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RING-CHAIN TAUTOMERISM AND THREE- TO FOUR-COMPONENT EQUILIBRIA IN FUSED-RING TETRAHYDRO-1,3-OXAZINES

Kalevi Pihlaja,*[,a] Aija Parkkinen,[a,b] Ferenc Fülöp,[a,c] Jorma Mattinen,[a] and Gábor Bernáth[c]

[a]Department of Chemistry, University of Turku, SF-20500 Turku, Finland; [b]Department of Chemistry in Biomedicine, University of Turku, SF-20500 Turku, Finland and [c]Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701 Szeged, POB 121, Hungary

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Abstract: The condensation of cis- (1) and trans-2-hydroxymethyl-4-cyclohexenyl-1-amine (2) and 2,3-diexo- (3) and 2,3-diendo-3-hydroxymethylbicyclo[2.2.1]heptylamine (4) with 8 different aromatic aldehydes led to ring-chain tautomeric equilibria between epimeric tetrahydro-1,3-oxazines and open-chain Schiff bases. In all cases the equilibrium mixtures consisted of two epimeric ring forms although the 2-axial epimers of the cyclohexene-fused derivatives had only a minor contribution to the ring-chain tautomeric equilibria. For the norbornane-fused derivatives the ring-chain tautomeric equilibria were taken equal to the ratio of the sum of the ring forms and the amount of the E-isomer of the open form in which case the simple equation, $\log K_X = 0.76\sigma^+ + \log K_{X=H}$ derived recently for ring-chain tautomerism in 1,3-oxazines prevailed again for each system studied.

Tetrahydro-1,3-oxazines and 1,3-oxazolidines are useful synthons in enantioselective syntheses.[1] Several of them and their thia-analogs are also important from a pharmacological point of view, both as potential drugs[2,3] and as starting materials in drug syntheses.[4] In spite of this, relatively little attention has been paid to the quantitative aspects of their ring-chain tautomerism[5], which can be of great importance to their synthetic applications[6] and to their pharmacological effects.[2d]

Recently a comparative study[7] on the ring-chain tautomerism in seven series of 2-aryl-substituted 1,3-oxazine derivatives (e.g. 1,3- and 3,1-benzoxazines and perhydrogenated analogs) were reported. In all cases the equation

$$\log K_X = (0.76\pm0.04)\sigma^+ + \log K_{X=H} \qquad (1)$$

where K_X = [ring]/[chain] and σ^+ is the Hammett constant was obeyed.[7]

Only two component equilibria were considered in the above studies.[7] Several recent reports[8], however, discuss oxazolidine and thiazolidine equilibria where two C-2 epimeric ring forms are in equilibrium with one open form. Sometimes, however, two open-chain forms might also be present.

Therefore the aim of this investigation was to study quantitatively the three- to four-component equilibria for some tetrahydro-1,3-oxazine derivatives and at the same time discuss the scope and limitations of equation (1) for these systems. As model compounds, four aminoalcohols (1-4) were chosen (Schemes 1 and 2). The ring system in cis- (1) and trans-2-hydroxymethyl-4-cyclohexenyl-1-amine[9] (2) is fairly flexible, but rather rigid in 2,3-diexo- (3) and 2,3-diendo-3-hydroxymethylbicyclo[2.2.1]heptylamine[10] (4).

