Pergamon

Tetrahedron 54 (1998) 9161–9168

TETRAHEDRON

Efficient Regioselective One-pot Synthesis of Partially Hydrogenated Thiazolo[3,2-*a*]pyridines

Aivars Krauze, Juris Popelis, Gunars Duburs*

Latvian Institute of Organic Synthesis, 21 Aizkraukles str., Riga, LV-1006, Latvia

Received 20 March 1998; revised 13 May 1998; accepted 3 June 1998

Abstract: 7*H*-Thiazolo[3,2-*a*]pyridin-3(2*H*)-ones, 7*H*-thiazolo[3,2-*a*]pyridin-3(2*H*)-imines, and 3-hydroxy-3-methyl(phenyl)-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines have been obtained in good yields by a one-pot synthesis.

Keywords: Pyridines; Cyclization; Bicyclic heterocyclic compounds; Thiazoles

INTRODUCTION

1,4-Dihydropyridines reveal diverse biological activities. Sulfur-containing 1,4- and 3,4-dihydropyridines and their annulated derivatives 4,7-dihydrothieno[2,3-*b*]pyridines and 4,7-dihydroisothiazolo[5,4-*b*]pyridines have been shown to have antihypertensive[1,2], vasodilator[2,3], calcium channel blocker[4-12] and antioxidant[13] activities.

2-Alkylthio-5-carbamoyl-3-cyano-1,4-dihydropyridines[14], on the one hand, and 8-ethoxycarbonyl-5,6-dihydrothiazolo[2,3-*c*][1,4]thiazine[15] and 7-alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazole derivatives[16], on the other, exhibit hepatoprotective activity. It would be useful to combine the structural moieties conferring this activity into one molecule – to synthesize hydrogenated thiazolo[3,2-*a*]pyridines.

Unfortunately, until now only a few 7*H*-dihydrothiazolo[3,2-*a*]pyridin-3(2*H*)-ones have been synthesized, by deamination of 3-cyano-2-carbamoylmethylthio-1,4-dihydropyridines.[17,18] It should be noted, firstly, that the dehydration of the 2-carbamoylmethylthio group to the 2-cyanomethylthio group and Thorpe cyclization are competing reactions, and secondly, that the substituents of the dihydropyridine ring significantly influence the

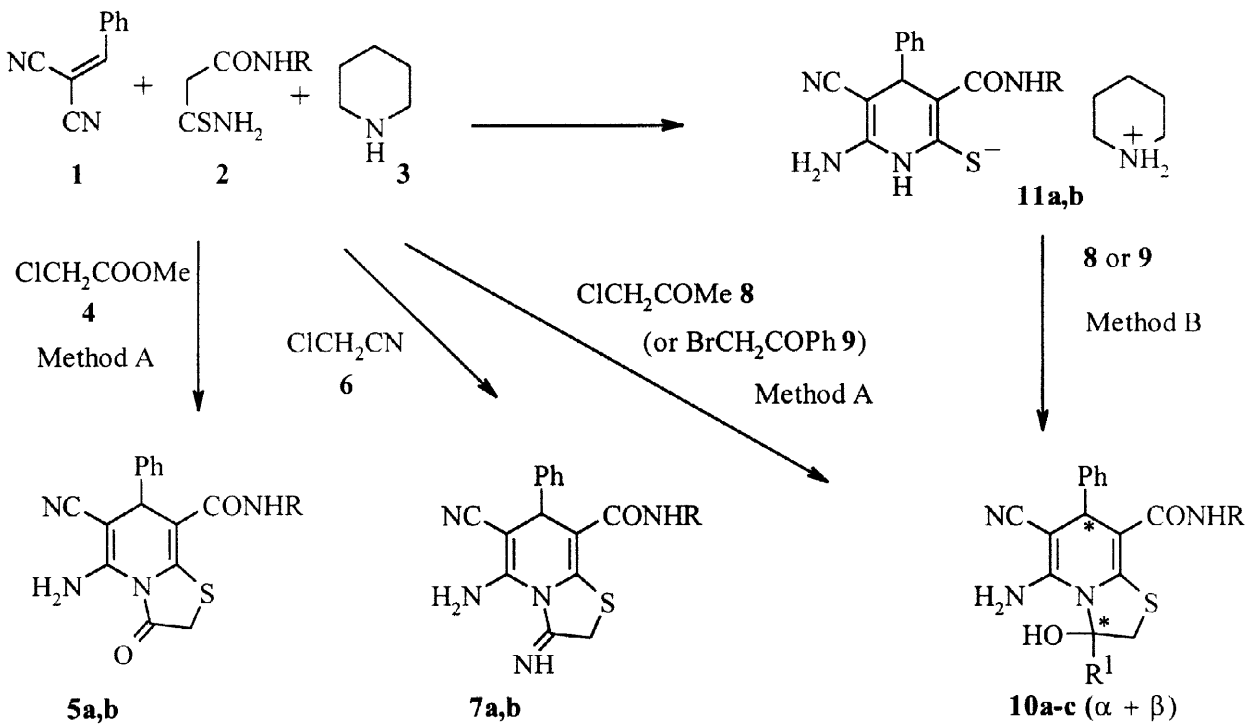
0040-4020/98/$19.00
PII: S0040-4020(98)00553-5

yield of deamination.[17,18] 6,8-Dicyano-spiro-2,3,4,7-tetrahydrothiazolo[3,2-*a*]pyridine-7,1'-cyclohexane[19] was reported to be formed by the treatment of the corresponding thione with dibromoethane, and 6,8-diethoxycarbonyl-2,3,4,7-tetrahydrothiazolo[3,2-*a*]pyridine[20] by the reaction of ethyl benzylideneacetoacetate with 2-ethoxycarbonylmethylenethiazolidine. The spectral data of the tetrahydrothiazolopyridine[21] do not completely satisfy the proposed structure, but the structure of 3-hydroxy-5-oxo-8-cyano-2,3,4,7-tetrahydrothiazolo[3,2-*a*]pyridine bromide obtained as a by-product was confirmed by X-ray analysis.[22]

