·H_2O	3	−46	0.5	3.8	−248	−303
80	3-NO_2		CH_3	CH_3	CH_3	42	145—147	$C_{27}H_{30}N_4O_6$ ·2HCl·H_2O	1	−32	0.8	2.5		
81	3-NO_2		CH_3	CH_3	CH_3	73	136—169	$C_{26}H_{29}N_3O_6S$ ·2HCl	1	−25	8.0	15.4	−190	−249
82	3-NO_2		CH_3	CH_3	CH_3	98	101—105	$C_{32}H_{31}N_3O_6$	1	−26	2.0	9.6	−197	−205
83	3-NO_2		$CH(CH_3)_2$	CH_3	CH_3	70.8	90—92	$C_{34}H_{35}N_3O_6$						
84	3-NO_2		n-C_6H_{13}	CH_3	CH_3	58	52—55	$C_{37}H_{41}N_3O_6$	1	−15	9.0	12.7	−174	
CD-349	3-NO_2	$CH_2CH(CH_3)ONO_2$	$(CH_2)_3ONO_2$	CH_3	CH_3				3	−41	0.5	9.1	−343	−380
Nif	2-NO_2	CH_3	CH_3	CH_3	CH_3				3	−36	0.3	7.0	−237	−259
Ben	3-NO_2		CH_3	CH_3	CH_3				3	−52	0.5	8.4	−399	−436
Nic	3-NO_2	CH_3		CH_3	CH_3				3	−31	0.8	5.3	−175	−178
Amlo	2-Cl	CH_2CH_3	CH_3	$CH_2OCH_2CH_2NH_2$	CH_3				3	−35	4.0	15.0	−347	−475
									1	−22	5.0	11.4	−194	−235
Nit	3-NO_2	CH_2CH_3	CH_3	CH_3	CH_3				3	−38	0.3	2.0	−153	−168
Man	3-NO_2	CH_2CH_2N  $NCH(Ph)_2$	CH_3	CH_3	CH_3				3	−31	6.0	12.3	−256	−398
FRC-8411	3-NO_2	CH_2  Ph	CH_3	CH_3	CH_3				3	−45	4.0	10.0	−426	−481
Nilv	3-NO_2	CH_3	$CH(CH_3)_2$	CN	CH_3				3	−28	0.3	7.6	−203	−189
Lac	2-$CH=CHCOOC(CH_3)_3$	CH_2CH_3	CH_2CH_3	CH_3	CH_3				1	−36	5.0	8.8	−295	−311

a) All compounds were analyzed for C, H, and N. Analytical results obtained for these elements were within 0.5% of the calculated values for the formulae shown. *b*) Drugs were orally administrated at a single dose in conscious SHRs (*p.o.*). *c*) Area of under the mean blood pressure curve after dosage to 12 h. *d*) Area of under the mean blood pressure curve after dosage to 24 h. *e*) F1, first eluted diastereomer; F2, second eluted diastereomer.

Table 2. Spectral Data for 1,4-Dihydropyridines I

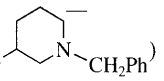
No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS m/z (M^+)	^{1}H-NMR ($CDCl_3$) δ (ppm)
1	—	—	480	2.19 (3H, s, C6-CH_3), 2.33 (3H, s, NCH_3), 2.61 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.49 (2H, s, NCH_2Ph), 3.61 (3H, s, $COOCH_3$), 4.14 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2N$), 5.00 (1H, s, C4-H), 6.10 (2H, brs, NH_2), 6.18 (1H, brs, NH), 7.14—8.13 (9H, m, Ar-H)
2	3430 3310	1670	508	1.08, 1.15 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.22 (3H, s, C6-CH_3), 2.31 (3H, s, NCH_3), 2.62 (2H, t, J=6 Hz, $OCH_2C\underline{H}_2N$), 3.50 (2H, s, NCH_2Ph), 4.15 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2N$), 4.92 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 5.00 (1H, s, C4-H), 6.22 (2H, brs, NH_2), 6.55 (1H, brs, NH), 7.10—8.16 (9H, m, Ar-H) [free][a]
3	—	1750 1675	449 (M^+ – )	—
4	3410 3300	1675	638 (M^+ – 2)	1.13—2.77 (8H, m, CH_2 (Pipe.)[b]), 2.20, 2.31 (3H×2, s×2, C6-CH_3, N-CH_3), 2.64 (2H, t, J=5 Hz, $OCH_2C\underline{H}_2N$), 3.19—3.61 (4H, m, NCH_2Ph, NC_2Ph, NCH_2-Pyrid.[b]), 4.16 (2H, t, J=5 Hz, $OC\underline{H}_2CH_2N$), 4.81 (1H, m, COOCH), 5.00 (1H, s, C4-H), 6.35 (3H, brs, NH, NH_2), 7.08—8.65 (8H, m, Ar-H)
5	—	1750	645	—
6	3440 3300	1675	523 (M^+ – 2)	1.08—1.32 (9H, m, $CH(C\underline{H}_3)_2$, $OCHC\underline{H}_3$), 2.01 (3H, s, C6-CH_3), 2.26 (3H, s, NCH_3), 2.30—2.50 (2H, m, $OCHC\underline{H}_2N$), 3.47, 3.70 (1H×2, d×2, J=14 Hz, NCH_2Ph), 4.84—5.25 (2H, m, $C\underline{H}(CH_3)_2$, $OC\underline{H}CH_3$), 4.98 (1H, s, C4-H), 6.20 (2H, brs, NH_2), 6.36 (1H, brs, NH), 7.10—8.18 (9H, m, Ar-H) [free][a]
7	—	—	—	0.75—1.60 (11H, m, $OCH_2C_5\underline{H}_{11}$), 0.86 (3H, m, $OCHC\underline{H}_3$), 2.20 (6H, m, C6-CH_3, NCH_3), 2.30—2.70 (2H, m, $OCHC\underline{H}_2N$), 3.12—3.60 (2H, m, NCH_2Ph), 3.82—4.15 (2H, m, $OC\underline{H}_2C_5H_{11}$), 4.85 (1H, s, C4-H), 5.04 (1H, m, $OC\underline{H}CH_3$), 6.40 (3H, brs, NH_2, NH), 7.04—8.16 (9H, m, Ar-H) [free][a]
8	—	—	—	0.91—1.30 (9H, m, $CH(C\underline{H}_3)_2$, $OCH_2CH(C\underline{H}_3)N$), 2.17 (3H, s, NCH_3), 2.35 (3H, s, C6-CH_3), 3.01 (1H, m, $OCH_2C\underline{H}(CH_3)N$), 3.54 (2H, m, NCH_2Ph), 3.90—4.23 (2H, m, $OC\underline{H}_2CH$), 4.94 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 5.05 (1H, s, C4-H), 5.98 (1H, brs, NH), 6.10 (2H, brs, NH_2), 7.10—8.18 (9H, m, Ar-H) [free][a]
9	3440 3310	1670	562 (M^+)	1.00—2.15 (8H, m, CH_2 (c.Hex.)[b]), 1.06, 1.28 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.80 (3H, s, NCH_3), 2.36 (3H, s, C6-CH_3), 2.99, 3.55 (1H×2, d×2, J=14 Hz, NCH_2Ph), 4.88—5.09 (3H, m, C4-H, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$), 6.01 (2H, brs, NH_2), 6.86 (1H, brs, NH), 7.05—8.19 (9H, m, Ar-H)
10	—	—	—	0.75—2.50 (19H, m, $C\underline{H}_2$ (c.Hex.),[b] $OCH_2C_5\underline{H}_{11}$), 1.83 (3H, s, NCH_3), 2.34 (3H, s, C6-CH_3), 3.00, 3.56 (1H×2, d×2, J=14 Hz, NCH_2Ph), 4.04 (2H, m, $COOCH_2$), 4.95 (2H, m, $COOC\underline{H}C\underline{H}N$), 5.07 (1H, s, C4-H), 6.11 (2H, brs, NH_2), 6.55 (1H, brs, NH), 7.00—8.20 (9H, m, Ar-H)
11F1	3440 3320	1670	506	1.20—2.88 (8H, m, CH_2 (Pipe.)[b]), 2.34 (3H, s, C6-CH_3), 3.43—3.58 (2H, m, NC_2Ph), 3.64 (3H, $COOCH_3$), 4.81 (1H, m, COOCH), 4.98 (1H, s, C4-H), 6.20 (2H, brs, NH_2), 6.31 (1H, brs, NH), 7.18—8.16 (9H, m, Ar-H)
11F2	3440 3320	1670	506	1.20—2.87 (8H, m, CH_2 (Pipe.)[b]), 2.33 (3H, s, C6-CH_3), 3.40—3.57 (2H, m, NCH_2Ph), 3.64 (3H, $COOCH_3$), 4.80 (1H, m, COOCH), 4.96 (1H, s, C4-H), 6.20 (2H, brs, NH_2), 6.32 (1H, brs, NH), 7.18—8.16 (9H, m, Ar-H)
12	3430 3310	1670	521 (M^++1)	1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.35—2.61 (8H, m, CH_2 (Pipe.)[b]), 2.34 (3H, s, C6-CH_3), 3.33—3.56 (2H, m, NCH_2Ph), 4.06 (2H, quar., J=7 Hz, $C\underline{H}_2CH_3$), 4.79 (1H, m, COOCH), 4.96 (1H, s, C4-H), 5.87 (1H, brs, NH), 6.06 (2H, brs, NH_2), 7.05—8.18 (9H, m, Ar-H)
13	3420 3320	1670	534	1.06, 1.27 (3H×2, d×2, J=3 Hz, $CH(C\underline{H}_3)_2$), 1.40—2.88 (8H, m, CH_2 (Pipe.)[b]), 2.32 (3H, s, C6-CH_3), 3.34—3.54 (2H, m, NCH_2Ph), 4.70—5.08 (3H, m, $COOC\underline{H}$, $C\underline{H}(CH_3)_2$, C4-H), 6.01 (1H, brs, NH), 6.13 (2H, brs, NH_2), 7.12—8.24 (9H, m, Ar-H)
14	3440 3330	1670	535 (M^++1)	—
15	3450 3320	1675	547 (M^++1)	0.30—2.90 (13H, $C\underline{H}_2$ (Pipe.),[b] $C\underline{H}$, $C\underline{H}_2$ (c.Pro.)[b]), 2.32 (3H, s, C6-CH_3), 3.37, 3.50 (2H, d, J=13 Hz, NCH_2Ph), 3.83 (2H, d, J=7 Hz, $COOCH_2$), 4.65—4.85 (1H, m, COOCH), 4.98 (1H, s, C4-H), 6.19 (2H, brs, NH_2), 6.40 (1H, brs, NH), 7.05—8.20 (9H, m, Ar-H) [free][a]
16	3445 3320	1680	577 (M^++1)	0.88 (3H, t, J=7 Hz, $O(CH_2)_5C\underline{H}_3$), 1.10—2.66 (16H, m, $C\underline{H}_2$ (Pipe.),[b] $OCH_2(C\underline{H}_2)_4CH_3$), 2.39 (3H, s, C6-$CH_3$), 3.39—3.59 (2H, m, NCH_2Ph), 4.00 (2H, t, J=7 Hz, $OC\underline{H}_2(CH_2)_4CH_3$), 4.70—4.88 (1H, m, COOCH), 4.96 (1H, s, C4-H), 5.80 (1H, brs, NH), 6.04 (2H, brs, NH_2), 7.05—8.18 (9H, m, Ar-H) [free][a]
17	3450 3330	1675	575 (M^++1)	0.95—2.64 (18H, m, CH_2 (c.Hex., Pipe.)[b]), 2.30, 2.38 (3H, s×2, C6-CH_3), 3.31—3.58 (2H, m, NCH_2Ph), 4.54—4.87 (2H, m, COOCH), 4.97 (1H, s, C4-H), 6.25 (2H, brs, NH_2), 6.65 (1H, brs, NH), 6.90—8.18 (9H, m, Ar-H) [free][a]
18	3430 3310	1670	607 (M^++1)	1.20—2.85 (8H, m, CH_2 (Pipe.)[b]), 2.32 (3H, s, C6-CH_3), 2.38, 2.48 (1H×2, d×2, J=11.4 Hz, NCH_2Ph), 4.60—4.85 (3H, m, $COOCH$, $COOCH_2$), 5.00 (1H, s, C4-H), 6.08—6.28 (3H, m, $N\underline{H}_2$, $OCH_2C\underline{H}$=CH), 6.42 (1H, brs, NH), 6.50 (1H, d, J=14 Hz, OCH_2CH=$C\underline{H}$), 7.15—8.20 (14H, m, Ar-H)
19	3430 3310	1670	551 (M^++1)	1.20—2.90 (8H, m, CH_2 (Pipe.)[b]), 2.38 (3H, s, C6-CH_3), 3.33 (3H, s, $COOCH_3$), 3.40—3.60 (4H, m, $NC\underline{H}_2Ph$, $COOCH_2C\underline{H}_2O$), 4.11—4.25 (2H, m, $COOC\underline{H}_2CH_2O$), 4.70—7.85 (1H, m, COOCH), 5.00 (1H, s, C4-H), 5.80 (1H, brs, NH), 6.03 (2H, brs, NH_2), 7.10—8.20 (9H, m, Ar-H) [free][a]
20	3430 3310	1675	591 (M^++1)	1.10—2.90 (17H, m, $C\underline{H}_2$ (Pipe.)[b]), $OCH_2(C\underline{H}_2)_4CH_2O\underline{H}$), 2.35 (3H, s, C6-$CH_3$), 3.35—3.75 (4H, m, $C\underline{H}_2OH$, $NC\underline{H}_2Ph$), 3.90—4.20 (2H, m, $COOCH_2$), 4.68—4.90 (1H, m, COOCH), 4.98, 4.99 (1H, s×2, C4-H), 5.91 (1H, brs, NH), 6.05 (2H, brs, NH_2), 7.10—8.16 (9H, m, Ar-H) [free][a]

Table 2. (continued)

