SYNTHESIS OF 4,7(2H)-DIHYDROTHIAZOLO[3,2-a]PYRIDINES FROM 3-CARBAMOYL-1,4-DIHYDROPYRIDINE-2(3H)-THIONES

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Abstract: γ-Dicyanobutyrothioamide 3, 3-carbamoyl substituted 1,4-dihydropyridine-2-thiolates 5, 3,4-dihydropyridine-2-thiolates 6 and 1,4-dihydropyridine2(3H)-thiones have been synthesized by Michael condensation of benzylidenemalononitrile 1 with thiocarbamoylacetamides 2. Use of stronger bases and elevated temperature is favourable for 3,4-dihydroisomers 6. The influence of the modification of the electrophilic ylidene component on the course of the subsequent intramolecular cyclization of Michael adducts of type 3 has been evaluated. The convenient method of synthesis of 4,7-(2H)dihydrothiazolo[3,2-a]pyridines 10 has been elaborated by alkylation of thiones 7 with the subsequent smooth intramolecular N-acylation of the possible intermediates - 1,4-dihydropyridines 9 containing 2-cyanomethylthio group.

Introduction

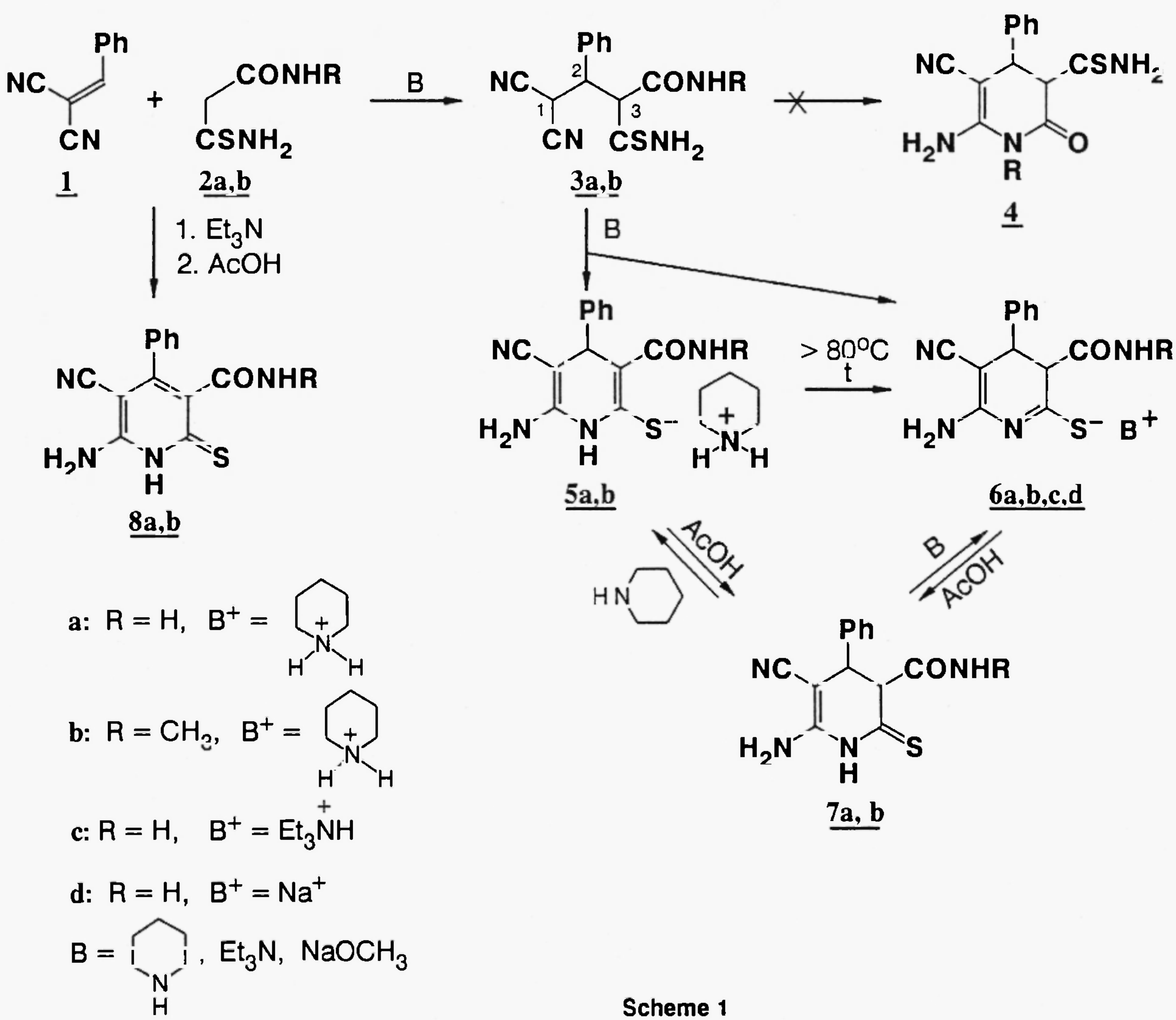
Hydrogenated 3-cyanopyridine-2-thiones synthesized from cyanothioacetamide are of a particular interest due to their high reactivity (1,2) and revealed cardiovascular (3,4), antioxidant and hehatoprotective (5,6) activities. Less attention has been paid to the use of thiocarbamoylacetamide 2a and N-methylthiocarbamoylacetamide 2b as methylene components in Michael and Knoevenagel reactions (7-10). Some 3-carbamoyl-substituted pyridine-2(1H)-thiones and 3-oxoisothiazolo[5,4-b]pyridines derived from thiones have also exhibited biological activity (11,12).

