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

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.003 Å
R factor = 0.048
wR factor = 0.130
Data-to-parameter ratio = 14.7

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

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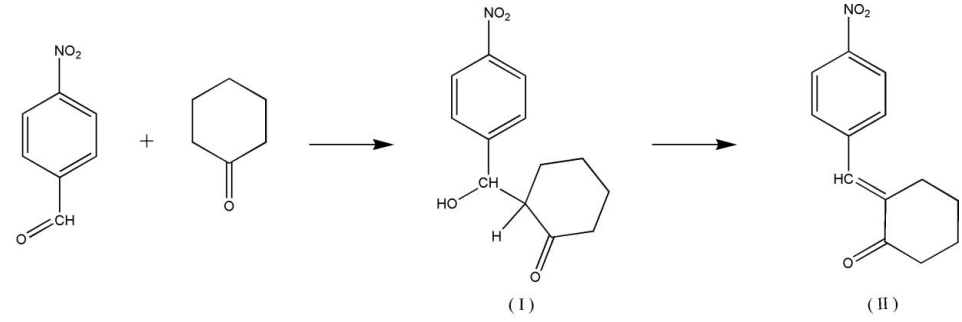
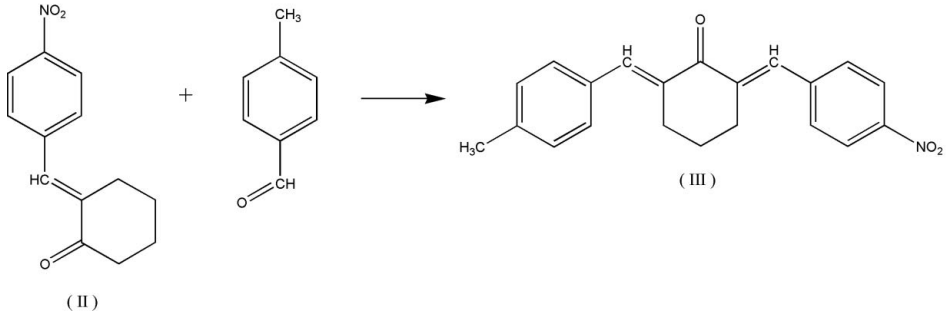
Both olefinic bonds in the title compound, $C_{21}H_{19}NO_3$, possess an *E* configuration, while the cyclohexyl ring adopts a sofa conformation. The aryl rings are not coplanar with the adjacent olefinic groups due to non-bonded interactions between the *ortho* H atoms of the aryl rings and the equatorial H atoms at positions 3 and 5 of the cyclohexyl ring.

Comment

A number of years ago, the theory of sequential cytotoxicity was proposed by one of the authors in regard to the design of antineoplastic agents (Dimmock *et al.*, 1993). This hypothesis states that, since a number of tumours are more susceptible to repeated chemical insults than the corresponding normal cells, compounds may be designed for sequential interactions with cellular constituents. In the present investigation, conjugated unsaturated ketones were synthesized because this class of compounds reacts preferentially or exclusively with thiols in contrast with hydroxy and amino groups (Baluja *et al.*, 1964; Dimmock *et al.*, 1983). Since amino and hydroxy substituents are present in nucleic acids, thiol alkylators may not produce unwanted genotoxic side effects.





A series of compounds, including the title compound, (III), was prepared in which the electronic charges at the sites of thiol interactions, namely the olefinic C atoms, were varied depending on the nature of the aryl substituents. In the case of

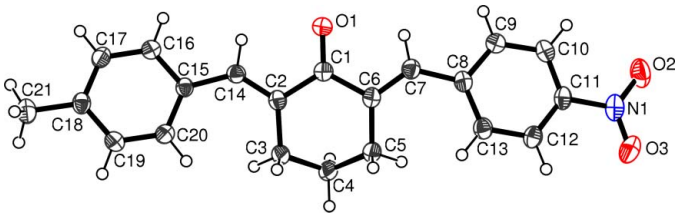


Figure 1
A general *ORTEP-3* (Farrugia, 1997) view of (III) with non-H-atom displacement ellipsoids drawn at the 50% probability level. For clarity, the H atoms are drawn as small spheres of arbitrary size.

