Novel 2-Amino-1,4-dihydropyridine Calcium Antagonists. I. Synthesis and Antihypertensive Effects of 2-Amino-1,4-dihydropyridine Derivatives Having Nitroxyalkoxycarbonyl Groups at 3- and/or 5-Position

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Novel 2-amino-1,4-dihydropyridine derivatives, which contain nitroxy-alkoxycarbonyl groups at the 3- and/or 5-position, were synthesized and their pharmaceutical effect was evaluated in spontaneously hypertensive rats. The structure–activity relationships are discussed in terms of potency, onset-rapidity, and duration of antihypertensive activity. Remarkably prolonged duration of antihypertensive action was observed when a tertiary amino group was introduced on either side of an ester chain.

Key words 1,4-dihydropyridine; calcium antagonist; antihypertensive effect; spontaneously hypertensive rat; structure–activity relationship

Nifedipine (Nif)[1] and nicardipine (Nic),[2] 1,4-dihydropyridine (DHP) calcium antagonists, are clinically very useful antihypertensives and many other analogs are also under development. Some of them are designed so as to provide an additional action favorable for lowering the blood pressure, such as antithrombotic,[3] α-adrenolytic,[4] and organic nitrite vasodilating effects.[5]

The vasodilating effects of alkyl nitrite particularly attracted our interest because its blood pressure-controlling action seemed to be more direct. Therefore, the introduction of a nitroxy group into the ester side chain of the DHP ring was examined. An amino group was also introduced into the ring at the 2-position instead of a methyl group in order to increase the hydrophilicity, which is required for gradual-onset and long-lasting antihypertensive activity.[6] Few 2-amino-1,4-dihydropyridine derivatives have been reported because of the difficulty in synthesizing the precursors, amidinoacetates.[5a,7]

Here we report the antihypertensive effects of newly synthesized 2-amino-1,4-dihydropyridine derivatives having nitroxyalkoxycarbonyl groups at the 3- and/or 5-position of the DHP ring, with special attention to the onset profile and the duration of action in spontaneously hypertensive rats (SHR).

Chemistry

2-Amino-1,4-dihydropyridine derivatives I were synthesized by the modified Hantzsch reaction[8] with amidinoacetates II and benzylideneacetoacetates III as shown in Chart 1. The results are listed in Tables 1 and 2.

The syntheses of the amidinoacetates II were achieved by the reaction of imidates VI with ammonium chloride.[9] 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 acetate in acetonitrile; this afforded better yields of II, which were then subjected to the next step without further purification due to their high hygroscopicity. The treatment of cyanoacetates V with ethyl or isopropyl alcohol in the presence of hydrogen chloride gave compounds VI, which were also subjected to the next reaction without further purification. Esterification of cyanoacetic acid with alcohols IV led to the cyanoacetates V as shown in Chart 2.

The benzylideneacetoacetates III, the other important synthetic intermediates, were obtained through the Knoevenagel reaction by employing acetoacetates VII and substituted benzaldehydes.[10] The acetoacetates VII were easily obtained by the reaction of the alcohols IV with diketene (Chart 3).[2,11]

The nitroxy-substituted alcohols IV were prepared either by the reaction of the corresponding haloalcohols with silver nitrate[12] or by the nitration of epoxides (or alcohols) with nitric acid.[13]

Pharmacology

Antihypertensive Effects in Conscious 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 *via* the left femoral artery for the

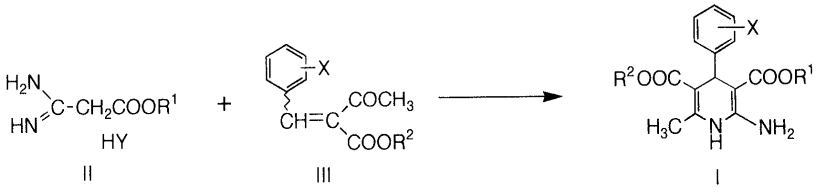

Chart 1

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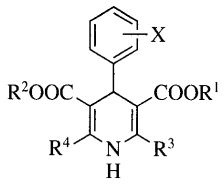
Table 1. Physical Properties and Antihypertensive Effects of 1,4-Dihydropyridines I



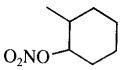
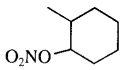
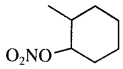
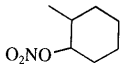
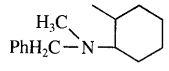
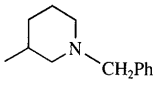
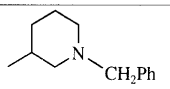
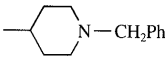
No.	X	R^1	R^2	R^3	R^4	Yield (%)	mp (°C) [RS][e]	Formula[a]	Antihypertensive effects[b]					
									Dose (mg/kg)	*dBP* (%)	T_{max} (h)	$T_{1/2}$ (h)	12 h*A*[c] (mmHg·%)	24 h*A*[d] (mmHg·%)
1	3-NO_2	$(CH_2)_3ONO_2$	$(CH_2)_3ONO_2$	NH_2	CH_3	65.9	145—146	$C_{20}H_{23}N_5O_{12}$	3	−30	4.0	7.6	−211	−230
2	3-NO_2	$(CH_2)_3ONO_2$	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	51.7	Oil	—	3	−20	4.0	7.2	−131	−129
3	3-NO_2	$(CH_2)_3ONO_2$	$CH_2CH_2ONO_2$	NH_2	CH_3	51.8	146—147	$C_{19}H_{21}N_5O_{12}$	3	−29	6.0	8.1	−164	−121
4	3-NO_2	$(CH_2)_3ONO_2$	CH_3	NH_2	CH_3	63.8	177—179 [T]	$C_{18}H_{20}N_4O_9$	3	−27	1.0	4.6	−118	−130
5	3-NO_2	$CH_2CH(CH_3)ONO_2$	$(CH_2)_3ONO_2$	NH_2	CH_3	43.5	47—56 [iPE]	$C_{20}H_{23}N_5O_{12}$	3	−14	0.5	1.0	+23	+13
6	3-NO_2	$(CH_2)_3ONO_2$		NH_2	CH_3	77	65—69	$C_{23}H_{27}N_5O_{12}$	3	−16	8.0	10.8	−139	−143
7	3-NO_2		n-C_6H_{13}	NH_2	CH_3	39.4	65—68	$C_{26}H_{33}N_4O_9$ ·1/2HCl	3	−17	7.0	9.5	−123	−122
8	3-NO_2		$CH(CH_3)_2$	NH_2	CH_3	49.3	94—98	$C_{23}H_{28}N_4O_9$ ·1/2HCl	3	−21	1.0	4.5		
9	3-NO_2	$(CH_2)_6ONO_2$	$(CH_2)_6ONO_2$	NH_2	CH_3	86.3	113—115	$C_{26}H_{35}N_5O_{12}$	1	−8	8.0	1.5		
10	3-NO_2	$(CH_2)_6ONO_2$	n-C_6H_{13}	NH_2	CH_3	62.7	62—65 [T–H]	$C_{26}H_{36}N_4O_9$ ·H_2O	1	−14	6.0	9.7		
11	3-NO_2	$(CH_2)_6ONO_2$	$CH(CH_3)_2$	NH_2	CH_3	93.1	125—127.5	$C_{23}H_{30}N_4O_9$	1	−34	3.0	7.6		
12	3-NO_2	$(CH_2)_6ONO_2$	CH_3	NH_2	CH_3	66.7	124—125	$C_{21}H_{26}N_4O_9$	1	−26	0.8	3.5		
13	2-NO_2	$(CH_2)_3ONO_2$	$CH_2CH_2ONO_2$	NH_2	CH_3	37.4	Oil	—	3	−14	0.5	8.7	−110	−115
14	2-NO_2	$(CH_2)_3ONO_2$	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	29.7	52—65 [iPE]	$C_{20}H_{23}N_5O_{12}$	3	−18	0.8	6.7	−138	−156
15	2,3-Cl_2	$(CH_2)_3ONO_2$	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	48.8	Oil	—	3	−19	2.0	5.7	−100	−104
16	2,3-Cl_2	$CH_2CH(CH_3)ONO_2$	$(CH_2)_3ONO_2$	NH_2	CH_3	28.0	60—64	$C_{20}H_{22}C_{12}N_4O_{10}$	3	−13	9.0	11.2	−105	−153
17	3-CN	$(CH_2)_3ONO_2$	$(CH_2)_3ONO_2$	NH_2	CH_3	16	160—161 [T]	$C_{21}H_{23}N_5O_{10}$	3	−14	3.0	6.6	−79	−79
18	3-NO_2	CH_2CH_3	$CH_2CH_2ONO_2$	NH_2	CH_3	66	179—180	$C_{18}H_{20}N_4O_9$	3	−22	2.0	4.4	−79	−70
19	3-NO_2	CH_2CH_3	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	54	171—173	$C_{19}H_{22}N_4O_9$	3	−31	3.0	6.4	−203	−236
20	3-NO_2	CH_2CH_3	$(CH_2)_6ONO_2$	NH_2	CH_3	79.3	106—108	$C_{22}H_{28}N_4O_9$	3	−42	4.0	11.4	−384	−483
21	3-NO_2	CH_2CH_3		NH_2	CH_3	82	88—91	$C_{22}H_{26}N_4O_9$ ·HCl	3	−22	5.0	14.8	−206	−274
22	3-NO_2	$CH(CH_3)_2$	$(CH_2)_3ONO_2$	NH_2	CH_3	62	114—115	$C_{20}H_{24}N_4O_9$	3	−22	4.0	6.4	−129	−157
23	2-NO_2	CH_2CH_3	$CH_2CH_2ONO_2$	NH_2	CH_3	56	Oil	—	3	−24	1.0	5.0	−137	−165
24	2-NO_2	CH_2CH_3	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	28.5	78—81	$C_{19}H_{23}ClN_4O_9$	3	−40	0.5	4.2	−187	−213
25	2,3-Cl_2	CH_2CH_3	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	40	71—73	$C_{19}H_{22}Cl_2N_3O_7$	3	−21	5.0	9.4	−179	−179
26	2,3-Cl_2	CH_2CH_3	$(CH_2)_3ONO_2$	NH_2	CH_3	64	62—63	$C_{19}H_{22}Cl_2N_3O_7$	3	−18	7.0	9.6	−138	−114
27	3-CF_3	CH_2CH_3	$CH_2CH(CH_3)ONO_2$	NH_2	CH_3	40	59—61	$C_{20}H_{22}F_3N_3O_7$	3	−12	0.8	3.6	−37	−33
28	3-CF_3	CH_2CH_3	$(CH_2)_3ONO_2$	NH_2	CH_3	61	20	$C_{20}H_{22}F_3N_3O_7$	3	−15	0.8	2.2	−101	−157
29	2-CF_3	CH_2CH_3	$(CH_2)_3ONO_2$	NH_2	CH_3	12	25	$C_{20}H_{22}F_3N_3O_7$	3	−28	4.0	10.6	−246	−321
30	3-CN	CH_2CH_3	$(CH_2)_3ONO_2$	NH_2	CH_3	30	143—144	$C_{20}H_{22}N_4O_7$	3	−22	1.0	3.0	−50	−62
31	3-NO_2	$(CH_2)_3ONO_2$	$CH_2CH_2N(CH_3)CH_2Ph$	NH_2	CH_3	17.9	53—56	$C_{27}H_{31}N_5O_9$	3	−7	23.0	>24.0	−30	−63
32	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$	$(CH_2)_3ONO_2$	NH_2	CH_3	11	Oil	—	3	−17	8.0	12.0	−164	−210
33	3-NO_2	$CH_2CH_2N(CH_3)CH_2Ph$	$(CH_2)_6ONO_2$	NH_2	CH_3	81.5	71—74	$C_{30}H_{37}N_5O_9$ ·2HCl	3	+9	0.3	0.4	−7	
34	3-NO_2	$CH(CH_3)CH_2N(CH_3)CH_2Ph$	$(CH_2)_6ONO_2$	NH_2	CH_3	30.2	58—60	$C_{31}H_{39}N_5O_9$ ·2HCl·H_2O	1	−16	1.0	1.4		
35	3-NO_2		$(CH_2)_6ONO_2$	NH_2	CH_3	14.2	100—102	$C_{34}H_{43}N_5O_9$ ·2HCl	1	−11	0.5	0.8		
36F1[f]	3-NO_2		$(CH_2)_6ONO_2$	NH_2	CH_3	20	102—105	$C_{32}H_{39}N_5O_9$ ·2HCl	3	−29	8.0	17.3	−299	−425