There are many publications on the reaction of benzylidenemalononitrile (**1**) with 2-cyano(benzoyl,carbamoyl,ethoxycarbonyl)methyl-1,3-thiazolin-4-one to yield 5-amino-2-benzylidene-3-oxo-7*H*-thiazolo[3,2-*a*]pyridines (proceeding through the partial destruction of **1** and the elimination of malononitrile), but not to form compounds of type **5**.[23-26]

We have devised an effective method for the preparation of partially hydrogenated thiazolo[3,2-*a*]pyridines (**5**, **7**, **10**) by a one-pot synthesis from benzylidenemalononitrile (**1**), *N*-substituted thiocarbamoylacetamides (**2a,b**), and an alkyl halide containing a carbofunctional group, in the presence of a basic catalyst. The reaction pathway was confirmed by the isolation of intermediates in a stepwise synthesis of the target thiazolo[3,2-*a*]-pyridines **5**, **7** and **10**.

RESULTS AND DISCUSSION



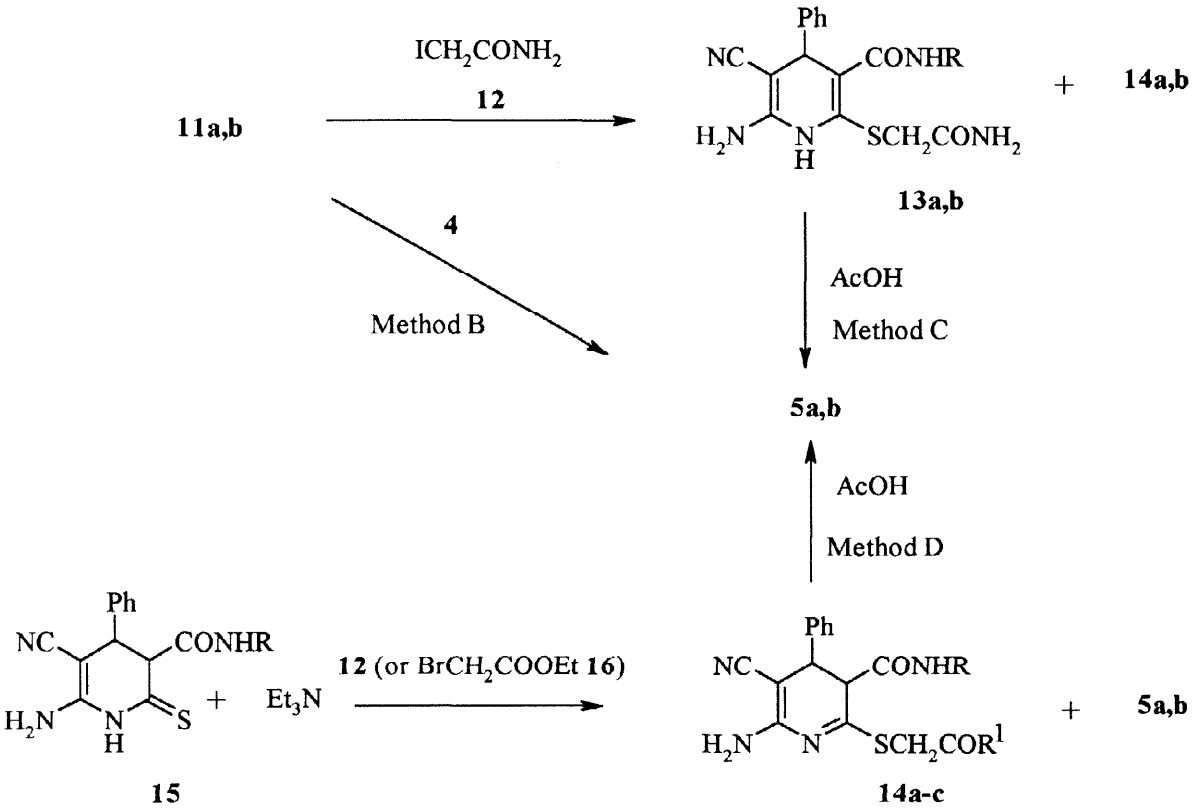
a: R = H, R^1 = Me; b: R = R^1 = Me; c: R = H, R^1 = Ph

Scheme 1

7*H*-Thiazolo[3,2-*a*]pyridin-3(2*H*)-ones **5a,b** were obtained (yields 93% and 85% respectively) from benzylidenemalononitrile (**1**) and thiocarbamoylacetamides **2a** or **2b** in the presence of an equimolar amount of piperidine (**3**) and methyl chloroacetate (**4**) after a brief heating at 30-40 °C. Use of chloroacetonitrile (**6**) instead

of 4 gave the corresponding thiazolo[3,2-*a*]pyridin-3-imines **7a,b** (yields 93% and 85%, respectively), while chloroacetone (**8**) or 2-bromoacetophenone (**9**) as alkylating agents afforded 3-hydroxy-2,3-dihydro-7*H*-thiazolo-[3,2-*a*]pyridines **10a-c** in 83-91% yields (Scheme 1).