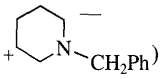
No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS m/z (M^+)	^{1}H-NMR ($CDCl_3$) δ (ppm)
21	3430 3325	1675	639	1.08—2.94 (10H, m, C$\underline{H}_2$ (Pipe.),[b] $OCH_2C\underline{H}_2N$), 2.19, 2.28 (3H×2, s×2, C6-CH_3, NCH_3), 3.25—3.59 (4H, NCH_2Ph), 4.15 (2H, t, J=6 Hz, OCH_2CH_2N), 4.75 (1H, m, COOCH), 4.98 (1H, s, C4-H), 6.29 (2H, br s, NH_2), 6.76 (1H, br s, NH), 6.95—8.18 (14H, m, Ar-H)
22		1675	652 (M^++1)	0.80—2.72 (8H, m, CH_2 (Pipe.)[b]), 1.22 (3H, m, $OCHC\underline{H}_3$), 2.06 (3H, m, C6-CH_3), 2.40 (3H, m, NCH_3), 3.29—3.43 (2H, m, NCH_2Ph), 3.85, 4.16 (4H, m, $OCH(CH_3)C\underline{H}_2NC\underline{H}_2Ph$), 4.79—5.25 (3H, m, C4-H), COOCH, NH), 7.13—8.10 (16H, m, NH_2, Ar-H) [free][a]
23		1750	509 (M^+ −  CH_2Ph)	—
24F1	3440 3300	1675	639 (M^+−2)	1.08—2.97 (8H, m, CH_2 (Pipe.)[b]), 2.17, 2.32 (3H×2, s×2, NCH_3, C6-CH_3), 2.61 (2H, t, J=6 Hz, $OCH_2C\underline{H}_2N$), 3.38, 3.70 (2H×2, m, NCH_2Ph, NCH_2-Pyrid.[b]), 4.16 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2N$), 4.80 (1H, m, COOCH), 4.99 (1H, s, C4-H), 6.34 (3H, br s, NH, NH_2), 7.01—8.60 (8H, m, Ar-H)
24F2	3440 3300	1675	639 (M^+−2)	1.20—2.82 (8H, m, CH_2 (Pipe.)[b]), 2.18, 2.33 (3H×2, s×2, NCH_3, C6-CH_3), 2.61 (2H, t, J=6 Hz, $OCH_2C\underline{H}_2N$), 3.37, 3.69 (2H×2, m, NCH_2Ph, NCH_2-Pyrid.[b]), 4.18 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2N$), 4.82 (1H, m, COOCH), 4.96 (1H, s, C4-H), 6.44 (3H, br s, NH, NH_2), 7.01—8.58 (8H, m, Ar-H)
25	3430	1670	644 (M^+−1)	1.14—2.90 (8H, m, CH_2 (Pipe.)[b]), 2.25, 2.30 (3H×2, s×2, C6-CH_3, NCH_3), 2.63 (2H, t, J=6 Hz, $OCH_2C\underline{H}_2N$), 3.32—3.51 (2H, m, NCH_2Ph), 3.70 (2H, s, NCH_2-Thio.[b]), 4.16 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2N$), 4.29 (1H, m, COOCH), 5.00 (1H, s, C-H), 6.22 (2H, br s, NH_2), 6.62 (1H, br s, NH), 6.78—8.20 (13H, m, Ar-H)
26	3440 3310	1670	506	0.92—3.04 (8H, m, CH_2 (Pipe.)[b]), 2.22 (3H, s, C6-CH_3), 3.30—3.50 (2H, m, NCH_2Ph), 3.57 (3H, s, $COOCH_3$), 4.74 (1H, m, COOCH), 5.72 (1H, s, C4-H), 6.30 (2H, br s, NH_2), 6.39 (1H, br s, NH), 7.05—7.76 (9H, m, Ar-H)
27	3430 3310	1660	560 (M^++2)	1.05, 1.07 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.34—2.72 (8H, m, CH_2 (Pipe.)[b]), 2.18 (3H, s, C6-CH_3), 3.31—3.56 (2H, m, NCH_2Ph), 4.75 (1H, m, COOCH), 4.95 (1H, Hept., J=6 Hz, $C\underline{H}(CH_3)_2$), 5.27 (1H, s, C4-H), 6.24 (2H, br s, NH_2), 6.55 (1H, br s, NH), 7.10—7.46 (8H, m, Ar-H)
28	3450 3330	1680	611 (M^++1)	1.08—1.25 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.10—2.80 (8H, m, CH_2 (Pipe.)[b]), 2.36 (3H, s, C6-CH_3), 4.22, 4.33 (1H, s×2, $CH(Ph)_2$), 4.70—5.05 (3H, m, COOCH, C4-H), 5.78 (1H, br s, NH), 6.03 (2H, br s, NH_2), 7.00—8.15 (14H, m, Ar-H) [free][a]
29	3450 3320	1680	651 (M^+−1)	0.78—0.92 (3H, m, $COO(CH_2)_5CH_3$), 1.10—2.80 (16H, m, $COOCH_2(CH_2)_4CH_3$, CH_2 (Pipe.)[b]), 2.30, 2.33 (3H, s×2, C6-CH_3), 3.90—4.12 (2H, m, $COOCH_2$), 4.25, 4.35 (1H, s, $CH(Ph)_2$), 4.70—4.95 (1H, m, COOCH), 4.90, 5.30 (1H, s×2, C4-H), 6.13 (2H, br s, NH_2), 6.25 (1H, br s, NH), 7.05—8.16 (14H, m, Ar-H) [free][a]
30	3430 3290	1670	536 (M^++1)	0.94—2.68 (8H, m, CH_2 (Pipe.)[b]), 1.05, 1.25 (3H×2, d×2, J=6 Hz, $CH(CH_3)_2$), 2.36 (3H, s, C6-CH_3), 3.34—3.62 (2H, m, NCH_2-Pyrid.[b]), 4.68—5.05 (2H, m, COOCH, $CH(CH_3)_2$), 4.96 (1H, s, C4-H), 6.15 (2H, br s, NH_2), 6.70 (1H, br s, NH), 7.15—8.62 (8H, m, Ar-H)
31	3430 3300	1670	578 (M^++1)	0.87 (3H, t, J=6 Hz, $COO(CH_2)_5CH_3$), 1.09—2.88 (16H, m, $COOCH_2(CH_2)_4CH_3$, CH_2 (Pipe.)[b]), 2.35 (3H, s, C6-H_3), 3.32—3.60 (2H, m, CH_2-Pyrid.[b]), 4.00 (2H, m, $COOCH_2$), 4.79 (1H, m, COOCH), 4.97 (1H, s, C4-H), 6.26 (3H, br s, NH_2, NH), 7.18—8.64 (8H, m, Ar-H) [free][a]
32	3440 3320	1680	541 (M^++1)	1.07, 1.27 (3H×2, d×2, J=6 Hz, $CH(CH_3)_2$), 1.43—2.85 (8H, m, CH_2 (Pipe.)[b]), 2.35 (3H, s, C6-CH_3), 3.68—3.80 (3H, m, NCH_2-Thio.[b]), 4.73—5.00 (3H, m, COOCH, $CH(CH_3)_2$, C4-H), 6.17 (3H, br s, NH, NH_2), 6.83—8.14 (7H, m, Ar-H)
33	3440 3310	1675	645	1.14—2.95 (10H, m, C$\underline{H}_2$ (Pipe.)[b]), $OCH_2C\underline{H}_2N$), 2.21, 2.28 (3H×2, s×2, C6-CH_3, NCH_3), 3.49 (2H, s, CH_2-Thio.[b]), 3.58—3.78 (2H, m, NCH_2Ph), 4.15 (2H, t, J=6 Hz, $OC\underline{H}_2CH_2N$), 4.77 (1H, m, COOCH), 4.99 (1H, s, C4-H), 6.22 (2H, br s, NH_2), 6.65—8.25 (13H, m, NH, Ar-H)
34	—	—	—	0.86—2.92 (19H, m, CH_2 (Pipe.),[b] $OCH_2C_5\underline{H}_{11}$), 2.34 (3H, s, C6-$CH_3$), 3.48 (2H, s, NCH_2Ph), 4.06 (2H, t, J=7 Hz, $COOCH_2$), 4.74 (1H, m, COOCH), 5.03 (1H, s, C4-H), 6.32 (2H, br s, NH_2), 6.74 (1H, br s, NH), 7.20—8.28 (9H, m, Ar-H)
35	—	—	610	0.78—2.70 (8H, m, CH_2 (Pipe.)[b]), 1.12, 1.29 (3H×2, d×2, $CH(C\underline{H}_3)_2$), 2.33 (3H, s, C6-CH_3), 4.18 (1H, s, NCH), 4.65—4.83 (1H, m, COOCH), 4.91—5.14 (1H, m, $C\underline{H}(CH_3)_2$), 5.01 (1H, s, C4-H), 6.00 (1H, br s, NH), 6.12 (2H, br s, NH_2), 7.12—8.28 (14H, m, Ar-H)
36	—	—	652	0.86—2.84 (19H, m, C$\underline{H}_2$ (Pipe.),[b] $OCH_2C_5\underline{H}_{11}$), 2.36 (3H, s, C6-$CH_3$), 4.08 (2H, t, J=7 Hz, $OC\underline{H}_2C_5H_{11}$), 4.21 (1H, s, NCH), 5.05 (1H, s, C4-H), 6.23 (2H, br s, NH_2), 6.40 (1H, br s, NH), 7.13—8.25 (14H, m, Ar-H)
37	—	—	563 (M^++1)	0.72—3.12 (17H, m, C$\underline{H}_2$ (Pyrr.),[b] $OCH_2C_5\underline{H}_{11}$), 2.30 (3H, s, C6-$CH_3$), 3.32—3.64 (2H, m, NCH_2Ph), 4.06 (2H, m, $OC\underline{H}_2C_5H_{11}$), 4.98 (1H, s, C4-H), 5.14 (1H, m, COOCH), 6.36 (2H, br s, NH_2), 6.96 (1H, br s, NH), 7.20—8.44 (9H, m, Ar-H) [free][a]
38	3450 3320	1675	597 (M^++1)	0.80—2.85 (6H, m, CH_2 (Pyrr.)[b]), 1.11, 1.31 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.29 (3H, s, C6-CH_3), 4.07, 4.23 (1H, s×2, $CH(Ph)_2$), 4.90—5.20 (3H, m, COOCH, C4-H), 6.16 (2H, br s, NH_2), 6.38 (1H, br s, NH), 7.10—8.20 (14H, m, Ar-H) [free][a]
39	3350 3420	1670	638	0.80—0.95 (3H, m, $O(CH_2)_5C\underline{H}_3$), 1.15—2.85 (14H, m, C$\underline{H}_2$ (Pyrr.),[b] $OCH_2(C\underline{H}_2)_4CH_3$), 2.37 (3H, s, C6-$CH_3$), 3.90—4.26 (3H, m, $COOCH_2$, $NCH(Ph)_2$), 4.98, 5.01 (1H, s×2, C4-H), 5.05—5.20 (1H, m, COOCH), 5.95—6.15 (3H, br s, NH, NH_2), 7.10—8.15 (14H, m, Ar-H) [free][a]
40	—	—	527 (M^++1)	0.96—3.00 (6H, m, CH_2 (Pyrr.)[b]), 1.06, 1.27 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.31 (3H, s, C6-CH_3), 3.64—4.01 (2H, m, NCH_2-Thio.[b]), 4.81—5.24 (2H, m, COOCH), 4.96 (1H, s, C4-H), 6.28 (2H, br s, NH_2), 6.63 (1H, br s, NH), 6.88—8.20 (7H, m, Ar-H)

Table 2. (continued)

