Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.029$
$wR(F^2) = 0.080$
$S = 1.056$
1725 reflections
128 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0416P)^2 + 0.5702P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.321$ e Å^{-3}
$\Delta\rho_{min} = -0.196$ e Å^{-3}
Extinction correction:
SHELXL96 (Sheldrick, 1996b)
Extinction coefficient: 0.0156 (14)
Scattering factors from International Tables for Crystallography (Vol. C)

The data collection nominally covered over a sphere of reciprocal space, by a combination of nine sets of exposures; each set had a different φ angle for the crystal and each exposure covered 0.3° in ω. The crystal-to-detector distance was 5.94 cm. Coverage of the unique set is over 99% complete to at least 26° in θ. Crystal decay was monitored by repeating the initial 100 frames of the first run at the end of data collection and analyzing the duplicate reflections. The data were corrected for Lorentz and polarization effects. All H atoms could be located by difference Fourier synthesis and were refined with fixed individual displacement parameters [U(H) = 1.2U_{eq}(C)] using a riding model with C—H(aromatic) = 0.95, C—H(secondary) = 0.99 or C—H(tertiary) = 1.0 Å.

Data collection: SMART (Siemens, 1995). Cell refinement: SMART. Data reduction: SAINT (Siemens, 1995). Program(s) used to solve structure: SHELXS86 (Sheldrick, 1990). Program(s) used to refine structure: SHELXL96 (Sheldrick, 1996b). Molecular graphics: XP in SHELXTL-Plus (Sheldrick, 1991).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA1235). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. & Kennard, O. (1993). Chem. Des. Autom. News, 8, 31–37.
Cremer, D. & Pople, J. A. (1975). J. Am. Chem. Soc. 97, 1354–1358.
Fieser, L. F., Fields, M. & Lieberman, S. (1944). J. Biol. Chem. 156, 191–201.
Halwax, E. & Vollenkle, H. (1983). Monatsh. Chem. 114, 687–698.
Horodniak, J. W., Wright, J. & Indictor, N. (1971). Org. Mass Spectrom. 5, 1287–1293.
Indictor, N., Horodniak, J. W., Jaffe, H. & Miller, D. (1969). J. Chem. Eng. Data, 14, 76–78.
McQueen, D. M. & Woodward, D. W. (1946). US Patent 2 481 434. Assignors to EI du Pont de Nemours & Company, Wilmington, USA.
Martin, E. L. (1947). US Patent 2 513 189. Assignor to EI du Pont de Nemours & Company, Wilmington, USA.
Minami, E. & Kojima, S. (1954). J. Chem. Soc. Jpn Ind. Chem. Sect. 57, 826–827.
Sheldrick, G. M. (1990). Acta Cryst. A46, 467–473.
Sheldrick, G. M. (1991). SHELXTL-Plus. Release 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1996a). SADABS. Program for Empirical Absorption Correction of Area Detector Data. University of Göttingen, Germany.
Sheldrick, G. M. (1996b). SHELXL96. Program for the Refinement of Crystal Structures. University of Göttingen, Germany.
Siemens (1995). SMART and SAINT. Data Collection and Processing software for the SMART System. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

(1R,2S,4S,11S)-4-Isopropyl-1-methyl-2-(α-N-morpholino-3-methoxybenzyl)cyclohexan-3-one†

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Abstract

The title compound, $C_{22}H_{33}NO_3$, was obtained by reacting (1R,4S)-2-(3-methoxybenzylidene)-1-methyl-4-isopropylcyclohexane-3-one (E/Z 68/31%), obtained from (−)-menthone and 3-methoxybenzaldehyde by Clasien–Schmidt condensation, with morpholine by Michael-type addition. The structure was elucidated by IR and ^{1}H NMR spectral analyses, and the stereochemistry was obtained through an X-ray diffraction study. The absolute configurations of the four chiral centres were determined as 1R, 2S, 4S and 11S. Both the cyclohexane and N-morpholino rings were found to be in chair conformations.

