the lone pair of the N atom. The bond angle C(3)—N(4)—C(5) of 121·8 (6)° confirms the sp^2 hybridization at N. The bond angle C(1)—C(8a)=C(8) of 131·6 (7)° is larger than the 120° value for alkene. The bond angle C(8)—S(1)—C(10), and bond lengths C(8)—S(1) and S(1)=O(2) are normal (Bandoli, Panattoni, Clemente, Tondello, Dondoni & Mangini, 1971). The stereochemistry determined at C(7) and S is in line with the prediction that the anion derived from (+)-(I) approaches alkyl *trans*-crotonate predominantly from the *re* face (Izumi & Tai, 1977).

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Structures of Colchicine Analogues. III. 2-Methoxy-5-(2′,3′-dimethoxyphenyl)- and 2-Methoxy-5-(3′,4′-dimethoxyphenyl)cyclohepta-2,4,6-trien-1-one

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Abstract. (4) and (5): $C_{16}H_{16}O_4$, M_r = 272·3, Cu $K\alpha$, λ = 1·5418 Å, T = 295 (1) K. 5-(2,3-Dimethoxyphenyl)-2-methoxycyclohepta-2,4,6-trien-1-one (4): orthorhombic, $P2_12_12_1$, a = 7·330 (1), b = 8·992 (1), c = 21·416 (1) Å, V = 1411·6 (4) Å^3, Z = 4, D_m (flotation) = 1·28 (1), D_x = 1·281 Mg m^{-3}, μ = 0·67 mm^{-1}, F(000) = 576. Final R = 0·032 for 1248 observed data. 5-(3,4-Dimethoxyphenyl)-2-methoxycyclohepta-2,4,6-trien-1-one (5): monoclinic, $C2/c$, a = 26·131 (5), b = 7·634 (1), c = 14·158 (2) Å, β = 104·78 (2)°, V = 2731 (1) Å^3, Z = 8, D_m (flotation) = 1·33 (1), D_x = 1·324 Mg m^{-3}, μ = 0·69 mm^{-1}, F(000) = 1152. Final R = 0·047 for 1584 observed data. Molecules of (4) and (5) assume a solid-state conformation that resembles that of isocolchicine rather than colchicine. The dihedral angle between the rings is 52·6° in (4) and 43·4° in (5) compared with 53° in colchicine.

Introduction. The potent antimitotic properties of colchicine (1) (Brossi, Yeh, Chrzanowska, Wolff, Hamel, Lin, Quin, Suffness & Silverton, 1988) and the bicyclic analogues (2) (Fitzgerald, 1976) and (3) (Banwell, Herbert, Buckleton, Clark, Rickard, Lin & Hamel, 1988) stem from the ability of these molecules to bind to the protein tubulin and thereby interfere with cellular processes that depend upon polymerization of that protein. On the basis of extensive physicochemical and structural studies (Banwell, Herbert, Buckleton, Clark, Rickard, Lin & Hamel, 1988), it has been argued that (1) and (2) undergo reversible binding to tubulin, giving an initial complex which is then converted into a more stable one. There is evidence suggesting that preliminary binding of (1) and (2) occurs with a skewed conformation of these molecules, while binding in the more stable complex involves a near-planar relationship between the tropone (*C*) and aryl (*A*) rings. The existence of two partial binding sites on the protein has been established, one for the trimethoxyphenyl *A* ring and one for the troponoid *C* ring. On the basis of the foregoing, it seems that conformational preferences

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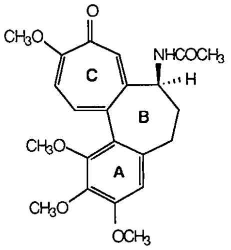
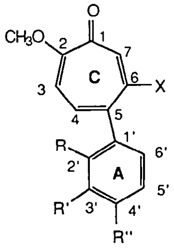
of *AC*-ring colchicine analogues will be an important determinant of antimitotic activity in such systems.

As part of a program directed towards producing therapeutically useful antimitotic agents, efficient synthetic routes to a number of *AC*-ring colchicine analogues have been developed (Banwell, Gravatt, Buckleton, Clark & Rickard, 1989; Banwell, Collis, Crisp, Lambert, Reum, Scoble, Gable, Mackay & Hamel, 1990). The X-ray structures of two such systems, compounds (4) and (5), are reported here as part of a continuing conformational study of potential antimitotic agents. It is expected that these results will further assist with the development of structure–activity relationships for such compounds and ultimately allow the rational design of new anticancer agents.



