Preparation of Novel Tricyclic Ring Systems Containing the Pyridazinone Ring

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Novel tricyclic ring systems, imidazo[3,4-*d*]pyridazino[4,5-*b*][1,4]thiazines **3**, imidazo[2,1-*b*]pyridazino[4,5-*e*][1,3,4]thiadiazines **15** and **18** were prepared by the reaction of 5-amino-4-chloropyridazin-3(2*H*)-ones **1** and 5(4)-(1-methylhydrazino)-4(5)-chloropyridazin-3(2*H*)-ones **13** (**16**) with isothiocyanates **2** and **7**.

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Sulfur-containing fused pyridazinones have recently drawn much attention due to their significant biological and pharmacological activities [1-7]. We previously reported that 5(4)-amino-4(5)-chloropyridazinones reacted with methyl dithiocarbamates and isothiocyanates to give 2-arylaminothiazolo[4,5-*d*]pyridazinones [8]. In continuation of our studies on the exploration of the new synthetic route of novel heterocyclic ring systems, we herein report the synthesis of sulfur-containing fused pyridazinones, which consist of novel tricyclic ring systems, formed by the double cyclization of 5(4)-amino-4(5)-chloropyridazin-3(2*H*)-one derivatives with isothiocyanates.

When 5-carboethoxymethylamino-4-chloropyridazin-3(2*H*)-ones **1** were allowed to react with an excess of isothiocyanates **2** in DMSO at 50° in the presence of sodium hydride, novel tricyclic heterocycles, 4-amino-2*H*,7*H*-imidazo[3,4-*d*]pyridazino[4,5-*b*][1,4]thiazine-3,6-dione-1-thiones **3**, were unexpectedly obtained in 35-55% yield, without anticipated isolation of thiazolo[4,5-*d*]pyridazinone **4** and pyridazino[4,5-*b*][1,4]thiazine **5**, though only trace of **3** was detected in the 1:1 reaction between **1** and **2**.

The structure of the product **3** was assigned by the analytical and spectral data. The ir spectra showed absorptions assignable to NH and the newly formed amide carbonyl groups at 3240-3200 cm^{-1} and 1680-1660 cm^{-1}, respectively, with disappearance of the carbethoxy carbonyl group. The mass spectra exhibited the parent ion peak corresponding to the elimination of ethanol and hydrogen chloride from one molecule of **1** with two molecule of **2**. The elemental analyses support the assigned structure **3**.

The formation of **3** is probably presumed to proceed by successive addition of isothiocyanates **2** to the amino group and methylene carbon of carboethoxymethylamino moiety of **1** followed by double cyclization with elimination of ethanol and hydrogen chloride.

We further examined the preparation of novel tricyclic ring systems by the reaction of 5(4)-amino-4(5)-chloropyridazin-3(2*H*)-ones **6** (**10**) [8] and 5(4)-(1-methylhydrazino)-

Scheme 1

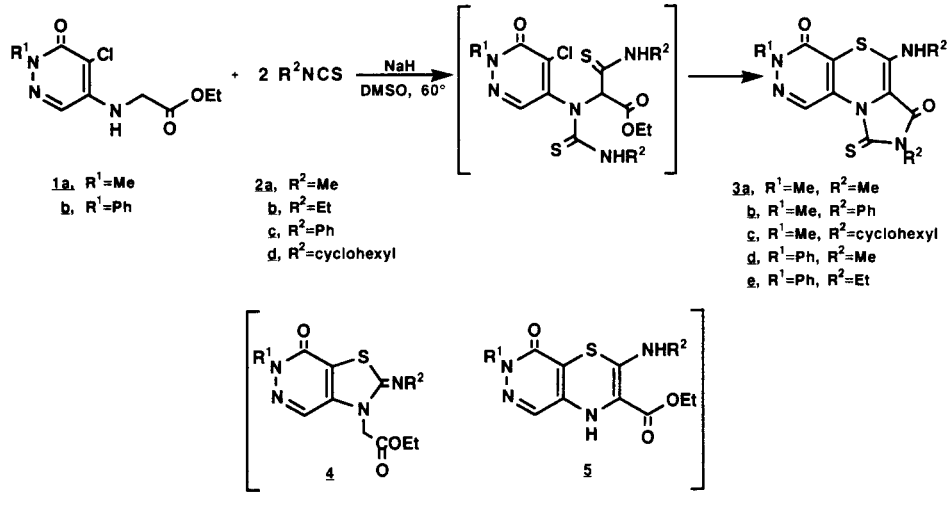


Table 1

2,7-Disubstituted 4-Amino-2*H*,7*H*-imidazo[3,4-*d*]pyridazino[4,5-*b*][1,4]thiazine-3,6-dione-1-thiones **3a-e**

