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SYNTHESIS OF 2-SULFANYL-4*H*-3,1-BENZOTHIAZINE DERIVATIVES BY THE REACTION OF 2-(BROMOMETHYL)PHENYL ISOTHIOCYANATES WITH THIOLS

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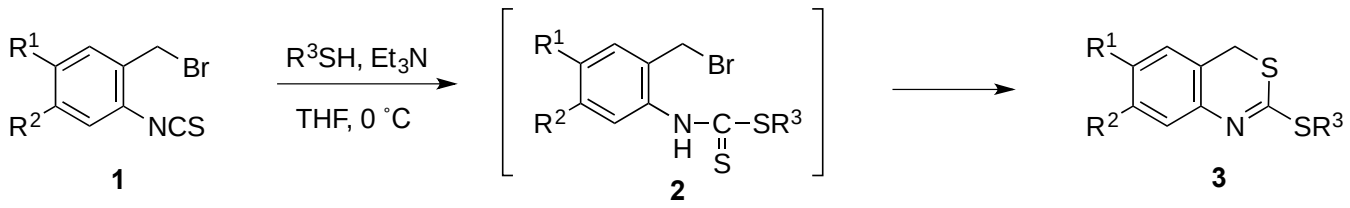
Abstract – The reaction of 2-(bromomethyl)phenyl isothiocyanates with thiols in the presence of triethylamine gave the corresponding 2-sulfanyl-4*H*-3,1-benzothiazines. The procedure was successfully applied to the preparation of 1,ω-bis[(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes using 1,ω-alkanedithiols.

Recently, several efficient syntheses of 2-sulfanyl-4*H*-3,1-benzothiazine derivatives have been reported,[1] because they have attracted much attention from a biological point of view.[1a,2] For example, Saito *et al*. have reported a synthesis by the reaction of 2-(oxiran-2-yl)phenyl isothiocyanates with thiols.[1a] We became interested in developing a facile synthetic route to 2-sulfanyl-4*H*-3,1-benzothiazines from readily available starting materials, which can be applicable to the synthesis of a novel type of 2-sulfanyl-4*H*-3,1-benzothiazine derivatives, 1,ω-bis[(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes. We have found that 2-sulfanyl-4*H*-3,1-benzothiazines (**3**) can be easily prepared by treating 2-(bromomethyl)phenyl isothiocyanates (**1**) with thiols in the presence of triethylamine[3] and the method can be successfully applied to the synthesis of 1,ω-bis[(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes (**4**) using 1,ω-alkanedithiols. In this paper the results of this investigation are reported.

One-pot synthesis of **3** from **1** and thiols was carried out as shown in Scheme 1. The starting materials were readily accessible by α-bromination of the respective 2-methylphenyl isothiocyanates,[3,4] and they were allowed to react with thiols in THF at 0 ˚C in the presence of an equivalent of triethylamine. The addition of thiols to the isothiocyanato carbon, generating the thiourea intermediates (**2**), followed by intramolecular cyclization by the nucleophilic attack of thiocarbonyl sulfur on the benzylic carbon proceeded rapidly and cleanly to afford 2-sulfanyl-4*H*-3,1-benzothiazines (**3**) in good yields as listed in

Table 1, whereas the progress of the reaction of **1a** with benzenethiol was somewhat slow to give the corresponding product (**3d**) only in moderate yield (Entry 4). In the cases of using 1,ω-alkanedithiols, the first 4*H*-3,1-benzothiazine ring was also formed rapidly, but the formation of the second one proceeded sluggishly. So, 2-(ω-sulfanylalkyl)sulfanyl-4*H*-3,1-benzothiazines (**3e**) and (**3g**) were isolated in fair yields along with low yields of the corresponding 1,ω-[bis(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes (**4b**) and (**4e**), respectively (Entries 5 and 7).



