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TAUTOMERIC STRUCTURE OF DIHYDROPYRIDAZINO-[3,4-b]QUINOXALINES IN SOLUTION AND SOLID STATE

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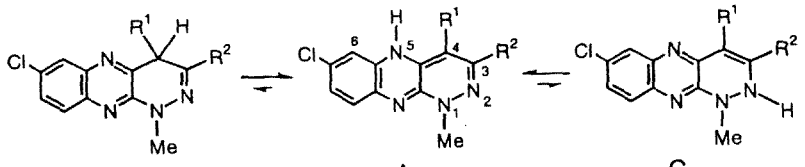
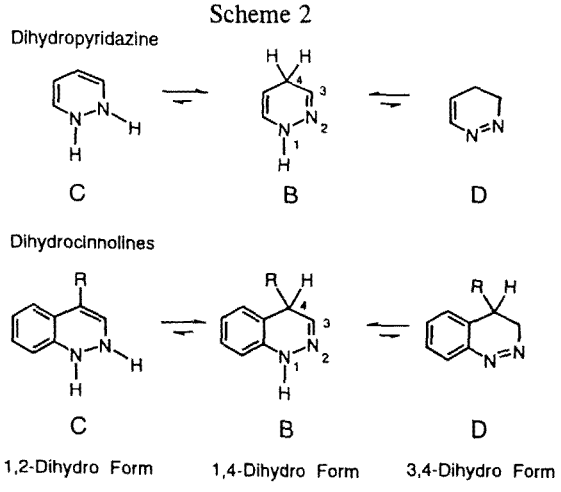
The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide (I) with β-diketones and β-ketoesters gave the dihydropyridazino[3,4-b]quinoxalines (IIIa-d), which were found to exist as the 1,5-dihydro form in solution and solid state by NMR spectroscopy and x-ray analysis.

In previous papers [1, 2], we reported that the 1,3-dipolar cycloaddition reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide (I) with acetylenedicarboxylates gave the dihydropyridazino[3,4-b]quinoxalines (IIa,b). Thereafter compounds IIa,b were clarified to exist as the 1,5-dihydro form A in a solution [3] (Scheme 1), while dihydropyridazine [4] and dihydrocinnolines [5] had been known to occur as the 1,4-dihydro form B in a solution (Scheme 2). In the present investigation, we found that the reaction of compound I with β-diketones and β-ketoesters in N,N-dimethylformamide also provided the dihydropyridazino[3,4-b]quinoxalines (IIIa-d). Moreover, compounds IIIa-d were found to exist as the 1,5-dihydro form A in solution and solid state by NMR spectroscopy and x-ray analysis. This paper describes the synthesis of the dihydropyridazino[3,4-b]quinoxalines IIIa-d together with their tautomeric structure in solution and solid state.

Scheme 1



Scheme 2



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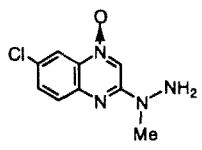
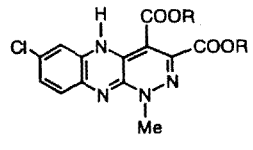
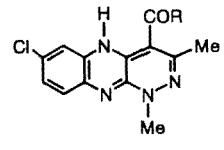
In the present investigation, we found that the reaction of compound I with β-diketones and β-ketoesters in DMF also provided the dihydropyridazino[3,4- *b*]quinoxalines (IIIa-d). Compounds IIIa-d were found to exist as the 1,5-dihydro form A in solution and solid state by the NMR spectroscopy and x-ray analysis. This paper describes the synthesis of the dihydropyridazino[3,4-*b*]quinoxalines IIIa-d together with their tautomeric structure in solution and solid state.



