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Studies on 1,4-Benzothiazines. IV.¹⁾ Reactions of 2-Acyl-4H-1,4-benzothiazines with Hydroxylamine, Hydrazine, Guanidine and Acetamidine

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2-Acyl-4-methyl-4H-1,4-benzothiazines (**1a**, **b**) reacted with hydroxylamine to give dihydroisoxazolo[4,5-*b*][1,4]benzothiazines (**3a**, **b**). However, the reaction of **1a** with hydrazine did not give the dihydropyrazolo[4,5-*b*][1,4]benzothiazine derivative corresponding to **3a**, but gave its dehydro compound (**6**). On the other hand, in the reaction of **1b** with hydrazine, formation of a pyrazole ring and opening of the thiazine ring occurred to afford a 4-(2-aminophenylthio)pyrazole derivative (**7**). Guanidine and acetamidine also reacted with **1a**, **b** to give 5-[2-(*N*-methylamino)phenylthio]pyrimidines (**10a—d**).

Keywords—2-acyl-4H-1,4-benzothiazine; dihydroisoxazolo[4,5-*b*][1,4]benzothiazine; pyrazolo[4,5-*b*][1,4]benzothiazine; 4-[2-(*N*-methylamino)phenylthio]-3-methylpyrazole; 2,4-disubstituted 5-[2-(*N*-methylamino)phenylthio]pyrimidine; autoxidation

The present paper deals with the reaction of 2-benzoyl-4-methyl-4H-1,4-benzothiazine (**1a**)³⁾ or its 2-(acetyl homologue (**1b**)¹⁾ with some nitrogen-containing nucleophiles such as hydroxylamine, hydrazine and amidine.

When a mixture of **1a** and hydroxylamine in ethanol was heated under basic conditions, the expected oxime (**2a**) was not isolated, but a new compound assigned as 9-methyl-3-phenyl-9H-3a,9a-dihydroisoxazolo[4,5-*b*][1,4]benzothiazine (**3a**) from the proton nuclear magnetic resonance (¹H-NMR) spectral data and the microanalysis was obtained. Similarly, **1b** reacted with hydroxylamine to give the 3-methyl homologue (**3b**) of **3a**.

From these observations, it was expected that the dihydropyrazolo[4,5-*b*][1,4]benzothiazine derivative might be produced by the reaction of **1a** or **1b** with hydrazine. Such a compound was not obtained from **1a** or **1b**, but when a mixture of **1a** and hydrazine dihydrochloride was refluxed in ethanol containing sodium ethoxide, the dehydro compound, 9-methyl-3-phenyl-9H-pyrazolo[4,5-*b*][1,4]benzothiazine (**6**) was isolated in fair yield. On the other hand, in the reaction of **1b** under similar conditions, we failed to isolate a product, but when a mixture of **1b** and 85% hydrazine hydrate in pyridine was heated, a compound assigned as 4-[2-(*N*-methylamino)phenylthio]-3-methylpyrazole (**7**) was obtained. The formation of **7** from **1b** is not surprising in view of the reported preparation of 4-(2-aminophenylthio)-3-phenyl-3-pyrazolin-5-one (**11**) from 2-ethoxycarbonyl-3-phenyl-4H-1,4-benzothiazine and hydrazine by Duro *et al.*,⁴⁾ while in the reaction of **1a** with hydrazine, it can be considered that the dihydropyrazolo[4,5-*b*][1,4]benzothiazine compound (**5**) was formed as an intermediate, then autoxidized to give **6** since the aromatization of the pyrazoline moiety would be promoted by the phenyl group at the 3-position.

Treatment of **6** with acetic anhydride in pyridine at room temperature gave a monoacetate (**8**), while **7** was converted to a diacetate (**9a**) by a similar procedure; the results of these acetylations support the assigned structures of **6** and **7**, respectively. Heating of an al-

kaline solution of the diacetate (**9a**) gave only a monoacetate, whose structure was established to be 4-[2-(*N*-acetyl-*N*-methylamino)phenylthio]-3-methylpyrazole (**9b**) by the ^1H -NMR and infrared (IR) spectral data.

Attempts to prepare pyrimido[5,6-*b*][1,4]benzothiazines by reactions of 2-acyl-4*H*-1,4-benzothiazines (**1a**, **b**) with guanidine or acetamidine were unsuccessful, in contrast to the reaction with hydroxylamine or hydrazine, but 2,4-disubstituted 5-[2-(*N*-methylamino)-phenylthio]pyrimidines (**10a**—**d**) were obtained in fair yields except in the reaction of **1a** with acetamidine.

Chart 1

Experimental

9-Methyl-3-phenyl-9H-3a,9a-dihydroisoxazolo[4,5-*b*][1,4]benzothiazine (3a)—A mixture of **1a** (1.0 g) and hydroxylamine·HCl (1.3 g) in 3.5% (w/v) KOH–EtOH solution (30 ml) was refluxed for 15 h, then allowed to stand overnight. A solid mass that formed in the reaction mixture was collected by filtration, washed with water and recrystallized from EtOH to give **3a** (0.5 g, 47.5%) as colorless needles. mp 148 °C. *Anal.* Calcd for C₁₆H₁₄N₂OS: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.17; H, 5.04; N, 10.00. ¹H-NMR (CDCl₃) δ: 3.16 (3H, s, N–CH₃), 5.15 (1H, d, *J* = 10.0 Hz, 9a–CH), 6.12 (1H, d, *J* = 10.0 Hz, 3a–CH).

