Tetrahedron Vol. 40, No. 11, pp. 2053 to 2060, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

STEREOCHEMICAL STUDIES—76
SATURATED HETEROCYCLES—63[1,2]

SYNTHESIS OF CIS- AND TRANS-N-METHYL- AND N-BENZYL-4,5- AND 5,6-TETRAMETHYLENETETRAHYDRO-1,3-OXAZINES; AN X-RAY STUDY OF N-BENZYL-CIS-4,5-TETRAMETHYLENETETRAHYDRO-1,3-OXAZINIUM-PICRATE

FERENC FÜLÖP and GÁBOR BERNÁTH*

Institute of Pharmaceutical Chemistry, University Medical School, POB 121, H-6701 Szeged, Hungary

GYULA ARGAY and ALAJOS KÁLMÁN

Central Research Institute for Chemistry, Hungarian Academy of Sciences, POB 17, H-1525 Budapest, Hungary

PÁL SOHÁR

EGYT Pharmacochemical Works, POB 100, H-1475 Budapest, Hungary

(*Received in UK 9 January* 1984)

Abstract - The corresponding cis- and trans-N-methyl- and N-benzyl-5,6- and 4,5-tetramethylenetetrahydro-1,3-oxazines (5a,b-8a,b) were synthesized from cis- and trans-N-methyl- and N-benzyl-2-aminomethyl-1-cyclohexanols (1a,b, 2a,b), and from cis- and trans-N-methyl- and N-benzyl-2-hydroxymethyl-1-cyclohexylamines (3a,b, 4a,b) by reaction with formaldehyde. The aminoalcohols 1a, 2a, 3a,b and 4a,b were prepared in considerably higher yields than in earlier procedures. NMR spectroscopy showed that the cis isomers of the synthesized oxazines were conformationally homogeneous in solution, and their preferred conformation (inside or outside) depended on the steric requirement of the groups attached to the anellation points, whereas a bulky C-2 substituent had no influence on the predominant conformation. The structure of N-benzyl-cis-4,5-tetramethylenetetrahydro-1,3-oxazinium-picrate (7b), determined by X-ray diffraction analysis, was in agreement with the predominant N-outside conformation of the corresponding base, established by means of NMR spectroscopy.

In previous works we made a systematic study of the synthesis and steric structure of stereoisomeric, six-membered cyclic compounds containing two hetero atoms in the 1,3-positions, fused with a cyclopentane, cyclohexane, cycloheptane or cyclooctane ring. Among others, a great number of dihydro-[3] and tetrahydro-1,3-oxazines,[4-6] tetrahydro-1,3-oxazin-4-ones,[7,8] 1,3-oxazin-2-ones[9,10] and 1,3-oxazine-2-thiones[11,12] were synthesized. Investigation on 2-aryl-substituted tetrahydro-1,3-oxazines led to the following general conclusions:

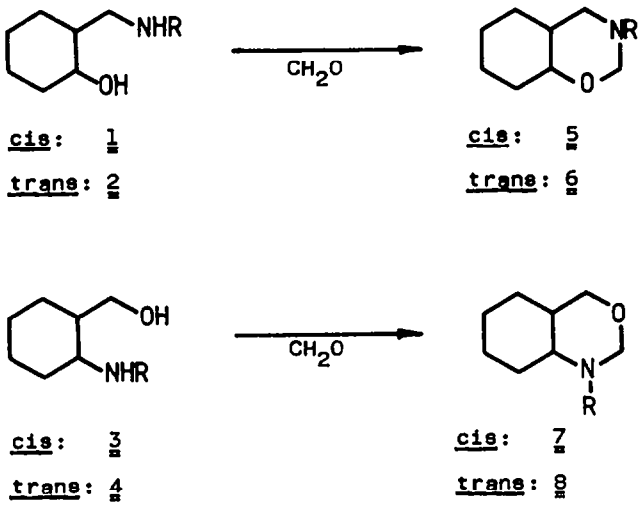
1. In all cases studied, the formation of 2-aryl-substituted 1,3-oxazines was a stereospecific process.[1]

2. The predominant conformation of the synthesized 1,3-oxazine cis isomers primarily depended on the steric requirement of the groups attached to the anellation points.[5]

3. The predominating conformation of the end-product was decisive for the configuration of the centre of chirality in position 2.[1]