I



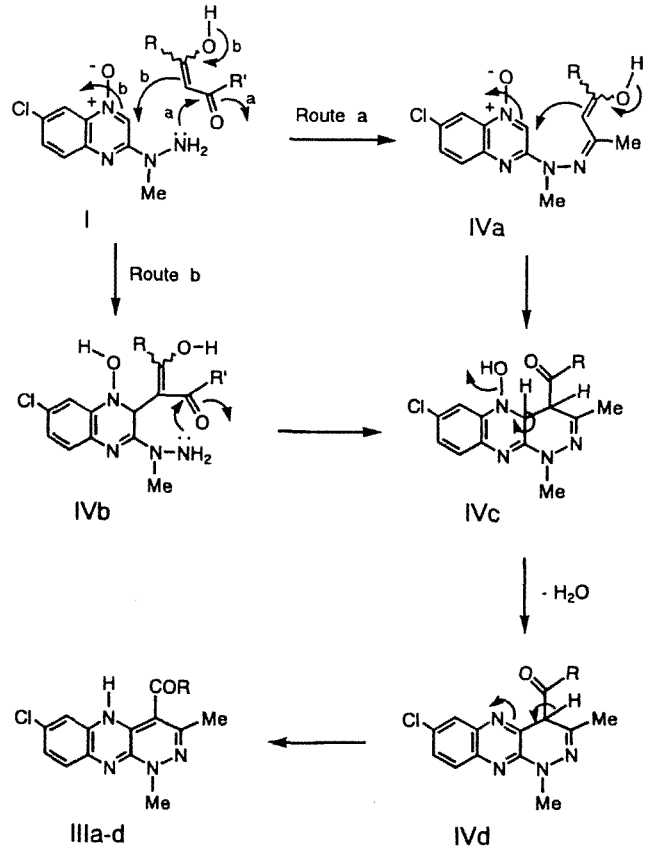
IIa R = Me
IIb R = Et



IIIa R = Me
IIIb R = Ph
IIIc R = OMe
IIId R = OEt

The reaction of the quinoxaline 4-oxide I with acetylacetone, benzoylacetone, methyl acetoacetate, or ethyl acetoacetate in DMF (Scheme 3) gave the 4-substituted 7-chloro-1,3-dimethyl-1,5-dihydropyridazino[3,4-*b*]quinoxalines IIIa, IIIb, IIIc, or IIId, respectively, presumably via intermediates IVa-d. The nucleophilic attack of hydrazines directed to the carbonyl carbon of acetylacetone [6, 7] as in route *a* and the nucleophilic attack of the active methylene carbon directed to the α-carbon of N-oxides [8, 9] as in route b have been reported by some research groups.

Scheme 3



IIIa R = Me, IIIb R = Ph, IIIc R = OMe, IIId R = OEt

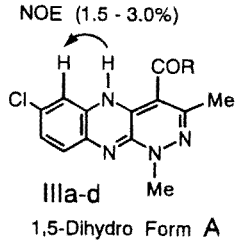
TABLE 1. NMR and IR Spectral Data for Compounds IIIa-d

Compound	R	^{13}C NMR δ(C=O), ppm	IR (KBr) ν(C=O), cm^{-1}
IIIa	Me	203,73	1575
IIIb	Ph	197,28	1575
IIIc	OMe	169,78	1650
IIId	OEt	169,37	1640

TABLE 2. ^{13}C-NMR Spectral Data for Compounds IIIa-d

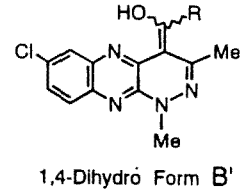
Carbon	Chemical shift (δ, ppm)			
	IIIa	IIIb	IIIc	IIId
C_3	158,10	157,58	159,20	159,29
C_4	112,16	114,97	104,45	104,63
C_{4a}	143,77	141,59	144,94	144,98
C_{5a}	130,80	131,96	131,22	131,28
C_6	120,31	119,50	119,92	119,91
C_7	135,50	135,28	135,37	135,36
C_8	129,49	128,48	128,94	128,90
C_9	121,28	121,29	121,26	121,25
C_{9a}	129,10	128,94	128,66	128,67
C_{10a}	148,82	149,06	148,52	148,57
N_1—Me	45,99	46,17	46,08	46,08
C_3—Me	25,80	23,52	25,38	25,59
C=O	203,73	197,28	169,78	169,37

