Influence of the structures of α-halo ketones and thioamides on the Hantzsch synthesis of thiazoles and thiazolo[5,4-*b*]indoles. A new approach to 4-acetyl-2-methyl-4*H*-thiazolo[5,4-*b*]indole

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In reactions with some α-halo ketones (3-bromo-1,1,1-trifluoropropan-2-one, 1-acetyl-2-bromoindolin-3-one, and α-bromoacetophenone), thioacetamide and a series of thioamides of aromatic and heteroaromatic acids are transformed into 4-hydroxy-Δ^2-thiazolines rather than into thiazoles (the expected Hantzsch reaction products). To the contrary, thiazoles are produced in the reactions of the same α-halo ketones with thioamides of phenylacetic, diphenylacetic, 3-indolylacetic, or cyanoacetic acids. The abnormal course of the Hantzsch reaction in the former case results from the fact that 4-hydroxy-Δ^2-thiazolines, which are intermediates in the thiazole synthesis, undergo virtually no dehydration under the Hantzsch reaction conditions. The ease of dehydration of hydroxythiazolines under the conditions of the thiazole synthesis and the possibility of the spontaneous thiazole synthesis depend on the nature of the substituent at position 2 and, consequently, on the structure of the starting thioamide. The Me, Ar, and Het substituents impede dehydration, whereas substituents containing the α-methylene (methine) unit at the C(2) atom of the thiazoline moiety substantially facilitate this reaction. The conditions for the dehydration of 4-acetyl-2-methyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indole under basic catalysis were found, and a new procedure was developed for the preparation of thiazoles and 2-R-thiazolo[5,4-*b*]indoles, whose synthesis presents difficulties or is impossible under standard conditions.

Key words: thiazoles, 2-R-thiazolo[5,4-*b*]indoles, Hantzsch reaction, thioamides, α-halo ketones, structure, 4-hydroxy-Δ^2-thiazolines, 2-R-4-acetyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indoles, dehydration.

The field of application of thiazole-containing compounds is gradually extended.[1—7] 2-R-Thiazolo[5,4-*b*]indoles, which we have synthesized earlier, and their derivatives are of interest for pharmacological studies.[8,9] One of the most commonly used procedures for the thiazole synthesis is based on the Hantzsch reaction (the reaction of α-halo ketones with thioamides), which proceeds, as a rule, under heating of the reaction components in ethanol over a short period of time and gives the target compounds in good yields.[10] However, 2-methyl-4-phenylthiazole can be prepared only by heating α-bromoacetophenone with thioacetamide in anhydrous EtOH in the presence of gaseous hydrogen chloride for many hours.[11] The formation of 4-hydroxy-Δ^2-thiazolines instead of thiazoles as the final products of the Hantzsch reaction was documented.[11,12] For example, heating of 3-bromo-1,1,1-trifluoropropan-2-one (**1a**) (trifluorobromoacetone) in EtOH with thioamides of acetic, benzoic, or pyridinecarboxylic acids affords 2-R-4-hydroxy-4-trifluoromethyl-Δ^2-thiazolines, which undergo dehydration to give 2-R-4-trifluoromethylthiazoles only under drastic conditions.[13] However, the reaction of trifluorobromoacetone **1a** with thiourea or phenylthiourea readily produces 2-amino- or 2-phenylamino-4-trifluoromethylthiazole, respectively. Under the same conditions, the reaction of trifluorobromoacetone **1a** with *N*,*N*′-diphenylthiourea affords 4-hydroxy-3-phenyl-2-phenylimino-4-trifluoromethylthiazolidine hydrobromide. The fact that 4-hydroxythiazolidines, which were prepared by the condensation of α-halo ketones with substituted thioureas, are easily subjected to dehydration giving rise to 2-imino-Δ^4-thiazolines has been documented earlier.[14]

In addition, we demonstrated that the reaction of 1-acetyl-2-bromo-3-indolinone (**1b**) (bromoindoxyl) with

