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Novel ring transformations of condensed [1,2,4]triazolo-[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thiones effected by dialkyl-acetylenedicarboxylates

Mónika Simó, Antal Csámpai,* Veronika Harmat, Orsolya Barabás and Gábor Magyarfalvy

Institute of Chemistry, Eötvös Loránd University, P.O. Box 32, Budapest 112, H-1518 Hungary

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Abstract—On heating with dialkyl-acetylenedicarboxylates in DMF condensed [1,2,4]-triazolo[4,3-*b*] pyridazine-6(5*H*)-one-3(2*H*)-thiones undergo unprecedented ring transformations yielding novel tetracyclic 1,3-diazepines and thiazolotriazole derivatives depending on the applied reaction temperature. The observed substrate selectivity was interpreted on the basis of the results of comparative theoretical calculations carried out at semiempirical level (AM1). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

For more than two decades there has been considerable interest in the chemistry and biological activity of pyridazine derivatives.[1–4] In connection with our program to investigate synthetic approaches to polycondensed pyridazines we reacted the tricyclic [1,2,4]-triazolo-[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thiones **1a**–**e**[5] with dimethylacetylene dicarboxylate (DMAD) in DMF at ambient temperature (Scheme 1) to furnish a series of novel tetracyclic systems (**2a**–**e**). These target compounds with an additional [1,3,4]-thiadiazine ring carrying two carbomethoxy groups seemed to be suitable precursors for a new class of molecules of potential biological activities by coupling with a wide variety of basic pharmacophoric units.

2. Results and discussion

Contrary to our expectations, the reactions conducted at 100°C took place with an unprecedented ring transformation yielding two types of isolable products (*cis*-**4a**,**c**,**d** and **5b**,**e**) both of them containing thiazolo [2,3-*b*][1,2,4]-triazole subunit (Scheme 1). Obviously, the unisolable tetracyclic diazepinone derivatives (*cis*-**4b**,**e**) undergo ring opening resulting in the bicyclic final products **5b**,**e**. Two interesting aspects of these new transformations involving the insertion of DMAD must be pointed out. On the first hand, the two carbomethoxy groups in the isolable tetracyclic diazepine derivatives can be found in the crowded *cis* arrangement (*cis*-**4a**,**c**,**d**) while their diastereomers (*trans*-**4a**,**c**,**d**) could not be isolated even in traces, and on the other, the tendency to splitting of the 1,3-diazepine ring is highly dependent on ring A.

Semiempirical (AM1) calculations were carried out for the diastereomeric condensed 1,3-diazepines *cis*-**4a**–**e** and *trans*-**4a**–**e**. Their relative heats of formation show that the formers are kinetic products ($\Delta H_{cis\text{-}\mathbf{4}-trans\text{-}\mathbf{4}}$ [kcal/mol]: **a** −3.65; **b** −3.87; **c** −3.50; **d** −3.47; **e** −4.07). According to the proposed mechanism (Scheme 1) the formation of *cis*-**4** can be interpreted by ring enlargement of the primarily formed tetracyclic 1,3,4-thiadiazine followed by the *trans*-annular recyclization in the resulting macrocyclic intermediate (**2**→**3**→*cis*-**4**). In the course of the latter step the nucleophilic triazole nitrogen attacks the carbon atom of the imino group from the less hindered side opposite to the carbomethoxy group bonded to the saturated skeletal carbon atom.

The same method was applied to reveal the cause of the increased tendency of unisolable diazepines *cis*-**4b**,**e** to undergo ring opening to **5b**,**e**. Calculations (Table 1: column 1) also show that—in accord with the experimental results—ring opening of type *cis*-**4**→**5** is highly exothermic process in each case studied. Since synchronous E2-elimination step must be ruled out because of the *cis* arrangement of the leaving acylamino group bonded to C4a and the involved H4 proton, we considered four types of zwitterionic intermediates (**4**/I–IV; Scheme 2) in which the split of C4a–N5 bond may occur. Their heats of formation relative to the corresponding *cis*-**4** (Table 1: columns 2–5) indicate that intramolecular protonation of the N2 atom (**4**/II) is the most favourable for each of the models. On the other hand, according to subsequent calculations the actual ring opening

Keywords: ring transformation; substrate selectivity; semiempirical calculations; structure determination.

* Corresponding author. Tel.: +36-1-209-055/6591; fax: +36-1-209-0602; e-mail: csampai@para.chem.elte.hu

