A New Tautomeric Zwitterion Form of 2-Acylamino-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalines in Solution

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The reaction of 2-acylamino-8-chloro-4-methyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalines **2a-d** with methyl iodide/base gave the 8-chloro-4,10-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalin-10-ium-2-acylamidates **4a-d**, respectively. Comparison of the nmr spectral data between compounds **2a-d** and **4a-d** in deuteriodimethyl sulfoxide or in deuteriotrifluoroacetic acid established that compounds **2a-d** existed as the zwitterionic tautomers **2'a-d** in solution.

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Introduction.

In previous papers, we reported the synthesis of the 2-(N-methyl) acylamino-4H-1,3,4-thiadiazino [5,6-b]-quinoxalines 1a,b (Chart 1) and their related compounds [1], and the nmr study of compounds 1a,b in deuteriodimethyl sulfoxide or deuteriotrifluoroacetic acid supported the formation of the N_5 -deuterized species $1a,b-D^+$ (Chart 1) in deuteriotrifluoroacetic acid [2]. Thereafter, we

Chart 1

1a,b R: a - CH₃, b - CF₃

1a,b-D+ in deuteriotrifluoroacetic acid

further reported the synthesis of the 2-acylamino-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalines **2a-d** (Chart 2) and their related compounds **3a-c** (Chart 3) [3]. In the course of the nmr study for compounds **2a-d**, we have found that there are remarkable differences in the ¹*H*-nmr spectral

Chart 2

$$CI$$
 $\begin{array}{c}
9 & 10 & 1 \\
N & O & 2 \\
7 & 6 & 5 & 4 \\
CH_3
\end{array}$
 $\begin{array}{c}
H \\
CR \\
O \\
O \\
R$

2a-d

R: $\mathbf{a} - OC_2H_5$, $\mathbf{b} - OC_4H_9(n)$, $\mathbf{c} - CF_3$, $\mathbf{d} - CH_3$

data of the aromatic protons between compounds 1a,b and 2a-d. Namely, the C₇-H and C₉-H protons of compounds 1a,b and 2a-d were observed in similar magnetic fields both in deuteriodimethyl sulfoxide and in deuteriotrifluoroacetic acid, but the C₆-H proton signals of compounds 2a-d in deuteriodimethyl sulfoxide (δ 9.53-9.41 ppm) were observed at much lower magnetic fields than those of compounds 1a,b in deuteriodimethyl sulfoxide (δ 7.61-7.57 ppm) (Table 1). The C_6 -H proton signals of compounds 2a-d in deuteriotrifluoroacetic acid (δ 8.43-7.97 ppm) or the N₄-methyl proton signals of compounds **2a-d** in deuteriodimethyl sulfoxide (δ 4.30-4.20 ppm) and in deuteriotrifluoroacetic acid (δ 4.77-4.50 ppm) were also observed at lower magnetic fields than those of compounds 1a,b [C₆-H in deuteriotrifluoroacetic acid (δ 7.32-7.29 ppm); N_4 -methyl in deuteriodimethyl sulfoxide (δ 3.37-3.36 ppm); N₄-methyl in deuteriotrifluoroacetic acid

3a R = COOC₂H₅ 3b R = CONHNH₂ 3c R = NH₂

Chemical Shift (8 ppm) in Deuteriodimethyl Sulfoxide

| Compound | C ₆ -H | C ₇ -H | C ₉ -H |
|----------|-------------------|-------------------|-------------------|
| 3a | 7.46 | 7.41 | 7.48 |
| 3b | 7.44 | 7.39 | 7.47 |
| 3c | 7.32 | 7.39 | 7.32 |

Table 1
Selected Proton Chemical Shifts for Compounds 1a,b and 2a-d in Deuteriodimethyl Sulfoxide and in Deuteriotrifluoroacetic Acid

