Tetrahydropyrimidin-2(1*H*)-ones with three neighbouring phenyl groups. Synthesis and allylic strain effects

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Abstract

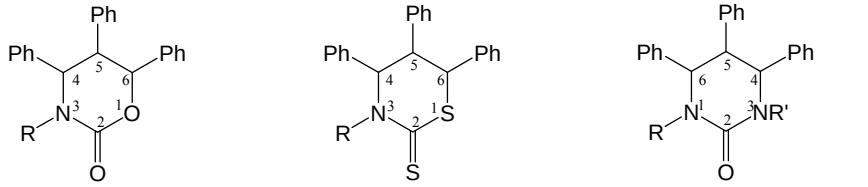
Favoured conformations of differently *N*-substituted *cis,trans*-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-ones and the allylic strain caused by different groups were studied. It was found that the diequatorial conformer is strongly preferred in equally *N,N'*-disubstituted products, where the effects of the two substituents negate each other. It was shown that a benzyl group gives rise to much stronger allylic strain than a methyl group. Additionally, unusual azetidine formation was observed upon acid hydrolysis of benzylideneamino azide *via* S_N2 mechanism. It was suggested that *N*-substitution does not significantly influence the ring geometry angle, while quaternisation affords serious increase of puckering.

Keywords: Tetrahydropyrimidin-2(1*H*)-ones, 1,2,3-triphenylpropane skeleton, favoured conformations, allylic strain, azetidines, ring geometry

Introduction

Compounds with a 1,2,3-triphenylpropane skeleton are useful models for conformational relationship studies due to their symmetry and the limited number of allowed conformations. Heterocyclic systems of this type are of special interest due to the tendency of phenyl groups to adopt axial *vs* equatorial position in the conformations of the various isomers. The conformational behaviour of tetrahydrooxazinones[1] and tetrahydrothiazinethiones[2] with three neighbouring phenyl groups (Figure 1) has been investigated. It was found that an *N*-substituent shifts the conformational equilibrium towards the conformer with an axial substituent at the carbon next to the nitrogen, due to the partial double character of the N-CO bond. The latter brings the *N*-substituent close to the equatorial one at the adjacent carbon, thus giving rise to allylic strain, $A^{(1,2)}$.[3] It has been observed that the effect is most clearly revealed in the case of *trans,cis* diastereoisomers,[4] while with the rest of the isomers either the same conformer is favoured for unsubstituted compounds or an equilibrium between both allowed forms exists.

Oxazinones and thiazinethiones showed similar patterns of behaviour and only slight differences were observed, probably due to the difference in C-O and C-S bond lengths. However, it has been found that in both series all *N*-substituents shift the equilibrium towards the sterically unfavoured diaxial form. Thus, an explicit comparison between the conformational preferences for a given configuration and the role of allylic strain, caused by different substituents, cannot be performed. The determination of the effects in tetrahydropyrimidinones (Figure 1), where the carbon-heteroatom bond lengths are equal and the effects of the two *N*-substituents are in concurrence, could provide more complete information about the allylic strain of different groups in these systems.



tetrahydro-1,3-oxazin-2-ones tetrahydro-1,3-thiazine-2-thiones tetrahydropyrimidin-2(1H)-ones

Figure 1. Heterocyclic compounds with triphenylpropane skeleton.

Tetrahydropyrimidinones are also useful as optically active chiral auxiliaries in a variety of organic reactions such as alkylation, aldol condensation, Michael addition and many others.[5] Among the broad range of procedures for direct asymmetric C-C bond formation, which now plays a key role in the preparation of complex natural products and pharmaceuticals,[6,7] the use of chiral auxiliaries is also considered as a methodology of great practical relevance,[8] despite their stoichiometric application. Different heterocyclic compounds, tetrahydropyrimidinones,[9-11] as well as their *O*-analogues,[12,13] have been widely applied as auxiliaries and the stereochemistry of the final product was fully controlled by the auxiliary used.

A study on the synthesis and allylic strain effects in differently *N*-substituted *cis,trans*-tetrahydropyrimidin-2(1*H*)-ones with triphenylpropane skeleton,[14] is presented herein.

