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Synthesis and spectroscopic studies of some hydrogenated thiazolo[2,3-*a*]isoquinolines

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Abstract—Dihydro-5*H*-thiazolo[2,3-*a*]isoquinolinones (**1–6**) and tetrahydro-5*H*-thiazolo[2,3*a*]isoquinolines (**7–12**) have been prepared from 3,4-dihydroisoquinoline derivatives under the action of α-mercapto alkanoic acids or ethylene sulfide, respectively. In the synthesis of compounds **2** and **5** isothiocarbostril (**13**) and *N*-thioacetyl-β-phenylethylamine derivatives (**14**), respectively, were also used as substrates and treated with bromoacetic acid derivatives. Spectral characteristics (IR, ^{1}H, ^{13}C NMR and MS) of compounds **1–12** are presented. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Among many types of thiazoloazines, synthesized in aromatic and saturated forms, whose chemistry has been intensely investigated,[1,2] the thiazolo[2,3-*a*]isoquinoline ring system has attracted much less attention. This type of heterocycle has been interesting for us in connection with our study on the sulfur-mediated synthesis of isoquinoline alkaloids.[3,4] We anticipated that the corresponding thiazoloisoquinoline derivatives could be useful as potential intermediates in this synthesis, in particular a stereogenic sulfur could be attractive for the preparation of chiral non-racemic alkaloids. Since little information could be obtained on the partially reduced thiazolo[2,3-*a*]isoquinoline heterocyclic system, we have undertaken a systematic study to learn more about this class of compounds.

In this paper, we describe the synthesis of compounds **1–12** and discuss their spectral characteristics.

2. Results and discussion

2.1. Synthesis

Two series of thiazolo[2,3-*a*]isoquinolines have been synthesized: the carbonyl derivatives **1–6** with amide functionality and the corresponding tetrahydro-analogs **7–12** (Scheme 1).

Of the many methods worked out for the construction of the 4-thiazolidinone ring system,[5] the cyclo-condensation of α-mercapto alkanoic acids or esters with Schiff bases has

1 $R^1=R^2=R^3=H$
2 $R^1=OCH_3$, $R^2=R^3=H$
3 $R^1=R^2=H$, $R^3=CH_3$
4 $R^1=OCH_3$, $R^2=H$, $R^3=CH_3$
5 $R^1=OCH_3$, $R^2=CH_3$, $R^3=H$
6 $R^1=OCH_3$, $R^2=R^3=CH_3$

7 $R^1=R^2=H$
8 $R^1=OCH_3$, $R^2=H$
9 $R^1=H$, $R^2=CH_3$
10 $R^1=OCH_3$, $R^2=CH_3$
11 $R^1=H$, $R^2=C_6H_5$
12 $R^1=OCH_3$, $R^2=C_6H_3(OCH_3)_2$

Scheme 1.

Keywords: thiazolo[2,3-*a*]isoquinolines; synthesis; IR; ^{1}H NMR; ^{13}C NMR; MS.

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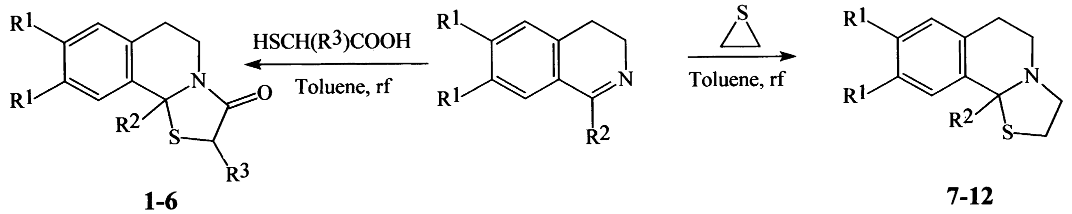
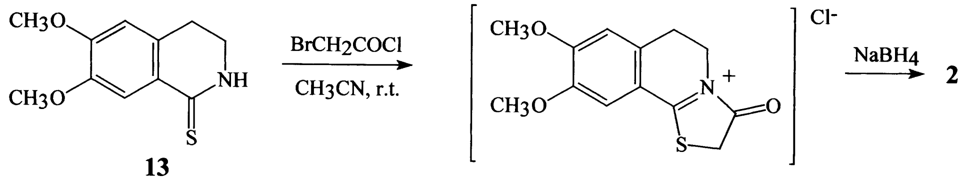


Scheme 2.



