Tetrahedron Vol. 48, No. 23, pp. 4957-4962, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Conformational Analysis of *s*-Triazolobenzothiazine Derivatives Prepared by Intermolecular 1,3-Dipolar Cycloaddition of Nitrilimines to 4-Aryl-2*H*-1,3-benzothiazines[1]

János Szabó*, Lajos Fodor, Ernest Bani-Akoto, Gizella S. Talpas, Gábor Bernáth

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University,
H-6701 Szeged, POB 121, Hungary,

and

Pál Sohár*

Spectroscopic Department, EGIS Pharmaceuticals, H-1475 Budapest, POB 100, Hungary

(*Received in UK* 12 *November* 1991)

Dedicated to Professor Gábor Fodor on the occasion of his 75th birthday

Key Words: 1,3,10b-Trisubstituted-8,9-dimethoxy-1,10b-dihydro-5*H*-1,2,4-triazolo[4,3-*c*][1,3]benzothiazines; cycloaddition of nitrilimines; reaction of 4-aryl-2*H*-1,3-benzothiazines; conformational analysis.

Abstract: *A series of new 1,3,10b-trisubstituted-8,9-dimethoxy-1,10b-dihydro-5H-1,2,4-triazolo[4,3-c] = [1,3]benzothiazines (**2a-i**) have been synthesized by thermal [3+2]-cycloaddition of nitrilimines to 4-aryl-6,7-dimethoxy-2H-1,3-benzothiazines (**1a-d**). Conformational analysis of the s-triazolobenzothiazine derivatives **2a-i** was performed by NMR spectroscopy.*

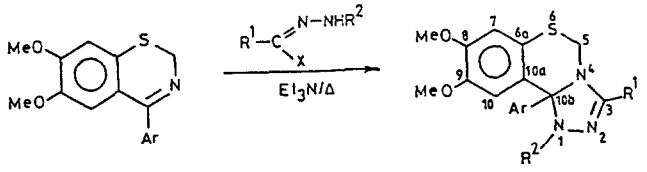
INTRODUCTION

The aim of the present work was to synthesize new 1,3,10b-trisubstituted-8,9-dimethoxy-5*H*-1,2,4-triazolo[4,3-*c*][1,3]benzothiazines that are structurally related to *s*-triazolo[3,4-*c*]isoquinolines,which have anti-inflammatory and cardiovascular activities [2,3]. Earlier, we reported[4-6] dipolar cycloadditions of nitrilimines to 6,7-dimethoxy-2*H*-1,3-benzothiazine and its 4-methyl derivative. In the present work, we have studied influence of bulky aryl substituents attached to the annelated 10b carbon atom on the conformational relations.

SYNTHESIS

For this purpose, compounds **2a-i** were synthesized by reacting 4-aryl-6,7-dimethoxy-2*H*-1,3-benzothiazines **1a-d** with nitrilimines, prepared from various hydrazonyl halides in the presence of triethylamine (Scheme 1).

As the attempted analogous cycloadditions of 2-methyl- and 2-phenyl-6,7-dimethoxy-4*H*-1,3-benzothiazines and the *cis*- and *trans*-4a,5,6,7,8,8a-hexahydro-2-phenyl-4*H*-1,3-benzothiazines failed, the currently unknown linearly fused isomeric *s*-triazolo-1,3-benzothiazine derivatives could not be prepared.



1a-d **2a-i**

a: Ar = Ph
b: Ar = 4-ClC_6H_4
c: Ar = 2-ClC_6H_4
d: Ar = 3,4-$(MeO)_2C_6H_3$

a: $R^1 = R^2 = Ar = Ph$
b: $R^1 = R^2 = Ph$, Ar = 4-ClC_6H_4
c: $R^1 = R^2 = Ph$, Ar = 2-ClC_6H_4
d: $R^1 = R^2 = Ph$, Ar = 3,4-$(MeO)_2C_6H_3$
e: R^1 = 4-ClC_6H_4, R_2 = Ar = Ph
f: $R^1 = CO_2Et$, R^2 = 4-ClC_6H_4, Ar = Ph
g: $R^1 = CO_2Et$, R^2 = 4-MeC_6H_4, Ar = Ph
h: $R^1 = CO_2Et$, R^2 = Ar = 4-ClC_6H_4
i: $R^1 = CO_2Et$, R^2 = 4-MeC_6H_4, Ar = 4-ClC_6H_4

