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Synthesis of 2-thio derivatives of 4-phenyl-9*H*-pyrimido[4,5-*b*]indole*

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The reaction of 3-benzylidene-2-ethoxyindolenine tetrafluoroborate with thiourea gives a mixture of 4-phenylpyrimido[4,5-*b*]indole-2(1*H*)-thione, its 3,4-dihydro derivative, and the corresponding disulfide, the product ratio depending on the reaction conditions. A number of transformations of the resulting compounds, in particular, those giving 2-alkylthio pyrimidoindole derivatives are described.

Key words: 4-phenyl-9*H*-pyrimido[4,5-*b*]indole-2(1*H*)-thione, 2-alkylthio derivatives of 4-phenyl-9*H*-pyrimido[4,5-*b*]indole, alkylation, oxidation, nucleophilic substitution, desulfurization.

The functional derivatives of pyrimido[4,5-*b*]indole, in particular, synthetically most available 2- and 4-amino-substituted derivatives, possess a broad spectrum of biological activities and present interest as a base for the development of new medicines.[1—3] The corresponding thio derivatives may also attract attention as biologically active substances, since compounds possessing antioxidant, antihypoxic, and hepatoprotector activities have been found in the series of related heterocyclic systems, 1,2,4-triazino[5,6-*b*]- and -[6,5-*b*]indoles.[4—6] In order to extend the range of functional derivatives of 4-phenylpyrimido[4,5-*b*]indole and to study their properties, we attempted to synthesize its 2-thio derivatives.

Previously, we carried out the reaction of 3-benzylidene-2-ethoxyindolenine tetrafluoroborate (**1**) with thiourea, which yielded a product identified as 4-phenylpyrimido[4,5-*b*]indole-2,4(1*H*)-thione (**2**)[7] (Scheme 1). A repeated detailed study of the reaction showed that this product is actually a mixture of thione **2**, its 3,4-dihydro derivative **3**, and disulfide **4**. Similar analytical and spectroscopic characteristics of compounds **2**—**4**, their poor solubility in most organic solvents, similar chromatographic behaviors of thiones **2** and **3**, and easy transformation into disulfide **4** make separation and identification of these compounds a difficult task. The presence of both thiones in the mixture can be detected by mass spectrometry, whereas disulfide **4** is not detected due to its very low volatility. All three components of the mixture can be observed by HPLC with mass selective detection (HPLC-MSD). In addition, the presence of disulfide **4** can be determined by TLC.

The intermediate formation of dihydro pyrimidoindole derivatives similar to compound **3** in the cyclocondensation of tetrafluoroborate **1** with amidines and guanidine has been proved previously.[8] Here the proof for the structure of compound **3** was based on chemical transformations and spectroscopic data. In addition to the intense molecular ion peak with *m/z* 279 (88%), its mass spectrum exhibits a line with *m/z* 202 (100%), indicating a typical easy elimination of the phenyl radical from the sp^3-hybridized C(4) atom of the molecular ion.[8] The ^{13}C NMR spectrum of compound **3** exhibits a signal for C(4) at δ 56.18, while the ^{1}H NMR spectrum contains a doublet for H(4) at δ 5.85 with $J = 2.5$ Hz due to spin—spin coupling with the proton of the neighboring N(3)H group. On selective decoupling of the signal at δ 9.11, the H(4) proton signal becomes a singlet, while the signal for the N(3)H group shows a clear-cut doublet structure with the same coupling constant under suppression of the lowest-field signal of the N(1)H group at δ 11.07. In addition, the last-mentioned signal exhibits the NOE; its intensity increases by 10% on application of an additional frequency onto the signal of the neighboring indole N(9)H group at δ 10.46. All NH groups undergo H—D exchange, the lowest exchange rate being typical of the N(3)H group. The signals for the aromatic protons of the indole fragment in compound **3** were assigned using double homonuclear resonance and published data. In particular, the doublet at δ 7.30 was assigned to the H(5) proton based on known data for indole,[9,10] pyrido[2,3-*b*]indol-2(1*H*)-one,[11] and benzopyrimido[4,5-*b*]indole-2,4(1*H*,3*H*)-dione[12] derivatives.

The aromatic proton signals in the ^{1}H NMR spectrum of thione **2** were also assigned using double resonance. When comparing the spectral patterns for compounds **2**

