Synthesis of 4*H*-1,3,4-Oxadiazino[5,6-*b*]quinoxalines from 2-Substituted Quinoxaline 4-Oxides

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The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **8** with acetic anhydride resulted in the intramolecular cyclization to give 8-chloro-2,4-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxaline **7a**, while the reaction of compound **8** with acetic anhydride/pyridine or acetic anhydride/acetic acid afforded 3-(2,2-diacetyl-1-methylhydrazino)-7-chloro-2-oxo-1,2-dihydroquinoxaline **9**, effecting no intramolecular cyclization. The reaction of 2-(2-acetyl-1-methylhydrazino)-6-chloroquinoxaline 4-oxide **10a** or 6-chloro-2-(1-methyl-2-trifluoroacetylhydrazino)quinoxaline 4-oxide **10b** with phosphoryl chloride provided compound **7a** or 8-chloro-4-methyl-2-trifluoromethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxaline **7b**, respectively. The reaction of compound **7b** with phosphorus pentasulfide gave 7-chloro-3-(1-methyl-2-trifluoroacetylhydrazino)-2-thioxo-1,2-dihydroquinoxaline **11**, whose dehydration with sulfuric acid in acetic acid afforded 8-chloro-4-methyl-2-trifluoromethyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **12**.

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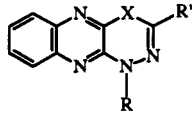
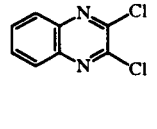
Several research groups have reported the synthesis of the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **1** [2,3] and 4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalines **2** [4], which are produced by the reaction of the 2,3-dichloroquinoxaline **3** with thioacyl or acyl hydrazides **4**, respectively (Chart 1). Thereafter, we reported a method for the synthesis of the 2-acylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **5** from the 2-thiocarbamoylhydrazinoquinoxaline 4-oxides **6** *via* an N_4-O-acylated intermediate **A** (Chart 2) [5,6]. In continuation of such type of investigation, we undertook the synthesis of the 4*H*-1,3,4-oxadiazino[5,6-*b*]-

Chart 1



1: X = S
2: X = O
R = Ph, H
R' = Me, Ph



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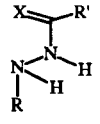
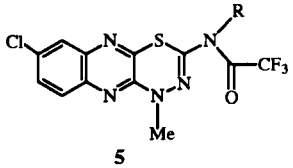


4

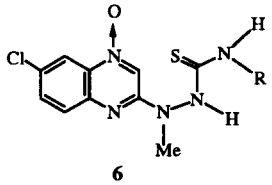
X = S, O
R = Ph, H
R' = Me, Ph

Chart 2



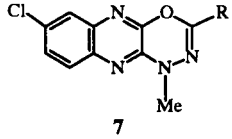
5

R = Me, Aryl



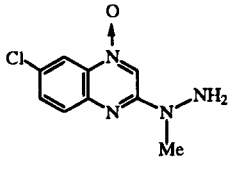
6

R = Me, Aryl



7

a: R = Me
b: R = CF_3



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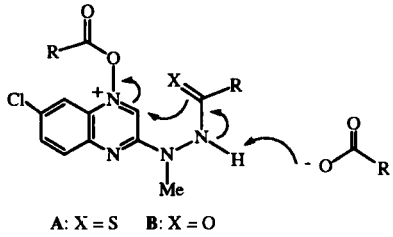