Table 1. (continued)

No.	X	R¹	R²	R³	R⁴	Yield (%)	mp (°C) [RS][e]	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·%)
36F2[f]	3-NO_2		$(CH_2)_6ONO_2$	NH_2	CH_3	20	111—115	$C_{32}H_{39}N_5O_8 \cdot 2HCl$	3	−27	5.0	13.1	−229	−264
37	3-NO_2		$(CH_2)_6ONO_2$	NH_2	CH_3	38.3	129—131	$C_{32}H_{39}N_5O_9 \cdot 2HCl$	3	−8	4.0	7.4		
38	2,3-Cl_2	$CH_2CH_2N(CH_3)CH_2Ph$	$(CH_2)_3ONO_2$	NH_2	CH_3	60	104—106	$C_{27}H_{30}Cl_2N_4O_7 \cdot 2HCl$	3	−28	1.0	9.4	−216	−267
39	3-NO_2	CH_2CH_3	$(CH_2)_3ONO_2$	NH_2	CH_3				3	−32	2.0	5.8	−203	−204
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
Nic	3-NO_2	CH_3	$CH_2CH_2N(CH_3)CH_2Ph$	CH_3	CH_3				3	−31	0.8	5.3	−175	−178
Amlo	2-Cl	CH_3	CH_2CH_3	$CH_2OCH_2CH_2NH_2$	CH_3				3	−35	4.0	15.0	−347	−475
									1	−22	5.0	11.4	−194	−235
Nilv	3-NO_2	CH_3	$CH(CH_3)_2$	CN	CH_3				3	−28	0.3	7.6	−203	−189

