INTRODUCTION OF ALKYL GROUPS AT THE α-POSITIONS OF PYRROLIDINES AND PIPERIDINES: SYNTHESIS OF (±)-CONIINE

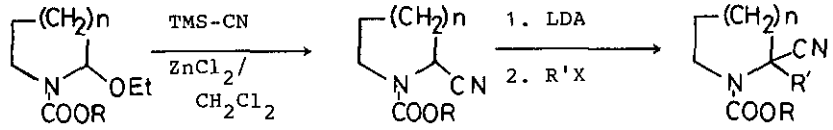
Tatsuo Nagasaka,* Hideki Hayashi, and Fumiko Hamaguchi
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

Abstract — The conversion of lactams to α-alkylated cyclic amines is described. Reactions of α-ethoxyurethanes with trimethylsilyl cyanide in the presence of Lewis acid afford the corresponding α-cyanourethanes, which, *via* carbanion, are alkylated to α-alkyl-α-cyanourethanes in moderate to high yields. Syntheses of (±)-coniine and *trans*-quinolizidine are carried out as model experiments for dealkoxycarbonylation and decyanation of 2-alkyl-1-alkoxycarbonyl-2-cyanopiperidines.

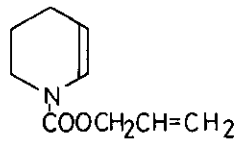
In the preceding paper,[1] a convenient method was reported for introducing various functional groups at the α-position of pyrrolidine derivatives, starting from 2-pyrrolidinone. The reaction of α-cyanopyrrolidine (*via* carbanion) with alkyl halide appears to hold promise as a general method for the carbon-carbon bond formation at the α-position of cyclic amines. The results of experiments conducted in this regard are discussed in the present paper.

α-Cyanourethanes (6-10) were obtained by reactions of the corresponding α-ethoxyurethanes (1-5)[2] with trimethylsilyl cyanide in the presence of zinc chloride. The yields of pyrrolidine derivatives (6, 7) generally exceeded those of piperidine derivatives (8, 9, 10). Those of piperidine series depended on the *N*-alkoxycarbonyl groups; for example, the methoxycarbonyl group afforded the best yield of 8, while *tert*-butoxycarbonyl and allyloxycarbonyl groups, low yields of the objective products (9 and 10), along with by-products (enamines and

Scheme 1



1	n=1, R=Me	6	n=1, R=Me (86%)	13~24
2	n=1, R=Et	7	n=1, R=Et (87%)	
3	n=2, R=Me	8	n=2, R=Me (68%)	
4	n=2, R=Bu-t	9	n=2, R=Bu-t (14%)	
5	n=2, R=$CH_2CH=CH_2$	10	n=2, R=$CH_2CH=CH_2$ (38%)	



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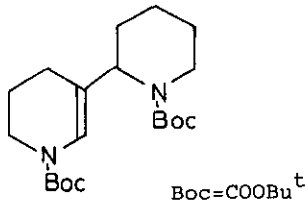

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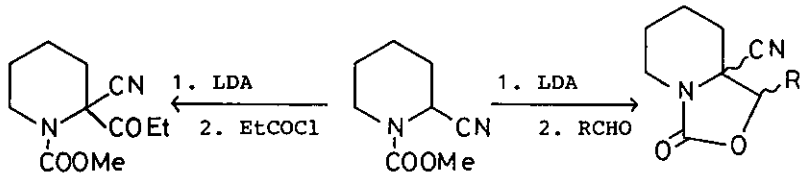
Table I. Reactions of Nitriles (6-10) with Alkyl Halides