(1)



(2) R = R' = R''= OCH_3, X = H
(3) R = R' = R''= OCH_3, X = Cl
(4) R = R' = OCH_3, R'' = X = H
(5) R' = R'' = OCH_3, R = X = H
(6) R = R'' = OCH_3, R' = X = H

Experimental. The syntheses of tropolone methyl ethers (4) and (5) were achieved by palladium-mediated cross coupling of 5-bromotropolone with the appropriate dimethoxyphenyltrimethylstannane (Banwell, Collis, Crisp, Lambert, Reum & Scoble, 1989). *O*-Methylation (with dimethyl sulfate/potassium carbonate) of the ensuing 5-aryl-tropolones then afforded the title compounds (4) and (5). Full synthetic details will be reported elsewhere (Banwell, Collis, Crisp, Lambert, Reum, Scoble, Gable, Mackay & Hamel, 1990). Light brown pseudo spherical crystals of (4) from benzene; yellow needles elongated along **a** from benzene (5). Crystals *ca* 0·40 mm diameter (4) and 0·50 × 0·17 × 0·12 mm (5) aligned on a Rigaku-AFC diffractometer; cell parameters determined by least squares for 25 reflections ($45 < 2\theta < 79°$); Cu $K\alpha$ radiation (graphite-crystal monochromator), $\lambda = 1{\cdot}5418$ Å; ω–2θ scan, scan rate 2° min^{-1}, scan range ($\Delta\omega$) $(1{\cdot}2 + 0{\cdot}5\tan\theta)°$, 10 s stationary background counts; three standard reflections monitored every 50 reflections showed no significant variations in intensity; data to $2\theta_{\max} = 130°$; 1430 unique data (h 0 to 8, k 0 to 10, l 0 to 25), 1248 having $I \geq 2\sigma(I)$ were used for structure refinement (4); 2290 unique data (h −30 to 30, k 0 to 8, l 0 to 16), 1584 having $I \geq 2\sigma(I)$ for structure refinement (5); intensities corrected for Lorentz and polarization effects and for absorption (5), transmission factors 0·829 to 0·928; no absorption correction for (4) due to spherical form of crystal. Structures solved by direct methods with *SHELX76* (Sheldrick, 1976); all atom sites located by difference and coordinates refined; full-matrix least-squares refinement (*SHELX76*) with anisotropic temperature factors given to C and O atoms, isotropic for H, converged at $R = 0{\cdot}032$, $wR = 0{\cdot}040$, $S = 1{\cdot}30$ (246 parameters varied) for (4) and $R = 0{\cdot}047$, $wR = 0{\cdot}054$, $S = 1{\cdot}44$ (246 parameters varied) for (5); function minimized $\sum w(|F_o| - |F_c|)^2$, with weights $k(\sigma^2|F_o| + m|F_o|^2)^{-1}$ for which k and m were 1·0, 0·0006 respectively for (4) and 1·093, 0·0007 for (5); an isotropic extinction correction of the form $F_c = F[1 - (g|F|^2/\sin\theta)]$ was applied to the calculated structure amplitudes, $g = 1{\cdot}7\,(1) \times 10^{-6}$ (4) and $2{\cdot}5\,(3) \times 10^{-7}$ (5). At convergence $(\Delta/\sigma)_{\max} = 0{\cdot}002{:}1$ (4) and (5); $(\Delta\rho)_{\max}$, $(\Delta\rho)_{\min} = +0{\cdot}11$, $-0{\cdot}13$ e Å^{-3} (4) and $+0{\cdot}17$, $-0{\cdot}21$ e Å^{-3} (5). Atomic scattering factors and anomalous-dispersion factors from *International Tables for X-ray Crystallography* (1974). Figures were prepared from the output of *ORTEP*II (Johnson, 1976). Calculations performed on VAX11/780 computer.

Discussion. Final atomic coordinates for the non-H atoms are given in Tables 1 and 2,* molecular conformations and numbering schemes are illustrated in Fig. 1 while selected torsion angles are given in Table 3 and bond lengths and angles in Table 4.

Molecules (4) and (5) both adopt a solid-state conformation that resembles isocolchicine rather than colchicine (1). This solid-state conformation is also adopted by (2) (Rossi, Lin & Lee, 1984), its 6-chloro derivative (3) (Banwell, Herbert, Buckleton, Clark, Rickard, Lin & Hamel, 1988) and the dimethoxy analogue (6) (Banwell, Collis, Crisp, Lambert, Reum, Scoble, Gable, Mackay & Hamel, 1990). The *A*-ring atoms in both structures are coplanar to within experimental error, whereas the *C*-ring atoms are coplanar to within ±0·06 (1) and ±0·03 (1) Å in (4) and (5) respectively. The dihedral angle between the normals to the two rings is 52·6 (3)° in (4) and 43·4 (3)° in (5) compared with 57·4° in (2) (Rossi, Link & Lee, 1984). The relative orientation of the two rings is also reflected in the torsion angle, C(2′)—C(1′)—C(5)—C(6), which ranges in value from 52 to 63° in molecules (1)–(6)