Scheme 1

STRUCTURE

The ^1H- and ^{13}C-NMR spectral data on the 10b-aryl-substituted triazolobenzothiazines **2a-i** are given in Tables 1 and 2. Detailed NMR conformational analyses of the 10b-unsubstituted and 10b-methyl analogues were reported earlier[5].

Table 1. ^1H-NMR chemical shifts (δ_{TMS} = 0 ppm, in $CDCl_3$ solution) of compounds **2a-i** at 250 MHz[a]

Com-pound	OCH_3, Pos. 8	2x*s*(2x3H) Pos. 9	H-7 *s*(1H)	H-10 *s*(1H)	CH_2 (H)[b] 2x*d*(2x1H)		ArH (Pos. 1, 3, 10b) 4-7 *m*'s(8-15H)
2a	3.80	3.27	6.52	6.42	4.41	4.61	6.85[c] 7.05[d,e] 7.45[f,g] 7.75[d,h]
2b	3.79	3.29	6.52	6.33	4.40	4.62	6.90[c] 7.0[i] 7.10[j] 7.45[k] 7.7[d,h]
2c	3.73	3.62	6.57[l]	6.50[l]	4.51	4.66	6.80[c] 6.90[i] 7.00[j] 7.4[k] 7.5[m] 7.8[n] 8.00[o]
2d	3.78	3.23	6.50[l]	6.47[l]	4.47	4.60	6.85[p] 6.95-7.1[q] 7.4[r] 7.52[s] 7.7[n]
2e	3.79	3.26	6.52	6.36	4.43	4.54	6.85[c] 7.05[d,e] 7.45[k] 7.65[n] 7.75[t]
2f	3.83	3.16	6.52	6.12	4.39	5.35	6.92[i] 7.08[j] 7.45[u] 7.65[t]
2g	3.82	3.06	6.51	6.00	4.41	5.36	6.86[i] 6.91[j] 7.45[u] 7.7[t]
2h	3.83	3.16	6.52	6.02	4.36	5.35	6.91[i] 7.10[j] 7.44[w] 7.63[t]
2i	3.82	3.05	6.51	5.91	4.37	5.37	6.83[i] 6.95[j] 7.43[w] 7.67[t]

[a] Characteristic IR bands (in KBr discs, cm^{-1}): $\gamma C_{(Ar)}H$ (phenyl): 768 and 754 (**2a**), 783 and 764 (**2b**), 757 (**2c**, coalesced with the $\gamma C_{(Ar)}H$ band of the *ortho*-disubst. ring), 760 (**2e**), 753 (**2f**), 766 (**2g**); $\gamma C_{(Ar)}H$ (*para*-disubst. ring): 832 (**2b,f,h**) 835 (**2e,i**) 859 (**2g**) 865 (**2h,i**); $\gamma C_{(Ar)}C_{(Ar)}$ (phenyl): 698±3 (**2a-f**), $\nu C{=}O$: 1711 (**2f**), 1717 (**2g**), 1713 (**2h**), 1712 (**2i**); Further ^1H-NMR signals: CH_3 (tolyl, **2g-i**): 2.22 *s*(3H); OCH_3 (veratryl, **2d**): 3.89 and 3.92, 2x*s*(2x3H), CH_3 (ethyl, **2f-i**): 1.39±0.01, *t*(3H ^3J:7.1±0.1 Hz); OCH_2 (ethyl, **2f-i**): 4.93±0.01, *qa*(2H). [b] *AB*-type spin-system, *J*(*A*,*B*): 13.5±0.1 Hz; [c] H-4 (1-Ph), ~*t*(1H); [d,f] Overlapping *m*'s of 4/6-H intensity; [e] H-2,3,5,6 (1-Ph); [g] H-3,4,5 (3-Ph + 10b-Ph); [h] H-2,6 (3-Ph + 10bPh); [i] H-2,6 (1-Ph), ~*d*(2H) for **2f-i**,$J \approx 9.0$ Hz; [j] H-3,5 (1-Ph), ~*t*(2H) for **2b,c**, *d* for **2g-i**; [k] H-3,4,5 (**2b,c**) or H-3,5 (**2e**) of 3-Ph + H-3,5 (**2b**), H-4,5 (**2c**), H-3,4,5 (**2e**) of 10b-Ph (5H); [l] Assigments are interchangeable; [m] H-3 (10b-Ph), ~*d*(1H); [n] H-2,6 (3-Ph), ~*d*(2H), [o] H-6 (10b-Ph), ~*d*(1H), $J \approx 8.5$ Hz; [p] Overlapping signals of H-4 (1-Ph) and H-5 (10b-Ph); [q] Overlapping signals of H-2,3,5,6 (1-Ph) and H-6 (10b-Ph); [r] H-3,4,5 (3-Ph); [s] H-2 (10b-Ph), ~*s*(1H); [t] H-2,6 (10b-Ph), ~*d*(2H); [u] H-3,4,5 (10b-Ph), *m*(3H); [w] H-3,5 (10b-Ph), ~*d*(1H), $J \approx 8.5$ Hz.

