Quinoxalines. XXVI.[1] Reactions of 2-Quinoxalinyl Thiocyanate with Nucleophiles

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2-Quinoxalinyl thiocyanate (1) possesses four electrophilic sites, *i.e.*, 2-position, 3-position, sulfur and cyano carbon, to receive nucleophilic attack. Grignard reagents attacked preferentially the sulfur atom to give sulfides (8—12). These sulfides were readily oxidazed to sulfoxides (13—17) with sodium bromite in acetic acid. Hydroxide and ethoxide ions were found to attack preferably the cyano carbon to give thiol (2), while amines (butylamine, piperidine and morpholine) and ethyl cyanoacetate carbanion attacked the carbon at the 2-position to afford the corresponding ipso-substitution products (4—7).

Keywords 2-quinoxalinyl thiocyanate; nucleophile; Grignard reagent; sulfur attack; oxidation; sodium bromite; carbanion; ipso-substitution; cyano carbon attack; amine

The reactions of N-heterocyclic thiocyanates with a few nucleophiles have been investigated mainly for synthetic purposes, to prepare thiols from thiocyanates.[2] However, no systematic investigation on the reaction between N-heterocyclic thiocyanate and various nucleophiles has been reported. Thus, we have initiated an investigation of the reaction of 2-quinoxalinyl thiocyanate (**1**) with nucleophiles.

Compound **1** possesses four reactive sites for nucleophilic attack, *i.e.*, the ring-carbon linked to the thiocyano group (site a), the sulfur atom (site b), the cyano carbon (site c), and the carbon at the 3-position (site d), (Fig. 1). The attack of nucleophiles on **1** took place at the sites a, b, and c, but the attack at the site d was not observed.

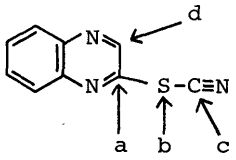

Fig. 1. Four Possible Sites for the Reaction of **1** with Nucleophiles

When a solution of **1** and sodium ethoxide in ethanol was stirred at room temperature, ethoxide ion attacked mainly the cyano carbon (site c) of **1** to give 2-quinoxalinethiol (**2**) (67%) as the major product, and also the carbon at the 2-position (site a) to afford 2-ethoxyquinoxaline (**3**) as a minor product. In the reaction of **1** with 2N NaOH, hydroxide ion attacked the site c of **1**, giving **2** as the sole product in good yield. In the reaction with amines, both primary and secondary aliphatic amines were found to attack exclusively the 2-position (site a) of **1**. Thus, butylamine, piperidine, and morpholine gave the corresponding 2-butylamino- (**4**, 68%), 2-piperidino- (**5**, 73%), and 2-morpholinoquinoxaline (**6**, 75%). No reactions between

