On the Reaction between 3*H*-1,2-Dithiolo[3,4-*b*]-pyridine-3-thione and Primary Alkyl and Arylalkylamines

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3*H*-1,2-Dithiolo[3,4-*b*]pyridine-3-thione (**10**) reacts with primary alkylamines to give 1,2-dihydro-2-thioxo-3-pyridinecarbothioamides **11a-g** and two minor products. Isothiazolo[5,4-*b*]pyridine-3(2*H*)-thiones **12a-g** and 3-imino-3*H*-1,2-dithiolo[3,4-*b*]pyridines **13a-g** were isolated and characterized. Further investigations allowed the synthesis of **12** and **13** in good yield.

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The chemistry and the biological activity of 2-substituted 1,2-benzisothiazol-3(2*H*)-ones **1** [1-3], of 1,2-benzisothiazole-3(2*H*)-thiones **2** [4-6] and of isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones **3** [7-10] have been largely examined. To the best of our knowledge, 2-substituted isothiazolo[5,4-*b*]pyridine-3(2*H*)-thiones **12** have not been reported in the literature (Figure 1).

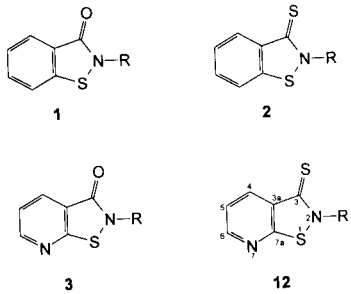
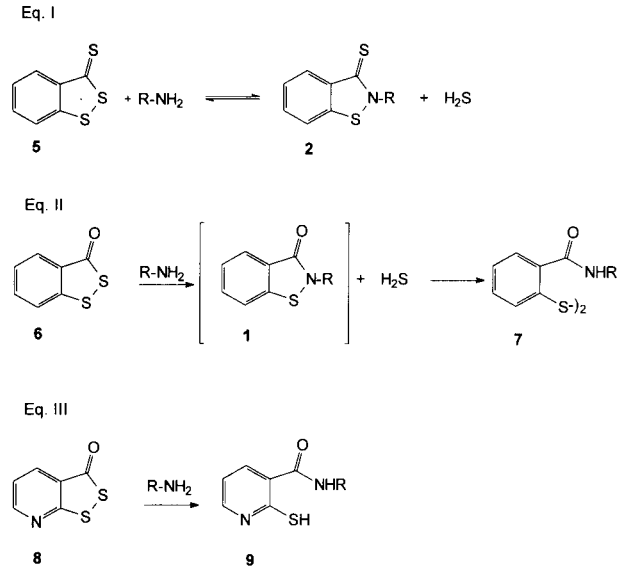


Figure 1

Compounds of type **2** were prepared by treatment of 3*H*-1,2-benzodithiole-3-thione **5** with primary alkylamines (Scheme I, Eq. I) [11] but the same reaction performed on 3*H*-1,2-benzodithiol-3-one **6** (Scheme I, Eq. II) [12] or 3*H*-1,2-dithiolo[3,4-*b*]pyridin-3-one **8** (Scheme I, Eq. III) [9] gave different results.

According to McClelland and co-workers [11] the substitution of sulphur for oxygen in the ketobenzoisothiazole system increases the stability of the S-N bond towards reducing agents. Therefore compounds **1** undergo reduction by hydrogen sulphide liberated during the reaction giving disulphides **7** whereas compounds **2** were stable under reaction conditions and could be isolated. As compound **8** reacts with amines to give **9** [9], we supposed that these compounds were derived from an "*in situ*" reduction of intermediates **3** which however were never isolated. This may be ascribed to the presence of a pyridine nitrogen adjacent to the isothiazolone ring, resulting in an increased reactivity of the S-N bond towards the reducing action of

Scheme I



the hydrogen sulphide. On the basis of these considerations we examined the reaction between 3*H*-1,2-dithiolo-[3,4-*b*]pyridine-3-thione (**10**) [9] and some primary alkyl and arylalkyl amines in order to synthetize a series of isothiazolo[5,4-*b*]pyridine-3(2*H*)-thione derivatives **12**, as potential fungicides and bactericides.

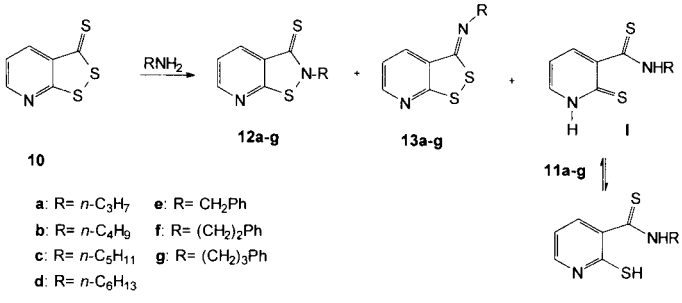
Results and Discussion.