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*) Compounds I were administered as a single dose in a conscious SHR (*p.o.*). *c*) Area under the mean blood pressure curve to 12 h after dosage. *d*) Area under the mean blood pressure curve to 24 h after dosage. *e*) Solvents for recrystallization. T: toluene, iPE: isopropyl ether, H: *n*-hexane, Ac: ethyl acetate, E: diethyl ether. *f*) 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*)	^{1}H-NMR ($CDCl_3$) δ (ppm)
1	3460 3380	1670	523 (M^+-2)	1.92—2.09 (4H, m, $CH_2CH_2CH_2ONO_2$), 2.33 (3H, s, C6-CH_3), 3.97—4.20 (4H, m, $COOCH_2$–), 4.33—4.43 (4H, m, –CH_2ONO_2), 4.91 (1H, s, C4-H), 6.73 (2H, br s, NH_2), 7.34—8.08 (4H, m, Ar-H), 8.47 (1H, br s, NH)
2	3450 3350	1710 1670	523 (M^+-2)	1.21—1.38 (3H, m, $CH_2CH(ONO_2)CH_3$), 1.95—2.13 (2H, m, $CH_2CH_2CH_2ONO_2$), 2.36 (3H, s, C6-CH_3), 4.0—4.20 (4H, m, $COOCH_2$), 4.35—4.46 (2H, t, J=6 Hz, CH_2ONO_2), 4.94 (1H, s, C4-H), 5.20—5.35 (1H, m, $CH_2CH(ONO_2)CH_3$), 6.27, 6.36 (2H, br s, NH_2), 6.80 (1H, br s, NH), 7.35—8.25 (4H, m, Ar-H)
3	3200 3130	1690	509 (M^+-2)	1.99 (2H, quin., J=6 Hz), $CH_2CH_2CH_2ONO_2$), 2.33 (3H, s, C6-CH_3), 3.95—4.40 (6H, m, $COOCH_2CH_2ONO_2$, $CH_2CH_2CH_2ONO_2$), 4.57—4.70 ($COOCH_2CH_2ONO_2$), 4.90 (1H, s, C4-H), 6.75 (2H, br s, NH_2), 7.30—8.10 (4H, m, Ar-H), 8.55 (1H, br s, NH) [P][a]
4	—	—	434 (M^+-2)	1.99 (2H, quin., J=6 Hz, $CH_2CH_2CH_2ONO_2$), 2.33 (3H, s, C6-CH_3), 3.62 (3H, s, $COOCH_3$), 3.95—4.20 (2H, m, $COOCH_2$), 4.31 (2H, t, J=6 Hz, $CH_2CH_2CH_2ONO_2$), 4.92 (1H, s, C4-H), 6.60 (1H, br s, NH), 6.70 (2H, br s, NH_2), 7.30—8.15 (4H, m, Ar-H)
5	3400 3300 3175	1675	523 (M^+-2)	1.20—1.50 (3H, m, $CH_2CH(ONO_2)CH_3$), 1.90—2.10 (2H, m, $CH_2CH_2CH_2ONO_2$), 2.40 (3H, s, C6-CH_3), 3.95—4.50 (6H, m, $CH_2CH_2CH_2ONO_2$, $CH_2CH(ONO_2)CH_3$), 4.95 (1H, s, C4-H), 5.10—5.40 (1H, m, $CH_2CH(ONO_2)CH_3$), 6.60, 6.65 (2H, br s, NH_2), 7.00—8.15 (5H, m, Ar-H, NH)
6	—	1740	518 (M^+-NO_2)	0.95—2.00 (8H, m, CH_2(c. Hex.)[b]), 2.05 (2H, m, $CH_2CH_2CH_2ONO_2$), 2.35, 2.38 (3H, s×2, C6-CH_3), 4.15 (2H, m, $CH_2CH_2CH_2ONO_2$), 4.40 (2H, m, $CH_2CH_2CH_2ONO_2$), 4.80 (1H, m, COOCH), 4.86, 4.92 (1H, s×2, C4-H), 5.19 (1H, m, $CHONO_2$), 6.20 (2H, br s, NH_2), 6.28 (1H, br s, NH), 7.14—8.16 (4H, m, Ar-H) [free][c]
7	3450 3330	1680	500 (M^+-NO_2)	0.78—1.00 (3H, m, $(CH_2)_5CH_3$), 1.05—2.30 (16H, m, $CH_2(CH_2)_4CH_3$, CH_2 (c.Hex)[b]), 2.36 (3H, s, C6-CH_3), 3.95—4.15 (2H, m, $CH_2C_5H_{11}$), 4.65—5.10 (3H, m, C4-H, $COOCHCHONO_2$), 6.00, 6.10 (1H, br, NH), 6.15, 6.21 (2H, br, NH_2), 7.15—8.20 (4H, m, Ar-H) [free][c]
8	3450 3330	1680	457 (M^+-HNO_2)	0.80—2.20 (14H, m, $CH(CH_3)_2$, CH_2 (c. Hex)[b]), 2.36 (3H, s, C6-CH_3), 4.65—5.10 (4H, m, $CH(CH_3)_2$, C4-H, $COOCHCHONO_2$), 5.91, 5.98 (1H, br, NH), 6.12, 6.20 (2H, br, NH_2), 7.15—8.20 (4H, m, Ar-H) [free][c]
9	3470 3360 3330	1720	607 (M^+-2)	1.15—1.90 (16H, m, $CH_2(CH_2)_4CH_2$), 2.33 (3H, s, C6-CH_3), 3.92—4.15 (4H, m, $COOCH_2$), 4.45 (4H, t, J=6 Hz, CH_2ONO_2), 4.98 (1H, s, C4-H), 6.18 (2H, br s, NH_2), 6.25 (1H, br s, NH), 7.30—8.15 (4H, m, Ar-H)
10	3420 3350 3320	1680 1660	502 (M^+-NO_2)	0.75—2.15 (19H, m, CH_2–C_5H_{11}, $CH_2(CH_2)_4CH_2$), 2.37 (3H, s, C6-CH_3), 3.90—4.15 (4H, m, $COOCH_2$), 4.35—4.55 (2H, m, CH_2ONO_2), 4.90 (1H, s, C4-H), 6.20 (2H, br s, NH_2), 7.25—8.15 (5H, m, NH, Ar-H)
11	3460 3330	1675	460 (M^+-NO_2)	0.90—1.95 (14H, m, $CH(CH_3)_2$, $CH_2(CH_2)_4CH_2$), 2.33 (3H, s, C6-CH_3), 3.90—4.15 (2H, m, $COOCH_2$), 4.42 (2H, t, J=6 Hz, CH_2ONO_2), 4.85—5.05 (2H, m, C4-H, $CH(CH_3)_2$), 6.20 (3H, br, NH_2, NH), 7.25—8.15 (4H, m, Ar-H)
12	3430 3350	1680 1660	476 (M^+-290)	1.15—1.48 (4H, m, $(CH_2)_2CH_2CH_2(CH_2)_2$), 1.50—1.80 (4H, m, $CH_2CH_2(CH_2)_2CH_2CH_2$), 2.34 (3H, s, C6-CH_3), 3.65 (3H, s, OCH_3), 3.90—4.12 (2H, m, $COOCH_2$), 4.42 (2H, t, J=6 Hz, CH_2ONO_2), 4.99 (1H, s, C4-H), 6.15 (3H, br s, NH, NH_2), 7.30—8.15 (4H, m, Ar-H)

Table 2. (continued)