No.	R^1	R^2	mp (°C) [a]	Yield (%)	IR (cm^{-1})	Mass (M^+)	^{1}H-NMR (ppm) (CF_3COOD)
3a	Me	Me	>300	54	3220 (NH), 1672 (C=O) 1625 (C=O)	309	3.49 (s, 3H, NCH_3), 401 (s, 6H, NCH_3 x 2), 11.16 (s, 1H, CH=)
3b	Me	Ph	>300	55	3200 (NH), 1680 (C=O) 1628 (C=O)	433	3.92 (s, 3H, NCH_3), 7.09-7.77 (m, 10H, Ph x 2), 11.05 (s, 1H, CH=)
3c	Me	cyclohexyl	263-265	32	3200 (C=O), 1660 (C=O) 1631 (C=O)	445	0.90-2.17 (m, 20H, CH_2 x 10), 2.33-2.54 (m, 2H, NCH x 2), 3.62 (s, 3H, NCH_3), 11.38 (s, 1H, CH=)
3d	Ph	Me	>300	54	3228 (NH), 1682 (C=O) 1641 (C=O)	371	3.32 (s, 3H, NCH_3), 3.40(s, 3H, NCH_3), 7.51 (s, 5H, Ph), 11.35 (s, 1H, CH=)
3e	Ph	Et	278-279	35	3240 (NH), 1681 (C=O) 1635 (C=O)	399	1.36 (t, 3H, J = 7 Hz, CH_3), 1.44 (t, 3H, J = Hz, CH_3), 3.71 (q, 2H, J = 7 Hz, CH_2), 4.19 (q, 2H, J = 7 Hz, CH_2), 7.58 (s, 5H, Ph), 11.31 (s, 1H, CH=)

No.	R^1	R^2	Formula	Analysis (%) Calcd. (Found) C	H	N
3a	Me	Me	$C_{11}H_{11}N_5O_2S_2$	42.71 (42.72)	3.58 (3.60)	22.64 (22.72)
3b	Me	Ph	$C_{21}H_{15}N_5O_2S_2$	58.18 (57.93)	3.49 (3.53)	16.15 (16.03)
3c	Me	cyclohexyl	$C_{21}H_{27}N_5O_2S_2$	56.60 (56.53)	6.11 (6.22)	15.72 (15.40)
3d	Ph	Me	$C_{16}H_{13}N_5O_2S_2$	51.74 (51.86)	3.53 (3.97)	18.85 (18.87)
3e	Ph	Et	$C_{18}H_{17}N_5O_2S_2$	54.12 (53.83)	4.29 (4.31)	17.53 (17.41)

[a] Recrystallization from dimethylformamide.

4(5)-chloropyridazin-3(2*H*)-ones **13** (**16**) [9] with 2,2-dimethoxyethylisothiocyanate **7**. The reactions of **6** and **10** with isothiocyanate **7** were successfully carried out in DMSO in the presence of sodium hydride to afford yellow crystalline products identified as thiazolo[4,5-*d*]pyridazinone **8** and **11** in 92 and 52% yields, respectively. Unfortunately, the cyclization of **8** and **11** to tricyclic compounds **9** and **12** in the presence of acidic catalyst resulted in failure.

