Monatsh Chem (2009) 140:387–396
DOI 10.1007/s00706-008-0038-x

ORIGINAL PAPER

Formation of novel 1,3-thiazole- and 1,2-thiazole-fused aporphines and study on the simultaneously occurring benzothiazole–benzisothiazole-type isomerization

Attila Sipos · Sándor Berényi

Received: 9 May 2008 / Accepted: 4 July 2008 / Published online: 3 September 2008

Abstract The synthesis and acid-catalyzed rearrangement of novel thiazolomorphinandienes have been presented. An isomerization was observed simultaneously with the backbone transformation. An extensive study was performed to determine the major effects of the isomerization of 2′-alkyl- and aryl-substituted thiazoloapocodeines into 3′-alkyl- and arylisothiazoloapocodeines. The obtained results provided another practical example of the reversible benzisothiazole–benzothiazole-type isomerization emphasizing the determining role of the thermal effects in the occurrence of these isomerization products. The obtained experimental results and the proposed mechanism were in agreement with the calculated DFT data.

Keywords Alkaloids · Photochemistry · Density functional calculations · Heterocycles

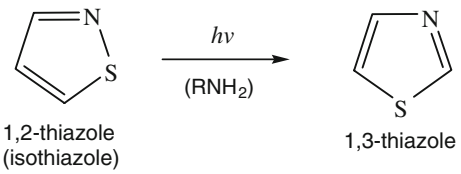
Introduction

In 1969 Lablache-Combier et al. [1] found that 1,2-thiazole (henceforth referred as isothiazole) photoisomerizes to 1,3-thiazole (henceforth referred as thiazole) in the presence of primary amines (Scheme 1).

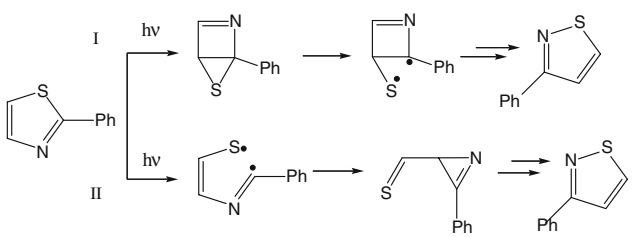
In the last decades the photoisomerization of thiazole moiety into isothiazoles [2–7] and isothiazoles to thiazole structures [8–12] became a widely studied area using different substitution patterns of these five-membered rings.

A general observation regarding the photoisomerization of pentaatomic aromatic heterocycles states that if the first excited singlet state of a molecule is populated, the molecule can convert into the corresponding triplet state or into the corresponding Dewar isomer (Scheme 2, first intermediate of Mechanism I). The efficiency of these processes will depend on energetic factors.

If the Dewar isomer is formed, the isomeric product is obtained. If the triplet state is formed, cleavage of the X–C_α bond can occur to give ring-opening products, decomposition products or ring contraction products. However, if the radical formed after the X–C_α cleavage shows a higher energy than the triplet state, the triplet state will not be able to give the biradical with high efficiency, and, then, it will be quenched in radiative and not radiative processes. In this case, the Dewar isomer could be responsible for the isomerization reaction, but the isomerized product will probably be produced in very low quantum yields.



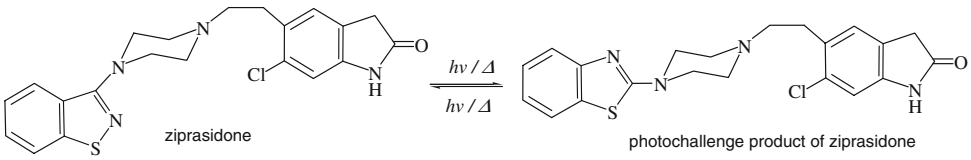
Scheme 1

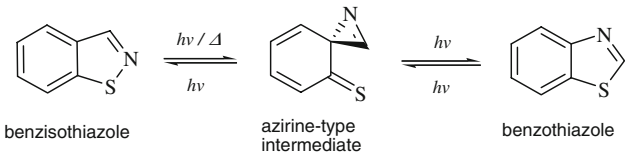


Scheme 2

A. Sipos (✉) · S. Berényi
Department of Organic Chemistry, University of Debrecen,
P.O. Box 20, 4010 Debrecen, Hungary
e-mail: asipos@puma.unideb.hu

Scheme 3





Scheme 4

In connection with the photo-induced isomerization of 2-phenylthiazole [2f] it was concluded that the singlet excited state could evolve, giving the Dewar thiazole (and then isothiazole according to Scheme 2, I. route), while the corresponding excited triplet state can be obtained. Furthermore, the triplet state cannot be converted into the biradical intermediates (Scheme 2, II. route) because these intermediates show a higher energy than the triplet state, thus preventing the formation of the cyclopropenyl derivatives.

A practical appearance of the isomerization of benzisothiazole moiety into the benzothiazole system was described by industrial researchers [13]. Sharp and colleagues investigated the photoisomerization of ziprasidone, an antipsychotic drug substance, and they observed the occurrence of a new compound having identical mass spectra with the one for the original compound. It was then proved that this phenomenon was caused by the photoisomerization of the benzisothiazole portion of ziprasidone (Scheme 3).

After the demonstration of the decisive role of benzisothiazole moiety in the formation of the photoisomerization product, the research group described a potential mechanism for the isomerization based on the pertinent literature [14] (Scheme 4).

The major step of this mechanism is the formation of an azirine. Sharp et al. emphasized the thermal dependence of this step; furthermore, it is also stressed that the complete isomerization process showed a significant thermal dependence. This conclusion was based on experimental results on photoconversion of a large scale of ziprasidone into the isomerization product. According to their observations, conversion was higher at elevated temperatures.