No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS m/z (M^+)	^{1}H-NMR ($CDCl_3$) δ (ppm)
41	3430 3300	1670	555 ($M^+ + 1$)	2.34 (3H, s, C6-CH_3), 2.61—3.77 (4H, m, CH_2 (Azet.)[b]), 3.66 (3H, s, $COOCH_3$), 4.29 (1H, s, $CH(Ph)_2$), 4.99 (1H, s, C4-H), 4.92—5.10 (1H, m, COOCH), 6.12 (2H, br s, NH_2), 6.23 (1H, br s, NH), 7.10—8.26 (14H, m, Ar-H)
42F1	—	—	568	1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.18 (3H, s, C6-CH_3), 2.93, 3.53 (2H×2, m, CH_2 (Azet.)[b]), 4.46 (2H, quar, J=7 Hz, $C\underline{H}_2CH_3$), 4.96—5.12 (1H, m, COOCH), 5.00 (1H, s, C4-H), 6.40 (2H, br s, NH_2), 6.64 (1H, br s, NH), 7.16—7.56 (14H, m, Ar-H) [free][a]
42F2	—	—	569 ($M^+ + 1$)	1.21 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.36 (3H, s, C6-CH_3), 2.63, 3.04, 3.50, 3.61 (1H×4, m, CH_2 (Azet.)[b]), 4.10 (2H, quar, J=7 Hz, $C\underline{H}_2CH_3$), 4.94—5.10 (1H, m, COOCH), 5.00 (1H, s, C4-H), 5.88 (1H, br s, NH), 6.08 (2H, br s, NH_2), 7.08—8.24 (1H, m, Ar-H)
43	3450 3310	1675	583 ($M^+ + 1$)	1.08, 1.26 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.35 (3H, s, C6-CH_3), 2.63, 3.06, 3.50, 3.62 (1H×4, t×4, J=8 Hz, CH_2 (Azet.)[b]), 4.26 (1H, s, $NCH(Ph)_2$), 4.87—5.04 (3H, m, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$, C4-$\underline{H}$), 6.04 (1H, br s, NH), 6.11 (2H, br s, NH_2), 7.10—8.17 (14H, m, Ar-H)
44	3400 3280	1685	583 ($M^+ + 1$)	—
45	3440 3360	1670	—	0.05—1.20 (5H, m, CH_2CH (c.Pro.)[b]), 2.32 (3H, s, C6-CH_3), 2.68, 3.08, 3.49, 3.63 (1H×4, m, CH_2 (Azet.)[b]), 3.73—3.93 (2H, m, $COOCH_2$), 4.27 (1H, s, $CH(Ph)_2$), 4.80—5.20 (2H, m, COOCH, C4-H), 6.20 (2H, br s, NH_2), 6.40 (1H, br s, NH), 7.10—8.30 (14H, m, Ar-H)
46	3430 3300	1670	625 ($M^+ + 1$)	0.87 (3H, t, J=6 Hz, $COO(CH_2)_5C\underline{H}_3$), 1.07—1.87 (8H, m, $COOCH_2(C\underline{H}_2)_4CH_3$), 2.34, 2.38 (3H, s×2, C6-CH_3), 2.61—3.69 (4H, m, CH_2 (Azet.)[b]), 4.02 (2H, m, $COOCH_2$), 4.28 (1H, s, $CH(Ph)_2$), 4.92 (1H, s, C4-H), 5.03 (1H, m, COOCH), 6.13 (2H, br s, NH_2), 6.21 (1H, br s, NH), 7.09–8.19 (14H, m, Ar-H) [free][a]
47	—	—	—	1.06—1.93 (10H, m, CH_2 (c.Hex.)[b]), 2.32 (3H, s, C6-CH_3), 2.64, 2.90, 3.05, 3.53 (1H×4, m, CH_2 (Azet.)[b]), 4.69, 4.92—5.10 (1H×2, m, COOCH), 5.00 (1H, s, C4-H), 6.23 (2H, br s, NH_2), 6.52 (1H, br s, NH), 7.09—8.24 (14H, m, Ar-H) [free][a]
48	3430 3300	1680	655 ($M^+ + 1$)	2.37 (3H, s, C6-CH_3), 2.64, 3.01 (1H×2, m, CH_2 (Azet.)[b]), 3.53 (2H, m, CH_2 (Azet.)[b]), 4.23, 4.33 (1H, s×2, $CH(Ph)_2$), 4.71 (2H, t, J=7 Hz, $COOCH_2$), 4.87—5.05 (2H, m, COOCH, C4-H), 5.88 (1H, br s, NH), 6.03 (2H, br s, NH_2), 6.19 (1H, dt, J=15, 7 Hz, $CH_2C\underline{H}$=CH), 6.52 (1H, d, J=15 Hz, CH_2CH=$C\underline{H}$), 7.10—8.20 (15H, m, Ar-H)
49	3450 3320	1680	598	2.35 (3H, s, C6-CH_3), 2.65, 3.03 (1H×2, m, CH_2 (Azet.)[b]), 3.35 (3H, s, OCH_3), 3.40—3.65 (4H, m, $OCH_2C\underline{H}_2OCH_3$, $C\underline{H}_2$ (Azet.)[b]), 4.10, 4.30 (3H, m, $C\underline{H}(Ph)_2$, $OC\underline{H}_2CH_2OCH_3$), 4.98—5.05 (2H, m, C4-H, COOCH), 6.05 (1H, br s, NH), 6.08 (2H, br s, NH_2), 7.10—8.20 (14H, m, Ar-H)
50	—	—	612 ($M^+ - {}^+COO$–  –N–$CH(Ph)_2$)	2.10—2.70 (11H, m, $C\underline{H}_2$ (Azet.),[b] $C\underline{H}_2$ (Pipera.)[b], $OCH_2C\underline{H}_2N$), 2.35 (3H, s, C6-CH_3), 3.03, 3.52 (1H×2, m, CH_2 (Azet.)[b]), 4.03—4.36 (4H, m, $CH(Ph)_2$, $COOCH_2$), 4.94—5.07 (2H, m, COOCH, C4-H), 5.72 (1H, br s, NH), 5.99 (2H, br s, NH_2), 7.10—8.20 (24H, m, Ar-H)
51	—	—	597 ($M^+ + 1$)	1.06, 1.23 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.56 (3H, s, $COOCHC\underline{H}_3$), 2.32 (3H, s, C6-CH_3), 2.86, 2.99 (1H×2, m, CH_2 (Azet.)[b]), 4.14 (1H, s, $CH(Ph)_2$), 4.80—5.10 (2H, m, COOCH, C4-H), 6.10 (3H, br s, NH_2, NH), 7.06—8.20 (14H, m, Ar-H)
52	—	—	—	1.10, 1.26 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.28 (3H, s, C6-CH_3), 2.60, 3.04 (1H×2, m, CH_2 (Azet.)[b]), 3.40—3.66 (2H, m, CH_2 (Azet.)[b]), 4.23 (1H, s, NCH), 4.86—5.12 (2H, m, COOCH), 5.00 (1H, s, C4-H), 6.42 (2H, br s, NH_2), 6.88—8.26 (13H, m, Ar-H)
53	3430 3300	1670	572	0.79, 1.19 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.30 (3H, s, C6-CH_3), 2.70—3.69 (4H, m, CH_2 (Azet.)[b]), 4.35, 4.38 (1H, s×2, $CH(Ph)_2$), 4.87, 5.10 (1H×2, m, COOCH), 5.29 (1H, s, C4-H), 5.81 (1H, br s, NH), 6.07 (2H, br s, NH_2), 7.01—7.56 (14H, m, Ar-H)
54	3450 3320	1680	606	1.05, 1.27 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.28 (3H, s, C6-CH_3), 2.64, 3.15 (1H×2, m, CH_2 (Azet.)[b]), 3.53 (2H, m, CH_2 (Azet.)[b], 4.35 (1H, s, $CH(Ph)_2$), 4.90—5.10 (2H, m, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$), 5.32 (1H, s, C4-H), 5.78 (1H, br s, NH), 6.08 (2H, br s, NH_2), 7.05—7.50 (13H, m, Ar-H)
55	—	—	625	1.07, 1.27 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.20 (3H, s, C6-CH_3), 2.62, 3.03, 3.52, 3.61 (1H×4, m, CH_2 (Azet.)[b]), 4.12 (1H, m, COOCH), 4.28 (1H, s, $NCH(Ph)_2$), 4.90 (1H, s, C4-H), 4.98 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 6.30 (2H, br s, NH_2), 6.96 (1H, br s, NH), 7.08—7.90 (14H, m, Ar-H)
56	—	—	563 ($M^+ + 1$)	1.10, 1.26 (3H×2, d×2, J=6 Hz, $CH(CH_3)_2$), 2.28 (3H, s, C6-CH_3), 2.68, 3.03, 3.53, 3.64 (1H×4, m, CH_2 (Azet.)[b]), 4.32 (1H, s, $NCH(Ph)_2$), 4.84—5.20 (2H, m, COOCH), 4.88 (1H, s, C4-H), 6.38 (2H, br s, NH_2), 6.88 (1H, br s, NH), 7.12—7.90 (14H, m, Ar-H)
57	—	—	520	0.96—1.32 (9H, m, $CH(CH_3)_2$, $NCH(Ph)CH_3$), 2.28 (3H, s, C6-CH_3), 2.50—3.92 (5H, m, CH_2 (Azet.),[b] $NCH(Ph)CH_3$), 4.80—5.12 (3H, m, COOCH, C4-H), 6.40 (2H, br s, NH_2), 7.03 (1H, br s, NH), 7.16—8.28 (9H, m, Ar-H)
58	3450 3320	1675	549 ($M^+ + 1$)	1.0—2.80 (9H, m, CH, CH_2 (Pipe.)[b]), 1.10, 1.25 (3H×2, d×2, J=6 Hz, $CH(CH_3)_2$), 2.32 (3H, s, C6-CH_3), 3.15, 3.96 (1H×2, d×2, J=13 Hz, NCH_2Ph), 4.10—4.30 (2H, m, $COOCH_2$), 4.90—5.07 (2H, m, COO–CH, C4-H), 6.21 (2H, br s, NH_2), 6.30 (1H, br s, NH), 7.15—8.15 (9H, m, Ar-H)
59	3450 3320	1680	591 ($M^+ + 1$)	0.78—0.98 (3H, m, $COO(CH_2)_5CH_3$), 1.15—2.80 (17H, m, $COOCH_2(CH_2)_4CH_3$, CH, CH_2 (Pipe.)[b]), 2.37 (3H, s, C6-CH_3), 3.16 (1H, d, J=14 Hz, NCH_2Ph), 3.85—4.30 (5H, m, NCH_2Ph, $COOCH_2$), 5.03, 5.06 (1H, s×2, C4-H), 5.90 (1H, br s, NH), 6.10 (2H, br s, NH_2), 7.10—8.18 (9H, m, Ar-H) [free][a]
60	—	—	925 ($M^+ + 1$)	0.92—3.06 (8H, m, CH_2 (Pipe.)[b]), 1.06, 1.24 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.28 (3H, s, C6-CH_3), 4.03—4.48 (3H, m, $COOCH_2CH$), 4.84—5.08 (1H, m, $C\underline{H}(CH_3)_2$), 4.96 (1H, s, C4-H), 6.20 (2H, br s, NH_2), 6.46 (1H, br s, NH), 7.06—8.14 (14H, m, Ar-H)

Table 2. (continued)

No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS m/z (M^+)	^{1}H-NMR ($CDCl_3$) δ (ppm)
61	3450 3320	1680	597 ($M^+ + 1$)	0.85—0.95 (3H, m, $O(CH_2)_5C\underline{H}_3$), 1.03—2.90 (17H, m, $C\underline{H}_2$, $C\underline{H}$ (Pipe.)[b], $OCH_2(C\underline{H}_2)_5CH_3$), 2.36 (3H, s, C6-$CH_3$), 3.61 (1H, m, NCH_2-Thio.[b]), 3.90—4.10 (3H, m, NCH_2-Thio.,[b] $COOCH_2$-Pipe.[b]), 4.15—4.28 (2H, m, $COOC\underline{H}_2C_5H_{11}$), 5.04, 5.06 (1H, s×2, C4-H), 6.08 (1H, br s, NH), 6.16 (2H, br s, NH_2), 6.73—8.18 (7H, m, Ar-H) [free][a]
62	—	1740	535 ($M^+ + 1$)	—
63	3440 3310	1670	577 ($M^+ + 1$)	0.89 (3H, t, J=6 Hz, $COO(CH_2)_5C\underline{H}_3$), 1.09—2.95 (14H, m, $COOCH_2(C\underline{H}_2)_4CH_3$, $C\underline{H}_2$ (Pyrr.)[b]), 2.33, 2.37 (3H, s×2, C6-H), 3.20—3.42 (2H, m, NCH_2Ph), 3.82—4.20 (5H, m, $COOCH_2CH$, $COOCH_2$), 5.01 (1H, s, C4-H), 6.21 (2H, br s, NH_2), 6.34 (1H, br s, NH), 7.10—8.15 (9H, m, Ar-H) [free][a]
64	—	—	610	0.78—3.20 (6H, m, CH_2 (Pyrr.)[b]), 1.10, 1.26 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.29 (3H, s, C6-CH_3), 3.52—3.84 (3H, m, $COOCH_2CH$), 4.74 (1H, m, $NCH(Ph)_2$), 4.84—5.12 (1H, m, $C\underline{H}(CH_3)_2$, 4.95 (1H, s, C4-H), 6.33 (2H, br s, NH_2), 6.93 (1H, br s, NH), 7.04—8.20 (14H, m, Ar-H)
65	3440 3320	1670	541 ($M^+ + 1$)	1.10, 1.25 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.31—3.11 (2H, m, CH_2 (Pyrr. C3, C4)[b]), 2.31 (3H, s, C6-CH_3), 2.66—3.11 (2H, m, CH_2-Thio.[b]), 3.54—4.28 (5H, m, CH_2 (Pyrr. C2),[b] $COOCH_2CH$), 4.92 (1H, h, $C\underline{H}(CH_3)_2$), J=6 Hz, 5.01 (1H, s, C4-H), 6.28 (2H, br s, NH_2), 6.52 (1H, br s, NH), 6.80—8.28 (7H, m, Ar-H) [free][a]
66	3450 3320	1680	583 ($M^+ + 1$)	0.89 (3H, m, $O(CH_2)_5C\underline{H}_3$), 1.01—2.00 (12H, m, CH_2 (Pyrr.),[b] $OCH_2(C\underline{H}_2)_4CH_3$), 2.31 (3H, s, C6-$CH_3$), 2.65—3.11 (2H, m, NCH_2-Thio.[b]), 3.50—4.34 (5H, $COOCH_2$, $COOCH_2CH$), 5.02 (1H, s, C4-H), 6.35 (3H, br s, NH_2, NH), 6.78—7.25 (14H, m, Ar-H)
67	—	—	598 ($M^+ + 1$)	1.13, 1.30 (3H×2, d×2, J=7 Hz, $CH(C\underline{H}_3)_2$), 1.76—2.02 (2H, m, C3-CH_2 (Azet.)[b]), 2.26, 2.28 (3H, s, C6-CH_3), 2.68—2.88 (1H, m, NCH_2), 3.22—3.60 (2H, $COOCH_2$), 4.40, 4.44 (1H, s×2, $NCH(Ph)_2$), 4.88—5.12 (2H, m, $COOCH_2C\underline{H}N$, $COOC\underline{H}$), 5.32 (1H, s, C4-H), 6.34 (2H, br s, C4-H), 6.34 (2H, br s, NH_2), 6.87 (1H, br s, NH), 7.08—8.24 (14H, m, Ar-H) [free][a]
68F2	3430 3310	1670	507 ($M^+ + 1$)	1.15—2.85 (8H, m, CH_2 (Pipe.)[b]), 2.32 (3H, s, C6-CH_3), 3.49—3.58 (2H, m, NCH_2Ph), 3.62 (3H, $COOCH_3$), 4.80 (1H, m, COOCH), 4.96 (1H, s, C4-H), 6.25 (2H, br s, NH_2), 6.58 (1H, br s, NH), 7.13—8.18 (9H, m, Ar-H)
69	3430 3300	1675	533	1.29 (6H, d, J=3 Hz, $CH(C\underline{H}_3)_2$), 1.15—2.90 (8H, m, CH_2 (Pipe.)[b]), 2.33 (3H, s, C6-CH_3), 3.38—3.65 (2H, m, NCH_2Ph), 4.75—5.05 (3H, m, C4-$\underline{H}$, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$), 6.20 (2H, br s, NH_2), 6.32 (1H, br s, NH), 7.16—8.17 (9H, m, Ar-H)
70	3410 3300	1670	521	1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.10—2.79 (8H, m, CH_2 (Pipe.)[b]), 2.38 (3H, s, C6-CH_3), 3.44—3.53 (2H, m, NCH_2Ph), 4.06 (2H, quar, J=7 Hz, $C\underline{H}_2CH_3$), 4.80 (1H, m, COOCH), 4.98 (1H, s, C4-H), 5.82 (1H, br s, NH), 6.05 (2H, br s, NH_2), 7.14—8.18 (9H, m, Ar-H)
71	3425 3300	1660	558	0.96, 1.28 (3H×2, d×2, J=3 Hz, $CH(C\underline{H}_3)_2$), 1.14—2.90 (8H, m, CH_2 (Pipe.)[b]), 2.24 (3H, s, C6-CH_3), 3.37—3.50 (2H, m, NCH_2Ph), 4.80 (1H, m, COOCH), 4.94 (1H, m, $C\underline{H}(CH_3)_2$), 5.27 (1H, s, C4-H), 6.14 (3H, br s, NH_2, NH), 7.14—7.44 (9H, m, Ar-H)
72	3440 3360 3300	1670	611 ($M^+ + 1$)	1.05, 1.28 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.40—2.70 (8H, m, CH_2 (Pipe.)[b]), 2.35 (3H, s, C6-CH_3), 4.25, 4.32 (1H, s×2, $CH(Ph)_2$), 4.73—5.05 (3H, m, COOCH, C4-H), 6.11 (3H, br s, NH_2, NH), 7.10—8.20 (14H, m, Ar-H)
73	3420 3300	1670	353	1.04, 1.29 (3H×2, d×2, J=7 Hz, $CH(C\underline{H}_3)_2$), 1.14—2.59 (8H, m, CH_2 (Pipe.)[b]), 2.34 (3H, s, C6-CH_3), 3.39—3.58 (2H, m, NCH_2-Pyrid.[b]), 4.72—5.04 (3H, m, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$, C4-$\underline{H}$), 6.25 (2H, br s, NH_2), 6.86 (1H, br s, NH), 7.20—8.58 (8H, m, Ar-H)
74	3430 3310	1675	540	1.04, 1.29 (3H×2, d×2, J=7 Hz, $CH(C\underline{H}_3)_2$), 1.42—2.80 (8H, m, CH_2 (Pipe.)[b]), 2.37 (3H, s, C6-CH_3), 2.68—2.78 (2H, m, NCH_2-Thio.[b]), 4.75—4.99 (3H, m, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$, C4-$\underline{H}$), 5.83 (1H, br s, NH), 6.06 (2H, br s, NH_2), 6.82—8.14 (7H, m, Ar-H)
75	3410	1670	521 ($M^+ + 1$)	1.00, 1.25 (3H×2, d×2, J=5 Hz, $CH(C\underline{H}_3)_2$), 1.90—2.90 (6H, m, CH_2 (Pyrr.)[b]), 2.30 (3H, s, C6-CH_3), 3.45–3.70 (2H, m, NCH_2Ph), 4.80—5.20 (3H, m, $COOC\underline{H}$, $C\underline{H}(CH_3)_2$, C4-$\underline{H}$), 6.05 (3H, br s, NH_2, NH), 7.10—8.20 (9H, m, Ar-H)
76	3440 3320 3270	1670	597 ($M^+ + 1$)	1.07, 1.33 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.60—2.90 (6H, m, CH_2 (Pyrr.)[b]), 2.33 (3H, s, C6-CH_3), 4.09, 4.22 (1H, s×2, $CH(Ph)_2$), 4.85—5.25 (3H, m, COOCH, C4-H), 6.20 (2H, br s, NH_2), 6.35 (1H, br s, NH), 7.10—8.30 (14H, m, Ar-H)
77	3440 3320	1675	583 ($M^+ + 1$)	1.04, 1.30 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.32 (3H, s, C6-CH_3), 2.65, 3.00 (1H×2, m, CH_2 (Azet.)[b]), 3.55 (2H, m, CH_2 (Azet.)[b]), 4.25 (1H, s, $CH(Ph)_2$), 4.85—5.05 (3H, m, $C\underline{H}(CH_3)_2$), $COOC\underline{H}$, C4-$\underline{H}$), 6.05 (1H, br s, NH), 6.11 (2H, br s, NH_2), 7.10—8.15 (14H, m, Ar-H)
78	3430 3320	1670	559 ($M^+ + 1$)	0.98, 1.24 (3H×2, d×2, J=7 Hz, $CH(C\underline{H}_3)_2$), 1.10—2.70 (6H, m, CH_2 (Pyrr.)[b]), 2.22 (3H, s, C6-CH_3), 3.48—3.68 (2H, m, NCH_2Ph), 3.80—4.12 (2H, m, $COOCH_2$), 4.85—5.05 (1H, m, $C\underline{H}(CH_3)_2$), 5.27 (1H, s, C4-H), 6.20 (2H, br s, NH_2), 6.38 (1H, br s, NH), 7.10—7.40 (8H, m, Ar-H)
79	3440 3310	1670	535 ($M^+ + 1$)	1.05, 1.25 (3H×2, d×2, J=6 Hz, $CH(C\underline{H}_3)_2$), 1.40—2.95 (6H, m, CH_2 (Pyrr.)[b]), 2.37 (3H, s, C6-CH_3), 3.28, 3.35 (1H, d, J=13 Hz, NCH_2Ph), 3.80—4.15 (3H, m, $COOCH_2CH$), 4.80—5.02 (2H, m, $COOC\underline{H}(CH_3)_2$, C4-H), 6.13 (2H, br s, NH_2), 6.26 (1H, br s, NH), 7.05—8.15 (9H, m, Ar-H) [free][a]
80	—	1680	507 ($M^+ + 1$)	1.03—2.84 (8H, m, CH_2 (Pipe.)[b]), 2.40 (6H, s, C2-CH_3, C6-CH_3), 3.38—3.59 (2H, m, CH_2-Pyrid.[b]), 3.66 (3H, s, $COOCH_3$), 4.84 (1H, m, COOCH), 5.08 (1H, C4-H), 6.06 (1H, br s, NH), 7.13—8.65 (8H, m, Ar-H) [free][a]

