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STRUCTURAL STUDIES ON 1,2-OXAZINES DERIVED FROM 3-METHYLCYCLOHEXANONE

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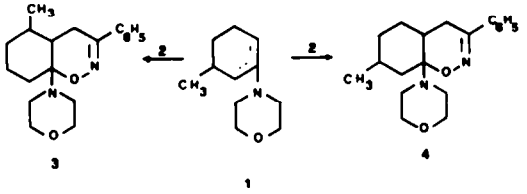
Abstract - The molecular structures of two isomeric 1,2-oxazines obtained by reaction of phenacyl bromide oxime with morpholine enamine of 3-methylcyclohexanone have been determined by spectroscopic and diffractometric techniques.
The oxazines result to be two diastereoisomers with cis fused ring conformation deriving from the Δ^6 enamine isomer.

It has been previously reported[1] that morpholine enamine of 3-methylcyclohexanone 1 reacts with phenacyl bromide oxime 2 to give two 1,2-oxazine isomers (m.p. 161-162°C and 165-166°C). Since morpholine enamine of 3-methylcyclohexanone exists as a ca. 1:1 mixture[2] of two structural isomers Δ^1 and Δ^6, it was at first supposed that the two 1,2-oxazine derivatives could be the structural isomers 3 and 4 shown in scheme 1.

Scheme 1.

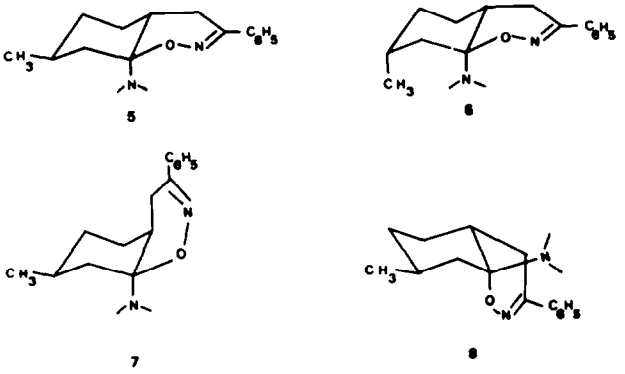


This hypothesis has been reexamined after the results from a separate investigation on the reaction of several enamines of 3-methylcyclohexanone with phenacyl bromide semicarbazone; in all the examined cases only the cyclocondensed 1,4-dihydropyridazine was obtained, whose structure derives from isomer Δ^6, as confirmed by single crystal X-ray structure determination[3].

On the basis of these results and of structural analogy between oxime and semicarbazone phenacyl bromide, it seemed reasonable to assume that the two 1,2-oxazine isomers obtained from enamine of 3-methylcyclohexanone are two diastereoisomers of general formula 4, hereafter 4a m.p. 161-162°C and 4b m.p. 165-166°C, derived from the enamine isomer Δ^6. The presence in 4 of three chiral centers gives rise to the existence of the four possible diastereoisomers shown in scheme 2.

^{1}H NMR spectra of 4a and 4b in $CDCl_3$ show that in both oxazines the methyl groups give rise to doublets centered at about δ = 0.87 (J = 6.2 Hz) and δ = 0.85 (J = 6.0 Hz) respectively; the chemical shifts and the coupling constants of these signals agree with the presence in the two oxazines of equatorial methyl groups[4-6], as further confirmed by ^{13}C NMR spectra. In fact the chemical shifts of the two methyl groups 19.86 p.p.m. for 4a and 20.22 p.p.m. for 4b are in the range generally found for equatorial orientation[6-7]. These data suggest the exclusion of diastereoisomer having the trans fused ring conformation 6 with axial methyl group and indicate the predominant pre-

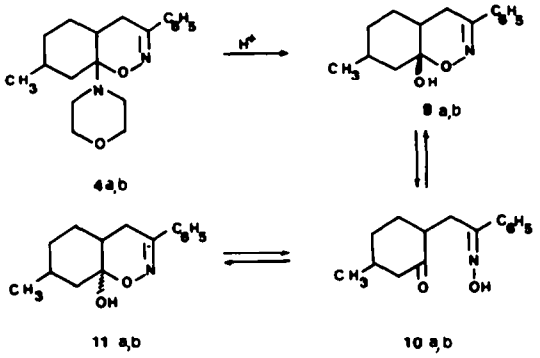
Scheme 2.



sence of the conformation with equatorial methyl group among those having the cis junction. The ^{13}C NMR spectra of 4a taken at variable temperature show a signal broadening at about -40°C, which partially splits at lower temperatures, confirming the cis junction of the rings in this isomer; no signal broadening or splitting was observed in the ^{13}C NMR spectra of 4b recorded down to a temperature of -130°C, although their absence cannot be considered decisive in determining the type of ring junction.

