NEW 5-SUBSTITUTED DERIVATIVES OF ETHYL 2,3-DIHYDRO-3-OXOISOTHIAZOLO[5,4-*b*]PYRIDINE-2-ACETATE

Victor Martinez-Merino*, Maria J. Gil, Alberto Gonzalez, Jose M. Zabalza, Javier Navarro, and Maria A. Mañu

Departamento de Quimica, Universidad Publica de Navarra, Cra. El Sadar s/n, 31006 Pamplona, Spain

Abstract - New series of ethyl 5-substituted 2,3-dihydro-3-oxoisothiazolo[5,4-*b*] pyridine-2-acetate was prepared either a) directly by reaction of 5-substituted 2-chlorothio-3-pyridinecarbonyl chlorides with ethyl glycinate or b) by oxidation of the correspondent 2-mercapto-3-pyridinecarboxamides. New 5-substituted 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acids as starting materials are described.

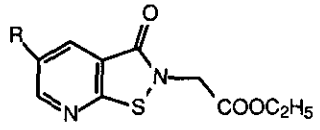
INTRODUCTION

Although isothiazole-3-ones fused with heterocyclic rings are relatively unknown in the literature, 2-substituted 3-oxoisothiazolo[5,4-*b*]pyridines are extensively investigated in view of their biological activity.[1-4] However, effects of substituents at 4-6 positions on bioactivity of these compounds remain unexplored. As for their derivatives substituted at 4-6 positions, methyl[5] or phenyl[6], 4,6-dimethyl[2,5] or diphenyl[7] and 5-amino-6-carbamoyl[3] derivatives have been reported.

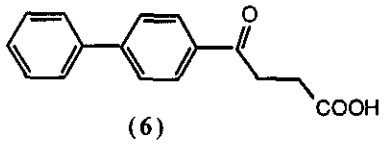
In this paper we report the synthesis of a series of ethyl 5-substituted 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]-pyridine-2-acetates (**1** to **5**) for their further study as antiinflamatory agents. Molecular modelling[8] preliminary studies showed close steric and electrostatic potential similarities between **3** and Cinopal® (fenbufen[9]) (**6**). On the other hand, ethyl 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetates are of interest as key intermediates in the synthesis of the oxicams,[10] another class of non steroidal antiinflamatory agents.

We have chosen 5-substituted derivative because the chemical stability of isothiazolone ring and consequently the metabolism of 3-oxoisothiazolo[5,4-*b*]pyridine system are conceivable to be strongly influenced by these

substituents. The selected NH_2, CH_3, C_6H_5, H and NO_2 substituents may be a suitable group for a preliminary biological screening because they show a wide range in σ_p Hammett constant (-0.66 to 0.71)[11] and also they change the hydrophobicity in three LogP units.[12] LogP and σ_p are not correlated ($r^2 < 0.05$) within that group of substituents.



(1) R= NH_2
(2) R= CH_3
(3) R= C_6H_5
(4) R= H
(5) R= NO_2



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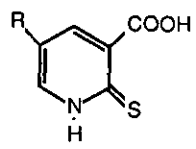
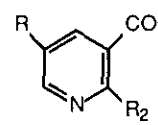
2-Substituted 3-oxoisothiazolo[5,4-*b*]pyridines are usually constructed by oxidation of a suitably substituted 2-mercapto-3-pyridinecarboxamides with sodium metaperiodate,[4] iodine,[5,6] potassium hexacyanoferrate (III)[5] or thionyl chloride.[1] Similarly 2,2'-dithiobis or 2,2'-trithiobis(3-pyridinecarboxamides) were oxidized to 3-oxoisothiazolo[5,4-*b*]pyridines by thionyl chloride.[1,13] An alternative route has recently been described by thermal rearrangement of 2-benzylsulfinyl-3-pyridinecarboxamides with trichloroacetic anhydride.[14] Now we report the synthesis of 2-substituted 3-oxoisothiazolo[5,4-*b*]pyridines in a single step by treatment of 2-chlorothio-3-pyridinecarbonyl chloride derivatives with an amine.

RESULTS AND DISCUSSION

Initially, 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acids (**7** to **9**) were prepared by several methods. 5-Phenyl derivative (**7**) was obtained by condensation of 3-dimethylamino-2-phenylacrolein with cyanothioacetamide in refluxing methanol-sodium methoxide for 8 h to give 3-cyano-5-phenylpyridine-2(1*H*)-thione which was refluxed in 37 % HCl for 8 h to give **7** (52% overall yield). Compound(**7**)was also prepared in 51% overall yield by treating 1,2-dihydro-2-oxo-5-phenyl-3-pyridinecarboxylic acid with phosphorus oxychloride/DMF to give 2-chloro-5-phenyl-3-pyridinecarboxylic acid (**10**) which was treated with thiourea (5 M) in diethylene glycol for 10 h at 150°C followed by hydrolysis of the isothioureido intermediate with concentrated HCl. While the reaction of **10** with thiourea in boiling water or in diluted HCl at 150 psi gave **7** in very poor yields (<10%), treatment of 2-bromo-5-methyl-3-pyridinecarboxylic acid with thiourea in boiling water for 3 h gave the 5-methyl derivative (**8**) in 77% yield.



