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# STEREOCHEMICAL STUDIES—XXXIII.[1] SATURATED HETEROCYCLES—IX[2]

## SYNTHESIS AND CONFORMATIONS OF STEREOISOMERIC *CIS*- AND *TRANS*-TETRAMETHYLENE- AND PENTAMETHYLENEDIHYDRO-1,3-OXAZINES

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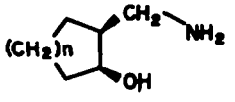
**Abstract**—By the reaction of *cis*- and *trans*-2-aminomethylcyclohexanol (1, 2), *cis*- and *trans*-2-hydroxymethylcyclohexylamine (3, 4) and the homologous cycloheptane derivatives (5–8) with ethyl *p*-chlorobenzimidate (11), *cis*- and *trans*-5,6-tetramethylene- and pentamethylene-2,3,5,6-tetrahydro-4*H*-1,3-oxazines (12, 13, 16, 17) and *cis*- and *trans*-4,5-tetramethylene- and pentamethylene-4,5-dihydro-6*H*-1,3-oxazines (14, 15, 18, 19) were prepared. The amidine intermediate of the ring-closure reaction was isolated, and the mechanism of the acid-catalysed reaction is discussed. It follows from the $^1$H NMR data that in the preferred conformations of the *cis*-tetramethylene-tetrahydrooxazines the methylene group of the hetero ring is *equatorial* and the hetero atom (O or N) *axial*. In contrast, the conformation equilibria of the *cis* pentamethylene derivatives, in accordance with earlier X-ray analysis, are shifted towards the conformer containing the methylene group in *isoclinal* and the hetero atom in *equatorial* position. The preferred conformations 12a and 14a of the tetramethylene derivatives 12 and 14 were also determined by X-ray crystal analysis.

Starting from *cis*- and *trans*-aminomethylcyclohexanol (1, 2), *cis*- and *trans*-hydroxymethylcyclohexylamine (3, 4) and the homologous cycloheptane derivatives (5–8), *cis*- and *trans*-5,6-tetramethylene- and pentamethylene-2,3,5,6-tetrahydro-4*H*-1,3-oxazines, *cis*- and *trans*-4,5-tetramethylene- and pentamethylene-2,3,4,5-tetrahydro-6*H*-1,3-oxazines[3,4] and the related tetramethylene- and pentamethylene-1,3-oxazin-2-ones[5,6] were prepared. The related *cis*- and *trans*-5,6-tetramethylene- and pentamethylene-2,3,5,6-tetrahydro-1,3-oxazin-4-ones[7] and 5,6-tetramethylene- and pentamethylene-5,6-dihydropyrimidin-4(3*H*)-ones[7] were also synthesized. It was shown by $^1$H NMR spectroscopy that the methylene or carbonyl group of the hetero ring is *equatorial*, while the hetero atom (O, N) attached to the cyclohexyl ring is *axial* in the preferred conformations of the *cis* isomers of the former tetramethylene-heterocycles.[3] The preferred conformations of the pentamethylene derivatives could not be deduced unequivocally purely from NMR data, and therefore X-ray studies were also performed.[8] The widespread investigation[9–12] on the conformational analysis of saturated and partly-saturated heterocycles prompted us to continue our earlier work in this field and to prepare and investigate the title compounds.

### *Synthesis and reaction mechanisms*

Though the ring closure 1,2- and 1,3-aminoalcohols with imidates to yield oxazolines[13–16] and dihydro-4*H*-1,3-oxazines[16–18] is a well-known method, the mechanisms of the reactions have not been investigated in detail. The formation of 2-phenyloxazoline by the reaction of 2-aminoethanol and ethyl benzimidate was formulated[13,14] with *N*-(2-hydroxyethyl)benzimidate 9 intermediate. Recently it was shown[19] that *N*-substituted amines and not, as suggested earlier, *N*-substituted imidates are the intermediates in the reactions of imidate salts with 1,2- and 1,3-aminoalcohols. In the reaction of ethyl benzimidate hydrochloride and 2-aminoethanol, the intermediate *N*-(2-hydroxyethyl)benzimidinium chloride 10 could also be isolated.

Contemporaneously with the above investigations[19] we prepared[20] the tetramethylene- and pentamethylenedihydrooxazines 12–19 by reacting the aminoalco-



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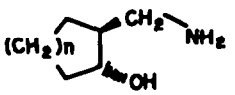

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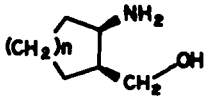

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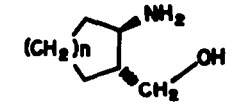

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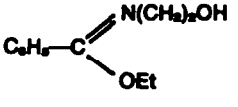

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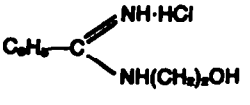

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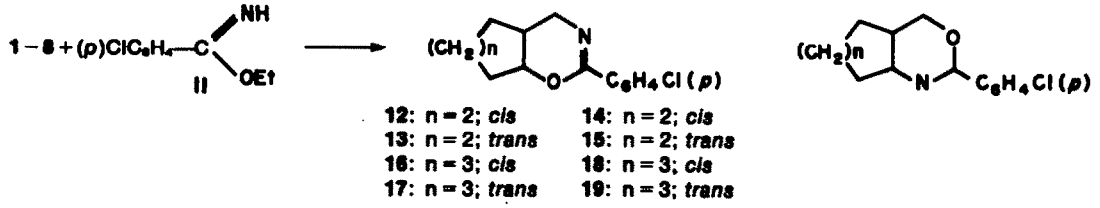
Scheme 1.