Table 2. ^{13}C-NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds **2a-i** in $CDCl_3$ solution at 20.14 MHz[a]

Compound	CH_2(5)	OCH_3(8,9)	C-3	C-6a	C-7	C-8	C-9	C-10	C-10a	C-10b	C-2',6' (1-Ph)	C-4' (1-Ph)
2a	45.4	55.8 55.9	149.6[b]	122.8	115.2	146.2	149.1[b]	111.6	127.6	90.2	120.7	122.2
2b	45.7	55.9[c]	149.7[b]	122.1	115.1	146.3	149.2[b]	111.7	127.9	89.9	121.1	122.6
2c	50.9	55.8 56.3	151.4	122.7	115.7	146.9	149.0	113.3	127.5[c]	89.4	120.1	121.9
2d	44.3	55.7[b] 56.2[b]	149.7[n]	122.3[o]	114.6	145.9	149.0[n]	111.1	126.9[p]	90.2	120.5	122.0
2e	45.6	55.8[c]	148.5	122.4[d]	115.2	146.2	149.1	111.6	127.2[b]	90.5	120.8	122.4[d]
2f	42.7	55.4 55.7	142.1[b]	120.4	113.4	145.8	149.4	111.0	126.8	92.7	122.8	129.0
2g	42.8	55.0 55.6	143.1	120.1	113.7	145.4	149.0	110.8	126.8	93.1	122.5	133.8
2h	42.9	55.3 55.7	141.8[b]	119.7	113.3	145.9	149.5	111.1	127.0	92.4	123.2	129.5
2i	43.2	55.3 55.8	142.2	119.7	113.8	145.7	149.4	111.1	127.1	93.0	123.1	134.5