The condensation of chalcones with thiocarbamoylacetamide 2a gave unexpected results. Cyclization of δ-ketosemithioamides (the intermediates of the above mentioned reaction) involves NH_2 of the carbamoyl group to give rise to 3-thiocarbamoyl-3,4-dihydropyridine-2(1H)-ones (13,14). By condensation of 2 with benzylidenemalononitrile 1 the alternative products 4 or 7 could be expected as well. Using cyanothioacetamide in this reaction 6-amino-3,5-dicyano-1,4-dihydropyridine-2(3H)-thiones have been characterized as easily oxidizable intermediates (15-18).

We have studied the influence of modification of electrophilic ylidene component on the course of cyclization, i.e., on the reaction direction of 2 with 1 (an alternative reaction), the variation of stability of 1,4-dihydropyridine-2(3H)-thiones 7 by introduction of a 3-CONHR group instead of the 3-CN group and alkylation of 7 with the subsequent intramolecular N-acylation of the possible intermediates 1,4-dihydropyridines 9 containing the carbofunctional group in 2-alkylthio substituent leading to the formation of hydrogenated thiazolo[3,2-a]pyridines 10.

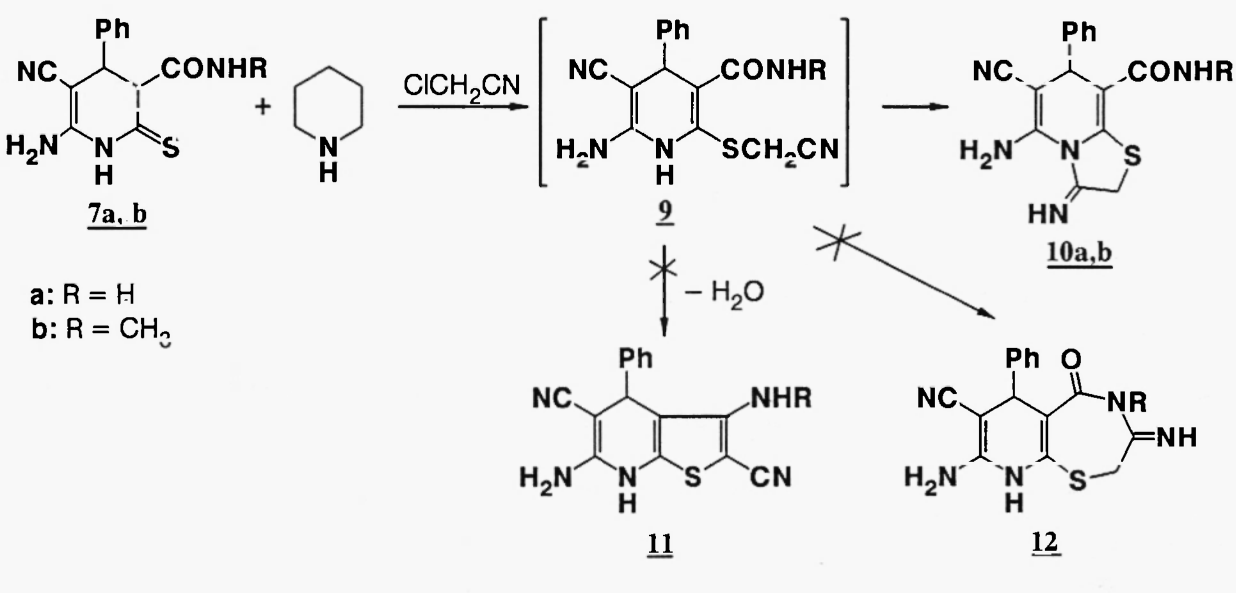
Results and discussions

Michael reaction of benzylidenemalononitrile 1 with amides 2 involving the subsequent cyclization proceeds smoothly on short heating to 30-40°C of the starting materials and depends on the base used and its quantity; as a result different reaction products 3, 5 and 6 could be obtained. In case of R=H, use of catalytic amounts of piperidine lead to γ-dicyanobutyrothioamide 3a, while equimolar amounts of piperidine gave rise to the mixture of 1,4-dihydropyridine-2-thiolates 5a and 3,4-dihydropyridine-2-thiolates 6a (method A). Treatment of γ-dicyanobutyrothioamide 3a with