No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS (*m/z*)	^{1}H-NMR ($CDCl_3$) δ (ppm)
13	3450 3325	1700 1670	509 (M^+-2)	1.85—2.13 (2H, m, $CH_2C\underline{H}_2CH_2ONO_2$), 2.30 (3H, s, C6-$CH_3$), 3.85—4.45 (6H, m, $COOC\underline{H}_2$-CH_2ONO_2, $COOC\underline{H}_2CH_2C\underline{H}_2ONO_2$), 4.53—4.65 (2H, m, $COOCH_2C\underline{H}_2ONO_2$), 5.70 (1H, s, C4-H), 6.40 (2H, br s, NH_2), 6.80 (1H, br s, NH), 7.15—8.80 (4H, m, Ar-H)
14	3350 3120	1700 1670	523 (M^+-2)	1.15—1.40 (3H, m, $CH_2CH(ONO_2)C\underline{H}_3$), 1.85—2.20 (2H, m, $CH_2CH_2ONO_2$), 2.30 (3H, s, C6-CH_3), 3.90—4.70 (6H, m, $C\underline{H}_2CH(ONO_2)CH_3$, $COOC\underline{H}_2CH_2C\underline{H}_2ONO_2$), 5.15—5.40 (1H, m, $CH_2C\underline{H}(ONO_2)CH_3$), 5.69 (1H, s, C4-H), 6.50 (2H, br s, NH_2), 7.00 (1H, br s, NH), 7.10—8.00 (4H, m, Ar-H)
15	3475 3350	1710 1670	547 (M^+-2)	1.13—1.40 (3H, m, $CH_2CH(ONO_2)C\underline{H}_3$), 1.90—2.10 (2H, m, $CH_2C\underline{H}_2CH_2ONO_2$), 2.30 (3H, s, C6-$CH_3$), 3.85—4.35 (6H, m, $C\underline{H}_2CH(ONO_2)CH_3$, $COOC\underline{H}_2CH_2C\underline{H}_2ONO_2$), 5.05—5.20 (1H, m, $CH_2C\underline{H}(ONO_2)CH_3$), 5.30 (1H, s, C4-H), 5.99 (1H, br s, NH), 6.16 (2H, br s, NH_2), 7.00—7.40 (3H, m, Ar-H)
16	3400 3380 3160	1700 1670	547 (M^+-2)	1.10—1.45 (3H, m, $CH_2CH(ONO_2)C\underline{H}_3$), 1.85—2.10 (2H, m, $CH_2C\underline{H}_2CH_2ONO_2$), 2.32 (3H, s, C6-$CH_3$), 3.85—4.40 (6H, m, $C\underline{H}_2CH(ONO_2)CH_3$, $COOC\underline{H}_2CH_2C\underline{H}_2ONO_2$), 5.15—5.40 (2H, m, $CH_2C\underline{H}(ONO_2)CH_3$, C4-$\underline{H}$), 6.70 (2H, br s, NH_2), 6.90—7.60 (4H, m, NH, Ar-H)
17	—	—	503 (M^+-2)	2.00 (4H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2ONO_2$), 2.34 (3H, s, C6-H), 3.93—4.21 (4H, m, $COOCH_2$), 4.40 (4H, quin., $J=6$ Hz, CH_2ONO_2), 4.81 (1H, s, C4-H), 6.75 (2H, br s, NH_2), 7.28—7.57 (4H, m, Ar-H), 8.59 (1H, br s, NH)
18	—	—	434 (M^+-2)	1.12 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 2.30 (3H, s, C6-CH_3), 3.94 (2H, m, $COOC\underline{H}_2CH_3$), 4.24 (2H, m, $COOC\underline{H}_2CH_2ONO_2$), 4.63 (2H, m, CH_2ONO_2), 4.83 (1H, s, C4-H), 6.73 (2H, br s, NH_2), 7.40—8.03 (4H, m, Ar-H), 8.82 (1H, br s, NH)
19	—	—	448 (M^+-2)	1.08—1.37 (6H, m, $COOCH_2C\underline{H}_3$, $CH_2CH(ONO_2)C\underline{H}_3$), 2.36 (3H, s, C6-$CH_3$), 3.14—4.33 (4H, m, $COOCH_2$), 4.92 (1H, s, C4-H), 5.24 (1H, m, $CH_2C\underline{H}(ONO_2)CH_3$), 6.62 (3H, br s, NH, NH_2), 7.52—8.46 (4H, m, Ar-H)
20	3460 3365	1705 1670	491 (M^+-2)	1.18—1.70 (8H, m, $OCH_2(C\underline{H}_2)_4CH_2ONO_2$), 1.22(3H, t, $J=8$ Hz, $COOCH_2C\underline{H}_3$), 2.37 (3H, s, C6-CH_3), 3.95—4.14 (4H, m, $COOCH_2$), 4.42 (2H, t, $J=8$ Hz, CH_2ONO_2), 4.98 (1H, s, C4-H), 5.97 (1H, br s, NH), 6.08 (2H, br s, NH_2), 7.30—8.15 (4H, m, Ar-H)
21	—	1740	488 (M^+-2)	0.92—2.50 (8H, m, CH_2 (c.Hex.)[b]), 1.24 (3H, t, $J=8$ Hz, $COOCH_2C\underline{H}_3$), 2.34, 2.37 (3H, s×2, C6-CH_3), 4.08 (2H, m, $COOC\underline{H}_2CH_3$), 4.76 (1H, m, $COOC\underline{H}CHONO_2$), 4.88, 4.92 (1H, s×2, C4-H), 5.14 (1H, m, $COOCHC\underline{H}ONO_2$), 6.11 (2H, br s, NH_2), 6.19 (1H, br s, NH), 7.14—8.13 (4H, m, Ar-H)
22	—	—	—	1.09, 1.30 (3H×2, d×2, $CH(C\underline{H}_3)_2$), 2.00 (2H, quin., $J=6$ Hz, $OCH_2C\underline{H}_2ONO_2$), 2.35 (3H, s, C6-$CH_3$), 4.12 (1H, Hept., $J=6$ Hz, $C\underline{H}(CH_3)_2$), 4.35 (2H, t, $J=6$ Hz, $COOCH_2$), 4.95 (3H, m, C4-H, CH_2ONO_2), 6.23 (2H, br s, NH_2), 6.59 (1H, br s, NH), 7.30—8.14 (4H, m, Ar-H)
23	3450	1700	437 ($M^+ + 1$)	—
24	—	1700	450 (M^+)	—
25	—	—	471 (M^+-2)	1.19 (3H, t, $J=8$ Hz, $COOCH_2C\underline{H}_3$), 1.26 (3H, d, $J=8$ Hz, $COOCH_2CH(ONO_2)C\underline{H}_3$), 1.28 (3H, s, C6-$CH_3$), 3.93—4.37 (4H, m, $COOC\underline{H}_2CH_3$, $COOC\underline{H}_2CH(ONO_2)CH_3$), 5.17—5.38 (1H, m, $COOCH_2C\underline{H}(ONO_2)CH_3$), 5.30 (1H, s, C4-H), 6.26 (2H, br s, NH_2), 6.70 (1H, br s, NH), 6.98—7.39 (3H, m, Ar-H)
26	—	—	473 (M^+)	1.19 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 2.02 (2H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2ONO_2$), 2.31 (3H, s, C6-$CH_3$), 3.99—4.37 (6H, m, $COOC\underline{H}_2CH_3$, $COOC\underline{H}_2CH_2C\underline{H}_2ONO_2$), 5,33 (1H, s, C4-H), 6.09 (1H, br s, NH), 6.14 (2H, br s, NH_2), 7.00—7.32 (3H, m, Ar-H)
27	—	—	471 (M^+-2)	1.21 (3H, t, $J=7$ Hz, $CH_2CH(ONO_2)C\underline{H}_3$), 1.27 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 2.36 (3H, s, C6-CH_3), 3.92—4.25 (4H, m, $COOC\underline{H}_2CH(ONO_2)CH_3$, $COOC\underline{H}_2CH_3$), 4.90 (1H, s, C4-H), 5.21 (1H, m, $COOCH_2C\underline{H}(ONO_2)CH_3$), 6.10 (2H, br s, NH_2), 6.23 (1H, br s, NH), 7.21—7.57 (3H, m, Ar-H)
28	—	—	473 (M^+)	1.23 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 2.02 (2H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2ONO_2$), 2.29 (3H, s, C6-$CH_3$), 3.98—4.36 (6H, m, $COOC\underline{H}_2CH_3$, $COOC\underline{H}_2CH_2ONO_2$), 4.90 (1H, s, C4-H), 6.24 (2H, br s, NH_2), 6.89 (1H, br s, NH), 7.24—7.65 (3H, m, Ar-H)
29	3450 3320	1710 1670	471 (M^+-2)	1.14 (3H, t, $J=6$ Hz, $COOCH_2C\underline{H}_3$), 1.99 (2H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2ONO_2$), 2.20 (3H, s, C6-$CH_3$), 3.90—4.25 (4H, m, $COOCH_2$), 4.31 (2H, t, $J=6$ Hz, CH_2ONO_2), 5.48 (1H, s, C4-H), 6.31 (3H, br s, NH_2), 6.90 (1H, br s, NH), 7.10—7.73 (4H, m, Ar-H)
30			428 (M^+-2)	1.24 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 2.00 (2H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2ONO_2$), 2.39 (3H, s, C6-$CH_3$), 4.01—4.24 (4H, m, $COOCH_2$), 4.34 (2H, t, $J=6$ Hz, CH_2ONO_2), 4.89 (1H, s, C4-H), 6.11 (2H, br s, NH_2), 6.22 (1H, br s, NH), 7.24—7.59 (4H, m, Ar-H)
31	—	—	569 (M^+)	1.83—2.05 (2H, m, $CH_2C\underline{H}_2CH_2ONO_2$), 2.25 (3H, s, NCH_3), 2.30 (3H, s, C6-CH_3), 2.65—2.75 (2H, m, $CH_2C\underline{H}_2N$), 3.56 (2H, s, NCH_2Ph), 4.00—4.40 (6H, m, $COOC\underline{H}_2CH_2C\underline{H}_2C\underline{H}_2ONO_2$, $COOC\underline{H}_2CH_2N$), 4.99 (1H, s, C4-H), 6.30 (2H, br s, NH_2), 6.49 (1H, br s, NH), 7.20—8.15 (9H, m, Ar-H)
32	3420 3300	1670	569 (M^+)	1.80 (2H, m, $CH_2C\underline{H}_2CH_2ONO_2$), 2.20 (3H, s, NCH_3), 2.31 (3H, s, C6-CH_3), 2.60—2.75 (2H, m, $COOCH_2C\underline{H}_2N$), 3.51 (2H, s, NCH_2Ph), 3.90—4.40 (6H, m, $COOC\underline{H}_2CH_2C\underline{H}_2ONO_2$, $COOC\underline{H}_2$-CH_2N), 4.99 (1H, s, C4-H), 6.25 (2H, br s, NH_2), 6.80 (1H, br s, NH), 7.15—8.10 (4H, m, Ar-H)
33	—	1750	565 (M^+-NO_2)	1.28 (4H, m, $(CH_2)_2C\underline{H}_2C\underline{H}_2(CH_2)_2$), 1.60 (4H, m, $CH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2$), 2.22 (3H, s, NCH_3), 2.32 (3H, s, C6-CH_3), 2.64 (2H, $J=6$ Hz, $COOCH_2C\underline{H}_2N$), 3.51 (2H, s, NCH_2Ph), 4.00 (2H, m, $COOC\underline{H}_2(CH_2)_5$), 4.16 (2H, m, $COOC\underline{H}_2CH_2N$), 4.39 (2H, t, $J=7$ Hz, CH_2ONO_2), 5.00 (1H, s, C4-H), 6.26 (2H, br s, NH_2), 6.71 (1H, br s, NH), 7.10—8.14 (9H, m, Ar-H)

Table 2. (continued)