Table 2. (continued)

No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS m/z (M^+)	^{1}H-NMR ($CDCl_3$) δ (ppm)
81	—	1680	512 ($M^+ + 1$)	1.15—2.78 (8H, m, CH_2 (Pipe.)[b]), 2.40 (6H, s, C2-CH_3, C6-CH_3), 3.65 (3H, s, $COOCH_3$), 3.59—3.83 (2H, m, CH_2-Thio.[b]), 4.48 (1H, m, COOCH), 5.09 (1H, s, C4-H), 5.74 (1H, br s, NH), 6.80—8.20 (7H, m, Ar-H) [free][a]
82	3330	1695	553	2.33, 2.36 (3H × 2, s × 2, C2-CH_3, C6-CH_3), 2.76, 3.05 (1H × 2, t, J=7 Hz, CH_2 (Azet.)[b]), 3.64 (5H, m, OCH_3, CH_2 (Azet.)[b]), 4.32 (1H, s, $CH(Ph)_2$), 5.08 (2H, m, COOCH, C4-H), 5.81 (1H, br s, NH), 7.12—8.18 (14H, m, Ar-H)
83	3335	1695	582 ($M^+ + 1$)	1.10, 1.26 (3H × 2, d × 2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.34, 2.36 (3H × 2, s × 2, C2-CH_3, C6-CH_3), 2.70, 3.01 (1H × 2, t, J=7 Hz, CH_2 (Azet.)[b]), 3.56 (2H, t, J=7 Hz, CH_2 (Azet.)[b]), 4.27 (1H, s, $CH(Ph)_2$), 4.85—5.10 (3H, m, $C\underline{H}(CH_3)_2$, $COOC\underline{H}$, C4-$\underline{H}$), 5.69 (1H, br s, NH), 7.10—8.17 (14H, m, Ar-H)
84	3335	1695	624 ($M^+ + 1$)	0.85 (3H, t, J=7 Hz, $O(CH_2)_5C\underline{H}_3$), 1.25 (6H, m, $O(CH_2)_2(C\underline{H}_2)_3CH_3$), 1.58 (2H, quar., $OCH_2C\underline{H}_2C_4H_9$), 2.34, 2.38 (3H × 2, s × 2, C2-CH_3, C6-CH_3), 2.75, 3.04 (1H × 2, t, J=7 Hz, CH_2 (Azet.)[b]), 3.58 (2H, t, J=7 Hz, CH_2 (Azet.)[b]), 4.04 (2H, m, $COOCH_2$), 4.30 (1H, s, $CH(Ph)_2$), 5.03 (1H, quin, J=7 Hz, COOCH), 5.08 (1H, s, C4-H), 5.77 (1H, br s, NH), 7.11—8.17 (14H, m, Ar-H)

a) NMR spectrum was measured as the free base. *b*) Ring name: c.Hex., cyclohexane; c.Pro., cyclopropane; Pipe., piperidine; Pyrid., pyridine; Thio., thiophene; Pyrr., pyrroridine; Azet., azetidine; Pipera., piperazine.

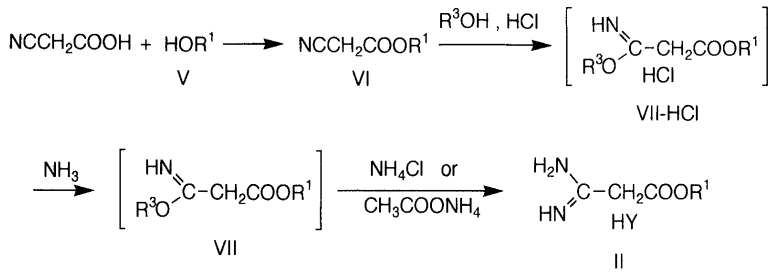


Chart 2

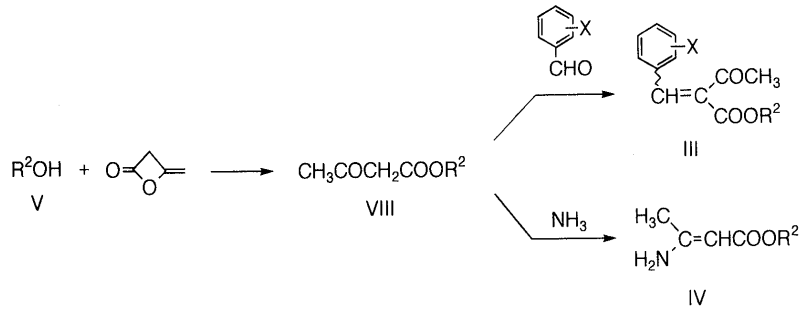


Chart 3

acetate in acetonitrile to afford better yields of compounds II, which were then subjected to the next step without further purification due to their high hygroscopicity. Chloroform was employed as a solvent in the preparation of the imidates VII because commonly used diethyl ether precipitated hydrochloride salts of the cyanoacetates VI possessing a basic amino group in the moiety represented by R^1. Compounds VII were also subjected to the next reaction without further purification. Esterification of cyanoacetic acid with the alcohols V provided the cyanoacetates VI (Chart 2).

Benzylideneacetoacetates III were obtained through the Knoevenagel reaction employing the acetoacetates VIII and substituted benzaldehydes.[7] Aminocrotonates IV were also prepared from compounds VIII with ammonia in tetrahydrofuran (THF).[2] The acetoacetates VIII were easily obtained by the reaction of diketene with the alcohols V[8] prepared from the corresponding halides and amines (Chart 3).

Pharmacology

Antihypertensive Effects in Conscious Spontaneously Hypertensive Rats (SHR): Male SHR, 23 weeks old, were anesthetized with sodium pentobarbital at the dose of 30 mg/kg i.p. An aortic cannula was surgically inserted with *via* the left femoral artery for the measurment of blood pressure and heart rate. The other end of the cannula was led under the skin and exteriorized at the back of the neck. The rats were placed in individual cages after surgery and allowed free access to tap water but not to food. When the rats had recovered from surgical stress, normally 2—3 d after surgery, the aortic cannula was connected to a pressure transducer, and blood pressure and heart rate were continuously recorded with a blood pressure measuring system that was developed in our laboratories. Compounds I were suspended in 0.3%

carboxymethyl cellulose (CMC) solution for oral administration. After blood pressure and heart rate were stabilized, a single oral dose of a test compound was given. Blood pressure and heart rate were monitored for up to 24 h after administration.

Results and Discussion

In the conversion of the imidates VI into the corresponding amidinoacetates II, the use of ammonium acetate instead of ammonium chloride in acetonitrile gave better yields of various 2-amino-1,4-dihydropyridine derivatives I. The antihypertensive activities of these products were then evaluated in SHR. The results are summarized in Table 1, in which the maximum rate of the blood pressure change, the time required for the maximum activity of the drug to appear after administration, and the half-life period of antihypertensive action of the drug, represented by *dBP*, T_{max}, and $T_{1/2}$ respectively, are shown as parameters of the pharmacological profiles of the drugs.

Among known drugs, CD-349, nifedipine (Nif), benidipine (Ben), nicardipine (Nic), nitrendipine (Nit), and nilvadipine (Nilv) were found to be highly potent, but exhibited rapid appearance of the effect, indicating acute onset. On the other hand, pharmacokinetic parameters for amlodipine (Amlo), manidipine (Man), and FRC-8411 revealed potent and long-lasting antihypertensive effects with gradual onset, which are desirable features from the viewpoint of the patients' quality of life.

The effects of 2-amino-1,4-dihydropyridines I on the potency and the mode of action varied considerably depending upon the substituents represented by R^1, R^2, R^3, and X. With regard to the ester side-chain R^1 at the 3-position, introduction of a tertiary amino group generally enhanced T_{max} and $T_{1/2}$, favoring gradual onset and long duration of action. In particular, the compounds containing cyclic amino moieties, such as piperidinyl, pyrrolidinyl and azetidinyl, induced higher potency than those with acyclic amino moieties. In the case of piperidinyloxy substituents as R^1, however, potency and mode of action of the drugs were quite different depending on the position of the oxygen atom. Piperidin-3-yloxy-substituted compounds such as I-**28** and I-**29** were more potent and gave remarkably larger values of T_{max} and $T_{1/2}$ than the piperidin-4-yloxy counterparts such as I-**35** and I-**36**, implying the existence of an optimum distance between the oxygen and the nitrogen atom. This was also supported by the comparison of I-**28** with I-**60**, and I-**43** with I-**35**, respectively. The best results were obtained for compound I-**43**, in which the 1-benzhydrylazetidin-3-yloxy group was introduced as R^1, while no clear effect of the fluorine atom on the benzhydryl group in I-**52** was seen. A reduction in potency was observed when a methyl group was introduced into the azetidine ring at the 3-position (I-**51**).

For R^2 at the 5-position, a small substituent such as a methyl group (I-**1** and I-**11**) was not effective in increasing T_{max} and $T_{1/2}$ values. Larger substituents such as isopropyl, *n*-hexyl, and cyclohexyl groups generally led to an increase in both T_{max} and $T_{1/2}$. Introduction of a tertiary amino group as R^1 also maintained relatively large T_{max} and $T_{1/2}$ values, but considerably reduced the absolute value of *dBP* as shown in I-**13**/I-**70**, I-**27**/I-**71**, I-**28**/I-**72**, I-**30**/I-**73**, I-**32**/I-**74**, I-**38**/I-**76**, and I-**43**/I-**77**, where R^1 and R^2 were reversed. This indicates that the two ester side-chains of 1,4-dihydropyridine might function differently in relation to the antihypertensive activities.

As far as R^3 is concerned, gradual onset was clearly apparent with 2-amino-substituted compounds such as I-**1**, I-**11**, I-**68**, and I-**41** compared with the 2-methyl counterparts, Nic, Ben, and I-**82**, though their potency was greatly decreased.

In general, a favorable substituent on the 4-phenyl ring (shown by X) was suggested to be an electron-withdrawing group such as a nitro group, a cyano group, a trifluoromethyl group, or a chlorine atom,[9] but we found that they affected the activity profile of the drug in different ways and their position was also important. A 2-nitro group did not show any better influence upon the antihypertensive action (compare I-**26** with I-**11**). The 2-chloro-substituted compound I-**53** lost its potency, but 2,3-dichloro-substituted compounds such as I-**54** and I-**71** exhibited almost the same antihypertensive profile, that is gradual onset and prolonged duration, as the 3-nitro compounds, I-**43** and I-**70**, though I-**71** was a little less potent than I-**70**. A 3-cyano group did not affect the values of T_{max} or $T_{1/2}$ very much, but greatly influenced *dBP*, resulting in a decrease in potency compared with a 3-nitro group (I-**56** and I-**43**). Comparison of I-**55** with I-**43** indicated that a 3-trifluoromethyl group had a similar influence on T_{max} value, but decreased both the antihypertensive activity itself and the duration of action. So far, 3-nitro and 2,3-dichloro substitutions have been found to be the most favorable for 2-amino-1,4-dihydropyridine derivatives.

These results suggest that 2-amino-1,4-dihydropyridine derivatives containing cyclic tertiary amino moieties possess high potency and prolonged duration of action with gradual onset of antihypertensive activities. In particular, 3-(1-benzhydrylazetidin-3-yl) 5-isopropyl 2-amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate I-**43** (CS-905) seems to be a promising candidate as an antihypertensive drug,[10] and it is now under clinical trial.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet 60SX spectrometer. Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL GSX-400 or a JEOL FX-200 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm. The following abbreviations are used: s = singlet, d = doublet, t = triplet, quar = quartet, quin = quintet, h = heptad, br = broad. Mass spectra were measured on a Hitachi M-80A spectrometer by the electron impact (EI), chemical ionization (CI) or secondary ion (SIMS) mass spectroscopy method. Column chromatography was performed on 200 mesh silica gel from Wako Chemicals.