| | | Chemical Shift (δ ppm) | | | | | |
|----------|------------------------------|------------------------|-------------------|-------------------|---------------------------------|--|--|
| Compound | Solvent | C ₆ -H | C ₇ -H | C ₉ -H | N ₄ -CH ₃ | | |
| 1a | deuteriodimethyl sulfoxide | 7.57 | 7.52 | 7.69 | 3.36 | | |
| | deuteriotrifluoroacetic acid | 7.29 | 7.34 | 7.50 | 3.53 | | |
| 1b | deuteriodimethyl sulfoxide | 7.61 | 7.57 | 7.72 | 3.37 | | |
| | deuteriotrifluoroacetic acid | 7.32 | 7.37 | 7.52 | 3.53 | | |
| 2a | deuteriodimethyl sulfoxide | 9.53 | 7.42 | 7.30 | 4.20 | | |
| | deuteriotrifluoroacetic acid | 8.42 | 7.68 | 7.76 | 4.77 | | |
| 2b | deuteriodimethyl sulfoxide | 9.52 | 7.42 | 7.30 | 4.20 | | |
| | deuteriotrifluoroacetic acid | 8.43 | 7.69 | 7.77 | 4.77 | | |
| 2c | deuteriodimethyl sulfoxide | 9.41 | 7.51 | 7.38 | 4.30 | | |
| | deuteriotrifluoroacetic acid | 7.97 | 7.47 | 7.50 | 4.59 | | |
| 2d | deuteriodimethyl sulfoxide | 9.51 | 7.34 | 7.30 | 4.24 | | |
| | deuteriotrifluoroacetic acid | 8.02 | 7.39 | 7.47 | 4.50 | | |

(δ 3.53 ppm)]. Such an extraordinary down field shift for the C₆-H proton signals of compounds 2a-d in deuteriodimethyl sulfoxide (8 9.53-9.41 ppm) was not observed for the C₂-ester, C₂-hydrazinocarbonyl, and C₂-amino derivatives 3a-c [C₆-H in deuteriodimethyl sulfoxide (δ 7.46-7.32 ppm)] (Chart 3). These results tempted us to study the structure of compounds 2a-d in solution. Accordingly, we initially tried to measure the NOE spectra of compounds 2a-d in deuteriodimethyl sulfoxide by irradiation at the NH proton signal. Among compounds 2a-d, the NOE spectrum was successfully obtained in compound 2c, showing the NOE between the N₁₀-H and C₉-H protons (Chart 4). Thus, compound 2c was found to occur as the zwitterionic tautomer 2'c in dimethyl sulfoxide (Chart 4). Moreover, the methylation of compounds 2a-d gave the zwitterionic compounds 4a-d (Scheme 1), and the ¹³C-nmr spectral data of compounds 2a-d and 4a-d in

NOE (%) in Deuteriodimethyl Sulfoxide

deuteriodimethyl sulfoxide (Table 2) or in deuteriotrifluoroacetic acid (Table 3) further ascertained that compounds $\bf 2a-d$ existed as the zwitterionic tautomers $\bf 2^a-d$ in deuteriodimethyl sulfoxide (Chart 8). The methylation of compounds $\bf 2a-d$ to the $\bf N_{10}$ -methyl derivatives $\bf 4a-d$ is described below together with the structural elucidation of

Table 2
Selected Carbon Chemical Shifts for Compounds 2a-d and 4a-d in Deuteriodimethyl Sulfoxide

| | | | | Chemical S | Shift (δ ppm) | | | |
|----------------------------------|---------------------------|-------|-------|------------|---------------|-------|-------|-------|
| | N ₁₀ -H Series | | | | yl Series | | | |
| Carbon | 2a | 2b | 2c | 2d | 4a | 4b | 4c | 4d |
| C_2 | 155.0 | 155.0 | 152.8 | 154.4 | 154.8 | 154.8 | 152.7 | 153.5 |
| C_{4a}^2 | 131.3 | 131.4 | 133.1 | 131.3 | 130.3 | 130.4 | 133.1 | 130.5 |
| C_{5a} | 120.7 | 120.7 | 120.0 | 121.5 | 120.8 | 120.9 | 120.1 | 120.9 |
| C ₄ | 120.3 | 120.3 | 120.3 | 120.0 | 120.1 | 120.1 | 120.3 | 120.3 |
| C ₆ C ₇ | 122.7 | 122.8 | 123.7 | 126.7 | 123.5 | 123.5 | 124.5 | 123.5 |
| C_8 | 131.7 | 131.6 | 132.5 | 134.2 | 132.0 | 132.0 | 132.3 | 132.0 |
| C ₉ | 115.6 | 115.8 | 115.8 | 117.7 | 115.6 | 115.6 | 116.3 | 115.6 |
| C _{9a} | 131.2 | 131.3 | 130.8 | 131.6 | 131.6 | 131.6 | 131.9 | 132.0 |
| C _{10a} | 149.8 | 149.8 | 149.1 | 149.3 | 149.1 | 149.2 | 149.1 | 149.2 |
| C = O | 159.3 | 159.5 | 159.7 | 175.3 | 159.2 | 159.3 | 159.7 | 175.6 |
| N ₁₀ -CH ₃ | | | | | 29.4 | 29.4 | 29.6 | 29.4 |
| N_4 -CH ₃ | 38.3 | 38.3 | 38.7 | 38.2 | 38.6 | 38.6 | 39.0 | 38.6 |