piperidine leads to the mixture of thiolates 5a and 6a too (method B). Acidification of salts 5 and 6 or their mixtures with an excess of acetic acid affords 5-cyano-3-carbamoyl-1,4-dihydropyridine-2(3H)-thiones 7 more stable to oxidation of the ring (contrary to 3,5-dicyano-1,4-dihydropyridine-2(3H)-thiones (15-18)). However, the treatment of the latter with piperidine small excesses yields again the mixture of salts 5 and 6 (method C). The relationship between thiolates 5 and 6 depends on the way they have been prepared. ^{1}H NMR spectra recorded in CD_3CN solution indicate: in case of R=H using method A more than 10:1 excess of thiolate 5a is obtained; in case of method B the relationship between 5a and 6a is approximately 2:1, and in case of method C it is about 1:3. The same relationship is observed in HMPA-d_{18} solution, but in DMSO-d_6 solution it is more shifted towards the formation of 5a. In case of R=CH_3 using both methods A and C considerable excess of thiolate 5b is gained. Using fractional crystallization isomers 5a,b are separable due to their poorer solubility in ethanol. Use of stronger bases – triethylamine (methods A and C) and sodium methylate (method C) in case of R=H gave rise to a considerable excess of thiolates 6c,d. The isomers 5 during the heating both in crystalline aggregation (colored from colourless to yellow) and in solution partially isomerize to isomers 6 which are detected by UV and ^{1}H NMR spectroscopy. Thus, the substitution of the strong electron withdrawing CN group in position 3 (only 1,4-dihydroisomers are observed) for a carbamoyl group leads to the alternative conjugated systems of thiolate anion in which either 3-carbamoyl group or the nitrogen atom of the cycle and the 5-CN group are involved.



