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(*E*,*E*)-2-(4-Fluorophenylmethylene)-6-(4-nitrophenylmethylene)cyclohexanone

J. Wilson Quail,[a]* Alireza Doroudi,[b] Hari N. Pati,[b] Umashankar Das[b] and Jonathan R. Dimmock[b]

[a]Saskatchewan Structural Sciences Centre, University of Saskatchewan, 110 Science Place, Saskatoon, Saskatchewan, Canada S7N 5C9, and [b]College of Pharmacy and Nutrition, University of Saskatchewan, 110 Science Place, Saskatoon, Saskatchewan, Canada S7N 5C9

Correspondence e-mail: quail@sask.usask.ca

Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.004 Å
R factor = 0.058
wR factor = 0.135
Data-to-parameter ratio = 13.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Both olefinic double bonds of the title compound, $C_{20}H_{16}FNO_3$, have the *E* configuration, while the cyclohexyl ring adopts the sofa conformation. Non-bonded interactions occur between one of the *ortho* H atoms of each of the aryl rings and the equatorial H atoms at positions 3 and 5 of the alicyclic ring.

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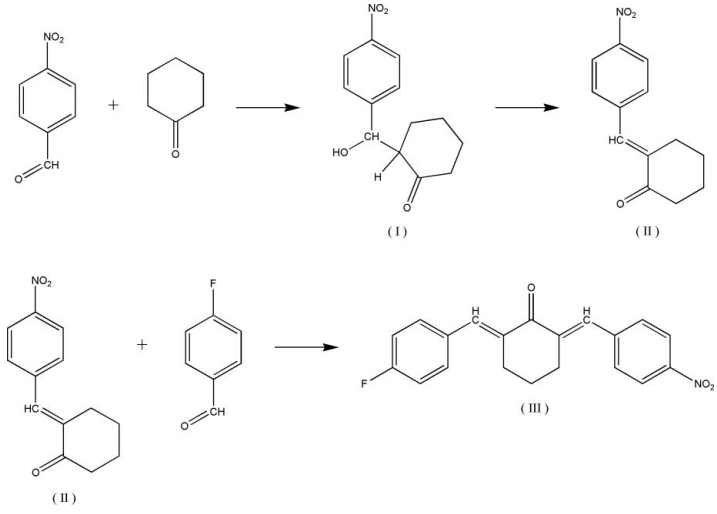
Comment

A major interest in our laboratories is the preparation and bioevaluation of various conjugated ketones as candidate cytotoxic and anticancer agents. Many of these compounds have a marked affinity for thiols over amino and hydroxy groups (Mutus *et al.*, 1989). Since thiols are not found in nucleic acids, conjugated enones may lack the genotoxic properties of various anticancer drugs (Benvenuto *et al.*, 1993). A number of 2,6-bis(arylidene)cyclohexanones display potent cytotoxicity towards different malignant cell lines and are well tolerated in mice (Dimmock *et al.*, 2003). Very recently, the insertion of a 4-nitro group into one of the aryl rings in a series of unsymmetrical 2,6-bis(arylidene)cyclohexanones has led to a series of compounds, some of which displayed selective toxicity to cancer cells over normal cells and which also reversed multidrug resistance in a colon cancer cell line (Dimmock *et al.*, 2005). As part of an extension of this project, the title compound, (III), was prepared. It was examined by X-ray crystallography in order to provide information pertaining to the molecular shape which may contribute to an understanding of any bioactivity observed, and also to provide direction for further synthetic chemical endeavours on a rational basis.



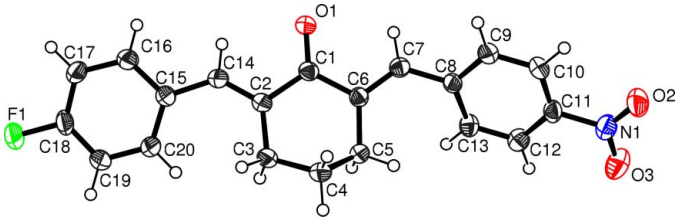


Figure 1
A view of (III), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary size.

A view of the molecular structure of (III) is presented in Fig. 1. The olefinic double bonds possess the *E* configuration. The cyclohexane ring is in a sofa conformation, with five of the C atoms (C1–C3/C5/C6) coplanar (r.m.s. deviation 0.0687 Å), while atom C4 is displaced 0.696 (4) Å from this plane. Nonbonded interactions between one of the *ortho* H atoms in the aryl rings and the equatorial H atoms (suffix e) at positions 3 and 5 of the cyclohexyl ring are apparent, as the H20···H3*B*e (d_1) and H13···H5*A*e (d_2) distances are 2.191 and 2.236 Å, respectively. These interactions contribute to the following two structural features. Firstly, the aryl rings are not coplanar with the adjacent olefinic linkages, the C2—C14—C15—C20 (θ_1) and C6—C7—C8—C13 (θ_2) torsion angles being −14.6 (5) and 38.9 (4)°, respectively. Secondly, instead of 120°, the bond angles C2—C14—C15 (ψ_1) and C6—C7—C8 (ψ_2) are 131.8 (3) and 127.4 (3)°, respectively.