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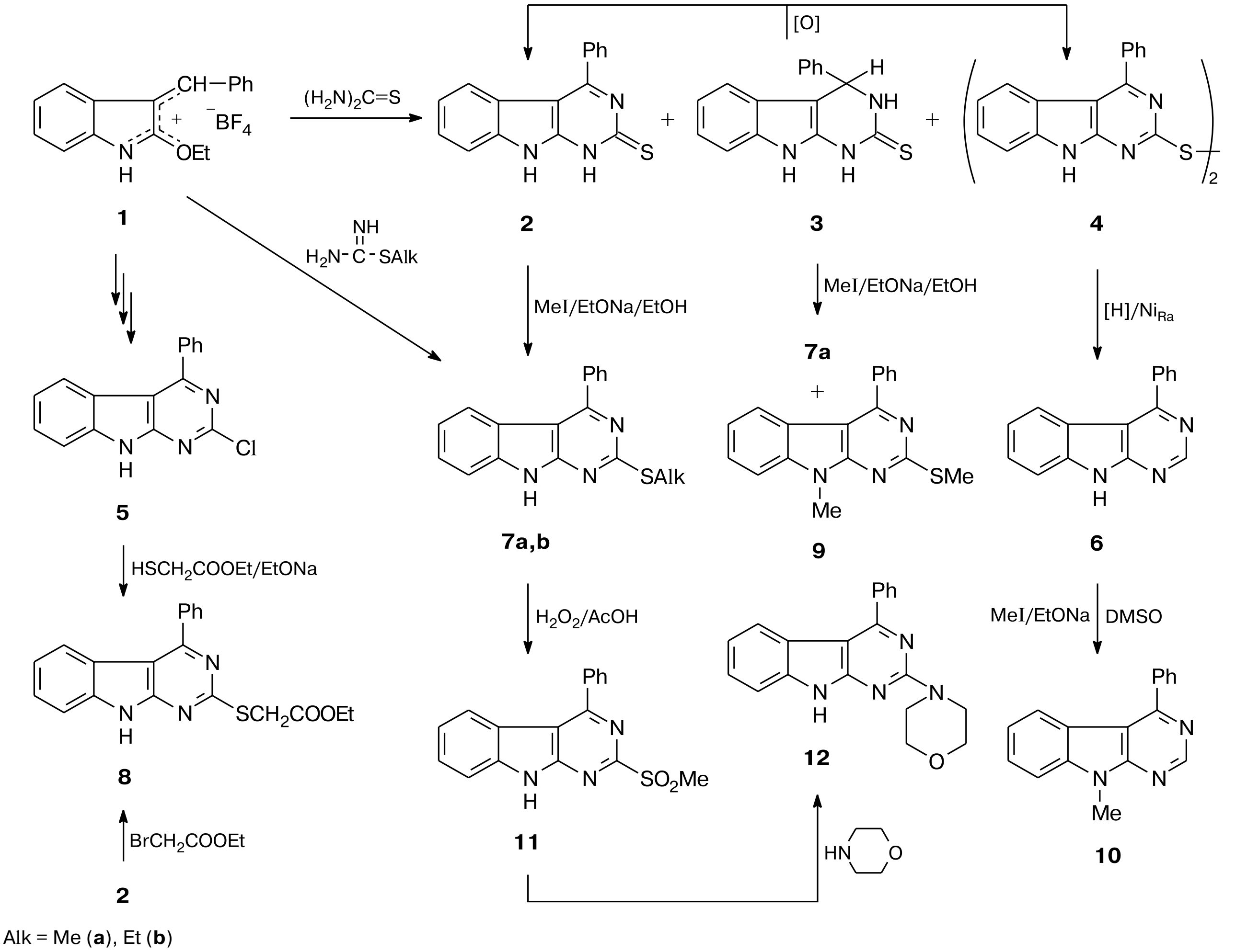
Scheme 1



and **3**, note the downfield shifts of the H(6), H(7), and H(8) proton signals in thione **2** by 0.2—0.4 ppm under the action of the annulated pyrimidine ring; conversely, the H(5) proton signal shifts upfield by 0.1 ppm. Apparently, the latter fact may be attributed to the influence of the neighboring phenyl group, which is rotated, due to steric requirements, in such a way that H(5) gets into its diamagnetic shielding area. The position of the N(9)H signal in the low-field part in the spectrum of thione **2** falls in the range typical of substituted pyrimidoindoles,[12—16] while an lower-field position of the N(1)H signal (δ 13.46) is analogous to those of the NH group in quinazolin-2- and quinazolin-4-thiones (δ ~14)[17].

We found that the ratio of compounds **2—4** in the products depends on the reaction conditions. Thus, an increase in the reaction time (6, 12, 24 h) or blowing air through the reaction mixture results in a substantial increase in the amount of disulfide **4**, which was detected by TLC. When the reaction is carried out under argon, a mixture of thiones **2** and **3** and traces of disulfide **4** are formed. The last-mentioned compound could have formed by stepwise oxidation—dehydrogenation of thione **3** in the presence of atmospheric oxygen during workup of the reaction mixture and product isolation.

A change in the product isolation procedure (see Experimental) with respect to that described previously[7] resulted in the preparation of pyrimidoindole-2-thione **2** in a satisfactory yield. It is also noteworthy that our attempts to synthesize thione **2** by heating 2-chloro-4-phenylpyrimido[4,5-*b*]indole (**5**) with thiourea or with its sodium salt in boiling ethanol or in DMSO at 120 °C were unsuccessful, unlike the behavior of chloropyrimidines in these reactions.[18]

Easy-to-oxidize derivative **3** has not been isolated in a pure form. However, when the condensation of salt **1** with thiourea was carried out under argon, we were able to obtain a product consisting of compound **3** and thione **2** impurity (~15%).

A similar formation of mixtures of dihydro- and tetrahydropyrimidines in the reactions of chalcones with thiourea is well known;[19] so is the ease of oxidation of 4,6-diphenylpyrimidine-2(1*H*)-thione with atmospheric oxygen to the corresponding disulfide.[20] Previously, we showed that the reactions of salt **1** with amidines and guanidines carried out under similar conditions afford 2-substituted pyrimido- and dihydropyrimido[4,5-*b*]indoles; the ease of dehydrogenation of the products depends on both the reaction temperature and the donor-acceptor properties of the substituents in the pyrimidine ring. The electron-donating substituents promote, while the electron-withdrawing substituents hamper dehydrogenation of the pyrimidine ring.[8]

Disulfide **4** was isolated in 5—10% yield by recrystallization from DMF of the product mixture formed upon the reaction of salt **1** and thiourea with access of air. Compound **4** was also prepared in a high yield upon oxidation of a mixture of thiones **2** and **3** with sodium nitrite in acetic acid. The reductive desulfurization of disulfide **4** with Raney nickel led to 4-phenyl-9*H*-pyrimido[4,5-*b*]indole (**6**) in a good yield. Previously,[13] we isolated this compound as a minor product upon the reaction of 2-chloropyrimidoindole **5** with hydrazine hydrate and upon hydrogenation of the corresponding 2-nitramino derivative.