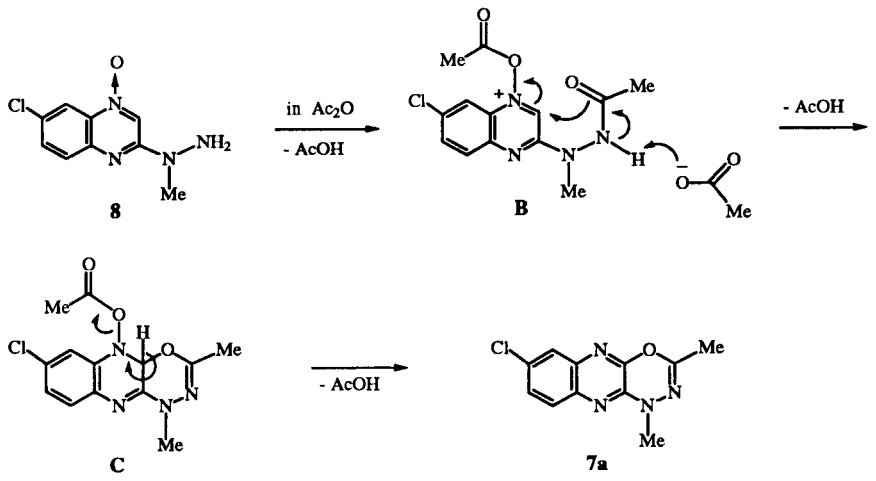
A: X = S **B**: X = O

quinoxalines **7** from 6-chloro-2-(1-methylhydrazino)-quinoxaline 4-oxide **8**. Namely, compound **8** would be acetylated with acetic anhydride to change into an intermediate **B**, which is converted into compound **7a**. This paper describes the synthesis of the 2-methyl- and 2-trifluoromethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxalines **7a,b** from compound **8** together with the conversion of the 2-trifluoromethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxaline **7b** into the 2-trifluoromethyl-4*H*-1,3,4-thiadiazino[5,6-*b*]-quinoxaline **12**.

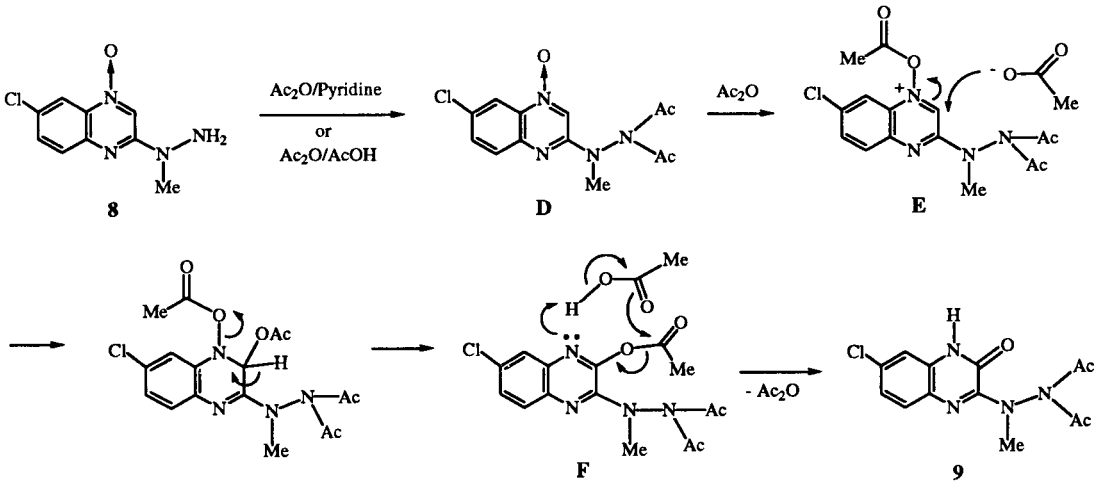
The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **8** with acetic anhydride gave 8-chloro-2,4-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxaline **7a** presumably *via* intermediates **B** and **C** (Scheme 1). Compound **7a** was obtained in a low yield (23%), so that we examined the reaction of compound **8** with acetic anhydride/pyridine or acetic anhydride/acetic acid. However, this reaction afforded 3-(2,2-diacetyl-1-methylhydrazino)-7-chloro-2-oxo-1,2-dihydroquinoxaline **9**, instead of compound **7a**, *via* intermediates **D-F** (Scheme 2a) or *via* intermediates **B-G** (Scheme 2b). The diacetylation of C_2-(1-methylhydrazino) group under the above reaction condition would prevent the construction of the 1,3,4-oxadiazine ring (Scheme 2a). On the other hand, an attack of acetoxy anion to the the C_3-carbon prior to the second acetylation of the C_2-(2-acetyl-1-methylhydrazino) group in an intermediate **B** (Scheme 2b) would provide an intermediate **G**, and subsequent migration of the acetyl group to the C_2-(2-acetyl-1-methylhydrazino) group affords compound **9**. Accordingly, we selected the efficient route as shown in Scheme 3.