The reactions of **10** with 1.2 equivalents of the appropriate amine gave **11a-g** in good yields (75-83%) and traces of almost equimolar **12a-g** and **13a-g** (Scheme II, Eq. I). All compounds were isolated by flash chromatography. Compounds **11a-g** were characterized by analytical and spectral data. The ir spectra showed bands at 3220-3100 cm^{-1} for NH group and at 1595-1590 cm^{-1} for C=S bond. All compounds **11a-d** showed some common signals in ^1H and ^{13}C nmr spectra; ^1H nmr: δ 3.85 (m, 2H, N-CH_2, J = 5.0 Hz), 6.95 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.67 (dd, 1H, 4-H, $J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 9.42 (dd,

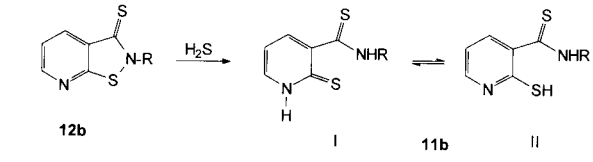
1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), ~ 12 (br s, 2H, NH and SH); ^{13}C nmr: δ C-7 (190.4), C-2 (172.0), C-6 (147.1), C-4 (138.2), C-3 (137.1), C-5 (114.2). The CH-NH coupling constants of 5.0 Hz and the chemical shifts of protons which resonate at about δ 12.0 are useful for a ready identification of **11**. Furthermore the large value of $J_{6,5}$ in ^{1}H nmr and the values of C-2 and C-6 in the ^{13}C nmr spectra, indicate the existence of two tautomeric forms **11 I** and **11 II** rapidly equilibrating on the nmr time scale.

Scheme II

Eq. I



Eq. II



The ir, ^{1}H and ^{13}C spectroscopy and mass spectrometry are helpful for the structural assignment of isomeric compounds **12a-g** and **13a-g**. The ir spectra of **12** and **13** showed bands at 1250-1280 cm^{-1} (C=S) and at 1605-1600 cm^{-1} (C=N) respectively. The ^{1}H nmr of **12a-d** showed typical signals at δ 4.40 (t, 2H, N-CH_2), 7.45 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.52 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz). Corresponding signals for **13a-d** were at δ 3.40 (t, 2H, N-CH_2), 7.21 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.21 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.58 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz). The ^{13}C signals of **12b** were assigned as follows: C-3 (184.0), C-7a (162.4), C-6 (153.3), C-4 (137.2), C-3a (129.3), C-5 (121.4), CH_2-N (48.7). Differently **13b** showed the following ^{13}C nmr spectra: C-3 (166.4), C-7a (159.5), C-6 (152.4), C-4 (134.3), C-3a (126.0), C-5 (119.8), CH_2-N (55.8). The chemical shifts of N-CH_2 (δ H) and C-3 (δ C) can be used for differentiating isomeric compounds **12** and **13**.

A good mass spectral feature is the presence of an ion peak at m/z 195 for compounds **12a-d** and **12g**, this could be attributed to a loss of the side chain which produced a five member ring containing nitrogen and sulphur. This peak was not observed for **12e-f** and **13a-g** where the formation of tricyclic ion is not possible.

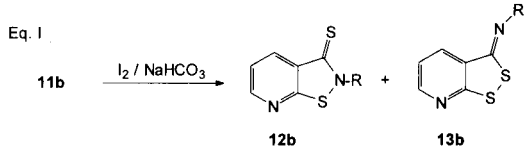
As compounds **12** are not the main products but are present in traces, we suspected their sensitivity towards reducing agents. That was confirmed by treatment of an ethanolic solution of **12b** with hydrogen sulphide which effected in a few seconds a complete conversion to **11b** (Scheme II, Eq. II). Probably the replacement of the benzene ring with a pyridine in compounds **2** decreases the stability of S-N bond. The occurrence of compounds **13** as reaction product, may be attributed to a "dynamic isomerism" like that between 1,2-benzisothiazole-3(2*H*)-thiones and 3-imino-3*H*-1,2-benzodithioles [13,14]. We have noted that pure compound **13b** rapidly establishes an equilibrium with **12b** upon being dissolved in a polar solvent (DMSO, DMF, acetone/water). We have observed the same behaviour for pure **12b** that rapidly interconverted with **13b** (Scheme III). Nevertheless both compounds **13b** and **12b** are stable after 1 hour at reflux in xylene so there is no evidence of isomerism in apolar solvents.