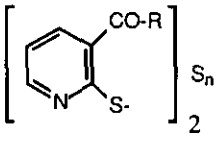
(7) R= C_6H_5
(8) R= CH_3
(9) R= NO_2



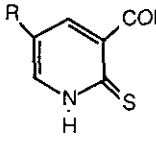
(10) R= C_6H_5, R_1=H, R_2=Cl
(11) R= NO_2, R_1=C_2H_5, R_2=Cl

When 1,2-dihydro-5-nitro-2-oxo-3-pyridinecarboxylic acid was esterified and then treated with phosphorus oxychloride/DMF, ethyl 2-chloro-5-nitro-3-pyridinecarboxylate (**11**) was obtained in 71% yield. However the treatment with phosphorus oxychloride/DMF before esterification gave bis(2-chloro-5-nitro-3-pyridinecarboxylic) anhydride.[15] This anhydride or ethyl ester (**11**) quickly reacted with sodium hydrosulfide at room temperature, and the sulfide intermediates were hydrolysed to give 5-nitro derivative (**9**) in 45% or 70% overall yields, respectively.

The reaction of 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid with thionyl chloride in toluene at reflux leads to 2,2'-dithiobis(3-pyridinecarbonyl chloride) (**12**) which reacts with amines in chloroform/pyridine or triethylamine to give the corresponding 2,2'-dithiobis(3-pyridinecarboxamides) (**14**).[13] *N*-Alkyl carboxamides (**14**) disproportionate under the reaction conditions to a mixture of 2-alkyl-3-oxoisothiazolo[5,4-*b*]pyridines and 1,2-dihydro-2-thioxo-3-pyridinecarboxamides (**15**).[13] Similarly, treatment of 5-nitro acid (**9**) with thionyl chloride in boiling xylene and then with ethyl glycinate gave a mixture of ethyl 2,3-dihydro-2-nitro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate (**5**) and *N*-(ethoxycarbonylmethyl)-1,2-dihydro-5-nitro-2-thioxo-3-pyridinecarboxamide (**16**). Iodine/$NaHCO_3$ oxidized this mixture to give pure **5** (80% overall yield). 3-Oxoisothiazolo[5,4-*b*]pyridines (**2**, **3** and **4**) were also obtained by the same method in 40-75% yield.

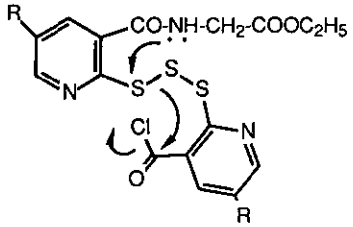


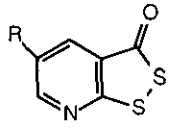
(12) n=0 R=Cl
(13) n=1 R=Cl
(14) n=0 R=NH-R_1 R_1=alkyl or aryl



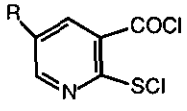
(15) R=H, R_1=alkyl
(16) R=NO_2, R_1=$CH_2COOC_2H_5$
(17) R=NH_2, R_1=$CH_2COOC_2H_5$

Otherwise, treatment of 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid with thionyl chloride in methylene dichloride/pyridine at 0 °C gives a mixture of 2,2'-dithiobis (**12**) and 2,2'-trithiobis(3-pyridinecarbonyl chloride) (**13**).[13] When the mixture of **12** and **13** was treated with ethyl glycinate, 1,2-dithiolo[5,4-*b*]pyridin-3-one (**18**) was also obtained probably through the rearrangement shown below. In the syntesis of 3-oxoisothiazolo[5,4-*b*]pyridines (**3**, **4** and **5**) from crude acid chlorides obtained in boiling xylene, corresponding 1,2-dithiolo[5,4-*b*]pyridin-3-ones were not detected, while **2** was accompanied with 5-methyl-1,2-dithiolo[5,4-*b*]pyridin-3-one (**19**) under the same conditions.