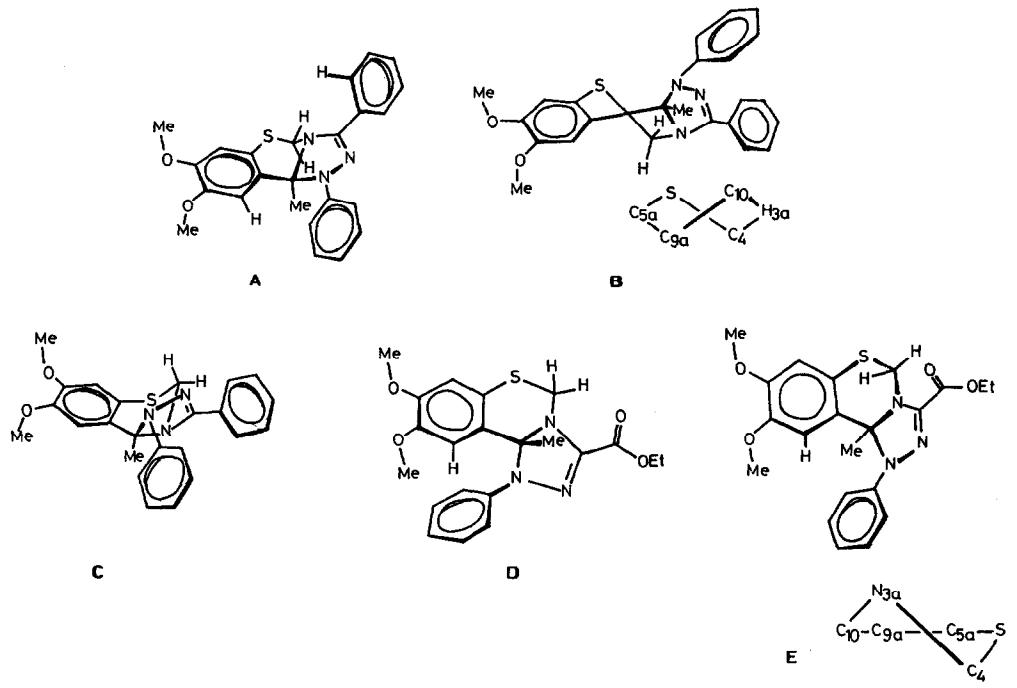
Compound	C-1' (3-Ph)	C-2',6' (3,10,b-Ph), C-3',5' (1,3,10b-Ph), C-4' (3,10b-Ph)	C-1' (1,10b-Ph)	
2a	—	128.1 128.3 128.4 128.7[c] 129.1	144.0	144.92
2b	129.6	128.0 128.3 128.5[d] 128.7 129.7[e,f] 130.4[g,h] 134.7[f,g]	142.9[g]	144.6[i]
2c	128.5[d]	126.9[g,j] 127.5[c,e,f] 127.9 128.7[d,k] 129.7 130.0[g,l] 131.4[f,g] 133.9[g,m]	139.9[g]	142.9[i]
2d	130.5	110.6[g,m] 112.5[g,j] 122.5[g,l,o] 127.9 128.3 128.6[c,q] 149.2[r] 149.4[r]	136.0[g]	144.9[i]
2e	129.5[p]	128,3[s] 129.0[t] 128.7[f,g] 129.2 135.5[e,f]	143.8	144.5
2f	127.5[b]	128.4 128.5 129.2[f,g] 129.6[i,u]	139.1[b]	142.3[b]
2g	—	128.1 128.8[f,g] 129.0 129.6	138.3[i]	140.8[g]
2h	—	128.6[c] 130.9[g,h] 135.4[f,g]	139.3[i]	141.1[b,g]
2i	—	128.5 129.3 131.2 135.2[f,g]	138.7[i]	140.9[g]

Further signals: CH_3 (Pos. 4' in 1-aryl substituent): 20.4 (**2g**), 20.6 (**2i**), OCH_3 (**2d**): 55.8[b], 55.9[b], CH_3(Et): 14.0 (**2f,g,h**), 14.2 (**2i**), OCH_2(Et): 61.7 (**2f, i**), 61.4 (**2g**), 61.8 (**2h**), C=O: 158.8 (**2f**), 158.9 (**2g**), 158.6 (**2h**), 159.0 (**2i**).

[a] The measuring frequency was 62.89 MHz for compound **2c**; [b,n,o,p] Interchangeable assignments; [c,d,s,t] Two overlapping lines; [e] 3-Aryl substituent; [f] C-4'; [g] 10b-Aryl substituent; [h] C-2',6'; [i] 1-Aryl substituent; [j] C-5'; [k] One of the two overlapping signals is the C-3' (10b-Aryl) line; [l] C-6'; [m] C-2'; [q] One of the two overlapping signals is the C-4' (3-Aryl) line; [r] C-3' or C-4' line of the 10b-Aryl substituent; [u] C-3',5'.