Scheme III

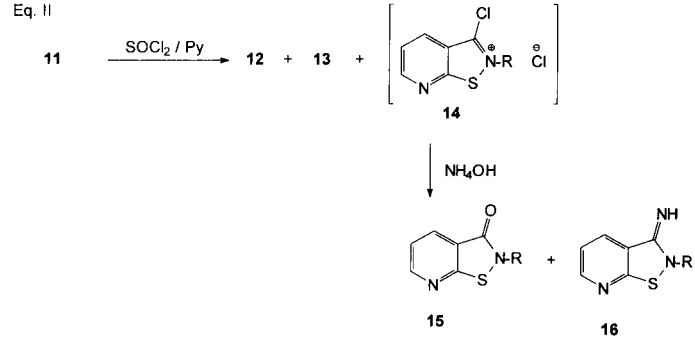
In order to attempt the synthesis of compounds **12** we tried ring closure of **11b** by iodine in ethanol in presence of sodium hydrogen carbonate [9]. The reaction gave a nearly equimolar mixture of **12b** and **13b** in good yield (Scheme IV, Eq. I).

Scheme IV

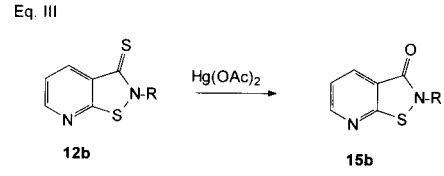
Eq. I



Eq. II



Eq. III



Then the cyclization of **11** was obtained by treatment with thionyl chloride and pyridine in chloroform at room temperature [15]. The reaction without any workup gave compounds **12** and **13** and very polar compounds **14** (Scheme IV, Eq. II). After ammonium hydrate workup the reaction gave, in addition to **12** and **13**, two new series of compounds, namely **15** and traces of substances having presumably structure **16**, that were isolated by flash chromatography. The ir spectra of **15** and **16** showed bands at 1650-1640 cm^{-1} (C=O) and at 3300 cm^{-1} (NH) and 1570 cm^{-1} (C=N) respectively. The ^1H nmr of **15a-d** showed typical signals at δ 3.92 (t, 2H, N-CH_2), 7.35 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 8.29 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz). Corresponding signals for **16a-c** were at δ 3.50 (t, 2H, CH_2-N), 5.0 (br s, 1H, NH), 7.26 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 7.97 (dd, 1H, 4-H, $J_{6,4}$ = 0.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.68 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz). The ^{13}C signals were assigned as follows: **15b**, C-3 (163.5), C-7a (162.0), C-6 (152.3), C-4 (134.6), C-5 (120.5), C-3a (119.5), CH_2-N (43.5), **16a**, C-3 (172.1), C-7a (157.0), C-6 (150.3), C-4 (129.3), C-3a (119.6), C-5 (118.3), CH_2-N (44.4). The values of N-CH_2 (δ H) and C-3 (δ C) allow us to distinguish **15** from **16** and **12**.

The identity of polar compounds **14** was assumed considering that reaction between 3-chloro-2-alkyl-1,2-benzisothiazolium chloride and ammonia gave 2-alkyl-3-imino-1,2-benzisothiazolines [16,17]. We surmise for our not isolated compounds, the structure indicate in Scheme IV, Eq. II.

2-Butylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15b**) was also obtained from the corresponding 3-thione **12b** by reaction with mercuric acetate (Scheme IV, Eq. III). Biological evaluation of all products synthesised is in progress.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba model 1106 Elemental Analyser. The ir spectra were recorded in nujol on a Perkin Elmer model 257 spectrophotometer. The 300 MHz ^1H and 75 MHz ^{13}C spectra were recorded on a Bruker ACE-300 spectrometer, in deuteriochloroform using tetramethylsilane as internal standard; chemical shifts are in δ (ppm) and coupling constants (J) in Hz. Mass spectra were obtained on a Finnigan MAT 8222 spectometer *via* the direct inlet. Electron ionisation was performed at 70 eV and 0.5 mA with a source temperature of 250°. The tlc analyses was run on silica gel 60 F_{254} Merck and visualised by uv (λ = 264 or 365 nm); flash column chromatography on silica gel 60 (60-200 μm, Merck) was performed as described in the original paper [18]. No attempt was made to optimise yields in the reactions described.

General Procedure for 1,2-Dihydro-2-thioxo-3-pyridinecarbothioamide Derivatives **11a-g**.

A mixture of 16 mmoles of 3*H*-1,2-dithiolo[3,4-*b*]pyridine-3-thione (**10**) and 19 mmoles of the appropriate amine was refluxed in 150 ml of ethanol for 30-60 minutes, the optimum reaction time being determined by tlc monitoring (eluant: *n*-hexane/ethyl acetate (6:4)). After cooling, the solvent was removed on a rotary evaporator and the residue was recrystallized from the suitable solvent.