(III), which was prepared by the route indicated in the scheme, the Hammett σ_p values for the nitro and methyl groups are 0.78 and −0.14, respectively (Perrin *et al.*, 1981), which are markedly divergent. Hence, thiolation should occur initially at C7 followed by a subsequent nucleophilic attack at C14.

The rate and extent of electrophilic interactions with thiols will be influenced by the topography of the molecules. The alicyclic ring of (III) adopts a sofa conformation. Atoms C1–C3/C5/C6 are coplanar, with an r.m.s. deviation of 0.0178 Å. Atom C4 deviates from this plane by 0.669 (3) Å. Both olefinic double bonds have an *E* configuration and the aryl rings are not coplanar with the adjacent olefinic double bonds and the planar portion of the alicyclic ring. The aryl rings are rotated to move atoms C13 and C20 in the opposite direction to the displacement of C4 from the plane of the other five atoms in the alicyclic ring. As a result, C2—C14—C15—C20 (Θ_1) and C6—C7—C8—C13 (Θ_2) torsion angles of 11.5 (3) and −18.2 (3)°, respectively, are observed. This lack of coplanarity is caused by non-bonded interactions between atom pairs H20/H3*e* and H13/H5*e* (the interatomic distances being 2.073 and 2.090 Å, respectively). These interactions also lead to the C2—C14—C15 (Ψ_1) and C6—C7—C8 (Ψ_2) angles being substantially greater than 120°, namely 132.85 (18) and 130.65 (18)°, respectively. The ability of the molecule to align at a binding site will be influenced by the stereochemistry of the alicyclic ring and the rotations of the phenylmethylene rings. These observations have implications in drug design. For example, both positive and negative correlations between Θ values and the potencies of various bioactive molecules have been observed (Pandeya & Dimmock, 1997). The data obtained from the X-ray crystallographic structure of (III) suggest that the placement of substituents on the olefinic C atoms or one or both of the *ortho* positions on the aryl rings will lead to varying Θ values, which may correlate with cytotoxicity.

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 (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 (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) (0.004 mol) and 4-methylbenzaldehyde (0.005 mol) in diethyl ether (40 ml) and methanol (4.0 ml) was stirred at room temperature for 5 min. Hydrogen chloride was passed into this solution for 20 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 added. The precipitate was collected and recrystallized from methanol to give (III) (m.p. 408–409 K) in 54% yield. Analysis calculated for $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20%; found: C 75.45, H 5.75, N 4.13%.

Crystal data

$C_{21}H_{19}NO_3$	D_x = 1.354 Mg m^{-3}
M_r = 333.37	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 4997 reflections
a = 7.5713 (3) Å	θ = 1.0–30.0°
b = 10.9972 (4) Å	μ = 0.09 mm^{-1}
c = 20.0451 (6) Å	T = 173 (2) K
β = 101.550 (2)°	Chip, yellow
V = 1635.22 (10) Å^3	0.25 × 0.15 × 0.10 mm
Z = 4	

Data collection

Nonius KappaCCD diffractometer	R_{int} = 0.038
φ scans and ω scans with κ offsets	θ_{max} = 26.4°
Absorption correction: none	$h = -9 \rightarrow 9$
6518 measured reflections	$k = -13 \rightarrow 13$
3354 independent reflections	$l = -24 \rightarrow 24$
2252 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0621P)^2 + 0.3697P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.048	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.130	$\Delta\rho_{max}$ = 0.26 e Å^{-3}
S = 1.03	$\Delta\rho_{min}$ = −0.24 e Å^{-3}
3354 reflections	Extinction correction: *SHELXL97*
228 parameters	Extinction coefficient: 0.0110 (18)
H-atom parameters constrained	

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

Data collection: *COLLECT* (Nonius, 2000); 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: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *PLATON* (Spek, 2003).

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