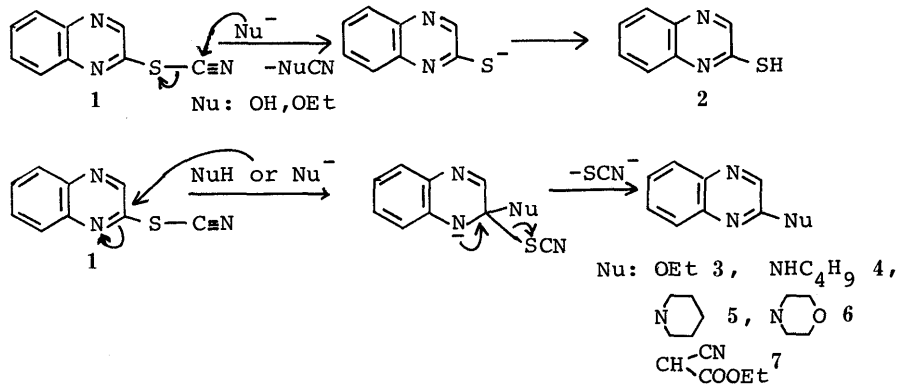

Chart 1

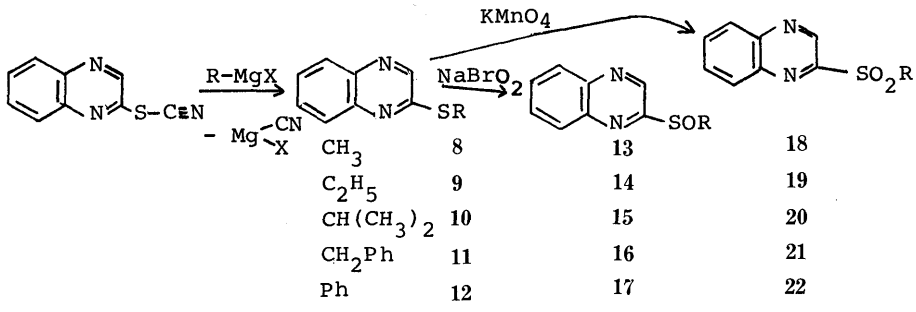

Chart 2

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TABLE I. Elemental Analysis, MS, IR, and ^{1}H-NMR Data for **9**—**11** and **13**—**17**

Compd.	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR ($CDCl_3$) ppm	MS *m/z*
9	$C_{10}H_{10}N_2S$	63.12 (63.01)	5.31 (5.38)	14.73 (14.67)	1085 (–S–)	1.41 (3H, t, J=7 Hz, CH_3), 3.33 (2H, q, J=7 Hz, CH_2), 7.40—8.10 (4H, m, C^{5-8}-H), 8.48 (1H, s, C^3-H)	190 (M^+), 175 (M^+-15), 162 (M^+-28), 157 (M^+-33)
10	$C_{11}H_{12}N_2S$	64.66 (64.81)	5.93 (6.00)	13.72 (13.65)	1080 (–S–)	1.49 (6H, d, J=7 Hz, CH_3), 4.20 (1H, m, CH), 7.40—8.10 (4H, m, C^{5-8}-H), 8.49 (1H, s, C^3-H)	204 (M^+), 189 (M^+-15), 171 (M^+-33)
11	$C_{15}H_{12}N_2S$	71.39 (71.72)	4.80 (4.87)	11.10 (10.91)	1085 (–S–)	4.49 (2H, s, CH_2), 6.90—8.20 (9H, m, C^{5-8}-H+Ph), 8.49 (1H, s, C^3-H)	252 (M^+), 219 (M^+-33), 175 (M^+-77)
13	$C_9H_8N_2OS$	56.22 (56.23)	4.20 (4.22)	14.58 (14.54)	1055 (SO)	3.03 (3H, s, CH_3), 7.65—8.35 (4H, m, C^{5-8}-H), 9.46 (1H, s, C^3-H)	192 (M^+), 176 (M^+-16), 146 (M^+-46)
14	$C_{10}H_{10}N_2OS$	58.22 (57.98)	4.90 (4.86)	13.58 (13.36)	1055 (SO)	1.32 (3H, t, J=7 Hz, CH_3), 3.20 (1H, q, J=7 Hz, 3.26 (1H, q, J=7 Hz, CH_2), 7.65—8.35 (4H, m, C^{5-8}-H), 9.40 (1H, s, C^3-H)	206 (M^+), 190 (M^+-16), 178 (M^+-28), 146 (178−32)
15	$C_{11}H_{12}N_2OS$	59.97 (59.68)	5.49 (5.51)	12.72 (12.53)	1060 (SO)	1.15 (3H, d, J=7 Hz, CH_3), 3.34 (1H, m, CH), 1.47 (3H, d, J=7 Hz, 7.60—8.30 (4H, m, C^{5-8}-H), 9.35 (1H, s, C^3-H)	220 (M^+), 204 (M^+-16), 178 (M^+-42), 162 (178−16), 130 (162−32)
16	$C_{15}H_{12}N_2OS$	67.13 (67.25)	4.52 (4.53)	10.44 (10.40)	1040 (SO)	4.15 (1H, d, J=13 Hz, CH_2), 6.80—7.40 (5H, m, Ph) 4.47 (1H, d, J=13 Hz, 7.60—8.30 (4H, m, C^{5-8}-H), 8.89 (1H, s, C^3-H)	268 (M^+), 252 (M^+-16), 219 (252−33)
17	$C_{14}H_{10}N_2OS$	66.11 (66.05)	3.97 (4.00)	11.02 (11.05)	1050 (SO)	8.30—9.25 (9H, m, C^{5-8}-H+Ph), 9.40 (1H, s, C^3-H)	254 (M^+), 237 (M^+-17), 222 (M^+-32)