Scheme 3.

been frequently used, also for the preparation of the known thiazolo[2,3-*a*]isoquinolinones along with other methods.[6–13] In our experiments, in which 3,4-dihydroisoquinolines were treated with α-mercapto acids in toluene at reflux for 5–8 h, lactams **1–6** were obtained in satisfactory yields (Scheme 2). The mechanism of this reaction has been proven[7] to be a two-step process involving the preliminary formation of corresponding (isoquino-1-ylthio)acetic acid, dehydrated in the next step to afford the thiazoloisoquinolinones.

In a similar procedure, in which 3,4-dihydroisoquinoline was treated with ethylene sulfide[14,15] instead of the mercapto acid, derivatives **7–12** have been synthesized (Scheme 2). This reaction has also been postulated[14] to be a two-step process, involving an intermediate iminium salt formed by thiirane ring opening due to nucleophilic attack of the imine nitrogen, followed by cyclization.

Several of the prepared thiazolo[2,3-*a*]isoquinolines were obtained in crystalline form, others as sticky oils. These compounds, when dissolved in organic solvents (e.g. for crystallization or chromatographic separation) turned out to be highly unstable and partially decomposed to give complex mixtures, yet in the solid state these heterocycles seemed to be relatively stable. In the reactions in which α-mercapto acids were used for the synthesis of compounds with two stereogenic centers (**3**, **4**, **6**), no significant diastereoselectivity was observed. However, when for the synthesis of **3** and **4**, methyl thiolactate was applied instead of the corresponding acid, the diastereoselectivity increased from ca. 1.5 to 85% and ca. 8 to 57%, respectively, as shown by the ^{1}H NMR spectra of the crude reaction products. Several attempts undertaken to separate the diastereomers failed due to the instability of these compounds in solution.

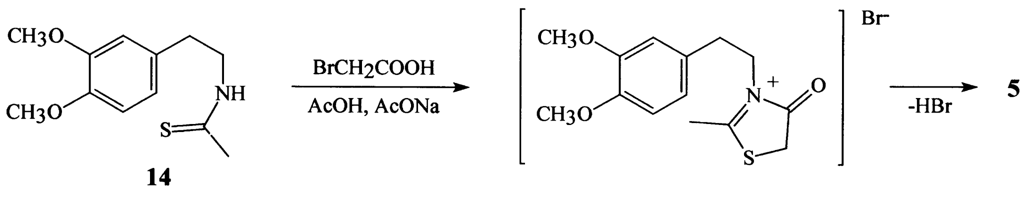
Compounds **2** and **5**, expected as the crucial intermediates *en route* to the isoquinoline alkaloids, have been prepared by two other methods, also in satisfactory yields. Compound **2** was obtained in a one-pot procedure involving addition of bromoacetyl chloride to 3,4-dimethoxydihydroisoquinolin-1-(2H)-thione (**13**) in acetonitrile at rt followed by sodium borohydride reduction of the intermediate acyliminium salt (Scheme 3).

In the synthesis of compound **5**, *N*-thioacetyl β-3,4-dimethoxyphenylethylamine (**14**), prepared from the corresponding *N*-acetyl derivative under the action of Lawesson reagent, was the substrate. Upon treatment with bromoacetic acid in acetic acid in the presence of sodium acetate, at reflux for 1 h, it was smoothly transformed into product **5**[13] (Scheme 4).

2.2. Spectral characteristics

IR spectra. The amide carbonyl absorption in IR spectra of compounds **1–6** was found in the region between 1670–1683 cm^{-1}.

^{1}H NMR spectra. Table 1 contains the proton NMR spectral data of thiazolino[2,3-*a*]isoquinolines **1–12**. In the spectra recorded in standard conditions, several features characteristic of all the thiazoloisoquinolines investigated can be found. Thus, they display resonance of the C-10b substituent. The H-10b benzylic proton in lactams appears as a singlet around 5.9–6.0 ppm while in the tetrahydro-derivatives in a more shielded region 5.7–5.8 ppm. The



Scheme 4.