Scheme 1

Refluxing of 1 and 2a during 3-4 h in the presence of a half equivalent of triethylamine is accompanied by H_2S evolution occurring due to the partial decomposition of 2a which lowers the yield of the desired product 8a. We succeeded to isolate a mixture of 7a and 8a (approximate ratio 10:1, yield 59%) and this fact differs from the results published in (9) and indicates the stability of 7a against 1 and air oxygen as oxidizing agents. The change of $CONH_2$ group for $CONHCH_3$ leads to the improvement of pyridine-2(1H)-thione 8b yield.
The structures of compounds 3, 5-8 are confirmed by spectroscopic methods. In the IR spectrum of compound 3a νCN is observed at 2266 cm^{-1}, it indicates that the cyano group is attached to sp^3-hybridized carbon atom. In the ^1H NMR spectrum of 3a the characteristic three adjacent proton systems of two stereoisomers are observed. The ^{13}C NMR spectrum of 3a reveals the chemical shifts of four CN groups and the characteristic δ C=O at 167.10 and 167.61 ppm and δ C=S at 199.15 ppm and 199.36 ppm, thus giving evidence for an open chain dicyanobutyrothioamide structure.
Theoretically the alternative route of intramolecular cyclization of intermediates 3 involving the carbamoyl group and giving rise to 3-thiocarbamoyl-1,4-dihydropyridine-2(3H)-ones 4 is possible, but this direction does not take place under such reaction conditions. Data of elemental analysis, ^1H NMR and IR spectra do not prove unambiguously the structure of compound 7a. In the UV spectra of compounds 7a,b one can observe the characteristic of 1,4-dihydropyridine-2(3H)-thiones (19) long-wave absorption (357 nm and 360 nm for 7a and 7b, respectively) which in case of alternative 3-thiocarbamoyl-1,4-dihydropyridine-2(1H)-ones 4 should be approximately at 280 nm (14). In the ^1H NMR spectra of thione 7b a characteristic quartet and doublet of 3-$CONHCH_3$ substituent with J=4.6 Hz are revealed. In case of alternative structure 4b these coupling constants could not been observed. In the ^1H NMR spectra of thiolates 5 the most characteristic are singlets of 4-H, but for thiolates 6 similarly to thiones 7 doublets of 3-H and 4-H with J=2.8-4.0 Hz are observed thus indicating the *trans*-arrangement for 3-CONHR and 4-Ph substituents (20,21). The doublet of 4-H is usually broadened due to the long-range coupling with 4-C_6H_5 protons. The structure of thione 7a is also supported by the data published in (10).
Thus, 3-carbamoyldihydropyridine-2-thiolates 5, 6 are formed instead of 3-thiocarbamoyldihydropyridine-2(1H)-ones 4.



Scheme 2

The treatment of thiones 7, thiolates 5, 6 or their mixture with chloroacetonitrile affords 92-97% yield of 5-amino-3-imino-(2H)4,7-dihydrothiazolo[3,2-a]pyridines 10. We did not succeed to isolate the intermediates of the reaction – 2-cyanomethylthio-1,4-dihydropyridines 9. Theoretically compounds 9 could undergo cyclization in which NH of 3-CONHR group is involved to form alternative thieno[2,3-b]pyridines 11 or 1,4-thiazepino[3,2-f]pyridines 12. The existing of thienopyridines 11 could be excluded since in the IR spectra only one νCN is observed and data of elemental analysis show that the elimination of water molecule did not occur. In the [1]H NMR spectra of thiazolopyridines 10a,b AB-multiplet characteristic of SCH_2 protons are observed thus confirming the occurrence of imino tautomeric form for compounds 10. In case of 8-(N-methylcarbamoyl)thiazolopyridine 10b characteristic coupling constants (q and d, J=4.5 Hz) of 8-$CONHCH_3$ substituent are observed thus excluding the existence of the alternative structure 12.

In conclusion a convenient method for the synthesis of hydrogenated thiazolo[3,2-a]pyridines has been elaborated; the enhancement of 1,4-dihydropyridine-2(3H)-thiones stability has been reached by the introduction of the 3-CONHR group instead of the 3-CN group; the promotion of intramolecular N-acylation of 1,4-dihydropyridines containing 2-cyanomethylthio group leading to the formation of hydrogenated thiazolo[3,2-a]pyridines has been revealed.