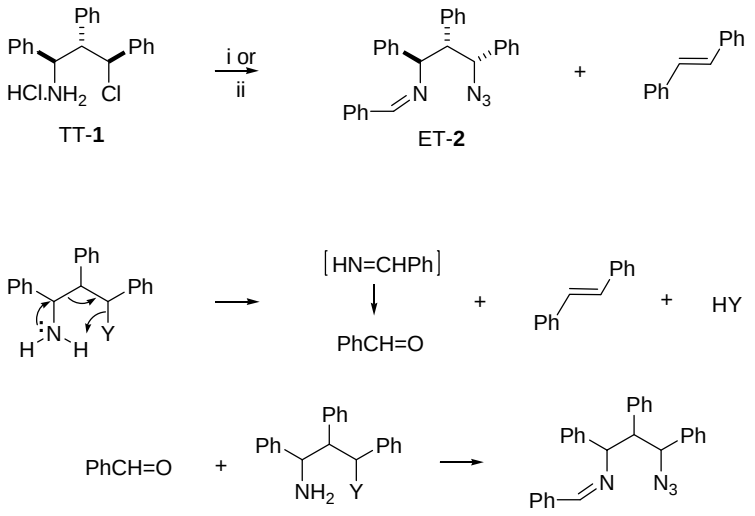
Results and Discussion

The triphenylated amino and methylamino propyl chlorides were obtained in our laboratory[15] as pairs of diastereoisomers, which differ in the relative configuration at C-1/C-2, that at C-2/C-3 being the same, *TT/ET* and *EE/TE* couples.[16] Since nucleophilic substitution of the chlorine atom with an azide group and subsequent routine transformations provides a relatively short method for tetrahydropyrimidin-2(1*H*)-one construction, *TT*-chlorides represent good candidates as starting materials in the synthesis of the *cis,trans*-pyrimidinones[14].

The transformation was first studied in the case of *TT*-amino chloride **1**, where, surprisingly, instead of the expected amino azide, the corresponding *ET* benzylideneamino compound **2** was

isolated, as shown in Scheme 1. The latter can be explained by a retroaldol cleavage of the starting chloride with elimination of benzylideneamine as a by-product, which hydrolyzes spontaneously to benzaldehyde and reacts with the free amino group. This suggestion is confirmed by the observed *trans*-stilbene formation.

As the retroaldol reaction requires a lone electron pair on nitrogen, the latter was inactivated as a Schiff base by performing the transformation in the presence of benzaldehyde as a co-reagent. Thus, the retroaldol cleavage was precluded, affording the product in a much higher yield with no *trans*-stilbene formation.

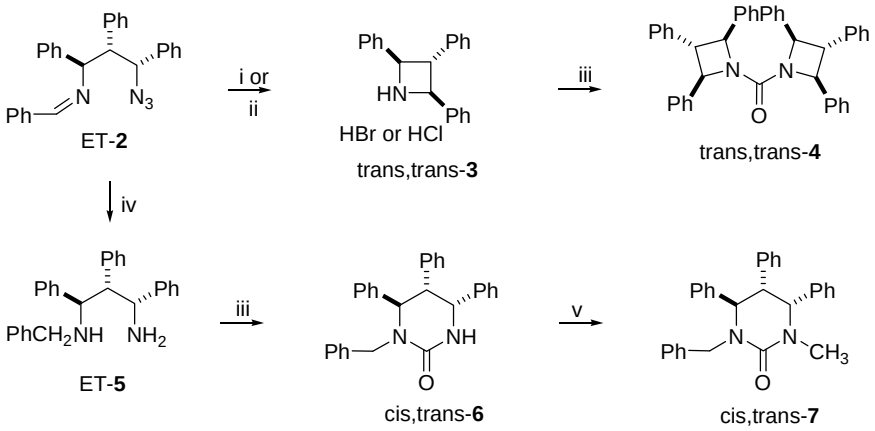


Scheme 1. i) NaN_3 (3 equiv), DMF, 70°C, 5 h; ii) NaN_3 (3 equiv), PhCHO (1.5 equiv), DMF, 70°C, 3-5 h, no *trans*-stilbene formation.

The assignment of the configuration of the product as *ET* is based on the observed coupling constants in the proton NMR spectra in comparison with those of a broad range of differently 1,3-bifunctionalysed compounds with triphenylpropane skeleton, as well as on the known fact that benzyl chlorides undergo similar reactions by S_N2 mechanism *via* inversion of the configuration.[17] An additional proof for the *ET* configuration of the azide **2** is the *cis,trans* configuration of pyrimidinone **6**, whose synthesis is described below (Scheme 2).

Azide **2** represents a direct precursor of the target diamine. In an attempt to hydrolyze both the azido and benzylideneamino groups of **2** under acidic conditions azetidine **3** was isolated as an unexpected product of intramolecular cyclisation (Scheme 2).

The ^1H and ^{13}C NMR spectra of compounds **3** and **4** show common signals for H-2/H-4 and C-2/C-4 resonances, which is a direct proof for their *trans,trans*-configuration[18] (Table 1). Methylation of azetidine **3** and comparison of the physical and spectral data of the product with those of the known *trans,trans*-1-methyl-azetidine,[2] gave an additional confirmation of its structure and stereochemistry.



Scheme 2. i) 4 N HBr/AcOH, rt, overnight; ii) 1 M HCl, EtOH, reflux, 2 h; iii) phosgene (1 equiv, 20% soln in toluene), pyridine (2.5 equiv), toluene, rt, 2 h; iv) $LiAlH_4$ (4 mmol, 16 equiv), dry ether, rt, 3 h; v) NaH (3 equiv), dry THF, rt, 15 min, CH_3I (15 equiv), rt, 1 h.

