Polycyclic *N*-Hetero Compounds. XXIX. Synthesis and Antidepressive Evaluation of 15-Thia-11,13-diazasteroidal Analogues and Their Precursors

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Syntheses of novel 15-thia-11,13-diazasteroidal skeleton **IV** and its D-homo analogues are described. Mesoionic derivatives of **IV** were also synthesized. Antidepressive activities of these compounds and their precursors were screened. D-Dihomothiadiazasteroid **IX** and 3,4,5,6-tetrahydrobenzo[*h*]quinazoline-4-thione (**V**) exhibited antireserpine action.

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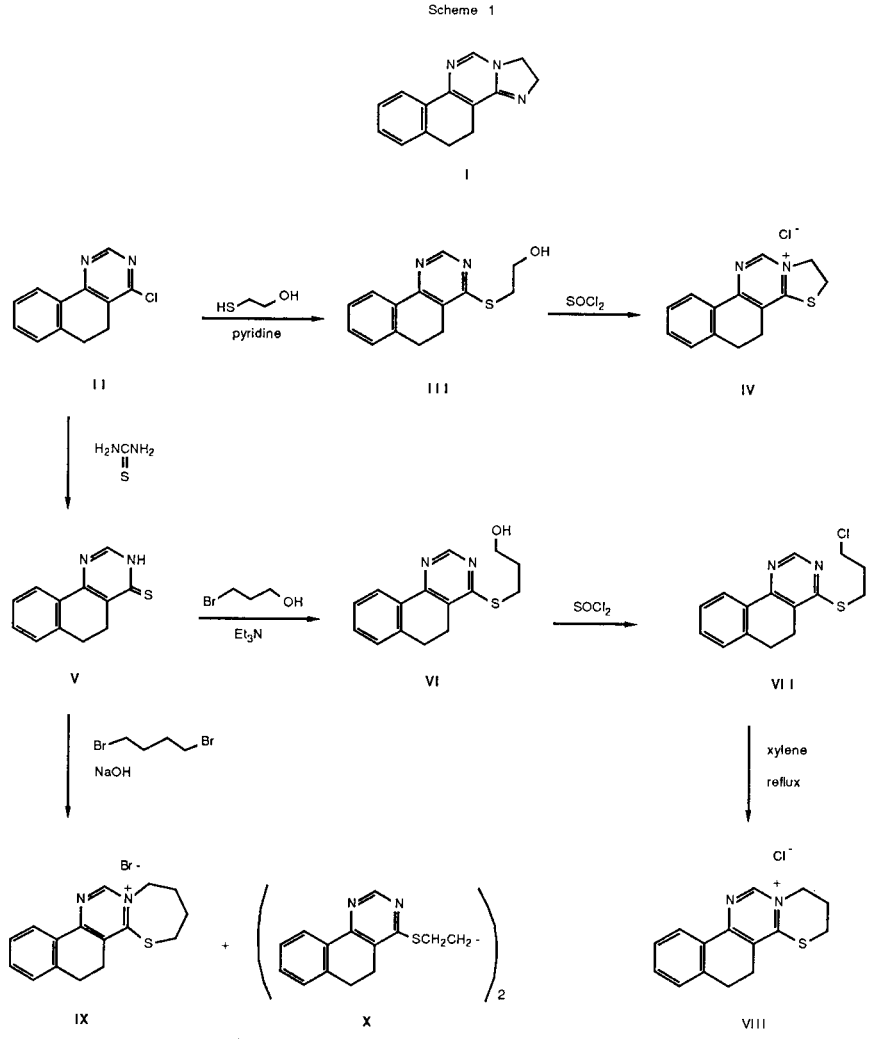
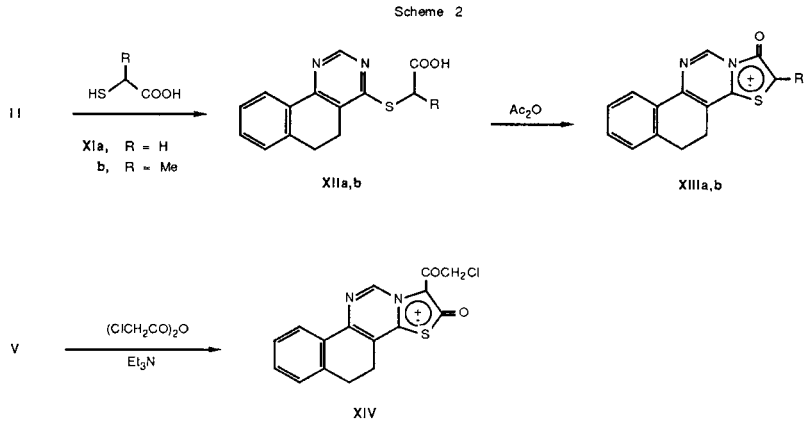
In the previous paper, we reported that 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (**I**) [1], corresponding to 11,13,15-triazasteroidal compound, and its D-homologue [2] exhibited antidepressive activity in mice. During the course of studies in this series, concerning the structure-activity relationship between azasteroid and antidepressive action, synthesis of 15-thia-11,13-diazasteroidal analogue was designed from a point of view of its similarity of the structure. Furthermore, since the ring system was not reported in literatures, additional interest prompted us to synthesize the thiadiazasteroidal skeleton.