Run	Starting Material	R'X	Products	yield(%)
1	6	n-PrI	13 (n=1, R=Me, R'=Pr-n)	38
2	7	n-PrI	14 (n=1, R=Et, R'=Pr-n)	30
3	7	$PhCH_2Br$	15 (n=1, R=Et, R'=CH_2Ph)	29
4	8	n-PrI	16 (n=2, R=Me, R'=Pr-n)	91
5	8	$PhCH_2Br$	17 (n=2, R=Me, R'=CH_2Ph)	64
6	8	MeI	18 (n=2, R=R'=Me)	61
7	8	$Br(CH_2)_3Cl$	19 (n=2, R=Me, R'=$(CH_2)_3Cl$)	65
8	8	$Br(CH_2)_4Cl$	20 (n=2, R=Me, R'=$(CH_2)_4Cl$)	91
9	8	MeCH(Br)COOEt	21 (n=2, R=Me, R'=CH(Me)COOEt)	45*1
10	8	$CH_2=CHCH_2Br$	22 (n=2, R=Me, R'=$CH_2CH=CH_2$)	71
11	8	n-$C_{11}H_{23}I$	23 (n=2, R=Me, R'=$C_{11}H_{23}$-n)	63
12	10	n-PrI	24 (n=2, R=cis-CH=CHMe, R'=Pr-n)	35

*1 diastreoisomers (1:1.2).

dimers, e. g., 11 and 12). Alkylation of α-cyanourethanes (6, 7, 8 and 10) via carbanion with alkyl halides afforded α-alkyl-α-cyanourethanes (13-24) in moderate to high yields, as shown in Scheme 1 and Table I. In this reaction, the piperidine series (Run 4-12) appeared reactive than that of pyrrolidine (Run 1-3). Alkylation of 1-allyloxycarbonyl-2-cyanopyrrolidine (10) caused migration of the double bond of the allyloxycarbonyl group with ordinary alkylation (Run 12). Alkylation using α-bromoester afforded a mixture of diastereomers (21) in 45% yield, that could be separated (Run 9). The reactions of α-cyanourethane (8) with acyl halide and aldehyde are shown in Scheme 2. The rection of 8 with propionyl chloride gave the objective ketone (25) in 31% yield along with numerous by-products. Reactions of 8 with propionaldehyde and benzaldehyde afforded oxazolones (26 and 27, respectively) in high yields; they could be separated to the diastereomers by column chromatography. (The stereochemical assignment of these isomers was not made). 1-Alkoxycarbonyl and 2-cyano groups were removed from 2-alkyl-1-alkoxycarbonyl-2-

Scheme 2



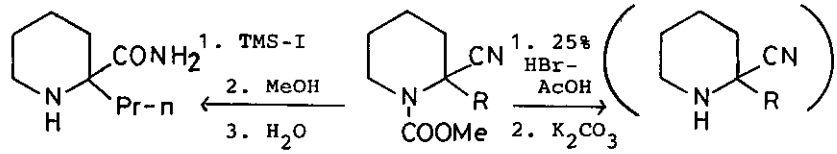
25 31%

8

26 R=Ph (8:7:5) 87%

27 R=Et (2:1) 89%

Scheme 3



28 63%

16 R=Pr-n

20 R=$(CH_2)_4Cl$

29 R=Pr-n

30 R=$(CH_2)_4Cl$

$NaBH_4$

$NaBH_4$

31 67% from 16

32 43% from 20

cyanopiperidine derivatives to give 2-alkylpiperidines, as shown in Scheme 3. Reaction of α-cyanourethane (16) with trimethylsilyl iodide[3] afforded α-carbamoylamine (28). That of α-cyanourethanes (16 and 20) with 25% hydrobromic acid in acetic acid gave the corresponding α-cyanoamines (29 and 30), which were, without purification, reduced with sodium borohydride in ethanol to obtain the α-alkylpiperidines (31 and 32). (±)-Coniine (31) was produced from 16 in 67% total yield and identified as hydrochloride and 3,5-dinitrobenzoate. trans-Quinolizidine (32) was also obtained from 20 in 43% total yield.

The data presented above clearly demonstrate the present method to be effective for bringing about the conversion of lactams to α-alkylated cyclic amines.