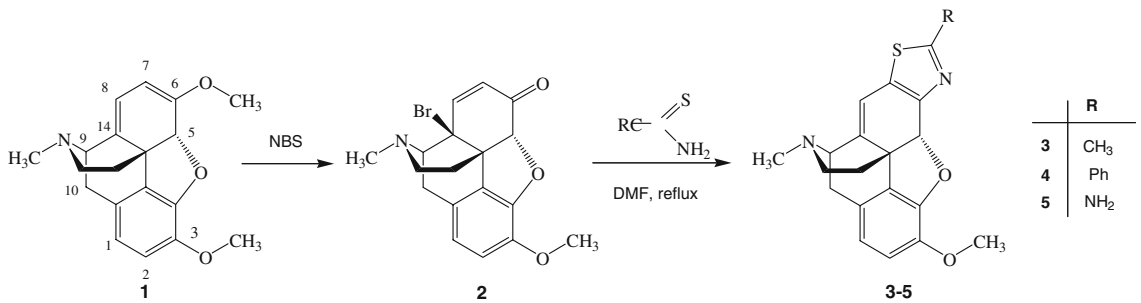
Results and discussion

Synthesis

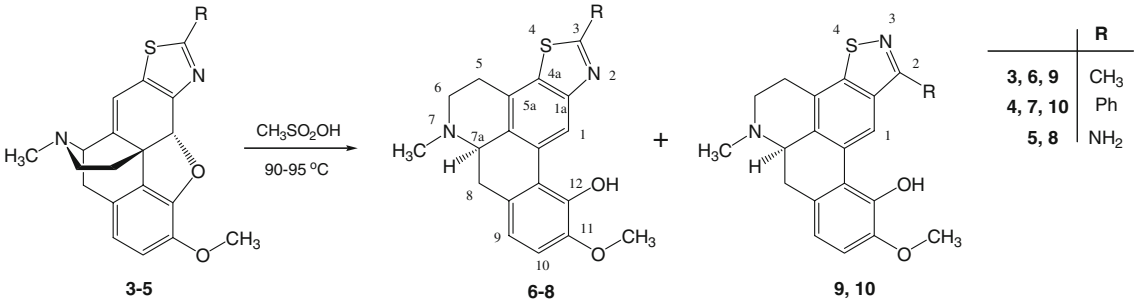
In one of our recent publications, we reported the synthesis of 2′-substituted thiazolomorphinandienes [15]. In the first step, thebaine (**1**) was converted into 14β-bromocodeinone (**2**) in a reaction with *N*-bromosuccinimide [16]. A Hantzsch-type thiazole synthesis was carried out to yield the aimed 2′-substituted thiazolomorphinandienes **3**–**5** (Scheme 5).

The morphinandiene structure of products **3**–**5** offered the possibility of rearrangement into compounds with aporphine backbone. This type of morphinandiene rearrangement has been studied in our laboratory for over 20 years [17–19], and it has been concluded that this reaction produces apocodeine derivatives almost quantitatively. In the acid-catalyzed rearrangement of compounds **3**–**5**, we observed different behaviour for compound **5**, and compounds **3**, **4** in point of the obtained products (Scheme 6).

In case of 2′-amino congener, the expected one-component crude product was obtained; however, in case of 2′-methyl and 2′-phenyl analogues, two-component reaction mixtures were found with components in approximately 1:1 ratio. After isolation and full ^{1}H- and ^{13}C- resonance assignments (obtained from COSY, TOCSY, HSQC and



Scheme 5



Scheme 6

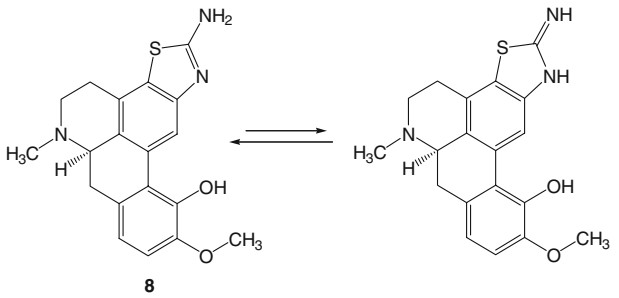


Fig. 1 Tautomer forms of 2′-aminothiazoloapocodeine (**8**)

HMBC spectra) of the products, it was revealed that in case of compounds **3** and **4** isothiazole-type apocodeines **9**, **10** were formed, beside the previously expected thiazoloaporphines **6**, **7**.

The explanation for the occurrence of isothiazoloaporphines **9**, **10** ('thiazoloaporphine' and 'isothiazoloaporphine' are used for simplification, for IUPAC names refer to the Experimental section) is an isomerization reaction that is simultaneous with the acid-catalysed rearrangement. The applied conditions for the acid-catalyzed rearrangement of the morphinandienes **3**, **4** were the following: 90–95 °C, polar solvent with strongly acidic character and no protection from light. These conditions are not in contradiction with those used by either Sharp et al. in their photoisomerization tests or other scientists studying photoisomerization of thiazoles and isothiazoles.

The reason for the difference in the behaviour of amino-derivative and its methyl- and phenyl-congeners could be justified via the significant willingness of 2-amino-benzothiazole moiety for tautomerization (Fig. 1).

The appearance of this imine-type tautomer means an extra stabilization for benzothiazole structure against benzisothiazole and may be an inhibitory effect of the isomerization.

Systematic study of isomerization

Initially, acid-catalysed rearrangement was repeated in inert atmosphere (nitrogen gas), but there was no significant change in the ratio of thiazolo- and isothiazolo-type products. In view of the above experimental results, our group decided to initiate an extensive study of the isomerization of 2′-phenylthiazoloapocodeine (**7**) into 3′-phenylisothiazoloapocodeine (**10**) to explore the photolytic and thermal dependences of this rearrangement. We aimed to investigate either the photoisomerization of the thiazoloapocodeine-type product in a variety of media or the effect of the application of different reaction conditions (i.e., application of microwave initiation) in comparison to the literature method for acid-catalyzed rearrangement[1] [20].

For rapid and accurate quantification of thiazolo- and isothiazoloapocodeines, a HPLC method was established on the basis methods for apomorphine. Aporphines were isolated from 0.5 ml of photoisomerization sample using a liquid–liquid extraction with diethyl ether. Analytes were separated on a 5-μm C18 Aquasil column (150 mm × 4.6 mm). The elution was achieved isocratically with a mobile phase of 2 mM·NH_4COOH buffer pH 3.8/acetonitrile (50/50, vol/vol) at a flow rate of 500 μl/min with UV detection at 254 nm. The average retention times for compounds **7** and **10** were found to be 5.9 and 6.6 min, respectively. The method was appropriately tested for specificity and accuracy prior to use for the analysis of different isomerization samples. After performing the irradiation of the samples, tests were carried out to determine the extent of decomposition and to demonstrate the appearance of the isothiazolo products. Representative chromatograms for the Et_2O extracts of two media (blank) and two photoisomerization samples are presented in Fig. 2.

[1] Provided the fundamental experimental method for the study of photoisomerization. Japanese scientists applied a Riko UVL-100HP (100 W) high-pressure mercury vapour lamp operated at wavelengths between 180 and 420 nm with a peak at 366 nm. Duration of the irradiation was 42 h. It means a total of 4,200 Wh of irradiation. In our photoisomerization studies the same quantity of irradiation was used.