Table 1. ^{1}H and ^{13}C NMR data of *trans,trans*-2,3,4-triphenylazetidines **3** and **4**, chemical shifts in δ, ppm, against TMS as an internal standard, *J* in Hz

Compd.	Solvent	C*H*-2 and C*H*-4[a] *C*H-2 and *C*H-4[a]	C*H*-3 *C*H-3	^3J (Hz)	Others
3 as HBr	CD_3OD	5.72, d, 2H 65.4	5.03, t, 1H 50.2	10.4	-
3 as HCl	$CDCl_3$	5.37, d, 2H	4.41, t, 1H	9.9	ca. 8.3[b], brs, N*H*
3	$CDCl_3$	5.06, d, 2H	3.64, t, 1H	8.5	2.79[b], brs, N*H*
4	$CDCl_3$	5.21, d, 4H 69.4	3.24, t, 2H 54.6	6.4	165.7, *C*=O

[a] Common signals. [b] Exchangeable signal.

The vicinal coupling values (^3J) in a series of cyclobutanes of known geometry have been correlated by Abraham *et al.*[19] with puckering angles. It was found that smaller couplings are observed for smaller puckering angles. Afterward, Kingsbury *et al.*[20] have applied these correlations to azetidines. The authors have found that very large ^3J are suggestive of axial hydrogens in a puckered ring. In a previous study in our laboratory,[2] *N*-methyl azetidines were investigated. It was shown that the conformations with e,e,e and e,a,e phenyls in puckered rings are preferred for *trans,trans* and *cis,cis* diastereoisomers,[21] respectively, while a planar ring is favoured for the *cis,trans* isomer. The coupling of 8.5 Hz, observed for the free base of **3** (Table 1) is suggestive of puckered ring. This value compared with 8.9 Hz for the corresponding *N*-methyl derivative shows that *N*-methylation does not significantly influence the ring geometry. In contrast, the larger couplings observed for the ammonium salts, 10.4 Hz and 9.9 Hz for the hydrobromide and hydrochloride of **3**, respectively (Table 1), and 10.9 Hz for the hydrochloride

of *N*-methyl derivative, indicate that the quaternisation of nitrogen results in a strongly biased preferred conformation with e,e,e phenyls in a puckered ring. This suggestion could be tested by the conformational behaviour of the *cis,trans*-isomer, as it was assumed that a planar ring is favoured for its *N*-methyl derivative. Thus, the transformation was performed with a diastereoisomeric mixture of chlorides **1**, *TT/ET* 4.7:1, and the hydrobromide of *cis,trans*-azetidine was obtained as an impurity. The latter shows very dissimilar couplings, J_{cis} 2.8 Hz and J_{trans} 11.0 Hz, which confirms that quaternisation affords a serious increase of the puckering angle.

Surprisingly, couplings of 8.4 Hz and 6.5 Hz were observed in the proton spectrum of the hydrobromide of *cis,trans*-azetidine in methanol-d_4, instead of a large and a small one as in deuterochloroform. The former are very similar to the couplings of 8.7 Hz and 5.4 Hz for the *N*-methyl derivative. It could be suggested that contrary to the *trans,trans*-isomer, where a puckered ring is favoured in deuteromethanol, the ring geometry in the case of the *cis,trans*-product depends on the solvent, and that protic solvents lead to a significant decrease of the puckering angle, while in aprotic the puckered ring is preferred.

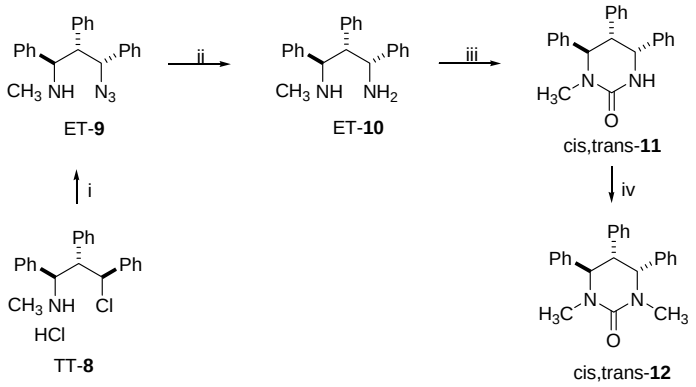
In the case of azetidine **4**, the ^3J value of 6.4 Hz is suggestive of a planar or slightly puckered ring. The latter compared with the *N*-methyl derivative (8.9 Hz), shows that an adjacent C=O group affords a decrease of the puckering angle, probably due to the partial double bond character of C-N.

The *trans,trans*-configuration of the product, which is the result of inversion at C-1, C-2 in azetidine, respectively, gives an indication that the nitrogen originates from the benzilideneamino group. The latter hydrolyzes to an amine as a first step, which afterwards attacks the carbon bearing the azide functionality, leading to cyclisation with inversion of the configuration at C-1. It could be suggested that the reaction goes *via* S_N2 mechanism with inversion of the configuration at C-1, bearing the azide functionality, and S_N1 does not take place as a parallel mechanism, as no *cis,trans*-azetidine formation was detected when pure *TT*-chloride was used.

When starting from the *N*-methylamino chloride **8** (Scheme 3), no retroaldol cleavage was observed, which most probably is due to the increased basicity at the nitrogen due to the *N*-alkyl substituent or/and to a faster than retroaldol reaction nucleophilic substitution in this case.