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin-Elmer 580B spectrometer. The [1]H NMR spectra of solutions in $CDCl_3$, CD_3CN or DMSO-d_6 were obtained with Bruker WH 90/DC (90 MHz) and AM-360 (360 MHz) spectrometers using TMS as internal standard. The UV spectra of solutions in ethanol were recorded on a Specord UV-vis instrument. The course of the reactions and the individuality of substances were monitored by TLC on Kieselgel 60 F Merck plates with dichloromethane-hexane-methanol (5:5:1) as eluent. Compounds are recrystallized from ethanol or DMF-ethanol (in case of 10a) mixture.

3-Carbamoyl-1,1-dicyano-2-phenyl-3-thiocarbamoylpropane 3a.

A mixture of benzylidenemalononitrile 1 (0.77 g, 5 mmol) and thiocarbamoylacetamide 2a (0.59 g, 5 mmol) in 15 ml of ethanol was dissolved on heating, cooled approximately to 30°C, two drops of piperidine were added and the resulting mixture filtered. The reaction mixture was stirred for 5 h at room temperature, cooled to 0°C, the precipitate was removed by filtration and washed with 5 ml of cooled ethanol to give 0.84 g (65%) of 3a as colourless crystals, mp 125-127°C; IR (ν/cm): 3420 sh., 3360, 3200 (NH, NH_2); 2266 (C≡N); 1696 sh., 1689 (C=O); [1]H NMR (CD_3CN, δ, ppm): isomer A: 4.01 (1H, dd, J=4.1 and 12.0 Hz, 2-H); 4.40 (1H, d, J=12.0 Hz, 3-H); 4.75 (1H, d, J=4.1 Hz, 1-H); 5.89 and 6.67 (2H, 2s, $CONH_2$); 7.4-7.5 (5H, m, 2-C_6H_5); 8.46 and 8.50 (2H, 2s, $CSNH_2$); isomer B: 4.16 (1H, dd, J=4.9 and 11.4 Hz, 2-H); 4.34 (1H, d, J=11.4 Hz, 3-H); 4.86 (1H, d, J=4.9 Hz, 1-H); 6.26 and 6.86 (2H, 2s, $CONH_2$); 7.4-7.5 (5H, m, 2-C_6H_5); 8.06 and 8.12 (2H, 2s, $CSNH_2$). The relationship A:B = 1:3. [13]C NMR ($CDCl_3$), δ, ppm): 28.16 and 28.30 (1-C); 45.79 and 46.01 (2-C); 60.20 and 61.03 (3-C); 112.55, 112.77, 113.05 and 113.14 (C≡N); 128.21 and 128.43, 128.36 and 128.58, 128.74 and 129.12, 135.03 and 135.13 (o-, p-, m- and α-C_6H_5); 167.10 and 167.61 (C=O); 199.15 and 199.36 (C=S). Anal. Calcd. For $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57; S 11.77. Found: C 57.28, H 4.40, N. 20.66, S 11.82.

Piperidinium 6-amino-5-cyano-3-carbamoyl(methylcarbamoyl)-4-phenyl-1,4- and 3,4-dihydropyridine-2-thiolates 5 and 6.

A. A mixture of benzylidenemalononitrile 1 (4.62 g, 30 mmol) and thiocarbamoylacetamide 2a (3.54 g, 30 mmol) was dissolved on heating under stirring in 60 ml of ethanol. Piperidine (3 ml, 30 mmol) was added at r.t., the reaction mixture stirred for 30 min, the precipitate removed by filtration and washed with 30 ml of ethanol to give a 9.1 g (85%) mixture of 5a and 6a (>10:1). A sample of 0.3 g was recrystallized from ethanol to yield 0.21 g of 5a as colourless crystals, mp 142-144°C; IR (ν/cm): 3386, 3320, 3216 (NH, NH_2); 2180 (C≡N); 1632 (C=O); [1]H NMR (DMSO-d_6, δ, ppm): 1.58 [6H, m, $CH_2)_3$]; 2.90 [4H, m, $N(CH_2)_2$]; 4.60 (1H, s, 4-H); 5.44 (2H, s, 6-NH_2); 5.62 (2H, br.s, +NH_2); 7.1-7.4 and 7.53 (7H, complex, 4-C_6H_5 and 3-$CONH_2$); 10.28 (1H, br.s, NH); UV (λ_{max}, nm): 330. Anal. Calcd. for $C_{15}H_{13}N_3OS$: C 60.48, H 6.49, N 19.59; S 8.97. Found: C 60.26, H 6.58, N 19.41, S 8.85.