Comment

The title compound, (I), was synthesized in two steps according to a previous method used for synthesizing some aminobenzylcyclanols (Özarslan, Ertan, Sayraç, Akgün, Demirdamar & Gümüşel, 1994).

(I)
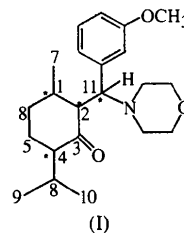
The stereochemistry of one of these compounds, which are ciramadol analogues with opiate analgesic activity, (1R,4S)-2-(α-N-pyrrolidino-3-benzyl)-1-methyl-

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† Alternative name: (1R,2S,4S,11S)-2-[(3-methoxyphenyl)(morpholino)methyl]-3-p-menthone.

4-isopropylcyclohexane-3-one, was studied by NMR spectroscopy (Burgemeister, Özarslan, Ertan, Akgün & Wiegrebe, 1994). In this study, the absolute configurations of C1 and C4 were assigned as 1R and 4S, respectively, by analogy to the literature values given for (−)-menthone which was used as the starting material. On the other hand, due to the diastereoselectivity of the Michael addition at C11 of (E)-(−)-2-benzylidenementhone, the product was in the form of one isomer. The absolute configurations at C11 and C2 were assigned as 2S and 11S, respectively, and trans to each other by NMR simulation, COSY-90 and NOE measurements. However, a suitable crystal for X-ray analysis could not be obtained. In the present study, a new derivative in the same class of compounds carrying a methoxyl group in the phenyl ring was synthesized and crystallized from methanol. In the previous study, the menthone ring adopted a boat conformation.

In the title compound, atoms C2, C3, C5 and C6 of the cyclohexane ring form a plane which has a maximum deviation of 0.003 Å, with C4 (−0.64 Å) and C1 (0.72 Å) lying on either side of the plane. Similarly, atoms C12, C13, C14 and C15 of the morpholino ring also form a plane which has a maximum deviation of 0.02 Å, with O1 (−0.65 Å) and N1 (0.70 Å) on either side of the plane. This shows that both rings adopt a chair conformation. The cyclohexane C—C bonds vary between 1.524 (3) and 1.557 (2) Å. The configuration of the three rings with respect to each other can be seen in the torsion angles about C11—C16, C11—N1 and C11—C2 (Table 1). This configuration brings the H atoms of C11 close to C7, those of C12 close to C1 and those of C2 close to C1; H11···H7A 2.48,
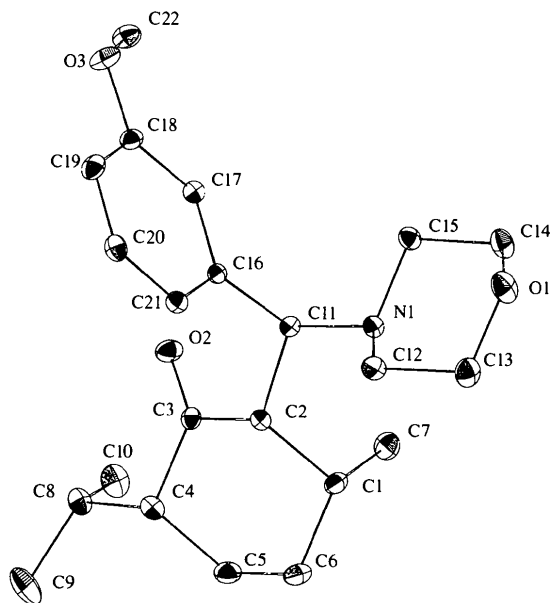

Fig. 1. ORTEPII (Johnson, 1976) drawing of the title compound. Displacement ellipsoids are plotted at the 50% probability level.

H12A···H1 2.28 and H2···H1 2.38 Å. H11 and H2 are axial, yet oppose each other with respect to the C atoms to which they are connected. These findings are in accordance with the results obtained from NOE difference experiments performed for the analogous compound in a previous study, confirming the absolute configurations of C11 and C2 as 11S and 2S, and those of C1 and C4 as 1R and 4S, respectively.