ET-Diamines **5** and **10**, easily obtained by hydrogenation of azides **2** and **9**, represent direct precursors of tetrahydropyrimidinones **6** and **11**, which after methylation gave the corresponding *N,N'*-disubstituted products **7** and **12,** as shown in Scheme 2 and Scheme 3. Thus, we had four products for comparison, which differ in the position and the type of *N*-substitution, with *cis,trans* configuration, the most useful isomer for allylic strain effect investigations in these hindered systems, where 1,3-parallel interactions between bulky groups lead to a strong limitation of the allowed conformations.

N,N'-Dimethyl pyrimidinone **12**, having equal *N*-substituents, the effects of which cancel each other, is a conformational analogue of the *N*-unsubstituted product, whose preparation by hydrolysis of **2** was unsuccessful.



Scheme 3. i) NaN_3 (3 equiv), DMF, 70°C, 3 h; ii) $LiAlH_4$ (4 mmol, 16 equiv), dry ether, rt, 3 h; iii) phosgene (1 equiv, 20% soln in toluene), pyridine (2.5 equiv), toluene, rt, 2 h; iv) NaH (3 equiv), dry THF, rt, 15 min, CH_3I (15 equiv), rt, 1 h.

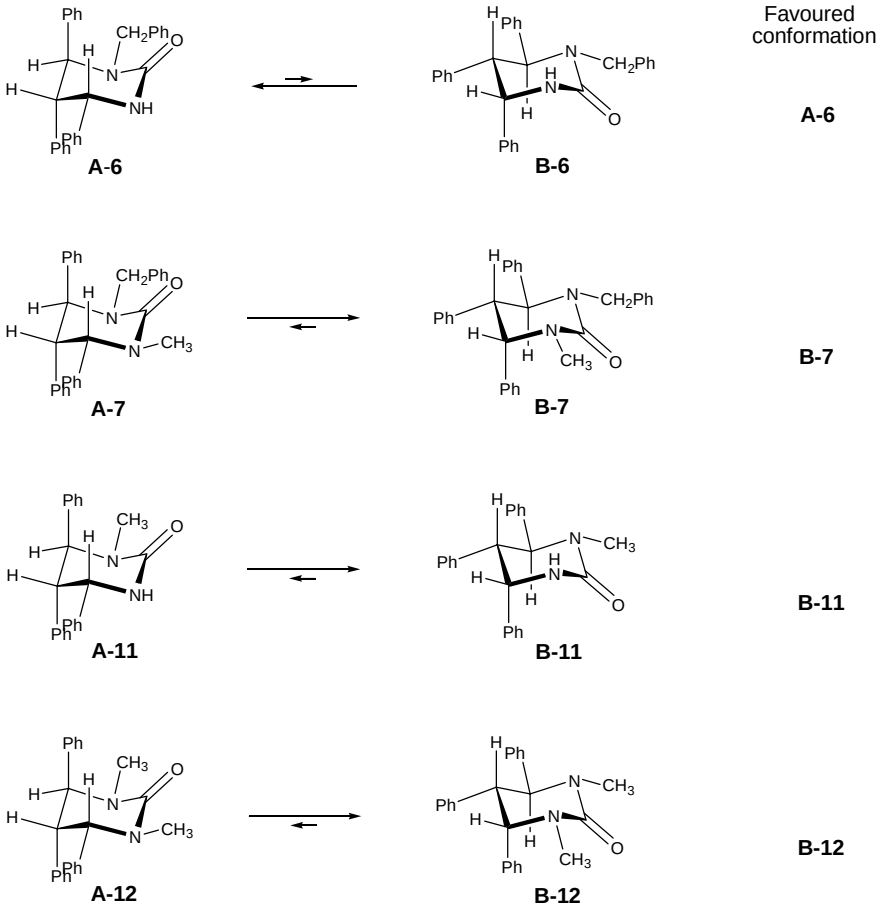
As can be seen on Table 2, small J_{cis} (3.0 Hz) and large J_{trans} (12.7 Hz) are observed for the dimethylated product **12.** These data show that the conformation with a,e,e phenyls (**B-12**) is strongly preferred for this derivative, as well as for the *N,N'*-unsubstituted and the equally *N,N'*-disubstituted compounds. This preferred conformation is in agreement with the classical stereochemical canons, as the diaxial form (e,a,a, **A-12**) is strongly disfavoured in the absence of other factors as a norm.

Table 2. ^1H and ^{13}C NMR data of differently 1,3-disubstituted *cis,trans*-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-ones in $CDCl_3$, chemical shifts in δ, ppm, against TMS as an internal standard, *J* in Hz

Compd	R_1	R_2	C*H*-4,d,1H *C*H-4	C*H*-5,dd,1H *C*H-5	C*H*-6,d,1H *C*H-6	J_{45} (Hz)	J_{56} (Hz)
6[a]	CH_2Ph	H	4.84 54.2	3.14 51.7	4.66 62.2	4.1	2.6
7[b]	CH_2Ph	CH_3	4.35	3.75	4.51	5.0	11.0
11[c]	CH_3	H	5.35 64.0	4.24 53.2	5.986 62.0	3.5	12.4
12[d]	CH_3	CH_3	5.41	4.23	5.82	3.0	12.7

[a] 3.61, d, 1H, *J* 14.4, ½ of CH_2; 5.56, d, 1H, *J* 14.4, ½ of CH_2; 5.23, brs, 1H, N*H*, exchangeable; 48.6, *C*H_2; 156.9, *C*=O. [b] 2.99, s, 3H, CH_3; 3.50, d, 1H, *J* 14.5, ½ of CH_2; 5.47, d, 1H, *J* 14.5, ½ of CH_2. [c] 2.94, s, 3H, CH_3; 33.2, *C*H_3; 151.5, *C*=O. [d] 2.81, s, 3H, CH_3; 2.82, s, 3H, CH_3.