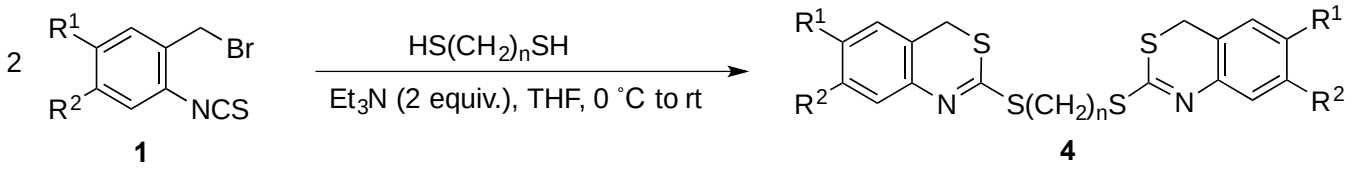
Scheme 1

Table 1. Preparation of 2-sulfanyl-4*H*-3,1-benzothiazines (**3**)

Entry	**1**	R^3	**3**	Yield/%[a]
1	**1a** (R^1 = R^2 = H)	Bn	**3a**	77
2	**1a**	$HO(CH_2)_2$	**3b**	99
3	**1a**	$EtOCOCH_2$	**3c**	89
4	**1a**	Ph	**3d**	56
5	**1a**	$HS(CH_2)_3$	**3e**	74[b]
6	**1b** (R^1 = H, R^2 = Cl)	$EtOCOCH_2CH_2$	**3f**	82
7	**1c** (R^1 = MeO, R^2 = H)	$HS(CH_2)_6$	**3g**	68[c]

[a] Isolated yields. [b] Compound **4b** was obtained in 7% yield. [c] Compound **4e** was obtained in 7% yield.

Subsequently, the preparation of 1,ω-bis[(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes (**4**) proved to be achieved by the reaction of **1** with 1,ω-alkanedithiols at a molar ratio of 2:1, as shown in Scheme 2. As mentioned above, the formation of the second 4*H*-3,1-benzothiazine ring was sluggish at 0 °C, though the reason for this is unclear. When the reaction temperature was raised to room temperature, it accelerated to give the desired products in satisfactory yields as compiled in Table 2.



Scheme 2

In conclusion, we have demonstrated that the reaction of 2-(bromomethyl)phenyl isothiocyanates with thiols in the presence of an equivalent of triethylamine provides a general and convenient method for the synthesis of 2-sulfanyl-4*H*-3,1-benzothiazine derivatives, including 1,ω-bis[(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes. The present method has advantages over previous methods because of the simplicity of the manipulations and the readily availability of the starting materials, and may provide interesting pharmacophores.

Table 2. Preparation of 1,ω-[bis(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes (**4**)

Entry	**1**	n in $HS(CH_2)_nSH$	**4**	Yield/%[a]
1	**1a** ($R^1 = R^2 = H$)	2	**4a**	85
2	**1a**	3	**4b**	70
3	**1a**	6	**4c**	64
4	**1b** ($R^1 = H$, $R^2 = Cl$)	3	**4d**	64
5	**1c** ($R^1 = MeO$, $R^2 = H$)	6	**4e**	74

[a] Isolated yields.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. High-resolution MS spectra (DART, positive) were measured by a Thermo Scientific Exactive spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. All chemicals used in this study were commercially available.

1-(Bromomethyl)-2-isothiocyanatobenzenes (1): prepared from the respective 1-isothiocyanato-2-methylbenzenes according to the previously reported procedure.[3,4] The physical, spectral, and analytical data for the new compound follow.

1-(Bromomethyl)-4-chloro-2-isothiocyanatobenzene (1b): yield: 69%; a pale-yellow liquid; R_f 0.50 (CH_2Cl_2–hexane 1:5); IR (neat) 2050 cm^{-1}; ^{1}H NMR (500 MHz) δ 4.47 (s, 2H), 7.23 (dd, J = 8.4, 2.3 Hz,

1H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H). Anal. Calcd for $C_8H_5BrClNS$: C, 36.60; H, 1.92; N, 5.33. Found: C, 36.47; H, 2.07; N, 5.23.