General Procedure for the Synthesis of 2-Amino-1,4-dihydropyridine Derivatives I 3-(1-Benzhydrylazetidin-3-yl) 5-Isopropyl 2-Amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (I-**43**) and Its Dihydrochloride (I-**44**): A solution of 1-benzhydrylazetidin-3-yl amidinoacetate acetic acid salt II-**20** (1.62 g), isopropyl 2-(3-nitrobenzylidene)acetoacetate III-**4** (1.39 g), and sodium methoxide (0.27 g) in isopropyl alcohol (80 ml) was refluxed for 4 h. After cooling, the

Table 3. Amidines II

$HN=C(NH_2)CH_2COOR \cdot CH_3COOH$

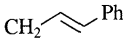
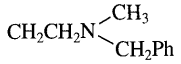
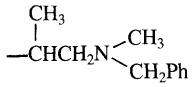
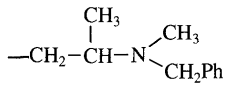
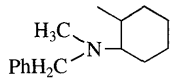
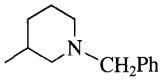
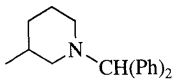
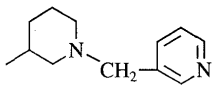
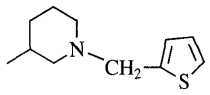
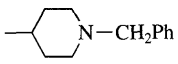
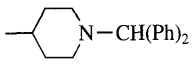
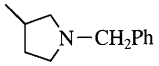
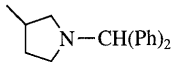
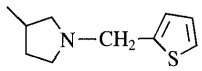
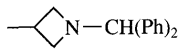
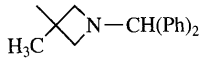
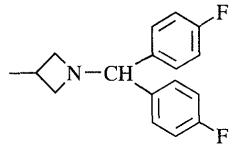
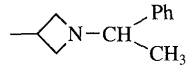
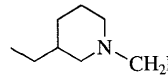
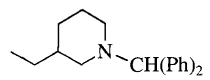
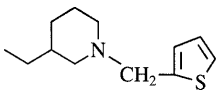
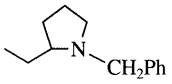
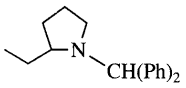
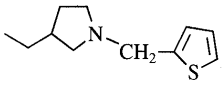
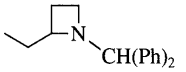
No.	R		Yield (%)	Appearance	MS m/z $M^+ + 1$	
1	CH_3	$(HCl)^{a)}$	59	Colorless crystals	116	(M^+)
2	CH_2CH_3	$(HCl)^{a)}$	76	Colorless crystals	130	(M^+)
3	CH_2CH_3		61.1	Colorless crystals	11—82	(M^+)
4	$CH(CH_3)_2$	$(HCl)^{a)}$	54	Colorless crystals	144	(M^+)
5	$CH(CH_3)_2$		48	Colorless crystals	144	(M^+)
6			47	Light yellow viscous oil	218	(M^+)
7			52	Colorless crystals	250	
8			15.5	Colorless crystals	264	
9			25	Colorless crystals	264	
10			31	Colorless crystals	304	
11			86	Light brown crystals	276	
12			96	Yellow viscous oil	353	
13			52.6	Brown viscous oil	277	
14			42	Light brown viscous oil	282	
15			100	Yellow viscous oil	276	
16			75	Yellow viscous oil	352	
17			28	Colorless crystals	268	
18			55	Light yellow crystals	338	
19			71.9	Colorless crystals	268	
20			87	Yellow crystals	324	
21			56	Colorless crystals	338	
22			96.6	Colorless crystals	360	
23			14.3	Colorless crystals	159	
24			56.5	Light yellow crystals	290	
25			43.6	Light yellow viscous oil	366	

Table 3. (continued)

No.	R	Yield (%)	Appearance	MS m/z $M^+ + 1$	
26		47.1	Yellow viscous oil	296	
27		41	Colorless crystals	277	$(M^+ + 2)$
28		19	Colorless crystals	352	$(M^+ + 2)$
29		48	Colorless crystals	282	
30		69	Light brown crystals	338	

a) Amidines were isolated as hydrochloric acid salts.

precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to give I-**43** (2.17 g, 74%) as a light yellow powder, mp 95—98 °C. I-**43** were recrystallized from benzene–*n*-hexane to give a light yellow powder, mp 120—124 °C.

Anhydrous hydrochloric acid was bubbled into a solution of I-**43** (0.87 g) in chloroform (20 ml) for 5 min. The solvent was removed under reduced pressure to give I-**44** (I-**43**·2HCl, 0.95 g) as a light yellow powder, mp 118—120 °C.

3-(1-Benzylpiperidin-3-yl) 5-Methyl 2-Amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (I-**11**F1 and I-**11**F2): A solution of 3-(1-benzylpiperidin-3-yl)amidinoacetate acetic acid salt II-**11** (1.68 g), methyl 2-(3-nitrobenzylidene)acetoacetate III-**1** (1.25 g), and sodium methoxide (0.27 g) in isopropyl alcohol (80 ml) was refluxed for 5 h. After cooling, the precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in ethyl acetoacetate, and the solution was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to give two fractions of I-**11**. The first fraction I-**11**F1 (0.87 g, 34%) was obtained as a light yellow powder, mp 94 °C. The second fraction I-**11**F2 (0.89 g, 35%) was obtained as a light yellow powder, mp 93 °C.

3-(1-Benzhydrylazetidin-3-yl) 5-Isopropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (I-**83**): A solution of 1-benzhydrylazetidin-3-yl crotonate IV-**1** (1.61 g) and isopropyl 2-(3-nitrobenzylidene)acetoacetate III-**4** (1.39 g) in isopropyl alcohol (50 ml) was refluxed for 10 h. After cooling, the precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was purified by column chromatography on silica gel to give I-**83** (2.06 g, 70.8%) as a light yellow powder, mp 90—92 °C.

Other 1,4-dihydropyridine derivatives I were also synthesized similarly, and are listed in Tables 1 and 2.

General Procedure for the Synthesis of Amidinoacetate Derivatives II 1-Benzhydrylazetidin-3-yl Amidinoacetate Acetic Acid Salt II-**20**: A solution of 1-benzhydrylazetidin-3-yl cyanoacetate VI-**17** (7.0 g) and ethyl alcohol (1.26 g) in chloroform (300 ml) was cooled in an ice-salt bath, and anhydrous hydrogen chloride was bubbled into it for 30 min. The mixture was allowed to stand overnight in an ice-salt bath. The solvent was removed under reduced pressure at room temperature and the residue was dissolved in chloroform (300 ml). The solution was cooled in an ice-salt bath and anhydrous ammonia was bubbled into it for 1 h. The precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in acetonitrile (50 ml), ammonium acetate (1.76 g) was added to the solution, and the whole was heated at 55 °C for 1 h. After cooling, the precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. Diethyl ether was added to the residue, and crystallization was induced by scratching. The crystals were collected by filtration and dried under reduced pressure in a desiccator to give II-**20** (7.6 g, 87%) as colorless crystals.

Other amidinoacetate derivatives II were also synthesized similarly, and are listed in Table 3.

General Procedure for the Synthesis of 2-Benzylideneacetoacetate Derivatives III Method A: 1-Benzylpiperidin-3-yl 2-(3-Nitrobenzylidene)acetoacetate III-**21**: A solution of 3-nitrobenzaldehyde (7.55 g) and 1-benzylpiperidin-3-yl acetoacetate VIII-**14** (13.75 g) in benzene (150 ml) containing a catalytic amount of piperidine was refluxed under azeotropic dehydration for 10 h. The reaction mixture was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give III-**21** (7.02 g, 34%) as a light brown oil.

Method B: Isopropyl 2-(3-Nitrobenzylidene)acetoacetate III-**4**: A solution of 3-nitrobenzaldehyde (15.1 g) and isopropyl acetoacetate (14.4 g) in isopropyl alcohol (50 ml) containing a catalytic amount of piperidinium acetate was stirred at 45—55 °C for 1 h. The mixture was allowed to stand overnight and crystals that separated were collected by filtration to give III-**4** (18.05 g, 65%) as colorless prisms, mp 91—95 °C.

Method C: 1-(Benzhydrylazetidin-3-yl) 2-(3-Nitrobenzylidene)acetoacetate III-**27**: A solution of 3-nitrobenzaldehyde (3.02 g) and 1-benzhydrylazetidin-3-yl acetoacetate VIII-**19** (6.46 g) in benzene (8 ml) and methyl alcohol (0.6 ml) containing a catalytic amount of piperidinium acetate was allowed to stand at room temperature for 1 d. Ethyl acetate was added to the mixture, then the organic layer was washed with water and dried on Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give III-**27** (3.2 g, 35%) as a light yellow oil.

Other 2-benzylideneacetoacetate derivatives III were also synthesized similarly, and are listed in Table 4.

1-(Benzhydrylazetidin-3-yl) Crotonate IV-1 Anhydrous ammonia gas was bubbled into a solution of 1-benzhydrylazetidin-3-yl acetoacetate VIII-**19**: (9 g) in THF (50 ml) for 1 h. The solvent was removed under reduced pressure to leave IV-1 (8.8 g, 98%) as a light yellow oil. IR (neat) cm^{-1}: 3430, 3340 (CO). MS m/z: 323 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, CH_3), 3.02, 3.62 (2H × 2, m, CH_2(Azet.)), 3.76 (2H, m, NH_2), 4.38 (1H, s, $CH(Ph)_2$), 4.52 (1H, s, CH=), 5.07 (1H, quin, J=6 Hz, COOCH), 7.11—7.46 (10H, m, Ar-H).

General Procedure for the Synthesis of Alcohol Derivatives V Method A: 2-(*N*-Benzyl-*N*-methylamino)ethyl Alcohol V-**1**: *N*-Methylbenzylamine (50 g) was added to a mixture of 2-bromoethyl alcohol (48.4 g) and K_2CO_3 (110.57 g) in *N*,*N*-dimethylformamide (DMF) (500 ml) and the whole was heated at 60 °C for 9 h, then added to water. The organic layer was extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was distilled to give V-**1** (38.35 g, 58%) as a colorless liquid, bp 110—120 °C (8 mm Hg).

Method B: 1-Benzhydryl-3-azetidinol V-**17**: A solution of benzhydryl-

Table 4. 2-Benzylideneacetoacetate III

$Ph(X)–CH=C(COCH_3)COOR$

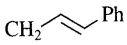
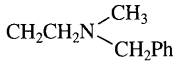
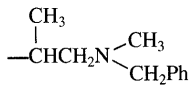
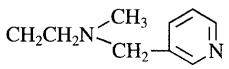
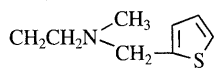
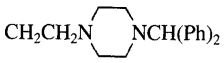
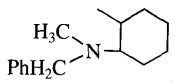
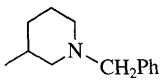
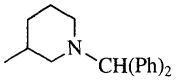
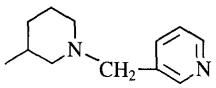
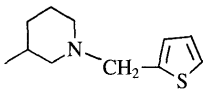
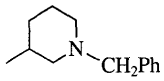
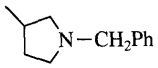
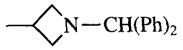
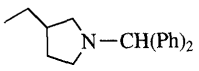
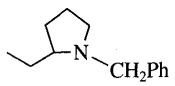
No.	X	R	Yield (%)	Method	Appearance (mp)	IR (KBr or neat) cm^{-1}	MS *m/z* M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
1	3-NO_2	CH_3	79	B	Colorless prisms	1720 (CO)	249	2.49 (3H, s, CH_3CO), 3.94 (3H, s, OCH_3), 7.28 (1H, s, =CH–), 7.57—8.33 (4H, m, Ar-H)
2	2-NO_2	CH_3	50	A	Light yellow oil	1730 (CO)	250 ($M^+ + 1$)	2.50 (3H, s, CH_3CO), 3.61 (3H, s, OCH_3), 7.10—8.28 (4H, m, Ar-H), 8.08 (1H, s, =CH–)
3	3-NO_2	CH_2CH_3	63	B	Colorless crystals (93—95 °C)	1725 (CO)	263	1.31 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.47 (3H, s, CH_3CO), 4.38 (2H, quar, J=7 Hz, $C\underline{H}_2CH_3$), 7.60 (1H, s, =CH–), 7.55—8.38 (4H, m, Ar-H)
4	3-NO_2	$CH(CH_3)_2$	65	B	Colorless prisms (91—95 °C)	1720 (CO)	270	1.30 (6H, d, J=5 Hz, $CH(C\underline{H}_3)_2$), 2.45 (3H, s, CH_3CO), 5.28 (1H, h, J=5 Hz, $C\underline{H}(CH_3)_2$), 7.58 (1H, s, =CH–), 7.52—8.41 (4H, m, Ar-H)
5	2-Cl	$CH(CH_3)_2$	100	B	Light yellow oil	1710 (CO)	267 ($M^+ + 1$)	1.19, 1.33 (3H × 2, d × 2, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.34, 2.45 (3H, s × 2, CH_3CO), 5.13 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 7.01—7.55 (4H, m, Ar-H), 7.82, 7.91 (1H, s × 2, =CH–Ar)
6	2,3-Cl_2	$CH(CH_3)_2$	89	B	Brown oil	1720 (CO)	301	1.16, 1.34 (3H × 2, d × 2, J=3 Hz, $CH(C\underline{H}_3)_2$), 2.24, 2.47 (3H, s × 2, CH_3CO), 5.02—5.26 (1H, m, $C\underline{H}(CH_3)_2$), 7.08—7.51 (3H, m, Ar-H), 7.80, 8.07 (1H, s × 2, =CH–Ar)
7	3-CN	$CH(CH_3)_2$	32	C	Colorless oil	2250 (CN) 1730 (CO)	257	1.31 (6H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.46 (3H, s, CH_3CO), 5.25 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 7.07—7.84 (5H, m, Ar-H, =CH–Ar)
8	3-CF_3	$CH(CH_3)_2$	52	C	Light yellow oil	1740 (CO)	300	[1] 1.34 (6H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.38 (3H, s, CH_3CO), 5.19 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 7.39—7.74 (5H, m, Ar-H, =CH–Ar) [2] 1.28 (6H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), 2.44 (3H, s, CH_3CO), 5.23 (1H, h, J=6 Hz, $C\underline{H}(CH_3)_2$), 7.44—7.78 (5H, m, Ar-H, =CH–Ar)
9	3-NO_2	*n*-C_6H_{13}	63.4	C	Light yellow oil	—	—	0.90 (3H, t, J=6 Hz, $O(CH_2)_5C\underline{H}_3$), 1.20—1.49 (6H, m, $O(CH_2)_2(C\underline{H}_2)_3CH_3$), 1.71 (2H, quin, J=6 Hz, $OCH_2C\underline{H}_2$), 2.40 (3H, s, $COCH_3$), 4.29 (2H, t, J=6 Hz, $COOCH_2$), 7.13—8.30 (5H, m, Ar-H, =CH–Ar)
10	3-NO_2		69.9	C	Light yellow oil	—	—	—[a]
11	3-NO_2		70.6	C	Light yellow oil	—	—	—[a]
12	3-NO_2		74.1	C	Light yellow oil	—	—	2.47 (3H, s, $COCH_3$), 4.95 (2H, d, J=7 Hz, $COOCH_2$), 6.24 (1H, dt, J=17, 7 Hz), CH_2-$C\underline{H}$=CH), 6.69 (1H, d, J=17 Hz, CH_2CH=$C\underline{H}$), 7.10—8.38 (10H, m, =CH–, Ar-H)
13	3-NO_2	$CH_2CH_2OCH_3$	73.4	C	Light yellow oil	—	—	2.46 (3H, s, CH_3CO), 3.32 (3H, s, OCH_3), 3.61 (2H, t, J=5 Hz, $CH_2C\underline{H}_2OCH_3$), 4.48 (2H, t, J=5 Hz, $COOC\underline{H}_2CH_2$), 7.40—8.40 (5H, m, Ar-H, =CH–Ar)
14	3-NO_2	$(CH_2)_6OH$	60.8	C	Light yellow oil	—	336 ($M^+ + 1$)	1.05—1.85 (8H, m, $OCH_2(C\underline{H}_2)_4CH_2OH$), 2.45 (3H, s, $COCH_3$), 3.19 (1H, br s, OH), 3.61 (2H, t, J=7 Hz, $C\underline{H}_2OH$), 4.30 (2H, t, J=7 Hz, $COOCH_2$), 7.14—8.37 (5H, m, Ar-H, =CH–Ar)
15	3-NO_2		63	C	Light yellow oil	1730 (CO) 1700 (CO)	383 ($M^+ + 1$)	2.24, 2.49 (3H × 2, s × 2, CH_3), 2.70 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.51 (2H, s, CH_2Ph), 4.44 (2H, t, J=6 Hz, $COOCH_2$), 7.05—8.46 (10H, m, Ar-H, =CH–)
16	3-NO_2		13	C	Light yellow oil	1720 (CO) 1700 (CO)	397 ($M^+ + 1$)	1.30 (3H, d, $CHC\underline{H}_3$), 2.22, 2.48 (3H × 2, s × 2, CH_3), 2.52—2.73 (2H, m, NCH_2Ph), 3.50 (2H, m, $CHC\underline{H}_2N$), 5.37 (1H, m, $C\underline{H}CH_2N$), 7.10—8.36 (10H, m, Ar-H, =CH–)
17	3-NO_2		46	C	Light brown oil	1725 (CO)	384 ($M^+ + 1$)	2.22, 2.46 (3H × 2, s × 2, CH_3), 2.72 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.41—3.61 (2H, s, CH_2-Pyrid.[b]), 4.45 (2H, t, J=6 Hz, $COOCH_2$), 7.14—8.60 (9H, m, Ar-H, =CH–)
18	3-NO_2		22	C	Light yellow oil	1720 (CO)	388	2.30, 2.49 (3H × 2, s × 2, CH_3), 2.71 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.74 (2H, s, CH_2-Thio.[b]), 4.43 (2H, t, J=6 Hz, $COOCH_2$), 6.78—8.34 (8H, m, Ar-H, =CH–)