Scheme 2.

hols 1–8 with ethyl *p*-chlorobenzimidate (11). The yield of the reaction in boiling chlorobenzene was only about 20%, which was raised to 50% by adding a catalytic amount of HCl, but owing to the high temperature a contaminated product was obtained. In boiling ethanol with acid-catalysis, the reaction furnished a pure product with a yield of over 70%.

The acid-catalysis is in accordance with the results of Neilson *et al.*[19] who observed that ethyl benzimidate and 2-aminoethanol do not react in ethereal solution, whereas ethyl benzimidate hydrochloride in methanol at room temperature gives the intermediate *N*-(hydroxyethyl)benzimidinium chloride (10); the latter, under the same mild conditions, but over a longer reaction time, yields 2-phenyloxazoline.

When 1 and ethyl *p*-chlorobenzimidate 11 were refluxed together in ethanol for 1.5 h, the amidine base 21 was isolated in an excellent yield. The structure of 21 was confirmed by hydrolysis, yielding *N*-(chlorobenzoyl)-*cis*-2-aminomethylcyclohexanol 22 (Scheme 3). Formation of amidine 21 was accelerated only moderately by a catalytic amount of acid, but the rate of the ring-closure step was considerably enhanced. With acid-catalysis in refluxing ethanol and amidine 21 furnished the dihydrooxazine 12 in nearly a quantitative yield in 12 h, while without acid the yield was merely about 10%.

As regards the relative rates of formation of the intermediate and product ($v_1$ and $v_2$, respectively), and the rates of the above proton-catalysed reactions [$v_1(H^+)$, $v_2(H^+)$], the following qualitative relations could be concluded:

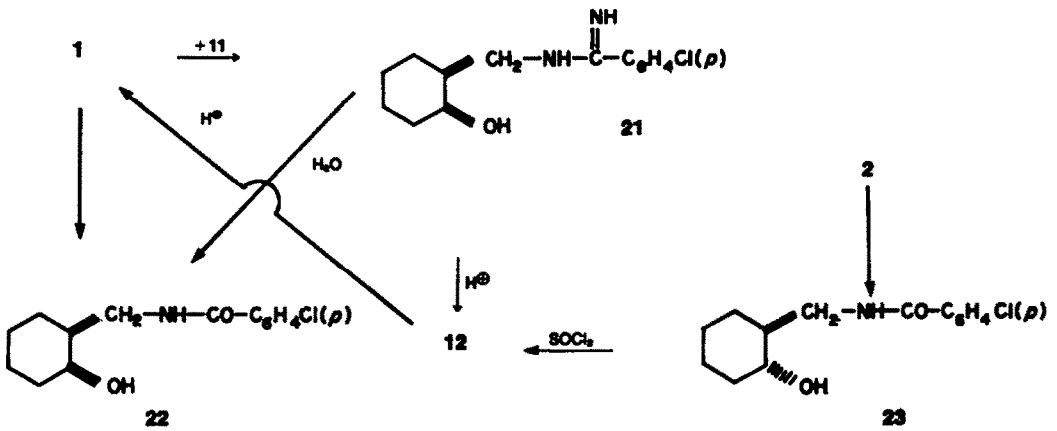
$$1 + 11 \xrightarrow[v_1]{v_1(H^+)} 21 \xrightarrow[v_2]{v_2(H^+)} 12$$

$$v_2 \ll v_2(H^+) \ll v_1 < v_1(H^+).$$

The mechanism of the reaction of 1,3-aminoalcohols and imidates, on the example of 1 and 11, can be represented by Scheme 4. With ethyl benzimidate and

Table 1. Physical and analytical data of compounds prepared

| Compound No. | M.p. °C | Found % C | H | N | Formula | Required % C | H | N |
|---|---|---|---|---|---|---|---|---|
| 12 | 77–78 | 67.6 | 6.6 | 5.6 | | | | |
| 13 | 104–105 | 67.3 | 6.6 | 5.9 | $C_{14}H_{16}ClNO$ | 67.4 | 6.5 | 5.6 |
| 14 | 82–84 | 67.0 | 6.5 | 5.9 | | | | |
| 15 | 108–109 | 67.6 | 6.6 | 5.6 | | | | |
| 16 | 67–68 | 68.3 | 7.0 | 5.3 | | | | |
| 17 | 106–107 | 68.3 | 7.0 | 5.4 | $C_{15}H_{18}ClNO$ | 68.3 | 6.9 | 5.3 |
| 18 | 121 | 67.9 | 7.0 | 5.5 | | | | |
| 19 | 85–86 | 68.5 | 6.9 | 5.4 | | | | |