Table 3
Selected Carbon Chemical Shifts for Compounds 2a-d and 4a-d in Deuteriotrifluoroacetic Acid

| | | | | Chemical S | Shift (δ ppm) | | | |
|-----------------------------------|-------------------------|------------|-------|------------|------------------------------------|-----------|-----------|-------|
| | N ₁₀ -H Seri | es | | | N ₁₀ -CH ₃ S | Series | | |
| Carbon | 2a | 2 b | 2c | 2d | 4a | 4b | 4c | 4d |
| C_2 | 142.8 | 142.9 | 140.5 | 142.3 | 142.2 | 142.1 | 140.1 | 141.6 |
| C_{4a} | 136.5 | 136.6 | 137.1 | 136.8 | 136.0 | 135.8 | 136.6 | 136.1 |
| C_{5a}^{7a} | 117.5 | 117.5 | 117.0 | 117.4 | 117.6 | 117.5 | 117.3 | 117.2 |
| C_6^{3u} | 118.2 | 118.3 | 117.6 | 118.1 | 118.6 | 118.4 | 118.1 | 118.3 |
| $\overset{\circ}{\mathrm{C}_{7}}$ | 127.3 | 127.3 | 127.3 | 127.3 | 126.6 | 126.4 | 126.7 | 126.5 |
| C ₈ | 139.3 | 139.1 | 139.5 | 139.2 | 139.4 | 139.3 | 139.8 | 139.3 |
| C ₉ | 118.3 | 118.4 | 118.3 | 118.2 | 117.5 | 117.3 | 117.5 | 117.2 |
| C_{9a} | 129.1 | 129.2 | 129.0 | 129.0 | 131.8 | 131.7 | 131.9 | 131.6 |
| C _{10a} | 148.7 | 148.8 | 148.4 | 148.7 | 148.1 | 148.0 | 147.9 | 147.9 |
| C = O | 155.0 | 155.2 | 158.4 | 176.2 | 155.1 | 155.1 | 158.1 | 176.2 |
| N ₁₀ -CH ₃ | | | ***** | | 29.9 | 29.7 | 29.9 | 29.7 |
| N ₄ -CH ₃ | 40.4 | 40.5 | 40.5 | 40.4 | 40.5 | 40.4 | 40.8 | 40.4 |

the zwitterionic tautomers 2'a-d and compounds 4a-d by nmr spectroscopy.

Synthesis of the N_{10} -Methyl Derivatives **4a-d**.

The reaction of compounds $2\mathbf{a}$ - \mathbf{d} with methyl iodide/base gave the N_{10} -methyl derivatives $4\mathbf{a}$ - \mathbf{d} , respectively (Scheme 1). The N_{10} -methyl structure of compounds $4\mathbf{a}$ - \mathbf{d} was supported by the NOE between the C_9 -H and N_{10} -methyl protons (Chart 5). The reaction of compound $2\mathbf{a}$ with N_1N_2 -dimethyl formamide dimethyl

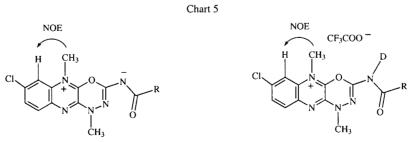
acetal also produced the N_{10} -methyl derivative **4a**, while the reaction of the N-(pyrazino[2,3-e][1,3,4]thiadiazin-2-yl) carbamate **5** with N,N-dimethylformamide dimethyl acetal resulted in the side-chain N-methylation to afford the N-(pyrazino[2,3-e][1,3,4]thiadiazin-2-yl)-N-methyl carbamate **6** (Chart 6) [4].