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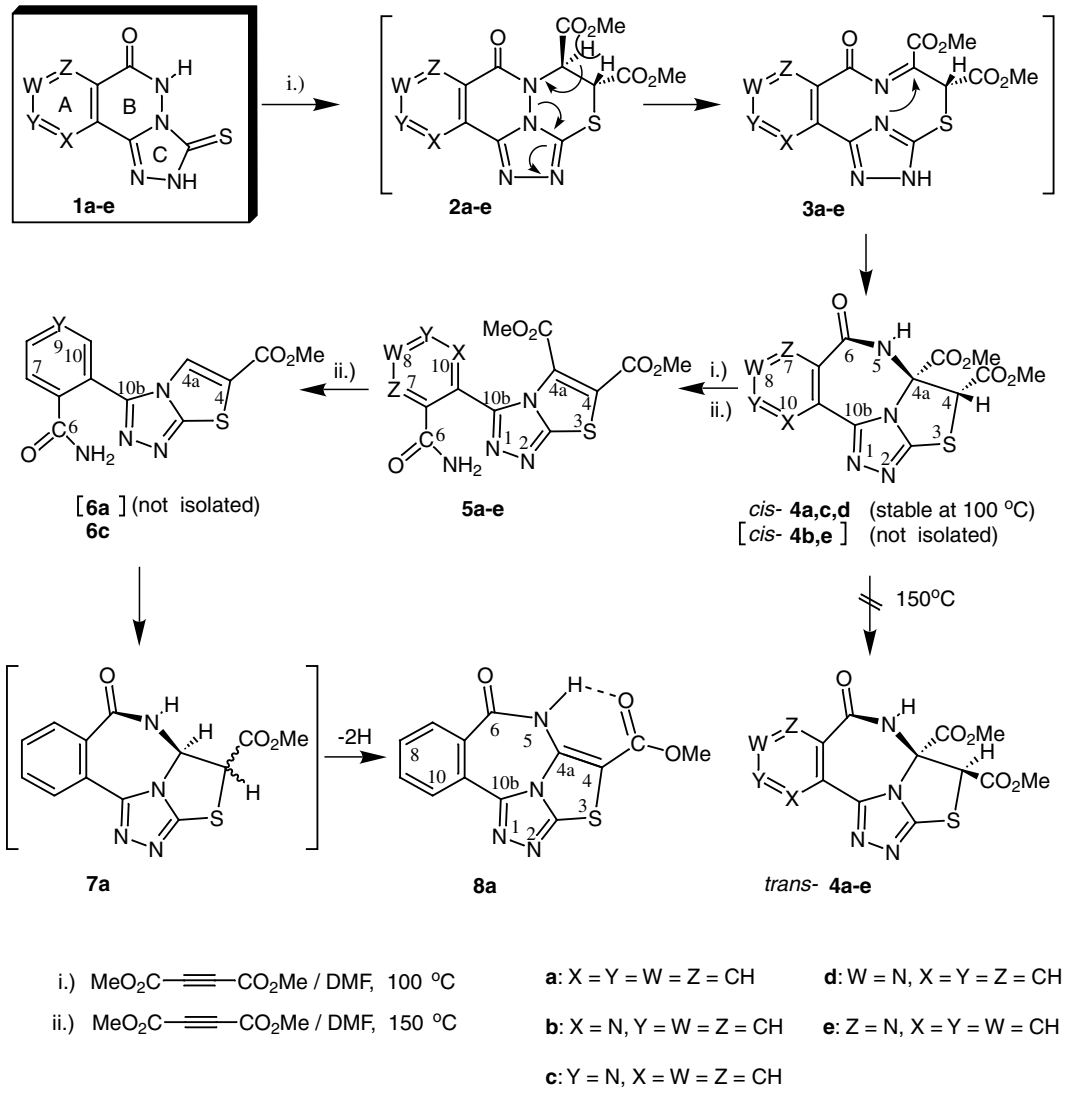


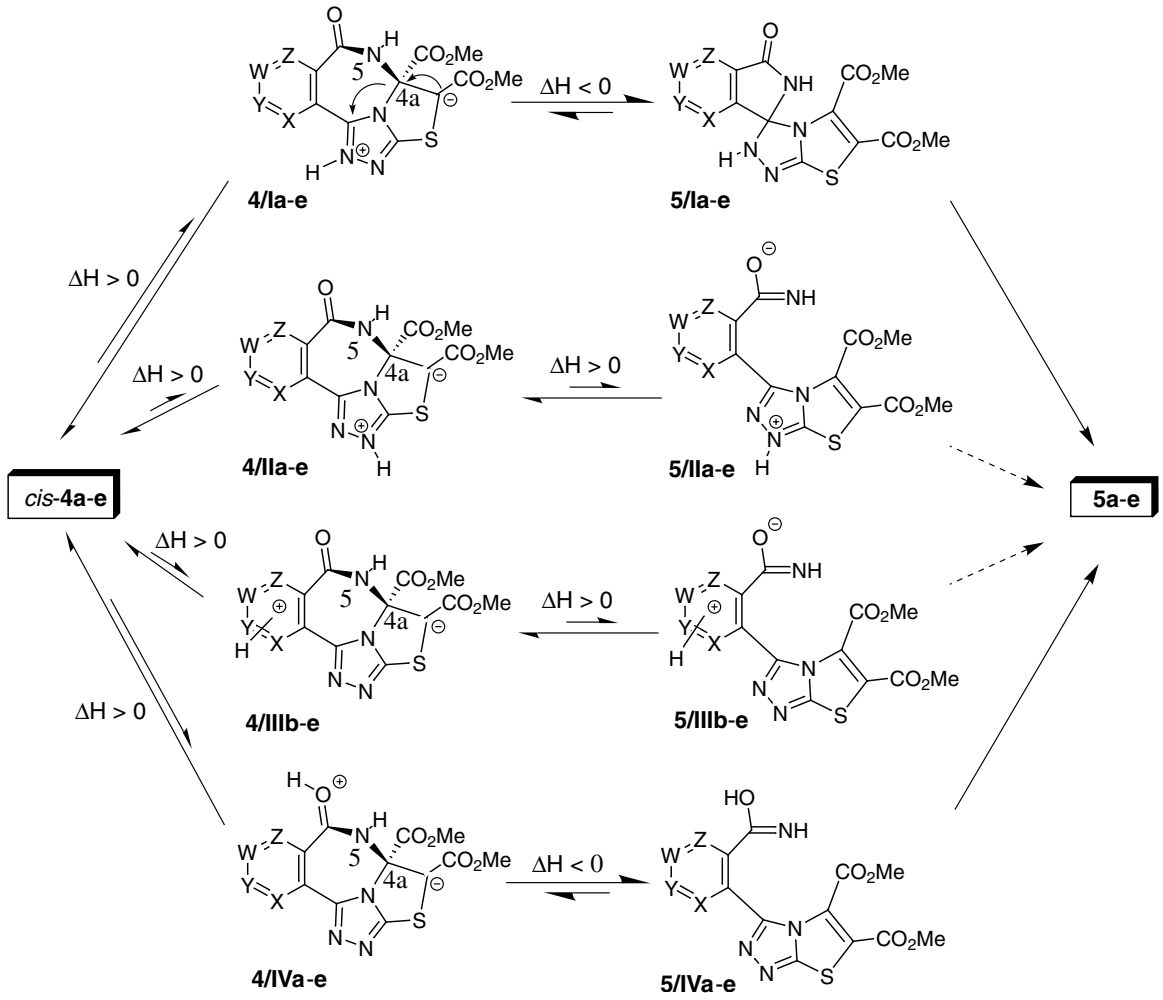
Scheme 1. The unanimous numbering of atoms refers to NMR assignments listed in Section 4.