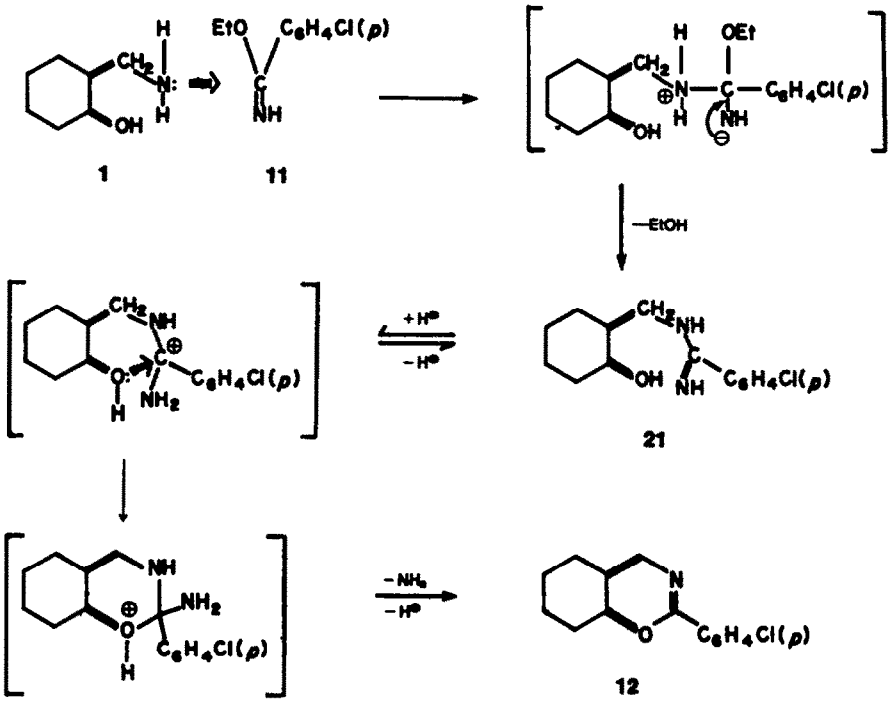



Scheme 3.

Table 2. IR and $^1$H NMR data of dihydrooxazines 12–19

| Compound No. | IR(KBr) cm$^{-1}$ | | $^1$H-NMR data in $CDCl_3$ solution ($\delta_{TMS}$ = 0 ppm) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Chemical shifts [$\delta$ ppm] | | | | | | Coupling constants (Hz) | | |
| | $\nu$(C=N) | $\gamma(C_{Ar}H)$[a] | $H_a$ | $H_b$ | $H_x$[b] | $H_M$, Cycloalkyl $CH_2$ | Aromatic protons[c] 2,6-H | 3,5-H | $J_{AB}$ | $J_{AM}$/ | $J_{BM}$/ |
| 12 | 1650 | 845, 840 | 3.65 | 3.37 | 4.38 (8) | 1.55[d] | 7.70 | 7.30 | 16 | 5 | 3 |
| 13 | 1640 | 840 | 3.72 | 3.15 | 3.85 (26) | 50–150[e] | 7.85 | 7.30 | 16 | 5 | 10 |
| 14 | 1645 | 830, 840, 845 | 4.25 | 4.10 | 3.65 (8) | 1.80[d], 1.50[d] | 7.75 | 7.37 | 11 | 4 | 4 |
| 15 | 1640 | 830, 840 | 4.25 | 3.90 | 3.00 (24) | 50–150[e] | 7.85 | 7.30 | 10 | 4 | 10 |
| 16 | 1650 | 840 | 3.60 | 3.35 | 4.45 (14) | 1.90[d], 1.60[d] | 7.83 | 7.28 | 16 | 5 | 5 |
| 17 | 1645 | 845 | 3.72 | 3.15 | 3.85 (20) | 1.65[d] | 7.85 | 7.32 | 16 | 5 | 10 |
| 18 | 1645 | 835 | 4.15 | 3.87 | 3.65 (16) | 60–140[e] | 7.85 | 7.30 | 10 | 4 | 7 |
| 19 | 1650 | 840 | 4.15 | 3.70 | 3.15 (22) | 1.65[d] | 7.87 | 7.30 | 11 | 5 | 11 |

[a] Out of plane deformation vibration of the $C_{Ar}$–H bonds, characteristic for *para* disubstituted aromatic rings.
[b] Halfbandwidth in Hz.
[c] Estimated from the *AA'BB'* multiplet of the *p*-disubstituted aromatic ring by *AB*-approximation ($J_{AB}$ = 9 Hz).
[d] Relative sharp maximum of overlapped multiplets.
[e] Multiplets in Hz.
[f] Estimated values by first order approximation.




Scheme 4.

a catalytic amount of acid instead of ethyl benzimidate hydrochloride,[19] the amidine intermediate 21 could also be isolated.

For conversion of the alicyclic *trans*-1,2-aminoalcohols into the corresponding *cis*-isomers, treatment of their *N*-benzoyl derivatives with thionyl chloride is a standard method,[16,21] which has been applied in several cases for preparation of the *cis*-2-aminomethylcyclanols from the *trans*-isomers.[22,23] Similar treatment of the *trans*-aminoalcohol 2 gave the *cis*-dihydrooxazine derivative 12, which was hydrolysed to the *cis*-aminoalcohol 1.

*Conformational analysis by* NMR *spectroscopy*

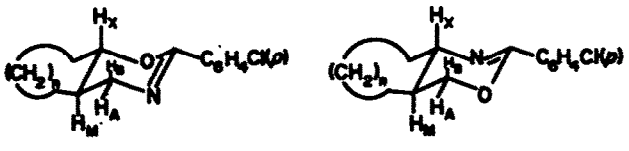
The conformational analysis is based[5] on the *ABMX* lines of the methylene protons in the hetero ring and of the anellated methine protons in the $^1$H NMR spectra. The parameters of the *ABMX* system, as well as some other characteristic IR and $^1$H NMR data of compounds 12–19, are given in Table 2.

The characteristically different *ABMX* parameters of the *cis* and *trans* isomers are due to the shift of the conformational equilibrium towards a preferred conformation. In the case of the *trans* isomers this preferred conformation is the chair–chair form, in which the methine protons are *axial*. Therefore, the coupling constants $J_{AM}$ and $J_{BM}$ differ significantly ($J_{AM}$ 4–5 Hz, $J_{BM}$ 10–11 Hz for compounds 13, 15, 17 and 19), as $J_{AM}$ and $J_{BM}$ correspond to an *equatorial-axial* and a *diaxial* interaction, respectively. The halfbandwidth of the anellated *X* proton attached to the hetero atom is large (20–26 Hz), and its chemical shift is relatively small, as $H_X$ is *axial* and among its interactions with the vicinal protons there are two *diaxial* ones.