The structure of 3-oxothiazolopyridines **5** and the reaction pathway is supported by the stepwise synthesis of the former (Scheme 2). The treatment of thiolates **11**[27] with iodoacetamide (**12**) gives 2-carbamoylmethylthio-1,4-dihydropyridines **13** containing less than 10% of the corresponding 3,4-dihydropyridines **14** and from which they are separable by fractional crystallization. The treatment of thiones **15**[27] with triethylamine and their subsequent reaction with iodoacetamide **12** (or ethyl bromoacetate **16**) yields 2-carbamoyl- (or ethoxycarbonyl-) methylthio-3,4-dihydropyridines **14** and **5** as the main products which are separable by fractional crystallization. On heating of 2-carbamoylmethylthio-1,4 (or 3,4)-dihydropyridines **13**, **14** or of their mixture in acetic acid, 6-amino-7*H*-thiazolo[3,2-*a*]pyridin-3(2*H*)-ones **5** are obtained (methods *C* and D). Compound **5a** is also obtained by the treatment of thiolate **11a** with methyl chloroacetate (**4**) (method B).



a: R = H, R^1 = NH_2; b: R = Me, R^1 = NH_2; c: R = H; R^1 = Et

Scheme 2

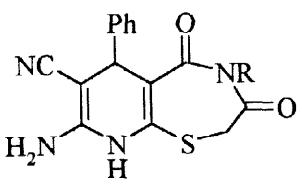
Similarly, 7*H*-thiazolo[3,2-*a*]pyridin-3(2*H*)-imines **7**[27] and 3-hydroxy-2,3-dihydro-7*H*-thiazolo[3,2-*a*]-pyridines **10** are obtained in high yields under mild reaction conditions by treatment of thiolates **11** with chloroacetonitrile (**6**), chloroacetone (**8**) or 2'-bromoacetophenone (**9**).

The high yields of the reduced thiazolo[3,2-*a*]pyridines **5**, **7** and **10** demonstrate the regioselectivity of the one-pot synthesis.

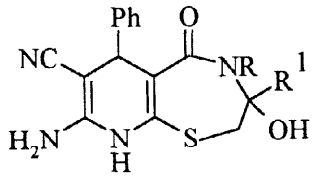
The structures of compounds **5**, **7** and **10** are proved by spectroscopic methods. In their IR spectra absorption bands for $\nu_{C\equiv N}$ at 2166-2190 cm^{-1} are seen; for **5** characteristic $\nu_{C=O}$ of the thiazol-2-one ring at

1714 cm $^{-1}$, and for **7** $\nu_{C=NH}$ at 1655-1656 cm^{-1} are observed. In the ^{1}H NMR spectra of **5**, **7**, and **10** the most characteristic are the C_7-H singlets at 4.39 - 4.62 ppm and AB-doublets of the SCH_2 group with J = 15.6 - 18.1 Hz. It is noteworthy that in the case of **5b** a surprising long-range coupling of one of the AB-system protons (J = 1.1 Hz) with C_7-H is observed. ^{1}H and ^{13}C NMR spectra reveal the existence of a mixture of two diastereoisomers in the case of 3-hydroxy-3-R^1-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines **10**(α+β), due to the asymmetric centres at positions 3 and 7. In the cases of compounds **10a** and **10b**, only one of the two (α, β) diasteroisomers shows the magnetic nonequivalence of the 2-CH_2 groups, while in the case of **10c**, with a sterically bulky phenyl group in the α-position to the 2-CH_2 protons, we observe magnetic nonequivalence of the protons of the AB-system in both diastereoisomers. In the ^{1}H NMR spectra of **13** the most characteristic are singlets of 4-H protons at 4.46 - 4.48 ppm, while in **14** doublets due to the 3-H and 4-H protons with J = 3.9 - 4.4 Hz are seen, indicating the *trans*-arrangement of the 3-CONHR and 4-Ph substituents. The doublets of 4-H are usually broadened due to long-range coupling with the 4-C_6H_5 *ortho* protons.

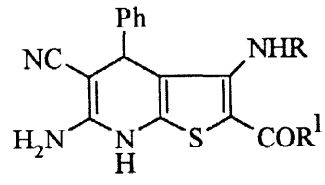
In principle, alternative routes of intramolecular cyclization of 2-alkylthio-3-carbamoyl-1,4-dihydropyridines (of type **13**) are possible, but they were not observed. Firstly, the nitrogen atom of the 3-carbamoyl group may be involved, giving pyrido[3,2-*f*]-1,4-thiazepines **17**, **18**, and secondly, condensation may occur between the active methylene group of the 2-alkylthio substituent and the carbonyl group of the 3-CONHR substituent giving rise to thieno[2,3-*b*]pyridines **19**.