TABLE II. IR and ^{1}H-NMR Spectral Data for **18**—**22**

Compd.	IR ν_{max}^{KBr} cm^{-1} (SO_2)	^{1}H-NMR ($CDCl_3$) ppm
18	1310, 1135	3.41 (3H, s, CH_3), 7.60—8.30 (4H, m, C^{5-8}-H), 9.52 (1H, s, C^3-H)
19	1310, 1115	1.41 (3H, t, J=7 Hz, CH_3), 3.56 (2H, q, J=7 Hz, CH_2), 7.80—8.40 (4H, m, C^{5-8}-H), 9.45 (1H, s, C^3-H)
20	1305, 1125	1.43 (6H, d, J=7 Hz, CH_3), 3.87 (1H, m, CH), 7.75—8.40 (4H, m, C^{5-8}-H), 9.43 (1H, s, C^3-H)
21	1315, 1125	4.75 (2H, s, CH_2), 7.20 (5H, s, Ph), 7.80—8.40 (4H, m, C^{5-8}-H), 9.10 (1H, s, C^3-H)
22	1335, 1150	7.35—8.25 (9H, m, C^{5-8}-H+Ph), 9.44 (1H, s, C^3-H)

organic thiocyanates and active methylene compounds have been reported. Compound **1** reacted with ethyl cyanoacetate in the presence of sodium hydride in hexamethylphosphoramide (HMPA) at room temperature to give ethyl α-cyano-2-quinoxalineacetate (**7**) in 75% yield. Compounds **3**—**7** are ipso-substitution products. We next examined the reaction of **1** with Grignard reagents. No reactions of N-heterocyclic thiocyanates with Grignard reagents have been reported. When **1** was stirred with Grignard reagents (3 eq) at room temperature, alkyl anions of Grignard reagents attacked the sulfur (site b) of **1** to afford sulfides. Thus, the reactions with methylmagnesium iodide and ethyl-, isopropyl-, benzyl-, and phenylmagnesium bromide gave the corresponding 2-methyl- (**8**, 85%), 2-ethyl-(**9**, 77%), 2-isopropyl- (**10**, 73%), 2-benzyl- (**11**, 73%), and 2-phenylthioquinoxaline (**12**, 85%). These sulfides were oxidized to sulfoxides, the corresponding 2-(methyl- (**13**, 69%), 2-(ethyl- (**14**, 88%), 2-(isopropyl- (**15**, 72%), 2-(benzyl- (**16**, 69%), and 2-(phenylsulfinyl)quinoxaline (**17**, 70%), with sodium bromite in acetic acid under cooling. Oxidation of sulfides with potassium permanganate in acetic acid afforded sulfones, the corresponding 2-(methyl- (**18**, 76%), 2-(ethyl- (**19**, 86%), 2-(isopropyl- (**20**, 74%), 2-(benzyl- (**21**, 85%), and 2-(phenylsulfonyl)quinoxaline (**22**, 88%). These products were characterized by comparison with authentic samples.

The experimental results may be summarized as follows. The actual reacting site among the three (sites a, b and c) in **1** varies with the reacting nucleophile. Hydroxide and ethoxide ion, being hard, attack preferentially the site c, the cyano carbon of **1**, to give thiol. Grignard reagents, being soft, attack the sulfur atom (site b), the softest reacting site for the nucleophile, to give sulfides. Amines and ethyl cyanoacetate carbanion, being relatively hard, attack the site a, the 2-position carbon of **1**, to give ipso-substitution products.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 diffraction grating IR spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in herz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and br s = broad singlet. Mass spectra (MS) were recorded on a JEOL JMS D-100 mass spectrometer. Samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Wakogel C-200 (200 mesh).

Reaction of 2-Quinoxalinyl Thiocyanate[3] (1) with 2 N NaOH A mixture of **1** (300 mg, 1.6 mmol) and 2 N NaOH (3 ml) was stirred for 2.5 h at room temperature. After neutralization of the mixture with AcOH, the resulting precipitate was collected and recrystallized from MeOH to give 220 mg (85%) of 2-quinoxalinethiol[4] (**2**), orange needles, mp 204—205 °C (lit.[4] 205 °C). *Anal.* Calcd for $C_8H_6N_2S$: C, 59.24; H, 3.73; N, 17.27. Found: C, 59.27; H, 3.67; N, 17.31. ^{1}H-NMR (in $CDCl_3$): 3.40 (1H, s, SH), 7.10—8.00 (4H, m, C^{5-8}-H), 8.62 (1H, s, C^3-H).