No.	IR (KBr) cm^{-1} NH	IR (KBr) cm^{-1} CO	MS (*m/z*)	^{1}H-NMR ($CDCl_3$) δ (ppm)
34	—	—	—	1.10, 1.79 (8H, m, $CH_2(CH_2)_4CH_2$), 1.29 (3H, d, J=7 Hz, $OCHCH_3$), 2.06, 2.25 (3H×2, s×2, C6-CH_3, NCH_3), 2.20—2.50 (2H, m, $OCHCH_2N$), 3.45, 3.69 (1H×2, d×2, J=14 Hz, NCH_2Ph), 4.15 (2H, t, J=6 Hz, $COOCH_2$), 4.40 (2H, t, J=6 Hz, CH_2ONO_2), 4.98 (1H, s, C4-H), 5.07 (1H, m, $OCHCH_3$), 6.28 (2H, br s, NH_2), 6.81 (1H, br s, NH), 7.10—8.14 (9H, m, Ar-H)
35	3440 3320	1680	637 (M^+-2)	0.96—2.00 (16H, m, $CH_2(CH_2)_4CH_2$, CH_2(c.Hex.)), 2.19 (3H, s, NCH_3), 2.39 (3H, s, C6-CH_3), 2.48—2.65 (1H, m, NCH), 3.00, 3.57 (1H×2, d×2, J=14 Hz, NCH_2Ph), 3.95—4.12 (2H, m, OCH_2), 4.41 (2H, t, J=6 Hz, CH_2ONO_2), 4.86—5.10 (1H, m, OCH), 5.05 (1H, s, C4-H), 5.95 (2H, br s, NH_2), 6.86 (1H, br s, NH), 7.05—8.15 (9H, m, Ar-H)
36F1	3450 3300	1640	591 (M^+-NO_2)	1.08—1.78 (16H, m, CH_2 (Pipe.),[b] $OCH_2(CH_2)_4CH_2ONO_2$), 2.38 (3H, s, C6-CH_3), 3.54 (2H, d, J=14 Hz, CH_2Ph), 4.02 (2H, m, $COOCH_2$), 4.40 (2H, t, J=7 Hz, CH_2ONO_2), 4.82 (1H, m, OCH), 4.98 (1H, s, C4-H), 5.68 (1H, br s, NH), 5.98 (2H, br s, NH_2), 7.20—8.15 (9H, m, Ar-H) [free][c]
36F2	3450 3300	1675	591 (M^+-NO_2)	1.14—1.87 (16H, m, CH_2(Pipe.),[b] $OCH_2(CH_2)_4CH_2ONO_2$), 2.38 (3H, s, C6-CH_3), 3.39, 3.52 (2H, d, J=13 Hz, CH_2Ph), 4.02 (2H, m, $COOCH_2$), 4.42 (2H, t, J=7 Hz, CH_2ONO_2), 4.82 (1H, m, OCH), 4.96 (1H, s, C4-H), 5.70 (1H, br s, NH), 6.00 (2H, br s, NH_2), 7.20—8.11 (9H, m, Ar-H)
37	—	—	—	1.12—2.80 (16H, m, CH_2 (Pipe.),[b] $CH_2(CH_2)_4CH_2$), 2.36 (3H, s, C6-CH_3), 3.49 (2H, s, CH_2Ph), 4.19 (2H, t, J=7 Hz, OCH_2), 4.45 (2H, t, J=7 Hz, CH_2ONO_2), 4.76 (1H, m, OCH), 5.03 (1H, s, C4-H), 6.31 (2H, br s, NH_2), 6.64 (1H, br s, NH), 7.16—8.23 (9H, m, Ar-H)
38	—	1750	165 ($M^+-CH_2CH_2N(CH_3)CH_2Ph$)	—

a) NMR spectrum was measured in Polysol solution. *b*) Ring name: c.Hex., cyclohexyl; Pipe., piperidine. *c*) NMR spectrum was measured as the free base.

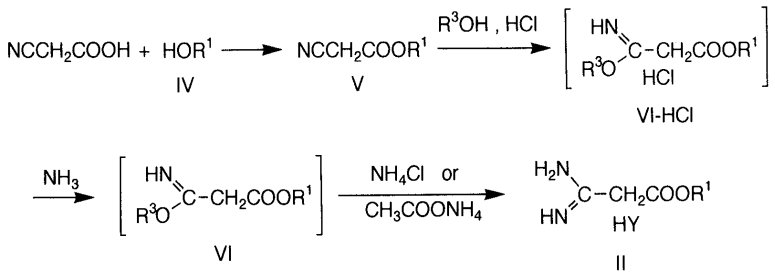


Chart 2

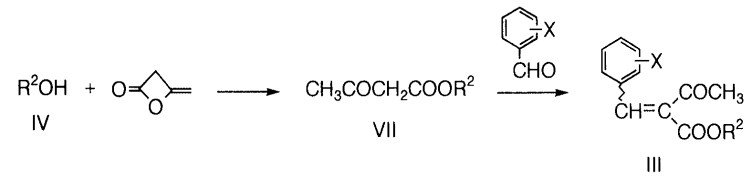


Chart 3

measurement 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 each suspended in 0.3% CMC solution for oral administration. After the blood pressure and heart rate had stabilized, a single oral dose of test compound was given. Blood pressure and heart rate were monitored for up to 24 h after administration.

Results and Discussion

Not many examples of amidinoacetates II have been reported though they are key intermediates in the preparation of 2-amino-1,4-dihydropyridines I. The use of ammonium acetate in acetonitrile for converting imidates VI into the corresponding amidinoacetates II enabled us to increase the yield and led to various 2-amino-1,4-dihydropyridine derivatives I, and their antihypertensive activities 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, nifedipine (Nif), nicardipine (Nic), nilvadipine (Nilv), and CD-349 exhibited high potency, but with rapid appearance of the effect indicating acute onset. On the other hand, pharmacokinetic pa-

rameters for amlodipine (Amlo) showed its potent and long-lasting antihypertensive effect with gradual onset, which is desirable features from the viewpoint of the patients' quality of life.

Effects of 2-amino-1,4-dihydropyridines I on the potency and the mode of action varied considerably depending on the substituents represented by X, R^1, and R^2. Favorable substituents on the 4-phenyl ring were reported to be electron-withdrawing such as a nitro group, a cyano group, a trifluoromethyl group, and a chlorine atom,[14] but the positions were also found to be important.

A 2-nitro group did not affect the duration very much, but greatly influenced appearance of the effect, showing unfavorable rapid onset compared with a 3-nitro group, as shown in I-**13**/I-**3**, I-**14**/I-**2**, and I-**24**/I-**19**. Comparison of I-**28** and I-**29** with I-**39** indicated that a 3-trifluoromethyl group led to a decrease in *dBP*, T_{max}, and $T_{1/2}$ values, while a 2-trifluoromethyl group resulted in larger T_{max} and $T_{1/2}$. 2,3-Dichloro-substituted compounds such as I-**16**, I-**25**, and I-**26** exhibited slower onset and more prolonged duration of action than those with a 3-nitro group, I-**5**, I-**19**, and I-**39**, respectively. A 3-cyano group did not improve the antihypertensive action, comparing I-**17** with I-**1**, and I-**30** with I-**39**.

With regard to the ester side-chain R^1 at the 3-position of DHP, introduction of a 6-nitroxy-hexyl group enhanced the potency, as shown by I-**11** and I-**12** at a dose of 1 mg/kg, and tertiary amino group-containing compounds such as I-**32** and I-**36** exhibited gradual onset and longer duration. For R^2 at the 5-position, a small substituent such as a methyl group (I-**4**, I-**12**) was not effective in increasing the T_{max} and $T_{1/2}$ values. Large substituents such as *n*-hexyl, 6-nitroxyhexyl, 2-nitroxycyclohexyl, and *N*-methyl-*N*-benzylaminoethyl generally resulted in an increase in both T_{max} and $T_{1/2}$. As a whole, remarkably prolonged duration of antihypertensive action was observed, mostly with gradual onset, when a tertiary amino group was introduced on either side of an ester chain (I-**31**, I-**32**, I-**36**). It is also interesting that the mode of drug-action was clearly distinguished when R^1 and R^2 were replaced with each other as in I-**2** and I-**5**, and in I-**31** and I-**32**, indicating that the function of one ester side-chain might be different from that of the other side-chain.

Further study on the optimum combination of substituents on 2-amino-1,4-dihydropyridines **I** is in progress with the aim of finding a potent and long-lasting antihypertensive drug with gradual onset.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet 60 SX spectrometer. Nuclear magnetic resonance (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 electron impact (EI), chemical ionization (CI) or secondary ion mass spectroscopy (SI-MS). 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. 3,5-Bis-(3-nitroxypropyl) 2-Amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate I-1 A solution of 3-nitroxypropyl amidinoacetate acetic acid salt II-**2** (14.76 g), 3-nitroxypropyl 2-(3-nitrobenzylidene)acetoacetate III-**5** (18.8 g), and sodium methoxide (3.0 g) in isopropyl alcohol (500 ml) was refluxed for 1.5 h. After cooling, the precipitate was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, and dried over Na_2SO_4. The solvent was removed under reduced pressure, then the residue was purified by column chromatography on silica gel, and recrystallized from toluene to give I-**1** (19.3 g, 65.9%) as a yellow powder. mp 145—146 °C.