17



18



19

Although the methylene group is activated by electron withdrawing groups, evidently the electrophilicity of the carbon atom of the CONHR substituent is insufficient due to the electron donating properties of the NHR group. Structure **19** is excluded by elemental analysis and spectroscopic data. The alternative cyclization leading to compounds of type **5**, **7**, **10** or of type **17** and **18** is determined by the competitive nucleophilicity of the NH of the dihydropyridine ring and that of the 3-CONHR substituent. In the first case nucleophilicity is partially diminished due to the double β-aminovinylketone type conjugation, but increased due to the electron donating properties of the 6-NH_2 group. In the second case nucleophilicity is diminished by the adjacent CO group and due to the effect of the 2-alkylthio substituent bearing electron withdrawing groups.

In the ^{1}H NMR spectra of **5b**, **7b** and **10b** the characteristic coupling constants of the $NHCH_3$ substituent (q and d, J = 4.5 - 4.6 Hz) are observed, thus supporting 3-oxo(imino)-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine **5b** or **7b** and 3-hydroxy-3-methyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine structures **10b** and excluding the alternative pyrido[3,2-*f*]-1,4-thiazepine structures of type **17** and **18**.

Taking into account earlier work[28], we can assume that on heating in acidic medium 3,4-dihydropyridines **14** first isomerize to 1,4-dihydropyridines **13** and then cyclize to **5**.

Conclusions

An effective regioselective method for the preparation of partially hydrogenated thiazolo[3,2-*a*]pyridines **5**,**7** and **10** has been elaborated by a one-pot synthesis from benzylidenemalononitrile **1**, an *N*-substituted

thiocarbamoylacetamide **2a** or **2b**, and an alkyl halide containing a carbofunctional group, in the presence of a basic catalyst.

Smooth intramolecular *N*-acylation (with loss of ammonia) of 2-carbamoylmethylthio-1,4- and -3,4-dihydropyridines (**13** and **14**) and cyclization of the probable intermediates 2-acetyl(benzoyl)methylthio-dihydropyridines (without subsequent dehydration) are the crucial steps of this method.

A change from the strongly electron-withdrawing CN group at position 3 and a CH_3 at position 6[29] for CONHR and NH_2 groups, respectively, in 2-alkylthiodihydropyridines leads to an increase in the nucleophilicity of the endocyclic nitrogen atom, which favours the existence of 1,4- and 3,4-dihydropyridine isomers, prevents the competing formation of 4,7-dihydrothieno[2,3-*b*]pyridines, and promotes intramolecular *N*-acylation.

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 (ν/cm^{-1}) with a Perkin-Elmer 580B spectrometer. The ^1H NMR spectra of solutions in $CDCl_3$, CD_3CN or DMSO-d_6 were obtained with a Bruker WH 90/DC (90 MHz) and AM-360 (360 MHz) spectrometers. Chemical shifts are expressed in δ (p.p.m. downfield from TMS) and coupling constants (*J*) in Hertz. The course of the reactions and the purity of the substances were monitored by TLC on Kieselgel 60F Merck plates with CH_2Cl_2-C_6H_{14}-MeOH (5:5:1) as eluent. Compounds were recrystallized from EtOH. Compounds **11** and **15** were synthesized as earlier described.[27]

5-Amino-6-cyano-3-oxo-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-8-(N-methyl)carboxamides **(5a, b)**: A mixture of benzylidenemalononitrile (**1**) (0.77 g, 5 mmol) and thiocarbamoylacetamide (**2a**) (0.59 g, 5 mmol) in methanol (10 ml) was heated until dissolution, then cooled to 30-40 °C. Piperidine (**3**) (0.55 ml, 5.5 mmol) and methyl chloroacetate (**4**) (0.53 ml, 6 mmol) were added and the reaction mixture was stirred at ambient temperature for 1 h. The precipitated crystals were removed by filtration, washed with hot EtOH (20 ml) and H_2O (20 ml) to give **5a** (1.45 g, 93 %) as colourless crystals, mp 263–265 °C; IR: 3488, 3422, 3372, 3316 (NH_2); 2186 (C≡N); 1714, 1668 (C=O); ^1H NMR (DMSO-d_6): 3.88 and 3.91 (2H, d and d, J = 18.0, 2-CH_2); 4.62 (1H, s, 7-H); 6.94 and 7.03 (2H, 2br.s, 3-$CONH_2$); 7.22 (2H, br.s, 5-NH_2); 7.24 - 7.34 (5H, m, 7-C_6H_5); ^{13}C NMR (DMSO-d_6): 32.56 (2-C); 39.30 (7-C); 65.63 (6-C); 104.99 (8-C); 119.43 (CN); 126.89, 127.19, 128.37, 143.38 (*p*-, *o*-, *m*- and *i*-C_6H_5); 144.16, 148.06 (5-C and 9-C); 167.01 (8-$CONH_2$); 174.02 (3-C=O). Anal. Calcd. for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94; S, 10.27. Found: C, 57.63; H, 3.82; N, 18.03; S, 10.33.