Scheme 2

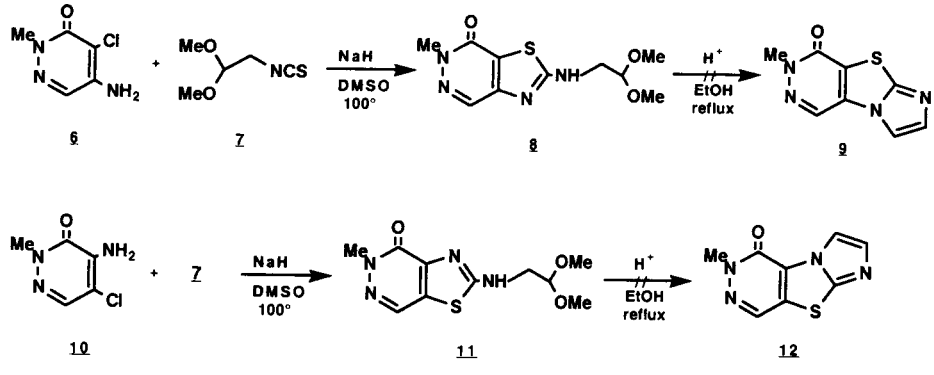


Table 2

2-Amino-4*H*-pyridazino[4,5-*e*][1,3,4]thiazin-8 (7*H*)-one **14** and 8-Substituted 5*H*-Imidazo[2,1-*b*]pyridazino[4,5-*e*][1,3,4]thiadiazin-9(8*H*)-one **15**

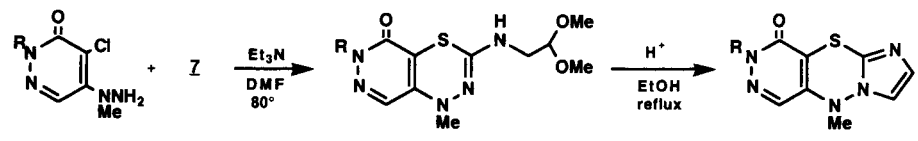
No.	R	mp (°C) [a]	Yield (%)	IR (cm^{-1})	Mass (M^+)	^{1}H-MNR (ppm) ($CDCl_3$)
14a	Me	125-126	21	3310 (NH) 1625 (C=O)	299	3.23 (s, 3H, NCH_3), 3.37 (s, 6H, OCH_3 x 2) 3.38-3.52 (m, 2H, CH_2), 3.71 (s, 3H, $CONCH_3$) 4.29-4.51 (m, 2H, CH and NH), 7.48 (s, 1H, CH=)
14b	Ph	159-160	12	3325 (NH) 1628 (C=O)	361	3.30 (s, 3H, NCH_3), 3.38 (s, 6H, OCH_3 x 2) 3.38-3.50 (m, 2H, CH_2), 4.41-4.59 (m, 2H, CH and NH), 7.25-7.58 (m, 5H, Ph), 7.64 (s, 1H, CH=)
14c	Bzl	115-116	10	3338 (NH) 1620 (C=O)	375	3.23 (s, 3H, NCH_3), 3.37 (s, 6H, OCH_3 x 2) 3.38-3.49 (m, 2H, CH_2), 4.33-4.62 (m, 2H, CH and NH), 5.25 (s, 2H, PhCH_2), 7.16-7.64 (m, 6H, Ph and CH=)
15a	Me	183-184	64	1636 (C=O)	235	3.30 (s, 3H, NCH_3), 3.76 (s, 3H, $CONCH_3$) 7.07 (s, 2H, CH= x 2), 7.54 (s, 1H, CH=)
15b	Ph	175-176	89	1630 (C=O)	297	3.37 (s, 3H, NCH_3), 7.10 (s, 2H, CH= x 2) 7.32-7.66 (m, 5H, Ph), 7.68 (s, 1H, CH=)
15c	Bzl	157-158	97	1628 (C=O)	311	3.28 (s, 3H, NCH_3), 5.28 (s, 2H, PhCH_2), 7.06 (s, 2H, CH= x 2), 7.15-7.51 (m, 5H, Ph), 7.55 (s, 1H, CH=)

No.	R	Formula	Analysis (%) Calcd. (Found) C	H	N
14a	Me	$C_{11}H_{17}N_5O_3S$	44.14 (44.50)	5.72 (5.70)	23.40 (23.25)
14b	Ph	$C_{16}H_{19}N_5O_3S$	53.17 (52.79)	5.30 (5.17)	19.38 (19.38)
14c	Bzl	$C_{17}H_{21}N_5O_3S$	54.38 (54.14)	5.64 (5.53)	18.65 (18.37)
15a	Me	$C_9H_9N_5OS$	45.95 (46.03)	3.86 (3.76)	29.77 (29.60)
15b	Ph	$C_{14}H_{11}N_5OS$	56.55 (56.16)	3.73 (3.76)	23.55 (23.29)
15c	Bzl	$C_{15}H_{13}N_5OS$	57.86 (57.83)	4.21 (4.22)	22.49 (21.99)

[a] Recrystallization from ethanol-isopropyl ether.