3-(3-Nitroxypropyl) 5-(2-Nitroxycyclohexyl) 2-Amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate I-6 A solution of 3-nitroxypropyl amidinoacetate acetic acid salt II-**2** (0.72 g), 2-nitroxycyclohexyl 2-(3-nitrobenzylidene)acetoacetate III-**8** (1.13 g), and sodium methoxide (0.16 g) in isopropyl alcohol (50 ml) was refluxed for 3 h. After cooling, the precipitate was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, 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-**6** (1.3 g, 77%) as a light yellow powder. mp 65—69 °C.

3-[2-(*N*-Benzyl-*N*-methylamino)ethyl] 5-(6-Nitroxyhexyl) 2-Amino-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate I-33 A solution of 2-(*N*-benzyl-*N*-methylamino)ethyl amidinoacetate acetic acid salt II-**6** (0.77 g), 6-nitroxyhexyl 2-(3-nitrobenzylidene)acetoacetate III-**7** (1.06 g), and sodium methoxide (0.14 g) in isopropyl alcohol (50 ml) was refluxed for 4 h. After cooling, the precipitate was filtered off and the solvent was removed 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 I-**33**-free (0.85 g, 56%) as a light brown oil. The I-**33**-free (0.75 g) was dissolved in chloroform (30 ml), and concentrated HCl (3 ml) was added to the solution. Toluene (200 ml) was then added and the solvent was removed under reduced pressure; this procedure was repeated twice. Next, isopropyl alcohol (100 ml) was added to the residue, and the solvent was removed under reduced pressure to give I-**33** (0.68 g, 81.5%) as a light yellow powder. mp 71—74 °C.

Other 2-amino-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. Ethyl Amidinoacetate Hydrochloride II-1-HCl A solution of ethyl cyanoacetate (28.3 g) and ethyl alcohol (12.0 g) in *n*-hexane (110 ml) was cooled at −30 °C, and anhydrous hydrogen chloride was bubbled into the solution for 1 h. The mixture was allowed to stand overnight on an ice-salt bath. The solvent was decanted, and the residue was washed with diethyl ether to give VI-**1**-HCl as a colorless mass, which was dried under reduced pressure at room temperature. The VI-**1**-HCl was added to a mixture of diethyl ether (300 ml) and a solution of K_2CO_3 (63.9 g) in water (200 ml). The diethyl ether layer was separated and dried over Na_2SO_4, then the solvent was removed under reduced pressure at room temperature to give VI-**1** (30.3 g, 76.1%) as a colorless oil. A mixture of VI-**1** (30 g) and ammonium chloride (10.1 g) in ethyl alcohol (120 ml) was refluxed for 8 h. The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was washed with diethyl ether and dried under reduced pressure at room temperature to give II-**1**-HCl (23.8 g, 76.0%) as colorless crystals. MS *m/z*: 130 (M^+).

Ethyl Amidinoacetate Acetic Acid Salt II-1-AcOH A solution of ethyl cyanoacetate (11.31 g) and ethyl alcohol (5.53 g) in chloroform (300 ml) was cooled in an ice-salt bath, and anhydrous hydrogen chloride was bubbled in until the solution was saturated. The mixture was allowed to stand overnight in a refrigerator. 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 the solution for 1 h. The precipitate was filtered off and the filtrate was evaporated under reduced pressure at room temperature to give VI-**1** as a colorless oil. A mixture of VI-**1** and ammonium acetate (7.71 g) in acetonitrile (100 ml) was stirred at 50—60 °C for 2 h. The solvent was removed under reduced pressure, then the residue was washed with diethyl ether and dried under reduced pressure at room temperature to give II-**1**-AcOH (11.6 g, 60.0%) as colorless needles. mp 104—108 °C. MS *m/z*: 130 (M^+).

3-Nitroxypropyl Amidinoacetate Acetic Acid Salt II-2 A solution of 3-nitroxypropyl cyanoacetate (18.8 g) and isopropyl alcohol (7.21 g) in diethyl ether (250 ml) was cooled on an ice-salt bath and anhydrous hydrogen chloride was bubbled into the solution for 30 min. The mixture was allowed to stand overnight in a refrigerator. The solvent was removed under reduced pressure at room temperature and the residue was

dissolved in diethyl ether (250 ml). The solution was cooled on an ice-salt bath and anhydrous ammonia was bubbled into it for 1 h. The precipitate was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in acetonitrile (150 ml), then ammonium acetate (7.18 g) was added to the solution, and the mixture was heated at 50—60 °C for 1 h. After cooling, the precipitate was filtered off and the solvent was removed under reduced pressure. Diethyl ether was added to the residue, and crystallization was induced by scratching. The crystals were collected by filteration and dried under reduced pressure in a desiccator to give II-**2** (25.22 g, 95.17%) as colorless crystals. MS *m/z*: 206 ($M^+ + 1$).

Other amidinoacetate derivatives II-**3**—II-**6** were also synthesized similarly.

2-Nitroxypropyl Amidinoacetate Acetic Acid Salt II-**3**: Light brown crystals, yield 85.3%. MS *m/z*: 207 ($M^+ + 2$).

6-Nitroxyhexyl Amidinoacetate Acetic Acid Salt II-**4**: Light brown crystals, yield 66.1%. MS *m/z*: 248 ($M^+ + 1$).

2-Nitroxycyclohexyl Amidinoacetate Acetic Acid Salt II-**5**: Light reddish brown crystals, yield 60.3%. MS *m/z*: 245 (M^+).

2-(*N*-Benzyl-*N*-methylamino)ethyl Amidinoacetate Acetic Acid Salt II-**6**: Colorless crystals, yield 52%. MS *m/z*: 250 ($M^+ + 1$).

1-(*N*-Benzyl-*N*-methylamino)propyl-2-yl Amidinoacetate Acetic Acid Salt II-**7**: Colorless crystals, yield 15.5%. MS *m/z*: 264 ($M^+ + 1$).

2-(*N*-Benzyl-*N*-methylamino)cyclohexyl Amidinoacetate Acetic Acid Salt II-**8**: Light brown crystals, yield 31.0%. MS *m/z*: 304 ($M^+ + 1$).

1-Benzylpiperidine-3-yl Amidinoacetate Acetic Acid Salt II-**9**: Light brown crystals, yield 86.0%. MS *m/z*: 276 ($M^+ + 1$).

1-Benzylpiperidine-4-yl Amidinoacetate Acetic Acid Salt II-**10**: Colorless crystals, yield 100%. MS *m/z*: 276 ($M^+ + 1$).

General Procedure for the Synthesis of 2-Benzylideneacetoacetate Derivatives III. Method A: 2-Nitroxyethyl 2-(3-Nitrobenzylidene)acetoacetate III-4 A solution of 3-nitrobenzaldehyde (7.55 g) and 2-nitroxyethyl acetoacetate (9.6 g) in benzene (150 ml) containing a catalytic amount of piperidine was refluxed under azeotropic dehydration for 11 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-**4** (9.71 g, 60%) as colorless crystals. mp 113—116 °C. IR (Nujol) cm^{-1}: 1725, 1690 (CO). MS *m/z*: 324 (M^+). ^{1}H-NMR (Polysol) δ: 2.40 (3H, s, CH_3), 4.59 (2H, t, J=7 Hz, $COOCH_2$), 4.82 (2H, t, J=7 Hz, CH_2ONO_2), 7.55—8.30 (4H, m, Ar-H), 7.75 (1H, s, =CHAr)

Method B: 3-Nitroxypropyl 2-(3-Nitrobenzylidene)acetoacetate III-5 A solution of 3-nitrobenzaldehyde (7.25 g) and 3-nitroxypropyl acetoacetate (9.84 g) containing a catalytic amount of piperidinium acetate in isopropyl alcohol (200 ml) was stirred at 45—55 °C for 10 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give III-**5** (6.9 g, 43%) as a light yellow oil. IR (neat) cm^{-1}: 1720 (CO).

Method C: 2-Nitroxycyclohexyl 2-(3-Nitrobenzylidene)acetoacetate III-8 A solution of 3-nitrobenzaldehyde (3.02 g) and 2-nitroxycyclohexyl acetoacetate (4.9 g) containing a catalytic amount of piperidinium acetate in benzene (8 ml) and methyl alcohol (0.6 ml) was allowed to stand at room temperature for 4 d. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give III-**8** (4.86 g, 64%) as a light brown oil. IR (neat) cm^{-1}: 1730 (CO). MS *m/z*: 379 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.12—2.40 (8H, m, CH_2 (c. Hex.)), 2.48 (3H, s, CH_3), 5.03 (2H, m, $COOCHCH$–ONO_2), 7.15—8.32 (5H, m, =CH–Ar-H).

Other 2-benzylideneacetoacetate derivatives III-**1**—III-**16** were also synthesized similarly.