Scheme 1



Scheme 2



As shown in Scheme 1, 4-chloro-5,6-dihydrobenzo[*h*]-quinazoline (**II**) [3] was used as starting material. Reaction of **II** with 2-mercaptoethanol gave 4-(2-hydroxyethylthio)-5,6-dihydrobenzo[*h*]quinazoline (**III**). Cyclization of **III** with thionyl chloride afforded 1,2,4,5-tetrahydrobenzo[*h*]-thiazolo[3,2-*c*]quinazolinium chloride (**IV**), corresponding to 15-thia-11,13-diazasteroidal skeleton. On the other hand, 4-thione derivative **V** was synthesized by heating of **II** with thiourea in 2-methoxyethanol. Treatment of **V** with 3-bromo-1-propanol in the presence of triethylamine afforded 4-(3-hydroxypropylthio)-5,6-dihydrobenzo[*h*]-quinazoline (**VI**), which was not cyclized with thionyl chloride, but gave 4-(3-chloropropylthio)-5,6-dihydrobenzo[*h*]quinazoline (**VII**). Mass spectrum of **VII** showed parent peak at 290 with M + 2 isotopic peak (relative intensity 3 to 1). Heating of **VII** in xylene gave D-homo-15-thia-11,13-diazasteroid **VIII**.

Similar reaction of **III** with 1,4-dibromobutane in the presence of 1.1 equivalent of 1*N* sodium hydroxide afforded D-dihomo-15-thia-11,13-diazasteroid **IX** and dimer **X**.

For the purpose of synthesis of novel meso-ionic thiadiazasteroid, compound **II** was allowed to react with mercaptoacetic acid derivatives **XIa,b**, and 2-(5,6-dihydro-4-benzo[*h*]quinazolinylthio)acetic acids **XIIa,b** were yielded. Cyclization of **XII** with acetic anhydride afforded meso-ionic compounds **XIIIa,b**. In pmr spectra of **XIII**, meso-ionic ring proton of **XIIIa** appeared at δ 5.58 as one-proton singlet, which was exchangeable with deuterium oxide, and methyl signal of **XIIIb** did at δ 2.45 as singlet.

Since Maki *et al.* [4] reported that synthesis of meso-ionic imidazo[2,1-*i*]purines by the reaction of adenines with chloroacetic anhydride, this method was applied to compound **V**. Reaction of **V** with chloroacetic anhydride in the presence of triethylamine gave meso-ionic compound **XIV** which showed positive Beilstein test. The pmr spectrum of **XIV** showed two-proton singlet at δ 4.85 attributable to methylene group of side chain.