Table 1. ^{1}H NMR spectral data of thiazolo[2,3-*a*]isoquinolines δ (ppm), J (Hz)

No.	H-2β [CH$_3$-2β]	H-2α [CH$_3$-2α]	H-3	H-3′	H-5a	H-5e	H-6ψa	H-6ψe	H-10b [CH$_3$-10b]
1[a]	3.84 (d, J=15.4)	3.61 (d, J=15.4)	–	–	3.11–3.21 (m)	4.40–4.47 (m)	2.77–2.85 (m) 2.97–3.08 (m)		6.05
2[b]	3.83 (d, J=15.4)	3.62 (d, J=15.4)	–	–	3.11[c] J=12.2 J=12.2 J=3.8	4.43[d] J=12.2 J=5.6 J=1.8	2.96[d] J=13.7 J=12.2 J=5.6	2.68–2.73 (m)	6.01
2[e]	4.45 (q, J=9)		–		2.50–3.40 (m)				6.05
3[f]	4.04 (q, J=6.87)	[1.52] (d, J=6.87)	–	–	3.15[d] J=12.7 J=10.2 J=4.1	4.43[d] J=12.7 J=5.5 J=2.2	2.77–2.85 (m) 2.94–3.07 (m)		5.98
4[f]	4.03 (q, J=6.87)	[1.53] (d, J=6.87)	–	–	3.06–3.19 (m)	4.39–4.48 (m)	2.67–2.73 (m) 2.89–3.01 (m)		5.93
5[b]	3.85 (d, J=15.4)	3.63 (d, J=15.4)	–	–	3.16[d] J=13.2 J=12.3 J=4.3	4.43[d] J=13.2 J=6.0 J=1.4	2.96[d] J=16.0 J=12.3 J=6.0	2.68[d] J=16.0 J=4.3 J=1.4	[1.95]
5[g]	3.08–3.85 (m)	3.63 (d, J=15.6)	–	–	3.14–3.17 (m)	4.40–4.51 (m)	2.91–2.98 (m)	2.66–2.71 (m)	[1.95]
6[b,f]	[1.66] (d, J=7.1) 3.92 (q, J=7.1)		–	–	3.25[c] J=12.8 J=12.8 J=4.4	4.42[d] J=12.8 J=6.4 J=1.3	2.60–2.72 (m) 2.87–3.04 (m)		[1.97]
7[a,b]	2.79–2.83 (m) 3.02–3.14 (m)		2.71[d] J=10.4 J=8.9 J=5.8	2.86–2.91 (m)	3.56[c] J=11.3 J=11.3 J=6.6	3.12–3.21 (m)	3.25[c] J=10.7 J=10.7 J=7.1	3.02–3.14 (m)	5.78
8[a]	3.01–3.12 (m) 2.64–2.70 (m)		2.84[d] J=14.6 J=11.2 J=3.9	2.64–2.70 (m)	3.49–3.61 (m)	3.14–3.28 (m)	3.18–3.28 (m)	3.01–3.12 (m)	5.72
9	2.78–2.83 (m)		3.04–3.20 (m)	2.70[h] J=15.6 J=2.8 J=2.8	3.67[d] J=12.8 J=10.5 J=7.3	3.48[d] J=12.8 J=6.9 J=1.4	3.26[c] J=10.3 J=10.5 J=6.9	3.04–3.20 (m)	[1.89]
10[a]	3.00–3.05 (m)	2.60[h] J=15.4 J=2.6 J=2.6	2.78–2.82 (m)		3.67[d] J=12.8 J=10.6 J=7.3	3.48[d] J=12.8 J=6.9 J=1.4	3.27[c] J=10.2 J=10.6 J=6.9	3.08[d] J=10.2 J=7.3 J=1.4	[1.78]
11	2.80–3.45 (m)								6.76–7.81 (m)
12	2.71–3.32 (m)								6.77 (d, J=8.5) 7.28 (d, J=2.2) 7.41 (dd, J=8.5, 2.2)

[a] Determined by HETCOR measurement.
[b] Determined by NOE difference spectroscopy.
[c] dt.
[d] ddd.
[e] Data from Ref. 11.
[f] Spectral data of the major isomer.
[g] Data from Ref. 13.
[h] td.

protons of C-10b methyl substituent resonate as singlets around 1.9 ppm, and protons of the aromatic C-10b substituent in **12** can be identified in the aromatic region.

The methylene group protons of the five-membered lactam ring are nonequivalent and give rise to two doublets centered at 3.6 and 3.8 ppm, respectively, with a geminal coupling constant J=15.4 Hz. A NOE difference experiment for lactam **2**, which shows the interaction between the H-10b proton (6.01 ppm) and that located at 3.83 ppm (H-2β) [and also with the one at 3.11 ppm, axial H-5], allowed identification of the protons to which the lower-field doublets correspond, on the same face of the molecule as the H-10b proton, for which a pseudo-axial orientation has been previously established by X-ray crystal analysis.[16]

The steric orientation of the four ethylene bridge protons of the six-membered isoquinoline moiety in lactams **1**–**6** can be easily assigned because of a nearly first-order AMX system present in the spectra of these compounds. Absorption of one of them, shifted by more than 1.5 ppm downfield from the others, was particularly useful for the assignment. Inspection of Dreiding models revealed that the H-5 equatorial proton falls within the deshielding zone of the amide carbonyl. This finding was additionally confirmed by the values of the three coupling constants, indicating the geminal, equatorial–pseudoaxial and equatorial–pseudoequatorial relationships with neighboring protons, respectively.