Thiolate 6a. IR and [1]H NMR selected from mixture of 5a and 6a. IR (ν/cm): 3386, 3320, 3216 (NH_2); 2162 (C≡N); 1648 (C=O); [1]H NMR (CD_3CN, δ, ppm): 1.63 [6H, m, $CH_2)_3$]; 3.00 [4H, m, $N(CH_2)_2$]; 3.92 (1H, d, J=3.5 Hz, 3-H); 4.06 (1H, br.d, J=3.5 Hz, 4-H); 4.67 (2H, br.s, +NH_2); 5.69 (2H, s, 6-NH_2); 7.1-7.4 (7H, complex, 4-C_6H_5 and 5-NH_2); UV (λ_{max}, nm): 342.

Thiolate 5b. In a similar manner starting with 2b (methanol was used instead of ethanol) mixture of 5b and 6b (>15:1 from [1]H NMR spectra) was obtained, and 5b separated by recrystallization. Yield of 5b as colourless crystals was 83%, mp 144-146°C; IR (ν/cm): 3334 sh., 3360, 3294, 3176 (NH, NH_2); 2165 (C=N); 1643 (C=O); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.58 [6H, m, $CH_2)_3$]; 2.58 [3H, d, J=4.8 Hz, NH<u>CH</u>$_3$; 2.90 [4H, m, $N(CH_2)_2$]; 4.61 (1H, s, 4-H); 5.42 (2H, s, 6-NH_2); ca. 6.6 (2H, br.s, +NH_2); 7.0-7.2 (5H, m, 4-C_6H_5); 7.42 (1H, s, NH); 10.72 (1H, q, J=4.8 Hz, <u>NH</u>CH_3); UV (λ_{max}, nm): 342. Anal. Calcd. for $C_{19}H_{25}N_5OS$: C 58.59, H 6.99, N 17.98; S 8.23. Found: C 59.02, H 6.79, N 18.03, S 8.32.

Thiolate <u>6b</u>. (DMSO-d_6, selected δ, ppm): 2.58 (3H, d, J=4.8 Hz, NH<u>CH</u>$_3$); 3.80 (1H, br.d, J=3.3 Hz, 4-H); 3.87 (1H, d, J=3.3 Hz, 3-H); 6.17 (2H, s, 6-NH_2); 8.12 (1H, q, J=4.8 Hz, <u>NH</u>CH_3).

B. A mixture of butyrothiamide <u>3</u> (0.27 g, 1 mmol) and piperidine (0.12 ml, 1.2 mmol) in 8 ml of ethanol was shortly heated and filtered. Afterwards the reaction mixture was kept at room temperature for 30 min, the precipitated crystals were removed by filtration and washed with 5 ml of ethanol to give 0.27 g (76%) of <u>5a</u> and <u>6a</u> (2:1 from ^{1}H NMR spectra).

C. A mixture of well crushed thione <u>7a</u> (0.55 g, 2.5 mmol) and piperidine (0.25 ml, 2.5 mmol) in 10 ml of ethanol was shortly heated to 50-60°C and stirred 15 min at r.t. The precipitated crystals were removed by filtration and washed with 5 ml of ethanol to give 0.69 g (97.0%) of <u>5a</u> and <u>6a</u> (1:3 from ^{1}H NMR spectra.

<u>Triethylammonium 6-amino-3-carbamoyl-5-cyano-4-phenyl-3,4-dihydropyridine-2-thiolate 6c</u>.