(18) R=H
(19) R=CH_3



(20)
R=CH_3, C_6H_5, H or NO_2

To eliminate the formation of dithiolopyridines and to improve yields, new 2-chlorothio-3-pyridinecarbonyl chlorides (**20**) were synthesised by treating crude 5,5'-disubstituted derivatives of disulfide (**12**) with dry chlorine and catalytic amounts of iodine. Sulfenyl chlorides (**20**) are unstable and decompose by thermal rearrangement under nitrogen atmosphere into disulfide acid chlorides. Whereas acyl disulfide (**12**) shows a multiplet at δ 8.45-8.65 ppm in ^{1}H-nmr ($CDCl_3$) assignable to H-4, H-6, H-4' and H-6', 2-chlorothio-3-pyridinecarbonyl chloride (**20**) shows two double doublets at δ 8.52 and 8.85 ppm assignable to H-4 and H-6 respectively (J_{45}=8.0, J_{46}=1.8 and J_{56}=4.6 Hz). Similarly, 5-nitro derivative of sulfenyl chloride (**20**) shows H-6 as a doublet at δ 9.59 ppm (J_{46}=2.2 Hz), 0.32 ppm larger than H-6 and H-6' of 5,5'-dinitro derivative of disulfide (**12**). On the other hand, the ir spectrum (KBr) reveals a carbonyl absortion at 1720-1730 cm^{-1} for disulfides (**12**) instead of 1680-1690 cm^{-1} for sulfenyl chlorides (**20**).

The reaction of crude **20** with ethyl glycinate afforded ethyl 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate derivatives (**2**, **3**, **4** and **5**) in 60-80% yields. 5-Amino derivative (**1**) was obtained in 63% overall yield by reduction of **5** with Fe/ammonium chloride to give *N*-(ethoxycarbonylmethyl)-1,2-dihydro-5-amino-2-thioxo-3-pydridinecarboxamide (**17**) which was easily oxidized to **1** with bromine. Other methods of reduction of **5** with iron (II) hydroxide, iron in acid solution, stannous chloride or hydrogen/Raney Ni or Pd-C gave worse yields.

EXPERIMENTAL

Melting points were determined in a Mettler FP82HT+FP80 apparatus and are uncorrected. Elemental analyses were obtained in a CHNS Carlo Erba EA1108 analyzer from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 6-12 h at about 30-70ºC). Infrared spectra were recorded on a FT-IR Nicolet 510M apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products; the frequencies are expressed in cm^{-1}. The ^{1}H-nmr spectra were obtained on a Varian Gemini (200 MHz) instrument at 20ºC, with tetramethylsilane as the internal reference, at a concentration of about 0.1 g/ml and deuteriochloroform or dimethyl sulfoxide-d_6 as solvent; the chemical shifts are reported in ppm from tetramethylsilane and are in δ units. The ms spectra were recorded in a radiofrequency ITD instrument linked to GC Perkin Elmer 8420. Thin layer chromatography (tlc) was carried out in silica gel (Schleicher & Schuell F1500/LS 254) with benzene:dioxane:acetic acid (90:25:4) as solvent and the plates were scanned under 254 and 366 nm ultraviolet light. Column chromatography was carried out in silica gel 60 Merck (70-230 mesh ASTM) with indicated solvents. Solvents were usually removed under vacuum, when stated, in a rotavapory

evaporator. The reactions carried out with thionyl chloride, chlorine, phosphorus oxychloride or sodium methoxide were protected from humidity with a calcium chloride tube.

Reaction of 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acids with thionyl chloride

Method A: A mixture of 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid,[1] **7**, **8** or **9** (5.0 mmol), xylene (20 ml) and $SOCl_2$ (3 ml, 40.9 mmol) was boiled for 2 h. The excess of reagent was removed in vacuum. Xylene was added to the residual material and solvent evaporated in vacuum again. This last operation was repeated until all the $SOCl_2$ was removed. The respective crude acid chlorides, ir 1720-1730 (CO) cm^{-1}, were used without further purification.

Two pure samples of acid chlorides were characterized from the yellow product which crystallized on cooling the reaction mixture. The yellow crystals were collected by filtration and washed with CS_2 and then with cold $CHCl_3$. 2,2'-Dithiobis(3-pyridinecarbonyl chloride) (**12**) had mp 212-214°C decomp.(reported 212-214°C from toluene);[13] ir 1725 (CO) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 7.25 (2H, dd, J_{45}=7.5 and J_{56}=5.0 Hz, H-5, H-5'), 8.45-8.65 (4H, m, H-4, H-4', H-6, H-6'). 2,2'-Dithiobis(5-nitro-3-pyridinecarbonyl chloride) had mp > 205°C decomp. under N_2 atm; ir 1720 (CO) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 9.20-9.35 (4H, m, H-4, H-4', H-6, H-6'). Anal. Calcd for $C_{12}H_4N_4O_6Cl_2S_2$: *C, 33.10; H, 0.92; N, 12.87; S, 14.71. Found: C, 33.22; H, 1.01;* N, 12.75; S, 14.60.

