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(5*S**,6*R**,7*R**,9*R**)-1-Benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]nonane-6-carbonitrile

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Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.005 Å
R factor = 0.085
wR factor = 0.287
Data-to-parameter ratio = 15.1

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

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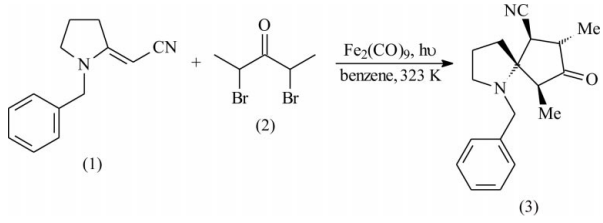
The racemic title compound, $C_{18}H_{22}N_2O$, isolated from the reaction of 2-(1-benzyl-2-pyrrolidinylidene)acetonitrile, 2,4-dibromo-3-pentanone and nonacarbonyldiiron, crystallizes in a centrosymmetric monoclinic space group with four symmetry-equivalent molecules per unit cell. All bond lengths and angles are within expected ranges.

Comment

The 1-azaspiro[4.4]nonane ring system is embedded in alkaloids such as cephalotaxine (Fig. 1). Certain esters of cephalotaxine, first discovered by Paudler *et al.* (1963), display antitumour activity and thus are important synthetic targets. Noyori and co-workers showed that polybromoketones undergo [3 + 2]-cycloaddition reactions with 1,3-dienes (Takaya *et al.*, 1978), aromatic olefins (Hayakawa *et al.*, 1978*a*) and enamines (Hayakawa *et al.*, 1978*b*) in the presence of $Fe_2(CO)_9$. We wished to investigate whether the Noyori annulation reaction could be used to couple 2-methylenepyrrolidines to α,α′-dibromoketones, to form 8-oxo-1-azaspiro[4.4]nonanes, synthetic precursors to the cephalotaxine azaspirocycle.



Preparation of the title compound involved heating a mixture of 2-(1-benzyl-2-pyrrolidinylidene)acetonitrile, (1), 2,4-dibromo-3-pentanone, (2), and diiron nonacarbonyl for 18 h with concomitant irradiation, as shown in the reaction scheme. The title compound, (3), selectively crystallized from an EtOAc/hexane solution to give large colourless crystals. We have characterized this compound using HRMS and NMR and FT–IR spectroscopy. The crystal structure of (3) is reported here.

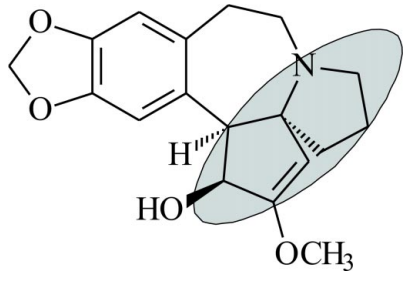


Figure 1
Cephalotaxine, with the 1-azaspiro[4.4]nonane ring system highlighted.

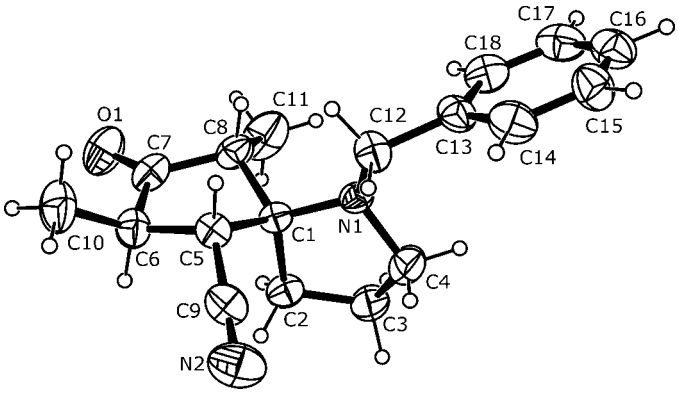


Figure 2
The molecular structure of (3), showing the labelling scheme. Displacement ellipsoids are drawn at the 50% probability level for all non-H atoms; spheres of arbitrary radii depict H atoms.

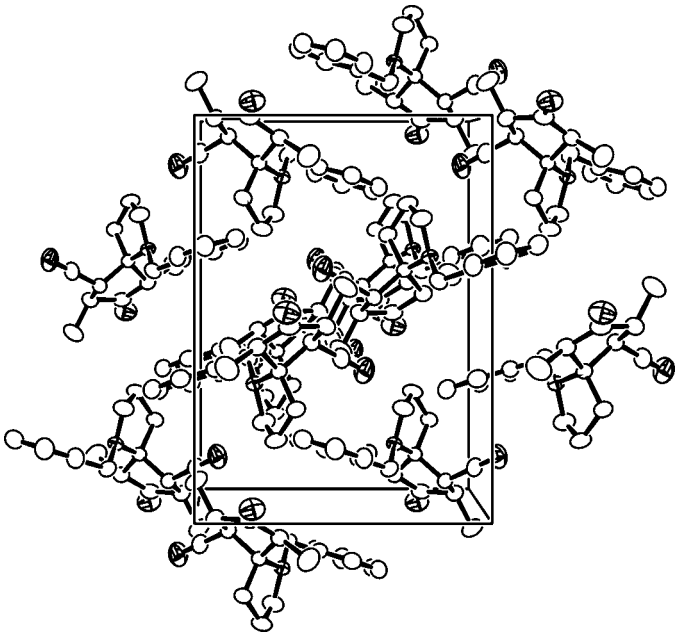


Figure 3
Packing diagram, viewed down the *a* axis.