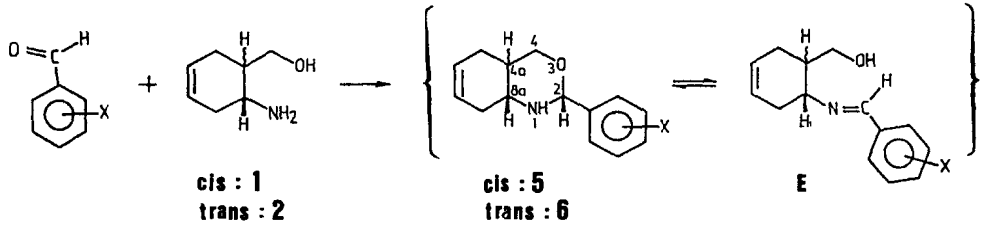
RESULTS AND DISCUSSION

Aminoalcohols 1 and 2 were prepared from cis- and trans-1,2,3,6-tetrahydrophtalic anhydride through ammonolysis, Hoffman degradation[11] and subsequent lithium aluminium hydride reduction.[9] 2,3-Diexo-3-hydroxymethylbicyclo[2.2.1]heptane (3) was prepared from norbornane through chlorosulfonyl isocyanate addition[12], hydrogen chloride hydrolysis of the azetidinone, and lithium aluminium hydride reduction.[10a] 2,3-Diendo-2-hydroxymethylbicyclo[2.2.1]heptylamine (4) was obtained from 5-norbornene-2,3-diendo-dicarboxylic anhydride by ammonolysis and Hofmann degradation.[10a] The resulting 3-endo-aminobicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid, after esterification and catalytic and lithium aluminium hydride reduction, furnished the aminoalcohol 4.[10b]

The reaction of aminoalcohols 1-4 with aromatic aldehydes occurs smoothly, in 2 h even at room temperature, with nearly quantitative yields. The tautomer ratios were determined by integrating the signals of suitable, well-separated protons, mainly those of H-2 methine (ca 8.3 ppm) and H-2-methylene protons (ca 5.3 ppm).

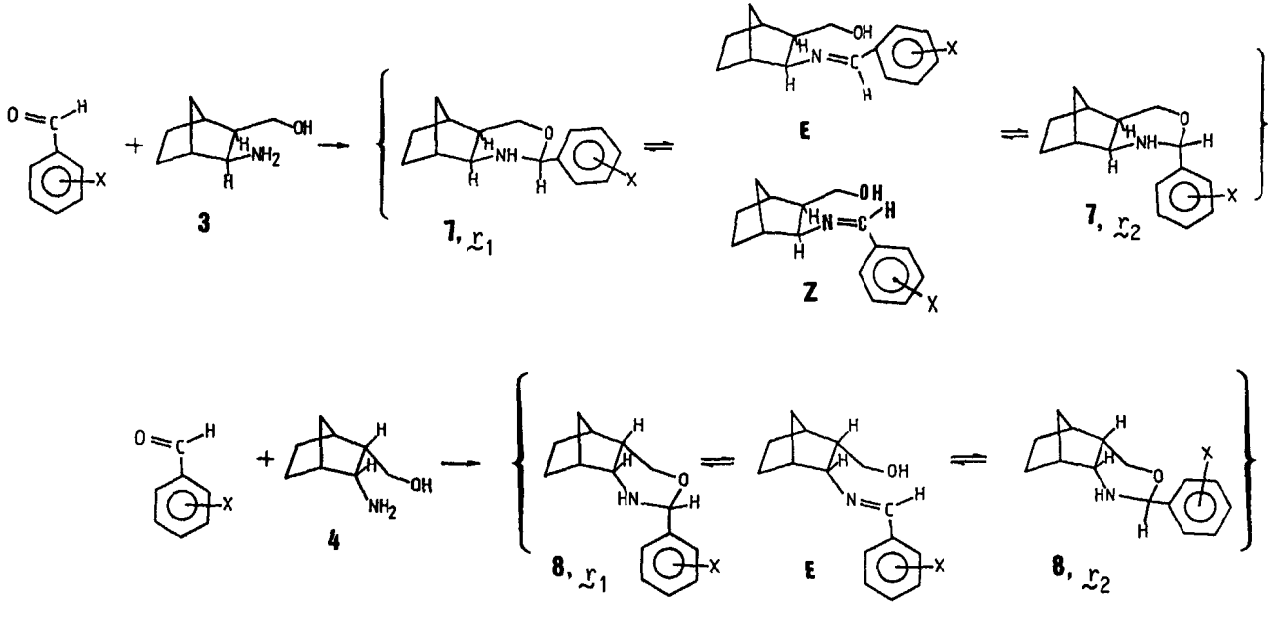
The condensation of cis- (1) and trans-2-hydroxymethyl-4-cyclohexenyl-1-amine (2) and 2,3-diexo- (3) and 2,3-diendo-3-hydroxymethylbicyclo[2.2.1]-heptylamine (4) with 8 different aromatic aldehydes led to ring-chain tautomeric equilibria between epimeric tetrahydro-1,3-oxazines[13] and open-chain Schiff bases (Schemes 1 and 2). In all cases, as shown for the condensation products with 2-p-nitrobenzaldehyde (Figs. 1-3), the equilibrium mixtures consisted of two epimeric ring forms. The 2-axial epimers of cyclohexene-fused derivatives, however, were not quantified since they made only a minor contribution to the ring-chain tautomeric equilibria. This is demonstrated in Fig. 1 which shows the ^{1}H NMR spectrum of the aryl protons of the reaction mixture of 1 with p-nitrobenzaldehyde in $CDCl_3$ solution in equilibrium state at 323 K.