EXPERIMENTAL[4]

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on a Hitachi 200-10 and a Hitachi M-80 spectrometer, respectively. ^{1}H-Nmr and ^{13}C-nmr spectra were recorded on a Varian EM-390 and/or a Brucker AM-400 spectrometer. Ir and ^{1}H-nmr spectra of the products are shown in Table II. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. Chromatographic separations were made using a silica gel (Wako-gel C-200) column. Thin-layer chromatography (TLC) was carried out with pre-coated silica gel plates (Kiesel 60 F-254, Merck).

General Procedure for Preparation of 2-Cyanourethanes --- A typical procedure is described for 2-cyano-1-methoxycarbonylpyrrolidine (6) : A solution of ethoxyurethane (1, 173 mg, 1 mmol) in CH_2Cl_2 (1 ml) was added at -10°C to a solution of $ZnCl_2$ (136 mg, 1 mmol) in CH_2Cl_2 (5 ml) under Ar atmosphere. Me_3SiCN (99 mg, 1.1 mmol) was added immediately followed by stirring at°0 C for 2 h and then at room temperature overnight. The reaction mixture was washed with H_2O, dried over $MgSO_4$ and evaporated under reduced pressure to give an oil , which, on chromatographic separation by elution with hexane-acetone (5:1), gave 133 mg (86%) of 6 as a colorless oil, bp 105-107°C (2 mmHg). MS m/z: 154 (M^+). Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.32; H, 6.68; N, 17.88.

2-Cyano-1-methoxycarbonylpiperidine (8) -- Chromatography by elution with benzene-acetone (20:1) gave the oil (68%) of 8, bp 103°C (2 mmHg). MS m/z: 168 (M^+). Anal.

Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.78; H, 7.28; N, 16.35.

1-tert-Butoxycarbonyl-2-cyanopiperidine (9) -- Chromatography by elution with hexane-acetone (20:1) and recrystallization from hexane gave colorless needles (14%) of 9, mp 52-52°C. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62,83; H, 8.63; H, 13.32. Found: C, 62.83; H, 8,80; N, 13.13.

1-Allyloxycarbonyl-2-cyanopiperidine (10) -- Chromatography by elution with benzene-acetone (20:1) gave the oil (38%) of 10, bp 132°C (10 mmHg). MS m/z: 194 (M^+). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.98; H, 7.37; N, 14.38.

General Procedure for Preparation of 2-Alkyl-2-cyanourethanes --- A typical procedure is described for 2-cyano-1-methoxycarbonyl-2-n-propylpyrrolidine (13) : A solution of n-BuLi (1.1 mmol) in hexane was added at -78°C to a solution of diisopropylamine (303 mg, 3 mmol) in THF (10 ml) under Ar atmosphere. This was followed 15 min later by the addition of a solution of 6 (160 mg, 1mmol) and HMPA (180 mg, 1 mmol) in THF (0.5 ml) and stirring at -78°C for 30 min. A solution of n-PrI (510 mg, 3 mmol) in THF (0.5 ml) was then added and the reaction mixture was stirred at -78° C for 1 h and then at room temp for 1 h. Neutralization was effected by adding an aqueous NH_4Cl solution, followed by extraction with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. Chromatographic separation by elution with hexane-acetone (20:1) gave 74 mg (38%) of 13 as a colorless oil, bp 94°C (2 mmHg). MS m/z: 196 (M^+). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.32; H, 8.21; N, 14.17.

2-Benzyl-2-cyano-1-ethoxycarbonylpyrrolidine (15) -- Chromatography by elution with hexane-acetone (5:1) gave the oil(29%) of 15, bp 130°C (2 mmHg). MS m/z: 258 (M^+). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02: N, 10.85. Found: C, 69.64; H, 7.16; N, 10.84.