The 2-aryl-substituted dihydro- and tetrahydro-1,3-oxazines we studied earlier were conformationally homogeneous systems, as shown by ^{1}H and ^{13}C NMR examinations at room temperature.[3,4,10] The conformational homogeneity of these oxazine derivatives has recently been supported by high-resolution (400 MHz) ^{1}H NMR measurements.[13]

In this paper we report the synthesis and structure elucidation of tetrahydro-1,3-oxazines containing no bulky 2-aryl substituent such as those present in the previously investigated compounds, which were possibly primarily responsible for the conformational homogeneity (Scheme 1).



cis: 1 trans: 2 cis: 5 trans: 6

cis: 3 trans: 4 cis: 7 trans: 8

a: R = CH_3; b: R = $CH_2C_6H_5$

Scheme 1.

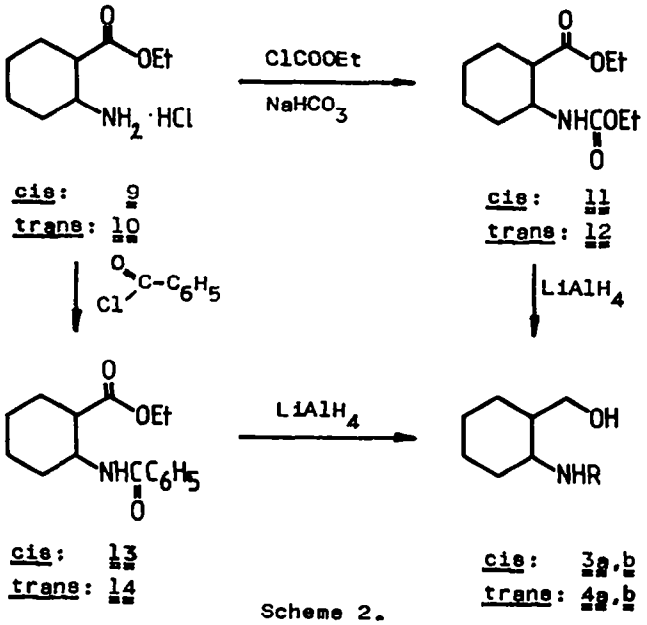
Crabb *et al.* described the results of investigations on closely analogous compounds in several publications.[14-16] In studies on the reactions of trans-2-amino-1-cyclanols and 2-amino-1-cycloalkanethiols,[15,16] they prepared a number of fused-skeleton oxazole and thiazole derivatives. When the starting compounds were unsubstituted 1,2-aminoalcohols, polycyclic products too were obtained, whereas the cyclization of trans-2-alkylamino-1-cyclanols with formaldehyde gave exclusively the fused-skeleton 1,3-oxazoles.[14] The structures of the compounds synthesized were supported by detailed ^{1}H and ^{13}C NMR analyses.

Conformational equilibria and barriers to ring and nitrogen inversion were determined by ^{1}H and ^{13}C NMR for numerous nearly analogous 2, 3 and 4-substituted 1,3-oxazine derivatives by Katritzky *et al.*[17]

Our N-methyl- and N-benzyl-cis- and trans-2-aminomethyl-1-cyclohexanols (1a,b, 2a,b) were prepared as described earlier,[6,18] from the appropriately substituted, stereoisomeric 2-hydroxy-1-cyclohexanecarboxamides. The very low yields (15-35%) previously observed for the N-methyl derivatives (1a, 2a) could be increased considerably (to 80%) by shortening the time of the lithium aluminium hydride reduction, and by improving the work-up.

Earlier, several synthetic routes had been elaborated[6] leading to N-methyl- and N-benzyl-cis- and trans-2-hydroxymethyl-1-cyclohexylamines (3a,b, 4a,b). The N-methyl derivatives 3a and 4a were prepared by the lithium aluminium hydride reduction of N-formyl- or N-ethoxycarbonyl derivative of the appropriate cis- and trans-2-amino-1-cyclohexanecarboxylic acids. The N-benzylaminoalcohols 3b and 4b were obtained by reducing the N-benzoyl derivatives of cis- and trans-2-amino-1-cyclohexanecarboxylic acid. Compound 3b was also synthesized by the successive reduction with sodium borohydride and then with lithium aluminium hydride of the Schiff base made from cis-2-amino-1-cyclohexanecarboxylic acid and benzaldehyde. The above reactions usually gave the products in very low yields.