On the other hand, heating of 5-(1-methylhydrazino)-4-chloropyridazin-3(2*H*)-ones **13** with **7** in DMF at 80° in the presence of triethylamine produced pyridazino[4,5-*e*]-[1,3,4]thiadiazines **14** in low yields, and the cyclization to the novel tricyclic heterocycles was successfully carried out in concentrated sulfuric acid-ethanol under reflux to afford imidazo[2,1-*b*]pyridazino[4,5-*e*][1,3,4]thiadiazines **15** in 64-97% yield. The ^{1}H-nmr spectra of **15** showed a singlet signal at 7.06-7.10 ppm region assignable to two sp^2 methine protons of the imidazole ring. The assigned structure **15** was also supported by the elemental analyses and mass spectral data.

Scheme 3

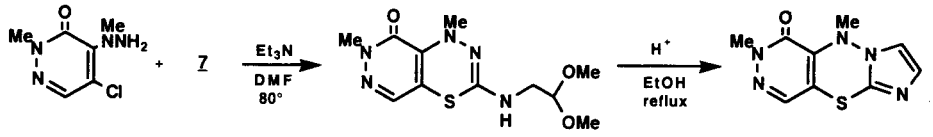


13a, R=Me
b, R=Ph
c, R=Bzl

14a-c

15a-c

Scheme 4



Analogously, when 4-(1-methylhydrazino)-5-chloropyridazin-3(2*H*)-one **16**, a regioisomer of **13**, was treated with **7** under the similar conditions, the novel tricyclic compound **18** was produced *via* pyridazinothiadiazine **17**, as is to be expected. The structure of **18** was assigned by their ir, ^{1}H-nmr, mass spectral data and the elemental analyses.

The application of hydrazinopyridazinone to the preparation of other tricyclic compounds is currently being investigated.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO IRA-1 grating ir spectrometer. The ^{1}H-nmr spectra were determined with a HITACHI R-600 spectrometer using tetramethylsilan as an internal standard. Mass spectra were measured with a JEOL JMS-DX 303 mass spectrometer.

5-Carboethoxymethylamino-4-chloropyridazin-3(2*H*)-one (**1**).

To a stirred solution of 2-substituted 4,5-dichloro-3(2*H*)-pyridazin-3(2*H*)-ones [10,11] (30 mmoles) and ethyl glycinate hydrochloride (12.56 g, 90 mmoles) in ethanol (100 ml) was added triethylamine (12.54 ml, 90 mmoles). The solution was refluxed for 2 days. After evaporation of the ethanol under reduced pressure, cold water (100 ml) was poured into the residue. Precipitated solid was collected and recrystallized from appropriate solvents to give compounds **1**.

Compound **1a** (3.38 g, 45%) had mp (ethanol) 190-191°; ir (potassium bromide): ν max cm^{-1} 3355 (NH), 1736 (C=O); ^{1}H-nmr (DMSO-d$_6$): δ 1.20 (t, 3H, J = 7 Hz, CH_2CH_3), 3.60 (s, 3H, NCH_3), 3.85-4.42 (m, 4H, CH_2CH_3 and NCH_2), 6.75 (br, 1H, NH), 7.77 (s, 1H, CH=); ms: m/z 245 (M$^+$).

Anal. Calcd. for $C_9H_{12}ClN_2O_3$: C, 44.00; H, 4.92; N, 17.10. Found: C, 43.96; H, 4.87; N, 17.13.

Compound **1b** (5.80 g, 63%) had mp (ethanol-isopropyl ether) 126-127°; ir (potassium bromide): ν max cm^{-1} 3335 (NH), 1738 (C=O); ^{1}H-nmr (DMSO-d$_6$): δ 1.30 (t, 3H, J = 7 Hz, CH_2CH_3), 3.96-4.53 (m, 4H, CH_2CH_3 and NCH_2), 5.48 (br, 1H, NH), 7.25-7.68 (m, 6H, Ph and CH=); ms: m/z 307 (M$^+$).

