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SYNTHESIS AND PROPERTIES OF 3-CYANO-4-(4-CYANOPHENYL)-1,4-DIHYDROPYRIDINE-2(3H)-THIONES

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Piperidinium 3-cyano-4-(4-cyanophenyl)-1,4-dihydropyridine-2(3H)-thiolates were obtained by the condensation of 1,3-dicarbonyl compounds, 4-cyanobenzaldehyde, and cyanothioacetamide in the presence of an equimolar amount of piperidine. The acidification of these thiolates gave the corresponding 1,4-dihydropyridine-2(3H)-thiones and pyridine-2(1H)-thione. Alkylation of 1,4-dihydropyridine-2-thiolates or the reaction mixture of the three-carbon condensation using iodacetamide gave 2-carbamoylmethylthio-1,4,5,6-tetrahydro- or 1,4-dihydropyridines, which were characterized by their conversion to 4,7-dihydrothieno[2,3-b]pyridines.

Keywords: pyridines, thienopyridines, alkylation, intramolecular cyclization.

3-Cyano-1,4-dihydropyridine-2(3H)-thiones have attracted attention as reactive compounds [1, 2] with cardiovascular [3, 4], hepatoprotective [5], and antioxidant activity [6]. The corresponding 2-alkylthio-1,4-dihydropyridines and 4,7-dihydrothieno[2,3-*b*]pyridines also display hepatoprotective [5], antioxidant [6], and even more pronounced cardiovascular activity [7-10].

In a continuation of our study of partially hydrogenated pyridine-2-thiones [2, 11], we synthesized 4-(4-cyanophenyl)-3-cyano-1,4-dihydropyridine-2(3H)-thiones **6** in an attempt to find new biologically active compounds. The alkylation of **6** gave 2-alkylthio-1,4-dihydropyridines **9**, while subsequent Thorpe–Ziegler cyclization gave 4,7-dihydrothieno[2,3-*b*]pyridines **10**.

For this purpose, we selected the asymmetric three-carbon condensation of a 1,3-dicarbonyl compound, aldehyde, and cyanoacetamide [12]. The condensation of acetylacetone **1a** and acetoacetate esters **1b,c** with 4-cyanobenzaldehyde **2** and cyanothioacetamide **3** in the presence of an equimolar amount of piperidine gives piperidinium 3-cyano-1,4-dihydropyridine-2-thiolates **5a,c** as the primary products with a slight impurity of unstable 6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiolates **4a,c** (as indicated by ^{1}H NMR spectroscopy), which undergo dehydrogenation upon recrystallization from ethanol to give thiolates **5a,c**.

Brief heating of 1,4-dihydropyridine-2-thiolates **5** with an excess of hydrochloric acid in ethanol at reflux gave 1,4-dihydropyridine-2(3H)-thiones in high yield. In the case of the 5-acetyl derivatives, recrystallization from ethanol gave a slight amount of less soluble pyridine-2(1H)-thione **7a**.

1,4,5,6-Tetrahydropyridine-2-thiolate (**4d**) or 1,4-dihydropyridine-2-thiolate (**5d**) could not be isolated in the condensation of ethyl benzoylacetate (**1d**) with **2** and **3** in the presence of an equimolar amount of piperidine. Acidification of the reaction mixture also did not give thione **6d** but 2-carbamoylmethylthio-6-hydroxy-1,4,5,6-tetrahydropyridine (**8**) was formed in 70% yield upon alkylation of the reaction mixture with iodacetamide. Brief heating of 6-hydroxy-1,4,5,6-tetrahydropyridine **8** in a solution of hydrochloric acid in ethanol at reflux gave a more stable derivative, 1,4-dihydropyridine **9d**, in 84% yield.