The NMR spectra of compounds IIIa-d were measured in deuteriodimethyl sulfoxide/trifluoroacetic acid (1:3) because of poor solubility in deuteriodimethyl sulfoxide to take the HMBC and HMQC spectra. The NOE between the C_6-H and N_5-H protons (1.5-3.0%)* clarified that compounds IIIa-d existed as the 1,5-dihydro form A in a solution, and the C=O carbon signals were observed in the corresponding resonance region (Table 1). Thus, the tautomeric structure of compounds IIIa-d in a solution was found to be similar to that of compounds IIIa,b in a solution. The carbon chemical shifts of compounds IIIa-d assigned by the HMBC and HMQC spectral data are shown in Table 2.



IIIa-d

1,5-Dihydro Form A



1,4-Dihydro Form B'

On the other hand, the IR spectra of compounds IIIa, IIIb, IIIc, and IIId showed the absorption bands at 1575, 1575, 1650, and 1640 cm^{-1}, respectively, and no other appreciable peaks were observed in the region of the C=O absorption bands

*The NOE in deuteriodimethyl sulfoxide/trifluoroacetic acid (1.8-2.3%) was inferior in intensity to that in deuteriodimethyl sulfoxide (13.9-15.2%) in a previous work [3].

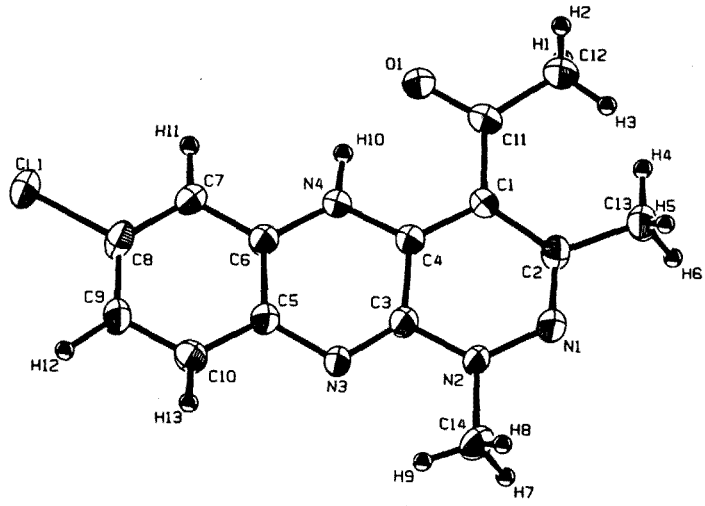


Fig. 1. X-ray structure of compound IIIa showing crystallographic numbering scheme.

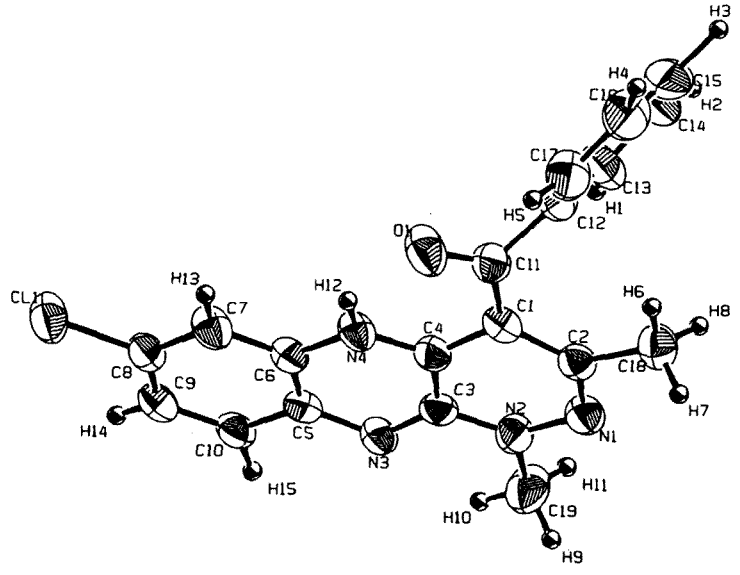


Fig. 2. X-ray structure of compound IIIB showing crystallographic numbering scheme.