In the spectra of hydrogenated-derivatives **7**–**12** interchange of the chemical shifts between the C-5 methylene group protons seems to result from changes in the conformation of the six-membered isoquinoline ring as compared with that of lactams **1**–**6**. Signals of the ethylene group protons of the five-membered ring overlap with those assigned to the isoquinoline moiety, forming ill-defined multiplets, unsuitable for interpretation, particularly in the case of compounds **11**, **12**. However, correlations given in Table 1 for compounds **7**–**10** were achieved in few cases with the help of HETCOR and NOE measurements and on the basis of fragments of the spectra, from which ^2J and ^3J values and splitting patterns could be established.

The two *para*-oriented H-7 and H-10 aromatic protons in the spectra of the compounds with methoxy substituents appear as singlets at 6.60–6.78 ppm, being shifted upfield as compared with the aromatic multiplets (6.78–7.81) of the unsubstituted analogs.

A series of long-range couplings over five bonds (1.0–1.4 Hz) is observed in the spectra of lactams **1**–**6**. A decoupling experiment with lactam **2** of established conformation, indicates a coupling between the H-10b and both C-2 methylene group protons on the one hand, and H-2β and H-5 axial protons on the other. In the spectrum of compound **5** with C-10 substituent, however only the long-range coupling between the H-2β and H-5 axial proton is present. The splitting pattern of the H-2 methine proton absorption in spectra of **3** and **4** (the major diastereomers), which is similar to that of the H-2β proton in **2**, implies the α-orientation of the C-2 methyl group. Another long-range coupling between the C-6 methylene group protons and aromatic ring protons is also evident and the signals are particularly well shaped in the 8,9-dimethoxy substituted derivatives.

^{13}C NMR spectra. The ^{13}C NMR spectral data of selected thiazolo[2,3-*a*]isoquinolines are listed in Table 2. The signals were assigned on the basis of HETCOR measurements and are in accordance with values expected on the basis of chemical shift considerations and literature data.[17,18] Resonances of C-2, C-3 and C-10b carbon nuclei of the fused heterocyclic ring system in the spectra of lactams **1**, **2** are found in the region characteristic of other thiazolidinone derivatives,[17] with a downfield shift of the C-10b carbon in **5**, due to the deshielding effect of the attached methyl substituent (a similar situation exists in the case of compound **10**). The ethylene bridge C-5 and C-6 carbons resonate in the area described for tetrahydroisoquinoline derivatives.[18] The HETCOR spectra of **1**, **2**, **5** additionally support these findings by showing a coupling between the C-5 carbon and the characteristic low-field equatorial H-5 hydrogen.

A comparison of the spectral data of hydrogenated analogs **7**, **8**, **10** with those of the amides **1**, **2**, **5** shows, as expected, that the C-2 carbons are shifted upfield by ca. 5 ppm, while the two methylene groups C-5, C-6 and methine C-10b carbons are deshielded by ca. 21.0, 4.0 and 13.0 ppm, respectively.

Mass spectra. Mass spectral data of compounds **1**–**12** are presented in Table 3 and Scheme 5. The electron impact mass spectra of all the thiazolo[2,3-*a*]isoquinolines studied