Table 4. (continued)

No.	X	R	Yield (%)	Method	Appearance (mp)	IR (KBr or neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
19	3-NO_2		22.8	C	Light yellow oil	—	513	—
20	3-NO_2		10	C	Light yellow oil	1725 (CO)	436	1.05—2.70 (8H, m, CH_2 (c.Hex.)[b]), 2.40, 2.48 (3H×2, s×2, CH_3), 3.46—3.60 (2H, m, NCH_2-Ph), 4.89—5.28 (2H, m, COOCHCHN), 7.09—8.75 (10H, m, Ar-H, =CH–)
21	3-NO_2		34	A	Light brown oil	1720 (CO) 1700 (CO)	409 (M^++1)	1.37—2.82 (8H, m, CH_2 (Pipe.)[b]), 2.44 (3H, s, CH_3), 3.50 (2H, m, NCH_2Ph), 5.15 (1H, s, COOCH), 7.14—8.33 (10H, m, Ar-H, =CH–)
22	3-NO_2		65	C	Light yellow oil	—	485 (M^++1)	—
23	3-NO_2		45	C	Yellow oil	1720 (CO)	409	1.39—2.85 (8H, m, CH_2 (Pipe.)[b]),2.44 (3H, s, CH_3), 3.52 (2H, s, N-CH_2), 5.14 (1H, quin, J=4 Hz, COOCH), 7.14—8.48 (8H, m, Ar-H)
24	3-NO_2		46	C	Light yellow oil	1725 (CO)	415 (M^++1)	1.38—2.85 (8H, m, CH_2 (Pipe.)[b]), 2.46 (3H, s, CH_3), 3.74 (2H, m, NCH_2), 5.16 (1H, m, COOCH), 6.81—8.34 (8H, m, Ar-H, =CH–)
25	2,3-Cl_2		75	A	Yellow oil	—	—	—[a]
26	3-NO_2		70	C	Yellow oil	—	471 (M^++1)	—
27	3-NO_2		35	C	Light yellow oil	1640 (CO)	457 (M^++1)	2.45 (3H, s, CH_3), 3.05, 3.65 (2H×2, m, CH_2), 4.35 (1H, s, $CH(Ph)_2$), 5.25 (1H, quin, J=6 Hz, COOCH), 7.10—8.40 (15H, m, Ar-H, =CH–)
28	2,3-Cl_2		59.7	C	Light yellow oil	—	—	1.20—2.85 (7H, m, OCH_2CH, CH_2 (Pyrr.)[b]), 3.44 (3H, s, CH_3), 3.51, 3.60 (1H×2, s×2, CH_2Ph), 4.00—4.12, 4.15, 4.25 (1H×2, m, $COOCH_2$), 7.10—7.60 (8H, m, Ar-H), 7.80, 7.88 (1H, s, =CH–)
29	3-NO_2		7.3	C	Light yellow oil	—	409 (M^++1)	—

a) Compounds were not purified and were used directly in the next reaction. *b*) Ring name: Pyrid., pyridine; Thio., thiophene; c.Hex., cyclohexane; Pipe., piperidine; Pyrr., pyrroridine.

amine (250 ml) and epichlorohydrin (134.36 g) was allowed to stand at room temperature for 3 d, then refluxed for 72 h. After cooling, separated crystals were collected by filtration and the filtrate was evaporated under reduced pressure. Acetone was added to the residue and the separated crystals were collected and combined with the previous crop. Diethyl ether (800 ml) and 1 N NaOH (860 ml) were added to the crystals and the diethyl ether layer was separated. It was washed with saturated aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure, *n*-hexane (500 ml) was added to the residue, and crystals that separated were collected by filtration and washed with *n*-hexane to give V-**17** (198.3 g, 57%) as colorless crystals, mp 104—106 °C.

Method C: 1-Thienyl-3-piperidinol V-**13**: 3-Piperidinol (30.3 g) and 2-thiophenecarboxyaldehyde (22.4 g) were dissolved in ethyl alcohol (200 ml) and cooled in an ice-salt bath. Sodium borohydride (7.57 g) was added to the solution little by little and the mixture was stirred for 4 h in an ice-salt bath. The solvent was removed under reduced pressure and ice-water was added to the residue. The mixture was made acid with concentrated HCl and the organic layer was extracted with ethyl acetate. The water layer was made alkaline with concentrated NH_4OH and the organic layer was extracted with ethyl acetate. The ethyl acetate extracts were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to give V-**13** (28.44 g, 72%) as a light brown oil.

Method D: 1-(*N*-Benzyl-*N*-methylamino)-2-propyl Alcohol V-**2**: A solution of propylene oxide (11.62 g) in ethyl alcohol (10 ml) was added dropwise to a solution of *N*-methylbenzylamine (60.5 g) in ethyl alcohol (50 ml) and the mixture was stirred at room temperature for 8 h. The solvent was removed under reduced pressure and the residue was distilled to give V-**2** (31.53 g, 88%) as a colorless liquid, bp 88—94 °C (3 mmH g).

Method E: 1-Benzhydryl-3-methyl-3-azetidinol V-**18**: Pyridine (1 ml) and phosphoric acid (0.5 ml) were added to a solution of 1-benzhydryl-3-azetidinol V-**17** (7.17 g) in dimethyl sulfoxide (DMSO) (35 ml) and dichloromethane (20 ml). Dicyclohexylcarbodiimide (12.5 g) was added, and the whole was stirred at room temperature for 2 h. Water (300 ml) was added, and the mixture was extracted with chloroform (200 ml) 2 times. The extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 1-benzhydryl-3-azetidinone (4.84 g, 67%) as a light yellow oil. MS m/z: 238 (M^++1).

A solution of 1 M methylmagnesium bromide in THF (60 ml) was added dropwise to a solution of 1-benzhydryl-3-azetidinone (7.26 g) in an ice-salt bath and the mixture was stirred for 1 h. Water was added, and the whole was extracted with diethyl ether. The extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give V-**18** (5.92 g, 76%) as a colorless oil.

Method F: (1-Benzhydrylazetidin-2-yl)methanol V-**27**: Methyl (1-

Table 5. Alcohols V

R–OH

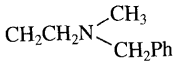
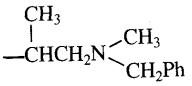
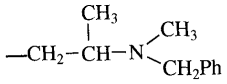
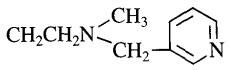
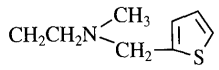
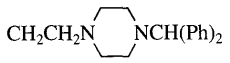
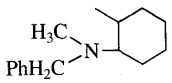
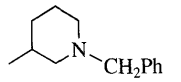
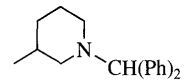
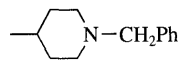
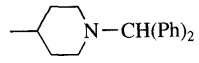
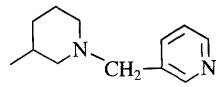
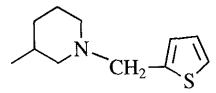
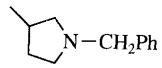
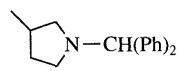
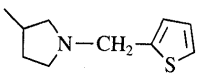
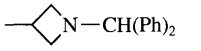
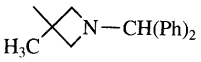
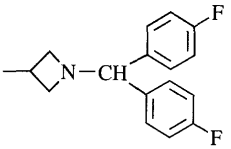
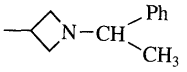
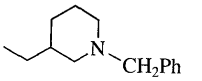
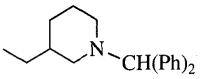
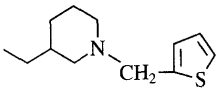
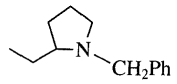
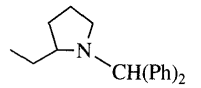
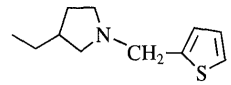
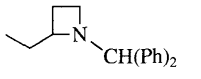
No.	R	Yield (%)	Method	Appearance (mp or bp)	IR (KBr or neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
1		58	A	Colorless liquid (bp 110—120 °C/8 mmHg)	3280 (OH)	164 (M^+-1)	2.24 (3H, s, CH_3), 2.59 (2H, t, J=5 Hz, $CH_2C\underline{H}_2N$), 2.86 (1H, s, OH), 3.56 (2H, s, CH_2Ph), 3.61 (2H, t, J=5 Hz, $C\underline{H}_2OH$), 7.30 (5H, m, Ar-H)
2		88	D	Colorless liquid (bp 88—94 °C/3 mmHg)	3420 (OH)	180 (M^++1)	1.14 (3H, d, J=6 Hz, $CHC\underline{H}_3$), 2.22 (3H, s, NCH_3), 2.24—2.46 (2H, m, CH_2Ph), 3.45, 3.66 (1H×2, d, J=12 Hz, $CHC\underline{H}_2Ph$), 3.53 (1H, br s, OH), 3.86 (1H, m, $C\underline{H}OH$), 7.30 (5H, m, Ar-H)
3		85	F	Colorless liquid	3400 (OH)	180 (M^++1)	0.93 (3H, d, J=4 Hz, $OCH_2CH(C\underline{H}_3)N$), 2.16 (3H, s, NCH_3), 2.88—3.07 (1H, m, $OCH_2C\underline{H}(CH_3)N$), 3.39 (2H, m, OCH_2), 3.46, 3.69 (1H×2, d×2, J=8 Hz, NCH_2Ph), 7.20—7.40 (5H, m, Ar-H)
4		57	A	Colorless liquid (bp 115—122 °C/3 mmHg)	3300 (OH)	167 (M^++1)	2.25 (3H, s, CH_3), 2.63 (2H, t, J=5 Hz, $CH_2C\underline{H}_2N$), 3.58 (2H, s, NCH_2-Pyrid.[a]), 3.65 (2H, t, J=5 Hz, $HOC\underline{H}_2$), 7.22—8.58 (4H, m, Ar-H)
5		29	C	Colorless liquid	3360 (OH)	172 (M^++1)	2.30 (3H, s, CH_3), 2.33—2.78 (1H, br, OH), 2.60 (2H, t, J=5 Hz, $CH_2C\underline{H}_2N$), 3.63 (2H, t, J=5 Hz, $HOC\underline{H}_2$), 3.80 (2H, s, NCH-Thio.[a]), 6.85—7.30 (3H, m, Ar-H)
6		66	A	Light yellow oil	3400 (OH)	296	2.25—2.74 (9H, m, OH, CH_2 (Pipera.)[a]), 3.54 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.68 (2H, t, J=6 Hz, $C\underline{H}_2OH$), 4.22 (1H, s, $CH(Ph)_2$), 7.10—7.46 (10H, m, Ar-H)
7		37	D	Colorless liquid (bp 134 °C/3 mmHg)	3450 (OH)	219	1.05—2.20 (8H, m, CH_2 (c.Hex.)[a]), 2.18 (3H, s, CH_3), 2.35 (1H, m, CHN), 3.38—3.51 (1H, br s, CH_2Ph), 3.71 (1H, d, J=16 Hz, $C\underline{H}OH$), 3.99 (1H, br s, OH), 7.31 (5H, m, Ar-H)
8		96	A	Colorless oil (bp 135—137 °C/5 mmHg)	3350 (OH)	—	1.43—2.57 (9H, m, CH_2 (Pipe.),[a] OH), 3.53 (2H, s, CH_2Ph), 3.83 (1H, m, $C\underline{H}OH$), 7.30 (5H, m, Ar-H), 11—67
9		79	A	Yellow oil	3340 (OH)	267	1.41—2.58 (9H, m, CH_2, OH), 3.80 (1H, m, $C\underline{H}OH$), 4.34 (1H, s, $CH(Ph)_2$), 7.13—7.40 (10H, m, Ar-H)
10		36	A	Colorless oil	3325 (OH)	—	1.30—2.81 (9H, m, CH_2 (Pipe.), [a] OH), 3.44 (2H, s, CH_2Ph), 3.42—3.72 (1H, m, $C\underline{H}OH$), 7.16 (5H, m, Ar-H)
11		44	A	Colorless crystals (mp 137—139.5 °C)	—	267	—
12		100	A	Light brown oil	3300 (OH)	192	1.44—2.60 (9H, m, CH_2 (Pipe.),[a] OH), 3.52 (2H, s, CH_2-Pyrid.[a]), 3.82 (1H, m, $C\underline{H}OH$), 7.23—8.51 (4H, m, Ar-H)
13		72	C	Light brown oil	3320 (OH)	197	1.46—2.61 (9H, m, CH_2 (Pipe.),[a] OH), 3.69 (2H, s, CH_2-Thio.[a]), 3.82 (1H, quin, J=4 Hz, $C\underline{H}OH$), 6.90, 7.21 (3H, m, Ar-H)
14		23.7	G	Light yellow oil	—	—	1.64—2.94 (6H, m, CH_2 (Pyrr.)[a]), 3.62 (2H, s, NCH_2Ph), 4.27—4.43 (1H, m, $HOC\underline{H}$), 7.25—7.45 (5H, m, Ar-H)
15		81	A	Light brown oil	3360 (OH)	253	1.64—2.19 (6H, m, CH_2), 2.94 (1H, br s, OH), 3.61 (1H, s, $CH(Ph)_2$), 4.30 (1H, m, $C\underline{H}OH$), 7.30 (10H, m, Ar-H)