These compounds can assume conformations of three different types[5], one of which is the rigid form containing *trans*-annelated hetero rings, denoted by "A" in Scheme 2. The other two families of conformations are those that can transform freely into each other by pseudorotation, requiring little energy of activation; in these conformations, the hetero rings are *cis*-annelated and they can be interconverted by inversion of the thiazine ring. Pseudorotation means here the change of the dihedral angle made by the atoms N(1)-C(10b)-N(4)-C(3) within a given segment (i.e. the relative twist of the hetero rings). The two families of conformations differ in the relation of the 10b-aryl group, which is *axial* to the *cis*(α) H-5' in one of them, and to the *trans*(β) H-5 in the other from. Both groups of conformations can each be characterized by two extreme forms, corresponding to the segment limits (*cis*: "B", "E", *trans*: "C" and "D", as denoted in Scheme 2).

It was found that the 3-carbethoxy derivatives in solution have a preferred conformation ("E") in which the 1-aryl group is near H-10 and the 9-methoxy group, and where its anisotropic effect gives rise to a considerable shielding of H-10 and the 9-methoxy hydrogens. On the other hand, in the predominant conformation of the 3-aryl analogues (denoted by "B" in Scheme 2), these groups are situated far from each other, and no extraordinary shielding effect can be observed. The results of our NMR measurements have been supported by those of X-ray studies[6], which showed that the conformations in the solid state are the same as those favoured in solution.



Relatively stable conformations of triazolobenzothiazines of type **2**

Scheme 2

The ^{1}H NMR spectra of the 10b-aryl-3-carbethoxy compounds (**2f-i**) show the characteristics of the "E" from, i.e. the same conformation as determined during the investigation of the 10b-H/Me analogues:

(a) the 9-methoxy group and H-10 are anomalously shielded; the average chemical shifts of these H atoms are 3.1 and 6.0 ppm, respectively, as compared with the usual values of about 3.8 and 6.8 ppm;

(b) the chemical shift difference for the 5-methylene hydrogens is about 1.0 ppm, whereas in the other conformation the average difference is 0.25 ppm[5].

Thus, it is clear that the preferred conformations of these compounds are the same as those previously proposed for the 10b-H/Me analogues, i.e. form "E".

In this conformation, the thiazine ring is in a twist form which approaches the *sofa* conformation containing C-5 in an *out-of-plane* position; the 10b-aryl group is *quasi axial*, lying parallel to the *α-axial* H-5[5], and hence it is not hindered sterically by any other group of the molecule. This is the reason why the aryl substituent occupying the place of the H/Me group does not give rise to a change in the conformation.

In the 3-aryl derivatives **2a-e** too, the introduction of the 10b-aryl substituent apparently leaves the skeletal conformation unaffected; similarly as for the 10b-H/Me derivatives, the preferred conformation of these 10b-aryl compounds is "B", that is, depending on the 3-substituent, compounds **2** undergo the same conformational change. This is indicated by a decrease in the chemical shift difference of the 5-methylene hydrogens to 0.16 ppm on average. Instead of the anisotropic effect of the coplanar carbonyl group causing a downfield shift, the 3-aryl ring causes an opposite shift of the H-5*eq* signal, which largely compensates the usual[7] difference δH-5*ax* < δH-5*eq*.

The small upfield shift of the 9-methylene signals (by *ca* 0.17 ppm) as compared to those for **2f-i** is a consequence of the shielding effect of the 1-aryl ring. The 1-aryl ring is nearly perpendicular to the triazoline ring because of the presence of the 10b-aryl substituent, the latter being nearly coplanar with the fused benzene ring; consequently, the 1-aryl group does not influence the shift of the H-10 signal, but it does have shielding effect on the 9-methoxy hydrogens.

This is supported by the fact that no upfield shift of the 9-methoxy signal was observed for **2c**, as in this molecule the presence of the *ortho* substituent on the 10b-aryl ring requires a mutually perpendicular arrangement of the ring and the molecular skeleton. This is evidenced by the downfield shift (by about 5 ppm) of the C-5 signal, since the 10b-aryl — H-5α interaction, otherwise causing an upfield shift ("steric compression shift"[8]), has been eliminated.

The results of pharmacological testing of the compounds prepared in this work will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected.