In a similar manner, starting from **2b** compound **5b** (yield 85 %) was obtained as colourless crystals, mp 210-212 °C; IR: 3418, 3320 (NH, NH_2); 2190 (C≡N); 1714, 1661 (C=O); ^1H NMR (CD_3CN): 2.55 (3H, d, J = 4.5, $NHCH_3$); 3.76 and 3.81 (2H, d and d, J = 18.3, 2-CH_2); 4.39 (1H, s, 7-H); 6.00 (1H, bs.s, $NHCH_3$); 6.58 (2H, br.s, 5-NH_2); 7.2 - 7.4 (5H, m, 4-C_6H_5); ^{13}C NMR (DMSO-d_6): 25.92 ($NHCH_3$); 32.53 (2-C); 38.90 (7-C); 65.48 (6-C); 105.04 (8-C); 119.45 (CN); 126.93, 127.04, 128.44, 142.63 (*p*-, *o*-, *m*- and *i*-C_6H_5); 144.04 and 148.19 (5-C and 9-C); 165.39 (8-$CONH_2$); 173.98 (3-C=O). Anal. Calcd. for $C_{16}H_{14}N_4O_2S$: C, 58.88; H, 4.32; N, 17.17; S, 9.82. Found: C, 58.57; H, 4.35; N, 17.00; S, 9.89.

B. A mixture of thiolate **11a** (1.07 g, 3 mmol) and methyl chloroacetate (**4**) (0.44 ml, 5 mmol) in MeOH (25 ml) was heated until dissolution of the thiolate and stirred for 1 h at ambient temperature. The precipitated crystals were filtered off and washed with hot ethanol (20 ml) and water (20 ml) to yield **5a** (0.90 g, 96 %).

C. The 2-carbamoylmethylthio-1,4-dihydropyridine **13a** (0.99 g, 3 mmol) in AcOH (5 ml) was heated for 5 min on a water bath, filtered, ethanol (5 ml) was added and the mixture kept for 1 h at room temperature. The

precipitated crystals were removed by filtration and washed with ethanol (10 ml) and water (10 ml) to give **5a** (0.91 g, 97 %) of as colourless crystals, mp 263 - 265 °C. Compound **5b** (80 %) was obtained similarly.

D. A sample of 2-carbamoylmethylthio-3,4-dihydropyridine **14b** (0.1 g, 0.3 mmol) in AcOH (1 ml) was heated for 5 min on water bath, filtered and similarly to the method **C** **5a** (0.07 g, 75 %) was obtained.

5-Amino-6-cyano-3-imino-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-8-(N-methyl)carboxamides **(7a, b)**: Similarly to **5a** (method A) using chloroacetonitrile (**6**) instead of methyl chloroacetate (**4**), compound **7a** (93 %) was obtained as colourless crystals, mp 218-219 °C.[27] The IR and ^{1}H NMR spectra of **7a** and **7b** were identical with those given in ref. 27. ^{13}C NMR (DMSO-d_6): 31.82 (2-C); 39.01 (7-C); 62.81 (6-C); 103.27 (8-C); 120.56 (CN); 126.67, 126.89, 128.36 and 145.56 (); 145.14, 150.46 and 165.35 (3-C, 5-C and 9-C); 167.33 (8-$CONH_2$); 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 compound **7b** (85 %) was obtained as colourless crystals, mp 201-203 °C.[27] ^{13}C NMR (DMSO-d_6): 25.99 ($NHCH_3$); 31.82 (2-C); 38.61 (7-C); 62.70 (6-C); 103.37 (8-C); 120.59 (CN); 126.71, 126.75, 128.41 and 144.81 (*p*-, *o*-, *m*- and *i*-C_6H_5); 145.01, 150.61 and 165.75 (3-C, 5-C and 9-C); 165.75 (8-$CONH_2$). 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.

5-Amino-6-cyano-3-hydroxy-3-methyl(phenyl)-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-8-(N-methyl)carboxamides **(10a,b,c)**: **A**. A mixture of benzylidenemalononitrile (**1**) (0.77 g, 5 mmol), thiocarbamoylacetamide (**2a**) (0.59 g, 5 mmol) in ethanol (10 ml) was heated until dissolution, then cooled to 40-50 °C. Piperidine (0.55 ml, 5.5 mmol) and chloroacetone (0.53 ml, 6 mmol) were added and the reaction mixture was stirred at ambient temperature for 1 h. The precipitated crystals were removed by filtration, washed with ethanol (20 ml) and water (20 ml) to give **10a** (1.48 g, 90 %) as colourless crystals, mp 216 - 218 °C; IR: 3446, 3416, 3318, 3170 (NH_2, OH); 2176, 2168 (C≡N); 1650, 1630 (C=O); ^{1}H NMR (DMSO-d_6): 1.62 and 1.69 (3H, s and s, 3-CH_3); 3.02, 3.14 and 3.19 (total 2H, d, s and s, J = 11.3, 2-CH_2); 4.48 and 4.51 (1H, s and s, 7-H); 6.28 and 6.32 (2H, s and s, 5-NH_2); 6.57 and 6.65 (2H, bs and bs, 8-$CONH_2$); 7.1 - 7.4 (5H, m, 7-C_6H_5); 7.79 and 7.85 (1H, s and s, 3-OH); ^{13}C NMR (DMSO-d_6): 21.87 , 22.11, 24.21 (3-CH_3); 43.67 (2-C, 7-C); 61.10 and 61.43 (6-C); 95.73 and 96.05 (3-C); 99.41 (8-C); 121.31 and 121.65 (CN); 126.29, 126.46, 126.69, 126.81, 128.20, 144.71 and 145.70 (*p*-, *o*-, *m*- and *i*-C_6H_5); 146.47 and 146.55 (5-C and 9-C); 167.85 and 168.02 (8-$CONH_2$). Anal. Calcd. for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06; S, 9.76. Found: C, 58.48; H, 4.95; N, 17.08; S, 9.62.