In the course of the present work the synthesis of aminoalcohols 3 and 4 was modified by using the ethyl esters instead of the above carboxylic acid derivatives, which were scarcely soluble in ether or tetrahydrofuran and therefore barely reducible with lithium aluminium hydride. Accordingly, the required aminoalcohols 3a,b and 4a,b were synthesized in very good yields by treatment of ethyl cis- or trans-2-amino-1-cyclohexanecarboxylate (9, 10) with ethyl chloroformate, followed by reduction with lithium aluminium hydride, or by acylation of the starting ethyl ester with benzoyl chloride and subsequent reduction (Scheme 2). As a further advantage of the method, the reaction times of the reduction steps could be decreased to 1 or 2 h and the final products were obtained as very pure compounds, without any contamination.

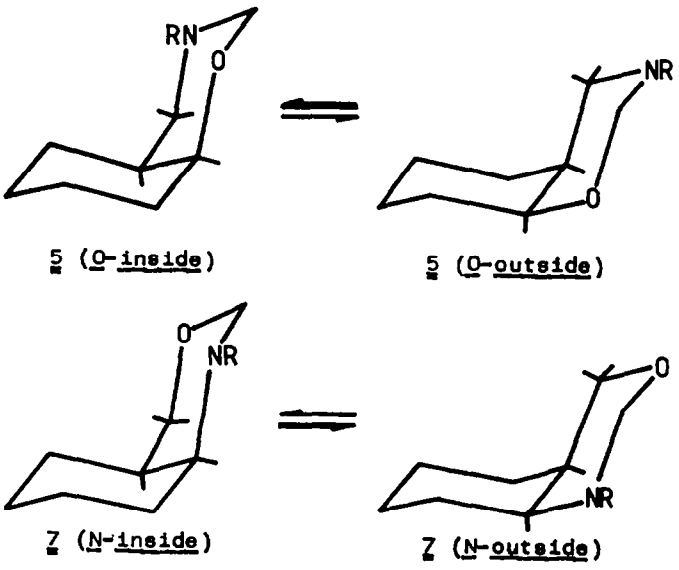


Scheme 2.

The N-substituted 1,3-oxazines 5a,b–8a,b were synthesized by treatment of the appropriate aminoalcohol 1a,b–4a,b with aqueous formaldehyde. Compounds 5–8 were isolated from the reaction mixture as oily products and were purified through their picrate or hydrochloride salts. For NMR spectroscopy the bases liberated from the salts were used.

Detailed conformational analysis by ^{1}H and ^{13}C NMR of the synthesized 1,3-oxazines has been reported earlier.[19] Hence, only the main results of this work are mentioned here.

The conformational analysis of the cis-1,3-oxazines 5 and 7 is based on a comparative NMR study of the cis-trans isomer pairs. There are two possible stable chair-chair conformations for the cis isomers. In the O- or N-inside conformation the hetero atom is axial with respect to the cyclohexane ring. In the case of the O- or N-outside conformation this position is equatorial (Scheme 3).



a: R = CH_3; b: R = $CH_2C_6H_5$

Scheme 3.

^{1}H and ^{13}C NMR data show that the cis isomers, similarly to the 2-aryl-substituted analogues, are conformationally homogeneous. In the case of trans derivatives 6a,b and 8a,b the J(4aH,5H)

and J(5H,6aH) couplings, respectively, are 11.7 and 12.1 Hz. In the cis-5,6-tetramethylene-1,3-oxazines 5a and 5b the J(4aH,5H) coupling is 3.3 Hz, and therefore the predominant conformation is O-inside. In contrast, in the cis-4,5-tetramethylene-1,3-oxazines (7a and 7b) the J(5H,6aH) coupling is 11 Hz, showing the predominance of the N-outside conformation, as in the case of the 2-(p-nitrophenyl)-substituted analogues.[5] It follows that the 2-aryl substitution does not influence the conformational conditions of cis-5,6-tetramethylenetetrahydro-1,3-oxazines.

X-ray analysis of N-benzyl-cis-4,5-tetramethylenetetrahydro-1,3-oxazinium-picrate (7b)

A perspective view of the molecular geometry assumed by the tertiary ammonium cation formed from 3-benzyl-cis-4,5-tetramethylene-2,3,4,5-tetrahydro-1,3-oxazine with picric acid is depicted in Fig. 1. Since the crystal has a centre of symmetry, both enantiomers are present; of these, the form bearing the heteroatoms N and O in the α-position is drawn. Accordingly, in the crystalline state 7b also has the N-outside conformation. The corresponding final relative atomic coordinates of this cation, together with those of the picrate anion, have been deposited. The bond lenghts and angles for both the cation and the picrate anion are given in Fig. 2. As shown by the puckering parameters[20] both cis-fused rings adopt an almost perfect chair conformation.