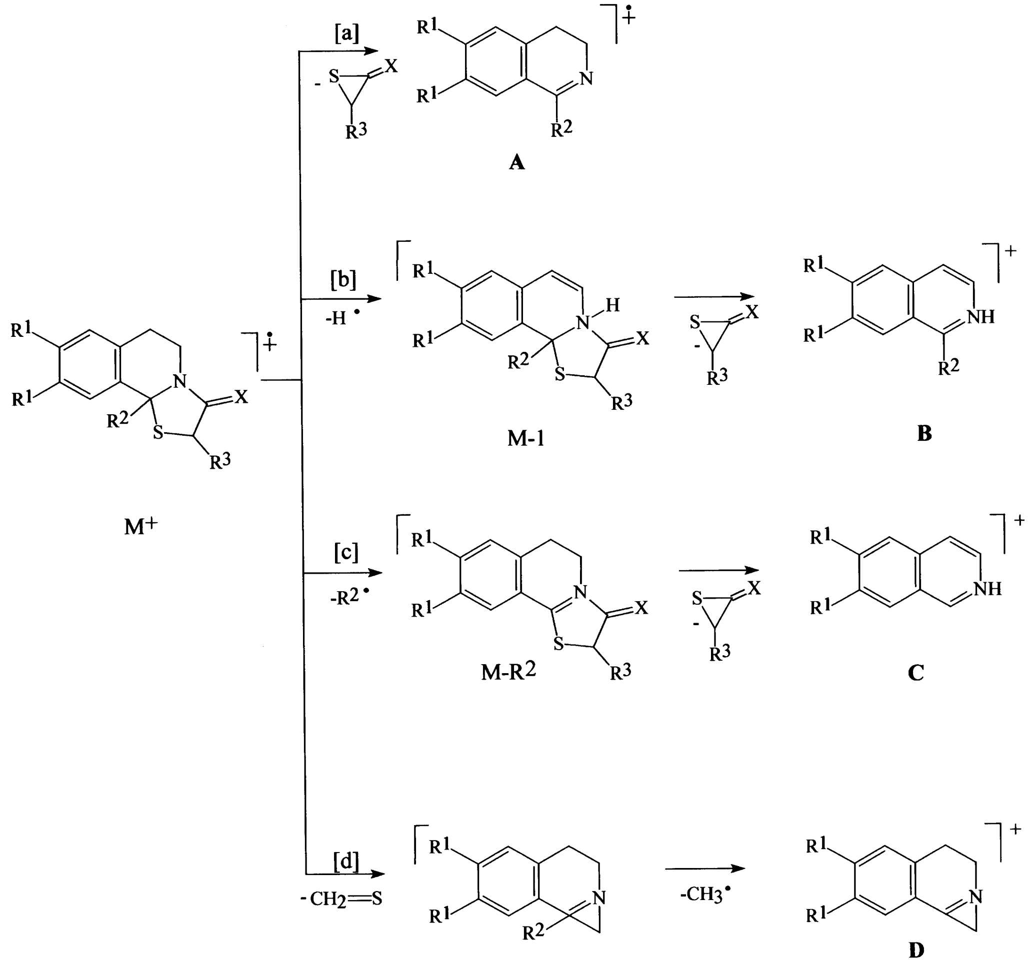
Table 2. ^{13}C NMR spectral data of representative thiazolo[2,3-*a*]isoquinolines δ (ppm)

No.	C-2	C-3	C-5	C-6	C-6a and C-10a	C-7 and C-10	C-8 and C-9	C-10b
1	33.99	169.79	39.63	28.13	133.27 135.29	125.57, 127.13 127.84, 129.0	125.57, 127.13 127.84, 129.0	59.34
2	33.96	169.75	39.68	27.66	148.45 148.74	108.14 111.57	125.39 126.90	59.23
5	33.88	169.29	36.71	27.76	148.44 148.65	108.04 110.34	125.58 126.77	68.03
7	29.34	43.86	60.58	32.38	132.72 133.89	126.06, 127.19 127.34, 128.53	126.06, 127.19 127.34, 128.53	73.29
8	28.92	43.98	60.44	32.29	147.46 148.16	109.86 111.04	124.92 125.82	73.35
10	29.31	47.39	58.95	32.72	124.18 132.04	110.11 110.67	147.68 147.74	81.58

Table 3. Mass spectral data of thiazolo[2,3-*a*]isoquinolines *m*/*z* (%)

No.	R^1	R^2	R^3	X	M^+	$(M-1)^+$	$(M-R^2)$	$M-(SCHR^3CX)$	$(M-1)-(SCHR^3CX)$	$(M-R^2)-(SCHR^3CX)$	$M-(CH_2S)$	$(M-1)-(SCH_2)$	$(M-R^2)-(SCH_2)$
1	H	H	H	O	205 (90)	204 (37)	–	131 (37)	130 (100)	–	–	–	–
2	CH_3O	H	H	O	265 (100)	264 (56)	–	191 (29)	190 (76)	–	–	–	–
3	H	H	CH_3	O	219 (89)	218 (49)	–	131 (58)	130 (100)	–	–	–	–
4	CH_3O	H	CH_3	O	279 (100)	278 (68)	–	191 (58)	190 (92)	–	–	–	–
5	CH_3O	CH_3	H	O	279 (16)	278 (>1)	264 (100)	205 (10)	204 (18)	190 (11)	–	–	–
6	CH_3O	CH_3	CH_3	O	293 (11)	292 (>1)	278 (100)	205 (7)	204 (13)	190 (10)	–	–	–
7	H	H	H	H_2	191 (100)	190 (64)	–	131 (25)	130 (93)	–	145 (22)	144 (9)	144 (9)
8	CH_3O	H	H	H_2	251 (84)	250 (100)	–	191 (66)	190 (66)	–	205 (11)	204 (2)	204 (2)
9	H	CH_3	H	H_2	205 (100)	204 (19)	190 (37)	145 (22)	144 (91)	130 (19)	159 (21)	158 (19)	144 (91)
10	CH_3O	CH_3	H	H_2	265 (62)	264 (28)	250 (12)	205 (100)	204 (68)	190 (51)	219 (8)	218 (7)	204 (68)
11	H	C_6H_5	H	H_2	267 (67)	266 (17)	190 (6)	207 (52)	206 (100)	130 (2)	221 (7)	220 (26)	–
12[a]	CH_3O	$(CH_3O)_2C_6H_3$	H	H_2	388 (M+1)	–	–	–	–	–	–	–	–