Experimental

(1R,4S)-2-(3-Methoxybenzylidene)-1-methyl-4-isopropylcyclo-hexan-3-one, (II) (mixture of diastereomers E/Z 68/31%). 3 g of (−)-menthone and 0.5 g (excess) of NaH were stirred for 30 min at 298 K in dry ether. 2.6 g of 3-methoxybenz-aldehyde were added dropwise over 2 h. A solid mass was decomposed with 50 ml N HCl. The supernatant layer was extracted with ether and washed with saturated NaHCO$_3$. Ether was evaporated at 15 Torr (1 Torr = 133.32 Pa) and the crude material was purified by column chromatography with ether/pentane (1:15) as eluent. To synthesize the title compound, (I), 1.09 g (4 mmol) of (II) were dissolved in an excess of morpholine and allowed to stand at room temperature. After standing for 3 d, 50 ml of ether were added to the reaction mixture. This solution was extracted three times with N HCl. The acid phases were combined and basified with NaOH. The resulting oily precipitate was dissolved in ether, washed with water and dried over Na$_2$SO$_4$. The ethereal solution was evaporated to dryness and purified with silica gel flash chromatography using ether/pentane (1:1) as eluent and crystallized from absolute MeOH. M.p. 351–352 K; $[\alpha]_D^{20}$ +84 (c1 in MeOH); IR(KBr): 1707 cm^{-1}, CO; ^{1}H NMR: δ 0.79 [9H, m, (CH$_3$)$_2$ and 1-CH$_3$], 1.56 (1H, m, H-1), 1.81 (1H, m, H-8), 1.99 [4H, m, (CH$_2$)$_2$], 2.05, 2.40 (2H each, m, 2 × N-CH$_2$, morpholine) 2.80 (1H, m, H-4), 3.36 (1H, dd, H-2, J_{2-11} 11.4, J 4.73 Hz) 3.63 (4H, m, 2 × O-CH$_2$, morpholine), 3.82 (3H, s, O-CH$_3$) 3.83 (1H, d, H-11, J_{11-2} 11.4 Hz) 6.63 (1H, m, H-4', phenyl) 6.71 (1H, s, H-2', phenyl), 6.75 (1H, d, H-6', phenyl) 7.20 (1H, m, H-5', phenyl). Melting points were determined in capillaries using a Thomas–Hoover Unimelt apparatus and are uncorrected. A Bellingham Stanler P20 Polarimeter was used for $[\alpha]_D^{20}$. IR spectra were obtained on a Perkin-Elmer FT-IR-1720X. ^{1}H NMR spectra were recorded on a Bruker ARX 400 MHz NMR instrument in CDCl$_3$, with TMS as the internal standard (chemical shifts in p.p.m.).

Crystal data

C$_{22}$H$_{33}$NO$_3$	Mo $K\alpha$ radiation
$M_r = 359.49$	$\lambda = 0.71073$ Å
Monoclinic	Cell parameters from 25
$P2_1$	reflections
$a = 8.493$ (1) Å	$\theta = 4.6$–16.5°
$b = 11.253$ (2) Å	$\mu = 0.076$ mm^{-1}
$c = 11.368$ (2) Å	$T = 153$ (2) K
$\beta = 108.46$ (2)°	Prismatic
$V = 1030.6$ (3) Å^3	0.35 × 0.28 × 0.23 mm
$Z = 2$	Colourless
$D_x = 1.159$ Mg m^{-3}	
D_m not measured	

Data collection

Siemens *P*3 four-circle diffractometer	$R_{int} = 0.015$
ω–2θ scans	$\theta_{max} = 27°$
Absorption correction: none	$h = 0 \rightarrow 10$
2507 measured reflections	$k = 0 \rightarrow 14$
2355 independent reflections	$l = -14 \rightarrow 13$
2354 reflections with	2 standard reflections
$I > 2\sigma(I)$	every 100 reflections
	intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + 0.0446P^2]$,
$R = 0.0305$	$P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.0704$	$\Delta\rho_{max} = 0.160$ e Å^{-3}
$S = 0.943$	$\Delta\rho_{min} = -0.155$ e Å^{-3}
2354 reflections	Extinction correction: none
367 parameters	Scattering factors from
H atoms: see below	*International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