Under mild acid hydrolysis both 4a and 4b lose the morpholine ring giving rise to only one of two possible epimeric carbinols 9a,11a and 9b,11b (scheme 3); these undergo, in several solvents,

Scheme 3.



a process of epimeric equilibration through the formation of the corresponding open chain tautomers 10a and 10b, as shown by IR and ^1H NMR spectra. This process can be readily followed by means of the methyl and hydroxy signals in the ^1H NMR spectra recorded in DMSO-d_6, a solvent able to reduce the rate of both epimerization and proton exchange, thus favouring the separation of the signals due to different hydroxy groups[8-10]. ^1H NMR spectra of the hydrolysis product of 4a recorded at room temperature immediately after dissolving the sample show the signals of only one epimeric carbinol 9a: a doublet due to the methyl group at δ = 1.06 (J = 7.3 Hz) and an OH signal due to the carbinolic group at δ = 6.40. After a few hours the signals due to the open-chain tautomer 11a appear as a doublet of a methyl group centered at δ = 0.87 (J = 6.6 Hz) and of a singlet due to the oximic OH group[11] at δ = 11.6. Finally the appearance of a doublet of a methyl group at δ = = 0.82 (J = 6.2 Hz) and of a carbinolic OH signal at δ = 6.60 indicates the presence of the other possible epimeric carbinol 11a. The results obtained for the hydrolysis product of 4b show the same trend. The formation of an open-chain tautomer is confirmed by I.R. spectra recorded in chloroform solution which show an absorption band at 1705 cm^{-1} for 10a and at 1700 cm^{-1} for 10b.

Spectroscopic data for both equilibria, summarized in Table 1, clearly show that the oxazines 4a and 4b give rise to different open forms and to different pairs of epimeric carbinols. From a glance at the projection of the configurations of the chiral centers C4a, C7, C8a in the diastereoisomers 5, 7 and 8 depicted in scheme 2, it is easy to infer that different pairs of epimeric carbinols are obtained only from the diastereoisomers 5 and 7 or 7 and 8; the possible structures for 4a and 4b are thus restricted to the two pairs of diastereoisomers 5, 7 and 7, 8, and there-

Table 1. ^{1}H-NMR spectral data[a]

Compound	Solvent	CH_3[b](δ)	$J_{CH_3,H}$(Hz)	OH(δ)
4a	$CDCl_3$	0.87	6.2	-
4b	$CDCl_3$	0.85	6.0	-
9a	DMSO-d_6	1.06	7.3	6.10
10a	DMSO-d_6	0.87	6.6	11.11
11a	DMSO-d_6	0.82	6.2	6.30
9b	DMSO-d_6	0.90	6.0	6.00
10b	DMSO-d_6	-	-	11.20
11b	DMSO-d_6	0.88	5.9	6.15

[a] TMS as internal standard; [b] Centre of CH_3 doublet.

fore one of the two oxazines must have the structure 7. The assignment of this structure to the isomer 4a was done on the basis of spectral data in Table 1; they show that the coupling constants of the methyl groups, which are indicative of their orientation, are very close in epimeric carbinols 9b and 11b, while they are significantly different in the case of 9a and 11a, indicating in the first case retention and in the second one inversion of conformation of the carbocyclic ring, when passing from one form to the other. An examination of the diastereoisomeric structures 5, 7, 8 shows that only 5 and 8 can give rise to a pair of epimeric carbinols which maintain the starting carbocyclic ring conformation, while 7 can give rise either to a pair of epimeric carbinols having identical carbocyclic ring conformation but opposite with respect to the starting one, or to a pair of carbinols having opposite carbocyclic ring conformation, one of them necessarily being that of the starting compound. On the basis of these facts structure 7 must therefore be assigned to oxazine 4a, while for 4b the choice remains between the structures 5 and 8.