The alkylation of thione **2** with methyl iodide and ethyl bromoacetate gave 2-methylthio-4-phenylpyrimidoindole **7a** and ethyl *S*-(4-phenylpyrimidoindolyl)thioglycolate **8** in good yields. An alternative method, *i.e.*, the reaction of salt **1** with *S*-methyl- and *S*-ethylisothioureas, respectively, gave 2-alkylthio derivatives **7a,b** in moderate yields, while ethylthioglycolate **8** was prepared by nucleophilic displacement of the chlorine atom in 2-chloropyrimidoindole **5** on treatment with ethyl thioglycolate. This reaction proceeds with difficulty, its completion requiring heating in DMSO for many hours. The retardation of nucleophilic substitution in the pyrimidoindole series (in relation to chloro and nitramino derivatives)[13] with respect to the pyrimidine analogs attests to substantial deactivating effect of the electron-releasing pyrrole fragment on the reactivity of the pyrimidoindole molecule. This conclusion is also confirmed by data on the mobility of the $MeSO_2$ group (see below).

We carried out methylation of dihydro derivative **3** (with a thione **2** impurity, see Experimental). The possibility of dehydrogenation of the dihydropyrimidine fragment was taken into account.[8] As expected, this gave 2-methylthiopyrimidoindole **7a**; however, a slight amount of 9-methyl-2-methylthio derivative **9** was isolated as hydroiodide. Apparently, *N*,*S*-dialkylation of dihydro derivative **3** followed by dehydrogenation also takes place. We demonstrated the possibility of alkylation at the indole nitrogen atom by conducting the reaction of the sodium salt of compound **6** with MeI (by analogy with Ref. 4), which gave 9-methyl-4-phenylpyrimidoindole **10**.

The oxidation of 2-methylthiopyrimidoindole **7a** with 30% H_2O_2 in acetic acid gave 2-methylsulfonyl derivative **11** in a good yield; a spectral feature of this product is a hypsochromic shift (17 nm) of the long-wavelength absorption band in the UV spectrum with respect to that in the spectrum of starting compound **7a**. A similar change in the UV spectra was noted for a structurally related heterocyclic system, 1,2,4-triazino[5,6-*b*]indole.[21]

In the reaction of compound **11** with morpholine (DMSO, 120 °C), the nucleophilic displacement of the $MeSO_2$ group to give 2-morpholino-4-phenylpyrimidoindole **12** proceeds with difficulty and not to completion; longer reaction times and higher temperatures result only in resinification of the reaction mixture. A similar outcome was attained in the reaction of derivative **11** with piperidine and benzylamine, which indicates a lower mobility of the $MeSO_2$ group located in the annulated pyrimidine ring compared to that in a nonannulated ring.[22]

Thus, we demonstrated that the reaction of 3-benzylidene-2-ethoxyindolenine tetrafluoroborate (**1**) with thiourea yields pyrimidoindole-2-thione **2**, its dihydro derivative **3**, and disulfide **4**. The product ratio depends on the reaction conditions. The transformation routes of thione **2** into some *S*-substituted pyrimidoindoles are presented. A substantial decrease in the nucleofugal properties of the chlorine atom and the methylsulfonyl group in position 2 of pyrimidoindole with respect to that for the same substituents in a nonannulated pyrimidine ring is noted.

Experimental

IR spectra were recorded for KBr pellets on a Specord M-80 spectrophotometer; UV spectra of solutions in ethanol were measured on an HP 8453 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 400 (400 MHz) in DMSO-d_6 using the residual signals of the solvent at δ 2.50 (^1H) and 39.50 (^{13}C) with respect to Me_4Si as internal standards. Mass spectra were recorded on a Finnigan MAT-8200 mass spectrometer (EI, 70 eV). The reactions were monitored and the purity of compounds was checked by TLC on Silufol UV-254 plates with UV detection.

The molecular mass of compound **4** was determined by an Agilent mass selective detector (model 1946c) connected to an Agilent 1100 series LC/MSD liquid chromatograph. The ions were generated in the mass detector by electrostatic spraying of a 0.05% solution of a sample of disulfide **4** in DMF at an atmospheric pressure (API-ES).

Reaction of 3-benzylidene-2-ethoxyindolenine tetrafluoroborate (1) with thiourea. *A.* Thiourea (0.76 g, 10 mmol) was dissolved in a solution of sodium ethoxide prepared from sodium (0.64 g, 28 mmol) and anhydrous ethanol (35 mL). Tetrafluoroborate **1** (3.0 g, 9 mmol) was added in small portions with stirring at 15—20 °C, the mixture was heated to boiling, kept for 6 h at a constant temperature, cooled, and neutralized by AcOH. The precipitate was filtered off, suspended in water (200 mL), filtered off again, and dried to give 0.87 g of (35%) **4-phenyl-9*H*-**