(Table 1). Hereupon, the absorption bands of compounds IIIa,b at 1575 cm^{-1} propose a question whether their tautomeric structure in a solid state is the 1,5-dihydro form A or others such as the 1,4-dihydro form B′. Accordingly, compounds IIIa,b were submitted to x-ray analysis, showing that compounds IIIa,b occurred as the 1,5-dihydro form A in a solid state (Figs. 1, 2, Tables 3-6). The bond length of C(1)-C(11) [1.472 Å (IIIa), 1.450 Å (IIIB)] longer than that of C(1)-C(4) [1.380 Å (IIIa), 1.410 Å (IIIb)] (Tables 4, 6) supported the tautomeric structure A, but not the tautomeric structure B′. Thus, the C=O absorption bands of compounds IIIa,b at 1575 cm^{-1} were attributed to the structure of the α,β-unsaturated β-aminoketone with hydrogen bond and observed at a lower wavenumber than the C=O absorption bands due to the α,β-unsaturated β-hydroxyketones with hydrogen bond (1639-1595 cm^{-1}) [10]. The C=O absorption bands of the α,β-unsaturated β-aminoesters IIIc,d were observed at a higher wavenumber (1650, 1640 cm^{-1}) than those of the α,β-unsaturated β-aminoketones IIIa,b (1575

TABLE 3. Positional Parameters and Their Estimated Standard Deviations for Compound IIIa

Atom	x	y	z	B_{eq}
Cl(1)	0,7540(3)	0,9366(2)	0,1980(3)	4,82(7)
O(1)	1,3225(6)	1,4305(5)	1,0303(7)	4,3(2)
N(1)	1,1003(7)	1,8192(6)	1,0225(8)	3,4(2)
N(2)	0,9690(7)	1,7321(6)	0,8575(8)	3,2(2)
N(3)	0,8223(7)	1,5296(6)	0,5965(8)	3,3(2)
N(4)	1,0565(7)	1,4035(6)	0,7561(9)	3,2(2)
C(1)	1,2113(8)	1,6212(7)	1,026(1)	2,7(2)
C(2)	1,214(1)	1,7673(8)	1,104(1)	2,9(2)
C(3)	0,9493(9)	1,5950(7)	0,761(1)	2,8(2)
C(4)	1,0795(8)	1,5404(7)	0,854(1)	2,5(2)
C(5)	0,8086(9)	1,3898(7)	0,504(1)	2,9(2)
C(6)	0,9254(8)	1,3243(7)	0,583(1)	2,7(2)
C(7)	0,9093(9)	1,1847(8)	0,493(1)	3,4(3)
C(8)	0,776(1)	1,1130(7)	0,320(1)	3,5(3)
C(9)	0,659(1)	1,1722(8)	0,235(1)	3,5(3)
C(10)	0,677(1)	1,3118(8)	0,330(1)	3,3(3)
C(11)	1,3388(9)	1,5582(8)	1,110(1)	3,4(3)
C(12)	1,488(1)	1,6358(9)	1,292(1)	5,3(3)
C(13)	1,351(1)	1,8778(8)	1,279(1)	4,1(3)
C(14)	0,846(1)	1,7992(8)	0,774(1)	4,5(3)