Method B: To an ice-cold and stirred solution of $SOCl_2$ (1.0 g, 8.4 mmol), pyridine (0.9 g, 11.4 mmol) and CH_2Cl_2 (15 ml), 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid,[1] **7**, **8** or **9** (5.0 mmol) was added in small portions and the mixture was stirred for 1 h at about 0°C. The solid material was collected by filtration and successively washed with several portions of cold $CHCl_3$ and CS_2. The resulting solid, a mixture of about 50% of corresponding derivatives of acid chlorides (**12**) and (**13**), was used without further purification.

Ethyl 5-amino-2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate (1)

To a suspension of **17** (0.38 g, 1.5 mmol) in 10 ml of CCl_4, a solution of bromine (0.30 g, 1.9 mmol) in 7 ml of CCl_4 was added dropwise with stirring at room temperature. The reaction mixture was stirred for 1 h and the precipitated product was filtered off. The solid material was suspended in 2M aqueous $NaHCO_3$ solution (10 ml) and extracted with $CHCl_3$ (3 x 20 ml). Organic layer was dried over Na_2SO_4 and evaporated and the residue was recrystallized from toluene to give 0.32 g (84 %) of **1**; mp 180-182°C; ir 1652 (CON), 1737 (COO), 3330, 3410 (NH_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 1.18 (3H, t, J=7.0 Hz, CH_3), 4.13 (2H, q, J=7.0 Hz, O-CH_2), 4.62 (2H, s, N-CH_2), 5.74 (2H, s, NH_2-5), 7.38 (1H, d, J=2.6 Hz, H-4), 8.27 (1H, d, J=2.6 Hz, H-6). Anal. Calcd for $C_{10}H_{11}N_3O_3S$: C, 47.43; H, 4.34; N, 16.60; S, 12.64. Found: C, 47.48; H, 4.40; N,

16.53; S, 12.55 .

Ethyl 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate derivatives (2, 3, 4 and 5). General procedures.

Method A: Crude acid chlorides were prepared from 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid,[1](7, 8 or 9)(5.0 mmol), and $SOCl_2$ in boiling xylene as described above and suspended in $CHCl_3$ (10 ml). A solution of ethyl glycinate hydrochloride (0.77 g, 5.0 mmol) and NEt_3 (1.01g, 10 mmol) in $CHCl_3$ (10 ml) was added dropwise at 0°C with stirring. The mixture was stirred at room temperature for 5 h and then the solvent was removed in vacuum. The solid residue was washed with water, collected and dried. The resulting solid, a mixture of the correspondent 3-oxoisothiazolo[5,4-*b*]pyridine and 2-thioxo-3-pyridinecarboxamide, was dissolved in EtOH (25 ml) and then solid $NaHCO_3$ (0.42g, 5 mmol) and iodine (0.63 g, 2.5 mmol) was added. The mixture was boiled for 2 h and then the solvent was removed in vacuum. The solid residue was washed with several portions of water, collected and recrystallized (**2**, **4** or **5**) or eluted by column chromatography with methylene dichloride and recrystallized (**3**).

Method B: Crude acid chlorides were prepared from 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid,[1] **7**, **8** or **9** (5.0 mmol), and $SOCl_2$ in boiling xylene as described above and suspended in dry $CHCl_3$ (30 ml); to the stirred mixture a catalytic amount of iodine was added and dry Cl_2 was passed over 45 min at -19°C. The solvent was removed in vacuum and the respective crude sulfenyl chloride (**20**) was dissolved in dioxane (10 ml). To the mixture, a freshly prepared solution of ethyl glycinate hydrochloride (3.08 g, 20 mmol) and NaOH (0.80 g, 20 mmol) in water (20 ml) was added dropwise with stirring at 0°C. Stirring was continued at room temperature for a further 3 h. Subsequently, water (70 ml) was added and then HCl (1 M) to bring pH 6. The resulting solid material was collected and recrystallized as indicated. An additional ammount of isothiazolo[5,4-*b*]pyridine was obtained by extraction of the aqueous filtrate with CH_2Cl_2 (3 x 50 ml).

Ethyl 2,3-dihydro-5-methyl-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate (2)

Prepared from **8**, mp 146-148°C (isopropanol), yield 0.52 g (41%) by method A and 0.71 g (61%) by method B; ir 1660 (CON), 1730 (COO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 1.21 (3H, t, J=7.1 Hz, CH_3), 2.44 (3H, s, CH_3-5), 4.15 (2H, q, J=7.1 Hz, O-CH_2), 4.72 (2H, s, N-CH_2), 8.17 (1H, d, J_{46}=2.0 Hz, H-4), 8.75 (1H, d, J_{46}=2.0 Hz, H-6). Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.76; N, 11.11; S, 12.69. Found: C, 52.23; H, 4.92; N, 11.09; S, 12.83.