O2—C3	1.213 (2)	C11—C16	1.533 (2)
N1—C15	1.465 (2)	C11—C2	1.540 (3)
N1—C12	1.472 (2)		
C15—N1—C12	108.6 (1)	C16—C11—C2	112.2 (2)
C15—N1—C11	111.9 (1)	O2—C3—C4	122.4 (2)
C12—N1—C11	116.9 (2)	O2—C3—C2	122.0 (2)
N1—C11—C16	113.8 (1)	C4—C3—C2	115.6 (2)
N1—C11—C2	111.7 (1)		
N1—C11—C16—C21	−71.0 (3)	C15—N1—C11—C16	−62.1 (2)
N1—C11—C16—C17	105.8 (2)	C16—C11—C2—C3	68.3 (2)
C12—N1—C11—C16	63.9 (2)	C16—C11—C2—C1	−168.6 (2)

The structure was solved by direct phase determination and refined by full-matrix least-squares techniques on F^2. The refinement was completed with anisotropic displacement parameters for all atoms except H atoms which were generated geometrically and refined isotropically.

Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976).

References

Burgemeister, T., Özarslan, Ö., Ertan, M., Akgün, H. & Wiegrebe, W. (1994). *Arch. Pharm. (Weinheim)*, **327**, 785–787.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Özarslan, Ö., Ertan, M., Sayraç, T., Akgün, H., Demirdamar, R. & Gümüşel, B. (1994). *Arch. Pharm. (Weinheim)*, **327**, 525–528.
Sheldrick, G. M. (1985). *SHELXS*86. *Program for the Solution of Crystal Structures*. University of Göttingen, Germany.
Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Three *trans*-2,6-Diaryl Derivatives of Oximes of *N*-Hydroxy-4-piperidone

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Abstract

In the solid state, *trans*-2,6-diphenyl-4-(hydroxyimino)-piperidinol, $C_{17}H_{18}N_2O_2$, (1), *trans*-2,6-bis(1-methyl-pyrrol-2-yl)-4-(hydroxyimino)piperidinol, $C_{15}H_{20}N_4O_2$, (2), and *trans*-2,6-bis(thien-2-yl)-4-(hydroxyimino)-piperidinol, $C_{13}H_{14}N_2O_2S_2$, (3), adopt conformations with an axial OH substituent on the ring N atom, in contrast to the preference for an equatorial conformation in solution. Molecules of all three structures are held together in chains by hydrogen bonding.

Comment

We have previously reported a ^{1}H and ^{13}C NMR study of the conformation of several oximes of 2,6-diaryl-piperidin-4-ones in solution (Díaz *et al.*, 1997). The crystal structures of three of these compounds, the diphenyl, (1), bis(1-methylpyrrol-2-yl), (2), and bis(thien-2-yl), (3), derivatives have been determined in order to establish their preferred conformation in the solid state.

(1)   (2)

(3)
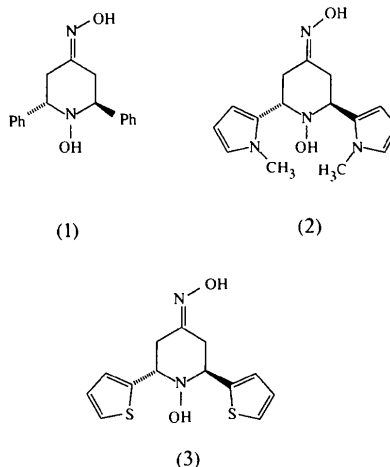
The molecular structures of compounds (1), (2) and (3) are shown in Figs. 1, 2 and 3, respectively. In each case, the hydroxyimino group displays a twofold orientational disorder. The crystals thus comprise a mixture of two forms, differing only in the orientation