Methyl 2-(3-Nitrobenzylidene)acetoacetate III-**1**, Method B: Colorless prisms, yield 79%. IR (Nujol) cm^{-1}: 1720 (CO). MS *m/z*: 249 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, s, CH_3CO), 3.94 (3H, s, OCH_3), 7.57—8.33 (5H, m, =CH–Ar-H)

Isopropyl 2-(3-Nitrobenzylidene)acetoacetate III-**2**, Method B: Colorless prisms, yield 65%. mp 91—95 °C. IR (Nujol) cm^{-1}: 1720 (CO). MS (EI) *m/z*: 270 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J=5Hz, $CH(C\underline{H}_3)_2$), 2.45 (3H, s, CH_3CO), 5.28 (1H, hept., J=5 Hz, $C\underline{H}(CH_3)_2$), 7.52—8.41 (5H, m, =CH–Ar-H).

n-Hexyl 2-(3-Nitrobenzylidene)acetoacetate III-**3**, Method C: A light yellow oil, yield 63.4%. III-**3** was not purified, but was subjected directly to the next reaction.

3-Nitroxypropyl 2-(3-Nitrobenzylidene)acetoacetate III-**5**, Method A: A light yellow oil, yield 53.7%. III-**5** was not purified, but was subjected directly to the next reaction.

2-Nitroxypropyl 2-(3-Nitrobenzylidene)acetoacetate III-**6**, Method A: A light yellow oil, yield 48.3%. IR (neat) cm^{-1}: 1720 (CO). MS *m/z*: 339 ($M^+ + 1$).

6-Nitroxyhexyl 2-(3-Nitrobenzylidene)acetoacetate III-**7**, Method B: A yellowish brown oil, yield 88%. IR (neat) cm^{-1}: 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.80 (8H, m, $CH_2(C\underline{H}_2)_4CH_2$), 2.46 (3H, s, CH_3CO), 4.31 (2H, t, J=6 Hz, $COOCH_2$), 4.42 (2H, t, J=6 Hz, CH_2ONO_2), 7.55—8.38 (5H, m, =CH–Ar-H).

3-Nitroxypropyl 2-(3-Trifluoromethylbenzylidene)acetoacetate III-**9**, Method A: A yellow oil, yield 67%. MS *m/z*: 362 ($M^+ + 1$).

2-Nitroxypropyl 2-(3-Trifluoromethylbenzylidene)acetoacetate III-**10**, Method A: A yellow oil, yield 81.8%. MS *m/z*: 362 ($M^+ + 1$).

3-Nitroxypropyl 2-(2-Trifluoromethylbenzylidene)acetoacetate III-**11**, Method A: A light yellow oil, yield 32%. MS *m/z*: 362 ($M^+ + 1$).

3-Nitroxypropyl 2-(3-Cyanobenzylidene)acetoacetate III-**12**, Method A: A yellow oil, yield 38%. MS *m/z*: 318 (M^+).

2-Nitroxyethyl 2-(2-Nitrobenzylidene)acetoacetate III-**13**, Method A: A reddish yellow oil, yield 87.0%. IR (neat) cm^{-1}: 1720 (CO).

2-Nitroxypropyl 2-(2-Nitrobenzylidene)acetoacetate III-**14**, Method B: A yellow oil. III-**14** was not purified, but was subjected directly to the next reaction.

3-Nitroxypropyl 2-(2,3-Dichlorobenzylidene)acetoacetate III-**15**, Method A: A yellow oil, yield 69%. MS *m/z*: 362 (M^+).

2-Nitroxypropyl 2-(2,3-Dichlorobenzylidene)acetoacetate III-**16**, Method A: A yellow oil, yield 85%. MS *m/z*: 362 (M^+).

General Procedure for the Synthesis of Alcohol Derivatives IV. 2-Nitroxyethyl Alcohol IV-1 2-Bromoethyl alcohol (24.2 g) in acetonitrile (50 ml) was added to a solution of silver nitrate (50.96 g) in acetonitrile (200 ml), and the solution was refluxed for 3 h. After cooling, the precipitate was filtered off and washed with acetonitrile. The filtrate was evaporated under reduced pressure, and ice-water and saturated aqueous NaCl were added to the residue. The precipitate was filtered off and washed with chloroform. The filtrate was extracted with chloroform and dried over Na_2SO_4. The solvent was removed under reduced pressure to give IV-**1** (19.2 g, 90.0%) as a colorless liquid. IR (neat) cm^{-1}: 3350 (OH). ^{1}H-NMR ($CDCl_3$) δ: 3.41 (1H, s, OH), 3.93 (2H, t, J=5 Hz, $HOC\underline{H}_2$), 4.61 (2H, t, J=5 Hz, CH_2ONO_2).

Other nitroxy-substituted alcohol derivatives IV-**2** and IV-**4** were also synthesized similarly.

3-Nitroxypropyl Alcohol IV-**2**: A colorless liquid, yield 78.3%. IR (neat) cm^{-1}: 3400 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.97 (2H, quin., J=6 Hz, $CH_2C\underline{H}_2CH_2$), 2.66 (1H, s, OH), 3.75 (2H, t, J=6 Hz, $C\underline{H}_2OH$), 4.60 (2H, t, J=6 Hz, CH_2ONO_2).

6-Nitroxyhexyl Alcohol IV-**4**: A colorless oil, yield quant. IR (neat) cm^{-1}: 3350 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.33—1.50 (4H, m, $C_2H_4(C\underline{H}_2)_2C_2H_4$), 1.50—1.63 (2H, m, $HOCH_2C\underline{H}_2$), 1.68—1.80 (2H, m, $C\underline{H}_2CH_2ONO_2$), 1.90 (1H, s, OH), 3.60—3.68 (2H, m, $HOC\underline{H}_2$), 4.42—4.49 (2H, t, J=7 Hz, CH_2ONO_2).

2-Nitroxycyclohexyl Alcohol IV-5 A solution of concentrated HNO_3 (6.85 ml) and NH_4NO_3 (46.4 g) in water (33.2 ml) was cooled in an ice-bath. 1,2-Epoxycyclohexane (46.4 g) was added dropwise at below 35 °C and the mixture was stirred at room temperature for 2 h, then neutralized with $NaHCO_3$. The organic layer was extracted 3 times with diethyl ether (100 ml). The extract was dried over Na_2SO_4 and the solvent was removed under reduced pressure at room temperature to give IV-**5** (13.05 g, 81.0%) as a colorless liquid. IR (neat) cm^{-1}: 3350 (OH). MS *m/z*: 162 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.28 (8H, m, CH_2), 3.35 (1H, br s, OH), 3.66 (1H, m, CHOH), 4.80 (1H, m, $CHONO_2$).

2-Nitroxypropyl Alcohol IV-3 This compound was synthesized similarly. A colorless liquid, yield 54%. IR (neat) cm^{-1}: 3420 (OH). MS *m/z*: 122 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6 Hz, CH_3), 2.94 (1H, s, OH), 3.69 (1H, dd, J=6, 13 Hz, CH_2), 3.80 (1H, dd, J=5, 13 Hz, CH_2), 5.20 (1H, m, $CHONO_2$).

2-(*N*-Benzyl-*N*-methylamino)ethyl Alcohol IV-6 2-Bromoethyl alcohol (50 g) was added to a mixture of *N*-methylbenzylamine (48.4 g) and K_2CO_3 (110.57 g) in dimethylformamide (DMF) (500 ml) at room temperature, and the mixture was stirred at 60 °C for 9 h, added to water and 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 IV-**6** (38.35 g, 58%) as a colorless liquid. bp 110—120 °C (8 mmHg). IR (neat) cm^{-1}: 3280 (OH). MS *m/z*: 164 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 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).

Other alcohol derivatives IV-**9** and IV-**10** were also synthesized similarly.

1-Benzyl-3-piperidinol IV-**9**: A colorless oil, yield 96%. bp 135—137 °C (5 mmHg). IR (neat) cm^{-1}: 3350 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.43—2.57 (9H, m, CH_2 (Pipe.), OH), 3.53 (2H, s, CH_2Ph), 3.83 (1H, m, $HOC\underline{H}$), 7.30 (5H, m, Ar-H).

1-Benzyl-4-piperidinol IV-**10**: A colorless oil, yield 36%. IR (neat) cm^{-1}: 3325 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.30—2.81 (9H, m, CH_2 (Pipe.), OH), 3.44 (2H, s, CH_2Ph), 3.42—3.72 (1H, m, $HOC\underline{H}$), 7.16 (5H, m, Ar-H).