of any zwitterions of types **4**/II and **4**/III is highly endothermic process (Scheme 2, Table 1: columns 7 and 8), but the analogous elementary steps starting from the N1-protonated and O-protonated forms (**4**/I and **4**/IV) are thermodynamically favoured (Scheme 2, Table 1: columns 6 and 9). It follows that the prerequisite of ring opening *cis*-**4**→**5** is the intramolecular proton migration yielding intermediates of types either **4**/I or **4**/IV. Finally, in these two groups the lowest heats of formation of **4**/I**b** and **4**/IV**e** (Table 1: columns 2 and 5) can be regarded to be the cause of the increased tendency of unisolable *cis*-**4b**,**e** to undergo ring opening yielding **5b**,**e**.

In order to obtain *cis*-**4b**,**e** the reactions could not be carried out at lower temperatures due to the bad solubility of the precursor thiones **1b**,**e**. On the other hand, the TLC-monitored reactions of **1b**,**e** yielding **5b**,**e** were completed in a few minutes referring to highly facile overall reactions. In the reaction mixtures obtained after the treatment of **1a**,**c**,**d** at 100°C only *cis*-**4a**,**c**,**d** with shorter R_f values

Table 1. Heat of reaction (ΔH [kcal/mol]) for ring opening of type *cis*-**4**→**5** (column 1) as overall process and for the possible elementary steps outlined in Scheme 2 (columns 2–9)

	5–*cis*-**4**	**4**/II–*cis*-**4**	**4**/II–*cis*-**4**	**4**/III–*cis*-**4**	**4**/IV–*cis*-**4**	**5**/I–**4**/I	**5**/II–**4**/II	**5**/III–**4**/III	**5**/IV–**4**/IV
A	−9.19	*23.74*	17.67	–	*25.96*	*−17.94*	56.98	–	*−17.09*
B	−12.41	***19.71***	16.53	21.82	*27.00*	*−16.53*	54.64	31.70	*−18.23*
C	−10.20	*24.22*	17.50	34.83	*27.69*	*−16.99*	53.70	23.95	*−17.11*
D	−9.07	*25.49*	18.23	24.87	*26.11*	*−18.45*	55.17	34.28	*−16.80*
E	−14.58	*25.15*	18.08	27.57	***21.79***	*−21.07*	55.82	14.37	*−15.44*



Scheme 2. The heats of reactions (ΔH) for these elementary steps are listed in Table 1.

could be detected by TLC. According to this monitoring, conversions of **1a**,**c**,**d** were completed after longer treatment (ca. 2.5 h for **1a**→*cis*-**4a**; and ca. 1 h for **1c**,**d**→*cis*-**4c**,**d**: Table 2).

When the reaction temperature was raised to 150°C, and a shorter reaction time (20 min) was applied (Table 2) **1a** got converted into a 1:6 mixture of **5a** and the tetracyclic monoester **8a** (overall yield: 56%), the reactions of three pyridopyridazinones (**1b**,**d**,**e**) gave exclusively the corresponding *bis*-carbomethoxythiazolo [2,3-*c*][1,2,4]-triazole (**5b**,**d**,**e**) as isolable final product (yields: 71, 54 and 75%) and the transformation of the fourth pyridopyridazinone **1c** resulted in a 7:5 mixture of *bis*-carbomethoxy derivative **5c**

Table 2. Conditions and product distributions for the ring transformation reactions of tricyclic- and tetracyclic precursors **1a**–**e** and *cis*-**4a**,**c**,**d**, respectively

Precursor	Reagent/solvent	Temperature [°C]	Reaction time	Products (yields)
1a	DEAD[a]/DMF	100	2.5 h	*cis*-**4a*** (78%)
	DMAD/DMF	100	2.5 h	*cis*-**4a** (84%)
	DMAD/DMF	150	20 min	**5a** (8%)+**8a** (48%)
1b	DMAD/DMF	100	5–10 min	**5b** (94%)
	DMAD/DMF	150	20 min	**5b** (71%)
1c	DMAD/DMF	100	1 h	*cis*-**4c** (80%)
	DMAD/DMF	150	20 min	**5c** (25%)+**6c** (35%)
1d	DMAD/DMF	100	1 h	*cis*-**4d** (75%)
	DMAD/DMF	150	20 min	**5d** (54%)
1e	DMAD/DMF	100	5–10 min	**5e** (85%)
	DMAD/DMF	150	20 min	**5e** (75%)
cis-**4a**	–/DMF	150	20 min	**5a** (14%)+**8a** (70%)
	–/DMF	150	40 min	**8a** (72%)
cis-**4c**	–/DMF	150	20 min	**5c** (40%)+**6c** (48%)
	–/DMF	150	40 min	**5c** (20%)+**6c** (56%)
cis-**4d**	–/DMF	150	20 min	**5d** (67%)

[a] Abbreviation refers to diethyl acetylenedicarboxylate.

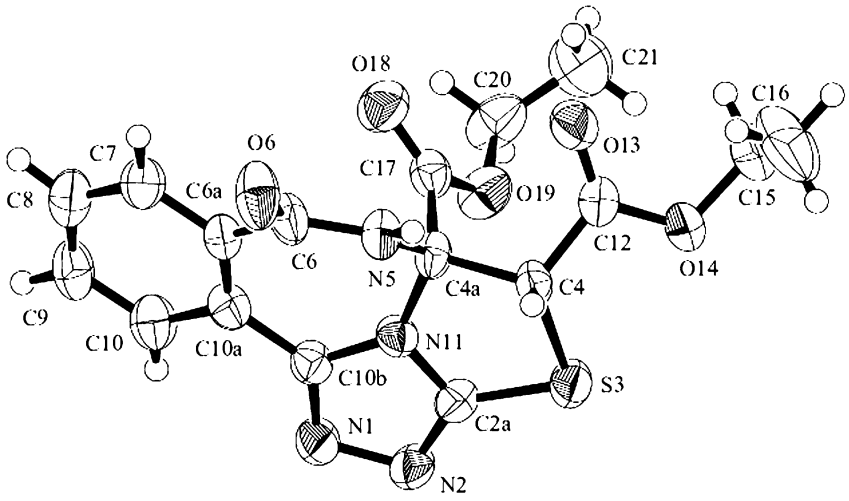


Figure 1. X-ray structure of *cis*-**4a**[*].