	Q	θ	φ
ring A	0.57 Å	4.0°	248.4°
ring B	0.58	4.4	75.5

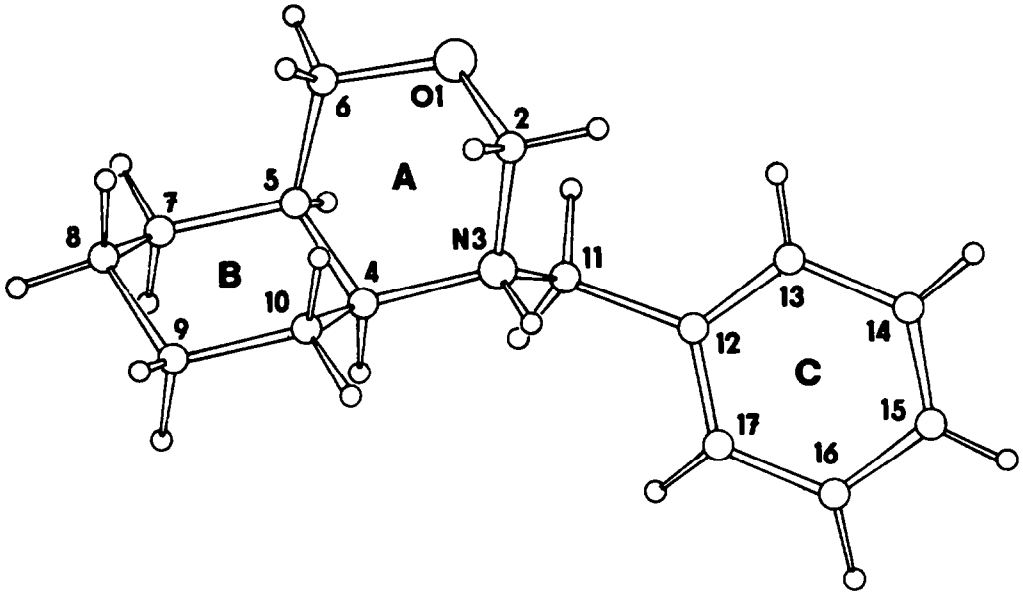


Figure 1. A perspective view of the N-benzyl-cis-4,5-tetramethylene-tetrahydro-1,3-oxazinium cation with atomic numbering and ring labelling. The bare numbers are for carbon atoms unless indicated otherwise.

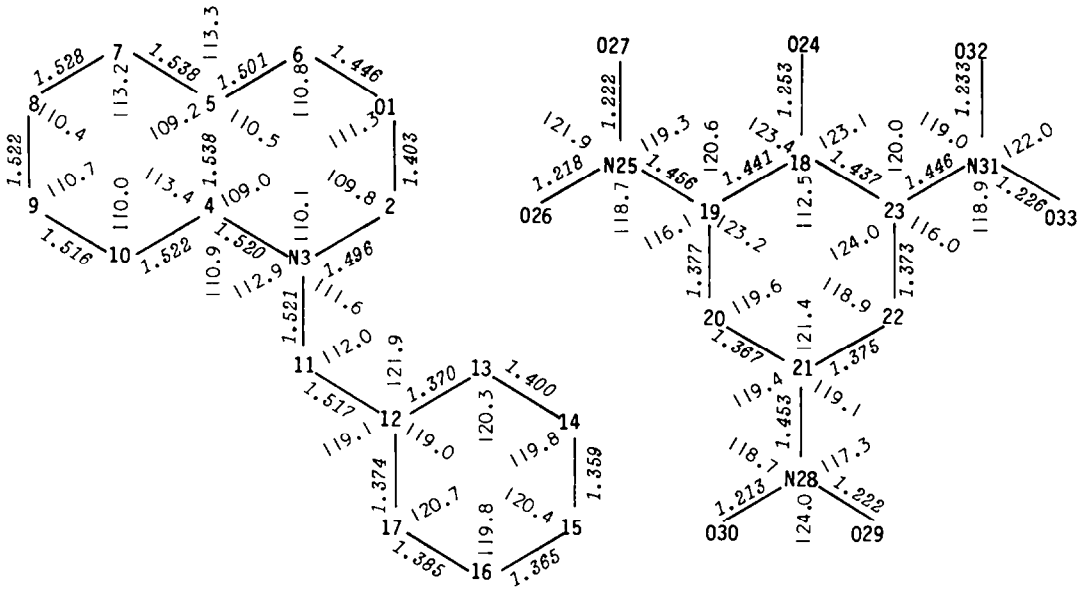


Figure 2. Bond lengths (Å) and angles (°) in compound 7b. E.s.d.'s are 0.002-0.004 Å and 0.2-0.4°, respectively.