The reaction of compound **8** with acetic anhydride in dioxane or with trifluoroacetic anhydride in chloroform gave 2-(2-acetyl-1-methylhydrazino)-6-chloroquinoxaline 4-oxide **10a** or 6-chloro-2-(1-methyl-2-trifluoroacetylhydrazino)quinoxaline 4-oxide **10b**, respectively, whose reaction with phosphoryl chloride provided compound **7a** or 8-chloro-4-methyl-2-trifluoromethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxaline **7b**, respectively.

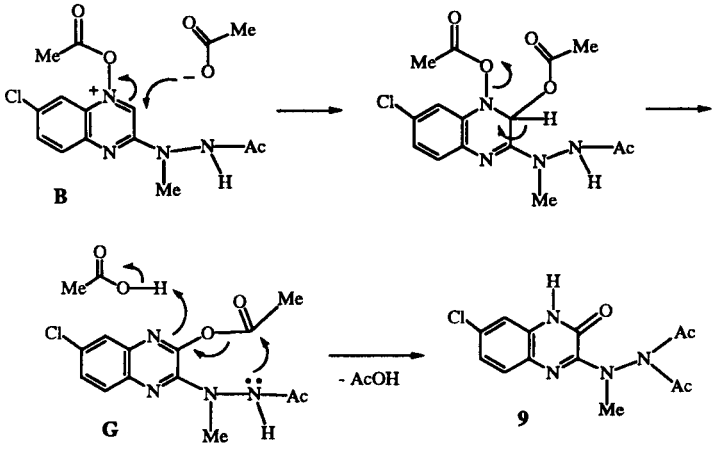
Scheme 1



Scheme 2a



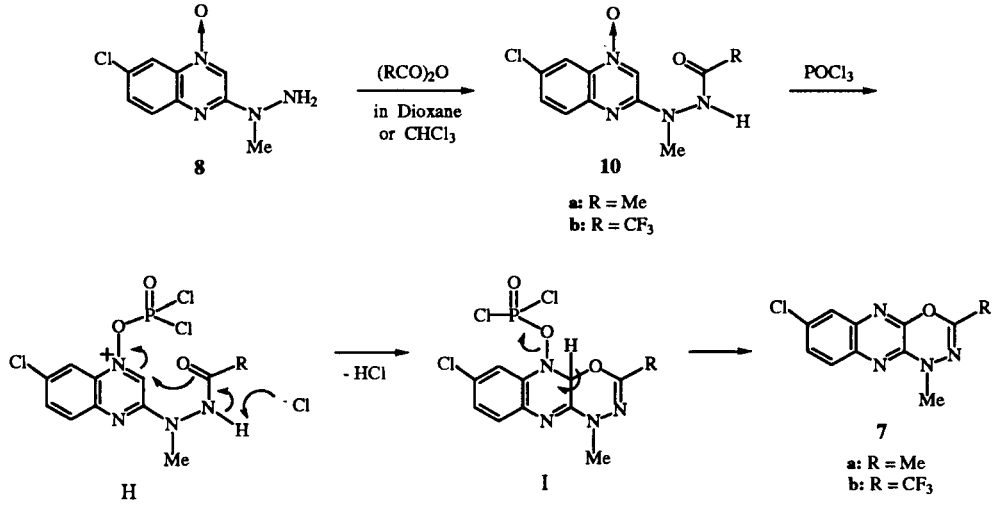
Scheme 2b



produced 8-chloro-4-methyl-2-trifluoromethyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **12** (Scheme 4).