and *mono* carbomethoxy compound **6c** (overall yield: 60%). Although on the basis of these observations no definitive statement can be made on the substrate selectivity, the intermediacy of *cis*-**4a**–**e** seems to be obvious. This view is supported by the results of control experiments in the course of which the isolated diazepines (*cis*-**4a**,**c**,**d**) were heated for 20 min in DMF at 150°C in the absence of DMAD (Table 2). These reactions afforded similar product distributions as did those performed in the presence of the reagent, but the yields were higher (**5a/8a**=1:5 with 84% overall yield; **5c/6c**=6:5 with 88% overall yield; **5d** 67%) probably due to a smaller degree of decomposition. After a longer treatment (40 min) of *cis*-**4a** at 150°C (Table 2) only **8a** could be isolated in 72% yield, and applying the same reaction time for *cis*-**4c** the product distribution was shifted towards **6c** (**5c/6c**=1:2.8 with 76% overall yield). These experiments refer to stepwise conversions starting from **5a**,**c** as outlined in Scheme 1.

Formation of **6a**,**c** can be explained by selective hydrolysis of the 4a-carbomethoxy group with the water impurity of the solvent and subsequent decarboxylation. The selective hydrolysis is probably assisted by the neighbouring carbamoyl group which can get close only to the 4a-carbomethoxy group by rotation of the C10a–C10b bond. This view is firmly supported by the dipole–dipole interaction between the two involved groups detected in **5e** by X-ray analysis (Fig. 2). Contrary to the carbamoylpyridyl derivative **6c** the carbamoylphenyl analogue **6a** could not be isolated due to its rapid cyclization followed by spontaneous dehydrogenation (**6a→7a→8a**) taking place easily under the applied conditions.

The ^{1}H- and ^{13}C NMR data of **1a**–**e** obtained in DMSO-d_6 indicate analogous structures in solution having both carbonyl- and thiocarbonyl groups. However, in solid phase, according to its deep red colour, **1d** must occur in a highly associated form due to strong hydrogen bonds involving the pyridine nitrogen and the proton attached to the triazole thione ring of enhanced acidity (**1a** is a white powder and **1b**,**c**,**e** are pale yellow crystals: Table 2). However, in the IR spectrum of **1d** taken in KBr pellet the amide-I band can be found in the same region as those of **1a**–**c**,**e** suggesting similar degree of involvement of the lactame moiety in hydrogen bonds for each triazolopyridazinones studied.

The structure identification of diazepines *cis*-**4a**,**c**,**d** is based on the single crystal X-ray- and NMR analysis of *cis*-**4a**[*], the *bis*-carboethoxy analogue of *cis*-**4a**. Its solid state structure (Fig. 1) does not change in solution as proved by ^{1}H- and ^{13}C NMR spectra obtained in DMSO-d_6. The spectral data assigned by 2D COSY, 2D HSQC and 2D HMBC methods unequivocally confirm the constitution and the considerable NOE (16.8%) detected between H4 and NH protons shows their *cis* arrangement. Consequently, the two carboethoxy groups must also be in *cis* position relative to each other. The upfield shift of the non-equivalent methylene- and methyl protons of the carboethoxy group attached to C4a atom refers to its position in the shielding region of the condensed benzene ring. This arrangement is also supported by DNOE experiment detecting interaction between H7 and the more upfield shifted methylene proton (3.4%). The constitution and stereostructure of *cis*-**4a**,**c**,**d** analogous to that of *cis*-**4a**[*] are evidenced by the followings: (i) the very similar H4, C2a, C4, C4a, C6 and C10b chemical shifts; (ii) the characteristic upfield shift observable on the methyl singlet of the carbomethoxy group bonded to C4a; (iii) the considerable NOE (15.2–17.6%) detected between H4 and NH protons; (iv) the smaller but characteristic NOE (2.7–3.0%) between the shielded methyl protons (in the carbomethoxy group bonded to C4a atom) and the H7 atom.

The structure of **5e** was also determined by single crystal X-ray diffraction (Fig. 2) showing the presence of a nearly planar trisubstituted thiazolo[2,3-*c*][1,2,4]trizole unit. The very similar IR, ^{1}H- and ^{13}C NMR data obtained for **5a**–**e** provide unambiguous evidence for their closely related structures. In monoester derivative **6c** a diagnostic NOE (4.2%) was measured between H4a and H10 protons which rules out the alternative structure containing the carbomethoxy group at position 4a.

In the 2D HMBC spectrum of monoester **8a** the NH proton gives correlation both to C4 and C4a atoms proving the existence of the condensed 1,3-diazepine ring. The

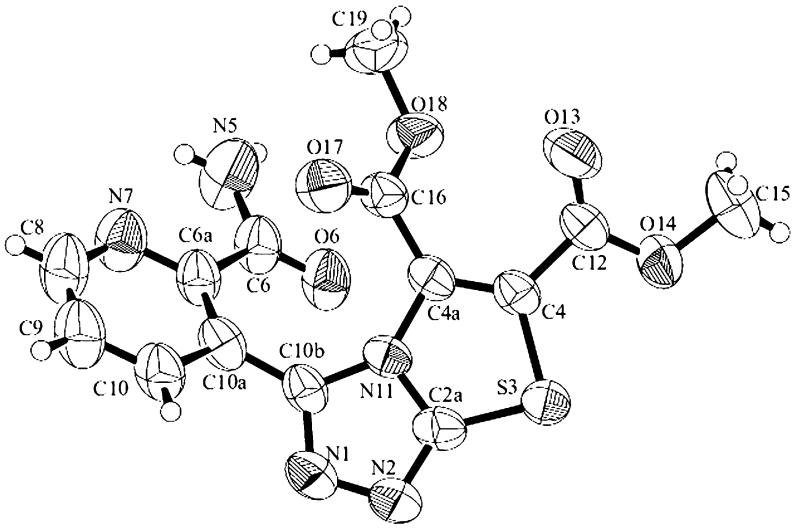


Figure 2. X-ray structure of **5e**.

downfield shifted NH resonance and the upfield shifted C4 signal of **8a** give further evidence for its tetracyclic structure having *N*-acylated β-enaminoester moiety. The low stretching frequency of the ester carbonyl group discernible in the IR spectrum also suggests the presence of the aforementioned structural element in **8a**.