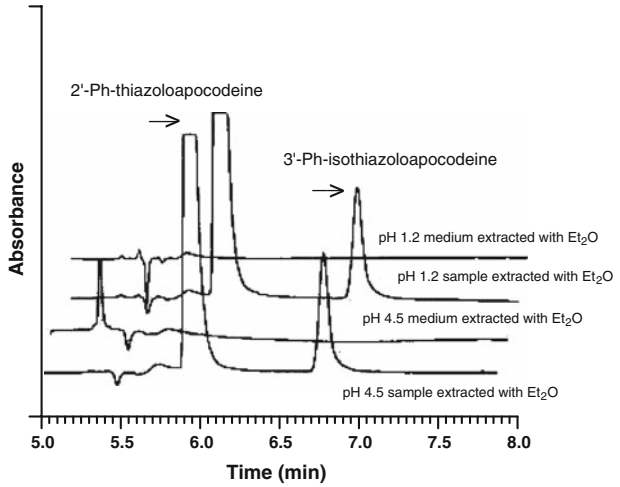


Fig. 2 Representative chromatograms for photoisomerization media and samples at pH 1.2 and 4.5

The first set of photoisomerization experiments was carried out in different media[2] with respect to their pH ranging from 1.2 to 10.0 at constant ambient temperature at an initial concentration of 0.5 mmol/l (the same as in Sharp's studies). We also applied the photoisomerization medium used by Sharp et al. (methanol:water = 3:2, pH = 5.5). The applied media was checked for interfering absorbancies in the range of the elution of the studied compounds, and there were no disturbing effects observed. The following graphs present the average results of three consecutive samplings and measurements (Fig. 3).

In the second step, we chose pH = 1.2 as a medium for the study of the thermal dependence of the isomerization. The reason for this decision was that the highest extent of isomerisation was observed at this pH, and the level of other decomposition products remained in an acceptable range. The elevated, constant temperature rearrangement studies of 2′-phenylthiazoloapocodeine (**7**) were performed at 35 and 50 °C (Fig. 4).

To protect reaction mixture from disturbing effects (i.e., atmospheric oxygen, sunshine, large amounts of heat), a novel method was developed involving microwave-initiated acid catalysis. Sample preparation was performed under inert atmosphere and protected from light. The microwave reactor maintained these conditions. The product mixture

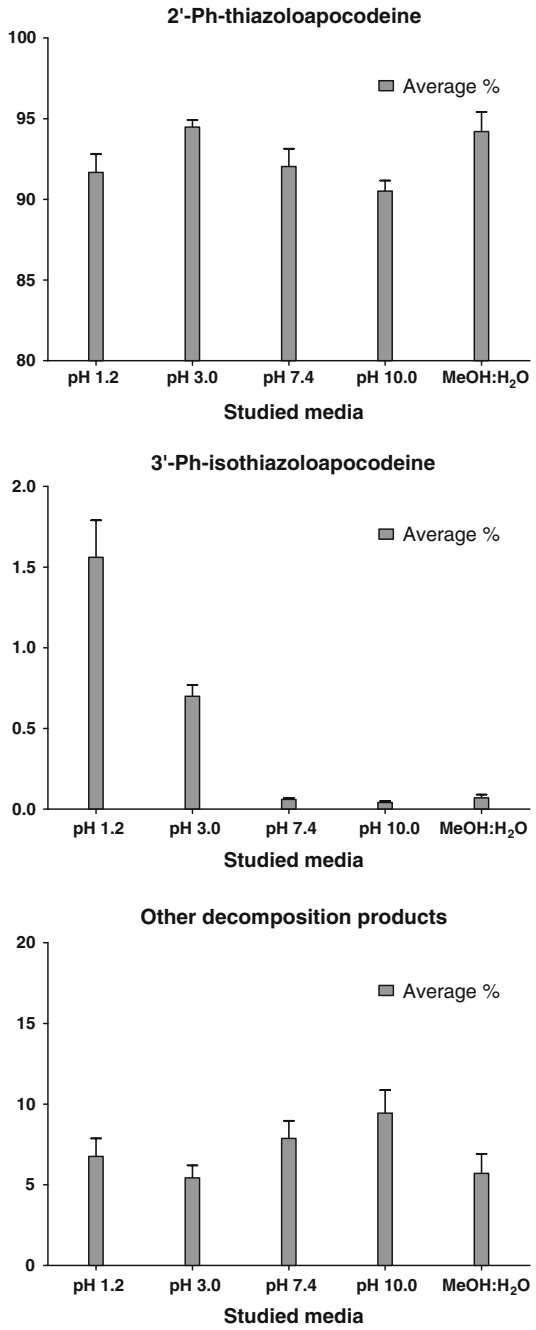


Fig. 3 Photoisomerization results in media with pH ranging from 1.2 to 10.0

was allowed to cool in the dark cavity. The workup was also performed in a dark place as much as possible.

Microwave-promotion was performed with three different settings. In the first experiment the target temperature was set to 90 °C with 5 min hold time. The observed ratio of thiazole-type vs. isothiazole-type products changed from approximately 1:1 to 3:2. The second set of reactions was performed under 70 °C target temperature with 10 min hold

[2] Applied media are commonly used in the pharmaceutical industry for dissolution tests, and their quality is in agreement with pharmaceutical requirements: pH = 1.2—0.1 N hydrochloride solution. pH = 3.0—0.05 M sodium chloride solution adjusted to pH 3.0 with hydrochloride solution. pH = 4.5, 6.8 and 7.4—0.05 M sodium dihydrogen phosphate buffer adjusted to the target pH with sodium hydroxide solution. pH = 10.0—0.05 M ammonium chloride solution adjusted to pH 10.0 with ammonia solution.