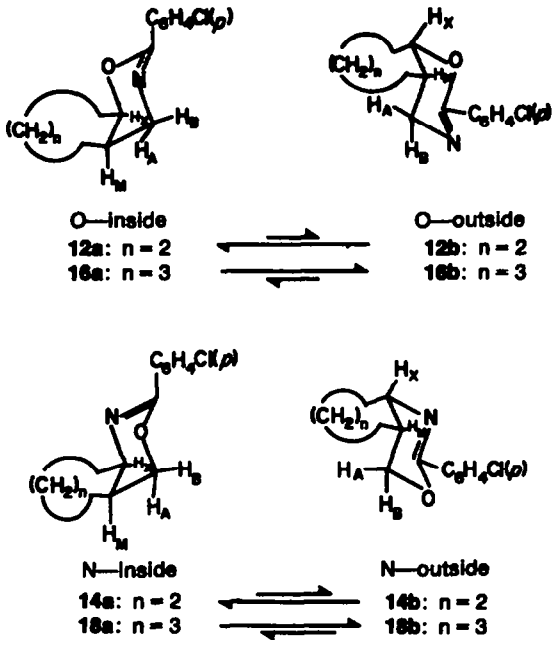
In the case of the *cis* isomers two chair–chair conformations are possible. In the *O*-inside (and *N*-inside) form (12a, 16a and 14a, 18a) the hetero atom attached to the cycloalkyl ring is *axial*, since $H_X$ is *equatorial*, so the other anellated hydrogen ($H_M$) is also *equatorial* relative to the hetero ring. In the *O*-outside (and *N*-outside) conformation (12b, 16b and 14b, 18b) the situation is reversed: the $H_X$ and $H_M$ protons are *axial* relative to the cycloalkyl and to the hetero ring, respectively.

In the case of the *cis* isomers the $H_X$ chemical shifts are increased by 0.50–0.65 ppm compared with their *trans* counterparts, whereas the halfbandwidth is simultaneously decreased (8 Hz for 12 and 14; 14 and 16 Hz for 16 and 18). Both data refer to the *equatorial* position of $H_X$, and consequently the predominance of the *O*-inside (*N*-inside) conformer. In accordance, $J_{AM}$ and $J_{BM}$ have similar and relative small values corresponding to the *diequatorial* and *axial-equatorial* interactions, respectively ($J_{AM}$5 and 4 Hz, $J_{BM}$3 and 4 Hz for 12 and 14, respectively; $J_{AM}$5 and 4 Hz, $J_{BM}$5 and 7 Hz for 16 and 18, respectively).

In the *O*-outside (*N*-outside) conformer (12b, 16b and




Scheme 5.




Scheme 6.

14b, 18b) the situation would be reversed: due to the *axial* position of $H_M$ relative to the hetero ring, the great difference between the values of $J_{AM}$ and $J_{BM}$ observed in the *trans* isomers should be unchanged.

The larger halfbandwidth of the $H_X$ signal and the larger value of the coupling constant $J_{BM}$ for compounds 16 and especially for 18 shows that the conformational equilibria in the case of these pentamethylene derivatives are shifted towards the conformers 16b and 18b. These results are in accordance with the conformation of related bicyclic 1,3-dioxanes,[24] where the tetramethylene derivatives the *O*-inside, but in the pentamethylene and hexamethylene homologues the *O*-outside conformer is preferred.

While in the case of the *cis*-tetramethyleneoxazines the preference for the *O*- and *N*- inside conformers (12a, 14a) follows unambiguously from a comparison of the halfbandwidths of the *cis* and *trans* isomers, a similar unequivocal conclusion cannot be drawn for the pentamethylene homologues, because in the case of the *cis* isomers 16 and 18 the halfbandwidths of the $H_X$ protons are increased (14 and 16 Hz, respectively). If the former values are with compared those of the corresponding *trans* isomers (20 and 22 Hz, respectively), the difference is not so expressed. Therefore, an unambiguous conclusion for the preferred conformation of the pentamethylene derivatives could not be drawn. Taking the above into account, we decided to determine the conformations of compounds 12, 14 and 18[8] by X-ray analysis. This X-ray analysis comprises part of a systematic study on related saturated heterocycles.

*X-Ray determination of the molecular structures of tetramethylene derivatives* 12 *and* 14

Figure 1 shows a perspective view of the structures computed from final fractional coordinates of the non-hydrogen atoms given with their e.s.d.'s in Table 3, and those of hydrogen atoms which are linked to the fused carbon atoms. The fractional coordinates of hydrogen atoms are presented in Table 4. The cooresponding bond

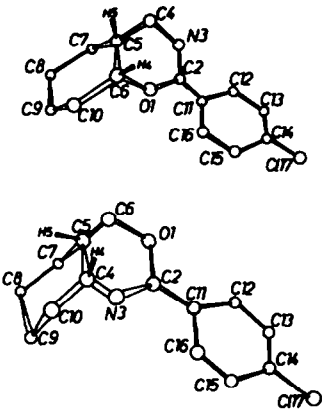


Fig. 1.