The X-ray crystal structure confirms that the substance produced is a racemic mixture of (5*S*,6*R*,7*R*,9*R*)- and (5*R*,6*S*,7*S*,9*S*)-1-benzyl-7,9-dimethyl-8-oxo-1-azaspiro[4.4]-nonane-6-carbonitrile (Fig. 2), as predicted by NOESY NMR experiments. Fig. 3 shows a packing diagram. There are no significant intermolecular interactions.

Experimental

2-(1-Benzyl-2-pyrrolidinylidene)acetonitrile, (1) (0.85 g, 4.3 mmol), dissolved in benzene (10 ml), and 2,4-dibromo-3-pentanone, (2) (1.57 g, 6.44 mmol, passed through a basic alumina column before use), dissolved in benzene (10 ml), were added to $Fe_2(CO)_9$ (1.49 g, 4.10 mmol). The resulting mixture was stirred overnight under N_2 at 323 K, with irradiation (a 400 W high-pressure Hg lamp was used, with an aqueous $CuSO_4$ solution (10% *w*/*v*) functioning as a filter, thereby blocking wavelengths less than 350 nm). The solution was diluted with EtOAc (30 ml) and then washed with saturated aqueous $NaHCO_3$ (40 ml) followed by a brine solution (40 ml). The organic layer was separated and dried ($MgSO_4$), filtered and concentrated *in vacuo*. A complete separation of all the products proved impossible even after extensive purification by radial chromatography (10% EtOAc/hexane). The title compound selectively crystallized from an EtOAc/hexane solution as large colourless crystals; R_F 0.49 (EtOAc–hexane, 20%); m.p. 381.5–383.5 K. Spectroscopic analysis, IR (KBr, ν_{max}/cm^{-1}): 3100–2800 (CH), 2237 (C≡N), 1747 (C=O) and 1076 (C—N); ^{1}H NMR (500 MHz; $CDCl_3$, p.p.m.): 7.25–7.35 (5H, *m*, aromatic H), 3.84 (1H, *d*, *J* = 13.3 Hz, ArCH_aH_b), 3.81 (1H, *d*, *J* = 13.3 Hz, ArCH_aH_b), 2.98–3.03 (1H, *m*, NCH_aH_bCH$_2$), 2.80–2.84 (1H, *m*, NCH_aH_bCH$_2$), 2.75 (1H, *d*, *J* = 11.4 Hz, C*H*C≡N), 2.36–2.46 (2H, *m*, 2 × CH$_3$CH), 1.99–2.11 (2H, *m*, CH$_2$CH_aH_bCH$_2$ and NCCH_aH_b), 1.88–1.93 (1H, *m*, NCCH_aH_b), 1.75–1.85 (1H, *m*, CH$_2$CH_aH_bCH$_2$), 1.27 (3H, *d*, *J* = 7.3 Hz, CHCHCH$_3$) and 1.14 (3H, *d*, *J* = 6.9 Hz, CCHCH$_3$); ^{13}C NMR (125 MHz; $CDCl_3$, p.p.m.): 213.71 (*C*=O), 138.94 (Ar *C*-1′), 128.52, 127.99, 127.29 (Ar *C*-2′, *C*-3′, *C*-4′), 119.69 (*C*≡N), 71.08 (*C*—N), 52.17 (NCH$_2$CH$_2$), 51.72 (*C*H$_2$Ar), 49.44 (C*C*HCH$_3$), 46.40 (CHCHCH$_3$), 40.88 (*C*HC≡N), 29.76 (NC*C*H$_2$), 22.16 (CH$_2$*C*H$_2$CH$_2$), 14.06 (CHCH*C*H$_3$) and 8.70 (CCH*C*H$_3$); *m*/*z* (EI): 282 (18%, M^+), 200 (13), 188 (14), 187 (100), 186 (28) and 91 (71, CH$_2$Ar); found: M^+ 282.1734; $C_{18}H_{22}N_2O$ requires 282.1732.

Crystal data

$C_{18}H_{22}N_2O$	D_x = 1.153 Mg m^{-3}
M_r = 282.38	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 25 reflections
a = 10.543 (3) Å	θ = 2–12°
b = 10.614 (4) Å	μ = 0.07 mm^{-1}
c = 14.570 (3) Å	T = 295 (2) K
β = 93.68 (2)°	Rectangular block, colourless
V = 1627.2 (8) Å^3	0.8 × 0.6 × 0.5 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 25.0°
$\omega/2\theta$ scans	$h = -1 \rightarrow 12$
Absorption correction: none	$k = -12 \rightarrow 12$
6534 measured reflections	$l = -17 \rightarrow 17$
2863 independent reflections	3 standard reflections
2336 reflections with $I > 2\sigma(I)$	frequency: 120 min
R_{int} = 0.067	intensity decay: 3%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.1715P)^2 + 0.8378P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.085	$(\Delta/\sigma)_{max}$ = 0.013
$wR(F^2)$ = 0.287	$\Delta\rho_{max}$ = 0.90 e Å^{-3}
S = 1.04	$\Delta\rho_{min}$ = −0.38 e Å^{-3}
2863 reflections	
190 parameters	
H-atom parameters constrained	

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*3 for Windows (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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