Typical Procedure for the Preparation of 2-Sulfanyl-4*H*-3,1-benzothiazines (3). 2-[(Phenylmethyl)sulfanyl]-4*H*-3,1-benzothiazine (3a). To a stirred solution of **1a** (0.11 g, 0.50 mmol) and BnSH (62 mg, 0.50 mmol) in THF (3 ml) at 0 °C was added Et_3N (51 mg, 0.50 mmol) dropwise. After complete consumption of the starting material (**1a**) had been confirmed by TLC analyses on silica gel (about 30 min), water (15 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to give **3a** (0.11 g, 77%); a colorless oil; R_f 0.22 (CH_2Cl_2–hexane 1:5); IR (neat) 1536 cm^{-1}; ^1H NMR (500 MHz) δ 3.90 (s, 2H), 4.50 (s, 2H), 7.11 (d, *J* = 6.9 Hz, 1H), 7.19–7.36 (m, 6H), 7.41 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR δ 30.32, 35.55, 120.22, 125.45, 126.65, 126.98, 127.30, 128.55, 128.57, 129.15, 137.27, 143.65, 160.07; MS *m/z* 271 (M^+, 73), 91 (100). Anal. Calcd for $C_{15}H_{13}NS_2$: C, 66.38; H, 4.83; N, 5.16. Found: C, 66.27; H, 4.85; N, 5.10.

2-[(2-Hydroxyethyl)sulfanyl]-4*H*-3,1-benzothiazine (3b): a pale-yellow solid; mp 147–149 °C (hexane–$CHCl_3$); IR (KBr) 3388, 1536 cm^{-1}; ^1H NMR (500 MHz) δ 3.28 (t, *J* = 4.6 Hz, 2H), 3.87 (s, 2H), 3.98 (t, *J* = 4.6 Hz, 2H), 5.12 (br s, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 30.29, 36.11, 63.15, 119.97, 125.02, 127.02, 127.10, 128.66, 143.01, 163.72. HR MS. Calcd for $C_{10}H_{12}NOS_2$ (M+H): 226.0360. Found: *m/z* 226.0359. Anal. Calcd for $C_{10}H_{11}NOS_2$: C, 53.30; H, 4.92; N, 6.22. Found: C, 53.35; H, 4.66; N, 6.47.

Ethyl 2-(4*H*-3,1-Benzothiazin-2-yl)sulfanylacetate (3c): a pale-yellow oil; R_f 0.41 (CH_2Cl_2–hexane 1:5); IR (neat) 1736, 1540 cm^{-1}; ^1H NMR (500 MHz) δ 1.28 (t, *J* = 6.9 Hz, 3H), 3.90 (s, 2H), 3.98 (s, 2H), 4.22 (t, *J* = 6.9 Hz, 2H), 7.10 (d, *J* = 6.9 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.31 (dd, *J* = 7.6, 6.9 Hz, 1H); ^{13}C NMR δ 14.16, 30.20, 33.59, 61.73, 119.80, 125.49, 126.84, 126.93, 128.56, 143.33, 158.84, 168.75. HR MS. Calcd for $C_{12}H_{14}NO_2S_2$ (M+H): 268.0466. Found: *m/z* 268.0459. Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24. Found: C, 53.75; H, 4.97; N, 5.15.

2-(Phenylsulfanyl)-4*H*-3,1-benzothiazine (3d): a colorless oil; R_f 0.08 (CH_2Cl_2–hexane 1:5); IR (neat) 1529 cm^{-1}; ^1H NMR (500 MHz) δ 3.89 (s, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.19 (td, *J* = 7.6, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.40–7.46 (m, 3H), 7.64 (dd, *J* = 7.6, 1.5 Hz, 2H); ^{13}C NMR δ 30.47, 119.37, 125.75, 126.83, 126.97, 128.49, 129.03, 129.29, 129.52, 135.09, 143.84, 162.11. HR MS. Calcd for $C_{14}H_{12}NS_2$ (M+H): 258.0411. Found: *m/z* 258.0397. Anal. Calcd for $C_{14}H_{11}NS_2$: C, 65.33; H, 4.31; N, 5.44. Found: C, 65.16; H, 4.50; N, 5.19.

2-(3-Sulfanylpropylsulfanyl)-4*H*-3,1-benzothiazine (3e): a pale-yellow oil; R_f 0.34 (AcOEt–hexane 1:5); IR (neat) 2540, 1536 cm^{-1}; ^1H NMR (500 MHz) δ 1.48 (t, *J* = 6.8 Hz, 1H), 2.06 (quint, *J* = 6.8 Hz, 2H), 2.67 (q, *J* = 6.8 Hz. 2H), 3.36 (t, *J* = 6.8 Hz, 2H), 3.89 (s, 2H), 7.10 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.19

(td, *J* = 7.6, 1.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.32 (td, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR δ 23.34, 29.47, 30.22, 33.41, 119.97, 125.45, 126.57, 126.90, 128.47, 143.54, 160.12. HR MS. Calcd for $C_{11}H_{14}NS_3$ (M+H): 256.0288. Found: *m/z* 256.0274. Anal. Calcd for $C_{11}H_{13}NS_3$: C, 51.73; H, 5.13; N, 5.48. Found: C, 51.51; H, 5.20; N, 5.35.