NMR Spectroscopy.

From the above NOE spectral data for compound 2c (Chart 4) and compounds 4a-d (Chart 5), compounds 2c

Scheme 1 CH₃I 1,8-diazabicyclo[5.4.0]-7-undecene in Dioxane CI N N R Tor 2a in CH₃O CH₃ CH₃O CH₃

R: $\mathbf{a} - OC_2H_5$, $\mathbf{b} - OC_4H_9(n)$, $\mathbf{c} - CF_3$, $\mathbf{d} - CH_3$



4a-d in deuteriodimethyl sulfoxide

4a-d - D+ in deuteriotrifluoroacetic acid

| | NOE (%) | | | | |
|--|----------------------------|------------------------------|--|--|--|
| 4a-d | deuteriodimethyl sulfoxide | deuteriotrifluoroacetic acid | | | |
| $\mathbf{a}: \mathbf{R} = \mathbf{OC}_2\mathbf{H}_5$ | 11.0 | 11.4 | | | |
| $\mathbf{b}: \mathbf{R} = \mathbf{OC_4H_9} - n$ | 17.1 | 10.7 | | | |
| $\mathbf{c}: \mathbf{R} = \mathbf{C}\mathbf{F}_3$ | 20.0 | 10.8 | | | |
| $\mathbf{d}: \mathbf{R} = \mathbf{C}\mathbf{H}_3$ | 20.0 | 10.4 | | | |

4a-d in deuteriodimethyl sulfoxide

and **4a-d** were supported to exist as the zwitterionic form. The HMQC and HMBC spectral data for compounds **4a-d** further secured the zwitterionic structure, showing the 3 J coupling between the N_{10} -methyl protons and C_{9a} carbon and between the N_{10} -methyl protons and C_{10a} carbon (Chart 7). The assignment of the annular carbons together with the C=O, N_{10} -methyl, and N_4 -methyl carbons for compounds **2a-d** and **4a-d** in deuteriodimethyl sulfoxide (Table 2) or in deuteriotrifluoroacetic

acid (Table 3) indicated that the chemical shifts for the individual carbons of compounds 2a-d and 4a-d had similar values in the respective solvents. Especially, the chemical shifts for the C_{9a} and C_{10a} carbons of the zwitterionic tautomers 2'a-d and compounds 4a-d in deuteriodimethyl sulfoxide were similar to those in deuteriotrifluoroacetic acid (Chart 8), indicating the formation of a coordinate bond at the N₁₀ atom in the zwitterionic tautomers 2'a-d and compounds 4a-d. However, the chemical shifts for the C₂-carbons of the zwitterionic tautomers 2'a-d and compounds 4a-d in deuteriodimethyl sulfoxide were observed at a lower magnetic field by 12 ppm in comparison with those in deuteriotrifluoroacetic acid, presumably due to the difference between the C2-amidate anion structure in deuteriodimethyl sulfoxide and the C2-(N-deuterio)acylamino structure in deuteriotrifluoroacetic acid. This structural difference due to the solvent change might influence the C₈-carbon chemical shifts. Namely, the chemical shifts for the C₈ carbon of the zwitterionic tautomers 2'a-d and compounds 4a-d in deuteriodimethyl sulfoxide were observed in a higher magnetic field by 7.6-5 ppm than those in deuteriotrifluoroacetic acid. The difference in the values for other carbons was less than 5 ppm when comparing the chemical shifts in deuteriodimethyl sulfoxide with those in deuteriotrifluoroacetic acid.

Chart 8

2'a-d in deuteriodimethyl sulfoxide

2'a-d - D+ in deuteriotrifluoroacetic acid

Chemical Shift (δ ppm)

$$CI \xrightarrow{\begin{array}{c} CH_3 \\ N \end{array}} \xrightarrow{} R$$

4a-d in deuteriodimethyl sulfoxide

4a-d - D+ in deuteriotrifluoroacetic acid

Chemical Shift (δ ppm)