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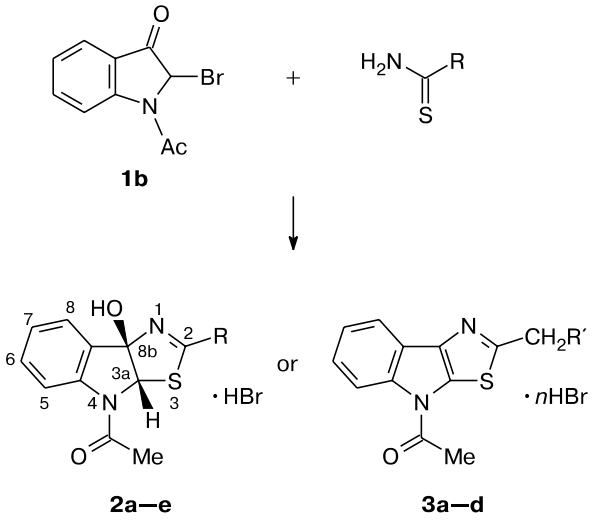
thioamides produces, depending on the nature of the latter compounds, either the corresponding hydroxydihydrothiazoloindoles **2a—d** (from thioamides of acetic, benzoic, or pyridinecarboxylic acids) or thiazoloindoles **3b—d** (from thioamides containing the α-methylene unit)[15] (Scheme 1). It should be noted that compounds **2a—d** undergo virtually no dehydration in an acidic medium. We succeeded in preparing only 4-acetyl-2-methyl-4*H*-thiazolo[5,4-*b*]indole hydrobromide (**3a**) in low yield from hydrobromide **2a**. An unsuccessful attempt[16] to synthesize 4-aryl-2-(*o*-hydroxyaryl)thiazoles by the Hantzsch reaction of α-haloacetophenones with thioamides of *o*-hydroxybenzoic acids deserves notice.

Scheme 1



2: R = Me (**a**), Ph (**b**), 3-pyridyl (**c**), 4-pyridyl (**d**), CH_2Ph (**e**)

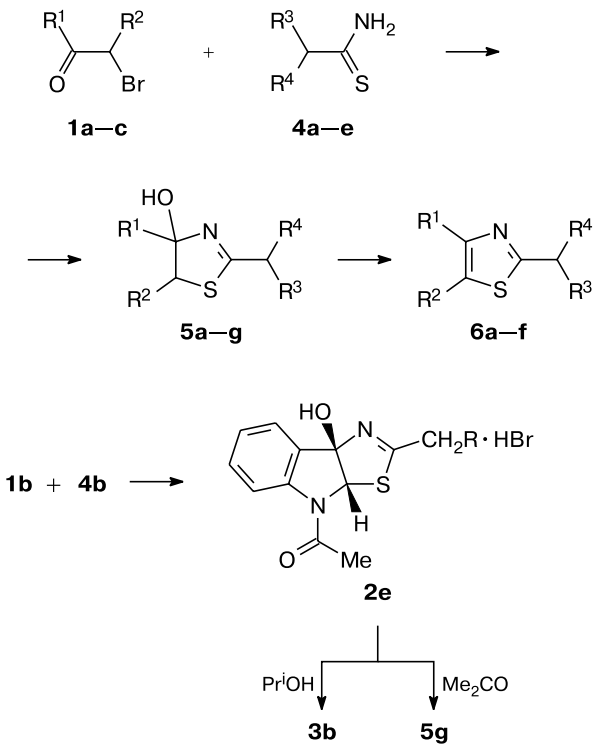
3: *n* = 1 (**a—c**), 0 (**d**); R′ = H (**a**), Ph (**b**), CH_2Ph (**c**), CN (**d**)

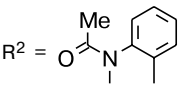
In the present study, we investigated the influence of the structures of the starting α-halo ketones and thioamides on the ease of the Hantzsch reaction and developed efficient procedures for the synthesis of thiazoles and 2-R-thiazolo[5,4-*b*]indoles, which are difficult, if at all, to synthesize under standard conditions.