The structural assignment of new compounds **7a,b** and **9-12** were based on the analytical and spectral data. In the nmr spectral data for compound **9**, the acetyl methyl protons were observed at δ 2.34 ppm (6H), and acetyl methyl carbon and acetyl carbonyl carbon were observed at δ 25.3 and 171.8 ppm, respectively (Chart 3). Moreover, the N_1-methylation of compound **9** gave 3-(2-acetyl-1-methylhydrazino)-7-chloro-1-methyl-2-oxo-1,2-dihydroquinoxaline **13** (Scheme 5). The nmr (NOE and C-H coupling) spectral data of compound **9** (Chart 3) and compound **13** (Chart 4) supported the respective structural assignment. In the nmr (NOE and C-H coupling) spectral data for compound **11** (Chart 5), the chemical shift due to the C_2=S (δ 169.1 ppm) and

Scheme 3



Furthermore, the reaction of compound **7b** with phosphorus pentasulfide gave 7-chloro-3-(1-methyl-2-trifluoroacetylhydrazino)-2-thioxo-1,2-dihydroquinoxaline **11**, whose reaction with sulfuric acid in acetic acid

Scheme 4

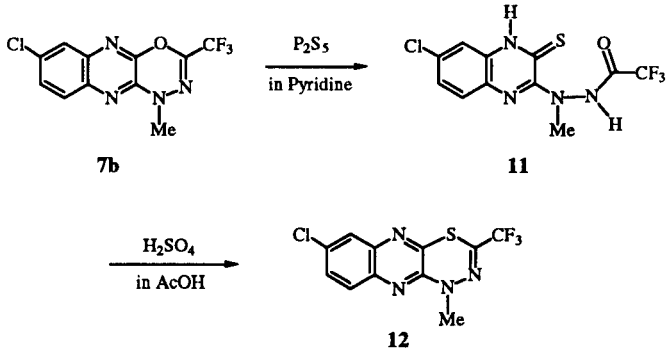


Chart 3

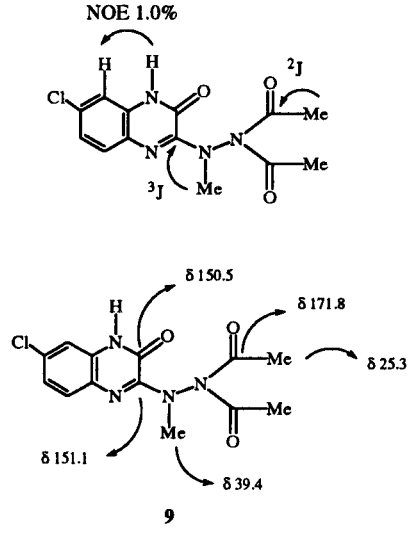
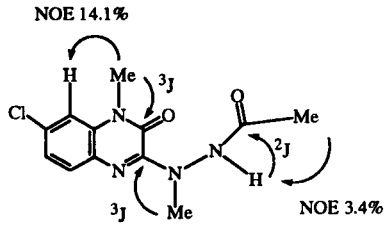
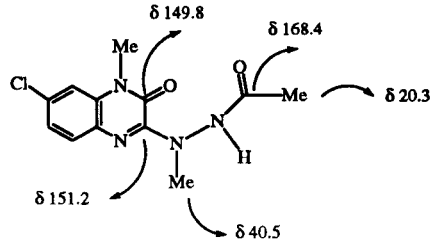