2-Cyano-1-methoxycarbonyl-2-n-propylpiperidine (16) -- Chromatography by elution with benzene-acetone (30:1) gave the oil (91%) of 16, bp 122°C (2 mmHg). MS m/z: 179 (M^+). Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.65; H, 8.76; N, 13.27.

2-Benzyl-2-cyano-1-methoxycarbonylpiperidine (17) -- Chromatography by elution with benzene gave the oil(84%) of 17, bp 140°C (2 mmHg). MS m/z: 258 (M^+). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 69.80; H, 7.00; N, 10.90. Found: C, 70.05; H, 7.08; N, 10.71.

2-Cyano-1-methoxycarbonyl-2-methylpiperidine (18) -- Chromatography by elution with benzene-acetone (30:1) gave the oil (61%) of 18, bp 111°C (2 mmHg). MS m/z: 182 (M^+). Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.77; N, 15.37. Found: C, 58.92; H, 7.90; N, 15.18.

2-(3-Chloropropyl)-2-cyano-1-methoxycarbonylpiperidine (19) -- Chromatography by elution with hexane-acetone (10:1) gave the oil (65%) of 19, bp 128-132° C (2 mmHg). MS m/z: 244 (M^+). Anal. Calcd for $C_{11}H_{17}ClN_2O_2$: C, 53.99; H, 7.00; N, 11.45. Found: C, 54.00; H, 7.16; N, 11.66.

2-(4-Chlorobutyl)-2-cyano-1-methoxycarbonylpiperidine (20) -- Chromatography by elution with hexane-acetone (10:1) gave the oil (91%) of 20, bp 145°C (2 mmHg). MS (CI) m/z: 259 (M^++1). Anal. Calcd for $C_{12}H_{19}ClN_2O_2$: C, 55.70; H, 7.40; N, 10.83. Found: C, 55.73; H, 7.42; N, 10.84.

2-Cyano-2-(1-ethoxycarbonylethyl)-1-methoxycarbonylpiperidine (21) -- Chromatography by elution with hexane-acetone (10:1) gave two isomers (ratio 1:1.2) in 45% yield. Minor product from the first crop: oil, bp 108-112°C (2 mmHg). MS(CI) m/z: 269 (M^++1). Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.92; H, 7.57; N, 10.26. Major product from the second crop: oil, bp 118-124° C (2 mmHg). MS(CI) m/z: 269 (M^++1).

2-Allyl-2-cyano-1-methoxycarbonylpiperidine (22) -- Chromatography by elution with hexane-acetone (30:1) gave the oil (71%) of 22, bp 140°C (2 mmHg). MS m/z: 208 (M^+). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46. Found: C, 63.73; H, 7.90; N, 13.38.

2-Cyano-1-methoxycarbonyl-2-n-undecylpiperidine (23) -- Chromatography by elution with hexane-acetone (30:1) gave the oil (63%) of 23. MS m/z: 322 (M^+). Anal. Calcd for $C_{19}H_{34}N_2O_2$: C, 70.80; H, 10.60; N, 8.60. Found: C, 70.83; H, 10.70; N, 8.50.

2-Cyano-2-n-propyl-1-(Z)-(1-propenyloxycarbonyl)piperidine (24) -- Chromatography by elution with hexane-acetone (40:1) gave the oil (20%) of 24, bp 107°C (2 mmHg). MS m/z: 236 (M^+).

2-Cyano-2-propionyl-1-methoxycarbonylpiperidine (25) -- Chromatography by elution with hexane-acetone (10:1) gave the oil (31%) of 25, bp 140-150°C (2 mmHg). MS m/z: 244 (M^+). Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.92; H, 7.14; N, 12.50. Found: C, 59.03; H, 7.28; N, 12.25.