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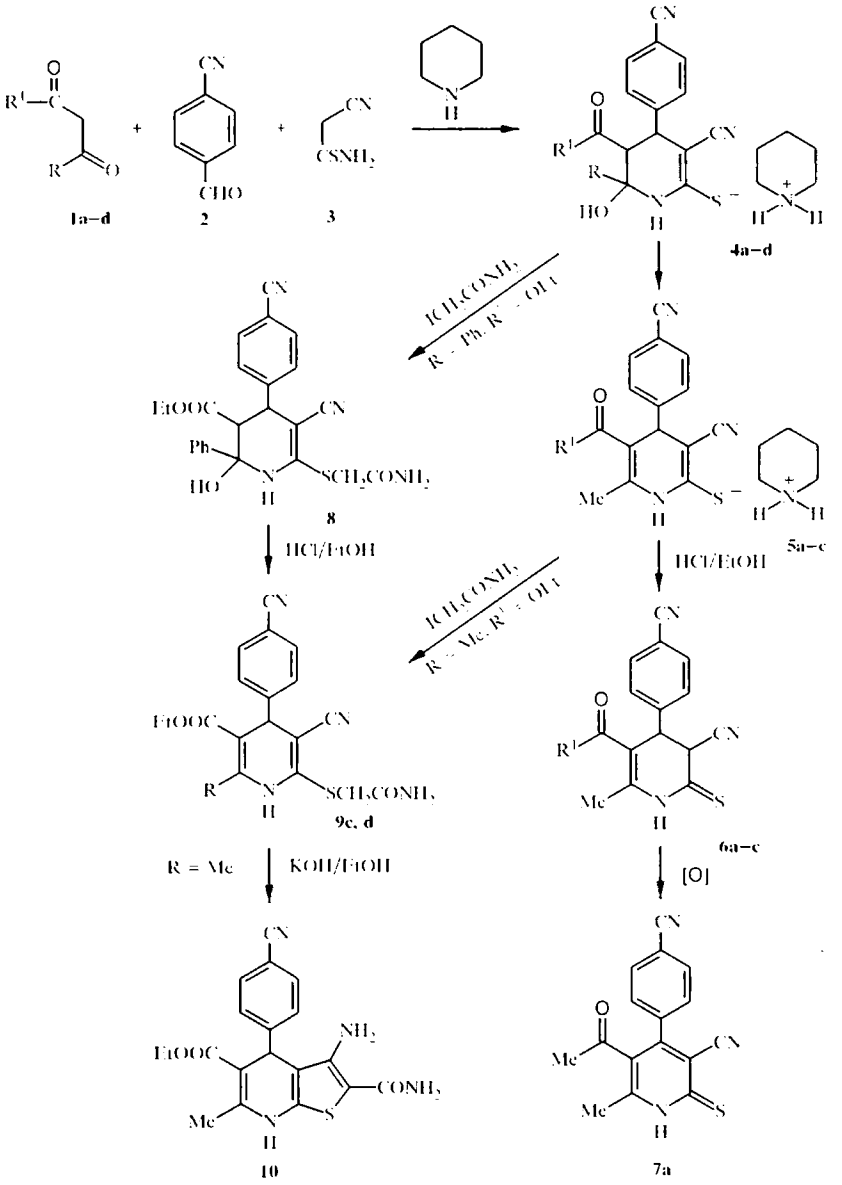

a R = Me, R^1 = Me; b R = Me, R^1 = OMe; c R = Me, R^1 = OEt; d R = Ph, R^1 = OEt

2-Carbamoylmethylthio-6-methyl-1,4-dihydropyridine **9c** was obtained in high yield by the alkylation of thiolate **5c** with iodacetamide. 2-Carbamoylmethylthio-3-cyano-1,4-dihydropyridine **9c** was characterized by its conversion to 4,7-dihydrothieno[2,3-*b*]pyridine **10** by the action of potassium hydroxide.