pyrimido[4,5-*b*]indole-2(1*H*)-thione (2), m.p. 325—329 °C (from DMF). The compound is hygroscopic. Found (%): C, 66.85; H, 3.75; N, 14.98; S, 11.15. $C_{16}H_{11}N_3S \cdot 0.5H_2O$. Calculated (%): C, 67.12; H, 4.22; N, 14.68; S, 11.20. MS, *m/z* (I_{rel} (%)): 278 $[M + 1]^+$ (21), 277 $[M]^+$ (86), 276 $[M - 1]^+$ (100). High-resolution MS, found: *m/z* 277.0666 $[M]^+$. $C_{16}H_{11}N_3S$. Calculated: M = 277.0674. ^{1}H NMR, δ: 7.07 (td, 1 H, H(6), ^3J = 7.9 Hz, ^4J < 1 Hz); 7.18 (d, 1 H, H(5), ^3J = 7.9 Hz); 7.37—7.44 (m, AB-part of an ABX-system, 2 H, H(7), H(8)); 7.63—7.71 (m, 3 H, Ph); 7.77 (d, 2 H, Ph, ^3J = 8.0 Hz); 12.22 (br.s, 1 H, N(9)H); 13.46 (br.s, 1 H, N(1)H). ^{13}C NMR, δ: 104.25; 112.05; 119.80; 120.42; 121.53; 127.52; 128.69; 129.02; 130.39; 131.24; 139.84; 151.34; 158.15; 178.79 (C(2)=S).

Keeping of the initial alcohol filtrate at 5 °C gave additionally 0.75 g of a product with m.p. 317—321 °C, representing a mixture of compounds **2—4**, according to MS and TLC data (benzene—acetone, 4 : 1). Recrystallization of this mixture from DMF gave 0.25 g (10%) of disulfide **4**, identical to that prepared by oxidation of a mixture of **2** and **3** (see below).

B. The reaction was carried out in a similar way but under argon; the product was isolated in air to give 1.6 g (64%) of a compound with m.p. 315—320 °C; according to ^{1}H NMR data, this was a mixture of 4-phenyl-9*H*-pyrimido[4,5-*b*]indole-2(1*H*)-thione (**2**) (15%) and 4-phenyl-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indole-2(1*H*)-thione (**3**) (85%). According to TLC data, the mixture also contained traces of disulfide **4**. MS (mixture), *m/z* (I_{rel} (%)): 279 ($[M]^+$ (**3**)) (88), 278 ($[M - 1]^+$ (**3**)) (27), 277 ($[M]^+$ (**2**)) (21), 276 ($[M - 1]^+$ (**2**)) (25), 219 (33), 218 (14), 203 (16), 202 ($[M - Ph]^+$ (**3**)) (100), 148 (9), 110 (12), 109 (13).

4-Phenyl-3,4-dihydro-9*H*-pyrimido[4,5-*b*]indole-2(1*H*)-thione (3). High-resolution MS, found: *m/z* 279.0839. $C_{16}H_{13}N_3S$. Calculated: M = 279.0831. ^{1}H NMR, δ: 5.85 (d, 1 H, H(4), ^3J = 2.5 Hz); 6.83 (ddd, 1 H, H(7), ^3J = 7.7 Hz, ^3J = 7.4 Hz, ^4J = 1.0 Hz); 6.90 (ddd, 1 H, H(6), ^3J = 7.8 Hz, ^3J = 7.4 Hz, ^4J = 1.3 Hz); 6.95 (d, 1 H, H(8), ^3J = 7.7 Hz); 7.30 (d, 1 H, H(5), ^3J = 7.8 Hz); 7.32—7.36 (m, 5 H, Ph); 9.11 (br.s, 1 H, N(3)H); 10.46 (br.s, 1 H, N(9)H); 11.07 (br.s, 1 H, N(1)H). ^{13}C NMR, δ: 56.18 (C(4)); 89.73; 111.37; 116.13; 119.38; 119.40; 126.62; 127.33; 128.29; 128.62; 131.64; 133.49; 144.07; 173.16 (C(2)=S).

Bis(4-phenyl-9*H*-pyrimido[4,5-*b*]indol-2-yl) disulfide (4). A solution of $NaNO_2$ (1.0 g, 14.5 mmol) in water (6 mL) was added dropwise with stirring at 80 °C to a suspension of a mixture of **2** and **3** (see above) (1 g, 3.6 mmol) in AcOH (70 mL). The reaction mixture was stirred for 5 h at this temperature and cooled, the precipitate was separated and suspended in water, and the suspension was washed with 10% NH_4OH. The precipitate was filtered off, washed with water, and dried *in vacuo* over P_2O_5. Yield 0.81 g (82%), m.p. 327—329 °C (from a DMF—DMSO mixture, 15 : 1). The compound is hygroscopic. Found (%): C, 66.92; H, 3.97; N, 14.94; S, 10.71. $C_{32}H_{20}N_6S_2 \cdot H_2O$. Calculated (%): C, 67.34; H, 3.89; N, 14.73; S, 11.24. Found: M = 552.1. $C_{32}H_{20}N_6S_2$. Calculated: M = 552.1. ^{1}H NMR, δ: 7.18 (ddd, 1 H, H(6), ^3J = 8.0 Hz, ^3J = 6.0 Hz, ^4J = 2.5 Hz); 7.45—7.49 (m, AB-part of an ABX-system, 2 H, H(7), H(8)); 7.59—7.64 (m, 3 H, Ph); 7.76 (d, 1 H, H(5), ^3J = 8.0 Hz); 7.85—7.88 (m, 2 H, Ph); 12.64 (br.s, 1 H, NH). ^{13}C NMR, δ: 108.41 (C(4a)); 111.89 (C(8)); 118.52 (C(4b)); 120.91 (C(6)); 121.55 (C(5)); 127.39 (C(7)); 128.56 (C_m, C_o); 130.20 (C_p); 137.34 (C_i); 138.37 (C(8a)); 157.17 (C(9a)); 159.28 (C(4)); 163.56 (C(2)).