9-Cyanohexahydro-1-phenyl-3H-oxazolo[3,4]pyridin-3-one (26) -- Chromatographic separation by elution with hexane-acetone (10:1) gave three isomers (ratio 8:7:5 in order of elution) in 87% yield. Oil from the first crop: MS m/z: 242

(M^+). Oil from the second crop: MS m/z: 242 (M^+). Colorless needles from the third crop: mp 118-119°C , recrystallized from hexane-acetone. MS m/z: 242 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.37; H, 6.12; N, 11.26.

9-Cyano-1-ethylhexahydro-3H-oxazolo[3,4]pyridin-3-one (27) -- Chromatographic separation by elution with hexane-acetone (10:1) gave two isomers (ratio 1:2 in order of elution) in 89% yield. Minor component from the first crop: Colorless prisms from isopropyl ether, mp 74-76°C. MS m/z: 194 (M^+). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61,57; H, 7.22; N, 14.19. Major component from the second crop: Colorless prisms from isopropyl ether, mp 88-89°C. MS m/z: 194 (M^+). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.74; H, 7.22; N, 14.45.

2-Carbamoyl-2-n-propylpiperidine (28) -- To a solution of 16 (158 mg, 0.75 mmol) was added Me_3SiI (225 mg, 1.125 mmol). After stirring the solution at room temp for 15 min, MeOH (24 mg, 75 mmol) was added followed by standing at 50°C for 1 h. Evaporation of the solvent under reduced pressure and chromatographic separation of the residue on alumina by elution with $CHCl_3$ gave a solid whose recrystallization from hexane gave 103 mg (63%) of 28 as colorless needles, mp 97-98°C. MS (CI) m/z: 170 (M^++1). Anal. Calcd for $C_9H_{18}N_2O_2$: C, 63.49; H, 10.66; N, 16.45. Found: C, 62.34; H, 10.52; N, 16.25.

(±)-Coniine (31) -- A solution of 16 (840 mg, 5 mmol) in 25% HBr-AcOH was stirred at room temp for 11 h followed by evaporation under reduced pressure. The residue was alkalified by an aqueous solution saturated with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3 and evaporated to give nitrile (29), which was refluxed for 2 h with $NaBH_4$ (190 mg, 5 mmol) in EtOH (10 ml). The reaction mixture was evaporated, dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3 and evaporated to give 400 mg (67%) of 31 as a colorless oil. HCl salt: Colorless needles from isopropyl alcohol, mp 216-218°C (lit.[5] 220° C). Anal. Calcd for $C_8H_{17}N\cdot HCl$: C, 58.70; H; 11.08; N, 8.56. Found: C, 58.85; H, 11.26; N, 8.55. 3,5-Dinitrobenzoate: Colorless needles from isopropyl ether, mp 105-107°C (lit.[5] 108°C). MS m/z: 321 (M^+). Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.06; H, 5.96; N, 13.08. Found: C, 55.86; H, 5.96; N, 13.00.

trans-Quinolizidine (32) -- By the method above, trans-quinolizidine(32) was obtained, following chromatographic separation on alumina by elution with hexane-acetone (5:1), in 43% yield from 20 as a colorless oil. MS(CI) m/z: 138 (M^++1).