Antidepressive activities of these 15-thia-11,13-diazasteroids and their precursors were screened by evaluating the inhibitory action of reserpine-induced hypothermia in mice [5]. 3,4,5,6-Tetrahydrobenzo[*h*]quinazoline-4-thione (**V**) and D-dihomo-15-thia-11,13-diazasteroid **IX** exhibited effective action. These data are shown in Table I.

EXPERIMENTAL

The melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spec-

Table I

Effects of **V** and **IX** on Reserpine-Induced Hypothermia in Mice

Compound	Body temperature (°C) mean value ± SD				
	Before administration	Time after administration			
		30 minutes	1 hour	2 hours	4 hours
saline	22.6 ± 0.6	23.5 ± 0.3	24.2 ± 0.4	25.4 ± 1.4	28.4 ± 1.5
V	22.7 ± 0.6	24.8 ± 0.9	26.3 ± 1.2 [a]	28.5 ± 1.6 [a]	31.3 ± 1.0 [a]
IX	22.5 ± 0.8	24.7 ± 1.0	25.8 ± 0.8 [a]	27.6 ± 0.7 [a]	28.7 ± 1.6

Five male ICR-JCL mice weighing 21 to 29 g were used in all experiments and test compounds (10 mg/kg, i. p.) were injected 18 hours following the administration of reserpine (2 mg/kg, i. p) to mice.
[a] Significantly different from the control at $p < 0.05$.

tra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer. The nmr spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm were measured relative to tetramethylsilane as an internal standard. The ms spectra were taken with a Shimadzu LKB-9000 instrument at 70eV.

IUPAC numbering was used in the experimental section.

4-(2-Hydroxyethylthio)-5,6-dihydrobenzo[*h*]quinazoline (**III**).

A mixture of 433 mg (2 mmoles) of **II**, 3 ml of 2-mercaptoethanol and 1 ml of pyridine was heated at 100° for 1 hour. After addition of water, the mixture was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The resulting viscous oil was recrystallized from benzene-*n*-hexane to give 418 mg (81%) of **III** as pale yellow needles, mp 78-80°; ms: m/z 258 (M^+); ir (potassium bromide): cm^{-1} 3390 (O-H); pmr (deuteriochloroform): 2.95 (4H, s, H-5 and 6), 3.45 (2H, t, J = 6 Hz, SCH_2), 4.00 (2H, m, OCH_2, changed to triplet on addition of deuterium oxide, J = 6 Hz), 7.41 (3H, m, H-7, 8 and 9), 8.31 (1H, m, H-10), 8.85 (1H, s, H-2).

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.08; H, 5.46; N, 10.84. Found: C, 64.82; H, 5.45; N, 10.63.

1,2,4,5-Tetrahydrobenzo[*h*]thiazolo[3,2-*c*]quinazolinium Chloride (**IV**) as the Monohydrate.

A solution of 258 mg (1 mmole) of **III** and 0.2 ml of thionyl chloride in 10 ml of alcohol-free, dry chloroform was stirred at room temperature for 10 hours. After evaporation of the solvent, the residue was triturated with 5 ml of water, and the mixture was evaporated to dryness. The resulting solid was recrystallized from diluted ethanol to give 177 mg (64%) of **IV** as yellowish needles, mp 203-205° dec; ms: m/z 241 (M $-H_2O$ -Cl), 213 (M $-H_2O$ -Cl $-(CH_2)_2$); ir (potassium bromide): cm^{-1} 3420 (water); pmr (DMSO-d_6): 3.05 (4H, m, H-4 and 5), 3.96 (2H, t, J = 8 Hz, SCH_2), 5.16 (2H, t, J = 8 Hz, NCH_2), 7.55 (3H, m, H-6, 7 and 8), 8.30 (1H, dd, J = 7.5 Hz, 1.5 Hz, H-9), 9.57 (1H, s, H-11).

Anal. Calcd. for $C_{14}H_{13}ClN_2S \cdot H_2O$: C, 57.03; H, 5.12; N, 9.50. Found: C, 56.89; H, 5.23; N, 9.35.

3,4,5,6-Tetrahydrobenzo[*h*]quinazoline-4-thione (**V**).