TABLE 4. Selected Bond Lengths and Bond Angles of IIIa

Bond length (Å)		Bond angle (°)	
O(1)—C(11)	1,256(8)	O(1)—C(11)—C(1)	119,7(7)
N(1)—N(2)	1,368(7)	N(1)—N(2)—C(3)	125,7(6)
N(1)—C(2)	1,295(9)	N(2)—N(1)—C(2)	118,6(6)
N(2)—C(3)	1,366(8)	N(3)—C(3)—C(4)	127,2(6)
N(3)—C(3)	1,306(8)	N(4)—C(4)—C(3)	113,2(6)
N(4)—C(4)	1,359(8)	C(2)—C(1)—C(4)	115,6(6)
C(1)—C(2)	1,460(9)	C(3)—N(3)—C(5)	115,9(6)
C(1)—C(4)	1,380(9)	C(4)—N(4)—C(6)	124,1(6)
C(1)—C(11)	1,472(9)	C(4)—C(1)—C(11)	118,9(6)

cm^{-1}). The above assignment of the C_4-ester C=O absorption bands for compounds IIIc,d enabled the assignment of the C_3- and C_4-ester C=O absorption bands for compounds IIa,b (Table 7).

In conclusion, we clarified the tautomeric structure of 1-methyldihydro-pyridazino[3,4-b]quinoxalines having the C_4-keto or C_4-ester group in solution and solid state.

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The IR spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The mass spectra (MS) were determined with a JEOL JMS-01S spectrometer. The NMR spectra were obtained with a XL-400 spectrometer at 400 MHz and measured in deuteriodimethyl sulfoxide/trifluoroacetic acid (1:3). Chemical shifts are given in δ scale. Elemental analyses were performed on a Perkin–Elmer 240B instrument.

Elemental analyses of the synthesized compounds IIIa-d for C, H, Cl, and N agreed with the calculated values.

4-Acetyl-7-chloro-1,3-dimethyl-1,5-dihydropyridazino[3,4-b]quinoxaline (IIIa). A solution of compound I (10 g, 44.5 mmole) and acetylacetone (6.68 g, 66.8 mmole) in N,N-dimethylformamide (100 ml) was refluxed in an oil bath for 3 hours. The reaction mixture was allowed to stand overnight to precipitate red prisms IIIa, which were collected by suction

TABLE 5. Positional Parameters and Their Estimated Standard Deviations for Compound IIIb

Atom	x	y	z	B_{eq}
Cl(1)	0,6441(2)	0,9424(1)	0,3688(5)	6,3(1)
O(1)	0,2457(4)	0,8718(4)	-0,767(1)	6,5(3)
N(1)	0,1851(4)	0,5270(4)	-0,882(1)	4,7(3)
N(2)	0,2626(4)	0,5273(4)	-0,648(1)	4,7(3)
N(3)	0,3961(4)	0,5937(4)	-0,294(1)	4,3(3)
N(4)	0,3581(5)	0,7752(5)	-0,433(1)	4,4(3)
C(1)	0,2097(5)	0,7018(5)	-0,789(1)	4,0(3)
C(2)	0,1610(5)	0,6111(5)	-0,940(1)	4,1(3)
C(3)	0,3221(5)	0,6064(5)	-0,500(1)	3,9(3)
C(4)	0,2964(5)	0,6975(5)	-0,578(1)	4,0(3)
C(5)	0,4518(5)	0,6764(5)	-0,141(1)	3,9(3)
C(6)	0,4367(5)	0,7687(5)	-0,207(1)	3,9(3)
C(7)	0,4949(6)	0,8506(6)	-0,052(2)	5,0(4)
C(8)	0,5710(5)	0,8400(5)	0,173(2)	4,5(3)
C(9)	0,5873(6)	0,7502(6)	0,244(2)	4,5(3)
C(10)	0,5294(6)	0,6689(5)	0,087(2)	4,5(3)
C(11)	0,1820(6)	0,7966(6)	-0,838(1)	4,7(3)
C(12)	0,0666(6)	0,8090(5)	-0,952(2)	4,7(3)
C(13)	-0,0222(6)	0,7582(7)	-0,846(2)	6,0(4)
C(14)	-0,1260(7)	0,7797(8)	-0,934(2)	7,3(5)
C(15)	-0,140(1)	0,8480(8)	-1,114(2)	7,8(6)
C(16)	-0,053(1)	0,8966(7)	-1,231(2)	7,7(5)
C(17)	0,0533(7)	0,8786(5)	-1,136(2)	6,3(4)
C(18)	0,0767(6)	0,6021(5)	-1,198(2)	5,2(3)
C(19)	0,2807(7)	0,4322(5)	-0,583(2)	7,0(4)