Anal. Calcd. for $C_{14}H_{14}ClN_3O_3$: C, 54.64; H, 4.59; N, 13.65. Found: C, 54.62; H, 4.36; N, 13.76.

Imidazo[3,4-*d*]pyridazino[4,5-*b*][1,4]thiazine (**3**).

Compound **1** (5 mmoles) was added to a solution of isothiocyanate **2** (15 mmoles) and 60% sodium hydride (0.60 g, 15 mmoles) in anhydrous dimethyl sulfoxide (20 ml). The reaction mixture was stirred for 3 hours at 60° under argon atmosphere. After removal of the dimethylsulfoxide, cold water (300 ml) was poured into the residue and the separated red crystals were filtered. The crude product was recrystallized from dimethylformamide. The results are summarized in Table 1.

2,2-Dimethoxyethylisothiocyanate (**7**).

This compound was synthesized according to a procedure used by Moore and Crossley [12]. To a stirred solution of sodium hydroxide (72 g, 1.8 moles) in water (160 ml) and carbon disulfide (110 ml, 1.8 moles), cooled to 10-15°, was added 2,2-dimethoxyethylamine (196 ml, 1.8 moles) over a period of 30 minutes. Stirring was continued, and the mixture was heated for 2 hours at 80°. The red solution was cooled to 35-40°, and then ethyl chlorocarbonate (175 ml, 1.8 moles) was added dropwise to the reaction mixture over a period of 1 hour. After stirring for further 30 minutes, the reaction mixture was extracted with ether (3 x 150 ml) and the extract was dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue was distilled under reduced pressure to give isothiocyanate **7** (225 g, 85%) as volatile liquid, bp 94°/25 mm; ir (film): ν max cm^{-1} 2120 (N=C=S); ^{1}H-nmr (deuteriochloroform): δ 3.45 (s, 6H, OCH_3 x 2), 3.60 (d, 2H, J = 5 Hz, CH_2), 4.60 (t, 1H, J = 5 Hz, CH); ms: CI m/z 148 (M+1)$^+$.

2-Aminothiazolo[4,5-*d*]pyridazin-4(5*H*)-one (**8**).

To a mixture of 5-amino-4-chloropyridazine **6** [8] (0.80 g, 5 mmoles) and 60% sodium hydride (0.40 g, 10 mmoles) in anhydrous dimethyl sulfoxide (20 ml) was added isothiocyanate **7** (1.4 g, 10 mmoles). The solution was stirred for 15 hours at 100° under argon atmosphere. The solvent was evaporated *in vacuo*, dichloromethane (100 ml) was added to the residue, and the solution was washed with water and dried over anhydrous magnesium sulfate. After removal of dichloromethane, the resulting crude product was recrystallized from ethanol-isopropylether to afford **8** (1.24 g, 92%), mp 132-133°; ir (potassium bromide): ν max cm^{-1} 3275 (NH), 1635 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.43 (s, 6H, OCH_3 x 2), 3.48-3.73 (m, 2H, CH_2), 3.84 (s, 3H, NCH_3), 4.60 (t, 1H, J = 5 Hz, CH), 7.05 (br, 1H, NH), 8.08 (s, 1H, CH=); ms: m/z 270 (M$^+$).

Anal. Calcd. for $C_{10}H_{14}N_4O_3S$: C, 44.43; H, 5.22; N, 20.73. Found: C, 44.51; H, 5.17; N, 20.77.

2-Aminothiazolo[4,5-*d*]pyridazin-7(6*H*)-one (**11**).

Compound **10** [8] (0.80 g, 5 mmoles) was allowed to react with isothiocyanate **7** (1.47 g, 10 mmoles) in the same manner as described for the preparation of **8** to give fused pyridazinone **11** (0.70 g, 52%), mp 220° (ethanol); ir (potassium bromide): ν max cm^{-1} 3200 (NH), 1660 (C=O); ^{1}H-nmr (DMSO-d$_6$): δ 3.33 (s, 6H, OCH_3 x 2), 3.42-3.62 (m, 2H, CH_2), 3.68 (s, 3H, NCH_3), 4.56 (t, 1H, J = 5 Hz, CH), 8.27 (s, 1H, CH=), 8.67 (br, 1H, NH); ms: m/z 270 (M$^+$).