3,9-Dimethyl-9H-3a,9a-dihydroisoxazolo[4,5-*b*][1,4]benzothiazine (3b)—A mixture of **1b** (1.0 g), hydroxylamine·HCl (0.8 g) and a methanol solution of MeONa [obtained from Na (0.26 g) and MeOH (60 ml)] in a sealed Pyrex tube was heated in an oil bath at a temperature of 120 °C for 3 h. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The insoluble mass in water was collected by filtration and recrystallized from EtOH to give **3b** (0.7 g, 65.3%) as colorless prisms. mp 120–124 °C. *Anal.* Calcd for C₁₁H₁₂N₂OS: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.10; H, 5.58; N, 12.71. ¹H-NMR (CDCl₃) δ: 1.83 (3H, s, C–CH₃), 3.07 (3H, s, N–CH₃), 4.61 (1H, d, *J* = 7.0 Hz, 3a–CH), 5.86 (1H, d, *J* = 7.0 Hz, 9a–CH).

9-Methyl-3-phenyl-9H-pyrazolo[4,5-*b*][1,4]benzothiazine (6)—Compound **1a** (2.0 g) and hydrazine·2HCl (2.8 g) were added to an ethanol solution of EtONa [prepared from Na (1.5 g) and EtOH (80 ml)]. The mixture was refluxed for 13 h, then filtered to remove NaCl, and the filtrate was concentrated under reduced pressure. Addition of a small amount of water to the residue gave a pale yellow solid, which was collected by filtration, washed with water and recrystallized from MeOH to give **6** (1.2 g, 57.5%) as colorless needles. mp 181 °C. *Anal.* Calcd for C₁₆H₁₃N₃S: C, 68.79; H, 4.69; N, 15.04. Found: C, 68.62; H, 4.81; N, 14.50. ¹H-NMR (CDCl₃) δ: 3.13 (3H, s, N–CH₃), 10.85 (1H, s, NH disappeared on deuterium exchange). IR ν_{max}^{KBr} cm^{–1}: 3480 (NH). MS *m/e*: 279 (M⁺).

1 (or 2)-Acetyl-9-methyl-3-phenyl-9H-pyrazolo[4,5-*b*][1,4]benzothiazine (8)—Compound **6** (0.1 g) was dissolved in pyridine (5 ml), and acetic anhydride (3 ml) was added to the solution. After standing overnight at room temperature, the mixture was concentrated under reduced pressure. Water was added to the resulting residue, and the semi-crystalline mass obtained was recrystallized from EtOH to give **8** (60 mg) as colorless leaflets. mp 143–145 °C. *Anal.* Calcd for C₁₈H₁₅N₃OS: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.05; H, 4.81; N, 13.25. ¹H-NMR (DMSO-*d*₆) δ: 2.50 (3H, s, COCH₃), 3.33 (3H, s, N–CH₃). IR ν_{max}^{KBr} cm^{–1}: 1715 (N–COCH₃).

4-[2-(*N*-Methylamino)phenylthio]-3-methylpyrazole (7)—A mixture of **1b** (10 g) and 85% hydrazine hydrate (5.7 g) in pyridine (20 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and a solution of the resulting residue in Et₂O was allowed to stand in a refrigerator for a few days to give a crystalline mass, which was recrystallized from cyclohexane to give **7** (4.5 g, 42.3%) as prisms. mp 61–64 °C. *Anal.* Calcd for C₁₁H₁₃N₃S: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.08; H, 5.77; N, 19.35. ¹H-NMR (DMSO-*d*₆) δ: 2.16 (3H, s, C–CH₃), 2.76 (3H, d, N–CH₃), 5.32 (1H, br, NHCH₃ disappeared on deuterium exchange), 7.71 (1H, s, pyrazole-3-H), 12.80 (1H, br, pyrazole–NH disappeared on deuterium exchange).

1 (or 2)-Acetyl-4-[2-(*N*-acetyl-*N*-methylamino)phenylthio]-3-methylpyrazole (9a)—Compound **7** (0.1 g) was dissolved in pyridine (10 ml), and acetic anhydride (5 ml) was added to the solution. After standing overnight at room temperature, the mixture was concentrated under reduced pressure. EtOH was added to the resulting residue, and the crystalline mass obtained was recrystallized from EtOH to give **9a** (0.7 g, 50.5%) as colorless needles. mp 138 °C. *Anal.* Calcd for C₁₅H₁₇N₃O₂S: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.29; H, 5.55; N, 13.98. ¹H-NMR (DMSO-*d*₆) δ: 1.72 (3H, s, C–CH₃), 2.09 (3H, s, pyrazole-1 or 2-COCH₃), 2.62 (3H, N–COCH₃ on the benzene ring), 3.09 (3H, s, N–CH₃), 8.64 (1H, s, pyrazole-3-H). IR ν_{max}^{KBr} cm^{–1}: 1630 (N–COCH₃ on the benzene ring), 1735 (COCH₃ at the 1 or 2-position of pyrazole ring).