Ethyl 2,3-dihydro-3-oxo-5-phenylisothiazolo[5,4-*b*]pyridine-2-acetate (3)

Prepared from **7**, mp 167-169°C (cyclohexane), yield 0.63 g (40%) by method A and 0.94 g (60%) by method

B; ir 1660 (CON), 1730 (COO) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 1.25 (3H, t, J=7.0 Hz, CH_3), 4.25 (2H, q, J=7.0 Hz, O-CH_2), 4.62 (2H, s, N-CH_2), 7.45-7.70 (5H, m, Ph-5), 8.52 (1H, d, J_{46}=2.2 Hz, H-4), 9.05 (1H, d, J_{46}=2.2 Hz, H-6). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.15; H, 4.46; N, 8.92; S, 10.19. Found: C, 61.35; H, 4.38; N, 8.71; S, 9.98.

Ethyl 2,3-dihydro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate (4)

Prepared from 1,2-dihydro-2-thioxo-3-pyridinecarboxylic acid,[1] mp 149-151°C (AcOEt-cyclohexane, 3:1 v/v), yield 0.89 g (75%) by method A and 0.95 g (80%) by method B; ir 1659 (CON), 1730 (COO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 1.20 (3H, t, J=7.0 Hz, CH_3), 4.15 (2H, q, J=7.0 Hz, O-CH_2), 4.73 (2H, s, N-CH_2), 7.53 (1H, dd, J_{45}=8.0 Hz, J_{56}=4.8 Hz, H-5), 8.32 (1H, dd, J_{45}=8.0 Hz, J_{46}=1.8 Hz, H-4), 8.86 (1H, dd, J_{46}=1.8 Hz, J_{56}=4.8 Hz, H-6). Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.42; H, 4.20; N, 11.76; S, 13.44. Found: C, 50.42; H, 4.33; N, 11.67; S, 13.37.

Ethyl 2,3-dihydro-5-nitro-3-oxoisothiazolo[5,4-*b*]pyridine-2-acetate (5)

Prepared from **9**, mp 196-198°C (isopropanol-acetone, 3:1 v/v), yield 1.13 g (80%) by method A and 1.09 g (77%) by method B; ir 1670 (CON), 1735 (COO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 1.23 (3H, t, J=6.9 Hz, CH_3), 4.20 (2H, q, J=6.9 Hz, O-CH_2), 4.83 (2H, s, N-CH_2), 8.90 (1H, d, J_{46}=2.4 Hz, H-4), 9.65 (1H, d, J_{46}=2.4 Hz, H-6). Anal. Calcd for $C_{10}H_9N_3O_5S$: C, 42.40; H, 3.18; N, 14.84; S, 11.30. Found: C, 42.41; H, 3.03; N, 14.67; S, 11.35.

1,2-Dihydro-5-phenyl-2-thioxo-3-pyridinecarboxylic acid (7)

Method A: To a freshly prepared solution of MeONa from Na (11.6 g, 0.5 mol) and dry MeOH (200 ml), solid cyanothioacetamide (10.3 g, 0.1 mol) was added in small portions and the mixture was stirred for 2 h at room temperature and then a solution of 3-dimethylamino-2-phenylacrolein[16] (17.5 g, 0.1 mol) in MeOH (100 ml) was also added dropwise. The mixture was boiled for 8 h. Solvent was removed in vacuum. The residual was diluted with water (150 ml) and acidified with HCl to pH 5. The solid material was collected by filtration and recrystallized from EtOH to yield 3-cyano-5-phenylpyridine-2(1*H*)-thione (12.7 g, 60%); mp 189-191°C (reported 205-209°C from acetone);[6] ir 2220 (CN), 2850-3150 (NH-CS) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 7.44-7.76 (5H, m, Ph-5), 8.28 (1H, d, J_{46}=2.2 Hz, H-6), 8.55 (1H, d, J_{46}=2.2 Hz, H-4), 14.5 (1H, br s, NH-CS). Anal. Calcd for $C_{12}H_8N_2S$: C, 67.92; H, 3.77; N, 13.21; S, 15.09. Found: C, 67.62; H, 3.68; N, 13.02; S, 15.31. This compound (10.6 g, 50 mmol) was boiled in 37% HCl (300 ml) for 8 h. On cooling yellow crystals were collected, washed with water and recrystallized from EtOH to give 9.9 g (86%) of **7**; mp 231-232°C (reported 268-270°C, the solvent was not indicated);[6] ir 1680 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 7.47-7.77 (5H,

m, *Ph-5*), 8.45 (1H, *d*, J_{46}=2.2 Hz, H-6), 8.70 (1H, d, J_{46}=2.2 Hz, H-4), 14.6 (2H, br s.). Anal. Calcd for $C_{12}H_9NO_2S$: C, 62.34; H, 3.90; N, 6.06; S, 13.85. Found: C, 62.25; H, 3.85; N, 5.97; S, 14.01.