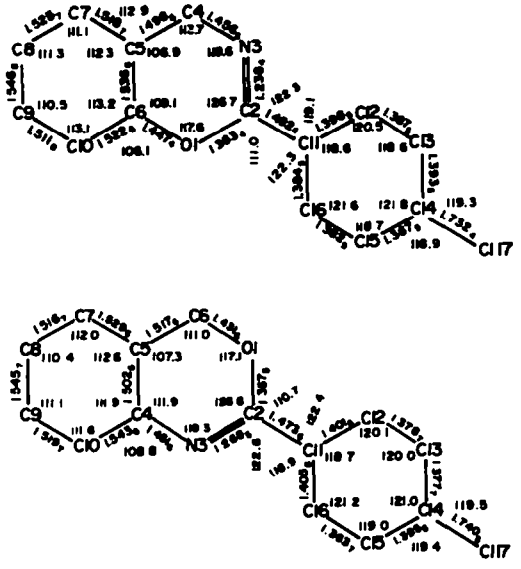


Fig. 2.

lengths and angles for 12 and 14, as can be seen in Fig. 2, agree well with each other and with those found in the literature. Bond distances C(2)–N(3) of 1.238(4) and 1.268(5) Å are somewhat different. Nevertheless, they indicate strong C=N double bonds in accordance with the low O(1)–C(2)–C(11) angles[25] of 111.0(3)° and 110.7(3)°, respectively. It is worth noting that the phenyl rings [means bond lengths: 1.385(5) and 1.387(7) Å] lie almost in the best planes determined by the O(1), C(2), C(11), N(3) moieties, as shown by the corresponding dihedral angles in Table 5. Each ether bridge is formed by significantly different C($sp^3$)–O and C($sp^2$)–O single bonds [mean bond lengths: 1.439 and 1.365 Å, respectively], indicating their different hybridization.

The cyclohexane ring fused to the 1,3-oxazine ring at C(5) and at either C(4) or C(6), thereby forming isomer 14 or 12, respectively has a chair conformation in both cases (see Table 6). In 12 it is somewhat more flattened than in 14; otherwise the mean bond lengths and angles agree well with each other: 1.526(5) vs 1.526(7) Å; 111.8(9)° vs 111.6(6)°. The conformation of each hetero ring can be characterized by the lowest asymmetry parameter:[26] $\Delta C_s(C5) = 10.5°$ for 12, and 4.7° for 14, which indicates a more and a less distorted sofa form. If

Table 3. Final fractional coordinates and anisotropic vibrational parameters (× $10^4$) for compounds 12 and 14. Estimated standard deviations are given in parentheses[a]

Molecule 12

| | x/a | y/b | z/c | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|---|---|---|
| O(1) | 3468(1) | 2018(2) | 4589(3) | 565(12) | 560(7) | 760(14) | -82(11) | -77(11) | 54(10) |
| C(2) | 3349(1) | 1065(3) | 3633(4) | 532(16) | 582(9) | 638(17) | 42(14) | 11(15) | -3(14) |
| N(3) | 3608(1) | 134(2) | 3642(4) | 644(16) | 693(9) | 752(17) | 37(13) | -28(15) | 152(14) |
| C(4) | 4093(2) | 14(4) | 4725(6) | 766(24) | 818(12) | 876(25) | 32(19) | -125(22) | 189(19) |
| C(5) | 4333(2) | 1172(3) | 5282(5) | 657(19) | 724(10) | 783(21) | 69(18) | -117(18) | 118(17) |
| C(6) | 3901(2) | 1916(3) | 5817(5) | 724(21) | 698(10) | 669(20) | 8(16) | -45(18) | 13(17) |
| C(7) | 4588(2) | 1803(4) | 4071(6) | 709(23) | 861(12) | 1003(28) | 0(22) | 83(23) | 52(19) |
| C(8) | 4777(2) | 3031(5) | 4624(8) | 916(33) | 1100(18) | 1277(38) | -117(31) | 127(31) | -361(28) |
| C(9) | 4326(2) | 3789(4) | 5045(7) | 941(31) | 989(15) | 1041(31) | -98(26) | -69(27) | -289(25) |
| C(10) | 4071(2) | 3176(4) | 6258(6) | 920(27) | 877(13) | 828(26) | -191(21) | -30(24) | -99(22) |
| C(11) | 2853(1) | 1233(3) | 2559(4) | 465(15) | 545(8) | 632(16) | 77(13) | 14(14) | 28(13) |
| C(12) | 2683(1) | 362(3) | 1460(4) | 609(18) | 650(9) | 701(18) | 0(16) | -22(16) | 52(15) |
| C(13) | 2212(2) | 486(4) | 470(5) | 700(20) | 725(10) | 756(21) | -20(17) | -52(18) | -25(17) |
| C(14) | 1920(1) | 1507(3) | 566(5) | 512(17) | 644(9) | 775(20) | 108(16) | 5(16) | -12(14) |
| C(15) | 2087(1) | 2387(3) | 1600(5) | 583(18) | 692(10) | 800(20) | 35(17) | 28(17) | 82(15) |
| C(16) | 2563(1) | 2241(3) | 2692(4) | 546(17) | 639(9) | 740(19) | -19(15) | -8(16) | 70(14) |
| Cl(17) | 1332(1) | 1678(1) | -663(1) | 705(7) | 920(5) | 1119(9) | 144(5) | -209(6) | -11(4) |