Table 5. (continued)

No.	R	Yield (%)	Method	Appearance (mp or bp)	IR (KBr or neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
16		56	C	Colorless oil	3350 (OH)	183	1.65—2.98 (7H, m, CH_2 (Pyrr.),[a] OH), 3.85 (2H, s, CH_2-Thio.[a]), 4.27—4.40 (1H, m, CHOH), 6.81—7.34 (3H, m, Ar-H)
17		57	B	Colorless crystals (mp 104—106 °C)	3080 (OH)	239	2.44 (1H, br s, OH), 2.90, 3.52 (2H × 2, dt × 2, J=6, 0.2 Hz, CH_2), 4.35 (1H, s, $CH(Ph)_2$), 4.45 (1H, quin, J=6 Hz, CHOH), 7.10—7.46 (10H, m, Ar-H)
18		76	E	Colorless oil	—	254 (M^++1)	1.50 (3H, s, CH_3), 2.15 (1H, br, OH), 2.97, 3.20 (2H × 2, d × 2, J=8 Hz, CH_2), 4.35 (1H, s, $CH(Ph)_2$), 7.15—7.45 (10H, m, Ar-H)
19		22	B	Light yellow oil	3360 (OH)	275	2.35 (1H, s, OH), 2.86, 3.46 (2H × 2, m, CH_2), 4.30 (1H, s, NCH), 4.40 (1H, quin, J=5 Hz, CHOH), 6.88—7.35 (8H, m, Ar-H)
20		88	B	Light yellow oil	—	—	1.38 (3H, d, J=7 Hz, $NCHCH_3$), 2.38 (1H, s, OH), 2.81—2.94 (2H, m, CH_2 (Azet.)[a]), 3.30 (1H, quar, J=7 Hz, $NCHCH_3$), 3.36—3.46, 3.68—3.80 (1H × 2, m, CH_2 (Azet.)[a]), 4.37—4.52 (1H, m, HOCH), 7.22—7.50 (5H, m, Ar-H)
21		73	A	Light brown oil	3400 (OH)	206 (M^++1)	1.25—2.75 (9H, m, CH_2 (Pipe.),[a] OH), 2.85 (1H, m, $HOCH_2CH$), 3.30, 4.05 (1H × 2, d × 2, J=14 Hz, CH_2Ph), 3.52, 3.85 (1H × 2, d × 2, J=4 Hz, CH_2OH), 7.20—7.40 (5H, m, Ar-H)
22		91.5	A	Light yellow oil	—	282 (M^++1)	—
23		32.4	C	Light yellow oil	—	211 (M^++1)	1.15—1.78 (7H, m, CH_2 (Pipe. C3, 4, 5),[a] OH), 2.23—3.00 (3H, m, CH_2, CH (Pipe. C2, 6)[a]), 3.55, 3.88 (1H × 2, dd × 2, J=4, 11 Hz, $HOCH_2$), 3.82, 4.11 (1H × 2, d × 2, J=15 Hz, NCH_2-Thio.[a]), 6.85—7.35 (3H, m, Ar-H)
24		100	A	Light yellow oil	3370 (OH)	192 (M^++1)	1.55—2.35 (4H, m, CH_2 (Pyrr. C3, C4)[a]), 2.57—3.01 (2H, m, NCH_2 (Pyrr. C5)[a]), 2.86, 2.92 (1H × 2, s × 2, NCH_2Ph), 3.34, 3.95 (1H × 2, d × 2, J=6 Hz, CH_2OH), 3.45 (1H, br s, OH), 3.63 (1H, dd, J=6, 2 Hz, $CHCH_2OH$), 7.30 (5H, m, Ar-H)
25		100	A	Light yellow oil	—	268 (M^++1)	—
26		90	C	Light brown oil	330 (OH)	198 (M^++1)	1.58—2.09 (4H, m, CH_2 (Pyrr. C3, C4)[a]), 2.29—2.51 (1H, m, NCH_2 (Pyrr. C5)[a]), 2.69—2.94 (2H, m, NCH_2 (Pyrr. C5),[a] OH), 3.07—3.18 (1H, m, $CHCH_2OH$), 3.43, 3.65 (1H × 2, dd × 2, J=11, 1 Hz, CH_2OH), 3.75, 4.10 (1H × 2, d × 2, J=14 Hz, NCH_2-Thio.[a]), 6.88—7.36 (3H, m, Ar-H)
27		100	F	Colorless oil	—	198 (M^++1)	1.92, 2.20 (1H × 2, m, C3-CH_2 (Azet.)[a]), 2.53, 3.00 (1H × 2, dd, J=11, 3 Hz, NCH_2), 2.83 (1H, quin, J=8.5 Hz, $NCHCH_2$), 3.35 (1H, td, J=8.5, 2.4 Hz, CH_2OH), 3.48 (1H, m, OH), 4.49 (1H, s, $NCH(Ph)_2$), 7.20—7.60 (10H, m, Ar-H)

a) Ring name: Pyrid., pyridine; Thio., thiophene; c.Hex., cyclohexane; Pipera., piperadine; Pyrr., pyrroridine; Azet., azetidine.

benzhydrylazetidin-2-yl)carboxylate (13 g) in ether (40 ml) was added dropwise to a mixture of lithium aluminum hydride (3.51 g) and diethyl ether (200 ml), and the whole was refluxed for 8 h, then allowed to cool. Water (10 ml) was added dropwise, and the reaction mixture was stirred for 0.5 h. Mg_2SO_4 was added and stirring was continued for 0.5 h. The precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was purified by column chromatography on silica gel to give V-**27** (11.9 g, quant.) as a colorless oil.

Table 6. Cyanoacetate VI

$NCCH_2COOR$

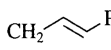
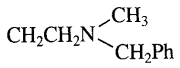
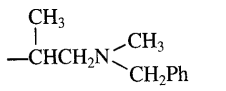
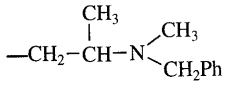
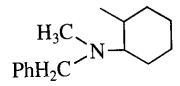
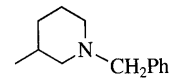
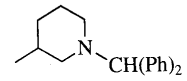
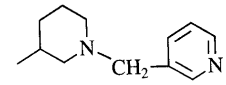
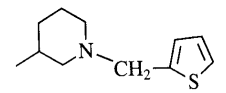
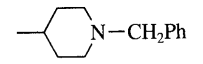
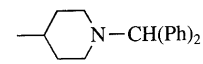
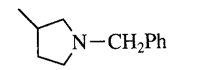
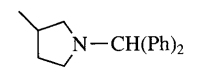
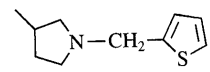
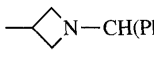
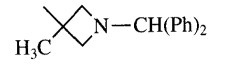
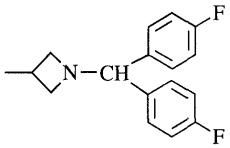
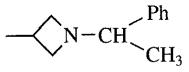
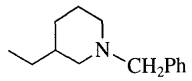
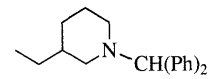
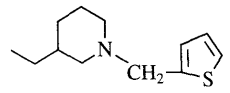
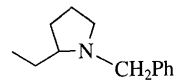
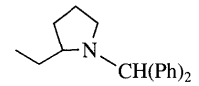
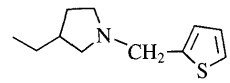
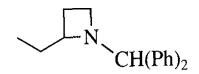
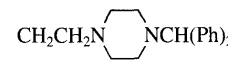
No.	R	Yield (%)	Appearance (mp or bp)	IR (neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
1	$CH(CH_3)_2$	80	Colorless liquid (bp 80—87 °C/21 mmHg)	2350 (CN) 1740 (CO)	—	1.31 (6H, d, J=6 Hz, CH_3), 3.45 (2H, s, CH_2), 5.10 (1H, h, J=6 Hz, CH)
2	$CH_2CH_2OCH_3$	40	Colorless liquid	2250 (CN) 1745 (CO)	144 (M^++1)	3.40 (3H, s, CH_3), 3.54 (2H, s, $NCCH_2$), 3.62 (2H, t, J=5 Hz, $CH_2C\underline{H}_2OCH_3$), 4.35 (2H, t, J=5 Hz, $COOC\underline{H}_2CH_2$)
3		57.7	Light yellow liquid	2260 (CN) 1745 (CO)	201	3.49 (2H, s, $NCCH_2$), 4.85 (2H, d, J=11 Hz, $COOCH_2$), 6.28 (1H, dt, J=22, 11 Hz, $CH_2C\underline{H}$=), 6.70 (1H, d, J=22 Hz, =CHPh), 7.14—7.54 (5H, m, Ar-H)
4		48	Light yellow oil	2250 (CN) 1740 (CO)	232	2.30 (3H, s, CH_3), 2.70 (2H, t, J=6 Hz, CH_2N), 3.43 (2H, s, CH_2Ph), 3.56 (2H, s, $NCCH_2$), 4.80 (2H, t, J=6 Hz, $COOCH_2$), 7.31 (5H, m, Ar-H)
5		63	Colorless oil	2260 (CN) 1750 (CO)	247 (M^++1)	1.27 (3H, J=7 Hz, $OCH(C\underline{H}_3)CH_2N$), 2.28 (3H, s, NCH_3), 2.38 (1H, dd, J=14, 5 Hz, $OCH(CH_3)C\underline{H}_2N$), 2.61 (1H, dd, J=14, 7 Hz, $OCH(CH_3)C\underline{H}_2N$), 3.42 (2H, s, $NCCH_2$), 3.49, 3.59 (1H×2, d×2, J=8 Hz, NCH_2Ph), 5.10—5.32 (1H, m, COOCH), 7.20—7.45 (5H, m, Ar-H)
6		66	Colorless oil	—	180	—
7		58	Light yellow oil	2260 (CN) 1740 (CO)	286	1.03—2.46 (8H, m, CH_2 (c.Hex.)[a]), 2.30 (3H, s, NCH_3), 3.46 (2H, s, $NCCH_2$), 3.54, 3.68 (1H×2, d×2, J=14 Hz, NCH_2Ph), 4.60 (1H, dt, J=4, 11 Hz, NCH), 4.99 (1H, dt, J=11, 5 Hz, OCH), 7.15—7.50 (5H, m, Ar-H)
8		85	Light yellow oil	2260 (CN) 1750 (CO)	258	1.23—2.84 (8H, m, CH_2 (Pipe.)[a]), 3.45 (2H, s, CH_2Ph), 3.56 (2H, s, $NCCH_2$), 4.95 (1H, m, COOCH), 7.13—7.34 (5H, m, Ar-H)
9		75.1	Light yellow oil	2270 (CN) 1755 (CO)	334	1.35—2.80 (8H, m, CH_2 (Pipe.),[a]3.54 (2H, s, $NCCH_2$), 4.36 (H, s, $NCH(Ph)_2$), 4.90—5.05 (1H, m, COOCH), 7.12—7.55 (10H, m, Ar-H)
10		54	Light brown oil	2260 (CN) 1740 (CO)	259	1.36—2.84 (8H, m, CH_2 (Pipe.)[a]), 3.49, 3.55 (2H×2, s×2, $NCCH_2$, NCH_2), 4.95 (1H, m, COOCH), 7.20—8.56 (4H, m, Ar-H)
11		81	Light yellow oil	2270 (CN) 1745 (CO)	264	1.44—2.81 (8H, m, CH_2 (Pipe.)[a]), 3.47 (2H, s, NCH_2), 3.77 (2H, s, $NCCH_2$), 4.94 (1H, quin, J=4 Hz, COOCH), 6.91, 7.22 (3H, m, Ar-H)
12		87	Yellow oil	—	—	1.64—2.20 (4H, m, CH_2 (Pipe.)[a]), 2.20—2.40, 2.60—2.78 (2H×2, m, CH_2 (Pipe.)[a]), 3.45, 3.50 (2H×2, s×2, $NCCH_2$, NCH_2Ph), 4.81—4.99 (1H, m, OCH), 7.20—7.50 (5H, m, Ar-H)
13		94	Yellow oil	—	334	1.64—2.20 (4H, m, CH_2 (Pipe.)[a]), 2.11—2.30, 2.55—2.78 (2H×2, m, CH_2 (Pipe.)[a]), 3.43 (2H, s, $NCCH_2$), 4.27 (1H, s, NCH), 4.80—4.96 (1H, m, OCH), 7.11—7.55 (10H, m, Ar-H)
14		48	Yellow oil	—	—	1.68—2.92 (6H, m, CH_2 (Pyrr.)[a]), 3.48 (2H, s, $NCCH_2$), 3.56—3.72 (2H, m, NCH_2Ph), 5.32 (1H, m, OCH), 7.20—7.60 (5H, m, Ar-H)
15		90.1	Light yellow oil	2270 (CN) 1755 (CO)	320	—
16		42.6	Light yellow oil	—	251	1.80—3.08 (6H, m, CH_2 (Pyrr.)[a]), 3.49 (2H, s, $NCCH_2$), 3.73—4.08 (2H, m, NCH_2-Thio.[a]), 5.28 (1H, m, OCH), 6.84—7.64 (3H, Ar-H)

Table 6. (continued)