Compound <u>6c</u> (colourless crystals) was obtained analogously to <u>6a</u>, in 93% (method A), 98% (method C) yields; mp 152-154°C; IR (ν/cm): 3442, 3400, 3308, 3206 (NH_2); 2154 (C≡N); 1646 (C=O); ^{1}H NMR (CD_3CN, δ, ppm): 1.21 (9H, t, CH_2<u>CH</u>$_3$); 3.05 (6H, q, <u>CH</u>$_2CH_3$); 3.94 (1H, d, J=3.5 Hz, 3-H); 4.07 (1H, br.s, J=3.5 Hz, 4-H); 5.59 (2H, br.s, 6-NH_2); 5.96 (1H, br.s, +NH); 6.55 and 7.2-7.4 (7H, complex, 4-C_6H_5 and $CONH_2$). Anal. Calcd. for $C_{19}H_{27}N_5OS$: C 61.10, H 7.29, N 18.75; S 8.58. Found: C 61.00, H 7.23, N 18.82, S 8.63.

<u>Sodium 6-amino-3-carbamoyl-5-cyano-4-phenyl-3,4-dihydropyridine-2-thiolate 6d</u>.

A mixture of thione <u>7a</u> (0.54 g, 2 mmol) and 10 ml of 0.4 N sodium methylate was stirred for 2 h at room temperature and cooled to 0°C. The precipitated crystals were separated by filtration and washed with 5 ml of cold methanol to give 0.15 g (24%) of <u>6d</u> as colourless crystals, mp 198-200°C; IR (ν/cm): 3484, 3400 sh., 3342, 3242, 3212, 3162 (NH_2); 2170 (C≡N); 1664 (C=O); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.46 (1H, d, J=1.6 Hz, 3-H); 3.86 (1H, br.s, J=1.6 Hz, 4-H); 5.50 (2H, s, 6-NH_2); 7.1-7.4 (7H, complex, 4-C_6H_5 and 3-$CONH_2$). Anal. Calcd. for $C_{13}H_{11}N_4OSNa$ x H_2O: C 50.00, H 4.19, N 17.94. Found: C 49.97, H 4.26, N 17.76.

<u>6-Amino-5-cyano-3-carbamoyl(methylcarbamoyl)-4-phenyl-1,4-dihydropyridine-2(3H)-thiones 7</u>.

A mixture of thiolates <u>5a</u> and <u>6a</u> (1.79 g, 5 mmol) was heated on a water bath with 10 ml of acetic acid until dissolution, filtered and 20 ml of 50% ethanol-water solution were added. The reaction mixture was kept for 30 min at 0°C, the precipitated crystals were removed by filtration and washed with 5 ml of cold ethanol and 20 ml of water to give 1.19 g (87%) of <u>7a</u> as yellow crystals; mp 222-224°C [221-223°C (14)]; IR (ν/cm): 3456, 3420, 3324, 3194 (NH, NH_2); 2176 (C≡N); 1682, 1644 (C=O); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.84 (1H, br.s, J=2.8 Hz, 4-H); 3.98 (1H, d, J=2.8 Hz, 3-H); 7.2-7.4 (5H, m, 4-C_6H_5). 11.64 (1H, s, NH); UV (λ_{max}, nm): 357. Anal. Calcd. for $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57, S 11.77. Found: C 57.24, H 4.52, N 20.52, S 11.90.

In a similar manner compound <u>7b</u> (yield 90%) was obtained as yellow crystals; mp 231-233°C; IR (ν/cm): 3420, 3330, 3180 (NH, NH_2); 2196 (C≡N); 1654, 1645 sh. (C=O); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.60 (3H, d, J=4.5 Hz, NH<u>CH</u>$_3$); 3.78 (1H, d, J=3.1 Hz, 3-H); 3.88 (1H, br.d, J=3.1 Hz, 4-H); 6.22 (1H, s, 6-NH_2); 7.2-7.5 (5H, m, 4-C_6H_5). 8.13 (1H, q, J=4.5 Hz, <u>NH</u>CH_3); 11.7 (1H, s, NH). UV (λ_{max}, nm): 360. Anal. Calcd. for $C_{14}H_{14}N_4OS$: C 58.72, H 4.93, N 19.57, S 11.20. Found: C 58.80, H 4.91, N 19.70, S 11.32.

<u>6-Amino-5-cyano-3-carbamoyl(methylcarbamoyl)-4-phenylpyridine-2(1H)-thiones 8</u>.