Scheme 1



X = pNO$_2$: a, mNO$_2$: b, mCl: c, pCl: d, H: e, pCH$_3$: f, pOCH$_3$: g, pN(CH$_3$)$_2$: h

Scheme 2



The tautomeric equilibria (Table 1) can be described with equation (1) when using σ^+ values given by Brown and Okamoto.[14] The intercept[7] (c) characterizes the sum of the steric and electronic effects of the substituents at C-4, C-5 and C-6. When the c values of 5 and 6 are compared with those of their fully saturated counterparts[7], no difference can be observed for the trans derivatives, while the unsaturation has a small destabilizing effect in the cis series ($\Delta c = 0.22$).

Table 1. Data for linear regression analysis of the ring-chain tautomeric equilibria of compounds 5-8 (cf Schemes 1 and 2).

Compound	5	6	7	8
No. of points	8	7	8	7
Slope ρ	0.79	0.75	0.77	0.84
SE[a] of ρ	0.02	0.03	0.07	0.06
Intercept c	0.57	1.32	-0.90	-1.57
SE[a] of c	0.02	0.02	0.05	0.03
Correlation coefficient	0.997	0.996	0.979	0.988

[a]Standard error.

For the norbornane-fused derivatives (7 and 8) the ring-chain tautomeric equilibria were best comparable with the earlier observations (cf equation 1) by taking the equilibrium constants equal to the ratio between the sum of the two ring forms and the amount of the E-isomer of the open-chain form despite the fact that in the case of diexo-norbornane derivatives both open-chain forms were present (cf Figure 2).

The relative mole fractions of the epimeric ring forms (7-8r_1,r_2), the Schiff base intermediates (7E,Z and 8E) and the aldehyde in the cyclizations of p-nitrobenzaldehyde with 3 and 4 in $CDCl_3$ solution at 293± 2 K are shown in Figs. 2 and 3, respectively, as a function of time. In the cyclization of 3 with p-nitrobenzaldehyde giving oxazine 7 two open-chain intermediates could be detected. Even in this case the E-form controls the tautomeric equilibria since the correlations shown in Table 2 gave practically equal slope values with each other and with our earlier data[7] despite the fact that the ratio $[r_1+r_2]/[E]$ was taken equal to the K-value also for 7.

In the case of the rigid diexo- and diendo-norbornane series the open form always clearly predominates (see Table 2 and the experimental section) - especially so in the diendo (8) derivatives. The chemical shifts and coupling constants (Table 2) are practically independent of the aryl substituents. The oxazine rings in 7 and 8 have practically the same conformation (Scheme 2) as in the case of their 2-unsubstituted analogs.[16]