N-Propyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11a**).

This compound was obtained as yellow crystals (dichloromethane/petroleum ether), mp 167-169°; ir: ν NH 3200, ν C=S 1590; ^1H nmr: δ 3.85 (m, 2H, N-CH_2, J = 5.0 Hz), 6.95 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.67 (dd, 1H, 4-H, $J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 9.42 (dd, 1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 12.28 and 12.45 (br s, 2H, NH and SH).

Anal. Calcd. for $C_9H_{12}N_2S_2$: C, 50.91; H, 5.70; N, 13.19. Found: C, 50.69; H, 5.54; N, 13.07.

N-Butyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11b**).

The compound was obtained as yellow crystals (ethanol/water), mp 141-143°; ^1H nmr: δ 3.82 (m, 2H, N-CH_2, J = 5.0 Hz), 6.95 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.67 (dd, 1H, H-4, $J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 9.42 (dd, 1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 12.3 (br s, 2H, NH and SH); ms: m/z (% ra) 226 (100), 169 (26), 155 (76), 154 (54), 137 (96), 124 (40), 78 (29), 72 (56).

Anal. Calcd. for $C_{10}H_{14}N_2S_2$: C, 53.06; H, 6.23; N, 12.38. Found: C, 52.83; H, 6.15; N, 12.46.

N-Pentyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11c**).

This compound was obtained as yellow crystals (ethyl acetate/*n*-hexane), mp 123-126°; ir: ν NH 3120, ν C=S 1590; ^1H nmr: δ 3.9 (m, 2H, N-CH_2, J = 5.0 Hz), 6.95 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.67 (dd, 1H, 4-H, $J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 9.42 (dd, 1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 12.3 and 12.45 (br s, 2H, NH and SH).

Anal. Calcd. for $C_{11}H_{16}N_2S_2$: C, 54.96; H, 6.71; N, 11.66. Found: C, 55.13; H, 6.51; N, 11.51.

N-Hexyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11d**).

This compound was obtained as yellow crystals (ethyl acetate/*n*-hexane), mp 122-124°.

Anal. Calcd. for $C_{12}H_{18}N_2S_2$: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.36; H, 6.84; N, 10.71.

N-Benzyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11e**).

This compound was obtained as yellow crystals (benzene/petroleum ether), mp 162-164°; ^1H nmr: δ 5.05 (d, 2H, N-CH_2), 6.95 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.65 (dd, 1H, 4-H, $J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 9.45 (dd, 1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 11.6 and 12.85 (br s, 2H, SH and NH).

Anal. Calcd. for $C_{13}H_{12}N_2S_2$: C, 59.97; H, 4.64; N, 10.76. Found: C, 59.67; H, 4.30; N, 10.52.

N-Phenethyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11f**).

This compound was obtained as yellow crystals (ethanol), mp 144-148°; ^1H nmr: δ 3.15 (t, 2H, CH_2-Ph), 4.15 (dt, 2H, N-CH_2), 6.94 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.65 (dd, 1H, 4-H,

$J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 9.35 (dd, 1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 12.45 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{14}N_2S_2$: C, 61.28; H, 5.14; N, 10.21. Found: C, 61.54; H, 5.07; N, 10.04.

N-(3-Phenylpropyl)-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11g**).

This compound was obtained as yellow crystals (ethyl acetate/*n*-hexane), mp 133-135°; ^{1}H nmr: δ 2.0 (m, 2H, CH_2-CH_2-CH_2), 2.7 (t, 2H, CH_2-Ph), 3.65 (dt, 2H, N-CH_2), 6.95 (dd, 1H, 5-H, $J_{6,5}$ = 7.5 Hz, $J_{4,5}$ = 6.0 Hz), 7.85 (dd, 1H, 4-H, $J_{4,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 8.40 (dd, 1H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 9.3 (br s, 1H, SH).

Anal. Calcd. for $C_{15}H_{16}N_2S_2$: C, 62.46; H, 5.59; N, 9.71. Found: C, 62.24; H, 5.65; N, 9.72.

General Procedures for Isothiazolo[5,4-*b*]pyridine-3(2*H*)-thiones **12a-g** and 3-Imino-3*H*-1,2-dithiolo[3,4-*b*]pyridines **13a-g**.

Method 1 (Scheme IV, Eq. I).