Ethyl 3-(7-Chloro-4*H*-3,1-benzothiazin-2-yl)sulfanylpropanoate (3f): a colorless oil; R_f 0.18 (CH_2Cl_2–hexane 1:5); IR (neat) 1733, 1534 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.27 (t, *J* = 7.6 Hz, 3H), 2.81 (t, *J* = 6.9 Hz, 2H), 3.44 (t, *J* = 6.9 Hz, 2H), 3.85 (s, 2H), 4.18 (q, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR δ 14.19, 26.45, 29.75, 34.48, 60.80, 118.45, 125.48, 126.40, 127.88, 133.87, 144.46, 162.12, 171.89. HR MS. Calcd for $C_{13}H_{15}ClNO_2S_2$ (M+H): 316.0232. Found: *m/z* 316.0228. Anal. Calcd for $C_{13}H_{14}ClNO_2S_2$: C, 49.44; H, 4.47; N, 4.43. Found: C, 49.17; H, 4.50; N, 4.34.

6-Methoxy-2-(6-sulfanylhexylsulfanyl)-4*H*-3,1-benzothiazine (3g): a colorless viscous oil; R_f 0.37 (AcOEt–hexane 1:5); IR (neat) 2563, 1608, 1542 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.33 (t, *J* = 6.8 Hz, 1H), 1.39–1.46 (m, 4H), 1.60–1.74 (m, 4H), 2.53 (q, *J* = 6.8 Hz, 2H), 3.21 (t, *J* = 6.8 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 2H), 6.63 (d, *J* = 3.0 Hz, 1H), 6.85 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 24.40, 27.68, 28.01, 29.06, 30.32, 31.05, 33.66, 55.38, 112.21, 113.32, 121.00, 126.48, 137.63, 157.02, 157.92. HR MS. Calcd for $C_{15}H_{22}NOS_3$ (M+H): 328.0863. Found: *m/z* 328.0861. Anal. Calcd for $C_{15}H_{21}NOS_3$: C, 55.01; H, 6.46; N, 4.28. Found: C, 54.94; H, 6.63; N, 4.14.

Typical Procedure for the Preparation of 1,ω-bis[(4*H*-3,1-benzothiazin-2-yl)sulfanyl]alkanes (4). 2-{3-[(4*H*-3,1-Benzothiazin-2-yl)sulfanyl]propylsulfanyl}-4*H*-3,1-benzothiazine (4b). To a stirred solution of **1a** (0.32 g, 1.4 mmol) and $HS(CH_2)_3SH$ (76 mg, 0.70 mmol) in THF (3 mL) at 0 °C was added Et_3N (0.14 g, 1.4 mmol) dropwise. The mixture was warmed to rt and stirring was continued overnight at the same temperature. After the resulting mixture was worked up as described above for the preparation of **3**, the residue was purified by column chromatography on silica gel to give **4b** (0.20 g, 70%); a colorless viscous oil; R_f 0.34 (AcOEt–hexane 1:5); IR (neat) 1537 cm^{-1}; ^{1}H NMR (500 MHz) δ 2.21 (quint, *J* = 6.9 Hz, 2H), 3.36 (t, *J* = 6.9 Hz, 4H), 3.89 (s, 4H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR δ 29.51, 30.18, 30.26, 119.98, 125.52, 126.34, 126.87, 128.48, 143.58, 160.11. HR MS. Calcd for $C_{19}H_{19}N_2S_4$ (M+H): 403.0431. Found: *m/z* 403.0428. Anal. Calcd for $C_{19}H_{18}N_2S_4$: C, 56.68; H, 4.51; N, 6.96. Found: C, 56.60; H, 4.51; N, 6.82.