The relative C-2 configurations for the ring forms were determined by 2D

COSY and NOESY experiments. In $7r_1$ and $8r_1$ the aryl group is anti and in

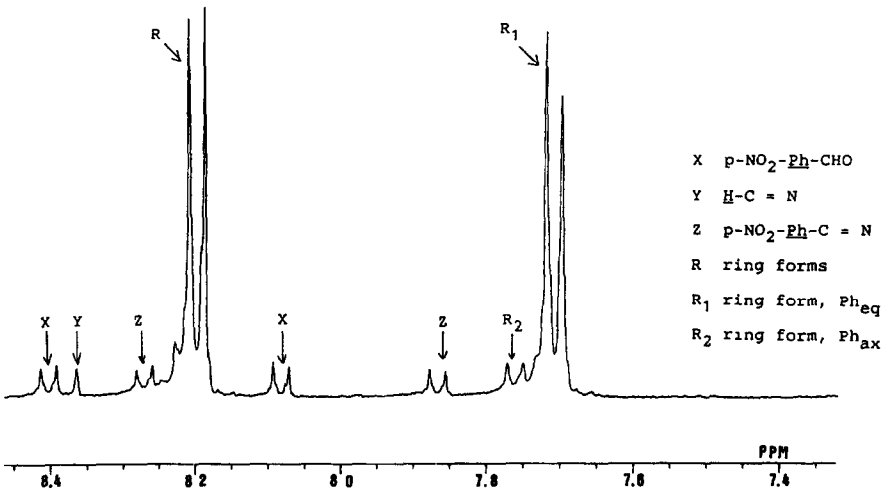


Figure 1. The ^1H NMR spectrum of the aryl protons of the reaction mixture of 1 with p-nitrobenzaldehyde in $CDCl_3$ saolution at 323 K.

Table 2. Selected chemical shifts and coupling constants for compounds 5, 6, 7 and 8.[a]

	Chem. shifts, ppm			J, Hz		
Compound	H-4_a	H-4_e	H-8a	$4a,4_a$	$4a,4_e$	$4_e,4_a$
5a	4.05	4.02	3.41	2.1	1.6	-11.5
5Eh	4.14	3.59	3.79	9.5	3.7	-12.0
6a	3.58	4.25	2.98	11.3	4.0	-11.3
6Eh	3.60	3.6	3.32	5.0	ca 1.0	-11.0
$7r_1a$	3.57	3.93	3.14	11.1	7.1	-11.0
$7r_2a$	3.45	3.90	2.58	11.9	7.2	-11.9
7Eā	3.70	3.63	3.65	4.8	5.8	-11.6
$8r_1a$	3.26	3.98	3.23	7.0	3.5	-11.3
$8r_2a$	4.14	4.11	2.46	7.0	4.0	-11.0
8Eā	3.73	3.78	3.89	7.0	6.7	-11.6

[a]The data were chosen from the most easily detectable p-$N(CH_3)_2$ or p-NO_2 derivatives.

$7r_2$ and $8r_2$ syn to the diexo and diendo protons, respectively. This is in agreement with the shielding and deshielding effects experienced by H-4_a in $8r_1$ and $8r_2$ when compared to $7r_1$ and $7r_2$, respectively. Similarly, H-8a is shielded by the aryl substituent both in $7r_2$ and $8r_2$ when compared to $7r_1$ and $8r_1$, respectively.

It can be concluded that the reactions of p-nitrobenzaldehyde (as well as those of other aromatic aldehydes) with aminoalcohol derivatives in question proceed via Schiff base intermediates and consist of two epimeric