Since spectroscopic data gave no further information, a single crystal X-ray investigation was carried out at this point on both compounds. A view of the molecular structures as determined by X-ray analysis is shown in Fig. 1; they confirm structure 7 for 4a and assign structure 8 to 4b.

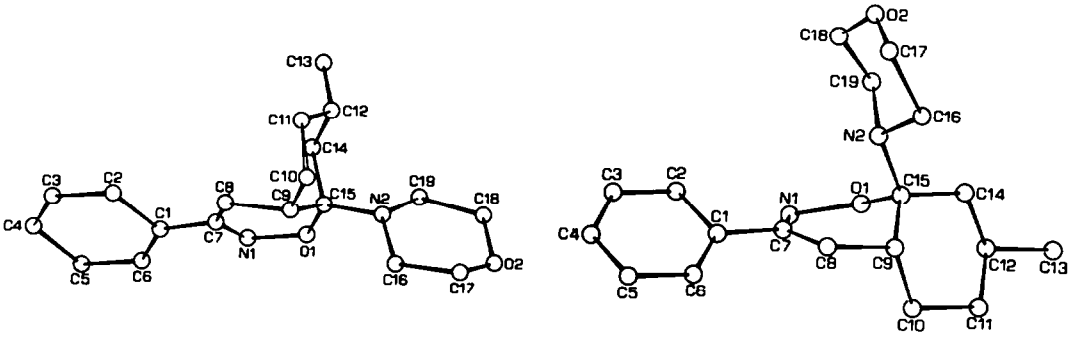


Fig. 1. A diagramatic view of the molecules of isomer 4a (left) and isomer 4b (right) with atoms labelling.

Structural results show that reaction of morpholine enamine of 3-methylcyclohexanone with phenacyl bromide oxime is highly regioselective. The two oxazines 4a and 4b necessarily derive from an axial and equatorial attack of 2 on the enamine isomer Δ^6, followed by cyclization and formation of cis fused systems as showed in scheme 4.

In the crystals of 4a the enantiomeric molecules are crystallographically independent, but related by pseudo elements of symmetry. The values of bond distances of the two independent 4a molecules and of the 4b are shown in Table 2. Corresponding values are generally very close, the few differences being rather ascribable to the quality of the diffraction data of crystals of 4a.

Slight conformation differences are present in the oxazine rings of molecules 4a and 4b as shown by deviations from the O-N-C-C least squares planes of C(9) and C(15) atoms: their values are respectively 0.30, -0.42 Å in 4a and 0.24, -0.50 Å in 4b.

The molecular packing is in both compounds regulated by normal van der Waals contacts. The mo-

Scheme 4.

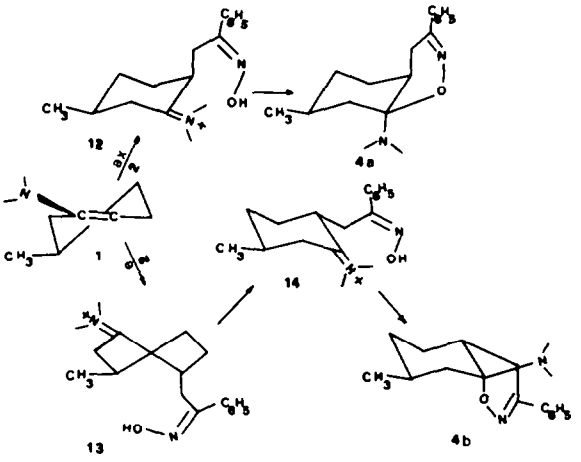


Table 2. Bond distances (Å) and angles (°) with estimated standard deviations in parentheses. First and second columns refer to the two molecules in the asymmetric unit of isomer 4a, third column refers to the molecule of isomer 4b.