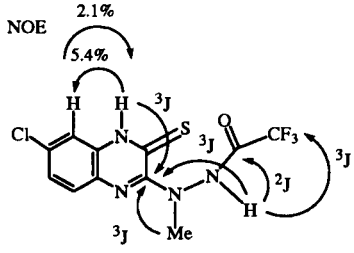
Chart 4

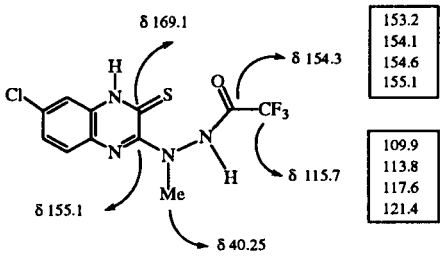




13

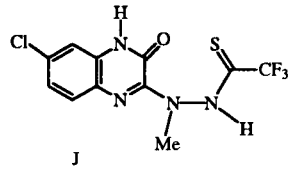
Chart 5





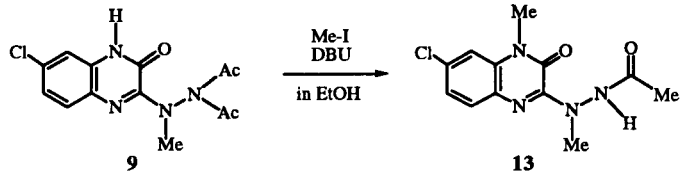
11

Chart 6



J

Scheme 5



9 13

trifluoroacetyl C=O (δ 154.3 ppm) carbons excluded the structure **J** (Chart 6).

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 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-2,4-dimethyl-4*H*-1,3,4-oxadiazino[5,6-*b*]quinoxaline **7a**.

From the Reaction of Compound **8** with Acetic Anhydride.

A solution of compound **8** (2 g) in acetic anhydride (50 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave yellow crystals **7a**, which were collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ ethanol afforded yellow needles (0.50 g, 23%), mp 162-163°; ir: ν cm^{-1} 3060, 1675, 1615, 1585, 1550, 1510; ms: m/z 248 (M^+), 250 ($M^+ + 2$); pmr: (deuteriodimethyl sulfoxide): 7.42 (dd, J = 2.0, 1.0 Hz, 1H, C_9-H), 7.39 (dd, J = 8.5, 1.0 Hz, 1H, C_6-H), 7.35 (dd, J = 8.5, 2.0 Hz, 1H, C_7-H), 3.13 (s, 3H, NCH_3), 1.92 (s, 3H, C_2-CH_3).

Anal. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; Cl, 14.26; N, 22.53. Found: C, 53.02; H, 3.68; Cl, 14.56; N, 22.41.

From the Reaction of Compound **10a** with Phosphoryl Chloride.

A suspension of compound **10a** (5 g) in phosphoryl chloride (100 ml) was refluxed in an oil bath for 30 minutes to give a clear solution. Evaporation of phosphoryl chloride afforded yellow crystals **7a**, which were washed with saturated sodium bicarbonate solution and then collected by suction filtration. Recrystallization from *N,N*-dimethylformamide/ethanol/water provided yellow needles (2.79 g, 60%).

3-(2,2-Diacetyl-1-methylhydrazino)-7-chloro-2-oxo-1,2-dihydroquinoxaline **9**.

From the Reaction of Compound **8** with Acetic Anhydride/Acetic Acid.

A solution of compound **8** (2 g) in acetic anhydride (30 ml)/acetic acid (20 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave crystals, which were triturated with water and then collected by suction filtration. Recrystallization from ethanol afforded colorless crystals **9** (1.70 g, 62%), mp 216-217°; ir: ν cm^{-1} 1730, 1710, 1670; ms: m/z 308 (M^+), 310 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 12.25 (brs, 1H, N_1-H), 7.49 (d, J = 9.0 Hz, 1H, C_5-H), 7.20 (dd, J = 9.0, 2.0 Hz, 1H, C_6-H), 7.19 (d, J = 2.0 Hz, 1H, C_8-H), 3.28 (s, 3H,

NCH_3), 2.34 (s, 6H, $COCH_3$); ^{13}C-nmr (deuteriodimethyl sulfoxide): 171.8 (acetyl C=O).

Anal. Calcd. for $C_{13}H_{13}ClN_4O_3$: C, 50.58; H, 4.24; Cl, 11.48; N, 18.15. Found: C, 50.65; H, 4.27; Cl, 11.37; N, 18.21.

From the Reaction of Compound **8** with Acetic Anhydride/Pyridine.

A solution of compound **8** (2 g) in acetic anhydride (30 ml)/pyridine (20 ml) was refluxed in an oil bath for 2 hours. Evaporation of the solvent *in vacuo* gave crystals, which were triturated with water and then collected by suction filtration. Recrystallization from ethanol gave colorless needles **9** (2.03 g, 74%).

2-(2-Acetyl-1-methylhydrazino)-6-chloroquinoxaline 4-Oxide **10a**.