Table II. Ir and ^{1}H-Nmr Spectra of Products

Product*1	Ir	^{1}H-Nmr
	ν (cm^{-1})	δ (ppm) ($CDCl_3$)
1	($CHCl_3$) 1700, 1110, 1090, 1065	1.17 (3H, t, J =7Hz, CH_3), 1.7-2.2 (4H, m, CH_2CH_2), 3.1-3.8 (4H, m, NCH_2, OCH_2CH_3), 3.67 (3H, s, OCH_3), 5.1-5.33 (1H, m, NCHOEt)
2	($CHCl_3$) 1690, 1100	1.15 (3H, t, J=7Hz, CH_3), 1.22 (3H, t, J=7Hz, CH_3), 1.53-2.4 (4H, m, CH_2CH_2) 3.1-3.77 (4H, m, CH_2N, OCH_2CH_3), 4.17 (2H, q, J=7Hz, OCH_2CH_3), 5.27 (1H, m, OCHN)
3	(neat) 1690, 1080 1060	1.17 (3H, t, J=7Hz, CH_3), 1.4-2.13 (6H, m, CH_2 x 3), 2.83-3.23 (1H, m, HCHN), 3.34 (2H, q, J=7Hz, OCH_2CH_3), 3.7 (3H, s, OCH_3), 3.73-4.07 (1H, m, HCHN), 5.33-5.57 (1H, m, OCHN)
4	(neat) 1700, 1090	1.18 (3H, t, J=7Hz, CH_3), 1.48 (9H, s, Bu-t), 1.21-1.98 (6H, m, CH_2 x 3), 2.91 (1H, m, HCHN), 3.43 (2H, q, J=7Hz, OCH_2CH_3), 3.86 (1H, m, HCHN), 5.43 (1H, m, OCHN)
5	(neat) 1700, 1080 1070	1.2 (3H, t, J=7Hz, CH_3), 1.38-2.15 (6H, m, CH_2 x 3), 2.78-3.2 (1H, m, HCHN), 3.43 (2H, q, J=7Hz, OCH_2CH_3), 3,78-4.08 (1H, m, HCHN), 4.48-4.75 (2H, m, $OCH_2CH=CH_2$), 5.1-5.58 (2H, m, $CH_2CH=CH_2$), 5.73-6.22 (1H, m, $CH_2CH=CH_2$)
6*2	(neat) 2230, 1720,	1.66-2.36 (4H, m, CH_2 x 2), 3.06-3.75 (2H, m, CH_2N), 3.72 (3H, s, OCH_3), 4.42-4.63 (1H, m, CHCN)
8	(neat) 2260, 1720	1.18-2.21 (6H, m, CH_2 x 3), 2.75-3.18 (1H, m, HCHN), 3.91-4.26 (1H, m, HCHN), 3.69 (3H, s, OCH_3). 5.27 (1H, br. CHCN)
9	(KBr) 2220, 1700	1.12-2.33 (6H, m, CH_2 x 3), 1.44 (9H, s, OBu), 2.69-3.09 (1H, m, HCHN), 3.88-4.15 (1H, m, HCHN), 5.16 (1H, br, CHCN)

(Continued)

10	(neat)	1700	1.16-2.09 (6H, m, CH_2 x 3), 2.72-3.15 (1H, m, HCHN), 3.91-4.24 (1H, m, HCHN), 4.59 (2H, d, J=7Hz, $OCH_2CH=CH_2$), 5.09-5.39 (3H, m, CH_2=CH), 5.69-6.12 (1H, m, CH=CH_2)
11	(neat)	1700, 1640	1.37-2.18 (4H, m, CH_2CH_2), 3.51-3.71 (2H, m, CH_2N), 4.48-4.72 (2H, m, $OCH_2CH=CH_2$), 4.9(1H, m, NCH=CH), 5.08-5.45 (2H, m, CH=CH_2), 5.72-6.18 (1H, m,CH=CH_2), 6.8 (1H, m, NCH=CH)
12	(neat)	1700	1.03-2.24 (28H, m, CH_2 x 5, CH_3 x 3), 3.24-3.6 (2H, m. HCHN), 3.72-4.15 (2H, m, HCHN x 2), 4.69 (1H, br. CH=C), 6.48-6.88 (1H, br d, NCH=C)
13	(neat)	1720	0.97 (3H, t, J=7Hz, CH_3), 1.13-2.69 (8H, m, CH_2 x 4), 3.18-3.75 (2H, m, CH_2N), 3.73 (3H, s, OCH_3)
15	(neat)	1700	1.33 (3H, t, J=7Hz, CH_3), 1.42-2.3 (4H, m, CH_2 x 2), 3.01-3.69 (4H, m, CH_2N, CH_2Ph), 4.22 (2H, q, J=7Hz, OCH_2CH_3), 7.26 (5H, s, Ph)
16	(neat)	2250, 1720	0.94 (3H, t, J=7Hz, CH_3), 1.15-2.21 (10H, m, CH_2 x 5), 2,83-3.42 (1H, m, HCHN), 3.21-4.03 (1H, m, HCHN), 3.69 (3H, s, OCH3)
17	(neat)	1700	1.5-1.9 (6H, m, CH_2 x 3), 2.68-2.9 (1H, m, HCHN), 3.8-3.9 (m, 1H, HCHN), 3.25 (2H, s, $PhCH_2$), 3.8 (3H, s, OCH_3), 7.2-7.3 (5H, s, Ph)
18	(neat)	2250, 1720	1.75-2.18 (6H, m, CH_2 x 3), 1.67 (3H, s, CH_3), 3.12-3.66 (2H, m, CH_2N), 3.66 (3H, s, OCH_3)
19	(neat)	2250, 1700	1.3-2.15 (10H, m, CH_2 x 5), 2.94-3.42 (1H, m, HCHN), 3.42-3.63 (2H, m, CH_2Cl), 3.73 (3H, s, OCH_3), 3.73-4.12 (1H, m, HCHN)
20	(neat)	2250, 1720	1.36-2.24 (12H, m, CH_2 x 6), 2.97-3.33 (1H, m, HCHN), 3.51 (2H, t, J=7Hz, CH_2Cl), 3.54-3.94 (1H, m, HCHN), 3.69 (3H, s, OCH_3)