For this purpose, we studied the condensation of α-bromoacetophenone (**1c**) with thioacetamide (**4a**) and thioamides containing the α-methylene (methine) unit **4b—e** (thioamides of phenylacetic, cyanoacetic, diphenylacetic, and 3-indolylacetic acids) under comparable conditions. The reactions of trifluorobromoacetone **1a** and bromoindoxyl **1b** with thioamide **4b** were studied under analogous conditions (Scheme 2).

It appeared that the cyclocondensation of bromo ketones **1a—c** with thioamides **4a,b,d,e** in the presence of 2 equiv. of triethylamine easily proceeds under mild conditions (20 °C, Me_2CO) and always stops at the formation

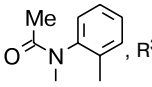
Scheme 2



1: R^1 = CF_3, R^2 = H (**a**), $R^1 + R^2$ =  (**b**), R^1 = Ph, R^2 = H (**c**);

4: $R^3 = R^4$ = H (**a**); R^3 = Ph, R^4 = H (**b**); R^3 = CN, R^4 = H (**c**), $R^3 = R^4$ = Ph (**d**), R^3 = 3-indolyl, R^4 = H (**e**);

5, 6: R^1 = Ph, $R^2 = R^3 = R^4$ = H (**a**); $R^1 = R^3$ = Ph, $R^2 = R^4$ = H (**b**); R^1 = Ph, $R^2 = R^4$ = H, R^3 = CN (**c**); R^1 = Ph, $R^2 = R^4$ = H, R^3 = 3-indolyl (**d**); $R^1 = R^3 = R^4$ = Ph, R^2 = H (**e**); R^1 = CF_3, $R^2 = R^4$ = H, R^3 = Ph (**f**);

$R^1 + R^2$ =  , R^3 = Ph, R^4 = H (**g**)

of hydroxythiazolines **5a,b,d—g**; the yields of the latter are 61—82% (method *A*, Table 1, see Scheme 2). Under the same conditions, the reaction of α-bromoacetophenone **1c** with thioamide **4c** also affords hydroxythiazoline **5c** (TLC data). However, we failed to isolate the latter compound in the individual state because it undergoes dehydration to give thiazole **6c** in the course of recrystallization from Pr^iOH.

Bromoindoxyl **1b** reacts with thioamide **4b** in Me_2CO at 20 °C and is almost quantitatively transformed into hydrobromide **2e**. The treatment of the latter with ammonium acetate gave free base **5g** in 86% yield (method *B*).

However, the reactions proceed differently if Pr^iOH is used as the solvent in the absence of bases. For example, heating of bromo ketones **1a—c** with thioamides **4b,d,e** over a short period of time affords thiazoles **6b,d—f** con-