1-(*N*-Benzyl-*N*-methylamino)-2-propyl Alcohol IV-7 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 IV-**7** (31.53 g, 88%) as a colorless liquid. bp 88—94 °C (3 mmHg). IR (neat) cm^{-1}: 3420 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, $J=6$ Hz, $CHC\underline{H}_3$), 2.22 (3H, s, NCH_3), 2.24—2.46 (2H, m, $CHC\underline{H}_2$), 3.45—3.66 (1H×2, d, $J=12$ Hz, NCH_2Ph), 3.53 (1H, br s, OH), 3.86 (1H, m, $HOC\underline{H}CH_3$), 7.30 (5H, m, Ar-H).

The alcohol derivative IV-**8** was also synthesized similarly.

2-(*N*-Benzyl-*N*-methylamino)cyclohexyl Alcohol IV-**8**: A colorless liquid, yield 37%. bp 134 °C (3 mmHg). IR (neat) cm^{-1}: 3450 (OH). MS *m/z*: 219 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.20 (8H, m, CH_2 (c. Hex.)), 2.18 (3H, s, CH_3), 2.35 (1H, m, NCH), 3.38—3.51 (2H, br s, CH_2Ph), 3.71 (1H, d, $J=16$ Hz, HOCH), 3.99 (1H, br s, OH), 7.31 (5H, m, Ar-H).

General Procedure for the Synthesis of Cyanoacetate Derivatives V. 3-Nitroxypropyl Cyanoacetate V-1 A solution of cyanoacetic acid (17.01 g) and 3-nitroxypropyl alcohol (24.2 g) in benzene (100 ml) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed under azeotropic dehydration for 16 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 V-**1** (30.64 g, 81%) as a colorless oil. IR (neat) cm^{-1}: 2270 (CN), 1770 (CO). MS *m/z*: 189 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 2.15 (2H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2$), 3.62 (2H, s, $NCCH_2$), 4.31 (2H, t, $J=6$ Hz, $COOCH_2$), 4.61 (2H, t, $J=6$ Hz, CH_2ONO_2)

Other cyanoacetate derivatives V-**2**—V-**4** were also synthesized similarly.

2-Nitroxypropyl Cyanoacetate V-**2**: A colorless oil, yield 44.9%. IR (neat) cm^{-1}: 2260 (CN), 1750 (CO).

6-Nitroxypropyl Cyanoacetate V-**3**: A light yellow oil, yield 100%. IR (neat) cm^{-1}: 2260 (CN), 1760 (CO). MS *m/z*: 231 ($M^+ + 1$).

2-Nitroxycyclohexyl Cyanoacetate V-**4**: A light yellow oil, yield 98.7%. IR (neat) cm^{-1}: 2270 (CN), 1755 (CO). MS *m/z*: 229 ($M^+ + 1$).

2-(*N*-Benzyl-*N*-methylamino)ethyl Cyanoacetate V-5 Dicyclohexylcarbodiimide (11.35 g) was added to a solution of cyanoacetic acid (4.25 g) and 2-(*N*-benzyl-*N*-methylamino)ethyl alcohol (8.25 g) in tetrahydrofuran (THF) (500 ml), and the mixture was stirred at room temperature for 5 h. The precipitate was filtered off, and washed with THF. The solvent was removed and the residue was purified by column chromatography on silica gel to give V-**5** as a light yellow oil (5.2 g, 48%). IR (neat) cm^{-1}: 2250 (CN), 1740 (CO). MS *m/z*: 232 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 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)

Other cyanoacetate derivatives V-**6**—V-**9** were also synthesized similarly.

1-(*N*-Benzyl-*N*-methylamino)propyl-2-yl Cyanoacetate V-**6**: A colorless oil, yield 63%. IR (neat) cm^{-1}: 2260 (CN), 1750 (CO). MS *m/z*: 247 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, $J=7$ Hz, $OCHC\underline{H}_3$), 2.28 (3H, s, NCH_3), 2.38 (1H, dd, $J=14$, 5 Hz, $OC\underline{H}CH_2$), 2.61 (1H, dd, $J=14$, 7 Hz, $OC\underline{H}CH_2$), 3.42 (2H, s, $NCCH_2$), 3.49, 3.59 (each 1H, each d, $J=8$ Hz, NCH_2Ph), 5.10—5.32 (1H, m, OCH), 7.20—7.45 (5H, m, Ar-H).

2-(*N*-Benzyl-*N*-methylamino)cyclohexyl Cyanoacetate V-**7**: A light yellow oil, yield 58%. IR (neat) cm^{-1}: 2260 (CN), 1740 (CO). MS *m/z*: 286 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.03—2.46 (8H, m, CH_2 (c. hex.)), 2.30 (3H, s, NCH_3), 3.46 (2H, s, $NCCH_2$), 3.54, 3.68 (each 1H, each d, $J=14$ Hz, NCH_2Ph), 4.60 (1H, dt, $J=4$, 11 Hz, NCH), 4.99 (1H, dt, $J=5$, 11 Hz, OCH), 7.15—7.50 (5H, m, Ar-H).

1-Benzylpiperidine-3-yl Cyanoacetate V-**8**: A light yellow oil, yield 85%. IR (neat) cm^{-1}: 2260 (CN), 1750 (CO). MS *m/z*: 258 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.23—2.84 (8H, m, CH_2 (Pipe.)), 3.45 (2H, s, NCH_2Ph), 3.56 (2H, s, NCCH2), 4.95 (1H, m, OCH), 7.15—7.50 (5H, m, Ar-H).

1-Benzylpiperidine-4-yl Cyanoacetate V-**9**: A yellow oil, yield 87%. ^{1}H-NMR ($CDCl_3$) δ: 1.64—2.78 (8H, m, CH_2 (Pipe.)), 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).

General Procedure for the Synthesis of Acetoacetate Derivatives VII. Isopropyl Acetoacetate VII-1 Diketene (63 g) and triethylamine (5 g) were alternately added dropwise to isopropyl alcohol (30.5 g) at below 40 °C (cooled on an ice-bath), and the mixture was stirred at room temperature for 5 h. Then 2 N HCl (90 ml) was added and the whole was extracted with ethyl acetate. The extract was washed with saturated aqueous Na_2CO_3 and dilute aqueous NaCl solution, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was distilled to give VII-**1** (55.8 g, 77.5%) as a colorless liquid. bp 89—91 °C (35 mmHg). IR (neat) cm^{-1}: 1710 (CO). MS *m/z*: 144 (M^+).

Other acetoacetate derivatives VII-**2**—VII-**7** were also synthesized similarly and isolated by column chromatography on silica gel.

n-Hexyl Acetoacetate VII-2: A colorless oil, yield 69.5%. MS *m/z*: 186 (M^+).

3-Nitroxypropyl Acetoacetate VII-**4**: A reddish yellow oil, yield 90.9%. IR (neat) cm^{-1}: 1740, 1720 (CO). MS *m/z*: 206 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (2H, quin., $J=6$ Hz, $CH_2C\underline{H}_2CH_2$), 2.13 (3H, s, CH_3), 3.48 (2H, s, $COCH_2COO$), 4.26 (2H, t, $J=6$ Hz, $COOCH_2$), 4.56 (2H, t, $J=6$ Hz, CH_2ONO_2).

2-Nitroxypropyl Acetoacetate VII-**5**: A light yellow oil, yield 70.5%. IR (neat) cm^{-1}: 1750, 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, $J=6$ Hz, $CH_2CHC\underline{H}_3$), 2.29 (3H, s, CH_3CO), 3.50 (2H, s, $COCH_2COO$), 4.19 (2H, each d, $J=11$, 6 Hz, $COOCH_2$), 5.35 (1H, m, $CH_2C\underline{H}CH_3$).

6-Nitroxyhexyl Acetoacetate VII-**6**: A light yellow oil, yield 78.2%. IR (neat) cm^{-1}: 1740, 1720 (CO). MS *m/z*: 248 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.52 (4H, m, $(CH_2)_2(C\underline{H}_2)_2(CH_2)_2$), 1.55—1.85 (4H, m, $CH_2C\underline{H}_2(CH_2)_2C\underline{H}_2CH_2$), 2.26 (3H, s, CH_3CO), 3.46 (2H, s, $COCH_2COO$), 4.14 (2H, t, $J=7$ Hz, $COOCH_2$), 4.45 (2H, t, $J=7$ Hz, CH_2ONO_2).

2-Nitroxycyclohexyl Acetoacetate VII-**7**: A colorless oil, yield 79%. IR (neat) cm^{-1}: 1740, 1720 (CO). MS *m/z*: 246 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.40 (8H, m, CH_2 (c. Hex.)), 2.26 (3H, s, CH_3), 3.45 (2H, s, $COCH_2COO$), 4.81—5.10 (2H, m, $COOCHCHONO_2$).

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