The lowest endocyclic torsion angles, which agree within experimental error, are found at the cis junction. The H(5)-C(5)-C(4)-H(4) torsion angle is -47.3(9)°. The benzyl group is bound axially (O(1)-C(2)-N(3)-C(11) = 65.2(2)°, C(5)-C(4)-N(3)-C(11) = -71.3(3)°) and the least squares plane of the phenyl ring is approximately parallel with that of the heteroring (their dihedral angle is 17.8(1)°). The formation of the tertiary ammonium base accounts for the visible increase in the C-N distances (cf. e.g. ref.[21]) around N(3) (their mean value is 1.512(2) Å). In the heteroring the (H_2)C-O distances differ significantly (Δ = 0.043 Å). The protonated N(3) denotes a strong hydrogen-bond to the deprotonated phenolic oxygen of the picrate anion (N(3)...O(24) = 2.676(2) Å, H(3)...O(24) = 1.76 Å, NH...O = 167.8(18)°). The ring distortion in the picrate anion (see Fig. 2) is similar to that observed in other picrate moieties.[22,23]

EXPERIMENTAL

The physical properties, analyses and yields of the compounds are listed in the Table.

Ethyl cis-2-ethoxycarbonylamino-1-cyclohexanecarboxylate (11)

Ethyl cis-2-amino-1-cyclohexanecarboxylate hydrochloride[24] (4.15 g; 0.02 mol) was dissolved in water (25 ml) and sodium hydrogen carbonate (2.52 g; 0.03 mol), and then ethyl chloroformate (2.1 ml; 0.022 mol) was added, with stirring. Stirring was continued for 1 h, and the oily product which separated

on standing overnight was extracted with benzene (3x30 ml). The combined benzene solution was dried (Na_2SO_4) and the solvent was evaporated to leave a pale-yellow oily product.

Ethyl trans-2-ethoxycarbonylamino-1-cyclohexanecarboxylate (12)

This compound was prepared analogously to 11, starting from ethyl trans-2-amino-1-cyclohexanecarboxylate hydrochloride.[25] The crystalline product (12) was filtered off and washed several times with water.

Table. Physical and analytical data on the starting compounds 1-4, 11-14 and the 1,3-oxazines 5-8

Compound	M.p.[a] °C	Yield[a] %	Found % C	H	N	Formula	Required % C	H	N
11	113-118[b]	92	59.3	8.9	5.7	$C_{12}H_{21}NO_4$	59.2	8.7	5.8
12	57-58[c] (57-59)	88 (85.7)							
13	85-87[c]	94	69.6	7.6	5.1	$C_{16}H_{21}NO_3$	69.8	7.7	5.1
14	130-131[c]	89	69.8	7.7	5.1				
1a	83-84[c] (82-84)	83 (13.9)							
2a	95-100[b] (88-94)[d]	81 (24.3)	66.9	12.0	9.7	$C_8H_{17}NO$	67.1	12.0	9.8
3a	43-44[c] (42-45)	87 (26.9)							
3b	64-66[c] (124-128)[d]	83 (52.5)	76.6	9.7	6.2	$C_{14}H_{21}NO$	76.7	9.7	6.4
4a	99-105[b,e]	79	67.2	12.0	9.6	$C_8H_{17}NO$	67.1	12.0	9.8
4b	81-83[c] (80-83)	74 (36.2)							
5a[g]	216-219[f]	92	56.3	9.5	7.5	$C_9H_{18}ClNO$	56.4	9.5	7.3
6a[g]	213-216[f]	84	56.6	9.6	7.4				
7a[h]	166-167[f]	84	46.8	5.4	14.7	$C_{15}H_{20}N_4O_8$	46.9	5.2	14.6
8a[h]	166-170[f]	78	47.0	5.3	14.8				
5b[h]	126-128[f]	79	54.7	5.2	12.4				
6b[h]	150-153[f]	84	54.9	5.3	12.2	$C_{21}H_{24}N_4O_8$	54.8	5.3	12.2
7b[h]	141-143[f]	82	54.7	5.2	12.2				
8b[h]	200-201[f]	80	55.0	5.3	12.4				