An *N*-alkylation should give rise to allylic strain, which should shift the conformational equilibrium towards the form with e,a,a phenyls, thus avoiding the interaction between the *N*-sustituent and the equatorial one on the neighbouring carbon.

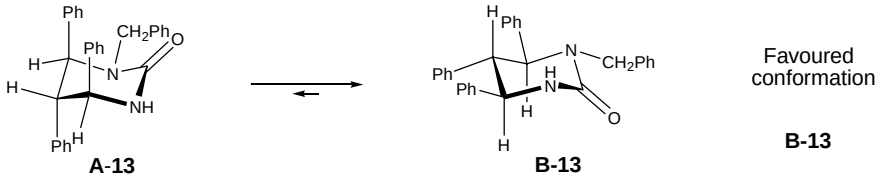


Scheme 4. Favoured conformations of differently *N*-substituted *cis,trans*-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-ones.

As can be seen on Table 2 and Scheme 4, the e,a,a conformer is strongly preferred for *N*-benzyl pyrimidinone **6** (**A-6**, Scheme 4) as a result of allylic strain. The effect of the latter is strong enough in this case to predominate over the steric restrictions for the diaxial conformer. Conversely, an *N*-methyl group does not change significantly the conformational preferences and the a,e,e form (**B-11**) is favoured again, while e,a,a (**A-11**) is very slightly populated, J_{trans} 12.4 Hz in **11** *vs* J_{trans} 12.7 Hz in **12**. This could be due to a relatively small allylic strain of the methyl group, which cannot bias the conformational equilibrium towards the sterically unfavoured diaxial form, or/and to a very strong steric preference for a conformation with equatorial phenyl groups. However, a comparison between the *N*-benzyl (**6**) and *N*-benzyl-*N'*-methyl (**7**) products, where **A-6** *vs* **B-7** are favoured, gives an indication that the effect of the methyl group is strong enough to eliminate the effect of allylic strain, caused by the benzyl group.

When performing the transformation with a diastereoisomeric mixture of chlorides **1**, *TT/ET* 4.7:1, *trans,trans*-pyrimidinone[22] **13** was isolated as an impurity (Scheme 5). The observed relatively small couplings, 3.2 Hz and 4.3 Hz, show that the triequatorial conformer **B-13** is favoured in this case, while the triaxial one (**A-13**) is only slightly populated. The latter

demonstrates that even the allylic strain of a benzyl group is not strong enough to predominate over the forceful steric restrictions of a triaxial conformation.



Scheme 5. Favoured conformation of *trans,trans*-1-benzyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one.

A comparison of the results, described herein, with those obtained for the corresponding pyrimidinones with two neighbouring phenyl groups,[23] where the effects are not clearly revealed, demonstrates the crucial role of the third phenyl in the conformational distribution in these highly hindered heterocyclic systems. The latter and the relative symmetry of triphenylated pyrimidinones make them explicit models for conformational relationship studies, allylic strain of different groups in particular.

It was found for tetrahydrooxazinones[1] and tetrahydrothiazinethiones[2] with three neighbouring phenyl groups, already studied in our laboratory, that the conformational preferences are strongly dependent on *N*-substitution as a result of allylic strain and that the effects are most clearly revealed in the case of the *cis,trans* diastereoisomer. When comparing the favoured conformations of pyrimidinones with those of oxazinones and thiazinethiones with the same configuration, it can be summarized that all heterocyclic compounds of these series have similar conformational behaviour and only slight differences are observed. Thus, while for *N*-unsubstituted, as judged from equally disubstituted pyrimidinones, the diequatorial conformer a,e,e (**B-12**) is strongly preferred, and for thiazinethiones e,a,a form is only slightly populated, in oxazinones both conformers are more or less equally populated, indicating a balance in the steric strain of the diaxial and diequatorial conformations. A possible explanation can be given by the shorter C-O bond in respect to C-N, which increases the steric interactions in the former fragment, thus making both forms almost equally allowed. *N*-Methylation in oxazinones and thiazinethiones leads to a strong preference for the diaxial conformer, e,a,a. This shows that the allylic strain of the methyl group is sufficient to fix the products in the sterically unfavoured diaxial conformations, especially in thiazinethiones, where the steric strain in both forms is not balanced as in the oxazinones. This observation is in agreement with the favoured e,a,a form for *N*-benzyl pyrimidinone (**A-6**), but is in contrast with the conformational preferences of the *N*-methyl derivative (a,e,e, **B-11**). A possible reason could be the existence of a proton at the second nitrogen, which accomplishes some steric interactions, thus decreasing the effect of methyl group allylic strain, which is relatively small, as it was shown above.