An ethanolic solution of iodine (6%) was added dropwise to a stirred mixture of 1.36 g (6 mmoles) of *N*-butyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11b**) and 0.86 g (10 mmoles) of sodium hydrogen carbonate in 100 ml of ethanol, until a persistent brown colour is noted. A precipitate was removed by filtration and washed with dichloromethane. Collected organic phases were evaporated under reduced pressure and the residue was purified through flash chromatography (*n*-hexane/ethyl acetate (9:1)) to give 0.475 g (36%) of pure **12b** and 0.455 g (34%) of pure **13b**.

2-Butylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12b**).

This compound was obtained as yellow crystals, mp 105-107°; Rf (*n*-hexane/ethyl acetate (6:4)) = 0.61; ir: ν C=S 1280; ^{1}H nmr: δ 4.40 (t, 2H, N-CH_2), 7.45 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.52 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.80 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 224 (55), 195 (36), 191 (46), 181 (37), 168 (100), 154 (28), 136 (11), 104 (36).

Anal. Calcd. for $C_{10}H_{12}N_2S_2$: C, 53.53; H, 5.39; N, 12.49. Found: C, 53.23; H, 5.41; N, 12.19.

N-Butyl-3-Imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13b**).

This compound was obtained as yellow crystals, mp 42-46°; Rf (*n*-hexane/ethyl acetate (6:4)) = 0.73; ir: ν C=N 1605; ^{1}H nmr: δ 3.40 (t, 2H, N-CH_2), 7.21 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.21 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.58 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 224 (25), 191 (56), 181 (19), 168 (100), 137 (12), 104 (75), 77 (15), 57 (37).

Anal. Calcd. for $C_{10}H_{12}N_2S_2$: C, 55.53; H, 5.39; N, 12.49. Found: C, 53.41; H, 5.31; N, 12.26.

Method 2 (Scheme IV, Eq. II).

To a stirred solution of 1 g (4.4 mmoles) of *N*-butyl-1,2-dihydro-2-thioxo-3-pyridinecarbothioamide (**11b**) in 10 ml of chloroform and 6.5 ml of pyridine, at room temperature, 6 ml of thionyl chloride was added dropwise. After being stirred for 10 minutes, solvent and excess reagent were removed in vacuum. The residue was treated with toluene and solvent removed. This operation was repeated until thionyl chloride was no more present. Then solid was treated with dilute ammonium hydroxide, and organic products were extracted with ethyl acetate (3 x 30 ml). Collected organic phases were dried over anhydrous sodium sulphate, solvent was removed under reduced pressure and the residue was flash-chromatographed (*n*-hexane/ethyl acetate (6:4)) to afford in order of elution a mixture of **13b** and **12b** (468 mg, 47% yield), pure **16b** (12 mg, 1.3% yield) and pure **15b** (38 mg, 4% yield). The mixture of **12b** and **13b** was then flash chromatographed (*n*-hexane/ethyl acetate (9:1)) to give pure products.

2-Propylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12a**).

This compound was obtained as yellow crystals, mp 125-127°; Rf (*n*-hexane/ethyl acetate (7:3)) = 0.58; ^{1}H nmr: δ 4.39 (t, 2H, N-CH_2), 7.45 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.50 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 210 (92), 195 (24), 181 (67), 168 (100), 154 (28), 141 (9), 137 (9), 104 (35).

Anal. Calcd. for $C_9H_{10}N_2S_2$: C, 51.40; H, 4.79; N, 13.32. Found: C, 51.28; H, 4.52; N, 12.98.

2-Pentylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12c**).

This compound was obtained as yellow crystals, mp 73-75°; Rf (*n*-hexane/ethyl acetate (8:2)) = 0.47; ^{1}H nmr: δ 4.39 (t, 2H, N-CH2), 7.42 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.52 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 238 (20), 205 (73), 195 (18), 181 (25), 168 (100), 154 (16), 104 (42), 43 (81).

Anal. Calcd. for $C_{11}H_{14}N_2S_2$: C, 55.43; H, 5.92; N, 11.75. Found: C, 55.36; H, 5.80; N, 11.41.

2-Hexylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12d**).

This compound was obtained as yellow crystals, mp 55-60°; Rf (*n*-hexane/ethyl acetate (92:8)) = 0.23; ^{1}H nmr: δ 4.41 (t, 2H, N-CH_2), 7.42 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.53 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 252 (17), 219 (77), 218 (23), 195 (13), 181 (22), 168 (100), 137 (11), 104 (34).

Anal. Calcd. for $C_{12}H_{18}N_2S_2$: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.36; H, 6.84; N, 10.71.

2-Benzylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12e**).

This compound was obtained as yellow crystals, mp 162-164°; Rf (*n*-hexane/ethyl acetate (85:15)) = 0.26; ^{1}H nmr: δ 5.60 (s, 2H, N-CH_2), 7.42 (m, 6H, 5-H and phenyl), 8.55 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 258 (40), 225 (12), 224 (12), 154 (15), 136 (6), 121 (6), 91 (100), 65 (17).