The data presented here are useful in the design of additional analogues. For example, the replacement of the equatorial H atoms at positions 3 and 5, or of one or more of the H atoms at C9, C13, C16 and C20, by substituents of varying sizes would likely lead to increases in the θ and ψ values. Correlations have been established between θ values and bioactivity (Pandeya & Dimmock, 1997). In addition, the increased ψ values would lead to variations in the relative locations of the aryl rings, which could affect the alignment (or possibly cause nonalignment) of these rings at a binding site and hence influence bioactivity.

Experimental

A solution of sodium hydroxide (0.015 mol) in water (5 ml) was added over a period of 15 min to a mixture of 4-nitrobenzaldehyde (0.041 mol) and cyclohexanone (0.061 mol) in water (50 ml). The mixture was stirred at room temperature overnight, after which time the precipitate was collected and triturated with diethyl ether (200 ml) for 30 min at room temperature. The solid was collected and dried to produce compound (I) [m.p. 428–429 K; literature m.p. 431–434 K (Vieweg & Wagner, 1979)] in 82% yield. A solution of (I) (0.032 mol) and hydrochloric acid (37% (*w*/*v*), 2 ml) in ethanol (200 ml) was heated at 313–318 K for 4 h. On cooling, the solvents were removed *in vacuo* and the residue was triturated with water (100 ml). The solid was collected by filtration and dried to produce compound (II) [m.p. 387–388 K; literature m.p. 391–393 K (Vieweg & Wagner, 1979)] in 64% yield. The structures of intermediates (I) and (II) were confirmed by ^{1}H NMR spectroscopy. A solution of (II) (0.002 mol) and 4-fluorobenzaldehyde (0.002 mol) in diethyl ether (10 ml) and methanol (0.5 ml) was stirred at room temperature for 5 min. Hydrogen chloride was passed into this solution for 15 min and stirring was continued at room temperature for 2 h. The precipitate was collected and dissolved in chloroform (10 ml) to which methanol (40 ml) was then added. The mixture was retained at room temperature for 24 h, after which time the precipitate was collected and dried to produce compound (III) (m.p. 442–443 K) in 33% yield. Analysis calculated for $C_{20}H_{16}FNO_3$: C 71.21, H 4.78, N 4.15%; found: C 70.61, H 4.76, N 4.05%.

Crystal data

$C_{20}H_{16}FNO_3$	D_x = 1.389 Mg m^{-3}
M_r = 337.34	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 3586 reflections
a = 15.5155 (7) Å	θ = 1.0–27.5°
b = 13.6328 (9) Å	μ = 0.10 mm^{-1}
c = 7.7777 (6) Å	T = 173 (2) K
β = 101.344 (3)°	Plate, yellow
V = 1613.13 (18) Å^3	0.20 × 0.15 × 0.02 mm
Z = 4	

Data collection

Nonius KappaCCD area-detector diffractometer	1813 reflections with $I > 2\sigma(I)$
φ scans, and ω scans with κ offsets	R_{int} = 0.063
Absorption correction: none	θ_{max} = 25.4°
5468 measured reflections	$h = -18 \rightarrow 18$
2950 independent reflections	$k = -16 \rightarrow 16$
	$l = -9 \rightarrow 9$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.047P)^2 + 0.7039P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.059	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.135	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
S = 1.03	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
2950 reflections	
226 parameters	
H-atom parameters constrained	

All H atoms were placed in calculated positions, with C—H distances in the range 0.95–0.99 Å, and included in the refinement in a riding-model approximation, with U_{iso}(H) constrained to be 1.2U_{eq}(C).

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3* for Windows (Farrugia, 1997); software used to prepare material for publication: *PLATON* (Spek, 2003).

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References

Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.
Benvenuto, J. A., Connor, T. A., Monteith, D. K., Laidlaw, J. W., Adams, S. C., Matney, T. S. & Theiss, J. C. (1993). *J. Pharm. Sci.* **82**, 988–991.
Dimmock, J. R., Das, U., Gul, H. I., Kawase, M., Sakagami, H., Baráth, Z., Ocsovsky, I. & Molnár, J. (2005). *Bioorg. Med. Chem. Lett.* **15**, 1633–1636.

Dimmock, J. R., Padmanilayam, M. P., Zello, G. A., Nienaber, K. H., Allen, T. M., Santos, C. L., De Clercq, E., Balzarini, J., Manavathu, E. K. & Stables, J. P. (2003). *Eur. J. Med. Chem.* **38**, 169–177.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Mutus, B., Wagner, J. D., Talpas, C. J., Dimmock, J. R., Phillips, O. A. & Reid, R. S. (1989). *Anal. Biochem.* **177**, 237–243.
Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307-326. New York: Academic Press.
Pandeya, S. N. & Dimmock, J. R. (1997). *An Introduction to Drug Design*, pp. 72–74. New Delhi: New Age International Publishers.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Vieweg, H. & Wagner, G. (1979). *Pharmazie*, **34**, 785–788.