In a similar manner [**2b** used instead of **2a** or bromoacetophenone (**9**) instead of chloroacetone (**8**)], compounds **10b** and **10c** were obtained.

Compound **10b** (yield 82 %), colourless crystals, mp 166-168 °C; IR: 3490, 3385, 3242 (NH_2, NH, OH); 2168 (C≡N); 1632 (C=O); ^{1}H NMR (DMSO-d_6): 1.62 and 1.69 (3H, s and s, 3-CH_3); 2.48 (3H, d, J = 4.7, N<u>H</u>CH_3); 3.02, 3.15 and 3.21 (total 2H, d, s and d, J = 11.2, 2-CH_2); 4.48 and 4.51 (1H, s and s, 7-H); 6.27 and 6.32 (2H, 2s, 5-NH_2); 6.97 (1H, q, J = 4.7, <u>NH</u>CH_3); 7.1 - 7.4 (5H, m, 7-C_6H_5); 7.76 and 7.82 (1H, 2s, 3-OH); ^{13}C NMR (DMSO-d_6): 21.81 and 24.34 (3-CH_3); 25.90 and 26.01 ($NHCH_3$); 38.53 and 38.77 (7-C); 39.38 (2-C); 60.87 and 61.20 (6-C); 95.64 and 96.06 (3-C); 99.50 (8-C); 121.37 and 121.70 (CN); 126.35, 126.50, 126.67, 128.26, 144.06 and 144.95 (*p*-, *o*-, *m*- and *i*-C_6H_5); 146.32, 146.39, 150.51 and 151.62 (5-C and 9-C); 166.30 and 166.47 (8-$CONH_2$). Anal. Calcd. for $C_{17}H_{18}N_4O_2S \cdot 0.5\ H_2O$: C, 58.10; H, 5.45; N, 15.94; S, 9.12; Found: C, 57.88; H, 5.35; N, 15.91; S 9.16.

Compound **10c** (yield 84 %), colourless crystals, mp 190 - 192 °C; IR: 3446, 3420, 3306, 3224, 3192 (NH_2, OH); 2166 (C≡N); 1648 (C=O); ^{1}H NMR (DMSO-d_6): 3.04 and 3.60, 3.30 and 3.41 (total 2H, d and d, J = 11.6, d and d, J = 12.2, 2-CH_2); 4.58 and 4.61 (1H, s and s, 7-H); 5.78 and 5.89 (2H, s and s, 5-NH_2); 6.7 and 6.76 (2H, bs and s, $CONH_2$); 7.1 - 7.5 (10H, m, 3,7-C_6H_5); 8.33 and 8.41 (1H, s and s, 3-OH); ^{13}C NMR (DMSO-d_6): 42.36 and 43.58 (2-C and 7-C); 60.88 and 61.62 (6-C); 95.35 and 96.55 (3-C); 98.96 and 99.78

(8-C); 121.24, 121.42 (CN); 124.46, 126.56, 126.70, 126.92, 128.23, 128.27, 128.34, 128.38, 141.32, 142.59, 145.66, 146.43, 147.18, 147.54, 150.63, 151.18 (*p*-, *o*-, *m*- and *i*-C_6H_5, 5-C and 9-C); 167.89 and 167.94 (8-$CONH_2$). Anal. Calcd. for $C_{21}H_{18}N_4O_2S$: C, 64.60; H, 4.65; N, 14.35; S, 8.20. Found: C, 64.57; H, 4.69; N, 14.28; S, 8.17.

B. A mixture of thiolate **11a** (1.07 g, 3 mmol) and chloroacetone (0.32 ml, 4 mmol) in ethanol (20 ml) was briefly heated to 40-50 °C, stirred at ambient temperature for 1 h and then treated as in method **A**; **10a** (0.90 g 91 %) was obtained. Similarly **10b** (83 %) and **10c** (86 %) were prepared.

***6-Amino-2-(carbamoylmethylthio)-5-cyano-4-phenyl-1,4-dihydropyridine-3-(N-methyl)carboxamides* (13)**: A mixture of thiolate **11a** (3.57 g, 10 mmol) and iodoacetamide **12** (2.22 g,12 mmol) in 40 ml of ethanol was briefly heated until dissolution of thiolate and then stirred for 1 h at ambient temperature. The precipitated crystals were removed by filtration and washed with hot ethanol (10 ml) and water (20 ml) to yield **13a** (2.56 g, 78 %) as colourless crystals; mp 240 - 242 °C ; IR: 3446, 3372, 3352, 3180 (NH_2); 2190 (C≡N); 1670, 1648 (C=O); ^{1}H NMR (DMSO-d_6): 3.42 and 3.60 (2H, d and d, J = 15.0, SCH_2); 4.48 (1H, s, 4-H); 5.70 (2H, s, 6-NH_2); 7.0 - 7.4 (7H, complex, 4-C_6H_5 and 5-$CONH_2$); 7.46 and 7.86 (2H, 2s, SCH_2CONH_2); 9.22 (1H, s, NH). Anal. Calcd. for $C_{15}H_{15}N_5O_2S$: C, 54.70; H, 4.59; N, 21.26; S, 9.73. Found: C, 54.51; H, 4.60; N, 21,19; S, 9.78.