[a] M^+ ion was determined by FAB technique.



Scheme 5.

reveal the presence of stable molecular ions of high abundance, except for compounds **5** and **6**, which due to easy elimination of methyl radical (leading to $M-R^2$ base peak) give M^+ ions of low intensity. In the spectra of all other compounds, the main fragmentation pathway is associated with the formation of isoquinolinium ions B (Scheme 5, path [b]). These ions of significant abundance may be formed by the loss of hydrogen atom to give $[M-1]^+$ cations, which subsequently undergo retro-cycloaddition with elimination of $SCHR^3CX$ molecule. A parallel fragmentation process, leading to isoquinolinum ions C (Scheme 5, path [c]) is also evidenced in the spectra; the R^2 substituent is eliminated prior to the retro-cycloaddition step giving $[M-R^2]^+$ ions. Abundant fragment ions corresponding to the dihydroisoquinolinium structure A (Scheme 5, path [a]), resulting from elimination of $SCHR^3CX$ molecule from M^+ ions, can also be found in the spectra of all the compounds investigated.

In the spectra of the tetrahydro-derivatives **7–12**, fragment ions resulting from elimination of thioformaldehyde from M^+, $[M-1]^+$ and $[M-R^2]^+$ ions, respectively, are observed (Table 3). The heterocycles **1–6** with amide functionality do not suffer such a fission, indicating greater stability of this type of ring system, observed also in other experiments. The structure of the fragment ions of the *m/z* 144 and *m/z* 204, found in the spectra of compounds **9** and **10**, respectively, could be presented either by formula B or D. The latter may arise from the molecular ions by the loss of thioformamide followed by methyl radical (Scheme 5, path [d]). Measurement of the metastable ions during the mass fragmentation of compound **10** revealed that both pathways are involved.

3. Conclusion

Two series of partially reduced thiazolo[2,3-*a*]isoquinolines (**1–12**) have been synthesized and their spectroscopic properties described.

For preparation of dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-ones (**1–6**) three different synthetic methods were applied in which 3,4-dihydroisoquinoline, isothiocarbostiril and *N*-thioacetyl-β-phenylethylamine derivatives, respectively, were used as the main building blocks. The corresponding tetrahydro-analogs **7–12** were obtained from 3,4-dihydroisoquinolines and ethylene sulfide.

Careful analysis of the spectral data (IR, NMR and MS) of the thiazolo[2,3-*a*]isoquinolines, compounds which had not been investigated systematically as yet, revealed several spectral features which may be considered as characteristic of this class of heterocycles.

4. Experimental

4.1. General

Melting points were determined on a Koffler block and are not corrected. IR spectra were recorded on Perkin–Elmer 180, in KBr pellets. NMR spectra were taken in $CDCl_3$ on Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.45 MHz), with TMS as internal standard. Mass spectra (EI) and FAB techniques were obtained by using Joel D-100, 75 eV. For FAB-mass spectra, 3-nitrobezyl alcohol was used as a matrix. Merck Silica gel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Silica gel 60_{254} for TLC.

4.2. Synthesis of 6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-ones (1–6). General procedure

α-Mercapto alkanoic acid, or ester, (3.3 mmol) was added to a solution of 3,4-dihydroisoquinoline (3.14 mmol) in dry toluene (40 ml) or xylene in the case of compound **6**, under an argon atmosphere. The reaction mixture was refluxed with azeotropic removal of water for 5–9 h (TLC monitoring). After evaporation of the solvent the residue was dissolved in dichloromethane, washed with 5% NaOH, 5% HCl, water and dried. The solvent was evaporated to give crude product, which was purified by crystallization or column chromatography on silica gel eluting with dichloromethane.