Anal. Calcd. for $C_{10}H_{14}N_4O_3S$: C, 44.43; H, 5.22; N, 20.73.

Found: C, 44.89; H, 5.24; N, 20.87.

2-Amino-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-8(7*H*)-one (**14**).

To a stirred solution of hydrazinopyridazine **13** (10 mmoles) and triethylamine (2.09 ml, 15 mmoles) in dimethylformamide (50 ml) was added isothiocyanate **7** (2.21 g, 15 mmoles). The reaction mixture was heated for 5-12 hours at 80°. After removal of the solvent *in vacuo*, the residue was dissolved into water (100 ml) and extracted with chloroform (3 x 70 ml). The extract was dried over anhydrous magnesium sulfate, evaporated, and the resulting crude product was purified by column chromatography on silica gel with chloroform as an eluent to give compound **14**. The results are shown in Table 2.

8-Substituted 5*H*-Imidazo[2,1-*b*]pyridazino[4,5-*e*][1,3,4]thiadiazin-9(8*H*)-one (**15**).

A solution of **14** (1 mmole) in concentrated hydrochloric acid (5 ml) and ethanol (5 ml) was refluxed for 30 minutes. After removal of ethanol, the residue was treated with water and neutralized with dilute sodium hydroxide. The separated solid was collected and recrystallized from ethanol-isopropyl ether to give **15**. The results are shown in Table 2.

5-Chloro-2-methyl-4-(1-methylhydrazino)pyridazin-3(2*H*)-one (**16**).

To a stirred solution of 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (17.90 g, 0.1 mole) in toluene (300 ml) was added dropwise methylhydrazine (15.96 ml, 0.3 moles) at room temperature. After being stirred for 24 hours, the precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with chloroform as an eluent to give compound **16** (4.10 g, 22%), mp 52-53° (ethanol); ir (potassium bromide): ν max cm^{-1} 3300, 3200 (NH), 1615 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.13 (s, 3H, NCH_3), 3.72 (s, 3H, $CONCH_3$), 4.73 (br, 2H, NH_2), 7.63 (s, 1H, CH=); ms: m/z 188 (M^+).

Anal. Calcd. for $C_6H_9ClN_4O$: C, 38.21; H, 4.81; N, 29.70. Found: C, 38.15; H, 4.59; N, 29.71.

2-Amino-4*H*-pyridazino[4,5-*e*][1,3,4]thiadiazin-5(6*H*)-one (**17**).

A mixture of compounds **16** (2.82 g, 15 mmoles), **7** (3.39 g, 23 mmoles) and triethylamine (3.21 ml, 23 mmoles) was heated for 12 hours and worked up in the same manner as described for the preparation of **14** to give fused pyridazinone **17** (0.93 g, 21%), mp 136° (ethanol-*n*-hexane); ir (potassium bromide): ν max cm^{-1} 3290 (NH), 1605 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.40 (s, 9H, OCH_3 x 2 and NCH_3), 3.69 (s, 3H, $CONCH_3$), 3.72-3.91 (m, 2H, CH_2), 4.21-4.62 (m, 2H, CH and NH), 7.30 (s, 1H, CH=); ms: m/z 299 (M^+).

Anal. Calcd. for $C_{11}H_{17}N_5O_3S$: C, 44.14; H, 5.72; N, 23.40. Found: C, 44.35; H, 5.63; N, 23.30.

7-Substituted 5*H*-Imidazo[2,1-*b*]pyridazino[4,5-*e*][1,3,4]thiadiazin-6(7*H*)-one (**18**).

Compound **17** (0.60 g, 2 mmoles) was worked up in the same manner as described above for the preparation of **15** to give **18** (0.44 g, 93%), mp 194° (ethanol-*n*-hexane); ir (potassium bromide): ν max cm^{-1} 1635 (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.39 (s, 3H, NCH_3), 3.78 (s, 3H, $CONCH_3$), 7.10 (d, 1H, J = 1 Hz, CH=), 7.21 (d, 1H, J = 1 Hz, CH=), 7.53 (s, 1H, CH=); ms: m/z 235 (M^+).

Anal. Calcd. for $C_9H_9N_5OS$: C, 45.95; H, 3.86; N, 29.77. Found: C, 46.22; H, 3.86; N, 29.67.

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