A solution of 2.17 g (10 mmoles) of **II** and 3.80 g (50 mmoles) of thiourea in 70 ml of 2-methoxyethanol was refluxed for 20 hours. After evaporation of the solvent, the residue was treated with 2*N* sodium hydroxide and the mixture was filtered. The alkaline filtrate was acidified with acetic acid. The precipitated yellow crystals were recrystallized from benzene to give 1.63 g (76%) of **V** as yellowish needles, mp 208-210°; ms: m/z 214 (M^+), 213 (M^+ -H); ir (potassium bromide): cm^{-1} 3150 (N-H); pmr (DMSO-d_6): 2.98 (4H, br s, H-5 and 6), 7.37 (3H, m, H-7, 8 and 9), 8.12 (1H, m, H-10), 8.36 (1H, s, H-2), 13.95 (1H, br, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07. Found: C, 67.13; H, 4.57; N, 13.02.

4-(3-Hydroxypropylthio)-5,6-dihydrobenzo[*h*]quinazoline (**VI**).

A solution of 428 mg (2 mmoles) of **V**, 0.72 ml (8 mmoles) of 3-bromopropanol and 1.12 ml (8 mmoles) of triethylamine in 20 ml of 2-methoxyethanol was heated at 80° for 8 hours. The reaction mixture was evaporated to dryness, and 25 ml of 1*N* sodium hydroxide was added to the residue, which was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The oily residue was chromatographed on silica gel. The chloroform-ethyl acetate (9:1, v/v) eluate was recrystallized from *n*-hexane to give 381 mg (70%) of colorless prisms, mp 72.5-73°; ms: m/z 272 (M^+); ir (potassium bromide): cm^{-1} 3280 (O-H); pmr (deuteriochloroform): 1.98 (2H, m, CH_2CH_2OH), 2.94 (4H, br s, H-5 and 6), 3.44 (2H, t, J = 6.3 Hz, SCH_2), 3.56 (2H, br q, J = 6 Hz, OCH_2, changed to triplet on addition of deuterium oxide), 7.30 (3H, m, H-7, 8 and 9), 8.27 (1H, m, H-10), 8.84 (1H, s, H-2).

Anal. Calcd. for $C_{15}H_{16}N_2OS$: C, 66.14; H, 5.92; N, 10.28. Found: C, 66.15; H, 5.89; N, 10.42.

4-(3-Chloropropylthio)-5,6-dihydrobenzo[*h*]quinazoline (**VII**).

A solution of 354 mg (1.3 mmoles) of **VI** and 0.26 ml (3.6 mmoles) of thionyl chloride in 10 ml of dry, alcohol-free chloroform was stirred at room temperature for 4 hours. After evaporation of the solvent, 5 ml of water was added to the residue, and the mixture was evaporated to dryness. The residue was recrystallized from diluted ethanol to give 201 mg (53%) of **VII** as ivory-colored granules, mp 76-76.5°; ms: m/z 290 (M^+): 292 ($M^+ + 2$) = 3:1; pmr (deuteriochloroform): 2.25 (2H, quin, J = 6 Hz, CH_2CH_2Cl), 2.93 (4H, m, H-5 and 6), 3.43, 3.72 (each 2H, t, J = 6 Hz, SCH_2, $ClCH_2$), 7.32 (3H, m, H-7, 8 and 9), 8.29 (1H, m, H-10), 8.88 (1H, s, H-2).

Anal. Calcd. for $C_{15}H_{15}ClN_2S$: C, 61.95; H, 5.19; N, 9.63. Found: C, 61.72; H, 5.15; N, 9.55.

2,3,5,6-Tetrahydro-1*H*-benzo[*h*][1,3]thiazino[3,2-*c*]quinazolinium Chloride (**VIII**) as the Monohydrate.