Table 1. Physicochemical characteristics, yields, and elemental analysis data for compounds **5a,b,d—g**, **6b,d—f**, and **7**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula	IR, ν/cm^{-1}		M^+
			C	H	N	S		OH, NH	C=N	
5a	79	104—105*	62.25 62.18	5.79 5.70	7.21 7.25	16.70 16.58	$C_{10}H_{11}NOS$	3150	1620	193
5b	74	116—117*	71.46 71.38	5.67 5.58	5.14 5.20	12.02 11.90	$C_{16}H_{15}NOS$	3115	1610	269
5d	77	161—163*	69.94 70.13	5.25 5.19	9.03 9.09	10.40 10.39	$C_{18}H_{16}N_2OS$	3225	1590	308
5e	80	160—162*	76.32 76.52	5.60 5.51	4.09 4.06	9.23 9.28	$C_{22}H_{19}NOS$	3150	1590	345
5f	61	104—107	50.63 50.57	3.87 3.83	5.38 5.36	12.36 12.26	$C_{11}H_{10}F_3NOS$	3120	1600	261
5g**	82	171—173	66.56 66.67	5.01 4.94	8.66 8.64	9.73 9.88	$C_{18}H_{16}N_2O_2S$	3100	1620	324
6b	83	72—74	76.31 76.49	5.25 5.18	5.51 5.57	12.82 12.75	$C_{16}H_{13}NS$	—	1590	251
6d	79	103—105	74.40 74.48	4.89 4.83	9.75 9.66	11.13 11.03	$C_{18}H_{14}N_2S$	3540, 3400	1640	290
6e	85	99—101	80.67 80.73	5.24 5.20	4.32 4.28	9.81 9.79	$C_{22}H_{17}NS$	—	1610	327
6f	56	41—43	54.40 54.32	3.33 3.29	5.70 5.76	13.29 13.17	$C_{11}H_8F_3NS$	—	1610	243
7**	62	128—130	62.48 62.61	4.42 4.35	12.25 12.17	13.99 13.91	$C_{12}H_{10}N_2OS$	—	1610	230

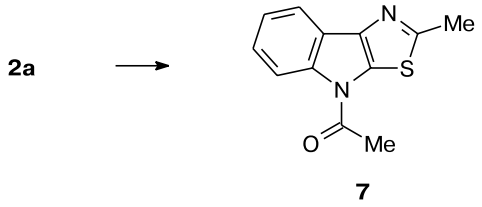
* The compound melts with decomposition.
** The absorption of the amide CO group in the IR spectra of compounds **5g** and **7** is observed at 1680 and 1675 cm^{-1}, respectively.

taining the α-methylene (methine) unit at the C(2) atom and 2-benzylthiazoloindole hydrobromide **3b** in 56—85% yields (method *A*). Thiazoles **6b,d—f** are also produced in 74—85% yields by dehydration of hydroxythiazolines **5b,d—f** performed with heating over a short period of time (1 min for compounds **5b,d,e** and 15 min for compound **5f**) in EtOH or Pr^{i}OH in the presence of an equimolar amount of HCl (method *B*). Hydrobromide **2e** is subjected to dehydration giving 2-benzylthiazoloindole **3b** in 95% yield by heating in Pr^{i}OH for 5 min.

Therefore, the available data[11—13] and the results obtained in the present study and our earlier investigations[15,17] show that hydroxythiazolines and their indole analogs, *viz.*, hydroxydihydrothiazoloindoles, are, as a rule, easily derived from α-halo ketones and thioamides in aprotic solvents at room temperature (sometimes, under heating in EtOH).[13,15] The reaction time and the yields of the products are virtually independent of the structure of the starting thioamide. In an acidic medium, hydroxythiazolines and hydroxydihydrothiazoloindoles containing the α-methylene (methine) unit at the C(2) atom are smoothly transformed into the corresponding thiazoles and thiazoloindoles. It is noteworthy that 2-benzylhydroxythiazolines **5b,f** and hydrobromide **2e**, which were prepared from structurally different α-halo ketones **1a—c** and the same thioamide of phenylacetic acid, are dehydrated under virtually the same conditions. The dehydration is not hindered by the trifluoromethyl group at position 4 of hydroxythiazoline **5f**. To the contrary, according to the published data,[11,13,15] intermediate hydroxy compounds prepared from thioacetamide and halo ketones **1a—c** are subjected to dehydration into the corresponding thiazoles under much more drastic conditions. As mentioned above, our attempt to perform the acid-catalyzed dehydration of compound **2a** failed, and the thermal dehydration performed by heating in chlorobenzene afforded 2-methylthiazoloindole hydrobromide **3a** in low yield (12%).[15] In the present study, we made an attempt to perform dehydration of hydroxy compound **2a** under conditions similar to those favorable for this reaction to proceed by the E1cb-type mechanism. We succeeded in increasing the yield of thiazoloindole **7** to 62% (method *A*) by heating compound **2a** in a mixture of acetic anhydride and pyridine for 15 min (Scheme 3). Thiazoloindole **7** was also synthesized in lower yield (54%) by storage of compound **2a** in a mixture of thionyl chloride and triethylamine in dioxane (method *B*).