R: $\mathbf{a} - OC_2H_5$, $\mathbf{b} - OC_4H_9(n)$, $\mathbf{c} - CF_3$, $\mathbf{d} - CH_3$

| Carbon | in deuteriodimethyl sulfoxide 2' a-d | in deuteriotrifluoroacetic acid 2' a-d | Difference in δ ppm | in deuteriodimethyl sulfoxide 4 a-d | in deuteriotrifluoroacetic acid 4 a-d | Difference in δ ppm |
|-----------|--------------------------------------|--|------------------------|-------------------------------------|---|----------------------------|
| C_{9a} | 131.6-130.8 | 129.2-129.0 | less than 2.6 | 132.0-131.6 | 131.9-131.6 | less than 2.6 |
| C_{10a} | 149.8-149.1 | 148.8-148.4 | less than 1.3 | 149.2-149.1 | 148.1-147.9 | less than 1.3 |
| C_2 | 155.0-152.8 | 142.9-140.5 | ca. 12 | 154.8-152.7 | 142.2-140.1 | ca. 12 |
| C_8 | 134.2-131.6 | 139.5-139.1 | 7.6-5 | 132.3-132.0 | 139.8-139.3 | 7.6-5 |

Conclusion.

The 2-acylamino-4H-1,3,4-oxadiazino[5,6-b]quinoxalines 2a-d were shown to occur as the zwitterionic tautomers 2'a-d in a dimethyl sulfoxide solution. The chemical shifts due to the C_6 -H protons of the zwitterionic tautomers 2'a-d in deuteriodimethyl sulfoxide were observed at a much lower magnetic field than those in deuteriotrifluoroacetic acid, presumably due to the difference between the C_2 -amidate anion structure in deuteriodimethyl sulfoxide and the C_2 -(N-deuterio)acylamino structure in deuteriotrifluoroacetic acid. This tendency was also observed in compounds 4a-d (Table 4).

in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

8-Chloro-4,10-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalin-10-ium-2-ethoxycarbonylamidate **4a**.

Method 1.

A solution of compound **2a** (2 g, 6.22 mmoles), 1,8-diazabicy-clo[5.4.0]-7-undecene (1.13 g, 7.46 mmoles), methyl iodide (971 mg, 6.84 mmoles) in dioxane (50 ml) was refluxed in an oil bath for 1 hour. The solution was allowed to stand overnight to precipitate colorless needles, which were removed by filtration. The filtrate was evaporated *in vacuo* to give colorless crystals **4a**, which were recrystallized from ethanol/water to give colorless needles

Table 4
Selected Proton Chemical Shifts for Compounds **4a-d** in Deuteriodimethyl Sulfoxide and in Deuteriotrifluoroacetic Acid

| | | Chemical Shift (d ppm) | | | | | |
|----------|------------------------------|------------------------|-------------------|-------------------|---------------------------------|--|--|
| Compound | Solvent | C ₆ -H | C ₇ -H | C ₉ -H | N ₄ -CH ₃ | | |
| 4a | deuteriodimethyl sulfoxide | 9.69 | 7.58 | 7.68 | 4.23 | | |
| | deuteriotrifluoroacetic acid | 8.22 | 7.42 | 7.55 | 4.49 | | |
| 4b | deuteriodimethyl sulfoxide | 9.70 | 7.54 | 7.69 | 4.23 | | |
| | deuteriotrifluoroacetic acid | 8.22 | 7.41 | 7.57 | 4.49 | | |
| 4c | deuteriodimethyl sulfoxide | 9.57 | 7.61 | 7.79 | 4.33 | | |
| | deuteriotrifluoroacetic acid | 8.01 | 7.42 | 7.58 | 4.53 | | |
| 4d | deuteriodimethyl sulfoxide | 9.81 | 7.57 | 7.69 | 4.23 | | |
| | deuteriotrifluoroacetic acid | 8.08 | 7.41 | 7.56 | 4.51 | | |

Thus, we have provided direct data supporting that compounds 2a-d exist as the zwitterionic tautomers 2'a-d in solution. Similar examples of the zwitterionic heterocycles have been reported by some researchers, as follows. The zwitterionic tautomer of 3-nitraminopyridine 7 in the solid state was confirmed by ir spectroscopy [5] (Chart 9), and the zwitterionic tautomer of 6-hydroxyquinoline 8 in solution was indicated by the study on the D-H exchange rate at the 5-position of compound 8 [6] (Chart 9).