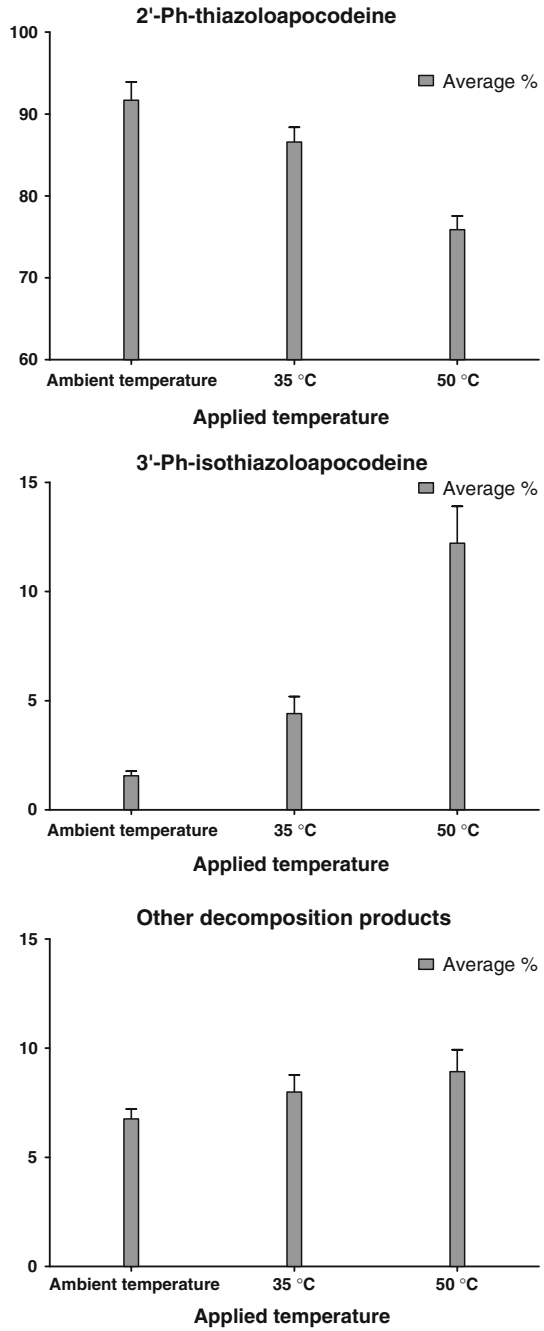


Fig. 4 *Graphs* presenting the thermal dependence of the isomerization

time. The amount of unreacted thiazolomorphinandienes increased to 10%. The ratio of two isomer products remained the same as in the first experiment. The third set of microwave-promoted rearrangements was carried out at 65 °C target temperature for 3 min of hold time. The amount of unreacted dienes increased up to 50%; however, a remarkable change in the product ratio was observed. The amount of benzisothiazole-type product dropped to 5% (Fig. 5).

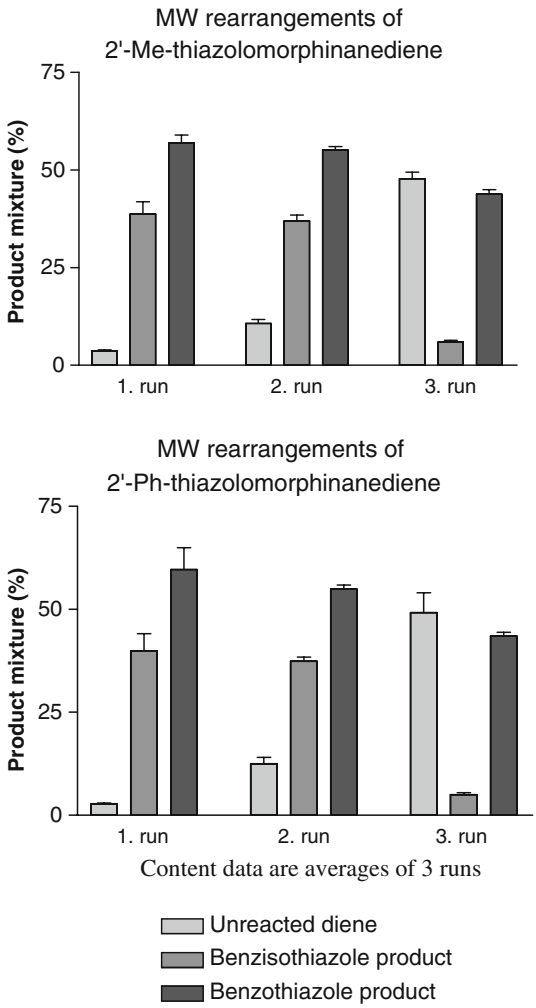


Fig. 5 *Graphs* presenting the contents of the product mixture of microwave-promoted rearrangements

Computational details

All the results presented in this work were obtained with ab initio DFT theory using the Gaussian 98 program[3] [21] with the standard 6-31G* basis set, as the electron correlation was expected to be critical in order to evaluate the reaction profile properly, we carried out these calculations by means of the hybrid functional developed by Becke and also Lee, Yang and Parr, which is customarily denoted as B3LYP [22–25]. Stationary points were characterised by frequency calculations [26]. All intermediates and products

[3] The model for thebaine (**1**) obtained at the B3LYP/6-31G* level was very much in accord with X-ray data (ref.: Mahler CH, Stevens ED, Tundell M-L, Nolan SP (1996) Acta Crystallogr C 52:3193) for compound **1**. All computations were performed using a dual-core Intel Xeon 5130 processor at 2.0 GHz. The CPU times for the geometry optimization steps were in the range of 4,812–7,332 s. The total time for geometry steps was 321 h.

have positive Hessian matrices. Transition structures show only one negative Eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration. Several reaction paths were checked by intrinsic reaction coordinate (IRC) calculations [27–29].

Both isomerization routes described in Scheme 2 were evaluated in DFT calculations by following the steps of the mechanisms by IRC calculations. There were several differences found in comparison to D'Auria's results regarding the photoisomerization of 2-phenylthiazole [2f].

Structures referring to the 2′-phenylthiazoloapocodeine (**7**) are illustrated in Fig. 6; the relative energy profile referring to these structures is reported in Fig. 7 presenting the proposed sequence of chemical changes; energy values and geometrical data (bond lengths and angles) are reported in Tables 1, 2 and 3.

In the ground state, the substrate shows bond lengths in agreement with the aromatic character of the molecule. For 2-phenylthiazole in the ground state, the calculated bond angles and distances predict a partial dienic character. This difference is clearly assigned to the presence of the fused aromatic system in compound **7**. The triplet states were clearly deformed in both cases. Both S_0 and T_1 states of 2-phenylthiazole and compound **7** are planar.

D'Auria reported that the triplet excited 2-phenylthiazole was found to be a π, π^* triplet; however, the biradical transition state structures were π, π triplets. The calculated energy levels for LSOMOs and HSOMOs (lowest and highest singly occupied molecular orbitals, respectively) suggested that the biradicals are very similar to the triplet species.