No.	R	Yield (%)	Appearance (mp or bp)	IR (neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
17		93	Colorles crystals (mp 98—101 °C)	2250 (CN) 1745 (CO)	306	3.10, 3.60 (2H × 2, m, CH_2 (Azet.)[a]), 3.46 (2H, s, $NCCH_2$), 4.37 (1H, s, $CH(Ph)_2$), 5.16 (1H, quin, J=6 Hz, COOCH), 7.10—7.50 (10H, m, Ar-H)
18		86.6	Yellow oil	—	321 (M^++1)	—
19		20	Light yellow oil	—	342	3.07, 3.53 (2H × 2, m, CH_2 (Azet.)[a]), 3.46 (2H, s, $NCCH_2$), 4.86 (1H, s, NCH), 5.13 (1H, m, COOCH), 6.82—7.68 (8H, m, Ar-H)
20		31	Light yellow oil	—	245 (M^++1)	1.56 (3H, d, J=7 Hz, $NCHC\underline{H}_3$), 3.07 (1H, quar, J=7 Hz), $NC\underline{H}CH_3$), 3.24—3.79 (4H, m, CH_2 (Azet.)[a]), 3.49 (2H, s, $NCCH_2$), 5.01—5.20 (1H, m, COOCH), 7.10—7.60 (15H, m, Ar-H)
21		44.5	Light yellow oil	2130 (CN) 1755 (CO)	273 (M^++1)	1.04—2.84 (9H, m, CH_2, CH (Pipe.)[a]), 3.39, 3.95 (1H × 2, d × 2, J=14 Hz, NCH_2Ph), 3.41 (2H, s, $NCCH_2$), 4.30, 4.38 (2H, dd, J=5, 9 Hz, $COOCH_2$), 7.10—7.40 (5H, m, Ar-H)
22		52.5	Light yellow oil	2270 (CN) 1755 (CO)	349 (M^++1)	—
23		48.4	Light yellow oil	2270 (CN) 1755 (CO)	279 (M^++1)	0.95—2.15 (9H, m, CH_2, CH (Pipe.)[a]), 3.41—3.80, 3.92—4.20 (2H × 2, m, NCH_2-Thio.[a]), 3.61 (2H, s, $NCCH_2$), 6.95—7.40 (3H, m, Ar-H)
24		81	Brown oil	2250 (CN) 1770 (CO)	259 (M^++1)	1.57—2.07 (4H, m, CH_2 (Pyrr. C3, C4)[a]), 2.21—2.39 (1H, m, $COOCH_2CH$), 2.82—3.03 (2H, m, CH_2 (Pyrr. C5)[a]), 3.42 (2H, s, $NCCH_2$), 3.49, 4.00 (1H × 2, d × 2, J=12 Hz, $COOCH_2$), 4.17 (2H, d, J=5 Hz, NCH_2Ph), 7.31 (5H, m, Ar-H)
25		32.7	Light yellow oil	—	334	—
26		99	Light brown oil	2250 (CN) 1740 (CO)	265 (M^++1)	1.56—2.02 (4H, m, CH_2 (Pyrr. C3, C4)[a]), 2.34—2.52 (1H, m, $COOCH_2CH$), 2.86—3.14 (2H, m, CH_2 (Pyrr. C5)[a]), 3.48 (2H, s, $NCCH_2$), 3.78—4.27 (4H, m, $COOCH_2$, NCH_2-Thio.[a]), 6.88—7.31 (3H, m, Ar-H)
27		95.5	Colorless oil	—	321 (M^++1)	1.96—2.16 (2H, m, C3-CH_2 (Azet.)[a]), 3.13 (2H, s, $NCCH_2$), 3.24—3.36, 3.42—3.60 (1H × 2, m, NCH_2), 3.65—3.88 (3H, m, $COOCH_2CH$), 4.44 (1H, s, $NCH(Ph)_2$), 7.16—7.57 (10H, m, Ar-H)
28		56	Light yellow oil	2250 (CN) 1740 (CO)	363	2.22—2.78 (8H, m, CH_2 (Pipera.)[a]), 2.65 (2H, t, J=6 Hz, CH_2N), 3.44 (2H, s, $NCCH_2$), 4.20 (1H, s, $CH(Ph)_2$), 4.30 (2H, t, J=6 Hz, COOCH), 7.04—7.50 (10H, m, Ar-H)

a) Ring name: Pipe., piperidine; Pyrid., pyridine; c.Hex., cyclohexane; c.Pro., cyclopropane; Thio., thiophene; Pyrr., pyrroridine; Azet., azetidine; Pipera., piperazine.

Method G: 1-Benzyl-3-pyrrolidinol V-**14**: Benzyl bromide (38.5 g) in DMF (50 ml) was added to the mixture of 3-pyrroline (75% purity, 18.75 g) and K_2CO_3 (55.2 g) in DMF (200 ml) on an ice bath, and the whole was stirred at room temperature for 8 h. It was poured into water and extracted with chloroform. The chloroform extract was washed with water and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 1-benzyl-3-pyrroline (9.84 g, 22.9%) as a colorless oil. MS m/z: 159 (M^+).

Sodium borohydride (1 M in THF, 200 ml) was added dropwise to a solution of 1-benzyl-3-pyrroline (7.9 g) in THF (50 ml) in an ice bath, and the mixture was stirred at room temperature for 1 h. Water (5 ml) and then 3 N NaOH (60 ml) were added. The reaction mixture was cooled in an ice bath, 60% NaOH (3.59 ml) was added and the whole was stirred at room temperature for 1 h. It was made alkaline with ice-water and KOH. The mixture was extracted with ethyl acetate, and the extract was washed with saturated aqueous NaCl, then dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give V-**14** (2.1 g, 23.7%) as a light yellow oil.

Other alcohol derivatives V were also synthesized according similarly, and are listed in Table 5.

Table 7. Acetoacetates VIII

CH_3COCH_2COOR

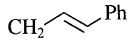
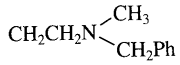
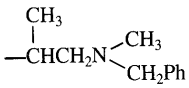
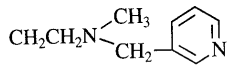
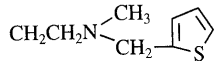
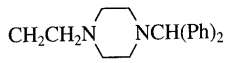
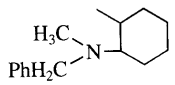
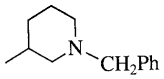
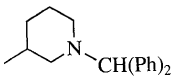
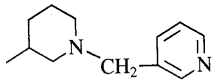
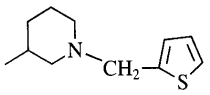
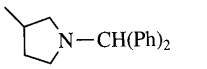
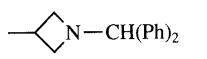
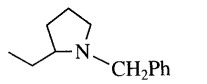
No.	R	Yield (%)	Appearance (bp)	IR (neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
1	$CH(CH_3)_2$	86	Colorless liquid (89—91 °C/35 mmHg)	1710 (CO)	144	—
2	n-C_6H_{13}	69.5	Colorless liquid	—	—	—[a]
3		100	Colorless liquid	—	—	—[a]
4		96.7	Colorless liquid	—	—	—[a]
5		70.8	Colorless liquid	—	—	2.28 (3H, s, $COCH_3$), 3.50 (2H, s, $COCH_2COO$), 4.79 (2H, d, J=6 Hz, $C\underline{H}_2CH=CH$), 6.27 (1H, dt, J=17, 6 Hz, $CH_2C\underline{H}=CH$), 6.68 (1H, dt, J=17 Hz, CH_2-$CH=C\underline{H}$), 7.10—7.44 (5H, m, Ar-H)
6	$CH_2CH_2OCH_3$	87.6	Colorless liquid	—	—	2.30 (3H, s, $COCH_3$), 3.41 (3H, s, OCH_3), 3.51 (2H, s, $COCH_2COO$), 3.60 (2H, t, J=4 Hz, $COOCH_2C\underline{H}_2$-O), 4.31 (2H, t, J=4 Hz, $COOC\underline{H}_2CH_2O$)
7	$(CH_2)_6OH$	40.4	Colorless liquid	—	—	1.29—1.71 (8H, m, $OCH_2(C\underline{H}_2)_4CH_2OH$), 1.76 (1H, s, OH), 2.26 (3H, s, CH_3CO), 3.45 (2H, s, $COCH_2COO$), 3.64 (2H, t, J=7 Hz, $C\underline{H}_2OH$), 4.15 (2H, t, J=7 Hz, $COOCH_2$)
8		63.6	Light yellow oil	1740 (CO) 1710 (CO)	250 (M^++1)	2.26, 2.28 (3H×2, s×2, CH_3), 2.69 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.45 (2H, s, CH_2Ph), 3.55 (2H, s, $COCH_2COO$), 4.26 (2H, t, J=6 Hz, $COOCH_2$), 7.30 (5H, m, Ar-H)
9		91	Light yellow oil	1730 (CO) 1715 (CO)	264 (M^++1)	1.24 (3H, d, J=6 Hz, $CH(C\underline{H}_3)$), 2.23, 2.28 (3H×2, s×2, $COCH_3$, NCH_3), 2.51—2.64 (2H, m, CH_2Ph), 3.44 (2H, s, $COCH_2$), 3.52 (2H, d, J=6 Hz, $CHC\underline{H}_2N$), 5.19 (1H, hex., $C\underline{H}(CH_3)CH_2$), 7.30 (5H, m, Ar-H)
10		80	Light brown oil	1740 (CO) 1715 (CO)	251 (M^++1)	2.30 (6H, s, CH_3), 2.70 (2H, t, J=6 Hz, $CH_2C\underline{H}_2N$), 3.50, 3.59 (2H×2, s×2, $COCH_2COO$, NCH_2-Pyrid.[b]), 4.29 (2H, t, J=6 Hz, $COOCH_2$), 7.26, 7.66, 8.54 (4H, m, Ar-H)
11		65	Light yellow oil	1740 (CO) 1720 (CO)	256 (M^++1)	2.29, 2.35 (3H×2, s×2, CH_3), 2.70 (2H, t, J=6 Hz, CH_2N), 3.49 (2H, s, $COCH_2COO$), 3.80 (2H, s, CH_2-Thio.[b]), 4.38 (2H, t, J=6 Hz, $COOCH_2$), 6.88—7.33 (3H, m, Ar-H)
12		59.1	Light brown oil	1740 (CO) 1720 (CO)	380	2.25 (3H, s, CH_3), 2.31—2.60 (8H, m, CH_2 (Pipe.)[b]), 2.65 (2H, t, J=6 Hz, CH_2N), 3.44 (2H, s, $COCH_2$-COO), 4.20 (1H, s, $CH(Ph)_2$), 4.24 (2H, t, J=6 Hz, $COOCH_2$), 7.10—7.49 (10H, m, Ar-H)
13		79	Light yellow oil	1740 (CO) 1720 (CO)	303	1.02—2.22 (8H, m, CH_2 (c.Hex.)[b]), 2.19, 2.29 (3H×2, s×2, CH_3), 2.60 (1H, dt, J=6, 11 Hz, CHN), 3.48 (2H, s, $COCH_2COO$), 3.50—3.71 (2H, m, CH_2Ph), 4.98 (1H, dt, J=6, 11 Hz, COOCH), 7.28 (5H, m, Ar-H)
14		100	Light yellow oil	1740 (CO) 1710 (CO)	276 (M^++1)	1.35—2.82 (8H, m, CH_2 (Pipe.)[b]), 2.26 (3H, s, CH_3), 3.43 (2H, s, $COCH_2COO$), 3.52 (2H, s, CH_2Ph), 4.94 (1H, m, COOCH), 7.14—7.34 (5H, m, Ar-H)
15		93	Light yellow oil	1750 (CO) 1725 (CO)	—	1.30—2.80 (8H, m, CH_2 (Pipe.)[b]), 2.25 (3H, s, CH_3), 3.40 (2H, s, $COCH_2COO$), 4.35 (1H, s, $CH(Ph)^2$), 4.85—5.05 (1H, m, COOCH), 7.10—7.50 (10H, m, Ar-H)
16		85	Brown oil	1740 (CO) 1715 (CO)	277 (M^++1)	1.38—2.80 (8H, m, CH_2 (Pipe.)[b]), 2.27 (3H, s, CH_3), 3.45 (2H, s, $COCH_2COO$), 3.54 (2H, s, NCH_2-Pyrid.[b]), 4.93 (1H, quin, J=4 Hz, COOCH), 7.22—8.52 (4H, m, Ar-H)

Table 7. (continued)

No.	R	Yield (%)	Appearance (bp)	IR (neat) cm^{-1}	MS m/z M^+	^{1}H-NMR ($CDCl_3$) δ (ppm)
17		85	Yellow oil	1715 (CO)	282 ($M^+ + 1$)	1.20—2.95 (8H, m, CH_2 (Pipe.)[b]), 2.29 (3H, s, CH_3), 3.45 (2H, s, $COCH_2COO$), 3.75 (2H, s, NCH_2-Thio.[b]), 4.94 (1H, m, COOCH), 6.86—7.32 (3H, m, Ar-H)
18		76.1	Light yellow oil	—	—	—[a]
19		93	Light yellow oil	1740 (CO) 1710 (CO)	324 ($M^+ + 1$)	2.29 (3H, s, CH_3), 3.05, 3.61 (2H × 2, m, CH_2 (Azet.)[b]), 3.45 (2H, s, $COCH_2COO$), 4.38 (1H, s, $CH(Ph)_2$), 5.11 (1H, quin, J = 5 Hz, COOCH), 7.10—7.49 (10H, m, Ar-H)
20		62.5	Light yellow oil	—	276 ($M^+ + 1$)	—

a) Compounds were not purified and were used directly in the next reaction. *b*) Ring name: Pyrid., pyridine; Thio., thiophene; Pipe., piperidine; c.Hex., cyclohexane; Azet., azetidine.

General Procedure for the Synthesis of Cyanoacetate Derivatives VI 1-Benzhydrylazetidin-3-yl Cyanoacetate VI-**17**: Dicyclohexylcarbodiimide (12.38 g) was added to a solution of cyanoacetic acid (4.25 g) and 1-benzhydryl-3-azetidinol V-**17** (11.95 g) in THF (400 ml) under stirring, and the mixture was heated at 55 °C for 11 h. After cooling, the precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to give VI-**17** (14.25 g, 93%) as colorless crystals, mp 98—101 °C.

Other cyanoacetate derivatives VI were synthesized similarly, and are listed in Table 6.

General Procedure for the Synthesis of Acetoacetate Derivatives VIII 1-Benzhydrylazetidin-3-yl Acetoacetate VIII-**19**: Diketene (6.3 g) was added to a solution of 1-benzhydryl-3-azetidinol V-**17** (11.95 g) and triethylamine (0.5 ml) in chloroform (30 ml) at room temperature and the mixture was stirred for 10 h. It was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give VIII-**19** (15.07 g, 93%) as a light yellow oil.

Other acetoacetate derivatives VIII were synthesized similarly, and are listed in Table 7.

Methyl (1-Benzhydrylazetidin-2-yl)carboxylate A mixture of benzhydryl-amine (143.4 g) and methyl 2,4-dibromobutanoate[11] (52 g) in acetonitrile (1000 ml) was refluxed for 30 h. After cooling, the precipitate was filtered off and the solvent was removed from the filtrate under reduced pressure. The residue was dissolved in toluene and hydrochloric acid gas was bubbled into the solution for 5 min. The separated crystals were filtered off and suspended in toluene (500 ml). Triethylamine (8.47 g) was added, and the mixture was stirred for 1h. The precipitate was filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give methyl (1-benzhydrylazetidin-2-yl)carboxylate (14 g, 24.9%) as a light yellow oil. IR (neat) cm^{-1}: 1740 (CO). MS m/z: 282 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 2.08—2.44 (2H, m, CH_2(Azet.C3)), 2.84—3.49 (2H, m, CH_2(Azet.C4)), 3.38 (3H, s, OCH_3), 3.54 (1H, t, J = 6 Hz, CHCOO), 4.48 (1H, s, $CH(Ph)_2$), 7.07—7.55 (10H, m, Ar-H).

Ethyl 2-(*N*-Benzyl-*N*-methylamino)-2-propionate was synthesized similarly. A light yellow oil (98%). IR (neat) cm^{-1}: 1730 (CO). MS m/z: 221 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, t, J = 6 Hz, $COOCH_2CH_3$; d, J = 6 Hz, $NCHCH_3$), 2.30 (3H, s, CH_3), 3.45 (1H, quar, J = 6 Hz, $NCHCH_3$), 3.61, 3.75 (1H × 2, d × 2, J = 12 Hz, NCH_2Ph), 4.20 (2H, quar, J = 6 Hz, $COOCH_2CH_3$), 6.89—7.42 (5H, m, Ar-H).

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