(Continued)

21 (minor component)	(neat)	1730, 1710	1.18 (3H, t, J=7Hz, OCH_2CH_3), 1.3 (3H, d, J=7.5Hz, CH_3CH), 1.51-2.15 (6H, m, CH_2 x 3), 2.72-3.15 (1H, m, CHCO), 3.69-4.06 (2H, m, CH_2N), 3.75 (3H, s, OCH_3), 4.09 (2H, q, J=7Hz, OCH_2CH_3)
21 (major component)	(neat)	1730, 1710	1.27 (3H, t, J=7Hz, OCH_2CH_3), 1.17 (3H, d, J=7.5Hz, CH_3CH), 1.51-2.15 (6H, m, CH_2 x 3), 2.97-3.39 (1H, m, CHCO), 3.48-4.06 (2H, m, CH_2N), 3.7 (3H, s, OCH_3), 4.14 (2H, q, J=7Hz, OCH_2CH_3)
22	(neat)	2250, 1720	1.55-2.1 (6H, m, CH_2 x 3), 2.8 (2H, d, J=6Hz, $CH_2CH=CH_2$), 3.05-3.25 (1H, m, HCHN), 3.85 (1H, m, HCHN), 3.7 (3H, s, OCH_3), 5.3 (2H, s, $CH=CH_2$), 5.5-6.25 (1H, m, $CH=CH_2$)
23	(neat)	1700	0.85 (3H, t, J=6Hz, CH_3), 1.1-1.35 (20H, m, CH_2 x 10), 1.55-2.05 (6H, m, CH_2 x 3), 2.95-3.45 (2H, m, CH_2N), 3.65 (3H, s, OCH_3)
24*3	($CHCl_3$)	2250, 1720, 1680	1.0 (3H, t, J=7Hz, CH_3), 1.42-1.68 (5H, m, $CH_3CH=C$, CH_2), 1.7-1.97 (4H, m, CH_2 x 2), 1.99-2.17 (4H, m, CH_2 x 2), 3.18-3.24 (1H, m, HCHN), 3.9-3.95 (1H, m, HCHN), 4.85-4.92 (1H, m, $CH_3CH=CH$), 6.95-6.98 (1H, d x q, J=8Hz, J=1.7Hz, $CH_3CH=CH$)
25	(neat)	2250, 1740	1.11 (3H, t, J=7Hz, $COCH_2CH_3$), 1.6-2.2 (6H, m, CH_2 x 3), 2.6-2.85 (2H, m, $COCH_2CH_3$), 3.0-3.33 (1H, m, HCHN), 3.85-4.2 (1H, m, HCHN), 3.7 (3H, s, OCH_3)
26 (from the 1st elution)	(neat)	1740	1.03-1.97 (6H, m, CH_2 x 3), 2.71-2.97 (1H, m, HCHN), 3.75-4.03 (1H, m, HCHN, 7.24-7.6 (5H, m, Ph)
26 (from the 2nd elution)	(neat)	1740	1.15-2.03 (6H, m, CH_2 x 3), 2.6-2.91 (1H, m, HCHN), 2.39-2.66 (1H, m, HCHN), 7.0-7.6 (5H, m, Ph)