Anal. Calcd. for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.85. Found: C, 60.17; H, 3.93; N, 10.63.

2-Phenethylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12f**).

This compound was obtained as yellow crystals, mp 111-115°; Rf (*n*-hexane/ethyl acetate (65:35)) = 0.70; ^{1}H nmr: δ 3.20 (t, 2H, CH_2-Ph), 4.62 (t, 2H, N-CH_2), 7.32 (m, 5H, phenyl), 7.49 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.55 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.80 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 272 (13), 239 (19), 181 (21), 168 (27), 154 (7), 105 (29), 104 (100), 77 (17).

Anal. Calcd. for $C_{14}H_{12}N_2S_2$: C, 61.73; H, 4.44; N, 10.28. Found: C, 61.86; H, 4.69; N, 9.95.

2-(3-Phenylpropyl)isothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12g**).

This compound was obtained as yellow crystals, mp 88-90°; Rf (*n*-hexane/ethyl acetate (8:2)) = 0.38; ^{1}H nmr: δ 2.18 (m, 2H, CH_2-CH_2-CH_2), 2.75 (t, 2H, CH_2-Ph), 4.42 (t, 2H, N-CH_2), 7.65 (dd,

1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.45 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.85 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 286 (9), 253 (100), 252 (38), 195 (17), 182 (19), 168 (26), 117 (32), 91 (76).

Anal. Calcd. for $C_{15}H_{14}N_2S_2$: C, 62.90; H, 4.93; N, 9.78. Found: C, 62.67; H, 4.93; N, 9.52.

N-Propyl-3-Imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13a**).

This compound was obtained as an oil; Rf (*n*-hexane/ethyl acetate (7:3)) = 0.75; ^{1}H nmr: δ 3.40 (t, 2H, N-CH_2), 7.21 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.21 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.58 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 210 (61), 181 (49), 177 (15), 168 (100), 137 (11), 104 (82), 77 (11), 43 (22).

N-Pentyl-3-imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13c**).

This compound was obtained as yellow crystals, mp 50-52°; Rf (*n*-hexane/ethyl acetate (8:2)) = 0.60; ^{1}H nmr: δ 3.40 (t, 2H, N-CH_2), 7.21 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.21 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.55 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 238 (6), 205 (52), 204 (35), 181 (13), 168 (75), 137 (13), 104 (47), 43 (100).

Anal. Calcd. for $C_{11}H_{14}N_2S_2$: C, 55.43; H, 5.92; N, 11.75. Found: C, 55.11; H, 6.01; N, 11.75.

N-Hexyl-3-imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13d**).

This compound was obtained as yellow crystals, mp 60-61°; Rf (*n*-hexane/ethyl acetate (9:1)) = 0.36; ^{1}H nmr: δ 3.40 (t, 2H, N-CH_2), 7.22 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.22 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.58 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 252 (11), 219 (71), 218 (27), 181 (18), 168 (90), 137 (11), 104 (35), 43 (100).

Anal. Calcd. for $C_{12}H_{16}N_2S_2$: C, 57.10; H, 6.39; N, 11.09. Found: C, 57.09; H, 6.10; N, 10.82.

N-Benzyl-3-imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13e**).

This compound was obtained as yellow crystals, mp 61-62°; Rf (*n*-hexane/ethyl acetate (85:15)) = 0.35; ^{1}H nmr: δ 4.60 (s, 2H, N-CH_2), 7.22 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 7.30-7.45 (m, 5H, phenyl), 8.32 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.61 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 258 (12), 136 (12), 91 (100), 65 (10).

Anal. Calcd. for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.85. Found: C, 60.33; H, 3.89; N, 10.74.

N-Phenethyl-3-imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13f**).

This compound was obtained as yellow crystals, mp 111-113°; Rf (*n*-hexane/ethyl acetate (65:35)) = 0.82; ^{1}H nmr: δ 3.12 (t, 2H, CH_2-Ph), 3.60 (t, 2H, N-CH_2), 7.22 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 7.40 (m, 5H, phenyl), 8.25 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.55 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 272 (13), 181 (100), 137 (16), 105 (88), 103 (20), 91 (6), 79 (27), 77 (28).

Anal. Calcd. for $C_{14}H_{12}N_2S_2$: C, 61.73; H, 4.44; N, 10.28. Found: C, 61.81; H, 4.68; N, 9.98.

N-(3-Phenylpropyl)-3-imino-3*H*-1,2-dithiolo[3,4-*b*]pyridine (**13g**).