The triplet state of 2′-phenylthiazoloapocodeine (**7**) shows a π, π^* character with the LSOMO at −6.37 eV and the HSOMO at −4.92 eV. The 1,2 biradical is a π, π triplet with the LSOMO at −6.69 eV and the HSOMO at −4.87 eV. The 1,5 biradical is a π, π triplet with the LSOMO at −5.24 eV and the HSOMO at −4.82 eV. It is clear from the energy diagram (Fig. 6) that the formation of the triplet species is significantly favoured over the formation of the Dewar isomer; furthermore, the formation of the 1,2-biradical is strongly favoured with respect to the formation of the 1,5-biradical, and this drives the reaction towards the formation of the isothiazole-type product **10**.

The reactions have all been carried out in protic solvents, which will favour acid–base equilibria and could stabilize the intermediates involved.

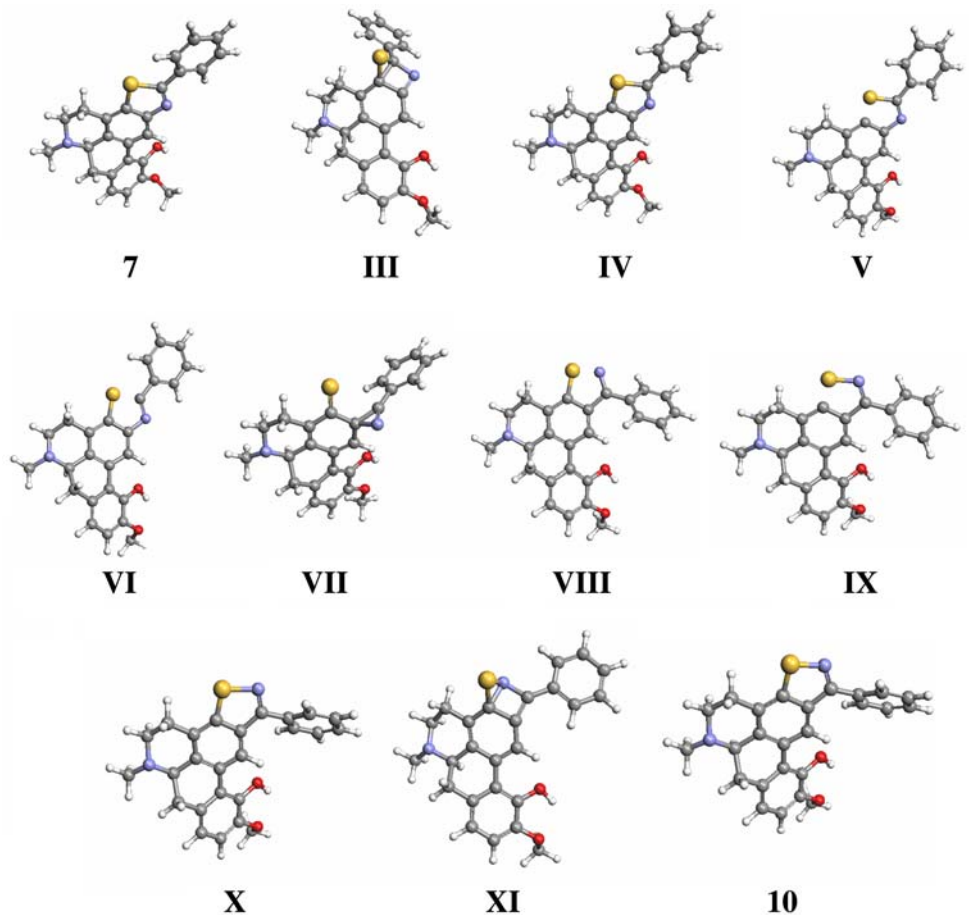


Fig. 6 Structures participating in the benzothiazole-benzisothiazole photoisomerization

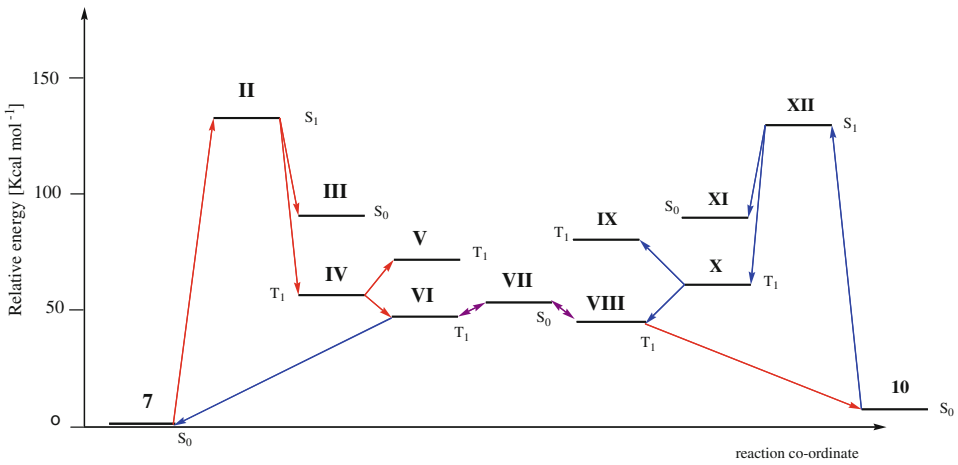


Fig. 7 Calculated relative energies and proposed sequence of isomerization-related structures

Table 1 Bond lengths and energies for five-membered structures

Structure	Electronic state	Bond length (Å)					Rel. energy (Kcal mol^{-1})
		3–4	2–3	1a–2	1a–4a	4–4a	
PTA (**7**)	S_0	1.7503	1.3267	1.4020	1.4369	1.6873	0
PTA (**IV**)	T_1	1.7878	1.4234	1.3121	1.4545	1.7124	54
PTA biradical 1,2 (**VI**)	T_1		1.4349	1.3045	1.4579	1.7101	46
PTA biradical 1,5 (**V**)	T_1	1.7842	1.4287	1.3111	1.4544		66
PITA biradical 1,2 (**VIII**)	T_1		1.4765	1.4610	1.4287	1.7018	52
PITA biradical 1,5 (**IX**)	T_1	1.6634	1.4810	1.4669	1.4356		77
PITA (**X**)	T_1	1.6507	1.4167	1.4023	1.4319	1.7054	57
PITA (**10**)	S_0	1.6411	1.3235	1.4677	1.4254	1.6954	9