4-Phenyl-9*H*-pyrimido[4,5-*b*]indole (6). Raney nickel (11 g) was added to a solution of the hydrate of disulfide **4** (0.75 g, 1.3 mmol) in DMF (80 mL), and the mixture was stirred for 2 h at 100—110 °C. The catalyst was separated and washed with hot DMF (20 mL), the combined DMF solutions were concentrated *in vacuo* and poured into water (100 mL). The precipitate was filtered off, washed with water, and dried *in vacuo* over P_2O_5. Yield 0.50 g (75%), m.p. 224—226 °C (from benzene). Found (%): C, 78.77; H, 4.61; N, 17.04. $C_{16}H_{11}N_3$. Calculated (%): C, 78.35; H, 4.52; N, 17.13. MS, *m/z* (I_{rel} (%)): 245 $[M]^+$ (50), 244 $[M - 1]^+$ (100), 122 (14). UV, λ_{max}/nm (logε): 252 (4.36), 303 (3.94). The ^{1}H and ^{13}C NMR data were reported previously.[13]

9-Methyl-4-phenylpyrimido[4,5-*b*]indole (10). Pyrimidoindole **6** (0.10 g, 0.4 mmol) was added to a solution of sodium ethoxide prepared from sodium (0.019 g, 0.8 mmol) and anhydrous ethanol (10 mL), the mixture was stirred for 10 min and concentrated to dryness *in vacuo* at 35 °C. The resulting sodium salt of pyrimidoindole **6** was dissolved in dry DMSO (10 mL), and MeI (0.17 g, 1.2 mmol) was added. The mixture was heated for 3 h at 100 °C, an additional portion of MeI (0.11 g, 0.8 mmol) was added, and the mixture was heated for additional 5 h, cooled, and poured into water (100 mL). The resulting precipitate was separated, washed with water on the filter, and dried. The product (0.086 g) dissolved in benzene, passed through a SiO_2/Al_2O_3 layer, and the eluate was concentrated to dryness to give 0.051 g (48%) of compound **10**, m.p. 160—163 °C (from hexane—benzene, 5 : 1). Found (%): C, 78.29; H, 5.21; N, 15.93. $C_{17}H_{13}N_3$. Calculated (%): C, 78.74; H, 5.05; N, 16.21. MS, *m/z* (I_{rel} (%)): 259 $[M]^+$ (63), 258 $[M - 1]^+$ (100), 243 (13). UV, λ_{max}/nm (logε): 254 (4.40), 302 (4.01). ^{1}H NMR, δ: 3.96 (s, 3 H, NMe); 7.25 (td, 1 H, H(6), ^3J = 7.7 Hz, ^4J = 0.8 Hz); 7.61 (td, 1 H, H(7), ^3J = 7.7 Hz, ^4J = 0.7 Hz); 7.63—7.68 (m, 3 H, Ph); 7.76 (d, 1 H, H(8), ^3J = 8.0 Hz); 7.83 (d, 1 H, H(5), ^3J = 7.7 Hz); 7.90—7.93 (m, 2 H, Ph); 9.04 (s, 1 H, H(2)). ^{13}C NMR, δ: 27.60 (Me); 110.08 (C(4a)); 110.33 (C(8)); 118.11 (C(4b)); 120.98 (C(6)); 121.83 (C(5)); 127.67 (C(7)); 128.57 (C_m); 128.65 (C_o); 129.92 (C_p); 138.03 (C_i); 139.66 (C(8a)); 154.00 (C(2)); 155.36 (C(9a)); 158.74 (C(4)).

2-Methylthio-4-phenyl-9*H*-pyrimido[4,5-*b*]indole (7a). ***A.*** Ground *S*-methylisothiourea sulfate (6.0 g, 22 mmol) was added to a solution of sodium methoxide (1.2 g, 22 mmol) in anhydrous THF (50 mL), and the mixture was stirred for 15 min. The resulting mixture was slowly added to a stirred suspension of tetrafluoroborate **1** (3.3 g, 10 mmol) in anhydrous THF (60 mL), and after 30 min, a solution of sodium methoxide (0.43 g, 8 mmol) in methanol (15 mL) was added. The mixture was stirred for 3 h at ~20 °C, refluxed for 3 h, and sodium methoxide (0.43 g, 8 mmol) was added. The mixture was refluxed for additional 3 h and left for ~14 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*, treated with water (100 mL), and extracted with chloroform (5×60 mL). The extract was dried over $MgSO_4$, concentrated *in vacuo*, and the residue was treated with methanol (3 mL), squeezed on the filter, washed with methanol (2×0.5 mL), and dried on the filter. Keeping methanol filtrates in a refrigerator gave an additional amount of compound **7a**. The total yield was 0.82 g (28%), m.p. ~270 °C. A sample for analysis was recrystallized from ethyl cellosolve with some ethanol added and dried *in vacuo* at 100 °C, m.p. 276—278 °C. Found (%): C, 70.04; H, 4.65; N, 14.31; S, 10.85. $C_{17}H_{13}N_3S$. Calculated (%): C, 70.08; H, 4.50; N, 14.42; S, 11.00. MS, *m/z* (I_{rel} (%)): 291 $[M]^+$ (100), 290 $[M - 1]^+$ (35), 245 (31), 244 $[M - SMe]^+$ (43), 219 (10). UV, λ_{max}/nm (logε): 268 (4.53), 329 (4.07). ^{1}H NMR, δ: 2.63 (s, 3 H, SMe); 7.16 (t, 1 H, H(6), $^3J = 7.9$ Hz); 7.46 (t, 1 H, H(7), $^3J = 7.9$ Hz); 7.52 (d, 1 H, H(8), $^3J = 7.9$ Hz); 7.62—7.68 (m, 3 H, Ph); 7.71 (d, 1 H, H(5), $^3J = 7.9$ Hz); 7.89—7.92 (m, 2 H, Ph); 12.35 (br.s, 1 H, N(9)H).