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 nmr spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given

(950 mg, 45%), mp 253-254°; ir: v cm⁻¹ 1695, 1665, 1550; ms: m/z 335 (M+), 337 (M+ + 2); pmr (deuteriodimethyl sulfoxide): 9.69 (d, J = 9.0 Hz, 1H, C_6 -H), 7.68 (d, J = 2.0 Hz, 1H, C_9 -H), 7.58 (dd, J = 2.0, 9.0 Hz, 1H, C_7 -H), 4.23 (s, 3H, N_4 -CH₃), 3.96 (q, J = 7.0 Hz, 2H, CH₂), 3.59 (s, 3H, N_{10} -CH₃), 1.17 (t, J = 7.0 Hz, 3H, CH₃); pmr (deuteriotrifluoroacetic acid): 8.22 (d, J = 9.0 Hz, 1H, C_6 -H), 7.55 (d, J = 2.0 Hz, 1H, C_9 -H), 7.42 (dd, J = 2.0, 9.0 Hz, 1H, C_7 -H), 4.49 (s, 3H, N_4 -CH₃), 4.28 (q, J = 7.0 Hz, 2H, CH₂), 3.69 (s, 3H, N_{10} -CH₃), 1.21 (t, J = 7.0 Hz, 3H, CH₃).

Anal. Calcd. for C₁₄H₁₄ClN₅O₃: C, 50.08; H, 4.20; Cl, 10.56; N, 20.86. Found: C, 49.85; H, 4.27; Cl, 10.69; N, 20.71.

Method 2.

A suspension of compound 2a (1 g) in N,N-dimethylformamide dimethyl acetal (10 ml) was refluxed in an oil bath for 5 hours to precipitate crystals 4a, which were collected by suction filtration and washed with n-hexane to give an analytically pure sample (0.70 g, 67%).

8-Chloro-4,10-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalin-10-ium-2-(*n*-butoxycarbonyl)amidate **4b**.

A solution of methyl iodide (670 mg, 4.72 mmoles) in dioxane (10 ml) was added to a refluxing solution of compound **2b** (1.5 g, 4.29 mmoles), 1,8-diazabicyclo[5.4.0]-7-undecene (783 mg, 5.15 mmoles) in dioxane (20 ml), and the solution was refluxed for 1 hour. The solvent was evaporated *in vacuo* to give an oily product, which was crystallized from ethanol/water to provide colorless needles **4b** (450 mg, 29%), mp 220-221°; ir: v cm⁻¹ 1690, 1660; ms: m/z 363 (M⁺), 365 (M⁺ + 2); pmr (deuteriodimethyl sulfoxide): 9.70 (d, J = 9.0 Hz, 1H, C₆-H), 7.69 (d, J = 2.0 Hz, 1H, C₉-H), 7.54 (dd, J =

2.0, 9.0 Hz, 1H, C_7 -H), 4.23 (s, 3H, N_4 -CH₃), 3.92 (t, J = 7.0 Hz, 2H, CH₂), 3.59 (s, 3H, N_{10} -CH₃), 1.55 (tt, J = 7.0, 7.0 Hz, 2H, CH₂), 1.35 (qt, J = 7.0, 7.5 Hz, 2H, CH₂), 0.90 (t, J = 7.5 Hz, 3H, CH₃); pmr (deuteriotrifluoroacetic acid): 8.22 (d, J = 9.0 Hz, 1H, C_6 -H), 7.57 (d, J = 2.0 Hz, 1H, C_9 -H), 7.41 (dd, J = 2.0, 9.0 Hz, 1H, C_7 -H), 4.49 (s, 3H, N_4 -CH₃), 4.24 (t, J = 7.0 Hz, 2H, CH₂), 3.69 (s, 3H, N_{10} -CH₃), 1.57 (tt, J = 7.0, 7.0 Hz, 2H, CH₂), 1.25 (qt, J = 7.0, 7.0 Hz, 2H, CH₂), 0.79 (t, J = 7.0 Hz, 3H, CH₃).

Anal. Calcd. for C₁₆H₁₈ClN₅O₃: C, 52.82; H, 4.99; Cl, 9.74; N, 19.25. Found: C, 52.53; H, 4.93; Cl, 9.83; N, 19.27.

8-Chloro-4,10-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalin-10-ium-2-trifluoroacetamidate **4c**.