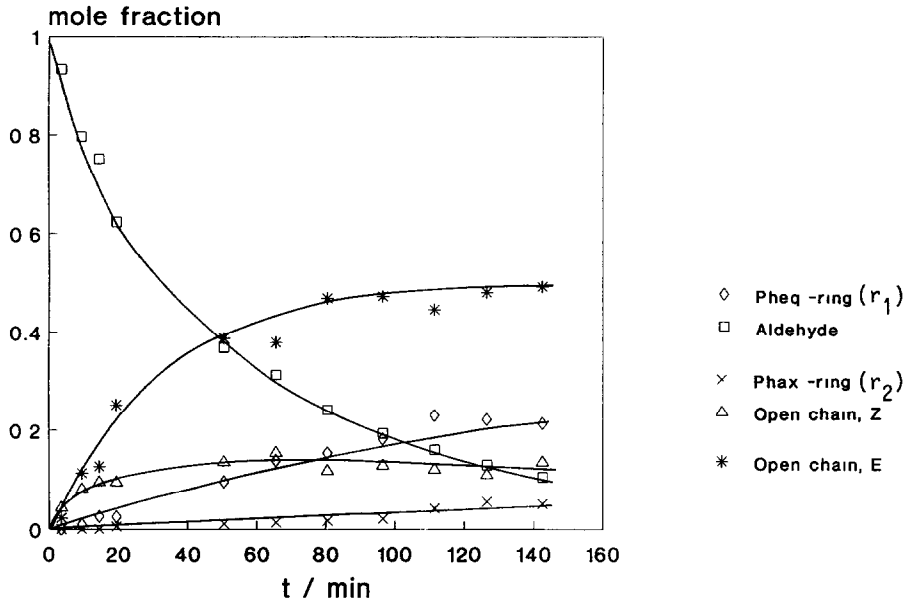


Figure 2. The relative mole fractions of the epimeric ring forms (r_1 and r_2), the open chain forms and aldehyde in $CDCl_3$ solution for the cyclization of p-nitrobenzaldehyde with 2,3-diexo-3-hydroxymethylbicyclo-[2.2.1]heptylamine (3) at 293±2 K against time.

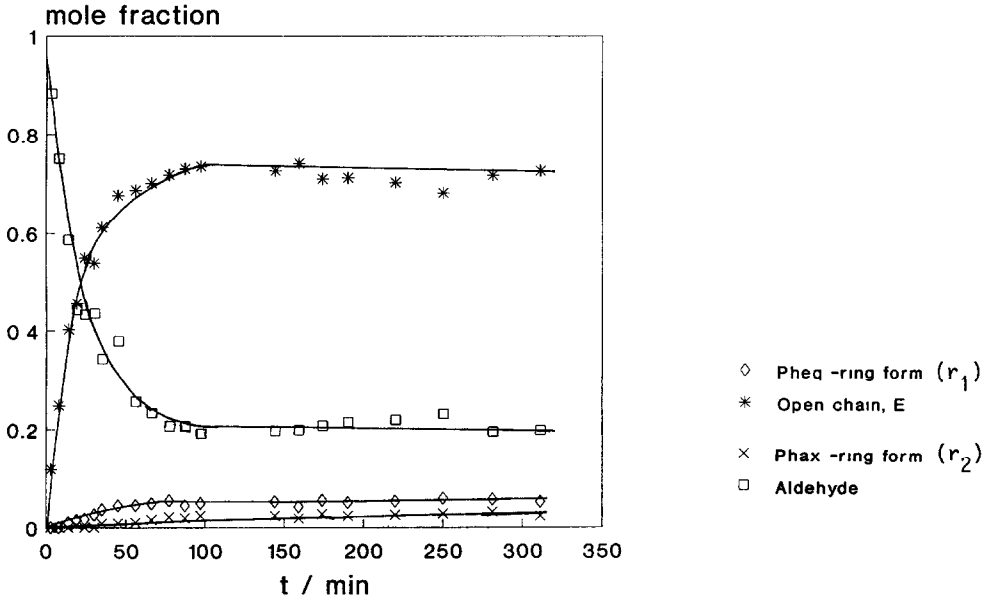


Figure 3. The relative mole fractions of the epimeric ring forms (r_1 and r_2), the open chain forms and aldehyde in $CDCl_3$ solution for the cyclization of p-nitrobenzaldehyde with 2,3-diendo-3-hydroxymethylbicyclo-[2.2.1]heptylamine (4) at 293±2 K against time.

ring forms and usually only one open chain form (E-isomer) at the equilibrium. The constant slope value obtained for equation (1) at a given temperature is, however, controlled by the ratio between the sum of both ring forms and the amount of the E-isomer of the open form (Table 1). In the systems we studied earlier[7] the contribution of the less stable ring epimer was so low that a good enough estimate for the slope and intercept could be obtained by inspecting the ratios of the amount of the predominant ring epimer to that of the E form of the Schiff base intermediate.

EXPERIMENTAL

General Methods. The ^{1}H NMR spectra were recorded on a JEOL GX 400 FT-NMR spectrometer in $CDCl_3$ (3-5 mg per 0.5 cm^3) at 293±2 K with Me_4Si as internal standard. The number of scans was 80 to improve S to N ratio for integration. The determination of the ring-chain tautomer ratios was based on the integrals of methylene and methine protons. The measurements were repeated several times at intervals to assure that the equilibria were established. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected.