A solution of compound **8** (5 g, 22.3 mmoles), acetic anhydride (2.73 g, 26.8 mmoles), and pyridine (1 ml) in dioxane (100 ml) was refluxed in an oil bath for 30 minutes to precipitate yellow needles **10a**. After cooling to room temperature, the yellow needles **10a** were collected by suction filtration and then washed with ethanol to give an analytically pure sample (5.22 g). Evaporation of the filtrate *in vacuo* provided additional yellow crystals **10a**, which were collected by suction filtration (0.57 g), total yield (5.79 g, 97%).

Compound **10a** had mp 278-279°; ir: ν cm^{-1} 3240, 3200, 1700, 1690; ms: m/z 266 (M^+), 268 (M^+ + 2); pmr (deuteriotrifluoroacetic acid): 8.99 (s, 1H, C_3-H), 8.47 (d, J = 2.0 Hz, 1H, C_5-H), 7.91 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 7.86 (d, J = 9.0 Hz, 1H C_8-H), 3.69 (s, 3H, NCH_3), 2.32 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{11}H_{11}ClN_4O_2$: C, 49.54; H, 4.16; Cl, 13.29; N, 21.01. Found: C, 49.59; H, 4.15; Cl, 13.51; N, 21.16.

6-Chloro-2-(1-methyl-2-trifluoroacetylhydrazino)quinoxaline 4-Oxide **10b**.

Trifluoroacetic anhydride (5.63 g, 26.8 mmoles) was added dropwise to a suspension of compound **8** (5 g, 22.3 mmoles) in chloroform (100 ml) under cooling in an ice-water bath to give a clear solution. The solution was heated at 70° for 1 hour to precipitate pale yellow crystals. Evaporation of the solvent *in vacuo* and trituration with sodium bicarbonate solution to neutralize trifluoroacetic acid provided yellow needles **10b**, which were collected by suction filtration and washed with ethanol/water (1:1) to provide analytically pure sample (4.49 g, 63%), mp 221-222°; ir: ν cm^{-1} 3140, 3100, 2940, 2850, 1740; ms: m/z 320 (M^+), 322 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 12.00 (brs, 1H, NH), 8.60 (s, 1H, C_3-H), 8.23 (dd, J = 0.8, 1.5 Hz, 1H, C_7-H), 7.76 (d, J = 1.5 Hz, 1H, C_8-H), 7.75 (d, J = 0.8 Hz, 1H, C_5-H), 3.34 (s, 3H, NCH_3).

Anal. Calcd. for $C_{11}H_8ClF_3N_4O_2$: C, 41.20; H, 2.51; N, 17.47. Found: C, 41.37; H, 2.66; N, 17.53.

8-Chloro-4-methyl-2-trifluoromethyl-4*H*-1,3,4-oxadiazino-[5,6-*b*]quinoxaline **7b**.

A suspension of compound **10b** (5 g) in phosphoryl chloride (100 ml) was refluxed in an oil bath for 40 minutes to give a clear solution. Evaporation of phosphoryl chloride *in vacuo* afforded crystals, which were dissolved in dioxane. The dioxane solution was poured onto crushed ice to precipitate yellow crystals, and addition of saturated sodium bicarbonate solution increased the amount of yellow crystals. The whole yellow crystals were collected by suction filtration, and recrystallization from ethanol/water provided yellow needles **7b** (4.20 g, 89%), mp 148-149°; ir: ν cm^{-1} 3080, 1680; ms: m/z 302 (M^+), 304 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 7.52 (dd, J = 1.0, 2.0 Hz, 1H, C_9-H), 7.49 (dd, J = 1.0, 9.0 Hz, 1H, C_6-H), 7.45 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 3.22 (s, 3H, NCH_3).

Anal. Calcd. for $C_{11}H_6ClF_3N_4O$: C, 43.66; H, 2.00; N, 18.51. Found: C, 43.83; H, 2.07; N, 18.61.

7-Chloro-3-(1-methyl-2-trifluoroacetylhydrazino)-2-thioxo-1,2-dihydroquinoxaline **11**.