The X-ray structures of *cis*-**4a*** and **5e** with their numbering are shown in Figs. 1 and 2, respectively. The central 1,3-diazepinone ring of *cis*-**4a*** is in boat conformation. The steric crowdance around C4a and the presence of two condensed aromatic rings cause slight distortion on the lactame moiety and on the junction of the benzene ring while the junction of the triazole ring remains planar (torsion angles for C6a–C6–N5–C4a, C6–C6a–C10a–C10b and C10a–C10b–N11–C4a are 11(1), −12(1) and −2(1)°, respectively). The 4- and 4a-ethoxycarbonyl groups are in pseudo-equatorial and pseudo-axial positions, respectively. For both *cis*-**4a*** and **5e** the S3–C4–C12–O14 torsion angle is small (−24.4(7) and 20.9(4)°, respectively) allowing the formation of S–O close-contact[6] (distance S3–O14 is 2.883(5) and 3.120(4) Å, respectively). In both structures dipole–dipole interactions with tandem character are detectable involving the alkoxycarbonyl- and carbamoyl groups. In *cis*-**4a*** distances O13–C17 and O18–C6 are 2.733(8) and 3.035(8) Å, respectively. In **5e** distances O13–C16, O17–C6a and C4a–O6 are 3.376(6), 3.418(7) and 3.266(6) Å, respectively. Although both compounds contain suitable donor and acceptor atoms, only crystal structure of *cis*-**4a*** shows intermolecular hydrogen bonds (between NH and N2 of the molecule in symmetry equivalent position $-x+1/2$, $y+1/2$, $-z+1/2$).

3. Conclusion

The extension of the reported facile and unprecedented ring transformation reactions by applying further electron-deficient acetylene derivatives and such substrates in which the 1,2,4-triazolo[4,3-*b*]pyridazine subunit is condensed to a variety of homo- and heterocycles may open up a convenient synthetic pathway to a great number of polycondensed 1,3-diazepines and thiazolo[2,3-*c*]-[1,2,4]triazoles. Moreover, the incorporated functionalities (alkoxycarbonyl- and related groups) make possible subsequent couplings (e.g. with hydrazines and amines) to produce a large number of new compounds with the aforementioned ring systems having considerable biological interest.[7–11] Finally, *cis*-**4a***, *cis*-**4a**,**c**,**d** and **8a** are the first representatives of a novel ring system which, according to our best knowledge, has not been described so far.

4. Experimental

Melting points (uncorrected) were determined with a Boetius microstage. The IR spectra were recorded in KBr pellets with a BRUKER IFS 55 FT-spectrometer. The ^{1}H- and ^{13}C NMR spectra were recorded in DMSO-d_6 solution in 5 mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 (^{1}H) and 125 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal reference. The standard Bruker microprogram NOEMULT.AU to generate NOE was used with a selective preirradiation time. DEPT spectra were run in a standard manner, using only the Θ=135° pulse to separate CH/CH$_3$ and CH$_2$ lines phased 'up' and 'down', respectively. The 2D HMQC and 2D HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND, respectively.

Single crystal X-ray diffraction measurements of *cis*-**4a*** and **5e** were accomplished by a Rigaku R-Axis IIC imaging plate detector. All data are deposited at the Cambridge Crystallographic Data Centre (deposition numbers: 157486 for *cis*-**4a*** and 157485 for **5e**).

4.1. Preparation of 1a–e

A mixture of 0.01 mol of the appropriate hydrazine (4-hydrazinophthalazine-1(2*H*)-one,[12] 8-hydrazinopyrido[2,3-*d*]pyridazine-5(6*H*)-one,[13] 5-hydrazinopyrido[2,3-*d*]-pyridazine-8(7*H*)-one,[13] 4-hydrazinopyrido[3,4-*d*]pyridazine-1(2*H*)-one,[14] 1-hydrazinopyrido[3,4-*d*]pyridazine-4(3*H*)-one,[14]

and phenylisothiocyanate (1.35 g; 0.01 mol) was stirred and heated at 150°C in DMF (25 mL) for 5 h. After cooling the precipitated crystals were filtered off, washed with EtOH (5 mL), and recrystallized from EtOH (50–100 mL) to obtain:

4.1.1. [1,2,4]Triazolo[4,3-*a*]phthalazine-6(5*H*)-one-3(2*H*)-thione (1a). Yield 89%; white powder, mp 303–306°C; [Found: C, 49.59; H, 2.74; N, 25.65; S, 14.69. $C_9H_6N_4OS$ requires C, 49.55; H, 2.77; N, 25.67; S, 14.67%]; ν_{max} (KBr) 3380–2600 br, 1635 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 14.29 and 13.32 (2×1H, 2×s, N*H*CO and N*H*CS), 8.21 (1H, d, *J*=7.4 Hz, H7), 8.10 (1H, d, *J*=7.3 Hz, H10), 7.93 (1H, t, *J*=7.3 Hz, H9), 7.82 (1H, t, *J*=7.3 Hz, H8); δ_C (125 MHz, DMSO-d_6) 162.0, 159.4, 141.2, 134.7, 132.8, 126.6, 124.5, 123.3, 121.2.