The cyano group stretching bands are most characteristic for these products. These bands are found at 2252-2254 cm^{-1} for 1,4-dihydropyridine-2(3H)-thiones **6**, indicating lack of conjugation of the nitrile group. The CN group stretching band is shifted with increasing conjugation to 2242 cm^{-1} for pyridine-2(1H)-thione **7a**, 2196-2206 cm^{-1} for 1,4,5,6-tetrahydro- and 1,4-dihydro-3-carbonitriles **5**, **8**, and **9**, and 2176-2178 cm^{-1} for 1,4-dihydropyridine-2-thiolates **5** (ν_{CN} is observed at 2222-2240 cm^{-1} for 4-CN-C_6H_4).

The ^1H NMR signal for 4-H at 4.42-4.64 ppm for 1,4-dihydropyridine-2-thiolates **5** and 1,4-dihydropyridines **9** and at 5.12 ppm for 4,7-dihydrothieno[2,3-*b*]pyridine **10** are the most characteristic evidence for the hydrogenated structure of these compounds. The ^1H NMR spectra of 1,4-dihydropyridine-2(3H)-thiones **6** show signals corresponding to *cis* and *trans* isomers in 3:2 ratio in the case of **6a** and 1:1 ratio in the case

of **6b**. In the case of **6b**, precise interpretation is difficult due to overlap of the *cis* and *trans* 3-H and 4-H protons and the *cis* and *trans* protons of the ethyl group. The signals with $^3J_{3,4}$ = 6.6-6.8 Hz were assigned to the *cis* isomer and the signals with $^3J_{3,4}$ = 2.4-2.6 Hz indicate *trans*-diequatorial arrangement of 4-H and 5-H [12, 13].

The ^{1}H NMR spectrum of 1,4,5,6-tetrahydropyridine **8** has characteristic doublets for 4-H and 5-H at 4.16 and 2.92 ppm with $^3J_{3,4}$ = 12.4 Hz, indicating *trans*-diaxial arrangement of 4-H and 5-H.

EXPERIMENTAL

The IR spectra were taken on a Perkin–Elmer 580B spectrometer for vaseline mulls. The ^{1}H NMR spectra were taken on a WH 90/DS spectrometer for solutions in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. The reaction course and purity of the products were checked by thin-layer chromatography on Silufol UV-254 plates with 1:1:2 acetone–hexane–chloroform as the eluent. Products **5-9** were recrystallized from ethanol, while **10** was recrystallized from 1:10 DMF–ethanol.

Piperidinium 5-Acetyl-3-cyano-4-(4-cyanophenyl)-6-methyl-1,4-dihydropyridine-2-thiolate (5a). A mixture of acetylacetone (3.0 g, 30 mmol) and *p*-cyanobenzaldehyde (3.93 g, 30 mmol) was dissolved with heating in ethanol (25 ml). Then, piperidine (1 ml, 10 mmol) was added and the mixture was stirred at room temperature for 15 min. A sample of cyanothioacetamide (3.0 g, 30 mmol) and piperidine (2 ml, 20 mmol) were added and the mixture was stirred for 15 min. The precipitate formed was filtered off and washed with cold ethanol (20 ml) to give 10.83 g (91%) of compound **5a**; mp >110°C (dec.). IR spectrum: 1620 (C=O), 2176, 2222 (C≡N), 2528 (NH_2^+), 3316 cm^{-1} (NH). ^{1}H NMR spectrum (DMSO-d_6): 1.60 (6H, m, $(CH_2)_3$); 1.98 (3H, s, 5-$COCH_3$); 2.28 (3H, s, 6-CH_3); 3.0 (4H, m, $N(CH_2)_2$); 4.42 (1H, s, 4-H); 7.24 and 7.70 (4H, dd and dd, 4-C_6H_4); 8.34 ppm (1H, s, NH). Found, %: C 63.05; H 6.68; N 13.96; S 7.87. $C_{21}H_{24}N_4OS\cdot H_2O$. Calculated, %: C 63.29; H 6.58; N 14.06; S 8.05.