[a] Literature[6] m.p.'s and yields in brackets
[b] B.p. at 400 Pa
[c] Recrystallized from n-hexane
[d] B.p. at 333 Pa
[e] M.p. of picrate 147-151 °C
[f] Recrystallized from ethanol-ether
[g] Hydrochloride
[h] Picrate

Ethyl cis-2-benzoylamino-1-cyclohexanecarboxylate (13)

Ethyl cis-2-amino-1-cyclohexanecarboxylate hydrochloride (4.15 g; 0.02 mol) was allowed to react with benzoyl chloride (2.55 ml; 0.022 mol) under Schotten-Baumann acylation conditions. After 2 h the benzene phase was separated and dried (Na_2SO_4), and the solvent was evaporated to yield snow-white, crystalline product.

cis-2-Methylaminomethyl-1-cyclohexanol (1a)

Lithium aluminium hydride (1.52 g; 0.04 mol) was suspended in dry tetrahydrofuran (200 ml) and, after stirring for 15 min, N-methyl-cis-2-hydroxy-1-cyclohexanecarboxamide (3.14 g; 0.02 mol) was added. The mixture was stirred and refluxed for 1.5 h, then cooled in ice, and water (1.6 ml) in tetrahydrofuran (30 ml) was added dropwise, followed by the addition of water (1.6 ml) in one portion, at room temperature. After stirring for 1 h, the inorganic material was removed by filtration and washed with tetrahydrofuran. Drying (over Na_2SO_4) of the filtrate and evaporation of the solvent gave 1a as a crystalline product.

cis-N-Methyl-5,6-tetramethylenetetrahydro-1,3-oxazine (5a)

cis-2-Methylaminomethyl-1-cyclohexanol (1a) (1.43 g; 0.01 mol) was shaken with 35% aqueous formaldehyde solution (10 ml) for an hour. The mixture was then basified with 10% aqueous potassium hydroxide solution and extracted with ether (3x30 ml). The combined extracts were dried (Na_2SO_4) and evaporated, to give an almost colourless oil which was purified as the hydrochloride salt.

The base liberated for purposes of spectroscopic examination was a colourless, viscous oil.

Crystal structure of N-benzyl-cis-4,5-tetramethylenetetrahydro-1,3-oxazinium-picrate (7b)

Crystal data: triclinic, a = 7.134(2) Å, b = 12.830(3) Å, c = 12.332(2) Å, α = 104.58(2)°, β = 87.41(3)°, γ = 104.37(2)°, U = 1058.0(9) Å^3, D_c = 1.445 g cm^{-3}, Z = 2, F(000) = 484, space group P$\bar{1}$. Intensities of 3224 independent reflexions were collected in the range $2\theta \leq 50°$ by an $\omega = 2\theta$ scan on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated MoK$_\alpha$ (λ = 0.71073 Å) radiation. Cell constants were determined by least squares refinement from the setting angles of 25 reflexions. After data reduction, 2720 reflexions with $I - 3.0\sigma(I) > 0$ were taken as observed. No absorption (μ = 1.05 cm^{-1}) correction was applied. The structure was solved by direct methods using the MULTAN program.[26] An E-map computed with the use of the phase set of 460 normalized structure factors having $E \geq 1.50$ revealed the positions of 30 non-hydrogen atoms (R = 0.36). The missing 3 atoms were located in a subsequent Fourier synthesis. Full matrix least squares refinement of positional and vibrational parameters reduced R to 0.095. At this stage H positions were generated from assumed geometries and were checked in a difference Fourier map. Further anisotropic refinement of the non-hydrogen atom positions, in which H positions were treated in isotropic mode, gave a final R = 0.050 (R_w = 0.061, R_{tot} = 0.060). Scattering factors were taken from International Tables for X-ray Crystallography.[27] All calculations were performed on a PDP 11/34 minicomputer with the use of the SDP-34 system of Enraf-Nonius with local modifications.

Acknowledgements

The authors wish to express their thanks to Mr. Cs. Kertész, Mr. M. Toldi and Mr. Gy. Tolnai for their technical assistance, and to Mrs. I. Szabó and Mrs. A. Varga for microanalyses.

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