4.1.2. Pyrido[2,3-*d*]-[1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thione (1b). Yield 79%; yellow powder, mp 297–299°C; [Found: C, 43.77; H, 2.30; N, 31.99; S, 14.54. $C_8H_5N_5OS$ requires C, 43.84; H, 2.30; N, 31.94; S, 14.60%]; ν_{max} (KBr) 3480–2500 br, 1629 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 14.37 and 14.23 (2×1H, 2×s, N*H*CO and N*H*CS), 9.06 (1H, d, *J*=4.8 Hz, H9), 8.04 (1H, d, *J*=7.8 Hz, H7), 7.84 (1H, dd, *J*=7.8, 4.8 Hz, H8); δ_C (125 MHz, DMSO-d_6) 162.2, 159.5, 155.8, 142.6, 141.6, 134.9, 119.0.

4.1.3. Pyrido[3,4-*d*]-[1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thione (1c). Yield 83%; yellow powder, mp 306–310°C; [Found: C, 43.82; H, 2.27; N, 31.90; S, 14.65. $C_8H_5N_5OS$ requires C, 43.84; H, 2.30; N, 31.94; S, 14.60%]; ν_{max} (KBr) 3027, 1614 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 14.42 and 13.82 (2×1H, 2×s, N*H*CO and N*H*CS), 9.51 (1H, s, H10), 9.01 (1H, d, *J*=5.8 Hz, H8), 7.96 (1H,, *J*=5.8 Hz, H7); δ_C (125 MHz, DMSO-d_6) 162.2, 158.6, 152.7, 146.0, 139.5, 132.9, 119.7, 119.1.

4.1.4. Pyrido[4,3-*d*]-[1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thione (1d). Yield 86%; red powder, mp >320°C; [Found: C, 43.90; H, 2.26; N, 31.99; S, 14.62. $C_8H_5N_5OS$ requires C, 43.84; H, 2.30; N, 31.94; S, 14.60%]; ν_{max} (KBr) 3041, 1646 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 14.57 and 13.76 (2×1H, 2×s, N*H*CO and N*H*CS), 9.32 (1H, s, H7), 9.02 (1H, d, *J*=5.8 Hz, H9), 8.13 1H, d, *J*=5.8 Hz, H10); δ_C (125 MHz, DMSO-d_6) 163.8, 160.1, 154.4, 152.9, 142.6, 134.2, 115.4, 107.3.

4.1.5. Pyrido[3,2-*d*]-[1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thione (1e). Yield 75%; yellow powder, mp 294–298°C; [Found: C, 43.88; H, 2.25; N, 31.95; S, 14.60. $C_8H_5N_5OS$ requires C, 43.84; H, 2.30; N, 31.94; S, 14.60%]; ν_{max} (KBr) 3400–2700 br, 1630 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 14.29 and 14.15 (2×1H, 2×s, N*H*CO and N*H*CS), 9.14 (1H, d, *J*=4.8 Hz, H8), 8.63 (1H, d, *J*=7.4 Hz, H10), 7.92 (1H, dd, *J*=7.4, 4.8 Hz, H9); δ_C (125 MHz, DMSO-d_6) 161.7, 161.2, 154.2, 149.4, 141.1, 132.1, 128.5, 121.2.

4.2. Reactions of 1a–e with DEAD and DMAD

Equimolar amounts (1–1 mmol) of the corresponding thione (**1a–e**) and dialkyl acetylenedicarboxylate (DEAD or DMAD) were stirred and heated at 100°C/150°C in DMF (20 mL) (Table 2). After the reaction time given in Table 2 the solvent was evaporated in vacuo. The crude products were separated and purified by flash chromatography (silica gel 40–63 μm, 50% cyclohexane/$CHCl_3$) followed by crystallization from EtOH to obtain:

4.2.1. (4*R,4a*R**)-4,4a-Dihydro-4,4a-*bis*-ethoxycarbonyl-1,2,5,10c-tetraaza-3-thiabenzo[6,7]cyclohepta[1,2,3,-*cd*]-pentalene-6(5*H*)-one (*cis*-4a*).** Yield 78% (after treatment of **1a** at 100°C); white cubes, mp 176–178°C; [Found: C, 52.67; H, 4.14; N, 14.45; S, 8.24. $C_{17}H_{16}N_4O_5S$ requires C, 52.59; H, 4.20; N, 14.42; S, 8.25%]; R_f (50% cyclohexane/$CHCl_3$) 0.38; ν_{max} (KBr) 3081, 3068, 1770, 1732, 1663 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 9.90 (1H, s, NH), 8.09 (1H, d, *J*=7.4 Hz, H7), 7.97 (1H, d, *J*=7.4 Hz, H10), 7.70 (1H, t, *J*=7.4 Hz, H8), 7.65 (1H, t, *J*=7.4 Hz, H9), 6.36 (1H, s, H4), 4.21 (2H, q, *J*=6.9 Hz, 4-$CO_2CH_2CH_3$), 3.98 (1H, dq, *J*=10.5, 6.9 Hz, 4a-$CO_2CH_aH_bCH_3$), 3.89 (1H, dq, *J*=10.5, 6.9 Hz, 4a-$CO_2CH_aH_bCH_3$), 1.21 (3H, t, *J*=6.9 Hz, 4-$CO_2CH_2CH_3$), 0.79 (3H, t, *J*=6.9 Hz, 4a-$CO_2CH_aH_bCH_3$); δ_C (125 MHz, DMSO-d_6) 167.9, 166.0, 165.6, 155.6, 149.9, 133.6, 133.4, 132.4, 131.9, 127.4, 122.3, 72.6, 64.2, 64.0 (two coalesced lines), 14.7, 14.1.