The structures of the resulting compounds were confirmed by IR spectroscopy, mass spectrometry, ^{1}H NMR spectroscopy, and elemental analysis (Tables 1—3). The

Scheme 3



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IR spectra of compounds **5a,b,e—g**, **6b,d—f**, and **7** show characteristic absorption bands of OH, NH, C=N, and N—COMe groups, whose positions are consistent with the known data. The EI mass spectra were studied for compounds **5b** and **6b**. Compound **5b** was also characterized by the fast atom bombardment (FAB) mass spectrum. The EI mass spectrum of thiazole **6b** has the intense peaks $[M]^+$ (*m/z* 251) and $[M - PhCH_2CN]^+$ (*m/z* 134). The EI mass spectrum of hydroxythiazoline **5b** has, along with the molecular ion peak $[M]^+$ (*m/z* 269), the peak $[M - H_2O]^+$ (*m/z* 251) with approximately equal intensity, as well as the peaks $[M - PhCH_2CN]^+$ (*m/z* 152), $[M - PhCH_2CN - H_2O]^+$ (*m/z* 134), $[PhCH_2CNH]^+$ (*m/z* 118), $[PhCO]^+$ (*m/z* 105), $[C_7H_7]^+$ (*m/z* 91), and $[Ph]^+$ (*m/z* 77). In the mass spectrum of compound **5b** measured with use of the soft ionization method (FAB), the quasimolecular ion peak $[MH]^+$ (*m/z* 270) and the peak $[M - H_2O]^+$ (*m/z* 252) have the maximum intensity (see Table 1).

The presence of the asymmetric C(4) atom in hydroxythiazolines **5b,d—f** results in the nonequivalence of the geminal protons (2 H) at position 5 of the heterocyclic moiety and the protons of the CH_2 group of the substituent at the C(2) atom. As a result, the signals for these protons in the ^{1}H NMR spectra of hydroxythiazolines are observed as an AB system with the spin-spin coupling constants ^2J ~12.5 and 15.5 Hz, respectively (see Table 2). The ^{1}H NMR spectrum of compound **5g** is characterized by the presence of two sets of analogous signals in a ratio of ~2 : 1, which correspond to protons of two conformers with respect to the N—COMe amide bond (see Table 3).

The above-considered data allowed us to make conclusions about the influence of the structures of α-halo ketones and thioamides on the ease of the Hantzsch reaction and about the optimal conditions for the thiazole synthesis. It was found that thioacetamide and thioamides of aromatic and heterocyclic acids are transformed into 4-hydroxy-Δ^2-thiazolines rather than into thiazoles (Hantzsch reaction products) in the reactions with such α-halo ketones as trifluorobromoacetone **1a**, bromoindoxyl **1b**, and bromoacetophenone **1c**. To the contrary, the reactions of the same α-halo ketones with thioamides of phenylacetic, diphenylacetic, 3-indolylacetic, and cyanoacetic acids produce thiazoles. In the former case, the abnormal course of the Hantzsch reaction is attributed to the fact that 4-hydroxy-Δ^2-thiazolines, which are intermediates in the thiazole synthesis, undergo virtually no dehydration under these conditions (except for 4-hydroxy-2-methyl-4-phenyl-Δ^2-thiazoline, which undergoes dehydration, though under more drastic conditions). The ease of dehydration of hydroxythiazolines under the conditions of the thiazole synthesis and the possibility of the spontaneous thiazole synthesis were demonstrated to depend on the nature of the substituent at position 2 and,