(Continued)

26 (from the 3rd elution)	(KBr)	1740	1.03-2.39 (6H, m, CH_2 x 3), 2.72-3.18 (1H, m, HCHN), 3.72-4.03 (1H, m, HCHN), 7.03-7.6 (5H, m, Ph)
27 (minor component)	(KBr)	1750	1.09 (3H, t, J=7.5Hz, CH_3), 1.27-2.09 (8H, m, CH_2 x 4), 2.88-3.27 (1H, m, HCHN), 3.72-4.0 (1H, m, HCHN), 4.51 (1H, t, J=7Hz, =CH-O)
27 (major component)	(KBr)	1750	1.09 (3H, t, J=7.5Hz, CH_3), 1.27-2.27 (8H, m, CH_2 x 4), 2.84-3.18 (1H, m, HCHN), 3.67-4.0 (1H, m, HCHN), 4.07 (1H, t x t, J=7.5Hz, CH-O)
28	(KBr)	3280, 3400 1680	0.85 (3H, t, J=7Hz, CH_3), 1.0-1.75 (10H, m, CH_2 x 5), 2.09-2.36 (1H, m, HCHN), 2.48-2.94 (3H, m, NH_2, HCHN), 6.17 (1H br, NH)
31	(neat)	2920, 2850, 2800, 1440	0.91 (3H, t, J=7.5Hz, CH_3), 1.03-1.97 (10H, m, CH_2 x 5), 2.3-2.75 (2H, m, CH_2N), 2.94-3,15 (1H, m, CHN)
31 (3,5-dinitrobenzoate)	(KBr)	1630	0.72-1.03 (3H, t, CH_3), 1.03-2.06 (12H, m, CH_2 x 6), 2.85-2.99 (1H, m, CHN), 8.5 (2H, d, J=3Hz, arom 2,5-H), 9.03 (1H, t, J=3Hz, arom 4-H)
32	(neat)	2950, 2850, 2800, 2750	1.03-2.09 (12H, m, CH_2 x 6), 2.63-2.91 (5H, m, CH_2N x 2, CHN)

*1 See reference 4.

*2 T. Shono, Y. Matsumura and K. Tsubata, Tetrahedron Lett., 1981, 22, 2411.

*3 ^{1}H- and ^{13}C-Nmr spectra of this compound were measured by a 400 MHz spectrometer.
^{13}C-Nmr ($CDCl_3$): 10.02 (q, $CH_2CH_2CH_3$), 13.89 (q, C=CHCH$_3$), 17,58 (t, $CH_2CH_2CH_2$), 22.5 (t, NC-C-CH_2), 33,19 (t, NCH_2CH_2), 37.63 (t, $CH_2CH_2CH_2$), 40.65 (t, CH_2N), 56.71 (s, NC-C), 107.28 (d, CH_3CH=C), 120.35 (s, CN), 135.57 (d, CH_3CH=CH), 152.86 (s, C=O)

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4 The syntheses of compounds 1-5, 7 and 14 are reported in our preceding papers (references 1 and 2).

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