PTA Phenylthiazoloapocodeine; *PITA* phenylisothiazoloapocodeine

Table 2 Bond and dihedral angles for five-membered structures

Structure	Bond angle (°)							Dihedral angle (°)	
	2–3–4	1a–2–3	2–1a–4a	1a–4a–4	3–4–4a	4–3–1′ (3–2–1′)	2–3–1′ (1a–2–1′)	1–1′–2–3	5a–4a–1a–2
PTA (**7**)	109.78	115.10	114.63	109.63	90.87	119.24	125.67	180.00	180.00
PTA (**IV**)	109.94	117.94	111.56	109.83	90.70	121.02	130.80	179.79	178.77
PTA biradical 1,2 (**VI**)	109.79	115.67	114.67	109.72	91.43	119.11	125.68	179.58	179.32
PTA biradical 1,5 (**V**)	109.72	115.03	114.53	109.55	90.79	119.28	125.69	179.48	179.61
PITA biradical 1,2 (**VIII**)	111.39	113.99	110.03	107.87	96.71	123.23	122.78	179.24	178.88
PITA biradical 1,5 (**IX**)	111.21	114.00	109.98	107.92	96.44	123.23	122.77	179.59	178.62
PITA (**10**)	111.45	114.01	109.93	107.64	96.77	123.39	122.60	180.00	180.00

PTA Phenylthiazoloapocodeine; *PITA* phenylisothiazoloapocodeine

With respect to the study of the thermal dependence, the above-presented results confirmed the determining role of the thermal effects in this type of isomerization reactions (in accordance with the comment of Sharp et al. regarding the photoisomerization of ziprasidone). On the basis of both the experimental results and the calculated data, we concluded that in the presented mechanism (Fig. 7, Scheme 7) the energy-demanding VI→VII and VIII→VII (i.e., the aziridine-formation) steps bore the thermal depending-character.

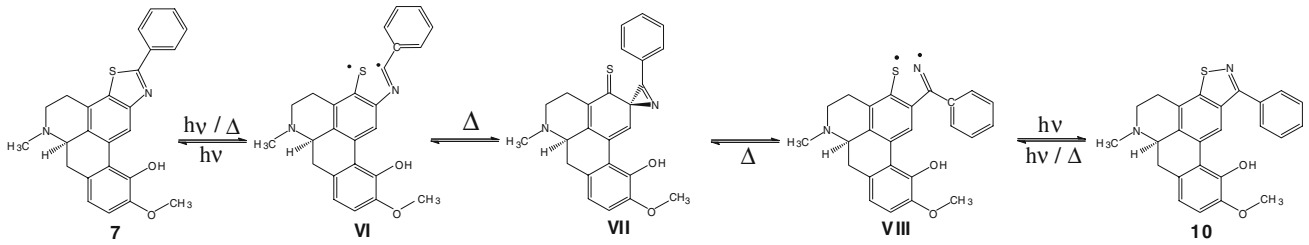
Conclusion

An extensive photoisomerization study was performed both by experimental and DFT (density functional theory)

Table 3 Structural properties and energies of three- and four-membered structures

Structure	Electronic state	Bond length (Å)		Bond angle (°)		Dihedral angle (°)		Rel. energy (Kcal mol^{-1})
PTA dewar (**III**)	S_0	1a-N	1.3332	1-1a-N	138.57	1-1a-4a-3	169.13	89
		N-3	1.5619	4a-S-3	51.19	1-1a-4a-S	130.33	
		4a-3	1.5058	S-3-N	109.61	5a-4a-1a-N	144.34	
		1a-3a	1.4794	S-3-4a	70.06	1-1a-N-3	165.41	
		3-S	1.9075	S-4a-3	58.75	5a-4a-3-N	121.11	
		4a-S	1.9854	1a-N-3	87.15	5a-4a-S-3	123.92	
				4a-3-N	89.23			
				1a-4a-3	81.64			
				4a-1a-N	97.42			
Aziridine intermediate (**VII**)	S_0	1a-N	1.7021	1a-N-3	63.90	1-2-3-S	173.23	49
		N-3	1.2723	N-3-1a	65.48	4a-3-2-N	141.57	
		1a-3	1.4802	N-2-S	148.14	1a-1-2-N	144.07	
		1a-4a	1.4534	1a-3-S	146.39	4a-3-2-2′	160.38	
		4a-S	1.7217			1a-1-2-2′	158.15	
PITA dewar (**XI**)	S_0	4a-3	1.3799	1-1a-3	145.88	1-1a-4a-N	162.79	91
		3-N	1.5063	3-S-N	50.77	1-1a-4a-S	138.27	
		N-4a	1.5187	S-3-N	63.79	5a-4a-1a-3	143.02	
		1a-4a	1.4834	S-3-2	112.30	3-1a-3a-N	5.00	
		N-S	1.9964	S-N-3	104.92	3-1a-4a-S	53.94	
		4a-S	1.9045	1a-N-S	65.44	1-1a-3-N	155.87	
				1a-3-N	94.53	1a-3a-N-S	117.13	
				1a-3a-N	112.49			
				4a-1a-3	91.18			

PTA Phenylthiazoloapocodeine; *PITA* phenylisothiazoloapocodeine



Scheme 7

calculations to determine the fundamental mechanism and determining factors of the unexpected benzothiazole–benzisothiazole-type isomerization explored during the formation of aporphine backbone. The experimental results from either reactions with modified parameters or target-specific photoisomerization studies and additional DFT calculation data revealed the main reasons responsible for this isomerization and provided further insight into the mechanism of long-studied thiazole-isothiazole rearrangement. Simultaneously with the presented study of the observed isomerization, we accomplished the *O*-demethylation of apocodeines **6–10** to obtain apomorphines with potential affinity to dopamine receptors. The pharmacological evaluation of these products will be published in due course.

Experimental

Melting points were determined with a Kofler hot-stage apparatus. Thin-layer chromatography was performed on pre-coated Merck 5554 Kieselgel 60 F_{254} foils using chloroform: methanol = 8:2 mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 360 spectrometer, chemical shifts are reported in ppm (δ) from internal TMS,

and coupling constants (*J*) are measured in Hz. Signal assignments were based on standard APT, DEPT, HSQC, HMQC, ^{1}H–^{1}H COSY and NOESY experiments. High-resolution mass spectral measurements were performed with a Bruker micrOTOF-Q instrument in the ESI (electrospray ionization) mode. Optical rotation was determined with a Perkin Elmer Model 241 polarimeter. Elemental analyses (C, H, N, S) were conducted using the Elemental Analyser Carlo Erba 1106; their results were found to be in good agreement (±0.2%) with the calculated values.