A solution of compound **2c** (1 g, 2.81 mmoles), 1,8-diazabicyclo[5.4.0]-7-undecene (527 mg, 3.47 mmoles), methyl iodide (452 mg, 3.18 mmoles) in dioxane (20 ml) was refluxed in an oil bath for 1 hour. The reaction mixture was allowed to stand overnight to precipitate colorless crystals, which were removed by filtration. The filtrate was evaporated *in vacuo* to provide an oily product, which was crystallized from ethanol/water to give colorless needles **4c** (860 mg, 83%), mp 260-261°; ir: v cm⁻¹ 1690, 1660; ms: m/z 359 (M⁺), 361 (M⁺ + 2); pmr (deuteriodimethyl sulfoxide): 9.57 (d, J = 9.0 Hz, 1H, C₆-H), 7.79 (d, J = 2.0 Hz, 1H, C₉-H), 7.61 (dd, J = 2.0, 9.0 Hz, 1H, C₇-H), 4.33 (s, 3H, N₄-CH₃), 3.65 (s, 3H, N₁₀-CH₃); pmr (deuteriotrifluoroacetic acid): 8.01 (d, J = 8.0 Hz, 1H, C₆-H), 7.58 (d, J = 2.0 Hz, 1H, C₉-H), 7.42 (dd, J = 2.0, 8.0 Hz, 1H, C₇-H), 4.53 (s, 3H, N₄-CH₃), 3.70 (s, 3H, N₁₀-CH₃).

Anal. Calcd. for $C_{13}H_9ClF_3N_5O_2$: C, 43.41; H, 2.52; N, 19.47. Found: C, 43.69; H, 2.74; N, 19.55.

8-Chloro-4,10-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalin-10-ium-2-acetamidate **4d**.

A solution of methyl iodide (535 mg, 3.77 mmoles) in dioxane (10 ml) was added to a refluxing solution of compound 2d (1 g, 3.43 mmoles), 1,8-diazabicyclo[5.4.0]-7-undecene (626 mg, 4.12 mmoles) in dioxane (20 ml), and the solution was refluxed in an oil bath for 1 hour. The solvent was evaporated *in vacuo* to give colorless crystals 4d, which were recrystallized from ethanol to afford colorless needles (270 mg, 26%), mp 272-273°; ir: v cm⁻¹ 1685, 1610; ms: m/z 305 (M+), 307 (M++2); pmr (deuteriodimethyl sulfoxide): 9.81 (d, J = 9.0 Hz, 1H, C₆-H), 7.69 (d, J = 2.0 Hz, 1H, C₉-H), 7.57 (dd, J = 2.0, 9.0 Hz, 1H, C₇-H), 4.23 (s, 3H, N₄-CH₃), 3.59 (s, 3H, N₁₀-CH₃), 2.03 (s, 3H, COCH₃); pmr (deuteriotrifluoroacetic acid): 8.08 (d, J = 9.0 Hz, 1H, C₆-H), 7.56 (d, J = 2.0 Hz, 1H, C₉-H), 7.41 (dd, J = 2.0, 9.0 Hz, 1H, C₇-H), 4.51 (s, 3H, N₄-CH₃), 3.70 (s, 3H, N₁₀-CH₃), 2.40 (s, 3H, COCH₃).

Anal. Calcd. for C₁₃H₁₂ClN₅O₂: C, 51.07; H, 3.96; Cl, 11.60; N, 22.91. Found: C, 50.79; H, 4.08; Cl, 11.72; N, 22.63.

REFERENCES AND NOTES

- [1] Y. Kurasawa, M. Sekine, H. S. Kim, and Y. Okamoto, J. Heterocyclic Chem., 33, 1859 (1996).
- [2] H. S. Kim, Y. Okamoto, and Y. Kurasawa, J. Heterocyclic Chem., 34, 1029 (1997).
- [3] H. S. Kim, T. E. Kim, S. U. Lee, D. I. Kim, S. W. Han, Y. Okamoto, T. Mitomi, and Y. Kurasawa, *J. Heterocyclic Chem.*, in press.
- [4] B. Koren, B. Stanovnik, and M. Tisler, *Heterocycles*, 23, 913 (1985).
 - [5] B. D. Batts and E. Spinner, Aust. J. Chem., 22, 2611 (1969).
- [6] V. Bressel, A. R. Katritzky, and J. R. Lea, J. Chem. Soc. (B), 11 (1971).