Materials. The aromatic aldehydes, cis-1,2,3,6-tetrahydrophtalic anhydride, norbornene, and 5-norbornene-2,3-diendo-dicarboxylic anhydride were commercial products. All aminoalcohols, cis- (1) and trans-2-hydroxymethyl-4-cyclohexenyl-1-amines[8] (2) and 2,3-diexo- (3) and 2,3-diendo-3-hydroxymethylbicyclo[2.2.1]heptylamines[10] (4) were prepared by known methods.

General Procedure to React Amino Alcohols with Aromatic Aldehydes. Amino alcohol (1 mmol) was dissolved in 10 cm^3 of absolute ethanol, and 1 mmol of aromatic aldehyde was added. After the mixture was allowed to stand for 2 h at room temperature the solvent was evaporated off. Some of the products crystallized after treating them with n-hexane from which they were also recrystallized. Oils were dried in a vacuum desiccator overnight. All compounds prepared gave satisfactory microanalyses (C, H, N).

Kinetic measurements. p-Nitrobenzaldehyde was dissolved in $CDCl_3$ in an NMR-tube and the mixture was thermostated to a preselected temperature after which an equivalent amount of the reactant aminoalcohol was added. The reactions were followed by the JEOL GX-400 NMR instrument which was preprogrammed to take the spectra automatically at given intervals. Selected parts of the spectra were integrated in respect with the Me_4Si-peak to calculate the relative mole fractions.

Melting points and the percentage(s) of the ring form(s) (%) are as follows:
5a: 104-105 °C, 94.5%. 5b: oil, 92.5%. 5c: oil, 87.95%. 5d: 72-73 °C, 83.1% (lit.[9] mp 75-77 °C). 5e: oil, 75.9%. 5f: oil, 67.25%. 5g: oil, 52.0%. 5h: 115-116 °C, 14.1%.
6a: 94-95 °C, 99.0%. 6b: oil, 97.9%. 6c: 60-61 °C, 97.7%. 6d: 82-83 °C, 96.1% (lit.[9,17] mp 83-85 °C). 6e: 50-51 °C, 95.0%. 6f: oil, 91.1%. 6g: oil, 85.0%. 6h: 98-99 °C, 55.2%.
7a: 64-66 °C, 28.4% (r_1), 12.9% (r_2). 7b: oil, 26.1% (r_1), 11.4% (r_2). 7c: oil, 13.7% (r_1), 4.3% (r_2). 7d: oil, 9.0% (r_1), 2.7% (r_2). 7e: oil, 6.15% (r_1), 1.6% (r_2). 7f: oil, 4.1% (r_1), 0.95% (r_2). 7g: oil, 2.7% (r_1), 0.65% (r_2). 7h: oil, 0.67% (r_1), 0.15% (r_2).
8a: oil, 8.7% (r_1), 3.6% (r_2). 8b: oil, 6.4% (r_1), 2.8% (r_2). 8c: oil, 4.5% (r_1), 1.5% (r_2). 8d: oil, 2.1% (r_1), 0.67% (r_2). 8e: oil, 1.7% (r_1), 0.41% (r_2). 8f: oil, 1.1% (r_1), 0.20% (r_2). 8g: oil, 0.70% (r_1), 0.05% (r_2). 8h: 99-100 °C, ring forms not detected.