Reaction of 1 with EtONa Compound **1** (300 mg, 1.6 mmol) was added to an EtONa–EtOH solution [prepared from Na (45 mg, 2 mmol) and dry EtOH (5 ml)], and the mixture was stirred for 3 h at room temperature. After removal of the EtOH, the residue was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was chromatographed on a column of SiO_2 with benzene. The crude product obtained from the benzene eluate was recrystallized from petr. benzine to give 40 mg (14%) of 2-ethoxyquinoxaline[5] (**3**), colorless needles, mp 60—61 °C (lit.[5] 61 °C). After neutralization of the aqueous layer with AcOH, the resulting

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precipitate was collected and recrystallized from MeOH to give 175 mg (67%) of **2**.

Reaction of 1 with Amines In a typical experiment, a mixture of **1** (300 mg, 1.6 mmol) and butylamine (3 ml) was heated for 1 h on a water bath. The excess amine was removed under reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was chromatographed on a column of SiO_2 eluting with benzene. The crude product obtained from the benzene eluate was recrystallized from petr. benzine to give 220 mg (68%) of 2-butylaminoquinoxaline[6] (**4**), colorless needles, mp 51—52 °C. *Anal.* Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.59; H, 7.47; N, 20.64. IR ν_{max}^{KBr} cm^{-1}: 3266, 3354 (NH). MS *m/z*: 201 (M^+), 186 ($M^+ - CH_3$), 172 ($186 - CH_2$), 158 ($172 - CH_2$). ^{1}H-NMR (in $CDCl_3$): 0.95 (3H, t, J=6 Hz, CH_3), 1.10—2.00 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 3.47 (1H, q, J=6 Hz, $NHC\underline{H}_2$), 5.04 (1H, br, NH), 7.05—7.95 (4H, m, C^{5-8}-H), 8.05 (1H, s, C^3-H). Picrate, mp 183—184 °C (lit.[6] 184 °C). 2-Piperidinoquinoxaline[7] (**5**) from piperidine had mp 62—63 °C (yellow plates) (lit.[7] mp 63 °C). Yield, 250 mg (73%). 2-Morpholinoquinoxaline[7] (**6**) from morpholine had mp 88—89 °C (yellow feathers) (lit.[7] mp 89 °C). Yield, 260 mg (75%).

Reaction of 1 with Ethyl Cyanoacetate Compound **1** (300 mg, 1.6 mmol) was added to a stirred mixture of ethyl cyanoacetate (295 mg, 2.6 mmol) and 50% NaH (in oil, 145 mg, 3.0 mmol) in HMPA (4 ml), and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured onto ice-water, neutralized with AcOH, and extracted with benzene. The benzene extract was chromatographed on a column of SiO_2 eluting with benzene. The crude product obtained from the benzene eluate was recrystallized from petr. benzine–benzene to give 290 mg (75%) of ethyl α-cyano-2-quinoxalineacetate[8] (**7**), yellow plates, mp 161—162 °C (lit.[8] 162 °C).

Reaction of 1 with RMgX In a typical experiment, a solution of MeMgI [prepared from MeI (680 mg, 4.8 mmol) and Mg (120 mg, 5.0 mmol) in dry ether (10 ml)] was added to a stirred solution of **1** (300 mg, 1.6 mmol) in dry benzene (20 ml), and the mixture was stirred for 4 h at room temperature. Aqueous NH_4Cl–NH_3 (a solution of NH_4Cl (3 g) and 28% NH_3 (1 ml) in water (15 ml)) was added to the reaction mixture. The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was combined with the benzene–ether solution, and the combined solution was dried over Na_2SO_4, then concentrated. The residue from the combined solution was chromatographed on a column of SiO_2 eluting with petr. benzine–benzene. The crude product obtained from the petr. benzine–benzene eluate was recrystallized from petr. benzine to give 240 mg (85%) of 2-methylthioquinoxaline[7,9] (**8**), yellow needles, mp 46—47 °C (lit.[7] 47 °C). (The reaction of **1** with MeMgI (2.5 mmol) gave 125 mg (44%) of **8** and 90 mg (30%) of **1**.) 2-Ethylthioquinoxaline[10] (**9**) from EtMgBr had mp 46—47 °C (colorless needles) (lit.[10] mp 47 °C). 235 mg (77%). 2-Isopropylthioquinoxaline[11] (**10**) from $Me_2CHMgBr$ was yellow oil. Yield, 240 mg (73%). 2-Benzylthioquinoxaline[10] (**11**) from $PhCH_2MgBr$ had mp 43—44 °C (colorless needles) (lit.[10] mp 44 °C). Yield, 295 mg (73%). 2-Phenylthioquinoxaline[3,10] (**12**) from PhMgBr had mp 88—89 °C (colorless needles) (lit.[3] mp 89 °C). Yield, 325 mg (85%).