4.2.1. 6,10b-Dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (1). Yield 65%; crystals, mp 80–83°C (from diethyl ether/hexane), (lit.[10] 92–93°C, from benzene); IR (cm^{-1}): 1671; HRMS: calcd for $C_{11}H_{11}NOS$ (M^+): 205.05614, found: 205.05728.

4.2.2. 8,9-Dimethoxy-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (2). Yield 87%; crystals, mp 160–162°C (from ethanol), (lit.[11] 173–174°C); IR (cm^{-1}): 1670; HRMS: calcd for $C_{13}H_{15}NO_3S$ (M^+): 265.07727, found: 265.07770.

4.2.3. 2-Methyl-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (3). Mixture of two diastereoisomers, d.e. 85%, Yield 57%; major isomer; crystals, mp 75–78°C (from diethyl ether), (lit.[10] 105–107°C, from 2-propanol); IR (cm^{-1}): 1677; HRMS: calcd for $C_{12}H_{13}NOS$ (M^+): 219.07179, found: 219.07041.

4.2.4. 8,9-Dimethoxy-2-methyl-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (4). Mixture of two diastereoisomers, d.e. 57%; Yield 62%; major isomer; oil, (lit.[10] 184–186°C from ethanol); IR (cm^{-1}): 1683; HRMS: calcd for $C_{14}H_{17}NO_3S$ (M^+): 279.09293, found: 279.09164.

4.2.5. 8,9-Dimethoxy-10b-methyl-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (5). Yield 67%; crystals, mp 124–125°C (from toluene/hexane), (lit.[13] 129–130°C); IR (cm^{-1}): 1674; HRMS: calcd for $C_{14}H_{17}NO_3S$ (M^+): 279.09293, found: 279.09381.

4.2.6. 8,9-Dimethoxy-2,10b-dimethyl-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (6). Mixture of two diastereoisomers, d.e. 6%; Yield 67%; major isomer; oil; IR (cm^{-1}): 1675; HRMS: calcd for $C_{15}H_{19}NO_3S$ (M^+): 293.10855, found: 293.10876.

4.3. Synthesis of 2,3,6,10b-tetrahydro-5*H*-thiazolo[2,3-*a*]isoquinolines (7–12). General procedure

To a solution of 3,4-dihydroisoquinoline (3.14 mmol) in dry toluene (40 ml) was added ethylene sulfide (0.37 ml, 6.2 mmol) and the mixture was refluxed for 30 h. After evaporation of the solvent, the residue was dissolved in dichloromethane, washed with 5% NaOH and dried. The solvent was evaporated to give crude product, which was chromatographed on a silica gel column eluting with dichloromethane.

4.3.1. 2,3,6,10b-Tetrahydro-5*H*-thiazolo[2,3-*a*]isoquinoline (7). Yield 85%; crystals, mp 83–84°C (from methanol/hexane); (lit.[8] 84–86°C, from benzene/ether 1:1); HRMS: calcd for $C_{11}H_{13}NS$ (M^+): 191.07687, found 191.07716.

4.3.2. 8,9-Dimethoxy-2,3,6,10b-tetrahydro-5*H*-thiazolo-[2,3-*a*]isoquinoline (8). Yield 86%; crystals, mp 117–118°C (from hexane/ethyl acetate); HRMS: calcd for $C_{13}H_{17}NO_2S$ (M^+): 251.09801, found: 251.09694.

4.3.3. 10b-Methyl-2,3,6,10b-tetrahydro-5*H*-thiazolo[2,3-*a*]isoquinoline (9). Yield 32%; oil; HRMS: calcd for $C_{12}H_{15}NS$ (M^+): 205. 09251, found: 205.09380.

4.3.4. 8,9-Dimethoxy-10b-methyl-2,3,6,10b-tetrahydro-5*H*-thiazolo[2,3-*a*]isoquinoline (10). Yield 66%; crystals, mp 139–140°C (from hexane/ethyl acetate); HRMS: calcd for $C_{14}H_{19}NO_2S$ (M^+): 265.11365, found: 265.11297.

4.3.5. 10b-Phenyl-2,3,6,10b-tetrahydro-5*H*-thiazolo[2,3-*a*]isoquinoline (11). Yield 68%; crystals, mp 101–103°C (from hexane); HRMS: calcd for $C_{17}H_{17}NS$ (M^+): 267.10818, found: 267.10556.