The same vicinal couplings, observed for *N*-benzyl and *N*-methyl oxazinones,[1] suggest that both groups provoke similar allylic strain in these systems, where the two fragments of the

molecule, C-N and C-O, are not equivalent. In contrast, the conformational preferences of equivalently built pyrimidinones show that a benzyl group gives rise to much stronger allylic strain than a methyl group.

Conclusions

Differently *N*-substituted *cis,trans*-pyrimidin-2(1*H*)-ones were prepared and the effects of allylic strain caused by different *N*-substituents were studied in these systems, where the classical stereochemical factors and the effects of *N*-substituents are clearly revealed due to the equality of the two carbon-hetero atom bond lengths and the relative symmetry of the molecule. It was observed that in the symmetrically *N,N'*-disubstituted compound **12**, which is a conformational analogue of the unsubstituted derivative, as the effects of the two groups cancel each other, the a,e,e conformation is strongly preferred. It was shown that a benzyl substituent shifts the conformational equilibrium towards the sterically unfavoured diaxial form (e,a,a-**6**), while the effect of a methyl group is relatively small and the e,a,a form is only very slightly populated. However, the latter effect is strong enough to eliminate that of the benzyl group in the *N*-benzyl-*N'*-methyl derivative **7**, where the a,e,e conformer is preferred again. Thus, a benzyl group gives rise to much stronger allylic strain than a methyl group. However, the former is not strong enough to predominate over the forceful steric restrictions of a triaxial conformation in *trans,trans*-pyrimidinone **13**.

Unusual azetidine formation was observed upon acid hydrolysis of benzylideneamino azide **2**, instead of the expected diamine. It was shown that the nitrogen originates from the benzylideneamino group and that the reaction goes *via* S_N2 mechanism**.** It was suggested for the *trans,trans*-isomer, based on NMR data analysis and on a comparison with known triphenylated *N*-methyl azetidines, that *N*-substitution does not significantly influence the ring geometry angle, while quaternisation affords a serious increase of puckering and strongly biases the equilibrium towards the conformer with e,e,e phenyls. It was observed in the case of *cis,trans*-azetidine, where a planar ring is assumed to be favoured for the *N*-methyl derivative, that the ring geometry of the hydrobromide depends on the solvent, and that a protic solvent leads to a significant decrease of the puckering angle, while in aprotic the puckered ring is preferred.

Experimental Section

General Procedures. All reagents were purchased from Aldrich, Merck and Fluka and were used without any further purification. Diethyl ether and toluene were dried over sodium wire, THF over $LiAlH_4$. Merck Silica gel 60 (0.040-0.063 mm) was used for the column chromatography isolation of the products. The melting points were determined in capillary tubes without corrections. The IR spectra were taken on a Bruker IFS 113v as solutions in chloroform

and were quoted in cm^{-1}. The NMR spectra were recorded on a Bruker DRX 250 spectrometer in deuterochloroform, the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The microanalyses were carried out by the microanalyses service of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

Preparation of azides 2 and 9. To a solution of chloride hydrochloride **1** or **8** (1 mmol) in dry DMF (5 ml), NaN_3 (3 mmol, 195 mg) was added and the mixture was stirred at 70°C for 3-5 h. The solvent was removed *in vacuo* and the residue was extracted with dichloromethane-water. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude product was dissolved in dry ether and 5% HCl in Et_2O (1 mmol HCl) was added to precipitate the hydrochloride of the corresponding azide **2** or **9**. The latter were not stable enough to be purified by chromatography or recrystallization and thus no analytical data are given.

***ET*-1-Azido-3-benzylideneamino-1,2,3-triphenylpropane hydrochloride (2).** (a) Starting from *TT*-3-amino-1,2,3-triphenylpropyl chloride hydrochloride **1**, 48% of azide hydrochloride **2** was isolated; m. p. 208-209 °C (147-149 °C as a base); IR 2100 (N_3), 1640 (CH=N); ^{1}H NMR 3.54 (dd, 1H, J_{12} 3.7, J_{23} 10.0, C*H*-2), 4.94 (d, 1H, J_{23} 10.0, C*H*-3), 5.21 (d, 1H, J_{12} 3.7, C*H*-1), 8.55 (s, 1H, C*H*=N); The ether solution, after addition of HCl and filtration of the main product, was evaporated and purified by column chromatography on silica gel to give *trans*-stilbene in 47% yield, whose physical and spectral data were identical with a commercial sample.

(b) When performing the reaction in the presence of benzaldehyde (1.5 mmol, 1.5 ml), 84% of azide **2** were isolated and no *trans*-stilbene formation was observed.

***ET*-1-Azido-3-methylamino-1,2,3-triphenylpropane hydrochloride (9).** Starting from *TT*-3-methylamino-1,2,3-triphenylpropyl chloride hydrochloride **8**, 92% of azide hydrochloride **9** was isolated; m. p. 238-239 °C; IR 2105 (N_3), 3425 (NH); ^{1}H NMR of the free base 1.83 (brs, 1H, N*H*, exchangeable), 2.19 (s, 3H, NCH_3), 3.69 (dd, 1H, J_{12} 3.5, J_{23} 10.7, C*H*-2), 4.41 (d, 1H, J_{12} 3.5, C*H*-1), 4.52 (d, 1H, J_{23} 10.7, C*H*-3).