Table 2. ^{1}H NMR spectroscopic data for hydroxythiazolines **5b,d—f** and thiazoles **6b,d—f**

Compound	δ (*J*/Hz)				
	4-OH (s, 1 H)	5-H (H_2)	2-CH (H_2)	4-R^1	R^2 (R^3)
5b	6.65	3.48, 3.35* (1 H each, ^2J = 12.0)	3.93, 3.91* (1 H each, ^2J = 15.3)	7.25—7.45 (m, 5 H)	7.25—7.45 (m, 5 H)
5d	6.60	3.42, 3.29* (1 H each, ^2J = 12.0)	4.04, 3.98* (2 H each, ^2J = 15.8)	7.25—7.45 (m, 5 H)	10.98 (s, NH); 6.95—7.55 (5 H, indole)
5e	6.72	3.51, 3.39* (1 H each, ^2J = 12.2)	5.44 (s, 1 H)	7.25—7.45 (m, 5 H)	7.25—7.45 (m, 10 H)
5f	7.50	3.61, 3.30* (1 H each, ^2J = 12.8)	3.92 (s, 2 H)	—	7.25—7.35 (m, 5 H)
6b	—	7.95 (s, 1 H)	4.38 (s, 2 H)	7.94 (d, 2 H, *J* = 8.0); 7.36 (m, 3 H)	7.41, 7.35 (both m, 2 H each); 7.26 (m, 1 H)
6d	—	7.87 (s, 1 H)	4.47 (s, 2 H)	7.95 (d, 2 H, *J* = 8.0); 7.42 (t, 2 H); 7.32 (t, 1 H)	11.03 (s, NH); 6.95—7.50 (m, 5 H, indole)
6e	—	8.03 (s, 1 H)	6.03 (s, 1 H)	7.91 (d, 2 H, *J* = 8.0); 7.25—7.45 (m, 3 H)	7.25—7.45 (m, 10 H)
6f	—	8.34 (s, 1 H)	4.40 (s, 2 H)	—	7.20—7.40 (m, 5 H)

* The AB system.

Table 3. ^{1}H NMR spectroscopic data for a mixture of the major (**5g$_{maj}$**) and minor conformers (**5g$_{min}$**) of 4-acetyl-2-benzyl-8b-hydroxy-3a,8b-dihydro-2*H*-thiazolo[5,4-*b*]indole **5g**

Compound	δ (*J*/Hz)				
	H(6)—H(8) (m)	H(5)	H(3a) (s)	C(2)H$_2$	NCOMe (s)
5g$_{maj}$	7.15—7.55	8.06 (d)	6.32	3.84, 3.79 (q, 2 H, ^2J = 16.0)	2.17
5g$_{min}$	7.15—7.55	7.15—7.55	5.80	3.77 (br)	2.40

consequently, on the structure of the starting thioamide. The Me, Ar, and Het substituents impede dehydration, whereas substituents containing the α-methylene (methine) unit at the C(2) atom substantially facilitates this process.

To summarize, we developed a two-step procedure for the preparation of thiazoles and 2-R-thiazolo[5,4-*b*]indoles, whose synthesis is difficult or impossible under the standard conditions. The first step resulting in the formation of hydroxythiazolines can be performed under rather mild conditions (see above), whereas the second rate-determining step should be carried out either under drastic conditions of acid catalysis (for example, according to the procedure described earlier[13] by prolonged heating in toluene in the presence of *p*-toluenesulfonic acid) or under conditions favorable for dehydration of intermediate hydroxythiazolines by the E1cb-type mechanism (in the presence of an appropriate base accompanied by the transformation of the hydroxy group into a good leaving group). In our opinion, the latter approach is preferable. For example, it is known that 2-methyl-4-phenylthiazole **6a** is produced by the Hantzsch reaction not only under acid catalysis but also in the presence of alkalis.[12] Apparently, the modification of this method would also be useful when the Hantzsch reaction is inhibited in an acidic medium.