A solution of compound **7b** (5 g, 16.5 mmoles) and phosphorus pentasulfide (2.75 g, 24.8 mmoles) in pyridine (100 ml) was refluxed in an oil bath for 1 hour. Evaporation of the solvent *in vacuo* gave an oily product, which was triturated with hot water to give yellow crystals **11** (5.38 g, 87%). Recrystallization from ethanol/water gave yellow needles, mp 256-257°; ir: ν cm^{-1} 3250, 1720; ms: m/z 336 (M^+), 338 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 14.23 (s, 1H, N_1-H), 11.97 (s, 1H, NH), 7.61 (d, J = 8.5 Hz, 1H, C_5-H), 7.49 (d, J = 2.0 Hz, 1H, C_8-H), 7.37 (dd, J = 8.5, 2.0 Hz, 1H, C_6-H), 3.34 (s, 3H, NCH_3); ^{13}C-nmr (deuteriodimethyl sulfoxide): 169.1 (C=S), 154.3 (trifluoroacetyl C=O).

Anal. Calcd. for $C_{11}H_8ClF_3N_4OS$: C, 39.24; H, 2.39; N, 16.64; S, 9.52. Found: C, 39.36; H, 2.43; N, 16.79; S, 9.78.

8-Chloro-4-methyl-2-trifluoromethyl-4*H*-1,3,4-thiadiazino-[5,6-*b*]quinoxaline **12**.

A solution of compound **11** (1 g) in concentrated sulfuric acid (0.1 ml)/acetic acid (30 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent gave an oily product, which was triturated with saturated sodium bicarbonate solution provided orange crystals. Recrystallization from ethanol afforded orange needles **12** (270 mg). Evaporation of the solvent *in vacuo* gave additional orange crystals **12** (60 mg), total yield (330 mg, 35%).

Compound **12** had mp 114-115°; ir: ν cm^{-1} 1620, 1600, 1570, 1540, 1520; ms: m/z 318 (M^+), 320 (M^+ + 2); pmr (deuteriodimethyl sulfoxide): 7.84 (d, J = 9.0 Hz, 1H, C_6-H), 7.75 (d, J = 2.0 Hz, 1H, C_9-H), 7.52 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 4.94 (s, 3H, NCH_3).

Anal. Calcd. for $C_{11}H_6ClF_3N_4S$: C, 41.46; H, 1.90; N, 17.58. Found: C, 41.32; H, 2.14; N, 17.43.

3-(2-Acetyl-1-methylhydrazino)-7-chloro-1-methyl-2-oxo-1,2-dihydroquinoxaline **13**.

A suspension of compound **9** (1 g, 3.25 mmoles), 1,8-diazabicyclo[5.4.0]-7-undecene (544 mg, 3.58 mmoles), and methyl iodide (508 mg, 3.58 mmoles) in ethanol (30 ml) was refluxed on a boiling water bath for 1 hour to give a clear solution. The solution was allowed to stand at room temperature to precipitate pale yellow needles **13**, which were collected by suction filtration and washed with *n*-hexane to provide analytically pure sample (670 mg, 74%), mp 238-239°; ir: ν cm^{-1} 3270, 1660; ms: m/z 280 (M^+), 282 (M^+ + 2); pmr (deuteriodimethyl sulfoxifde): 10.40 (s, 1H, NH), 7.44 (d, J = 2.0 Hz, 1H, C_8-H), 7.43 (d, J = 8.5 Hz, 1H, C_5-H), 7.25 (dd, J = 2.0, 8.5 Hz, 1H, C_6-H), 3.53 (s, 3H, N_1-CH_3), 3.25 (s, 3H, NCH_3), 1.82 (s, 3H, $COCH_3$); ^{13}C-nmr (deuteriodimethyl sulfoxide): 168.4 (acetyl C=O).

Anal. Calcd. for $C_{12}H_{13}ClN_4O_2$: C, 51.34; H, 4.67; Cl, 12.63; N, 19.96. Found: C, 51.45; H, 4.78; Cl, 12.85; N, 19.83.

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