Piperidinium 3-Cyano-4-(4-cyanophenyl)-5-methoxycarbonyl-6-methyl-1,4-dihydro-2-thiolate (5b) was obtained in 86% yield analogously to **5a** using methyl acetoacetate instead of acetylacetone; mp >105°C (dec.). IR spectrum: 1697 (C=O), 2176, 2228 (C≡N), 2510 (NH_2^+), 3244, 3334 cm^{-1} (NH). ^{1}H NMR spectrum ($CDCl_3$): 1.66 (6H, m, $(CH_2)_3$); 2.35 (3H, s, 6-CH_3); 3.03 (4H, m, $N(CH_2)_2$); 3.54 (3H, s, OCH_3); 4.56 (1H, s, 4-H); 6.68 (1H, br. s, NH); 6.88 (2H, br. s, NH_2^+); 7.30 and 7.52 ppm (4H, two d, 4-C_6H_4). Found, %: C 63.31; H 6.19; N 14.06; S 8.01. $C_{21}H_{24}N_4O_2S$. Calculated, %: C 63.61; H 6.10; N 14.13; S 8.09.

Piperidinium 4-(4-Cyanophenyl)-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridine-2-thiolate (5c) was obtained in 82% yield analogously to **5a** using ethyl acetoacetate instead of acetylacetone; mp 141-143°C. IR spectrum: 1692 (C=O), 2178, 2224 (C≡N), 2504 (NH_2^+), 3182, 3248 cm^{-1} (NH). ^{1}H NMR spectrum ($CDCl_3$): 1.18 (3H, t, $CH_2C\underline{H}_3$); 1.62 (6H, m, $(CH_2)_3$); 2.33 (3H, s, 6-CH_3); 2.98 (4H, m, $N(CH_2)_2$); 3.98 (2H, q, $C\underline{H}_2CH_3$); 4.57 (1H, s, 4-H); 6.62 (1H, br. s, NH); 7.32 and 7.52 (4H, two d, 4-C_6H_4); 7.85 ppm (2H, br. s, NH_2^+). Found, %: C 64.23; H 6.38; N 13.49; S 7.99. $C_{22}H_{26}N_4O_2S$. Calculated, %: C 64.38; H 6.36; N 13.65; S 7.81.

5-Acetyl-3-cyano-4-(4-cyanophenyl)-6-methyl-1,4-dihydropyridine-2(3H)-thione (6a) and 5-Acetyl-3-cyano-4-(4-cyanophenyl)-6-methylpyridine-2(1H)-thione (7a). A sample of piperidinium salt **5a** (3.81 g, 10 mmol) was dissolved with heating in 0.5 M (25 ml) hydrochloric acid in ethanol. A precipitate crystallized out after 5-10 min. The precipitate was filtered off and washed with ethanol (10 ml) and water (20 ml) to give 2.72 g (92%) of product, which was recrystallized from ethanol, separating out 0.05 g (2%) of insoluble **7a**; mp >270°C (dec.). IR spectrum: 1697 (C=O), 2232, 2242 (C≡N), 3186 cm^{-1} (NH). ^{1}H NMR spectrum (DMSO-d_6): 1.90 (3H, s, 5-$COCH_3$); 2.44 (3H, s, 6-CH_3); 7.62 and 8.02 (4H, two d, 4-C_6H_4); 14.40 ppm (1H, br. s, NH). Found, %: C 65.28; H 4.01; N 14.25; S 10.88. $C_{16}H_{11}N_3OS$. Calculated, %: C 65.51; H 3.78; N 14.32; S 10.93. A sample of compound **6a** (1.83 g, 62%) crystallized out of the filtrate; mp >175°C (dec.). IR spectrum: 1653 (C=O), 2234, 2252 (C≡N), 3276 cm^{-1} (NH). ^{1}H NMR spectrum in $CDCl_3$: 2.18 (1.8H, s, *cis*-$COCH_3$); 2.24 (1.2H, s, *trans*-$COCH_3$); 2.50 (1.8H, s, *cis*-6-CH_3); 2.56 (1.2H, s, *trans*-6-CH_3); 4.20 (0.4H, d, J = 2.6 Hz, *trans*-3-H); 4.28 (0.6H, d, J = 6.6 Hz, *cis*-3-H); 4.38 (0.6H, d, J = 6.6 Hz, *cis*-4-H); 4.46 (0.4H, d, J = 2.6 Hz, *trans*-4-H); 7.3-7.7 (4H, m, *cis*- and *trans*-C_6H_4); 8.68 ppm (1H, br. s, *cis*- and *trans*-NH). Found, %: C 64.95; H 4.44; N 14.29; S 10.84. $C_{16}H_{13}N_3OS$. Calculated, %: C 65.07; H 4.44; N 14.23; S 10.86.