This compound was obtained as an oil; Rf (*n*-hexane/ethyl acetate (8:2)) = 0.48; ^{1}H nmr: δ 2.15 (m, 2H, CH_2-CH_2-CH_2), 2.85 (t, 2H, CH_2-Ph), 3.50 (t, 2H, N-CH_2), 7.22 (dd, 1H, 5-H, $J_{6,5}$ = 4.5 Hz, $J_{5,4}$ = 7.5 Hz), 7.30-7.42 (m, 5H, phenyl), 8.23 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 7.5 Hz), 8.55 (dd, 1H, 6-H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 286 (5), 253 (20), 252 (54), 182 (14), 137 (4), 104 (5), 91 (100), 65 (10).

Anal. Calcd. for $C_{15}H_{14}N_2S_2$: C, 62.90; H, 4.93; N, 9.78. Found: C, 62.76; H, 4.77; N, 9.85.

Compounds **15a-g** and **16a-c** were isolated as by-products in small quantity.

2-Propylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15a**).

This compound had Rf (*n*-hexane/ethyl acetate (7:3)) = 0.26; ^{1}H nmr: δ 3.91 (t, 2H, N-CH_2), 7.38 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 8.29 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,5}$ = 5.0 Hz); ms: m/z (% ra) 194 (32), 177 (5), 165 (52), 152 (100), 138 (20), 137 (14), 110 (12), 82 (10).

2-Butylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15b**).

This compound had Rf (*n*-hexane/ethyl acetate (6:4)) = 0.44; ^{1}H nmr: δ 3.95 (t, 2H, N-CH_2), 7.35 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 8.29 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 208 (29), 191 (17), 165 (48), 152 (100), 138 (24), 137 (23), 110 (12), 82 (9).

2-Pentylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**15c**).

This compound had Rf (*n*-hexane/ethyl acetate (8:2)) = 0.17; ^{1}H nmr: δ 3.92 (t, 2H, N-CH_2), 7.35 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 8.29 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 222 (26), 205 (14), 166 (20), 165 (57), 152 (100), 137 (22), 110 (11), 84 (26).

2-Hexylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15d**).

This compound had Rf (*n*-hexane/ethyl acetate (7:3)) = 0.33; ^{1}H nmr: δ 3.92 (t, 2H, N-CH_2), 7.47 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 8.30 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 236 (25), 219 (10), 166 (25), 165 (83), 152 (100), 137 (21), 111 (12), 98 (16).

2-Benzylisothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15e**).

This compound had Rf (*n*-hexane/ethyl acetate (6:4)) = 0.48; ^{1}H nmr: δ 5.10 (s, 2H, N-CH_2), 7.35-7.45 (m, 6H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz and phenyl), 8.36 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 242 (23), 184 (1), 165 (2), 138 (4), 111 (5), 91 (100), 77 (5), 65 (11).

2-Phenethylisothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**15f**).

This compound had Rf (*n*-hexane/ethyl acetate (65:35)) = 0.27; ^{1}H nmr: δ 3.05 (t, 2H, CH_2-Ph), 4.18 (t, 2H, N-CH_2), 7.35-7.40 (m, 6H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz and phenyl), 8.28 (dd, 1H, 4-H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.71 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 256 (10), 165 (53), 152 (16), 138 (14), 110 (10), 104 (100), 91 (19), 77 (11).

2-(3-Phenylpropyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15g**).

This compound had Rf (*n*-hexane/ethyl acetate (8:2)) = 0.48; ^{1}H nmr: δ 2.10 (m, 2H, CH_2-CH_2-CH_2), 2.70 (t, 2H, CH_2-Ph), 3.92 (t, 2H, N-CH_2), 7.35-7.40 (m, 6H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz

and phenyl), 8.28 (dd, H-4, 1H, $J_{6,4}$ = 1.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.78 (dd, H-6, 1H, $J_{6,5}$ = 1.5 Hz, $J_{6,4}$ = 4.5 Hz); ms: m/z (% ra) 270 (66), 166 (65), 165 (28), 152 (25), 138 (33), 137 (50), 118 (100), 91 (50).

2-Propyl-3-imino-3*H*-isothiazolo[5,4-*b*]pyridine (**16a**).

This compound had Rf (*n*-hexane/ethyl acetate (7:3)) = 0.41; ^{1}H nmr: δ 3.50 (t, 2H, CH_2-N), 5.0 (br s, 1H, NH), 7.26 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 7.97 (dd, 1H, 4-H, $J_{6,4}$ = 0.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.68 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 193 (62), 177 (16), 164 (100), 151 (87), 136 (41), 110 (4), 108 (5), 92 (11).

2-Butyl-3-imino-3*H*-isothiazolo[5,4-*b*]pyridine (**16b**).