4.2.2. (4*R,4a*R**)-4,4a-Dihydro-4,4a-*bis*-methoxycarbonyl-1,2,5,10c-tetraaza-3-thiabenzo[6,7]cyclohepta[1,2,3,-*cd*]-pentalene-6(5*H*)-one (*cis*-4a).** Yield 84% (after treatment of **1a** at 100°C);white needles, mp 193–195°C; [Found: C, 50.05; H, 3.30; N, 15.58; S, 8.82. $C_{15}H_{12}N_4O_5S$ requires C, 50.01; H, 3.38; N, 15.54; S, 8.88%]; R_f (50% cyclohexane/$CHCl_3$) 0.30; ν_{max} (KBr) 3186, 3090, 1771, 1751, 1663 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 9.89 (1H, s, NH), 8.09 (1H, d, *J*=7.4 Hz, H7), 7.99 (1H, d, *J*=7.4 Hz, H10), 7.71 (1H, t, *J*=7.4 Hz, H8), 7.65 (1H, t, *J*=7.4 Hz, H9), 6.38 (1H, s, H4), 3.77 (3H, s, 4-CO_2CH_3), 3.50 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 167.8, 166.5, 166.2, 155.6, 149.8, 133.7, 133.4, 132.1, 132.0, 127.4, 122.2, 72.6, 63.8, 55.1, 54.8.

4.2.3. (4*R,4a*R**)-4,4a-Dihydro-4,4a-*bis*-methoxycarbonyl-1,2,5,9,10c-pentaaza-3-thiabenzo[6,7]cyclohepta[1,2,3,-*cd*]-pentalene-6(5*H*)-one (*cis*-4c).** Yield 80% (after treatment of **1c** at 100°C); yellow powder, mp 200–202°C; [Found: C, 46.48; H, 3.09; N, 19.42; S, 8.90. $C_{14}H_{11}N_5O_5S$ requires C, 46.55; H, 3.06; N, 19.38; S, 8.86%]; R_f (50% cyclohexane/$CHCl_3$) 0.26; ν_{max} (KBr) 3190, 3085, 1775, 1750, 1681 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 10.04 (1H, s, NH), 9.18 (1H, s, H10), 8.82 (1H, d, *J*=5.8 Hz, H8), 7.95 (1H, d, *J*=5.8 Hz, H7), 6.40 (1H, s, H4), 3.79 (3H, s, 4-CO_2CH_3), 3.53 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 166.5, 166.2, 166.0, 156.2, 153.0, 148.4, 147.9, 138.5, 119.0, 117.1, 72.8, 63.8, 55.3, 54.9.

4.2.4. (4*R,4a*R**)-4,4a-Dihydro-4,4a-*bis*-methoxycarbonyl-1,2,5,8,10c-pentaaza-3-thiabenzo[6,7]cyclohepta[1,2,3,-*cd*]-pentalene-6(5*H*)-one (*cis*-4d).** Yield 75% (after treatment of **1d** at 100°C); yellow powder, mp 210–213°C; [Found: C, 46.50; H, 3.05; N, 19.33; S, 8.85. $C_{14}H_{11}N_5O_5S$ requires C, 46.55; H, 3.06; N, 19.38; S, 8.86%]; R_f (50% cyclohexane/$CHCl_3$) 0.22; ν_{max} (KBr) 3181, 3079, 1766, 1746, 1676 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 10.06 (1H, s, NH), 9.38 (1H, s, H7), 8.84 (1H, d, *J*=5.8 Hz, H9), 7.98 (1H, d,

J=5.8 Hz, H10), 3.77 (3H, s, 4-CO_2CH_3), 3.52 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 166.5, 165.9, 165.4, 156.8, 154.2, 153.0, 148.1, 129.0, 125.6, 119.6, 72.8, 63.2, 54.7, 54.3.

4.2.5. 3-(2′-Carbamoylphen-1′-yl)-5,6-*bis*-methoxycarbonylthiazolo[2,3-*c*]-[1,2,4]triazole (5a). Yield 8% (after treatment of **1a** at 150°C); yellow powder, mp 201–202°C; [Found: C, 49.47; H, 3.40; N, 15.50; S, 8.85. $C_{15}H_{12}N_4O_5S$ requires C, 50.01; H, 3.38; N, 15.54; S, 8.88%]; R_f (50% cyclohexane/$CHCl_3$) 0.46; ν_{max} (KBr) 3368, 3179, 1748, 1723, 1684 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.04 (1H, s, NH_aH_b), 7.34 (1H, s, NH_aH_b), 7.87 (1H, d, J=7.4 Hz, H7), 7.67 (2H, t, J=7.4 Hz, H8 and H9), 7.53 (1H, d, J=7.4 Hz, H10), 3.85 (3H, s, 4-CO_2CH_3), 3.30 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 168.5, 160.5, 157.9, 155.6, 149.1, 136.0, 132.7, 131.4 (two coalesced lines), 128.7, 126.8, 126.7, 125.2, 54.6, 54.0.

4.2.6. 3-(3′-Carbamoylpyrid-2′-yl)-5,6-*bis*-methoxycarbonylthiazolo[2,3-*c*]-[1,2,4]triazole (5b). Yields are listed in Table 2; yellow powder, mp 190–191°C; [Found: C, 46.52; H, 3.06; N, 19.41; S, 8.81. $C_{14}H_{11}N_5O_5S$ requires C, 46.55; H, 3.06; N, 19.38; S, 8.86%]; R_f (50% cyclohexane/$CHCl_3$) 0.52; ν_{max} (KBr) 3375, 3151, 1742, 1729, 1690 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.71 (1H, d, J=7.8 Hz, H9), 8.08 (2H, s, NH_aH_b and d, J=4.2 Hz, H7: partly overlapping signals), 7.64 (1H, dd, J=7.8, 4.2 Hz, H8), 7.60 (1H, s, NH_aH_b), 3.91 (3H, s, 4-CO_2CH_3), 3.68 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 168.6, 160.4, 158.9, 155.4, 150.1, 149.6, 142.7, 137.7, 134.0, 127.7, 126.3, 125.5, 54.8, 54.4.