Acid hydrolysis of 2. (a) A solution of *ET*-1-azido-3-benzylideneamino-1,2,3-triphenylpropane hydrochloride **2** (1 mmol, 450 mg) in 4 N HBr in glacial acetic acid (1 ml) was kept at room temperature overnight. The solvent was removed *in vacuo* and the residue that formed was recrystallized from EtOH-Et_2O to afford the hydrobromide of ***trans,trans*-2,3,4-triphenylazetidine (3)** as white crystals in 94% yield; m. p. 172-173 °C (76-77 °C as a base); IR (tabl) 3450 (NH); NMR data (CD_3OD) are summarized on Table 1; Anal. calc. C 68.86, H 5.50, N 3.82, Br 21.82, for $C_{21}H_{20}NBr$, found C 68.62, H 5.38, N 3.58, Br 22.02.

(b) When starting from a diastereoisomeric mixture of *TT/ET*-3-amino-1,2,3-triphenylpropyl chloride hydrochlorides **1** (4.7:1), the hydrobromide of ***cis,trans*-2,3,4-triphenylazetidine** was isolated as an impurity in 11% overall yield; m. p. 183-184 °C; ^{1}H NMR 3.83 (dd, 1H, J_{23} 2.8, J_{34} 11.0, C*H*-3), 5.45 (d, 1H, J_{23} 2.8, C*H*-2), 6.22 (d, 1H, J_{34} 11.0, C*H*-4), 8.76 (brs, N*H*, exchangeable); ^{1}H NMR (CD_3OD) 4.04 (dd, 1H, J_{23} 8.4, J_{34} 6.5, C*H*-3), 5.13 (d, 1H, J_{34} 6.5, C*H*-4), 5.52 (d, 1H, J_{23} 8.4, C*H*-2); ^{13}C NMR (CD_3OD) 58.0 (*C*H-3), 59.0 (*C*H-2), 64.0 (*C*H-4);

Anal. calc. C 68.86, H 5.50, N 3.82, Br 21.82, for $C_{21}H_{20}NBr$, found C 68.71, H 5.36, N 3.71, Br 21.94.

(c) A solution of *ET*-1-azido-3-benzylideneamino-1,2,3-triphenylpropane hydrochloride **2** (1 mmol, 450 mg) in ethanol (10 ml) and 1 M aq. HCl (10 ml) was refluxed with stirring for 2 h. The solvent was removed *in vacuo* and the residue was recrystallized from EtOH-Et_2O to give the hydrochloride of azetidine **3** as white crystals in 92% yield; m. p. 166-167 ^oC; NMR data are summarized on Table 1. The free base has identical physical and spectral data with that obtained from the hydrobromide of **3**.

General procedure for hydrogenation of azides 2 and 9

To a stirred suspension of $LiAlH_4$ (4 mmol, 144 mg) in dry ether (20 ml) azide hydrochloride **2** or **9** (1 mmol) was added. After 3 h stirring at room temperature the excess of $LiAlH_4$ was quenched with water. The hydroxides formed were removed by filtration and washed with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness.

***ET*-3-Benzyl-1,2,3-triphenylpropane-1,3-diamine (5).** was prepared from *ET*-1-azido-3-benzylideneamino-1,2,3-triphenylpropane **2**, 88% yield of **5**; m. p. 223-224 ^oC as a dihydrochloride; IR 3430 (NH); ^1H NMR 1.66 (brs, 3H, NH_2 + N*H*, exchangeable), 3.36 (dd, 1H, J_{12} 6.5, J_{23} 8.4, C*H*-2), 3.51 (q, 2H, *J* 13.2, NCH_2), 3.99 (d, 1H, J_{23} 8.4, C*H*-3), 4.60 (d, 1H, J_{12} 6.5, C*H*-1); Anal. calc. C 72.25, H 6.50, N 6.02, Cl 15.23, for $C_{28}H_{30}N_2Cl_2$, found C 72.11, H 6.63, N 5.91, Cl 15.41.

***ET*-3-Methyl-1,2,3-triphenylpropane-1,3-diamine (10).** was prepared from *ET*-1-azido-3-methylamino-1,2,3-triphenylpropane **9**, 92% yield of **10**; m. p. 46-47 ^oC; IR 3430 (NH); ^1H NMR 1.50 (brs, 3H, NH_2 + N*H*, exchangeable),2.08 (s, 3H, NCH_3), 3.03 (dd, 1H, J_{12} 5.9, J_{23} 7.6, C*H*-2), 3.86 (d, 1H, J_{23} 7.6, C*H*-3), 4.20 (d, 1H, J_{12} 5.9, C*H*-1); Anal. calc. C 83.50, H 7.64, N 8.85, for $C_{22}H_{24}N_2$, found C 83.34, H 7.79, N 8.66.