3-Cyano-4-(4-cyanophenyl)-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridine-2(3H)-thione (6c) was obtained in 84% yield from salt **5c** analogously to **6a**; mp 114-116°C. IR spectrum: 1638, 1696 (C=O), 2226, 2252 (C≡N), 3125, 3200 cm^{-1} (NH). ^1H NMR spectrum ($CDCl_3$): 1.17 and 1.22 (3H, two t, *cis*- and *trans*-$CH_2\underline{CH_3}$); 2.52 and 2.56 (3H, two s, *cis*- and *trans*-6-CH_3); 3.9-4.6 (4H, m, *cis*- and *trans*-(3-H and 4-H) and *cis*- and *trans*-$C\underline{H_2}CH_3$); 7.1-7.7 (4H, m, *cis*- and *trans*-C_6H_4); 9.03 and 9.06 (1H, two br. s, *cis*- and *trans*-NH). Found, %: C 62.49; H 4.81; N 12.80; S 9.66. $C_{17}H_{15}N_3O_2S$. Calculated, %: C 62.75; H 4.65; N 12.91; S 9.85.

2-Carbamoylmethylthio-3-cyano-4-(4-cyanophenyl)-5-ethoxycarbonyl-6-hydroxy-5-phenyl-1,4,5,6-tetrahydropyridine (8). A mixture of ethyl benzoylacetate (5.76 g, 30 mmol) and 4-cyanobenzaldehyde (3.93 g, 30 mmol) in ethanol (15 ml) and piperidine (0.5 ml) was stirred for 10 min at room temperature. Then, cyanothioacetamide (3.0 g, 30 mmol), ethanol (20 ml), and piperidine (2.7 ml) were added and stirred for 2 h at room temperature. A sample of iodacetamide (6.1 g, 33 mmol) was added. The reaction mixture was briefly heated and then stirred for 1 h at room temperature. The precipitate formed was filtered off and washed with ethanol (30 ml), water (30 ml), and an additional 10 ml of ethanol to give 9.65 g (70%) of compound **8**; mp >190°C (dec.). IR spectrum: 1667, 1740 (C=O), 2196, 2240 (C≡N), 3164, 3356 cm^{-1} (NH, OH). ^1H NMR spectrum (DMSO-d_6): 0.48 (3H, t, $CH_2\underline{CH_3}$); 2.92 (1H, d, J = 12.4 Hz, 5-H); 3.38 (2H, q, $C\underline{H_2}CH_3$); 3.56 (2H, br. s, SCH_2); 4.16 (1H, d, J = 12.4 Hz, 4-H); 6.48 (1H, s, OH); 7.2-7.9 (11H, m, 4-C_6H_4, 6-C_6H_5, $CONH_2$); 9.24 ppm (1H, br. s, NH). Found, %: C 62.34; H 4.83; N 12.21; S 6.95. $C_{24}H_{22}N_4O_5S$. Calculated, %: C 62.32; H 4.79; N 12.11; S 6.93.