2-{2-[(4*H*-3,1-Benzothiazin-2-yl)sulfanyl]ethylsulfanyl}-4*H*-3,1-benzothiazine (4a): a white solid; mp 110–112 °C (hexane–Et_2O); IR (KBr) 1533 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.60 (s, 4H), 3.90 (s, 4H), 7.11 (d, *J* = 7.6 Hz, 2H), 7.20 (td, *J* = 7.6, 1.5 Hz, 2H), 7.23 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.30 (td, *J* = 7.6, 1.5 Hz, 2H); ^{13}C NMR δ 30.29, 31.34, 119.98, 125.66, 126.72, 126.94, 128.57, 143.55, 159.70. HR MS. Calcd for $C_{18}H_{17}N_2S_4$ (M+H): 388.0274. Found: *m/z* 388.0280. Anal. Calcd for $C_{18}H_{16}N_2S_4$: C, 55.64; H, 4.15; N,

7.21. Found: C, 55.53; H, 4.26; N, 7.07.

2-{6-[(4*H*-3,1-Benzothiazin-2-yl)sulfanyl]hexylsulfanyl}-4*H*-3,1-benzothiazine (4c): a pale-yellow viscous oil; R_f 0.52 (AcOEt–hexane 1:5); IR (neat) 1535 cm^{-1}; ^1H NMR (500 MHz) δ 1.48–1.51 (m, 4H), 1.73–1.76 (m, 4H), 3.23 (t, *J* = 6.9 Hz, 4H), 3.88 (s, 4H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.18 (td, *J* = 7.6, 1.5 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR δ 28.21, 29.17, 30.31, 31.25, 120.10, 125.44, 126.48, 126.91, 128.50, 143.72, 160.64. HR MS. Calcd for $C_{22}H_{25}N_2S_4$ (M+H): 445.0900. Found: *m/z* 455.0913. Anal. Calcd for $C_{22}H_{24}N_2S_4$: C, 59.42; H, 5.44; N, 6.30. Found: C, 59.50; H, 5.46; N, 6.19.

7-Chloro-2-{3-[(7-chloro-4*H*-3,1-benzothiazin-2-yl)sulfanyl]propylsulfanyl}-4*H*-3,1-benzothiazine (4d): a white solid; mp 87–88 °C (hexane–Et_2O); IR (KBr) 1524 cm^{-1}; ^1H NMR (500 MHz) δ 2.21 (quint, *J* = 6.9 Hz, 2H), 3.34 (t, *J* = 6.9 Hz, 4H), 3.86 (s, 4H), 7.03 (d, *J* = 7.6 Hz, 2H), 7.14 (dd, *J* = 7.6, 2.3 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR δ 29.40, 29.82, 30.19, 118.46, 125.46, 126.33, 127.86, 133.84, 144.51, 162.25. HR MS. Calcd for $C_{19}H_{17}Cl_2N_2S_4$ (M+H): 469.9573. Found: *m/z* 469.9569. Anal. Calcd for $C_{19}H_{16}Cl_2N_2S_4$: C, 48.40; H, 3.42; N, 5.94. Found: C, 48.31; H, 3.60; N, 5.76.

2-{6-[(6-Methoxy-4*H*-3,1-benzothiazin-2-yl)sulfanyl]hexylsulfanyl}-4*H*-3,1-benzothiazine (4e): a pale-yellow solid; mp 77–79 °C (hexane–Et_2O); IR (KBr) 1608, 1536 cm^{-1}; ^1H NMR (500 MHz) δ 1.47–1.49 (m, 4H), 1.70–1.76 (m, 4H), 3.21 (t, *J* = 6.8 Hz, 4H), 3.81 (s, 6H), 3.85 (s, 4H), 6.62 (d, *J* = 3.0 Hz, 2H), 6.84 (dd, *J* = 8.4, 3.0 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 28.22, 29.19, 30.48, 31.22, 55.52, 112.37, 113.47, 121.15, 126.69, 137.83, 157.27, 158.76. HR MS. Calcd for $C_{24}H_{29}N_2O_2S_4$ (M+H): 505.1112. Found: *m/z* 505.1096. Anal. Calcd for $C_{24}H_{28}N_2O_2S_4$: C, 57.11; H, 5.59; N, 5.55. Found: C, 57.02; H, 5.62; N, 5.44.

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