This compound had Rf (*n*-hexane/ethyl acetate (6:4)) = 0.30; ^{1}H nmr: δ 3.55 (t, 2H, CH_2-N), 4.9 (br s, 1H, NH), 7.25 (dd, 1H, 5-H, $J_{5,6}$ = 5.0 Hz, $J_{5,4}$ = 8.0 Hz), 7.95 (dd, 1H, 4-H, $J_{6,4}$ = 0.5 Hz, $J_{5,4}$ = 8.0 Hz), 8.70 (dd, 1H, 6-H, $J_{6,4}$ = 1.5 Hz, $J_{5,6}$ = 5.0 Hz); ms: m/z (% ra) 207 (36), 191 (83), 164 (100), 151 (61), 137 (16), 136 (35), 104 (6), 92 (10).

2-Pentyl-3-imino-3*H*-isothiazolo[5,4-*b*]pyridine (**16c**).

This compound had Rf (*n*-hexane/ethyl acetate (8:2)) = 0.17; ms: m/z (% ra) 221 (29), 205 (78), 165 (22), 164 (100), 151 (69), 137 (19), 136 (38), 92 (13).

Synthesis of Isothiazolo[5,4-*b*]pyridin-3(2*H*)-one (**15b**) from Isothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12b**).

A solution of 0.135 g of isothiazolo[5,4-*b*]pyridine-3(2*H*)-thione (**12b**) (0.6 mmole) in 2 ml of chloroform was added to a stirred suspension of mercuric acetate (0.41 g, 1.3 mmoles) in glacial acetic acid (5 ml). Stirring was continued at room temperature for 30 minutes then a solution of sodium hydrogen carbonate was added and organic products were extracted with ethyl acetate (3 x 20 ml). The combined organic phases were dried (anhydrous sodium sulphate) and evaporated under reduced pressure. The residue was purified through flash chromatography (*n*-hexane/ethyl acetate (6:4)) to give 32 mg (26%) of pure **15b**, mp 68-69°; ir: ν C=O 1640.

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.55; H, 5.75; N, 13.17.

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REFERENCES AND NOTES

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[1] L. L. Bambas, The Chemistry of Heterocyclic Compounds, A. Weissburger, ed, Wiley-Interscience, New York, 1952, pp 253-270.

[2] M. Davis, Benzisothiazoles, in Advances in Heterocyclic Chemistry, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1972, pp 43-98.

[3] M. Davis, Recent Advances in the Chemistry of Benzisothiazoles and Other Polycyclic Isothiazoles, in Advances in Heterocyclic Chemistry, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1985, pp 105-133.

[4] L. L. Bambas, The Chemistry of Heterocyclic Compounds, A. Weissburger, ed, Wiley-Interscience, New York, 1952, pp 271-273.

[5] A. Baruffini, P. Borgna and F. Gialdi, *Farmaco Ed. Sci.*, **23**, 3 (1968).

[6] P. Borgna, L. Vicarini, M. L. Carmellino and G. Pagani, *Farmaco Ed. Sci.*, **38**, 10 (1983).

[7] J. L. Rainey and M. C. Seidel, U. S. Patent, 3,965,107 (1974); *Chem. Abstr.*, **85**, 160072h (1976).

[8] K. H. Baggaley, German Offen. 2,718,707 (1976); *Chem. Abstr.*, **88**, 50843q (1978).

[9] K. H. Baggaley, L. J. A. Jennings and A. W. R. Tyrrell, *J. Heterocyclic Chem.*, **19**, 1393 (1982).

[10] B. Shroot and J. Maignan, German Offen. DE 3,342,538 (1982); *Chem. Abstr.*, **101**, 116736c (1984).

[11] E. W. McClelland, L. A. Warren and J. H. Jackson, *J. Chem. Soc.*, 1582 (1929).

[12] E. W. McClelland and J. Longwell, *J. Chem. Soc.*, 3310 (1923).

[13] E. W. McClelland and C. E. Salkeld, *J. Chem. Soc.*, 1143 (1936).

[14] H. Böshagen, H. Feltkamp and W. Geiger, *Chem. Ber.*, **100**, 2435 (1967).

[15] A. Monge, V. Martinez-Merino and E. Fernandez-Alvarez, *J. Heterocyclic Chem.*, **22**, 1353 (1985).

[16] Farbenfabriken Bayer A.G., Netherlands Appl. 6,610,677 (1967); *Chem. Abstr.*, **68**, 59572v (1968).

[17] H. Böshagen, W. Geiger and H. Medenwald (Farbenfabriken Bayer A.G.), South African 69 07,624 (1969); *Chem. Abstr.*, **72**, 90444m (1970).

[18] C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923-2924 (1978).