Experimental

The elemental analysis for C, H, N, S was carried out on an EA-1108 analyzer (CHNS/O, TDK detector). The ^{1}H NMR spectra were measured on a Varian Unity+400 spectrometer (400 MHz) in DMSO-d$_6$. The EI mass spectra were obtained on a Finnigan SSQ-710 instrument by the direct injection of samples into the ion source (the ionizing electron energy was 70 eV, the temperature of the ionization chamber was 150 °C, samples were heated to 350 °C, the heating rate was 163 deg min^{-1}) and by the FAB method in the *o*-nitrobenzyl alcohol matrix (xenon as the ionization gas). The IR spectra were recorded on a Perkin—Elmer 457 instrument (Nujol mulls). The course of the reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates (before chromatography of compounds **5a,b,d,e**, the plates were kept in Et$_3$N vapor for 3 min) using a 20 : 1 : 3 chloroform—acetone—hexane mixture as the eluent; visualization was carried out with UV light and iodine vapor. The melting points of compounds **3b**[15] and **6c**[18] are consistent with those described earlier.

2-(R^{3}R^{4}CH)-4-R^1-4-Hydroxy-Δ^2-thiazolines (5a,b,d—f), 4-acetyl-2-benzyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indole (5g), and 2-cyano-4-phenylmethylthiazole (6c) (general procedure). Method *A*. Bromo ketone **1a—c** (10 mmol) was added to a solution of the corresponding thioamide **4a—e** (10 mmol) and Et$_3$N (2.02 g, 20 mmol) in acetone (20 mL). The reaction solution was stirred at 20 °C for 30 min and then diluted with water (30 mL). The crystals that precipitated were filtered off, washed with aqueous acetone (1 : 1), and recrystallized from Pr^{i}OH, and compounds **5a,b,d—g** were obtained (see Tables 1—3). After dilution of the reaction mixture with water, thiazole **6c** was extracted with dichloromethane (3×15 mL). The extract was washed with water and dried with Na$_2$SO$_4$. The solvent was removed *in vacuo*, and the residue was recrystallized from a 5 : 1 petroleum ether—benzene mixture in the presence of activated carbon. Compound **6c** was obtained in a yield of 1.12 g (55%), m.p. 42—44 °C (*cf.* lit. data[18]: m.p. 42—44 °C). Found (%): C, 65.91; H, 4.08; N, 13.89; S, 15.94. $C_{11}H_8N_2S$. Calculated (%): C, 66.00; H, 4.00; N, 14.00; S, 16.00. MS (FAB, 70 eV, *m/z*): 200 [M]$^+$.

Method *B*. A suspension of hydrobromide **2e** (1.50 g, 3.70 mmol) and NaOAc (0.61 g, 7.40 mmol) in dioxane (12 mL) and water (5 mL) was stirred without heating for 15 min. The resulting emulsion was diluted with water (30 mL) and stirred for 5 min. The precipitate was filtered off and washed with water. Compound **5g** was obtained in a yield of 1.03 g (86%).

4-R^1-2-(R^{3}R^{4}CH)-5-R^2-Thiazoles 6b,d—f (general procedure). Method *A*. Thioamide **4b,d,e** (10 mmol) was dissolved on heating in Pr^{i}OH (30 mL). Then compound **1a** (1.91 g, 10 mmol) or compound **1c** (1.99 g, 10 mmol) was added to the solution. The reaction mixture was refluxed for 3 min (in the case of **1a**, for 15 min) and cooled. Aqueous NH$_3$ was added to the reaction mixture to pH = 8, and then water (30 mL) was added. The crystals that precipitated were filtered off and recrystallized from Pr^{i}OH. The yields of compounds **6b**, **6d**, and **6e** were 2.13 g (85%), 2.35 g (81%), and 2.55 g (78%), respectively. In the case of thiazole **6f**, the solvent was removed *in vacuo* and the residue was recrystallized from aqueous Pr^{i}OH. Compounds **6b,d—f** were prepared (see Tables 1 and 2).