B. Thione **2** (1.0 g, 3.6 mmol), and, after 15 min, MeI (2.52 g, 18 mmol) were added with stirring to a solution of sodium ethoxide prepared from sodium (0.09 g, 3.9 mmol) and anhydrous ethanol (25 mL). The resulting suspension was heated for 2 h at 80 °C and cooled, and the precipitate was separated, washed with ethanol, and dried. The yield of compound **7a** was 0.63 g (60%), m.p. 276—278 °C. The product was identical to that obtained by method ***A***.

C. Compound **3** (2.0 g, 7.2 mmol) containing thione **2** (~15%, see above) and MeI (5.0 g, 35 mmol) were added with stirring to a solution of sodium ethoxide prepared from sodium (0.17 g, 7.5 mmol) and anhydrous ethanol (40 mL). The suspension was heated for 2 h at 80 °C and cooled, the precipitate was separated, washed with ethanol, and dried to give 0.51 g of compound **7a**. Long-term keeping of the alcohol filtrate in a refrigerator, separation of the precipitate, and recrystallization from ethyl cellosolve gave additionally 0.31 g of compound **7a**. The total yield of compound **7a** was 39%, m.p. 275—277 °C.

Long-term keeping of the ethyl cellosolve mother solution in a refrigerator gave 0.21 g (3%) **9-methyl-2-methylthio-4-phenyl-9*H*-pyrimido[4,5-*b*]indole hydroiodide (9)**, m.p. 215—220 °C; 273—277 °C (from ethanol). Found (%): C, 50.14; H, 3.80; I, 29.48; N, 9.48; S, 7.06. $C_{18}H_{15}N_3S \cdot HI$. Calculated (%): C, 49.89; H, 3.72; I, 29.29; N, 9.70; S, 7.40.

Treatment of hydroiodide **9** (0.1 g, 0.23 mmol) with 10% NH_4OH (8 mL) gave 0.07 g of **9-methyl-2-methylthio-4-phenyl-9*H*-pyrimido[4,5-*b*]indole (9)**, m.p. 220—223 °C (from ethanol). Found (%): C, 70.56; H, 4.98; N, 13.67; S, 10.16. $C_{18}H_{15}N_3S$. Calculated (%): C, 70.80; H, 4.95; N, 13.76; S, 10.48. MS, *m/z* (I_{rel} (%)): 305 $[M]^+$ (100), 259 (31), 258 $[M - SMe]^+$ (19), 231 (14). ^{1}H NMR, δ: 2.78 (s, 3 H, SMe); 4.11 (s, 3 H, NMe); 7.10 (td, 1 H, H(6), $^3J = 8.0$ Hz, $^4J = 0.8$ Hz); 7.42 (td, 1 H, H(7), $^3J = 8.0$ Hz, $^4J = 1.0$ Hz); 7.63 (d, 1 H, H(8), $^3J = 8.0$ Hz); 7.64—7.69 (m, 3 H, Ph); 7.80 (d, 1 H, H(5), $^3J = 8.0$ Hz); 8.01—8.04 (m, 2 H, Ph).

2-Ethylthio-4-phenyl-9*H*-pyrimido[4,5-*b*]indole (7b). Ground *S*-ethylisothiourea hydrobromide (1.02 g, 5.5 mmol) was added with stirring to a solution of sodium methoxide (0.3 g, 5.5 mmol) in anhydrous THF (15 mL), and the mixture was stirred for 20 min. Tetrafluoroborate **1** (1.7 g, 5 mmol) in anhydrous THF (30 mL) was slowly added with stirring to the resulting suspension. After 1 h, more sodium methoxide (0.22 g, 4 mmol) in a THF (5 mL) and methanol (3 mL) mixture was added, and the reaction mixture was stirred for 2 h at ~20 °C, refluxed for 2 h, and concentrated *in vacuo*. The residue was treated with water (10 mL) and extracted with chloroform (5×60 mL), and the extract was washed with water and dried over $MgSO_4$. After the extract was concentrated *in vacuo*, the residue was treated with methanol (5 mL), and the precipitate was filtered off, washed with methanol (2×0.5 mL), and dried on the filter. Yield 0.44 g (29%), m.p. 246—248 °C. The sample for analysis was recrystallized from methyl cellosolve and dried *in vacuo* over P_2O_5, m.p. 253—255 °C. Found (%): C, 68.70; H, 5.43; N, 11.98; S, 9.18. $C_{18}H_{15}N_3S \cdot 0.5C_4H_{10}O_2$. Calculated (%): C, 68.54; H, 5.75; N, 11.99; S, 9.15. MS, *m/z* (I_{rel} (%)): 305 $[M]^+$ (100), 290 $[M - Me]^+$ (36), 276 $[M - Et]^+$ (24), 245 (38), 244 $[M - SEt]^+$ (67), 219 (18). ^{1}H NMR, δ: 1.40 (t, 3 H, Me, $^3J = 7.2$ Hz); 3.22 (q, 2 H, CH_2, $^3J = 7.2$ Hz); 7.14 (td, 1 H, H(6), $^3J = 8.0$ Hz, $^4J = 1.0$ Hz); 7.44 (td, 1 H, H(7), $^3J = 8.0$ Hz, $^4J = 1.0$ Hz); 7.51 (d, 1 H, H(8), $^3J = 8.0$ Hz); 7.61—7.66 (m, 3 H, Ph); 7.70 (d, 1 H, H(5), $^3J = 8.0$ Hz); 7.88—7.91 (m, 2 H, Ph); 12.37 (br.s, 1 H, N(9)H).