Molecule 14

| | x/a | y/b | z/c | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|---|---|---|
| O(1) | 9943(6) | 608(3) | 1955(1) | 806(17) | 750(9) | 701(16) | 25(12) | 154(14) | 110(14) |
| C(2) | 8972(9) | 1798(4) | 2011(2) | 700(20) | 832(9) | 570(18) | -33(14) | 27(16) | 2(17) |
| N(3) | 9322(7) | 2752(3) | 1678(2) | 764(19) | 686(9) | 614(16) | -43(13) | 123(15) | -80(15) |
| C(4) | 10823(9) | 2610(4) | 1166(2) | 686(21) | 707(10) | 720(21) | -14(18) | 106(19) | -98(18) |
| C(5) | 10812(9) | 1267(4) | 935(2) | 669(21) | 686(10) | 705(20) | -35(15) | 120(18) | 23(16) |
| C(6) | 11665(9) | 420(4) | 1401(2) | 714(23) | 765(12) | 816(24) | -35(20) | 123(21) | 77(19) |
| C(7) | 8272(9) | 878(4) | 609(2) | 741(22) | 700(10) | 656(20) | -69(17) | 121(18) | -11(17) |
| C(8) | 7389(11) | 1792(5) | 99(2) | 837(26) | 809(12) | 775(25) | -18(19) | 90(23) | -42(22) |
| C(9) | 7320(10) | 3161(5) | 349(2) | 855(27) | 817(13) | 778(26) | 126(20) | 123(24) | 57(23) |
| C(10) | 9865(10) | 3552(4) | 658(2) | 852(27) | 797(12) | 746(24) | 107(20) | 159(22) | -74(20) |
| C(11) | 7347(7) | 1043(4) | 2516(2) | 629(18) | 606(9) | 804(17) | -69(13) | 13(17) | -14(14) |
| C(12) | 7253(9) | 853(4) | 2940(2) | 824(23) | 710(11) | 600(20) | -9(16) | 85(19) | 22(19) |
| C(13) | 5651(10) | 929(5) | 3394(2) | 868(26) | 765(12) | 666(23) | 19(17) | 111(21) | -12(21) |
| C(14) | 4122(9) | 1973(4) | 3428(2) | 740(22) | 670(10) | 697(19) | -51(14) | 49(18) | -62(17) |
| C(15) | 4157(10) | 2962(4) | 3007(2) | 722(25) | 734(11) | 699(24) | -39(16) | 118(21) | 23(19) |
| C(16) | 5778(9) | 2899(4) | 2565(2) | 782(23) | 698(11) | 618(21) | -8(15) | 105(18) | 3(18) |
| Cl(17) | 2092(1) | 2062(1) | 4000(1) | 922(8) | 859(5) | 777(7) | -94(4) | 227(6) | -90(5) |

[a] The anisotropic vibrational parameters are given in the form:

$$\exp\left[-2\pi^2 \sum_i \sum_j h_i h_j a_i^* a_j^* U_{ij}\right] \quad \text{with } U_{ij} \text{ in } Å^2$$

these $\Delta C_s$ values are compared to the atomic deviations from the best planes of the 1,3-oxazine rings (see Table 5), it is clear that the ring conformation in 12 is a transition between sofa and skew forms, while in 14 it resembles a half-flattened boat.

The nearly-identical conformations of the isomer pair around the *cis*-junctions are depicted in the Newman projections (Fig. 3). In each case the hetero atom, O(1) or N(3), is *axial*, while the methylene group bound to C(5) is *equatorial* (12a and 14a), as inferred from the $^1$H NMR studies. It is a noteworthy fact that the predominant conformation of each isomer in the crystalline state is proactically identical with that in solution.

As regards structure 18, where the hetero atom N(3) was found by X-ray analysis[8] to assume an *equatorial* position, the torsion angle H–C(4)–C(5)–H is only 40.6°, while in both 12 and 14 it is considerably nearer to 60° (52.8° and 53.9°). The different conformation of the

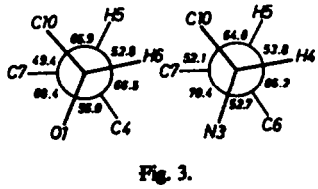



Fig. 3.

Table 6. Endocyclic torsion angles for compounds 12 and 14

| | Heterocyclic | | Isocyclic | |
|---|---|---|---|---|
| (12) | C(4)-C(5)-C(6)-O(1) | = -56.0° | C(7)-C(5)-C(6)-C(10) | = -49.4° |
| | C(5)-C(6)-O(1)-C(2) | = 37.5 | C(5)-C(6)-C(10)-C(9) | = 49.8 |
| | C(6)-O(1)-C(2)-N(3) | = -8.7 | C(6)-C(10)-C(9)-C(8) | = -53.1 |
| | O(1)-C(2)-N(3)-C(4) | = 0.0 | C(10)-C(9)-C(8)-C(7) | = 56.9 |
| | C(2)-N(3)-C(4)-C(5) | = -22.8 | C(9)-C(8)-C(7)-C(5) | = -57.1 |
| | N(3)-C(4)-C(5)-C(6) | = 49.6 | C(8)-C(7)-C(5)-C(6) | = 53.0 |
| (14) | N(3)-C(4)-C(5)-C(6) | = -52.7 | C(10)-C(4)-C(5)-C(7) | = -52.1 |
| | C(4)-C(5)-C(6)-O(1) | = 56.0 | C(4)-C(5)-C(7)-C(8) | = 54.1 |
| | C(5)-C(6)-O(1)-C(2) | = -31.9 | C(5)-C(7)-C(8)-C(9) | = -55.2 |
| | C(6)-O(1)-C(2)-N(3) | = 1.4 | C(7)-C(8)-C(9)-C(10) | = 56.4 |
| | O(1)-C(2)-N(3)-C(4) | = 2.2 | C(8)-C(9)-C(10)-C(4) | = -55.2 |
| | C(2)-N(3)-C(4)-C(5) | = 25.4 | C(9)-C(10)-C(4)-C(5) | = 53.1 |

hetero atom N(3) in 18b from those in 12a and 14a may be regarded as the effect of the cycloheptane ring, which has a twist chair (TC) conformation. In this (TC) conformation the $C_2$ axis crosses C(5), which thus maintains two *isoclinal* substituents: C(6) and H(20).