2-Carbamoylmethylthio-3-cyano-4-(4-cyanophenyl)-5-ethoxycarbonyl-6-methyl-1,4-dihydropyridine (9c). A mixture of salt **5c** (4.10 g, 10 mmol) and iodacetamide (2.03 g, 11 mmol) in ethanol (50 ml) was briefly heated on a water bath and filtered. The precipitate formed was filtered off and washed with ethanol (15 ml), water (20 ml), and an additional 5 ml of ethanol to give 2.79 g (73%) of compound **9c**, mp 184-186°C. IR spectrum: 1646, 1683, 1704 (C=O), 2196, 2228 (C≡N), 3160, 3348 cm^{-1} (NH, NH_2). ^1H NMR spectrum (DMSO-d_6): 1.07 (3H, t, $CH_2\underline{CH_3}$); 2.35 (3H, s, 6-CH_3); 3.64 and 3.74 (2H, two d, J = 15 Hz, SCH_2); 3.95 (2H, q, $C\underline{H_2}CH_3$); 4.64 (1H, s, 4-H); 7.38 and 7.78 (4H, two d, 4-C_6H_4); 7.62 and 7.90 (2H, two br. s, $CONH_2$); 10.49 ppm (1H, s, NH). Found, %: C 59.59; H 4.65; N 14.43; S 8.53. $C_{19}H_{18}N_4O_3S$. Calculated, %: C 59.67; H 4.74; N 14.65; S 8.39.

2-Carbamoylmethylthio-3-cyano-4-(4-cyanophenyl)-5-ethoxycarbonyl-6-phenyl-1,4-dihydropyridine (9d). A sample of tetrahydropyridine **8** (4.625 g, 10 mmol) in 0.5 M hydrochloric acid (40 ml, 20 mmol) in ethanol was heated at reflux for 10 min. The mixture was stirred at room temperature for 1 h. The precipitate formed was filtered off and washed with ethanol (25 ml) to give 3.72 g (84%) of compound **9d**; mp 202-204°C. IR spectrum: 1680, 1686 sh (C=O), 2196, 2236 (C≡N), 3206, 3260, 3304, 3412 cm^{-1} (NH, NH_2). ^1H NMR (DMSO-d_6): 0.68 (3H, t, $CH_2\underline{CH_3}$); 3.68 (2H, q, $C\underline{H_2}CH_3$); 3.74 (2H, two d, J = 15 Hz, SCH_2); 4.62 (1H, s, 4-H); 7.3-7.9 (11H, m, 4-C_6H_4, 6-C_6H_5 and $CONH_2$); 10.82 ppm (1H, s, NH). Found, %: C 64.65; H 4.55; N 12.50; S 7.31. $C_{24}H_{20}N_4O_3S$. Calculated, %: C 64.85; H 4.53; N 12.60; S 7.21.

2-Amino-2-carbamoyl-4-(4-cyanophenyl)-5-ethoxycarbonyl-6-methyl-4,7-dihydrothieno[2,3-*b*]-pyridine (10). A mixture of dihydropyridine **9c** (1.91 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in ethanol (20 ml) was briefly heated until the solid dissolved and then stirred for 3 h at room temperature. A sample of water (20 ml) was added over 30 min. The precipitate formed was filtered off and washed with water (50 ml) and ethanol (10 ml) to give 1.22 g (64%) of compound **10**; mp 216-218°C. IR spectrum: 1662, 1702 (C=O), 2228 (C≡N), 3168, 3324, 3420 cm^{-1} (NH, NH_2). ^1H NMR spectrum (DMSO-d_6): 1.14 (3H, t, CH_2CH_3); 2.33 (3H, s, 6-CH_3); 3.93 (2H, q, CH_2CH_3); 5.12 (1H, s, 4-H); 6.32 and 6.52 (4H, two br. s, $CONH_2$ and 3-NH_2); 7.46 and 7.72 (4H, two d, 4-C_6H_4); 9.85 ppm (1H, s, NH). Found, %: C 59.44; H 4.69; N 14.52; S 8.29. $C_{19}H_{18}N_4O_3S$. Calculated, %: C 59.67; H 4.74; N 14.65; S 8.39.

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