C(1) - C(2)	1.41(1)	1.41(1)	1.36(1)	C(9) - C(10)	1.54(1)	1.57(1)	1.52(1)
C(1) - C(6)	1.38(1)	1.41(1)	1.40(1)	C(10)- C(11)	1.57(2)	1.50(1)	1.53(1)
C(1) - C(7)	1.54(1)	1.48(1)	1.46(1)	C(11)- C(12)	1.57(2)	1.56(2)	1.53(1)
C(2) - C(3)	1.42(1)	1.41(1)	1.41(1)	C(12)- C(13)	1.54(2)	1.57(2)	1.53(1)
C(3) - C(4)	1.37(1)	1.37(1)	1.37(1)	C(12)- C(14)	1.53(1)	1.52(1)	1.51(1)
C(4) - C(5)	1.36(2)	1.37(1)	1.37(1)	C(14)- C(15)	1.55(1)	1.52(1)	1.55(1)
C(5) - C(6)	1.39(1)	1.41(1)	1.40(1)	C(15)- N(2)	1.44(1)	1.44(1)	1.47(1)
C(7) - N(1)	1.27(1)	1.30(1)	1.30(1)	N(2) - C(16)	1.50(1)	1.48(1)	1.47(1)
C(7) - C(8)	1.47(1)	1.51(1)	1.51(1)	C(16)- C(17)	1.54(1)	1.55(1)	1.51(1)
C(8) - C(9)	1.57(2)	1.57(1)	1.52(1)	C(17)- O(2)	1.46(1)	1.46(1)	1.43(1)
C(9) - C(15)	1.53(1)	1.53(1)	1.54(1)	O(2) - C(18)	1.42(1)	1.42(1)	1.46(1)
C(15)- O(1)	1.46(1)	1.50(1)	1.42(1)	C(18)- C(19)	1.52(1)	1.53(1)	1.48(1)
O(1) - N(1)	1.43(1)	1.40(1)	1.43(1)	N(2) - C(19)	1.47(1)	1.47(1)	1.45(1)
C(2) - C(1) - C(6)	119.0(7)	118.3(7)	119.9(6)	C(10)- C(11)- C(12)	111.9(7)	112.9(7)	111.9(6)
C(2) - C(1) - C(7)	118.1(6)	120.5(7)	120.2(7)	C(11)- C(12)- C(13)	110.2(7)	107.7(7)	111.7(6)
C(6) - C(1) - C(7)	122.8(7)	121.2(7)	119.8(6)	C(11)- C(12)- C(14)	111.8(7)	110.0(7)	110.5(6)
C(1) - C(2) - C(3)	119.2(7)	119.1(7)	120.9(8)	C(13)- C(12)- C(14)	109.7(7)	111.9(8)	112.6(6)
C(2) - C(3) - C(4)	119.0(8)	122.1(8)	119.3(7)	C(12)- C(14)- C(15)	110.3(7)	111.4(7)	114.5(6)
C(3) - C(4) - C(5)	121.9(8)	119.5(8)	119.9(7)	C(9) - C(15)- O(1)	110.4(7)	108.8(6)	109.3(5)
C(4) - C(5) - C(6)	119.6(8)	120.7(8)	121.4(8)	C(14)- C(15)- O(1)	107.7(6)	107.5(6)	103.2(6)
C(5) - C(6) - C(1)	121.3(8)	120.4(8)	118.5(7)	C(9) - C(15)- N(2)	110.8(6)	112.3(6)	111.1(5)
C(1) - C(7) - N(1)	111.3(6)	114.4(7)	113.6(6)	C(14)- C(15)- N(2)	111.7(7)	112.1(6)	114.2(5)
C(1) - C(7) - C(8)	119.1(7)	118.4(7)	120.3(7)	O(1) - C(15)- N(2)	106.1(6)	104.9(6)	107.7(4)
N(1) - C(7) - C(8)	129.6(7)	127.2(7)	126.0(6)	C(9) - C(15)- C(14)	110.1(7)	110.9(6)	110.9(5)
N(1) - O(1) - C(15)	119.5(6)	120.6(6)	116.7(6)	C(15)- N(2) - C(16)	116.1(6)	114.1(6)	115.2(5)
C(7) - N(1) - O(1)	116.1(6)	117.0(6)	116.7(6)	C(15)- N(2) - C(19)	116.0(6)	117.1(6)	113.6(5)
C(7) - C(8) - C(9)	112.4(7)	112.1(7)	113.2(7)	C(16)- N(2) - C(19)	108.2(6)	109.7(6)	110.8(5)
C(8) - C(9) - C(10)	112.1(6)	109.8(7)	113.1(6)	N(2) - C(16)- C(17)	108.7(7)	108.1(6)	108.1(5)
C(8) - C(9) - C(15)	106.9(6)	107.9(7)	105.5(5)	C(16)- C(17)- O(2)	108.5(7)	111.2(7)	111.3(6)
C(10)- C(9) - C(15)	110.9(7)	108.4(7)	110.9(6)	C(17)- O(2) - C(18)	107.5(6)	108.9(6)	109.4(6)
C(9) - C(10)- C(11)	112.8(7)	114.1(8)	110.1(6)	O(2) - C(18)- C(19)	111.9(7)	112.2(7)	112.2(6)
C(10)- C(11)- C(12)	111.9(7)	112.9(7)	111.9(6)	C(18)- C(19)- N(2)	110.2(6)	109.2(7)	106.9(6)
C(11)- C(12)- C(13)	110.2(7)	107.7(7)	111.7(6)				