Method *B*. The corresponding 4-R^1-2-(R^{3}R^{4}CH)-hydroxy-Δ^2-thiazoline **5b,d—f** (5 mmol) and concentrated (d = 1.18 g mL^{-1}) HCl (0.45 mL, 5 mmol) in Pr^{i}OH (3.5 mL) were added to Pr^{i}OH (12 mL). The reaction solution was refluxed for 1 min (in the case of compound **5f**, for 15 min). Aqueous NH$_3$ was added to the reaction mixture to pH = 8, and then water (20 mL) was added. The crystals that precipitated were filtered off and washed with water. The yields of compounds **6b**, **6d**, **6e**, and **6f** were 1.00 g (80%), 1.23 g (85%), 1.36 g (83%), and 0.90 g (74%), respectively.

4-Acetyl-2-benzyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indole hydrobromide (2e). Bromo ketone **1b** (2.54 g, 10 mmol) was added to a solution of thioamide **4b** (1.51 g, 10 mmol) in acetone (30 mL) at 20 °C. The reaction mixture was stirred for 20 min. The crystals were filtered off and washed with acetone. Compound **2e** was obtained in a yield of 3.85 g (95%), m.p. 162—165 °C (decomp.). Found (%): C, 53.29; H, 4.20; N, 7.02; S, 7.98. $C_{18}H_{16}N_2O_2S \cdot HBr$. Calculated (%):

C, 53.33; H, 4.20; N, 6.91; S, 7.90. MS: (FAB, 70 eV, *m/z*): 324 $[M - HBr]^+$.

4-Acetyl-2-benzyl-4*H*-thiazolo[5,4-*b*]indole hydrobromide (3b). A solution of hydrobromide **2e** (1.00 g, 2.50 mmol) in Pr^iOH (15 mL) was refluxed for 5 min. The reaction mixture was concentrated to 5 mL, diluted with acetone (15 mL), and cooled to 10 °C. The crystals that precipitated were filtered off and washed with acetone. Compound **3b** was obtained in a yield of 0.92 g (95%), m.p. 195—197 °C (*cf.* lit. data[15]: m.p. 195—197 °C). Found (%): C, 56.01; H, 3.93; N, 7.17; S, 8.32. $C_{18}H_{14}N_2OS \cdot HBr$. Calculated (%): C, 55.81; H, 3.88; N, 7.24; S, 8.27. MS (FAB, 70 eV, *m/z*): 306 $[M - HBr]^+$.

4-Acetyl-2-methyl-4*H*-thiazolo[5,4-*b*]indole (7). Method *A*. Pyridine (5 mL) and 4-acetyl-2-methyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indole hydrobromide **2a** (5.50 g, 17.5 mmol) were successively added with stirring to Ac_2O (25 mL).[15] The reaction mixture was refluxed for 15 min and concentrated *in vacuo*. Water (30 mL) was added to the residue, and the reaction mixture was stirred at 25 °C for 45 min. The reaction product was extracted with dichloromethane (3×15 mL), and the extract was washed with water (20 mL). Dichloromethane was removed *in vacuo*. The residue was successively recrystallized from EtOH and a 1 : 1 heptane—benzene mixture. Compound **7** was obtained in a yield of 2.34 g (see Table 1).

Method *B*. Compound **2a** (3.15 g, 10 mmol) and Et_3N (3.03 g, 30 mmol) were added to dioxane (15 mL) at 25 °C. A solution of $SOCl_2$ (1.19 g, 10 mmol) in dioxane (5 mL) was added to the reaction solution for 3 min. The reaction mixture was stirred at ~20 °C for 30 min and then concentrated *in vacuo*. The residue was treated as described in the method *A*. Compound **7** was obtained in a yield of 1.17 g (54%).

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