To the filtrate water (5 ml) was added and after 1h a crude product was separated by filtration which after recrystallization from ethanol yielded 8 % of **14a**.

In a similar manner compound **13b** (yield 76 %) was obtained as colourless crystals; mp 207 - 208 °C; IR: 3444, 3282, 3214 (NH, NH_2); 2182 (C≡N); 1682, 1640 (C=O); ^{1}H NMR (DMSO-d_6): 2.56 (3H, d, J = 4.5 Hz, $NHCH_3$); 3.44 and 3.60 (2H, d and d, J = 15.0, SCH_2); 4.46 (1H, s, 4-H); 5.68 (2H, s, 6-NH); 7.1 - 7.4 (5H, m, 4-C_6H_5); 7.46 and 7.86 (2H, bs and bs, $CONH_2$); 7.92 (1H, q, J = 4.5, $NHCH_3$); 9.08 (1H, s, NH). Anal. Calcd. for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.35; S, 9.34. Found: C, 55.73; H, 5.04; N, 20.25; S, 9.38.

To the filtrate water (20 ml) was added and after 1h **14b** (yield 9 %) was separated by filtration.

***6-Amino-2-(carbamoylmethylthio)-5-cyano-4-phenyl-3,4-dihydropyridine-3-(N-methyl)carboxamides* (14).** A mixture of thione **15a** (0.54 g, 2 mmol) and iodoacetamide (0.41 g, 2.2 mmol) in ethanol (25 ml) was heated until dissolution, and,with stirring and at ambient temperature triethylamine (0.28 ml, 2 mmol) was added. After 30 min water (25 ml) was added and the reaction mixture was cooled to 0 °C. The precipitated crystals were removed by filtration and washed with 50 % ethanol (20 ml) and water (20 ml) to yield **14a** (0.37 g, 56%) as yellow crystals, mp 117 - 119 °C ; IR: 3446, 3396, 3324, 3290, 3196 (NH); 2162 (C≡N); 1680, 1674 sh. (C=O); ^{1}H NMR (DMSO-d_6): 3.44 (1H, d, J = 3.6, 3-H); 3.66 and 3.78 (2H, d and d, J = 15, SCH_2); 3.88 (1H, bd, J = 3.6, 4-H); 6.52 (2H, s, 6-NH_2); 7.1 - 7.4 (7H, complex, 4-C_6H_5 and 3-$CONH_2$); 7.46 and 7.68 (2H, s and s, SCH_2CONH_2). Anal. Calcd. for $C_{15}H_{15}N_5O_2S$: C, 54.70; H, 4.59; N, 21.26; S, 9.73. Found: C, 54.50; H, 4.51; N, 21.09; S, 9.66.

The filtrate was concentrated to half of its volume and **5a** (0.14 g, 22 %) was obtained.

In a similar manner compound **14b** (90 %) was obtained as yellow crystals, mp 129 - 131 °C; IR: 3446, 3386 sh., 3318, 3196 (NH, NH_2); 2168 (C≡N); 1686 (C=O); ^{1}H NMR (DMSO-d_6): 2.60 (3H, d, J = 5.0, $NHCH_3$); 3,44 (1H, d, J = 4.4, 3-H); 3.68 and 3.78 (2H, d and d, J = 15.0, SCH_2); 3.86 (1H, bd, J = 4.2, 4-H); 6.53 (2H, s, 6-NH_2); 7.22 - 7.48 (2H, 2bs, $CONH_2$); 7.3 - 7.4 (5H, m, 4-C_6H_5); 8.18 (1H, q, J = 5.0, $NHCH_3$). Anal. Calcd. for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.35; S, 9.34. Found: C, 55.71; H, 5.03; N, 20.19; S, 9.16.

Similarly, **14c** (45 %) was obtained as yellow crystals (after separation of a 35 % yield of **5a**), mp 243 - 245 °C; IR: 3360, 3308, 3220, 3194 (NH_2); 2186 (C≡N); 1733, 1680 (C=O); ^{1}H NMR (DMSO-d_6): 1.19 and 4.12 (total 5H, t and q, C_2H_5); 3.47 (1H, d, J = 3.6, 3-H); 3.76 (1H, d, J = 3.6, 4-H); 3.98 and 4.02 (2H, d and d, J = 16, SCH_2); 6.48 (2H, s, 6-NH_2); 7.1 - 7.3 (5H, m, 4-C_6H_5); 7.18 and 7.52 (2H, bs and bs, 3-$CONH_2$). Anal. Calcd. for $C_{17}H_{16}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63; S, 8.95. Found: C, 56.96; H, 5.00; N, 15.84; S 9.08.