A mixture of benzylidene malononitrile <u>1</u> (1.54 g, 10 mmol), N-methylthiocarbamoylacetamide <u>2b</u> (1.32 g, 10 mmol) and triethylamine (0.7 ml, 5 mmol) in 30 ml of methanol was refluxed for 3 h. Afterwards 10 ml of acetic acid was added and the reaction mixture was refluxed for 1 h and cooled to 0°C. The precipitated crystals were removed by filtration and washed with 20 ml of ethanol and 20 ml of water to give 1.17 g (41%) of <u>8b</u> as yellow crystals; mp >300°C (decomp.); IR (ν/cm): 3396, 3315, 3250, 3210 (NH, NH_2); 2215 (C≡N); 1660 sh., 1648 (C=O); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.36 (3H, d, J=5.0 Hz, NH<u>CH</u>$_3$); 7.1-7.5 (7H, complex, 4-

C_6H_5 and 6-NH_2);. 7.78 (1H, q, J=5.0 Hz, NHCH$_3$); 12.58 (1H, br.s, NH). Anal. Calcd. for $C_{14}H_{12}N_4OS$: C 59.14, H 4.25, N 19.70, S 11.28. Found: C 58.79, H 4.31, N 19.58, S 11.20.
In a similar manner (2b was used instead of 2b) mixture of 7a and 8a (>10:1 from ^{1}H NMR spectra, yield 59%) was obtained. IR and ^{1}H NMR of 8a selected from mixture of 7a and 8a. IR (ν/cm): 2208; ^{1}H NMR (DMSO-d_6, δ, ppm): 12.6 (1H, br.s, NH).

5-Amino-6-cyano-3-imino-8-carbamoyl(methylcarbamoyl)-7-phenyl-(2H)4,7-dihydrothiazolo[3,2-a]pyridines 10.
A. A mixture of thione 7a (0.82 g, 3 mmol), piperidine (0.3 mol, 3 mmol) and chloroacetonitrile (0.32 ml, 5 mmol) in 10 ml of ethanol was heated to 50-60°C and stirred at ambient temperature for 30 min. Afterwards the precipitated crystals were removed by filtration and washed with 10 ml of ethanol and 20 ml of water to give 0.91 g (97%) of 10a as colourless crystals; mp 218-219°C. IR (ν/cm): 3440, 3324, 3128 (NH, NH_2); 2174 (C≡N); 1668 (C=O); 1656 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.86 and 3.92 (2H, d and d, J=15.6 Hz, SCH_2); 4.58 (1H, s, 7-H); 6.89 (2H, br.s, 5-NH_2); 7.2-7.3 (5H, m, 7-C_6H_5);. 8.16 (2H, br.s, 8-$CONH_2$);. 9.54 (1H, s, 3-N=H). Anal. Calcd. for $C_{15}H_{13}N_5OS$: C 57.86, H 4.21, N 22.49, S 10.30. Found: C 57.78, H 4.19, N 22.40, S 10.24.
In a similar manner (methanol was used instead of ethanol) compound 10b (yield 92%) was obtained as colourless crystals; mp 201-203°C; IR (ν/cm): 3436, 3252, 3110 (NH, NH_2); 2190 (C≡N); 1665 (C=O); 1655 (C=N); ^{1}H NMR (DMSO-d_6, δ, ppm): 2.50 (3H, d, J=4.5 Hz, NHCH$_3$); 3.88 and 3.91 (2H, d and d, J=16.1 Hz, SCH_2);.4.59 (1H, s, 7-H); 7.2-7.3 (5H, m, 7-C_6H_5);. 7.37 (1H, q, J=4.5 Hz, NHCH$_3$);. 8.16 (2H, s, 5-NH_2); 9.56 (1H, s, 3-N=H). Anal. Calcd. for $C_{16}H_{15}N_5OS$: C 59.06, H 4.65, N 21.52, S 9.85. Found: C 58.72, H 4.77, N 21.30, S 9.80.
B. Similarly to method **A** using thiolates 5a, 6a or their mixture instead of thione 7a and piperidine the yield of 10a was 95-97%.

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Received on July 15, 1997