4.3.6. 8,9-Dimethoxy-10b-(3,4-dimethoxyphenyl)-2,3,6,10b-tetrahydro-5*H*-thiazolo[2,3-*a*]isoquinoline (12). Yield 20%; oil; HRMS: calcd for $C_{21}H_{26}NO_4S$ $(M+1)^+$: 388.15826, found: 388.16087.

4.4. Reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione with bromoacetyl chloride

A mixture of 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione (0.45 mg, 2 mmol) and bromoacetyl chloride (0.2 ml, 2.4 mmol) in dry acetonitrile (30 ml) was stirred at room temperature for 1 h. The solvent was evaporated and the residue was dissolved in methanol (10 ml) and sodium borohydride (0.2 g, mmol) was added portionwise at 0°C. The reaction mixture was stirred for 1 h at room temperature, then the solvent removed under reduced pressure and the residue treated with 5% aq. sodium hydroxide. The solution was extracted with dichloromethane, the extract washed with water, dried and solvent evaporated. The crude product was digested with diethyl ether to give pure compound **2** (0.39 g, Yield 73%).

4.5. Reaction of the *N*-thioacetyl-β-(3,4-dimethoxyphenyl)ethylamine with bromoacetic acid[13]

To a solution of *N*-thioacetyl-β-(3,4-dimethoxyphenyl)-ethylamine[19] (1.3 g, 5.4 mmol) in acetic acid (30 ml) was added bromoacetic acid (0.834 g, 6 mmol) and sodium acetate (0.615 g, 7.5 mmol) and the mixture was refluxed for 7 h. After evaporation of the solvent, the residue was dissolved in dichloromethane, washed with water and dried. The solvent was evaporated to give crude product (1.47 g, Yield 98%), which was purified by chromatography on a silica gel column, eluting with dichloromethane and crystallization, to give pure compound **5**.

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References

1. Katritzky, A. R. *Comprehensive Heterocyclic Chemistry*, 1984, Vol. 6, pp. 668–710.
2. Katritzky, A. R. *Comprehensive Heterocyclic Chemistry II*, 1996, Vol. 8, pp. 280–285.
3. Representative example: Brózda, D. *Pol. J. Chem.* **1994**, *68*, 2665–2670.
4. Representative example: Chrzanowska, M.; Józkowiak, J.; Rozwadowska, M. D.; Sulima, A. *Pol. J. Chem.* **1998**, *72*, 2399–2404.
5. Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175–203.
6. Schneider, W.; Kämmerer, E. *Arch. Pharm.* **1966**, *299*, 847–857.
7. Nair, M. D.; Malik, P. A.; Mehta, S. R. *Indian J. Chem.* **1967**, *5*, 221–223.
8. Wimmer, T. L.; Day, F. H.; Bradsher, C. K. *J. Org. Chem.* **1975**, *40*, 1198–1201.
9. (a) Singh, H.; Lal, K. B.; Malhotra, S. C. *Indian J. Chem.* **1979**, *17B*, 4–6. (b) Singh, H.; Singh Bal, M. *Indian J. Chem.* **1979**, *18B*, 312–315. (c) Singh, H.; Lal, K. *J. Chem. Soc., Perkin Trans.* **1972**, 1799–1803.
10. Menendez, J. C.; Delgado-Iribarren, A.; Söllhuber, M. M. *An. Real Acad. Farm.* **1987**, *53*, 238–248.
11. Menendez, J. C.; Söllhuber, M. M. *Heterocycles* **1990**, *31*, 2065–2071.
12. Sheehan, S. M.; Beall, L. S.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4761–4764.
13. Padwa, A.; Beall, L. S.; Heidelbaugh, T. M.; Liu, B.; Sheehan, S. M. *J. Org. Chem.* **2000**, *65*, 2684–2695.
14. Potekhin, A. A.; Sokolov, W. W.; Ogloblin, K. A.; Esacov, S. M. *Khim. Geterocycl. Soedin.* **1983**, *6*, 776–785.
15. Sokolov, W. W.; Salfetnikowa, N.; Potekhin, A. A. *Zh. Org. Khim.* **1996**, *32*, 870–878.
16. Kosturkiewicz, Z.; Sulima, A. *Pol. J. Chem.* **1998**, *72*, 2500–2503.
17. Woolston, C. R. J.; Lee, J. B.; Swinbourne, F. *J. Magn. Reson. Chem.* **1993**, *31*, 348–351.
18. Hughes, D. W.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2252–2259.
19. Lete, E.; Collado, M. I.; Sotomayor, N.; Vicente, T.; Villa, M. J. *J. Heterocycl. Chem.* **1995**, *32*, 1751–1758.