## EXPERIMENTAL

*2-(p-Chlorophenyl)-cis-5,6-tetramethylene-5,6-dihydro-4* H-1,3-*oxazine* (12). *cis*-2-Aminomethylcyclohexanol[27] (1) (1.29 g; 0.01 mol) and ethyl *p*-chlorophenylbenzimidate (11) (1.83 g; 0.01 mol) were refluxed in EtOH (50 ml) with a catalytic amount of hydrogen chloride until TLC (Merck Kieselgel HF, benzene: EtOH 4:1) showed the absence of starting materials (about 24 h). Evaporation left a colourless crystalline residue. Recrystallisation from light petroleum gave prisms, m.p. 77° (1.8 g; 72%). The physical and analytical data of the related derivatives 12–19, prepared from the corresponding 1,3-aminoalcohols,[6,27] are listed in Table 1.

*B-(p-Chlorobenzimino)-cis-2-aminomethylcyclohexanol* 21

(a) *cis*-2-Aminomethylcyclohexanol (1) (0.65 g; 5 mmol) and ethyl *p*-chlorophenylbenzimidate (11) (0.92 g; 5 mmol) were refluxed in 20 ml EtOH for 1.5 h. Evaporation gave 0.97 g (73%) white crystals, which recrystallised from EtOH as cubic prisms, m.p. 146–150° (with decomposition). (Found: C, 62.98; H, 7.42; N, 10.80. $C_{14}H_{19}ClN_2O$ requires: C, 63.03; H, 7.18; N, 10.53%).

(b) Under identical conditions with a catalytic amount of HCl, in a 1 h reflux the yield was 73%.

(c) In a 1 h reflux without acid-catalysis, the yield was 62%.

(d) With a catalytic amount of HCl in 24 h at room temp., the yield was 36%.

(e) In 24 h at room temperature without acid-catalysis, the yield was 16%.

*2-(p-Chlorophenyl)-cis-5,6-tetramethylene-5,6-dihydro-4* H-1,3-*oxazine* (12) *from amidine* 21. *N-(p*-Chlorobenzimino)-*cis*-2-aminomethylcyclohexanol (21) (200 mg; 0.75 mmol) was dissolved in 10 ml EtOH and, after addition of a catalytic amount of HCl, refluxed for 12 h. Evaporation afforded a colourless oil which, on trituration with $Et_2O$, furnished a crystalline solid (170 mg; 91%); this recrystallised from petroleum ether as colourless plates, m.p. 77–78°, identical with 12 obtained from 1 with 11.

(b) Without proton catalysis under the same conditions, the yield was 10%.

*2-(p-Chlorophenyl)-cis-5,6-tetramethylene-5,6-dihydro-4* H-1,3-*oxazine* (12) *from* 23. 23[27] (1.24 g; 5 mmol) was added in portions to thionyl chloride (5 ml) at 0°. The reaction mixture was maintained for 24 h at room temp., and the thionyl chloride was evaporated. The residue was dissolved in $H_2O$ (10 ml), made alkaline with $Na_2CO_3$, and the ethereal extract was dried ($Na_2SO_4$), evaporated, and the residue (0.93 g; 74%) crystallised from light petroleum to furnish 12, m.p. 76–78°. The product is identical with 12 prepared from 1 with 11.

*N-(P-Chlorobenzoyl)-cis-2-aminomethylcyclohexanol* (22) *by hydrolysis of amidine* 21. 21 (100 mg; 0.41 mmol) was refluxed (6 h) in 50% EtOH (10 ml), then evaporated and the residue was crystallised from benzene to give 22 (73 mg; 73%), m.p. 154–155°, identical with an authentic sample[28] of 22 prepared from 1 by Schotten–Baumann acylation.

*cis-2-Aminomethylcyclohexanol* (1) 1,3-*oxazine* 12. 12 (0.5 g; 2 mmol) was refluxed (10 h) in a mixture of EtOH (10 ml) and conc. HCl (10 ml). The EtOH was then distilled off and the residue extracted with $Et_2O$. The water phase was made alkaline ($Na_2CO_3$) and extracted ($Et_2O$), the extract was dried ($Na_2SO_4$), evaporated and the residual oil (215 mg; 83%), after distillation, furnished 1 (190 mg), identical with an authentic sample.[27]

*Crystal structure determinations on* 2-(p-*chlorophenyl*)-*cis*-5,6-*tetramethylene*-5,6-*dihydro*-4H-1,3-*oxazine* (12) *and* 2-(p-*chlorophenyl*)-*cis*-4,5-*tetramethylene*-4,5-*dihydro*-6H-1,3-*oxazine* (14)

Crystal data: $C_{14}H_{16}NOCl$, MW 249.74.

| | 12 | 14 |
|---|---|---|
| Crystal symmetry: | monoclinic | monoclinic |
| Space group: | C2/c | $P2_1/c$ (from systematic absences) |
| *a*: | 26.004(5) | 5.352(3) Å |
| *b*: | 11.305(1) | 10.539(4) |
| *c*: | 8.770(1) | 21.937(9) |
| *β*: | 99.41(1) | 95.53(2)° |
| U: | 2543.47 | 1241.59 Å$^3$ |
| $D_c$: | 1.304 | 1.347 g. cm$^{-3}$ |
| $D_m$: | 1.29 | 1.34 (by flotation) |
| Z:: | 8 | 4 |
| F(000) | 1056 | 528 |
| $N(F_{tot})$ | 1979 | 2273 |
| $N(F_{obs})$ | 1966 | 1736 |
| $R_{obs}$ | 0.091 | 0.119 |
| g | $2.35 \times 10^{-3}$ | $1.85 \times 10^{-2}$ (in the weighting scheme) |
| k | 2.628 | 1.000 of $w = k/(\sigma(F) + gF^2)$ |