Method B: A mixture of **10** (5.0 g, 21.4 mmol), thiourea (19.0 g, 250 mmol) and diethylene glycol (50 ml) was stirred for 10 h at 150°C, thereafter 15% HCl (250 ml) was added and the new mixture was refluxed for 2 h. On cooling yellow crystals were collected, washed with water and recrystallized from EtOH to give 3.8 g (76%) of **7**.

1,2-Dihydro-5-methyl-2-thioxo-3-pyridinecarboxylic acid (8)

A suspension of 2-bromo-5-methyl-3-pyridinecarboxylic acid[17] (10.0 g, 46 mmol), thiourea (4.6 g, 60 mmol) and 35% HCl (0.1 ml) in water (200 ml) was refluxed with vigorous stirring for 3 h. The cold suspension was filtered off. The solid material was suspended in water (300 ml) and then NaOH (1 M) was added with stirring to bring pH 6. After filtering, the solution was brought to about pH 2-3 by the addition of HCl. The yellow precipitate was collected by filtration and recrystallized from 90% EtOH to give 6.0 g (77%) of **8**; mp 225-227°C; ir 1690 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 2.23 (3H, s, CH_3-5), 8.06 (1H, d, J_{46}=2.2 Hz, H-6), 8.42 (1H, d, J_{46}=2.2 Hz, H-4), 14.7 (2H, br s.). Anal. Calcd for $C_7H_7NO_2S$: C, 49.70; H, 4.14; N, 8.20. Found: C, 49.59; H, 4.15; N, 7.98.

1,2-Dihydro-5-nitro-2-thioxo-3-pyridinecarboxylic acid (9)

Method A: To a stirred solution formed by 90% sodium hydrosulfide monohydrate (3.37 g, 41 mmol) and 95% EtOH (50 ml), compound (**11**) (4.72 g, 20 mmol) was added in small portions at room temperature. The mixture stands with stirring for 1 h. Subsequently, the solid material was filtered and dissolved in water (50 ml). The solution was acidified to pH 2 by slow addition of 35% HCl. The resulting yellow solid material was collected by filtration, washed with cold water and recrystallized from isopropanol to give 4.0 g (87%) of ethyl 1,2-dihydro-5-nitro-2-thioxo-3-pyridinecarboxylate; mp 145-147°C; ir 1340 (NO_2), 1710 (CO), 3150-3300 (HNCS) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 1.43 (3H, t, J=7.2 Hz, CH_3), 4.45 (2H, q, J=7.2 Hz, CH_2), 5.8 (1H, br s, *NH-CS*), 8.94 (1H, d, J_{46}=2.6 Hz, *H-6*), 9.18 (1H, d, J_{46}=2.6 Hz, *H-4*). Anal. Calcd for $C_8H_8N_2O_4S$: C, 42.10; H, 3.50; N, 12.28; S, 14.03. Found: C, 42.12; H, 3.32; N, 12.24; S, 13.84. A mixture of the above compound (3.88 g, 17 mmol) and potassium hydroxide (1.91 g, 34 mmol) in 95% EtOH (50 ml) was stirred for 2 h at room temperature. The solvent was removed under vacuum and the residue was dissolved in water (50 ml). The solution was acidified to pH 2 by slow addition of 35% HCl. The yellow solid material was collected by filtration, washed with water and recrystallized from *n*-butanol to give 2.72 g (80%) of **9**; mp 199-201°C; ir 1350 (NO_2), 1690 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 8.44 (1H, d, J_{46}=2.8 Hz, H-6), 8.65-8.75 (3H,

br s. + d, J_{46}=2.8 Hz, H-4, NH, OH). Anal. Calcd for $C_6H_4N_2O_4S$: C, 36.00; H, 2.00; N, 14.00; S, 16.00. Found: C, 36.23; H, 1.96; N, 14.07; S, 16.21.

Method B: A mixture of bis(2-chloro-5-nitro-3-pyridinecarboxylic) anhydride[15] (5.8 g, 15 mmol), 90% sodium hydrosulfide monohydrate (4.92 g, 60 mmol) and 95% EtOH (200 ml) was stirred for 1 h at room temperature. Subsequently, NaOH (2.4 g, 60 mmol) was added and the solution was stirred for 2 h at 20°C. The solid material was filtered and dissolved in water (50 ml) and the solution was acidified with 15% HCl to pH 2. The yellow solid material was collected and recrystallized from *n*-butanol to give 2.7 g (45%) of **9**.