lar volumes are 418 Å^3 in 4b and 439 Å^3 in 4a, the lower value corresponding to the isomer with the higher melting point.

EXPERIMENTAL

I.R. spectra were determined with a Perkin-Elmer mod. 325 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian FT 80 A spectrometer. Chemical shifts were measured in p.p.m. (δ) from internal TMS standard. Exchangeable proton were detected by D_2O addition. ^{13}C NMR spectra at low temperatures were recorded in CHF_2Cl in a sealed tube using HMDS as internal standard and a small quantity of $(CD_3)_2CO$ as the lock signal.

Preparation 1,2-oxazine 4a and 4b

General procedure. The preparation of 1,2-oxazines 4a (m.p. 161-162°C) and 4b (165-166°C) was carried out as previously reported[1], refluxing the phenacyl bromide oxime 2 with the morpholine enamine of 3-methylcyclohexanone in anhydrous chloroform in the presence of triethylamine for ca. 90 min. The chloroform solution was evaporated and the residue extracted several times with water and ether. The ether extract was dried over Na_2SO_4 and slowly evaporated to give by fractional crystallization the crude 1,2-oxazines 4a and 4b, which were each purified by chromatography on a silica gel column eluting with petroleum ether (b.p. 40-70°C) diethyl ether (5:1).

Preparation hydroxy-1,2-oxazines 9a and 9b

The hydroxy-1,2-oxazines 9a and 9b were obtained as crystalline products on dissolving the corresponding 1,2-oxazines 4a and 4b (0.4 mmol) in a 2% solution of hydrochloric acid in ethanol and then diluting with water.

X-ray crystallographic structure determinations

4a $C_{19}H_{26}N_2O_2$ M = 314.19 crystallizes in triclinic space group $P\bar{1}$ with a = 10.159(5); b = = 19.297(10); c = 9.561(5) Å; α = 89.08(8)°; β = 98.07(8)°; γ = 93.07(8)°; U = 1757 Å^3; dm = = 1.18 g.cm^{-3}; Z = 4; dc = 1.19 g.cm^{-3}; CuKα λ = 1.5418 Å; μ = 5.35 cm^{-1}.

3582 independent reflections up to 2θ = 100° were measured by the θ-2θ scan technique on a Siemens automatic diffractometer; they were corrected for Lorentz and polarization factors. The structure was solved by Multan 80 set of programs[12] and refined by block-diagonal least-squares methods using 2371 reflections having $I \geq 2.5\sigma(I)$ to a conventional R factor of 0.101.

4b $C_{19}H_{26}N_2O_2$ M = 314.19 crystallizes in monoclinic space group $P2_1/c$ with a = 11.261(6); b = = 13.312(7); c = 14.700(6) Å; β = 107.71(10)°; V = 1671 Å^3; dm = 1.22 g.cm^{-3}; Z = 4; dc = 1.25 g.cm^{-3}; MoKα λ = 0.71069 Å; μ = 1.0 cm^{-1}.

2971 independent reflections up to 2θ = 50° were measured by the θ-2θ scan technique on a Siemens automatic diffractometer; they were corrected for Lorentz and polarization factors. The structure was solved by Multan 80 set of programs and refined by block-diagonal least-squares method using 1816 reflections having $I \geq 2.5\sigma(I)$ to a conventional R factor of 0.092.

A list of refined atomic coordinates and observed and calculated structure factors has been deposited at the Cambridge Crystallographic Data Center.

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