Ethyl *S*-(4-phenyl-9*H*-pyrimido[4,5-*b*]indol-2-yl)thioglycolate (8). ***A.*** Thione **2** (1.0 g, 3.6 mmol) was added with stirring to a solution of sodium (0.09 g, 3.8 mmol) in anhydrous ethanol (15 mL), and the mixture was concentrated to dryness *in vacuo* at 35 °C. The residue was dissolved in dry DMF (25 mL), ethyl bromoacetate (0.63 g, 3.8 mmol) was added, and the mixture was heated for 0.5 h at 100 °C. Then the reaction mixture was cooled and poured into water (250 mL), and the precipitate was separated, washed on the filter with water, and dried. The product was formed in a quantitative yield, m.p. 209—222 °C. After recrystallization from ethanol, the yield of compound **8** was 0.87 g (70%), m.p. 228—230 °C. Found (%): C, 66.34; H, 4.72; N, 11.68; S, 8.70. $C_{20}H_{17}N_3O_2S$. Calculated (%): C, 66.09; H, 4.71; N, 11.56; S, 8.82. MS, *m/z* (I_{rel} (%)): 363 $[M]^+$ (26), 291 (32), 290 $[M - CO_2Et]^+$ (100), 244 (27). IR, ν/cm^{-1}: 1236 (C—OEt); 1736 (C=O); 3400 (N—H). ^{1}H NMR, δ: 1.15 (t, 3 H, Me, $^3J = 7.2$ Hz); 4.07 (q, 2 H, CH_2, $^3J = 7.2$ Hz); 7.16 (t, 1 H, H(6), $^3J = 8.0$ Hz); 7.46 (t, 1 H, H(7), $^3J = 8.0$ Hz); 7.53 (d, 1 H, H(8), $^3J = 8.0$ Hz); 7.73 (d, 1 H, H(5), $^3J = 8.0$ Hz); 7.62—7.67 (m, 3 H, Ph); 7.87—7.92 (m, 2 H, Ph); 12.33 (br.s, 1 H, N(9)H).

B. Ethyl thioglycolate (0.34 g, 2.8 mmol) was added with stirring to a solution of sodium (0.07 g, 3 mmol) in anhydrous ethanol (2 mL) and the mixture was concentrated to dryness *in vacuo*. The residue was dissolved in dry DMSO (4 mL), 2-chloro-4-phenyl-9*H*-pyrimido[4,5-*b*]indole (**5**) (0.70 g, 2.5 mmol) was added,[13] and the mixture was heated for 40 h at 120 °C. After cooling, ethyl acetate (50 mL) and then chloroform (100 mL) were added to dissolve the product. The organic extract was washed several times with water, and the remaining product was extracted from the collected aqueous solutions with chloroform. The combined organic extracts (~250 mL) were dried over $MgSO_4$ and concentrated *in vacuo* to dryness. The residue was transferred onto a filter, washed with a minimum quantity of 50% aqueous ethanol, and recrystallized from ethanol to give 0.78 g (86%) of compound **8**, m.p. 225—228 °C. The product was identical to the compound prepared by method ***A***.

2-Methylsulfonyl-4-phenyl-9*H*-pyrimido[4,5-*b*]indole (11). A 30% solution of H_2O_2 (10 mL, 87 mmol) was added with stirring at 60 °C to a solution of 2-methylthiopyrimidoindole **7a** (2.54 g, 8.7 mmol) in AcOH (430 mL). The mixture was stirred for 6 h at this temperature and concentrated *in vacuo* to 60 mL, and the precipitate that formed was separated, washed with 10% NH_4OH and water, and dried. Yield 2.04 g (72%), m.p. 283—285 °C (from ethanol). Found (%): C, 63.10; H, 4.02; N, 12.90; S, 9.72. $C_{17}H_{13}N_3O_2S$. Calculated (%): C, 63.15; H, 4.05; N, 13.00; S, 9.90. MS, *m/z* (I_{rel} (%)): 323 $[M]^+$ (80), 260 (32), 244 $[M - SO_2Me]^+$ (100), 190 (28). IR, ν/cm^{-1}: 1311, 1130 (SO_2Me); 3400 (N—H). UV, λ_{max}/nm (logε): 259 (4.50), 312 (4.06). ^{1}H NMR, δ: 3.48 (s, 3 H, Me); 7.29 (ddd, 1 H, H(6),

^3J = 8.0 Hz, ^3J = 7.4 Hz, ^4J = 1.0 Hz); 7.63 (td, 1 H, H(7), ^3J = 7.4 Hz, ^4J = 1.0 Hz); 7.68—7.72 (m, 4 H, H(8) + Ph); 7.90 (d, 1 H, H(5), ^3J = 8.0 Hz); 7.98—8.01 (m, 2 H, Ph); 13.10 (br.s, 1 H, N(9)H).