Symmetry-independent reflections for both compounds were collected from h01 → h, 10, 1 crystal layers on a Stoe-Göttinger semi-automatic two-circle diffractometer[29] using Ni-filtered CuK$\bar{\alpha}$ ($\bar{\lambda}$ = 1.5418 Å) radiation. The lattice parameters were determined and refined from Weissenberg and precision photographs. No absorption correction was applied in either case. Both crystal structures were solved by direct methods. Blocked full-matrix least-squares refinement of the positional and anisо-

Table 4. Fractional coordinates ($\times 10^4$) for hydrogen atoms of compounds 12 and 14. [$\bar{U}_i$12 = 0.119(5), $\bar{U}_i$14 = 0.095(6) Å$^2$.] They are numbered according to the carbon atoms to which they are linked

| | Molecule 12 | | | | Molecule 14 | | |
|---|---|---|---|---|---|---|---|
| | x/a | y/b | z/c | | x/a | y/b | z/c |
| H(4a) | 4016(2) | -486(4) | 5712(6) | H(4) | 12758(9) | 2824(4) | 1315(2) |
| H(4b) | 4368(2) | -461(4) | 4156(6) | H(5) | 12130(9) | 1175(4) | 595(2) |
| H(5) | 4647(2) | 1023(3) | 6233(5) | H(6a) | 13469(9) | 639(4) | 1659(2) |
| H(6) | 3800(2) | 1474(3) | 6818(5) | H(6b) | 11456(9) | -560(4) | 1336(2) |
| H(7a) | 4916(2) | 1289(4) | 3837(6) | H(7a) | 6898(9) | 855(4) | 938(2) |
| H(7b) | 4307(2) | 1890(4) | 3025(6) | H(7b) | 8450(9) | -56(4) | 415(2) |
| H(8a) | 5072(2) | 2938(5) | 5638(8) | H(8a) | 8671(11) | 1755(5) | -251(2) |
| H(8b) | 4942(2) | 3466(5) | 3721(8) | H(8b) | 5534(11) | 1521(5) | -94(2) |
| H(9a) | 4478(2) | 4632(4) | 5491(7) | H(9a) | 5948(10) | 3213(5) | 677(2) |
| H(9b) | 4040(2) | 3930(4) | 4019(7) | H(9b) | 6795(10) | 3802(5) | -26(2) |
| H(10a) | 3732(2) | 3679(4) | 6431(6) | H(10a) | 11195(10) | 3585(4) | 318(2) |
| H(10b) | 4345(2) | 3148(4) | 7324(6) | H(10b) | 9711(10) | 4482(4) | 858(2) |
| H(12) | 2921(1) | -411(3) | 1380(4) | H(12) | 8431(9) | 28(4) | 2910(2) |
| H(13) | 2077(2) | -200(4) | -357(5) | H(13) | 5605(10) | 172(5) | 3725(2) |
| H(15) | 1858(1) | 3180(3) | 1642(5) | H(15) | 2927(10) | 3769(4) | 3032(2) |
| H(16) | 2689(1) | 2926(3) | 3418(4) | H(16) | 5857(9) | 3879(4) | 2248(2) |

Table 5. Equations of atomic planes in the form $AX + BY + CZ = D$ where $X$, $Y$, $Z$ are orthogonal (Å) coordinates related to the axes a*, b, c. Deviations (Å $\times 10^3$) of relevant atoms from the planes are given in square brackets. Values for molecule 12 precede those for molecule 14

Plane (1): O(1), C(2), N(3), C(4), C(5), C(6)
0.4006 X + 0.4394 Y - 0.8040 Z = 2.4645
0.8860 X + 0.2472 Y + 0.3922 Z = 6.3596
[O(1) 72,-27; C(2) 84,-108; N(3) -25,13; C(4) -185, 213;
C(5) 327,-340; C(6) -272, 248; C(7) 1843, -1870; C(10) 275, -414]

Plane (2): O(1), C(2), N(3), C(11)
0.5035 X + 0.3963 Y - 0.7678 Z = 3.4453
0.7904 X + 0.2572 Y + 0.5559 Z = 6.4533
[O(1) 0, -2; C(2) 0, 7; N(3) 0, -3; C(4) 2, -77; C(5) 534, -727;
C(6) -192, 5; C(7) 2045, -2227; C(10) 360, -817; C(11) 0, -2;
C(12) 75, 210; C(16) -56, -272]

Plane (3): C(11), C(12), C(13), C(14), C(15), C(16)
0.4818 X + 0.4436 Y - 0.7557 Z = 3.3792
0.7118 X + 0.4519 Y + 0.5378 Z = 6.4290
[O(1) 13, -339; C(2) - 42, -47; N(3) -107, 137; C(11) -13.1;
C(12) 13, -6; C(13) -3, 4; C(14) -8, 4; C(15) 8, -10;
C(16) 3,8; Cl(17) -24, 3]

Dihedral angles (°) between planes (1)-(2) 6.7, 10.9;
(2)-(3) 3.1, 12.1; (1)-(3) 5.4, 17.6

tropic vibrational parameters of non-hydrogen atoms resulted in the final conventional R values given above. The fractional coordinates of hydrogen atoms were generated from assumed geometries with C–H constrained to 1.08 Å and were included in Sf calculations with a mean isotropic thermal parameter. A bonded hydrogen atom scattering factor was employed[30] with complex neutral scattering factors for the remaining atoms.[31,32] All calculations were performed with program SHELX[33] adapted on a CDC 3300 computer in Budapest.

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