4.2.7. 3-(4′-Carbamoylpyrid-3′-yl)-5,6-*bis*-methoxycarbonylthiazolo[2,3-*c*]-[1,2,4]triazole (5c). Yield 25% (after treatment of **1c** at 150°C); yellow powder, mp 168–169°C; [Found: C, 46.57; H, 3.08; N, 19.38; S, 8.86. $C_{14}H_{11}N_5O_5S$ requires C, 46.55; H, 3.06; N, 19.38; S, 8.86%]; R_f (50% cyclohexane/$CHCl_3$) 0.55; ν_{max} (KBr) 3365, 3162, 1748, 1730, 1695 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.93 (1H, d, J=5.8 Hz, H8), 8.79 (1H, s, H10), 8.37 (1H, s, NH_aH_b), 7.84 (1H, d, J=5.8 Hz, H7), 7.75 (1H, s, NH_aH_b), 3.89 (3H, s, 4-CO_2CH_3), 3.44 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 167.0, 160.4, 157.9, 155.2, 153.0, 152.5, 146.4, 142.6, 126.9, 126.3, 122.2, 122.0, 54.8, 54.2.

4.2.8. 3-(3′-Carbamoylpyrid-4′-yl)-5,6-*bis*-methoxycarbonylthiazolo[2,3-*c*]-[1,2,4]triazole (5d). Yield 54% (after treatment of **1c** at 150°C); yellow cubes, mp 184–186°C; [Found: C, 46.50; H, 3.01; N, 19.33; S, 8.89. $C_{14}H_{11}N_5O_5S$ requires C, 46.55; H, 3.06; N, 19.38; S, 8.86%]; R_f (50% cyclohexane/$CHCl_3$) 0.50; ν_{max} (KBr) 3358, 3070, 1739, 1729, 1690 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 9.10 (1H, s, H7), 8.91 (1H, d, J=5.8 Hz, H9), 8.32 (1H, s, NH_aH_b), 7.67 (1H, d, J=5.8 Hz, H10), 7.62 (1H, s, NH_aH_b), 3.92 (3H, s, 4-CO_2CH_3), 3.45 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 167.0, 160.7, 158.2, 156.0, 152.6, 149.4, 148.5, 143.0, 127.2, 126.6, 126.5, 121.0, 54.8, 53.9.

4.2.9. 3-(2′-Carbamoylpyrid-3′-yl)-5,6-*bis*-methoxycarbonylthiazolo[2,3-*c*]-[1,2,4]triazole (5e). Yields are listed in Table 2; yellow cubes, mp 177–178°C; [Found: C, 46.59; H, 3.09; N, 19.42; S, 8.82. $C_{14}H_{11}N_5O_5S$ requires C, 46.55; H, 3.06; N, 19.38; S, 8.86%]; R_f (50% cyclohexane/$CHCl_3$) 0.48; ν_{max} (KBr) 3495, 3377, 1733, 1728, 1692 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.86 (1H, d, J=4.8 Hz, H8), 8.34 (1H, s, NH_aH_b), 8.11 (1H, d, J=7.8 Hz, H10), 7.82 (1H, dd, J=7.8, 4.8 Hz, H9), 7.71 (1H, s, NH_aH_b), 3.89 (3H, s, 4-CO_2CH_3), 3.47 (3H, s, 4a-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 166.4, 160.5, 158.2, 154.8, 151.2, 149.2, 147.9, 141.9, 127.0, 126.6, 126.4, 123.4, 54.7, 54.3.

4.2.10. 3-(4′-Carbamoylpyrid-3′-yl)-6-methoxycarbonylthiazolo[2,3-*c*]-[1,2,4]triazole (6c). Yield 35% (after treatment of **1c** at 150°C); yellow powder, mp 222–224°C; [Found: C, 47.51; H, 3.02; N, 23.12; S, 10.52. $C_{12}H_9N_5O_3S$ requires C, 47.54; H, 2.99; N, 23.09; S, 10.55%]; R_f (50% cyclohexane/$CHCl_3$) 0.42; ν_{max} (KBr) 3297, 3058, 1729, 1688 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 8.91 (1H, s, H10), 8.89 (1H, d, J=5.8 Hz, H8), 8.58 (1H, s, H4a), 8.26 (1H, s, NH_aH_b), 7.82 (1H, s, NH_aH_b), 7.76 (1H, d, J=5.8 Hz, H7), 3.90 (3H, s, 4-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 168.1, 161.8, 157.2, 152.8, 151.7, 146.2, 143.9, 125.5, 124.9, 122.6, 120.7, 54.2.

4.2.11. 4-Methoxycarbonyl-1,2,5,10c-tetraaza-3-thiabenzo[6,7]cyclohepta[1,2,3-*cd*]pentalene-6(5*H*)-one (8a). Yield 48% (after treatment of **1a** at 150°C); yellow powder, mp 280–283°C; [Found: C, 51.98; H, 2.63; N, 18.58; S, 10.69. $C_{13}H_8N_4O_3S$ requires C, 52.00; H, 2.69; N, 18.66; S, 10.66%]; R_f (50% cyclohexane/$CHCl_3$) 0.31; ν_{max} (KBr) 3271, 1688, 1657 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 9.85 (1H, s, NH), 8.38 (1H, d, J=7.4 Hz, H10), 8.35 (1H, d, J=7.4 Hz, H7), 7.77 (1H, t, J=7.4 Hz, H9), 7.61 (1H, t, J=7.4 Hz, H8), 3.87 (3H, s, 4-CO_2CH_3); δ_C (125 MHz, DMSO-d_6) 164.0, 162.6, 154.1, 147.8, 135.3, 134.8, 132.7, 131.6, 128.4, 126.7, 125.2, 93.3, 53.9.

4.3. Thermal transformation of *cis*-4a,c,d

The corresponding condensed 1,3-diazepine (1 mmol) was dissolved in DMF (25 mL) and the solution was heated at 150°C for the period of time given in Table 2 then the solvent was evaporated in vacuo. The crude products were separated and purified by flash chromatography (silica gel 40–63 μm, 50% cyclohexane/$CHCl_3$) followed by crystallization from EtOH to obtain **5a**,**c**,**d**, **6c** and **8a** with the yields listed in Table 2.

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