TABLE 6. Selected Bond Lengths and Bond Angles of IIIb

Bond length (Å)		Bond angle (°)	
O(1)—C(13)	1,235(7)	O(1)—C(11)—C(1)	122,9(6)
N(1)—N(2)	1,396(6)	N(1)—N(2)—C(3)	125,9(6)
N(1)—C(2)	1,301(8)	N(2)—N(1)—C(2)	115,9(6)
N(2)—C(3)	1,350(7)	N(3)—C(3)—C(4)	125,8(6)
N(3)—C(3)	1,314(7)	N(4)—C(4)—C(3)	115,2(6)
N(4)—C(4)	1,342(8)	C(2)—C(1)—C(4)	115,6(6)
C(1)—C(2)	1,432(8)	C(3)—N(3)—C(5)	116,2(6)
C(1)—C(4)	1,410(8)	C(4)—N(4)—C(6)	122,9(6)
C(1)—C(11)	1,450(8)	C(4)—C(1)—C(11)	117,3(6)

TABLE 7. IR Spectral Data for Compounds IIa,b

Compound	R	ν (C=O) (KBr), cm^{-1}	
		C_3-Ester	C_4-Ester
IIa	Me	1735	1660
IIb	Et	1745	1665

filtration and then washed with ethanol and n-hexane to provide an analytically pure sample (5.01 g, 42%), mp 223-224°C; MS: *m/z* 288 (M^+), 290 (M^+ + 2); PMR: 11.63 (1H, s, N_5-H), 6.71 (1H, d, J = 8.5 Hz, C_9-H), 6.67 (1H, d, J = 2.0 Hz, C_6-H), 6.64 (1H, dd, J = 8.5 Hz, J = 2.0 Hz, C_8-H), 3.41 (3H, s, N_1-CH_3), 2.25 (3H, s, C_4-$COCH_3$), 2.09 (3H, s, C_3-CH_3).

4-Benzoyl-7-chloro-1,3-dimethyl-1,5-dihydropyridazino[3,4-b]quinoxaline (IIIb). A solution of compound I (10 g, 44.5 mmole) and benzoylacetone (10.82 g, 66.8 mmole) in N,N-dimethylformamide (100 ml) was refluxed in an oil bath for

3 hours, and evaporation of the solvent *in vacuo* afforded an oily product. Crystallization from ethanol provided red prisms IIIb, which were collected by suction filtration (6.07 g, 39%), mp 184-185°C; MS: *m/z* 350 (M^+), 352 ($M^+ + 2$); PMR: 8.88 (1H, s, N_5-H), 7.46 (2H, d, J = 7.5 Hz, o-H), 7.34 (1H, dd, J = 7.5 Hz, J = 7.5 Hz, p-H), 7.18 (2H, dd, J = 7.5 Hz, m-H), 6.59 (1H, d, J = 8.5 Hz, C_9-H), 6.52 (1H, dd, J = 8.5 Hz, J = 2.0 Hz, C_8-H), 6.47 (1H, d, J = 2.9 Hz, C_6-H), 3.45 (3H, s, N_1-CH_3), 1.45 (3H, s, C_3-CH_3).