General procedure for reaction with phosgene

To a solution of **3**, **5** or **10** (1 mmol) in dry toluene (5 ml), pyridine (0.2 ml, 2.5 mmol) and phosgene (0.5 ml, 1 mmol as a 20% solution in toluene), were added under argon atmosphere. After 2 h stirring at room temperature the solution was washed with brine, with 5% aq. HCl and again with brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford the crude product **4**, **6** or **11**, respectively, which was purified by column chromatography on silica gel, using diethyl ether as a mobile phase.

Bis(*trans,trans*-2,3,4-triphenylazetidin-1-yl)methanone (4). was prepared from the hydrobromide or hydrochloride of *trans,trans*-2,3,4-triphenylazetidine **3**, 74 % yield; m. p. 243-245 ^oC; IR 1620 (C=O); NMR data are summarized on Table 1; TOF MS ES+ 619.27390 (M+Na), $C_{43}H_{36}N_2ONa$; Anal. calc. C 86.54, H 6.08, N 4.69, for $C_{43}H_{36}N_2O$, found C 86.72, H 6.18, N 4.43.

***cis,trans*-1-Benzyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one (6).** was prepared from *ET*-3-benzyl-1,2,3-triphenylpropyl-1,3-diamine **5**, 68% yield; m. p. 212.5-213 ^oC; IR 1640

(C=O), 3200 (NH); NMR data are summarized on Table 2, the most important HMBC cross peak 5.561/62.211; MS (CI) m/z 419.05 $(M+1)^+$; Anal. calc. C 83.22, H 6.26, N 6.42, for $C_{29}H_{26}N_2O$, found C 83.17, H 6.41, N 6.40.

***trans,trans*-1-Benzyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one (13).** When starting from a diastereoisomeric mixture of *TT/ET*-3-amino-1,2,3-triphenylpropyl chloride hydrochlorides **1** (4.7:1), *trans,trans*-pyrimidinone **13** was isolated as an impurity in 7% overall yield; m. p. 179-180°C; IR 1645 (C=O); ^{1}H NMR 3.28 (dd, 1H, *J* 3.2, 4.3, C*H*-5), 3.77 (d, 1H, *J* 14.5, ½ of CH_2), 4.48 (d, 1H, *J* 3.2, C*H*), 4.86 (d, 1H, *J* 4.3, C*H*), 4.94 (brs, N*H*, exchangeable), 5.40 (d, 1H, J 14.5, ½ of CH_2); ^{13}C NMR 49.6 (*C*H_2), 54.1 (*C*H-5), 61.4 (*C*H), 77.2 (*C*H); Anal. calc. C 83.22, H 6.26, N 6.42, for $C_{29}H_{26}N_2O$, found C 83.19, H 6.37, N 6.31.

***cis,trans*-1-Methyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one (11).** was prepared from *ET*-3-methyl-1,2,3-triphenylpropyl-1,3-diamine **10**, 70% yield; m. p. 188-189°C; IR 1705 (C=O); 3445 (NH), NMR data are summarized on Table 2; MS (EI) m/z 342 (M^+, 12), 327 (M^+-CH_3, 62), 267 (21), 238 (48), 180 (100), 77 (11), 72 (18),43 (21), 15 (37); Anal. calc. C 80.67, H 6.48, N 8.18, for $C_{23}H_{22}N_2O$, found C 80.81, H 6.62, N 8.06.

General procedure for N-methylation

To an oil-free suspension of NaH (3 mmol, 114 mg 55-60% in oil) in dry THF (10 ml) heterocyclic compound **3, 6** or **11** (1.5 mmol) was added. The mixture was stirred at room temperature 15 min and methyl iodide (15 mmol, 0.8 ml) was then added. After 1 h stirring at room temperature the excess of NaH was quenched with water and the solvent was removed *in vacuo*. The residue formed was extracted with dichloromethane-water. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness to afford the corresponding methylated product in quantitative conversion.

***trans,trans*-1-Methyl-2,3,4-triphenylazetidine** was prepared from hydrobromide or hydrochloride of *trans,trans*-2,3,4-triphenylazetidine **3**; identical physical and spectral data with those of the known product.[2]

***cis,trans*-1-Benzyl-3-methyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one (7).** was prepared from *cis,trans*-1-benzyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one **6**; 96%; m. p. 144-6°C; IR 1620 (C=O); NMR data are summarized on Table 2; MS(CI) m/z 433.20 $(M+1)^+$; Anal. calc. C 83.30, H 6.52, N 6.48, for $C_{30}H_{28}N_2O$, found C 83.24, H 6.61, N 6.29.

***cis,trans*-1,3-Dimethyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one (12).** was prepared from *cis,trans*-1-methyl-4,5,6-triphenyl-tetrahydropyrimidin-2(1*H*)-one **11**; 97%; m. p. 121-122°C; IR 1690 (C=O); NMR data are summarized on Table 2; ESI m/z 358 (M+1, 714), 380 (M+Na, 875), 396 (M+K, 586); Anal. calc. C 80.86, H 6.79, N 7.86, for $C_{24}H_{24}N_2O$, found C 80.78, H 6.83, N 7.58.

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