A solution of 151 mg (0.52 mmole) of **VII** in 5 ml of xylene was refluxed for 5 hours. After cooled, the precipitated crystals were collected and recrystallized from diluted ethanol to give 107 mg (67%) of **VIII** as pale brown needles, mp 257-260° dec; ms: m/z 255 (M $-H_2O$ -Cl), 213 (M $-H_2O$ -Cl $-(CH_2)_3$); ir (potassium bromide): cm^{-1} 3350 (water); pmr (DMSO-d_6): 2.31 (2H, m, H-2), 3.01 (4H, m, H-5 and 6), 3.54 (2H, t, J = 6 Hz, H-3), 4.60 (2H, br t, J = 5.5 Hz, H-1), 7.49 (3H, m, H-7, 8 and 9), 8.27 (1H, br d, J = 7.5 Hz, H-10), 9.37 (1H, s, H-12).

Anal. Calcd. for $C_{15}H_{15}ClN_2S \cdot H_2O$: C, 58.33; H, 5.54; N, 9.07. Found: C, 58.40; H, 5.38; N, 9.09.

1,2,3,4,6,7-Hexahydrobenzo[*h*][1,3]thiazepino[3,2-*c*]quinazolinium Bromide (**IX**) as the Monohydrate and 1,4-Bis(5,6-dihydro-4-benzo[*h*]-quinazolinylthio)butane (**X**).

A solution of 428 mg (2 mmoles) of **V**, 2.2 ml of 1*N* sodium hydroxide and 864 mg (4 mmoles) of 1,4-dibromobutane in 15 ml of 2-methoxyethanol-water (1:1, v/v) was heated at 100° for 5 hours under nitrogen. After cooled, the precipitated crystals were collected and recrystallized from benzene-cyclohexane to give 308 mg (64%) of **X**, mp 206-209°; ms: m/z 482 (M^+), 269 (M^+ -213), 241 (M^+ -241), 213 (M^+ -269); pmr (deuteriochloroform): 1.96 (4H, m, SCH_2CH_2), 2.92 (8H, m, H-5 and 6), 3.37 (4H, br t, J = 7 Hz, 2 x SCH_2), 7.30 (6H, m, H-7, 8 and 9), 8.29 (2H, m, H-10), 8.89 (2H, s, H-2).

Anal. Calcd. for $C_{28}H_{26}N_4S_2$: C, 69.67; H, 5.42; N, 11.60. Found: C, 69.90; H, 5.36; N, 11.48.

The mother liquor consisted of diluted 2-methoxyethanol was evaporated, and the residue was recrystallized from dioxane to give 242 mg (33%) of **IX** as pale orange powder, mp 247-250° dec; ms: m/z 269 (M $-H_2O$ -Br), 213 (M $-H_2O$ -Br $-(CH_2)_4$); ir (potassium bromide): cm^{-1} 3300, 3220 (water); pmr (DMSO-d_6): 2.10 (4H, m, H-2 and 3), 3.20 (4H, m, H-6 and 7), 3.45 (2H, m, H-4), 4.85 (2H, m, H-1), 7.54 (3H, m, H-8, 9 and 10), 8.39 (1H, m, H-11), 9.75 (1H, s, H-13).

Anal. Calcd. for $C_{16}H_{17}BrN_2S \cdot H_2O$: C, 52.31; H, 5.21; N, 7.62. Found: C, 52.05; H, 5.30; N, 7.39.

2-(5,6-Dihydro-4-benzo[*h*]quinazolinylthio)acetic Acid (**XIIa**).

A mixture of 648 mg (3 mmoles) of **II**, 0.42 ml (6 mmoles) of mercaptoacetic acid (**XIa**) and 1.04 g (7.5 mmoles) of potassium carbonate in 20 ml of 2-methoxyethanol-water (1:1, v/v) was heated at 100° for 10 hours. After evaporation of the solvent, *ca.* 10 ml of water was added to the residue. The solution was acidified with acetic acid and the precipitated crystals were recrystallized from ethanol to give 801 mg (98%) of **XIIa** as colorless needles, mp 205-207° dec; ms: m/z 272 (M^+); ir (potassium bromide): cm^{-1} 1720 (C=O); pmr (DMSO-d_6): 2.91 (4H, m, H-5 and 6), 4.10 (2H, s, SCH_2), 7.39 (3H, m, H-7, 8, and 9), 8.23 (1H, m, H-10), 8.88 (1H, s, H-2).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.74; H, 4.44; N, 10.28. Found: C, 61.68; H, 4.43; N, 10.22.