The microwave-induced reactions were carried out in a Discover model microwave reactor manufactured by CEM Corporation. Controlled temperature, power, pressure and time settings were used for all reactions.

Acid-catalyzed rearrangement of morphinandienes (general procedure)

A mixture of the diene (1 g) and methanesulfonic acid (5 cm^3) was stirred for 20 min at 0 °C. Then the reaction mixture was heated at 90–95 °C for 30 min. After cooling to room temperature, the product mixture was added dropwise, with stirring and external ice-cooling, to a solution of potassium hydrogen carbonate (10 g) in water (50 cm^3). After extraction with chloroform (3 × 15 cm^3), the combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated in vacuum. In case of necessity, the residue was submitted to purification by means of column chromatography (Kieselgel 40, chloroform:methanol = 1:1) to yield appropriate apocodeines.

(7aR)-12-Hydroxy-3-methyl-11-methoxy-thiazolo[4,5-k]-5, 6, 7a, 8-tetrahydro-4H-dibenzo [de,g]quinoline (6) (2′-methylthiazolo-apocodeine)

Column chromatography was applied to separate compounds **6** and **9**. Compound **6** was the first eluted fraction. Grey plate shape crystals; R_f (chloroform:methanol = 8:2) 0.67; m.p. 170–173 °C; yield: 216 mg (44%); $[\alpha]_D^{25}$ –109 $cm^2\ g^{-1}$ (c 0.1, chloroform); HR-MS (ESI) *m/z* (%) found: 353.1309 (M^++1, 100), calculated: 353.1321 (M^++1); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.95 (s, H1), 6.77 (2d, $J_{9–10}$ 7.2 Hz, H9, H10), 6.71 (br s, 12-OH), 3.92 (s, 11-OCH_3), 3.52-2.92 (m, $H5_a$, $H6_a$, $H6_b$, $H7_a$), 2.85 (s, 3-CH_3), 2.81–2.51 (m, $H5_b$, $H8_a$, $H8_b$, NCH_3) ppm; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 169.6 (C3), 152.9 (C1′), 148.5 (C11), 142.6 (C12), 136.7–114.4 (Ar, 9C), 60.4 (OCH_3), 58.6 ($C7_a$), 53.1 (C6), 40.7 (NCH_3), 35.1 (C8), 24.2 (C5), 22.2 (C-**C**H_3) ppm.

(7aR)-12-Hydroxy-11-methoxy-3-phenyl-thiazolo[4,5-k]-5, 6, 7a, 8-tetrahydro-4H-dibenzo [de,g]quinoline (7) (2′-phenylthiazolo-apocodeine)

Column chromatography was applied to separate compounds **7** and **10**. Compound **7** was the first eluted fraction. Off-white plate shape crystals, R_f (chloroform:methanol = 8:2) 0.59; m.p. 162–164 °C; yield: 188 mg (39%); $[\alpha]_D^{25}$ –206 $cm^2\ g^{-1}$ (c 0.1, chloroform); HR-MS (ESI) *m/z* (%) found: 415.1479 (M^++1, 100), calculated: 415.1484 (M^++1); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.91 (s, H1), 7.77–7.19 (m, 5H, 3-Ph), 6.68 (2d, $J_{9–10}$ 7.7 Hz, H9, H10), 6.12 (br s, 12-OH), 3.83 (s, 11-OCH_3), 3.09–2.41 (m, $H5_a$, $H6_a$, $H6_b$, $H7_a$), 2.38 (s, NCH_3), 2.30–2.07 (m, $H5_b$, $H8_a$, $H8_b$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 166.7 (C3), 154.2 (C1′), 149.1 (C11), 142.7 (C12), 135.4–112.1 (Ar, 15C), 59.0 (OCH_3), 56.5 ($C7_a$), 52.8 (C6), 41.2 (NCH_3), 35.1 (C8), 27.4 (C5) ppm.

(7aR)-3-Amino-12-hydroxy-11-methoxy-thiazolo[4,5-k]-5, 6, 7a, 8-tetrahydro-4H-dibenzo [de,g]quinoline (8) (2′-aminothiazolo-apocodeine)

Pale yellow cubic crystals were obtained by the recrystallization of crude apocodeine from anhydrous ether; m.p. 109–111 °C (ether); yield: 488 mg (89%); $[\alpha]_D^{25}$ −203 $cm^2\ g^{-1}$ (c 0.1, methanol); HR-MS (ESI) *m/z* (%) found: 354.1261 (M^++1, 100), calculated: 354.1274 (M^++1); ^{1}H NMR (360 MHz, DMSO-d6): δ = 8.87 (s, 12-OH), 8.29 (s, H1), 7.41 (s, 3-NH_2), 6.82 (2d, $J_{9\text{-}10}$ 8.4 Hz, H9, H10), 3.84 (s, 11-OCH_3), 3.31-2.78 (m, $H5_a$, $H6_a$, $H6_b$, $H7_a$), 2.47 (s, NCH_3), 2.66–2.09 (m, $H5_b$, $H8_a$, $H8_b$) ppm; ^{13}C NMR (90 MHz, DMSO-d6): δ = 162.9 (C3), 148.3 (C1′), 148.1 (C11), 143.4 (C12), 135.2–114.5 (Ar, 9C), 60.3 ($C7_a$), 56.4 (OCH_3), 52.4 (C6), 42.4 (NCH_3), 35.8 (C8), 28.8 (C5) ppm.

(7aR)-12-Hydroxy-2-methyl-11-methoxy-isothiazolo[4,5-k]-5, 6, 7a, 8-tetrahydro-4H-dibenzo [de,g]quinoline (9) (3′-methylisothiazolo-apocodeine)

Column chromatography was applied to separate compounds **6** and **9**. Compound **9** was the second eluted fraction. Grey plate shape crystals, R_f (chloroform:methanol = 8:2) 0.44; m.p. 142–147 °C, yield: 167 mg (44%); $[\alpha]_D^{25}$ +16 $cm^2\ g^{-1}$ (c 0.1, chloroform); HR-MS (ESI) *m/z* (%) found: 353.1315 (M^++1, 100), calculated: 353.1321 (M^++1); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.98 (s, H1), 6.77 (2d, $J_{9–10}$ 7.9 Hz, H9, H10), 6.44 (br s, 12-OH), 3.92 (s, 11-OCH_3), 3.52–2.83 (m, $H5_a$, $H5_b$, $H6_b$, $H7_a$, $H8_b$), 2.60 (s, 2-CH_3), 2.55 (m, $H8_a$), 2.51 (s, NCH_3), 2.41 (m, $H6_a$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 158.7 (C2), 147.9 (C11), 142.9 (C12), 142.7 ($C5_a$), 138.2 ($C4_a$), 133.8–114.6 (Ar, 8C), 60.6 ($C7_a$), 56.4 (OCH_3), 52.1 (C6), 41.2 (NCH_3), 34.0 (C8), 23.8 (C5), 19.5 (C-**C**H_3) ppm.