4-[2-(*N*-Acetyl-*N*-methylamino)phenylthio]-3-methylpyrazole (9b)—A solution of **9a** (1.0 g) in aq. EtOH–NaOH (50% EtOH 5 ml + 5% NaOH 3 ml) was refluxed for 1.5 h. After being neutralized with acetic acid, the reaction mixture was concentrated under reduced pressure, and water was added to the residue. The resulting solid mass was collected by filtration, washed with water and recrystallized from water to give **9b** (0.7 g, 81.3%) as colorless needles. mp 148 °C. *Anal.* Calcd for C₁₃H₁₅N₃OS: C, 59.75; H, 5.79; N, 16.08. Found: C, 59.96; H, 5.79; N, 16.18. ¹H-NMR (CDCl₃) δ: 1.95 (3H, s, C–CH₃), 2.32 (3H, s, N–COCH₃), 3.31 (3H, s, N–CH₃), 7.71 (1H, s, pyrazole-3-H). IR ν_{max}^{KBr} cm^{–1}: 1630 (COCH₃).

2-Amino-5-[2-(*N*-methylamino)phenylthio]-4-phenylpyrimidine (10a)—Compound **1a** (2.7 g) and guanidine·HCl (1.2 g) were added to a methanol solution of MeONa [prepared from Na (0.53 g) and MeOH (50 ml)]. The resulting mixture was refluxed for 7 h, and the solvent was removed under reduced pressure. The residue was washed with water, and recrystallized from MeOH to give **10a** (1.4 g, 45.1%) as colorless needles. mp 135 °C. *Anal.* Calcd for C₁₇H₁₆N₄S: C, 66.21; H, 5.23; N, 18.17. Found: C, 66.20; H, 5.10; N, 18.07. ¹H-NMR (CDCl₃) δ: 2.61 [3H, d (singlet on treatment with D₂O), N–CH₃], 4.4 (1H, br, NH disappeared on deuterium exchange), 5.41 (2H, s, NH₂ disappeared on deuterium exchange), 8.10 (1H, s, pyrimidine-4-H).

2-Methyl-5-[2-(*N*-methylamino)phenylthio]-4-phenylpyrimidine (10b)—A mixture of **1a** (2.7 g) and acetamidine·HCl (1.2 g) in a methanol solution (50 ml) containing MeONa (prepared from Na 0.53 g) was refluxed for 20 h. The reaction mixture was treated as described for the preparation of **10a**. Yield, 0.8 g (25.8%). Colorless

needles (from MeOH). mp 138 °C. *Anal.* Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67. Found: C, 70.38; H, 5.45; N, 13.58. 1H -NMR ($CDCl_3$) δ : 2.70 (3H, s, $C-CH_3$), 2.75 [3H, d (singlet on treatment with D_2O), $N-CH_3$], 4.7 (1H, br, NH disappeared on deuterium exchange), 8.03 (1H, s, pyrimidine-4-H).

2-Amino-5-[2-(*N*-methylamino)phenylthio]-4-methylpyrimidine (10c)—A mixture of **1b** (2.0 g) and guanidine $\cdot$ HCl (1.2 g) in a methanol solution (50 ml) containing MeONa (prepared from Na 0.53 g) was refluxed for 5 h. The reaction mixture was treated as described for the preparation of **10a**. Yield, 1.4 g (58.3%). Colorless needles (from MeOH). mp 202—204 °C. *Anal.* Calcd for $C_{12}H_{14}N_4S$: C, 58.51; H, 5.73; N, 22.74. Found: C, 58.50; H, 5.60; N, 22.70. 1H -NMR ($DMSO-d_6$) δ : 2.33 (3H, s, $C-CH_3$), 2.80 (3H, d, $N-CH_3$), 5.42 (1H, br, NH disappeared on deuterium exchange), 8.13 (1H, s, pyrimidine-4-H).

2,4-Dimethyl-5-[2-(*N*-methylamino)phenylthio]pyrimidine (10d)—A mixture of **1b** (2.0 g) and acetamidine $\cdot$ HCl (1.2 g) in a methanol solution (50 ml) containing MeONa (prepared from Na 0.53 g) was refluxed for 5 h. The reaction mixture was treated as described for the preparation of **10a**. Yield, 1.53 g (64%). Colorless needles (from MeOH). mp 146—148 °C. *Anal.* Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13. Found: C, 63.61; H, 6.09; N, 17.05. 1H -NMR ($DMSO-d_6$) δ : 2.50 (6H, singlet due to overlap of two CH_3 -signals on the pyrimidine ring), 2.72 (3H, d, $N-CH_3$), 5.62 (1H, br, NH disappeared on deuterium exchange), 7.71 (1H, s, pyrimidine-4-H).

References and Notes

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