Preparation of Sulfides (9, 10, 11) In a typical experiment, a solution of 2-chloroquinoxaline[5] (**23**) (5.0 g, 0.03 mol) in dimethylformamide (30 ml) was added to a mixture of 2-propanethiol (3.0 g, 0.04 mol) and 10% NaOH (20 ml), and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with benzene. The benzene extract was purified by SiO_2 column chromatography with petr. benzine–benzene. Compound **10** was obtained from petr. benzine–benzene eluate in 78% yield (4.81 g). Compound **9** from ethanethiol was obtained in 78% yield (4.53 g). Compound **11** from phenylmethanethiol was obtained in 90% yield (7.01 g).

Oxidation of Sulfides (8—12) with Sodium Bromite In a typical experiment, 65% sodium bromite (1.2 eq) was added gradually to a stirred solution of **8** (1.0 g) in AcOH (10 ml) under cooling, and the mixture was stirred for 2 h on a cold water bath. The reaction mixture was diluted with water, neutralized with Na_2CO_3, and extracted with benzene. The benzene extract was chromatographed on a column of SiO_2 with petr. benzine–benzene then benzene as eluents. The crude product obtained from the petr. benzine–benzene eluate was recrystallized from benzene to give 95 mg (8%) of 2-(methylsulfonyl)quinoxaline[7,12] (**18**), colorless plates, mp 125—126 °C (lit.[7] 126 °C). The crude product obtained from the benzene eluate was recrystallized from petr. benzine–benzene to give 750 mg (69%) of 2-(methylsulfinyl)quinoxaline[13] (**13**), colorless needles, mp 104—106 °C (lit.[13] 102—103 °C). 2-(Ethylsulfinyl)quinoxaline[11] (**14**) from **9** had mp 54—55 °C (colorless needles) (lit.[11] mp 55 °C). Yield, 950 mg, (88%). 2-(Isopropylsulfinyl)quinoxaline (**15**) from **10** was yellow oil. Yield, 775 mg (72%). 2-(Benzylsulfinyl)quinoxaline (**16**) from **11** had mp 77—79 °C (colorless needles). Yield, 735 mg (69%). 2-(Phenylsulfinyl)quinoxaline (**17**) from **12** had mp 122—123 °C (colorless prisms). Yield, 750 mg (70%).

Preparation of Sulfones In a typical experiment, a solution of 3% $KMnO_4$ (about 45 ml) was added dropwise to a stirred solution of **11** (1.5 g) in AcOH (10 ml) until the purple color of the permanganate persisted. The reaction mixture was made alkaline with 20% $NaHSO_3$ (100 ml). The resulting precipitate was collected and recrystallized from petr. benzine–benzene to give 1.44 g (85%) of 2-(benzylsulfonyl)-quinoxaline (**21**), colorless needles, mp 140—142 °C. *Anal.* Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.35; H, 4.26; N, 9.85. Found: C, 63.60; H, 4.33; N, 9.80. MS *m/z*: 284 (M^+), 220 ($M^+ - SO_2$), 129 ($220 - PhCH_2$). Compound **18** was obtained in 76% yield (1.34 g). 2-(Ethylsulfonyl)quinoxaline[11] (**19**) had mp 122—123 °C (colorless needles) (lit.[11] mp 123 °C). Yield, 1.51 g (86%). 2-(Isopropylsulfonyl)quinoxaline[11] (**20**) had mp 105—106 °C (colorless needles) (lit.[11] mp 106 °C). Yield, 1.29 g (74%). 2-(Phenylsulfonyl)quinoxaline[3] (**22**) had mp 136—136.5 °C (colorless needles) (lit.[3] mp 136.5 °C). Yield, 1.49 g (88%).

Acknowledgement The authors are greatly indebted to the staff of the central analysis room of this college for elemental analysis and mass spectral measurement.

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