2-Chloro-5-phenyl-3-pyridinecarboxylic acid (10)

A suspension of 1,2-dihydro-2-oxo-5-phenyl-3-pyridinecarboxylic acid[16] (10.0 g, 46.5 mmol), DMF (2 ml, 25.6 mmol) and $POCl_3$ (20 ml, 0.21 mol) in monochlorobenzene (130 ml) was boiled for 4 h. The solvents were removed in vacuum. The residual oil was treated with xylene and solvent was evaporated in vacuum again. To the residue in an ice-bath with stirring, water (50 ml) was added in drops and then 10% NaOH was added dropwise to bring pH 12. The ice-cold mixture was stirred for 2 h. After acidification to pH 2 with 15% HCl, the solid material was collected by filtration, washed with cold water, dried and recrystallized from EtOH to give 7.3 g (67%) of **10**; mp 226-228°C; ir 1710 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 7.48-7.81 (5H, m, Ph-5), 8.43 (1H, d, J_{46}=2.2 Hz, H-4), 8.86 (1H, d, J_{46}=2.2 Hz, H-6). Anal. Calcd for $C_{12}H_8NO_2Cl$: C, 61.67; H, 3.43; N, 6.00. Found: C, 61.54; H, 3.51; N, 6.10.

Ethyl 2-chloro-5-nitro-3-pyridinecarboxylate (11)

A mixture of 1,2-dihydro-5-nitro-2-oxo-3-pyridinecarboxylic acid[15] (9.0 g, 49 mmol), toluene (90 ml) and $SOCl_2$ (36 ml, 0.49 mol) was refluxed for 2 h. The excess of reagent was removed in vacuum. Toluene was added to the residual material and solvent was evaporated in vacuum again. This last operation was repeated until all the $SOCl_2$ was removed. The mixture of above crude solid in EtOH (90 ml) was refluxed for 3 h. The white product which crystallized on cooling the solution, was collected by filtration and recrystallized from EtOH to give 8.6 g (83%) of ethyl 1,2-dihydro-5-nitro-2-oxo-3-pyridinecarboxylate; mp 180-182°C; ir 1350 (NO_2), 1660 (CON), 1740 (COO), 3100-3200 (NH-CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6): 1.28 (3H, t, J=7.0 Hz, CH_3), 4.24 (2H, q, J=7.0 Hz, CH_2), 8.59 (1H, d, J_{46}=2.2 Hz), 8.86 (1H, d, J_{46}=2.2 Hz), 12.20 (1H, br s, NHCO). Anal. Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.77; N, 13.21. Found: C, 45.28; H, 3.81; N, 13.12. A stirred mixture of above compound (10.0 g, 46.5 mmol), DMF (4 ml, 51.2 mmol) and $POCl_3$ (37 ml, 0.40 mol) in monochlorobenzene (110 ml) was boiled for 4 h. The solvents were removed in vacuum. The residual oil was treated with xylene and solvent was evaporated in vacuum again. Subsequently, water (200 ml) was

added dropwise with stirring in an ice-bath and then the suspension was stirred at room temperature for a further 3 h. The white solid material was collected by filtration, dried and recrystallized from isooctane to give 9.25 g (85%) of **11**; mp 37-39°C; ir 1350 (NO_2), 1740 (CO) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 1.43 (3H, t, J=7.2 Hz, CH_3), 4.46 (2H, q, J=7.2 Hz, CH_2), 8.88 (1H, d, J_{46}=2.6 Hz, H-4), 9.29 (1H, d, J_{46}=2.2 Hz, H-6). Anal. Calcd for $C_8H_7N_2O_4Cl$: C, 41.65; H, 3.03; N, 12.14. Found: C, 41.67; H, 2.92; N, 12.07.

***N*-(Ethoxycarbonylmethyl)-1,2-dihydro-5-nitro-2-thioxo-3-pyridinecarboxamide (16)**

Compound (**9**) (1.0 g, 5 mmol) was treated with $SOCl_2$ (3 ml, 40.9 mmol) in boiling xylene (20 ml) and then with ethyl glicinate hydrochloride (0.77 g, 5.0 mmol) according to above method A of the synthesis of **5**, but the solid mixture of **16** and **5** was eluted by column chromatography with ethyl acetate/hexane (4:1, v/v) and recrystallized from isopropanol to give 0.57 g (40%) of **16**; mp 197-199°C; ir 1346 (NO_2), 1637 (CON), 1744 (COO) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 1.20 (3H, t, J=7.2 Hz, CH_3), 4.06-4.17 (4H, m, N-CH_2, O-CH_2), 8.78 (2H, m, H-4, H-6), 10.62 (1H, t, J=5.5 Hz, CONH). Anal. Calcd for $C_{10}H_{11}N_3O_5S$: C, 42.10; H, 3.85; N, 14.73; S, 11.22. Found: C, 42.05; H, 3.98; N, 14.55; S, 11.39 .