REFERENCES

1. Meyer H., Bossert F., Vater W., Stoepel K.: Ger.Offen. 2 260 860 (1972), *C.A.* **1974**, *81*, 91 364.
2. Adachi I., Yamamori T., Hiramatsu Y., Sakai K., Mihara S.M., Kawakami M., Masui M., Uno O., Ueda M.: *Chem. Pharm. Bull.* **1988**, *36*: 4389-4402.
3. Krauze A.A., Vitolina R.O., Romanova M.R., Dubur G.Ya.: *Khim.-Farm. Zh.* (in Russian). **1988**, *22*, 955-959.
4. Shinichi Y., Takao G., Hiromitsu M., Senichi, N.: Japan. Pat. 01 287 089 (1990), *C.A.* **1991**, *114*, 228 895.
5. Atwal K.S., Rovnyak G.C., Schwartz J., Moreland S., Hedberg A., Gougontas J.Z., Malley M.F., Floyd D.M.: *J. Med. Chem.* **1990**, *33*, 1510-1515.
6. Atwal K.S., Rovnyak G.C., Kimball B.D., Floyd D.M., Moreland S., Swanson B.N., Gougontas J.Z., Smillie K.M., Malley M.F., Schwartz J.: J. *Med. Chem.* **1990**, *33*, 2629-2635.
7. Mihara S., Fujimoto M.: *Japan. J. Pharmacol.* **1991**, *56*, 249-259.
8. Dessy C., Salomone S., Morel N., Goldfraid T.: *Eur. J. Pharmacol.* **1993**, *231*, 435-442.
9. Ueda M., Matsumura S., Masui M., Matsuura E., Uno O., Kawakami M., Ninomiya M., Adachi I.: *Arzneim.Forsch./ Drug Res.* **1993**, *43*, 1270-1275.
10. Nakajima M., Ueda M., Matsumura S., Masui M., Matsuura E., Uno O., Kawakami M., Ninomiya M., Adachi I.: *Arzneim.Forsch./ Drug Res.* **1993**, *43*, 1270-1275.
11. Ueda M., Matsumura S., Masui M., Matsuura E., Kawakami M., Fugimoto H., Umeda T., Kagawa H., Hirohata S., Shima K., Adachi I.: *Arzneim.Forsch./ Drug Res.* **1993**, *43*, 1282-1290.
12. Ueda M., Masui M., Kawakami M., Matsunaga K., Gemba T., Ninomiya M., Nakano A., Torii M., Adachi I., Ito H.: *Arzneim.Forsch./ Drug Res.* **1993**, *43*, 1291-1303.
13. Kirule I.E., Krauze A.A., Velena A.H., Antipova D.Yu., Arnicane G.Ya., Vucina I.A., Dubur G.Ya.: *Khim.-Farm. Zh.* (in Russian). **1992**, Nr 11/12, *26*, 59-62.
14. Krauze A.A., Odinecs A.G., Verreva A.A., Germane S.K., Kozhukhov A.N., Dubur G.Ya.: *Khim.-Farm. Zh.* (in Russian), **1991**, Nr 7, *25*, 40-43.
15. Hasegawa M., Nakayama A., Hosokami T., Kurebayashi Y., Ikeda T., Shimoto Y., Ide S., Honda Y., Suzuki N.: *Chem. Pharm. Bull.* **1995**, *43*, 78-83.
16. Hasegawa M., Nakayama A., Hokohama S., Hosokami T., Kurebayashi Y., Ikeda T., Shimoto Y., Ide S.: *Chem. Pharm. Bull.* **1995**, *43*, 1125-1131.
17. Krauze A., Duburs G.: *Latv. J. Chem.* **1994**, 92-94.
18. Krauze A., Duburs G.: *Chem. Heterocycl. Comp.* **1996**, *32*, 982-983.
19. Dyachenko V.D., Krivokolysko S.G., Struchkov Yu.T., Litvinov V.P.: *Izv. Akad. Nauk., Ser. Chim.* (in Russian). **1996**, 2535-2540.
20. Meyer H., Bossert F., Horstmann H.: *Liebigs Ann. Chem.* **1977**, 1888-1894.
21. Elmoghayar M.R.H., El-Agamey A-G.A., Nasr M.Y.A-S., Sallam M.M.M.: *J. Heterocycl. Chem.* **1984**, *21*, 1885-1887.
22. Shestopalov A.M., Bogomolova O.R., Rodinovskaya L.A., Litvinov V.P., Bujnicki B., Mikalajczyk M., Nesterov V.N., Struchkov Yu.T.: *Heteroat. Chem.* **1993**, *4*, 593-602.
23. Elgemeie G.E.H., Elfahham H.A., Hassan S.M.E., Elnagdi M.H.: *Z. Naturforsch.* **1983**, *38b*, 781-785.
24. Osman S.A.M., Elgemeie G.E.H., Nawar G.A.M., Elnagdi M.H.: *Monatsh. Chem.* **1986**, *117*, 105-110.
25. Abdul-Latif F.F., Shaker R.M.: *Phosphorus Sulfur Silicon*, **1990**, *48*, 217-221.
26. Elnagdi M.H., Elmoghayar M.R.H., Elghandour A.H.H., Sadek K.U.: *Coll. Czech. Chem. Commun.* **1990**, *55*, 745-751.
27. Krauze A., Popelis J., Duburs G.: *Heterocycl. Commun.* **1997**, *3*, 515-520.
28. Krauze A.A., Liepinsh E.E., Pelcher Yu.E., Kalme Z.A., Dubur G.Ya.: *Chem. Heterocycl. Comp.* **1987**, *23*, 61-65.
29. Krauze A.A., Liepinsh E.E., Pelcher Yu.E., Dubur G.Ya.: *Chem. Heterocycl. Comp.* **1987**, *23*, 102-106.