^{1}H- and ^{13}C-NMR spectra were recorded at room temperature in deuterochloroform solution, in 5 ml (^{1}H) and 5 or 10 ml (^{13}C) tubes, on Bruker WM-250 (^{1}H, ^{13}C) and WP-80-SY (^{13}C) FT spectrometers controlled by as ASPECT 2000 computer at 250 (^{1}H) and 63 or 20 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and tetramethylsilane as internal standard.

General procedure for synthesis of the *s*-triazolobenzothiazines **2a-i**

The appropriate compound **1** (3.3 mmoles) and the substituted hydrazonyl chloride (3.3 mmoles) were dissolved in benzene (20 ml). The solution was stirred and refluxed while a benzene solution (10 ml) of triethylamine (3.3 mmoles) was added dropwise over a period of 1 hour. Refluxing was then continued for 10 hours. The reaction mixture was subsequently washed with dilute hydrochloric acid and then with water, and the benzene solution was dried over anhydrous sodium sulphate. After evaporation of the solvent, the product was crystallized from an appropriate solvent (Table 3).

Table 3. Physical and analytical data on compounds **2a-i**

Compound	Yield (%)	M.p. (°C)[a]	Formula	M.w.	Analysis Calcd. / Found (%) C	H	N
2a	52	167-168	$C_{29}H_{25}N_3O_2S$	479.58	72.62 / 72.41	5.26 / 5.38	8.76 / 8.58
2b	47	173-174	$C_{29}H_{24}ClN_3O_2S$	514.03	67.76 / 67.47	4.71 / 5.00	8.17 / 8.19
2c	53	214-215	$C_{29}H_{24}ClN_3O_2S$	514.03	67.76 / 68.03	4.71 / 4.95	8.17 / 8.15
2d	53	189-191	$C_{30}H_{29}N_3O_4S$	527.62	68.29 / 68.20	5.54 / 5.77	7.96 / 7.69
2e	45	198-199	$C_{29}H_{24}ClN_3O_2S$	514.03	67.76 / 67.49	4.71 / 4.95	8.17 / 8.03
2f	78	187-188	$C_{26}H_{24}ClN_3O_4S$	509.99	61.23 / 61.24	4.74 / 4.92	8.24 / 8.24
2g	60	169-171	$C_{27}H_{27}N_3O_4S$	489.58	66.23 / 66.47	5.56 / 5.72	8.58 / 8.51
2h	57	151-153	$C_{26}H_{23}Cl_2N_3O_4S$	544.45	57.35 / 57.65	4.26 / 4.43	7.72 / 7.81
2i	49	143-144	$C_{27}H_{26}ClN_3O_4S$	524.02	61.88 / 62.10	5.00 / 5.03	8.02 / 8.05

[a] Solvent: ethanol (**2a,d,h,i**), acetone (**2b**), ethanol — acetone (**2c**), ethyl acetate (**2e,f,g**)

REFERENCES AND NOTES

1. This paper is regarded as Part 202 of the series Saturated Heterocycles, Part 201: Huber, I.; Szabó, Á.; Fülöp, F.; Bernáth, G. *Tetrahedron* submitted for publication.
2. Cavallito, C. J.; Gray, A. P.; Fr. Pat. 2135297 *Chem. Abstr.* **1973**, *79*, 96989.
3. Geigy, J. R., AG; Neth. Pat. 6614979; *Chem. Abstr.* **1968**, *68* , 69003.
4. Fodor, L.; El-Gharib, M. S.; Szabó, J.; Bernáth, G.; Sohár, P. *Heterocycles* **1984**, *22*, 537.
5. Sohár, P.; Fodor, L.; Szabó, J.; Bernáth, G. *Org. Magn. Reson.* **1984**, *22*, 720.
6. Kálmán, A.; Argay, Gy.; Sohár, P.; Fodor, L.; Szabó, J.; Bernáth, G. *J. Mol. Struct.* **1985**, *129*, 271.
7. Sohár, P. *Nuclear Magnetic Resonance Spestroscopy* (CRC Press, Boca Raton, Florida, **1983**), Vol. *2*, p. 25.
8. Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315.