4,5-Dihydrobenzo[*h*]thiazolo[3,2-*c*]quinazolinium-1-olate (**XIIIa**).

To a solution of 272 mg (1 mmole) of **XIIa** in 1 ml of dry pyridine, was added 0.14 ml (1.5 mmoles) of acetic anhydride in 7 ml of benzene at room temperature, and the mixture was allowed to stand under argon for 1 hour. The precipitated brownish crystals were collected on a filter, washed with cold benzene and dried to give 157 mg (62%) of **XIIIa**, mp 108-111° dec; ms: m/z 254 (M^+); ir (potassium bromide): cm^{-1} 1645 (C=O); pmr (deuteriochloroform): 3.11 (4H, m, H-4 and 5), 5.58 (1H, s, H-2), 7.40 (3H, m, H-6, 7 and 8), 8.37 (1H, m, H-9), 9.59 (1H, s, H-11).

Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.01. Found: C, 65.90; H, 4.15; N, 10.88.

2-(5,6-Dihydro-4-benzo[*h*]quinazolinylthio)propionic Acid (**XIIb**).

Similar procedure was carried out as described in the synthesis of **XIIa** (reflux time, 19 hours). The precipitated crystals were recrystallized from ethanol to give colorless needles (74%), mp 197-200° dec; ms: m/z 286 (M^+); ir (potassium bromide): cm^{-1} 1715 (C=O); pmr (DMSO-d_6): 1.61 (3H, d, J = 7.5 Hz, CH_3), 2.87 (4H, m, H-5 and 6), 4.60 (1H, q, J = 7.5 Hz, SCH), 7.37 (3H, m, H-7, 8 and 9), 8.28 (1H, m, H-10), 8.88 (1H, s, H-2).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.92; N, 9.78. Found: C, 63.05; H, 4.94; N, 9.62.

2-Methyl-4,5-dihydrobenzo[*h*]thiazolo[3,2-*c*]quinazolinium-1-olate (**XIIIb**).

The same procedure was carried out as described in the synthesis of **XIIIa**, reddish needles (79%), mp 202-205°; ms: m/z 268 (M^+); ir (potassium bromide): cm^{-1} 1640 (C=O); pmr (deuteriochloroform): 2.45 (3H, s, CH_3), 3.11 (4H, br s, H-4 and 5), 7.39 (3H, m, H-6, 7 and 8), 8.35 (1H, m, H-9), 9.49 (1H, s, H-11).

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.50; N, 10.43. Found: C, 67.03; H, 4.39; N, 10.41.

1-Chloroacetyl-4,5-dihydrobenzo[*h*]thiazolo[3,2-*c*]quinazolinium-2-olate (**XIV**).

To a solution of 214 mg (1 mmole) of **V** and 1.4 ml of triethylamine in 20 ml of 1,2-dimethoxyethane, was added 456 mg (2.5 mmoles) of chloroacetic anhydride in 10 ml of 1,2-dimethoxyethane. The mixture was stirred at 40-50° for 6 hours. The reaction mixture was concentrated and the oily residue was chromatographed on silica gel. The benzene-ethyl acetate (4:1, v/v) eluate was triturated with benzene and the insoluble crystals were filtered. The crystals were washed with benzene and dried to give 122 mg (37%) of **XIV** as orange granules, mp 249-252° dec, which showed a positive Beilstein test; ms: m/z 330 (M^+) 332 ($M^+ + 2$) = 3:1; ir (potassium bromide): cm^{-1} 1675, 1610 (C=O); pmr (deuteriochloroform): 3.13 (4H, br s, H-4 and 5), 4.85 (2H, s, CH_2Cl), 7.48 (3H, m, H-6, 7 and 8), 8.45 (1H, m, H-9), 9.50 (1H, s, H-11).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S$: C, 58.09; H, 3.35; N, 8.46. Found: C, 57.87; H, 3.18; N, 8.30.

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