Reaction of 2-methylsulfonylpyrimidoindole 11 with morpholine. A solution of sulfone **11** (0.2 g, 0.6 mmol) and morpholine (0.16 g, 1.8 mmol) in dry DMSO (18 mL) was heated for 6 h at 120 °C, cooled, and poured into water (150 mL), and the precipitate was separated, washed with water, and dried over P_2O_5 to give 0.18 g of a mixture of **2-morpholino-4-phenyl-9*H*-pyrimido[4,5-*b*]indole (12)**[13] and starting sulfone **11** in ~1 : 1 ratio (^{1}H NMR data and TLC (benzene—acetone, 4 : 1)). ^{1}H NMR (compound **12**), δ: 3.70—3.73 (m, 4 H, NCH_2); 3.81—3.85 (m, 4 H, OCH_2); 7.04 (td, 1 H, H(6), ^3J = 7.7 Hz, ^4J = 1.1 Hz); 7.29 (td, 1 H, H(7), ^3J = 7.7 Hz, ^4J = 1.1 Hz); 7.39 (d, 1 H, H(8), ^3J = 7.7 Hz); 7.56 (d, 1 H, H(5), ^3J = 7.7 Hz); 7.58—7.63 (m, 3 H, Ph); 7.86—7.89 (m, 2 H, Ph); 11.79 (br.s, 1 H, N(9)H).

References

1. PCT Int. Appl. 93 20078; *Chem. Abstrs*, 1994, **121**, 134139.
2. PCT Int. Appl. 98 42708; *Chem. Abstrs*, 1998, **129**, 290145.
3. PCT Int. Appl. 00 66585; *Chem. Abstrs*, 2000, **133**, 350241.
4. A. B. Tomchin, O. Yu. Uryupov, T. I. Zhukova, T. A. Kuznetsova, M. V. Kostycheva, and A. V. Smirnov, *Khim.-Farm. Zh.*, 1997, **31**, Issue 3, 19 [*Pharm. Chem. J.*, 1997, **31**, Issue 3 (Engl. Transl.)].
5. A. B. Tomchin and A. V. Kropotov, *Khim.-Farm. Zh.*, 1998, **32**, Issue 1, 22 [*Pharm. Chem. J.*, 1998, **32**, Issue 1 (Engl. Transl.)].
6. S. V. Okovityi, *Biomeditsin. Khim.* [*Biomed. Chem.*], 2004, **50**, 293 (in Russian).
7. V. P. Borovik, L. S. Filatova, and V. P. Mamaev, *Izv. Sib. Otd. Akad. Nauk SSSR. Ser. Khim. Nauk*, 1975, No. 3, 137 [*Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1975, Issue 3 (Engl. Transl.)].
8. V. P. Borovik, L. Yu. Ivanovskaya, and V. P. Mamaev, *Izv. Sib. Otd. Akad. Nauk SSSR. Ser. Khim. Nauk*, 1977, No. 6, 110 [*Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1977, Issue 6 (Engl. Transl.)].
9. T. J. Batterham, *NMR Spectra of Simple Heterocycles*, Wiley-Interscience, New York, 1973, 250.
10. B. Hoefgen, M. Decker, P. Mohr, A. M. Schramm, S. A. F. Rostom, H. El-Subbagh, P. M. Schweikert, D. R. Rudolf, M. U. Kassack, and J. Lehmann, *J. Med. Chem.*, 2006, **49**, 760.
11. J.-P. Buisson, E. Bisagni, C. Monneret, P. Demerseman, C. Leon, and N. Platzer, *J. Heterocycl. Chem.*, 1996, **33**, 973.
12. E. K. Panisheva, M. L. Alekseeva, and V. G. Granik, *Khim.-Farm. Zh.*, 2004, **38**, Issue 3, 29 [*Pharm. Chem. J.*, 2004, **38**, Issue 3 (Engl. Transl.)].
13. V. P. Borovik and O. P. Shkurko, *Izv. Akad. Nauk. Ser. Khim.*, 2002, 1974 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 2129].
14. V. P. Borovik, M. M. Shakirov, and O. P. Shkurko, *Khim. Geterotsikl. Soedin.*, 2003, 1531 [*Chem. Heterocycl. Compd.*, 2003, **39**, 1348 (Engl. Transl.)].
15. Y.-M. Zhang, T. Razler, and P. F. Jackson, *Tetrahedron Lett.*, 2002, **43**, 8235.
16. B. Dotzauer and R. Troschütz, *Synlett*, 2004, 1039.
17. T. Nishio, M. Fujisawa, and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2523.
18. M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1951, 1218.
19. S. K. Naik, R. K. Benera, and A. Nayak, *Ind. J. Chem., Sect. B*, 1982, **21**, 1124.
20. F. G. Baddar, F. H. Al-Hajjar, and N. R. El-Rayyes, *J. Heterocycl. Chem.*, 1976, **13**, 257.
21. I. S. Ioffe, A. B. Tomchin, and E. N. Zhukova, *Zh. Obshch. Khim.*, 1969, **39**, 2111 [*J. Gen. Chem. USSR*, 1969, **39** (Engl. Transl.)].
22. Z. Budesinsky and J. Vavrina, *Collect. Czech. Chem. Commun.*, 1972, **37**, 1721.

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