Methyl 7-Chloro-1,3-dimethyl-1,5-dihydropyridazino[3,4-b]quinoxaline-4-carboxylate (IIIc). A solution of compound I (3 g) and methyl acetoacetate (10 ml, excess) in N,N-dimethylformamide (50 ml) was refluxed in an oil bath for 5 hours. The reaction mixture was allowed to stand overnight to precipitate brown needles IIIc, which were collected by suction filtration and then washed with ethanol to furnish an analytically pure sample (740 mg, 18%), mp 215-216°C; MS: *m/z* 304 (M^+), ($M^+ + 2$); PMR: 10.59 (1H, s, N_5-H), 6.63 (1H, d, J = 2.0 Hz, C_6-H), 6.63 (1H, d, J = 8.5 Hz, C_9-H), 6.58 (1H, dd, J = 2.0 Hz, J = 8.5 Hz, C_8-H), 3.56 (3H, s, ester CH_3), 3.38 (3H, s, N_1-CH_3), 1.99 (3H, s, C_3-CH_3).

Ethyl 17-Chloro-1,3-dimethyl-1,5-dihydropyridazino[3,4-b]quinoxaline-4-carboxylate (IIId). A solution of compound I (3 g) and ethyl acetoacetate (10 ml, excess) in N,N-dimethylformamide (50 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave yellow crystals IIId, whose crystallization from N,N-dimethylformamide/ethanol afforded brown needles (1.05 g, 25%), mp 192-193°C; MS: *m/z* 318 (M^+), 320 ($M^+ + 2$); PMR: 10.65 (1H, s, N_5-H), 6.62 (1H, d, J = 1.5 Hz, C_6-H), 6.62 (1H, d, J = 8.5 Hz, C_9-H), 6.57 (1H, dd, J = 1.5 Hz, J = 8.5 Hz, C_8-H), 4.03 (2H, q, J = 7.0 Hz, ester CH_2), 3.38 (3H, s, N_1-CH_3), 2.02 (3H, s, C_3-CH_3), 1.02 (3H, t, J = 7.0 Hz, ester CH_3).

X-Ray Analysis of IIIa and IIIb. A crystal was mounted on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data were measured with graphite-monochromated Cu Kα (λ = 1.54179 Å) radiation at 23°C. Approximate atomic coordinates were obtained by the direct method using MITHRIL [11]. The parameters of non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were located from a difference Fourier synthesis, and refined with isotropic temperature factors.

The crystal data of IIIa are as follows: chemical formula $C_{14}H_{13}ClN_4O$; M.W. 288.74; triclinic; space group $P\bar{1}$; Z = 2; until cell dimensions a = 9.626(1) Å, b = 10.005(1) Å, c = 7.8647(9) Å, α = 101.43(1)°, β = 113.25(1)°, γ = 101.17(1)°, V = 650.3(2) Å^3; D_{cal} = 1.474 gcm^{-3}; μ (Cu Kα) = 26.36 cm^{-1}; crystal size 0.1 × 0.1 × 0.1 mm. Of the total of 2488 reflection up to the 2θ range of 140.1° (unique reflections: 2333), 1267 were measured as above the 3σ (I) level and were used. The final R value was 0.070. The positional para-meters for IIIa are listed in Table 3. The selected bond lengths and bond angles for IIIa are listed in Table 4.

The crystal data of IIIb are as follows: chemical formula $C_{19}H_{15}ClN_4O$; M.W. 350.81; triclinic; space group $P\bar{1}$; Z = 2; unit cell dimensions a = 12.511(2) Å, b = 14.037(2) Å, c = 4.709(2) Å, α = 94.93(2)°, β = 95.48(2)°, γ = 97.62(1)°, V = 811.8(6) Å^3; D_{cal} = 1.435 gcm^{-3}; μ (Cu Kα) = 22.16 cm^{-1}; crystal size 0.2 × 0.2 × 0.4 mm. Of the total of 3063 reflections up to the 2θ range of 140.1° (unique reflections: 2922), 1376 were measured as above the 3σ (I) level and were used. The final R value was 0.064. The positional parameters for IIIb are listed in Table 5. The selected bond lengths and bond angles for IIIb are listed in Table 6.

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