***N*-(Ethoxycarbonylmethyl)-1,2-dihydro-5-amino-2-thioxo-3-pydridinecarboxamide (17)**

A suspension of **5** (1.0 g, 3.5 mmol), iron (1.16 g, 20 mmol) and ammonium chloride (0.53 g, 10 mmol) in 50% EtOH/water (100 ml) was refluxed for 3 h. The resulting warm suspension was filtered and the solid material was extracted with boiling EtOH. Combined filtrates and washings were concentrated at about 50 ml by evaporation in vacuum. The crystalline product obtained on cooling was filtered and recrystallized from EtOH to give 0.67 g (75 %) of **17**; mp 190-192°C; ir 1652 (CON), 1723 (COO), 2850-3220 (NHCS, NHCO), 3290, 3417 (NH_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6) 1.20 (3H, t, J=7.2 Hz, CH_3), 4.05-4.20 (4H, m, N-CH_2, O-CH_2), 5.44 (2H, s, NH_2-5), 7.34 (1H, d, J_{46}=2.8 Hz, H-6), 8.15 (1H, d, J_{46}=2.8 Hz, H-4), 11.67 (1H, t, J=5.5 Hz, CONH), 13.60 (1H, br s, CSNH). Anal. Calcd for $C_{10}H_{13}N_3O_3S$: C, 47.06; H, 5.10; N, 16.47; S, 12.55. Found: C, 47.13; H, 5.34; N, 16.29; S, 12.39 .

1,2-Dithiolo[5,4-*b*]pyridin-3-one (18)

1,2-Dihydro-2-thioxo-3-pyridinecarboxylic acid[1] (0.93 g, 6 mmol) was treated with $SOCl_2$ (1.20 g, 10.1 mmol), pyridine (1.08 g, 13.68 mmol) at about 0°C (method B of 3-pydinecarbonyl chlorides) and then with ethyl glicinate hydrochloride (0.92 g, 6.0 mmol) according to above method A of the synthesis of **4**, but the resulting solid mixture was eluted by column chromatography with AcOEt/hexane (1:1, v/v). The first fractions of eluents were separated, evaporated in vaccuum and the solid material was recrystallized from MeOH to give 0.15 g (15%) of **18**; mp 97-99°C (reported 97-99°C from EtOH)[6]; ms (m/z) for $C_6H_3NOS_2$: 169 (M^+, 100),

141 (M^+-28, 50), 105 (M^+-64, 100).

5-Methyl-1,2-dithiolo[5,4-*b*]pyridin-3-one (19)

Compound (**8**) (0.85 g, 5.0 mmol) was treated with $SOCl_2$ (3 ml, 40.9 mmol) in boiling xylene (20 ml) and then with ethyl glicinate hydrochloride (0.77 g, 5.0 mmol) according to above method A of the synthesis of **2**, but the solid mixture was eluted by column chromatography with AcOEt/hexane (1:1, v/v). The first fractions of eluents were separated, evaporated in vaccuum and the solid material was recrystallized from isooctane to give 0.11 g (12%) of **19**; mp 116-118°C ; ir 1670 cm^{-1}; ^{1}H-nmr ($CDCl_3$): 2.28 (3H, s, 5-CH_3), 7.98 (1H, d, J_{46}=2.2 Hz, H-4), 8.62 (1H, d, J_{46}=2.2 Hz, H-6); ms (m/z) for $C_7H_5NOS_2$:183 (M^+, 100), 155 (M^+-28, 38), 119 (M^+-64, 30).

2-Chlorothio-3-pyridinecarbonyl chloride derivatives (20)

These compounds were prepared following method B of synthesis of isotiazolo[5,4-*b*]pyridines (**2**) to (**5**). Two pure samples were characterized by recrystallization of crude 5-hydrogen and 5-nitro sulfenyl chlorides from toluene and $CHCl_3$ respectively. 2-Chlorothio-3-pyridinecarbonyl chloride had mp > 72°C decomp. under N_2 atm; ir 1687 (CO) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 7.37 (1H, dd, J_{45}=8.0 and J_{56}=4.8 Hz, H-5), 8.52 (1H, dd, J_{45}=8.0 and J_{46}=1.8 Hz, H-4), 8.85 (1H, dd, J_{46}=1.8 and J_{56}=4.8 Hz, H-6). Anal. Calcd for $C_6H_3NOCl_2S$: C, 34.61; H, 1.44; N, 6.73; S, 15.38. Found: C, 34.80; H, 1.56; N, 6.69; S, 15.26. 2-Chlorothio-5-nitro-3-pyridinecarbonyl chloride had mp > 93°C(decomp.)under N_2 atm; ir 1680 (CO) cm^{-1}; ^{1}H-nmr ($CDCl_3$) 9.22 (1H, d, J_{46}=2.2 Hz, H-4), 9.59 (1H, d, J_{46}=2.2 Hz, H-6). Anal. Calcd for $C_6H_2N_2O_3Cl_2S$: C, 28.46; H, 0.79; N, 11.07; S, 12.65. Found: C, 28.62; H, 0.78; N, 10.95; S, 12.93

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