(7aR)-12-Hydroxy-11-methoxy-3-phenyl-isothiazolo [4,5-k]-5, 6, 7a, 8-tetrahydro-4H-dibenzo [de,g] quinoline (10) (2′-phenylisothiazolo-apocodeine)

Column chromatography was applied to separate compounds **7** and **10**. Compound **10** was the second eluted

fraction. White plate shape crystals; R_f (chloroform:methanol = 8:2) 0.43; m.p. 179–183 °C, yield: 159 mg (33%); $[\alpha]_D^{25}$ +15 cm^2 g^{-1} (c 0.1, chloroform); HR-MS (ESI) *m/z* (%) found: 415.1499 (M^++1, 100), calculated: 415.1485 (M^++1); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.23 (s, H1), 8.11–7.43 (m, 5H, 2-Ph), 6.70 (2d, J_{9-10} 7.9 Hz, H9, H10), 3.59 (s, 11-OCH_3), 3.31–2.77 (m, $H5_a$, $H5_b$, $H6_b$, $H7_a$, $H8_b$), 2.63–2.51 (m, $H6_b$, $H8_a$, NCH_3) ppm; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 157.0 (C2), 149.2 (C11), 144.4 ($C4_a$), 142.4 (C12), 141.2 ($C5_a$), 133.8–113.3 (Ar, 14C), 60.2 (OCH_3), 56.9 ($C7_a$), 52.1 (C6), 40.9 (NCH_3), 35.4 (C8), 29.3 (C5) ppm.

General procedure for microwave-promoted acid-catalyzed rearrangement

A mixture of the diene (1 g) and methanesulfonic acid (5 cm^3) was stirred in the pressurized glass vial, equipped with a magnetic stirring bar, for 20 min at 0 °C carefully protected from sunlight under nitrogen atmosphere. The vial was inserted into the microwave cavity of the microwave reactor, irradiated at the pre-set target temperature for the previously set hold time and subsequently cooled by rapid gas-jet cooling. The product mixture was allowed to cool to room temperature in the microwave cavity; the following workup procedure was the same as in case of thermal activation.

Conditions for photoisomerization studies

Compound **7** (20.7 mg; 0.5 mmol/dm^3) was dissolved in the corresponding medium[4] (100 cm^3) and outgassed with helium for 1 h. The solution was irradiated with a 125 W high-pressure mercury-arc (Helios-Italquartz, Milan) surrounded by a Pyrex water jacket. After previously determined irradiation time mixture[5] was analyzed by the described HPLC method in order to determine the extent of isomerization.

Acknowledgments The authors are grateful to Prof. Sándor Antus for substantial discussions and to the National Science Foundation (Grant OTKA reg. No. T049436 and NI61336) for the financial support. We thank the Péter Pázmány Programme (NKTH, RET006/2004) for allowing us to use the microwave reactor and to Szabolcs Fekete for the valuable technical help.

References

1. Catteau JP, Lablache-Combier A, Pollet A (1969) J Chem Soc D 1018
2. Vernin G, Poite J-C, Metzger J, Aune J-P, Dou HJM (1971) Bull Soc Chim Fr 1103
3. Vernin G, Jauffred R, Ricard C, Dou HJM, Metzger J (1972) J Chem Soc Perkin Trans 2 1145
4. Maeda M, Kojima M (1973) Tetrahedron Lett 14:3523
5. Pavlik JK, Pandit CR, Samuel CJ, Day AC (1992) J Org Chem 58:3407
6. Pavlik JW, Tongcharoensirikul P, Bird NP, Day AC, Barltrop JA (1994) J Am Chem Soc 116:2292
7. D'Auria M (2002) Tetrahedron 58:8037
8. D'Auria M (1998) Targets Heterocycl Syst 2:233
9. Pavlik JW, Tongcharoensirikul P, French KM (1998) J Org Chem 63:559
10. Zlotin SG, Bobrov AV, Chunikhin KS (1999) Russ Chem Bull 48:1339
11. Pavlik JW, Tongcharoensirikul P (2000) J Org Chem 65:3626
12. Zlotin SG, Bobrov AV (2000) Russ Chem Bull 49:956
13. Sharp RT, Leeman KR, Bryant DE, Horan GJ (2003) Tetrahedron Lett 44:1559
14. Gilchrist TL (1985) Heterocyclic chemistry. Longman Scientefic & Technical Publishers, UK, p 214
15. Tóth M, Gyulai Zs, Berényi S, Sipos A (2007) Lett Org Chem 4:539
16. Conroy H (1955) J Am Chem Soc 77:5960
17. Berényi S, Hosztafi S, Makleit S, Szeifert I (1982) Acta Chim Acad Sci Hung 110:363
18. Berényi S, Makleit S, Rantal F (1985) Acta Chim Acad Sci Hung 120:201
19. Csutorás Cs, Berényi S, Makleit S (1996) Synth Commun 26:2251
20. Maeda M, Kojima M (1978) J Chem Soc Perkin Trans 1 685
21. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA Jr., Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (1998) Gaussian 98, Revision A.3, Gaussian, Pittsburgh
22. Becke AD (1993) J Chem Phys 98:5648
23. Becke AD (1998) Phys Rev A 38:3098
24. Lee WY, Parr RG (1980) Phys Rev B 37:785
25. Vosko SH, Wilk L, Nusair M (1980) Can J Phys 58:1200
26. McIver JW, Komornicki AK J Am Chem Soc 94: 2625
27. González C, Schlegel HB (1989) J Chem Phys 90:2154
28. González C, Schlegel HB (1990) J Phys Chem 94:5523
29. Fukui K (1981) Acc Chem Res 14:363

[4] See Footnote 2.

[5] See Footnote 1.