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REFERENCES

1. (a) J. D. Morrison, (Ed.) Asymmetric Synthesis, Academic Press, New York, 1983; (b) J. W. ApSimon and T. L. Collier, Tetrahedron 42, 5157 (1986).
2. (a) B. Paul and W. Korytnyk, J. Med. Chem. 19, 1002 (1976); (b) H. T. Nagasawa, D. J. W. Goon, R. T. Zera and D. L. Yuzon, J. Med. Chem. 25, 491 (1982); (c) H. T. Nagasawa, D. J. W. Goon, W. P. Muldon and R. T. Zera, J. Med. Chem. 27, 591 (1984); (d) J. C. Robert, H. T. Nagasawa, R. T. Zera, R. F. Fricke and D. J. W. Goon, J. Med. Chem. 30, 1891 987).
3. (a) R. Bognár, Z. Gyorgydeák, L. Szilágyi, G. Horváth, G. Czira and L. Radics, Liebigs Ann. Chem., 450 (1976); (b) R. Bognár, Z. Györgydeák, L. Szilágyi, P. Sándorand L. Radics, Liebigs Ann. Chem., 701 (1979); (c) L. Szilágyi and Z. Györgydeák, J. Am. Chem. Soc. 101, 427 (1979).
4. (a) Y. Roble, J.-P. Fernandez, R. Dubief, J.-P. Chapat, H. Sentenac-Roumanou, M. Fatome and J.-D. Laval, Eur. J. Med. Chem. 17, 235 (1982); (b) M. Oya, T. Bata, E. Kato, Y. Kavashima and T. Watanabe, Chem. Pharm. Bull. 30, 440 (1982); (c) N. Margoum, P. Tronche, P. Bastide, J. Bastide and C. Rubat, Eur. J. Med. Chem. 19, 415 (1984); (d) B. Refouvelet, P. Tronche, J. Couquelet, J.-F. Robert, G. Claudet-Bonnefoy and J. Panouse-Perrin, Eur. J. Med. Chem. 22, 11 (1987).
5. (a) R. Valters and W. Flitsch, Ring Chain Tautomerism, Plenum, New York, 1985; (b) A. F. McDonagh and H. E. Smith, J. Org. Chem. 33, 1 (1968); (c) J. V. Paukstelis and L. L. Lambing, Tetrahedron Lett., 299 (1970); (d) M. E. Alva Astudillo, N. C. J.Chokotho, T. C. Jarvis, C. D. Johnson, C. C. Lewis and P. D. McDonell, Tetrahedron, 41, 5919 (1985); (e) F. Fülöp, K. Pihlaja, J. Mattinen and G. Bernáth, Tetrahedron 43, 1863 (1987); (f) A. Parkkinen, F. Fülöp and K. Pihlaja, Tetrahedron 47, 000 (1991).
6. (a) J. E. Saavedra, J. Org. Chem. 50, 2271 (1985); (b) J. Knabe and W. Buchheit, Arch. Pharm. (Weinheim) 318, 593 and 727 (1985); (c) F. Fülöp, I. Huber and G. Bernáth, Acta Chim. Hung. 124, 667 (1987).
7. (a) F. Fülöp, K. Pihlaja, J. Mattinen and G. Bernáth, J. Org. Chem. 52, 3821 (1987) and references cited therein; (b) A. Parkkinen, F. Fülop and K. Pihlaja, Acta Chem. Scand. 45, 000 (1991).
8. (a) S. L. Spassov, L. Markova, O. Argirov and T. Obretenov, J. Mol. Struct. 147, 105 (1986); (b) F. Ponticelli, E. Marinello and M. C. Misalle, Org. Magn. Reson. 20, 138 (1982); (c) W. Ando, Y. Igarashi and L. Huang, Chem. Letters, 1361 (1987).
9. G. Bernáth, G. Stájer, A. E. Szabo, F. Fülop and P. Sohár, Tetrahedron 41, 1353 (1985).
10. (a) G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár, J. Heterocyclic Chem. 20, 1181 (1983); (b) G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár, J. Heterocyclic Chem. 21, 1373 (1984).
11. A recent synthesis of the intermediate 1S,2R-2-amino-4-cyclohexene-1-carboxylic acid: N. Tamura, Y. Kawano, Y. Matsushita, K. Yoshioka and M. Ochiai, Tetrahedron Lett. 27, 3749 (1986).
12. E. J. Moriconi and W. C. Crawford, J. Org. Chem. 33, 370 (1968).
13. All compounds in question were racemates. In the formulas one of the enantiomers is given. See: F. Fülöp, G. Bernáth, J. A. Szabó and Gy. Dombi, J. Chem. Educ. 60, 95 (1983).
14. H. C. Brown and Y. Okamoto, J. Am. Chem. Soc. 80, 4979 (1958).
15. For easy comparison of the spectroscopic data, the same numbering was used for the ring and the chain forms.
16. F. Fülöp, G. Stájer, G. Bernáth and P. Sohár, Tetrahedron 41, 5159 (1985).
17. G. Argay, A. Kálmán, B. Ribár and G. Bernáth, Acta Cryst. C42, 1884 (1986).