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* Lists of structure amplitudes, anisotropic thermal parameters, H-atom coordinates, torsion angles and short intermolecular approaches have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52719 (34 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final atomic coordinates* (×10⁴) *and equivalent isotropic temperature factors for the non-*H *atoms of* (4) *with e.s.d.'s in parentheses*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}(Å²)
C(1)	7321 (3)	5186 (3)	1008 (1)	3·52 (4)
C(2)	5705 (3)	6105 (3)	863 (1)	3·36 (4)
C(3)	3913 (3)	5704 (3)	886 (1)	3·51 (4)
C(4)	3082 (3)	4314 (3)	1010 (1)	3·40 (4)
C(5)	3819 (3)	2948 (3)	1115 (1)	3·18 (4)
C(6)	5747 (3)	2664 (3)	1142 (1)	3·49 (4)
C(7)	7177 (3)	3601 (3)	1101 (1)	3·79 (5)
C(1′)	2579 (3)	1641 (2)	1182 (1)	3·10 (4)
C(2′)	2689 (3)	701 (3)	1693 (1)	3·30 (4)
C(3′)	1470 (3)	−499 (3)	1755 (1)	3·71 (4)
C(4′)	201 (3)	−769 (3)	1291 (1)	4·03 (5)
C(5′)	120 (4)	154 (3)	776 (1)	4·25 (5)
C(6′)	1271 (4)	1358 (3)	723 (1)	3·83 (5)
O(1)	8832 (2)	5778 (2)	1026 (1)	5·32 (4)
O(2)	6260 (2)	7494 (2)	702 (1)	4·25 (3)
C(2‴)	4954 (4)	8481 (3)	428 (2)	4·77 (6)
O(2′)	3894 (3)	1052 (2)	2165 (1)	4·38 (3)
C(2″)	5213 (5)	−61 (4)	2323 (2)	6·03 (8)
O(3′)	1611 (3)	−1301 (2)	2293 (1)	5·41 (4)
C(3″)	348 (6)	−2479 (5)	2393 (2)	6·92 (9)

Table 2. *Final atomic coordinates* (×10⁴) *and equivalent isotropic temperature factors for the non-*H *atoms of* (5) *with e.s.d.'s in parentheses*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}(Å²)
C(1)	5436 (1)	−499 (3)	3750 (2)	3·62 (5)
C(2)	5778 (1)	1051 (3)	3844 (2)	3·72 (5)
C(3)	5653 (1)	2758 (4)	3904 (2)	3·98 (5)
C(4)	5159 (1)	3596 (3)	3856 (2)	3·84 (5)
C(5)	4668 (1)	2890 (3)	3759 (2)	3·39 (4)
C(6)	4561 (1)	1072 (3)	3732 (2)	3·81 (5)
C(7)	4880 (1)	−335 (3)	3743 (2)	3·87 (5)
C(1′)	4208 (1)	4093 (3)	3662 (2)	3·38 (5)
C(2′)	3822 (1)	3737 (3)	4169 (2)	3·60 (5)
C(3′)	3389 (1)	4836 (3)	4077 (2)	3·60 (5)
C(4′)	3333 (1)	6311 (3)	3480 (2)	3·51 (5)
C(5′)	3713 (1)	6664 (3)	2976 (2)	3·68 (5)
C(6′)	4145 (1)	5565 (3)	3073 (2)	3·70 (5)
O(1)	5617 (1)	−1969 (2)	3695 (1)	5·07 (4)
O(2)	6279 (1)	516 (2)	3847 (1)	5·10 (4)
C(2‴)	6682 (1)	1798 (5)	3904 (3)	5·82 (8)
O(3′)	3006 (1)	4600 (3)	4576 (1)	4·81 (4)
C(3″)	3125 (1)	3386 (6)	5362 (3)	6·28 (8)
O(4′)	2891 (1)	7302 (2)	3437 (1)	4·91 (4)
C(4″)	2838 (2)	8890 (5)	2909 (4)	6·61 (9)

Table 3. *Selected torsion angles* (°) *with e.s.d.'s in parentheses; values for colchicine* (1), *isocolchicine* (1*a*), (2) *and* (6) *are included for comparison*

	(1)		(1*a*)		(2)*	(6)		(4)	(5)
C(3′)—C(2′)—O(2′)—C(2″)	−79	−94	−90	−85	−76	9	12	62·2 (3)	
C(4′)—C(3′)—O(3′)—C(3″)	−68	−76	74	−84	−67			−1·3 (4)	−164·6 (3)
C(5′)—C(4′)—O(4′)—C(4″)	14	−4	−8	23	8	−5	−5		−5·9 (4)
C(2′)—C(1′)—C(5)—C(6)	54	52	53	63	58	62	63	55·1 (3)	43·0 (3)
C(2′)—C(1′)—C(5)—C(4)	−129	−127	−131	−124	−124	−121	−118	−127·3 (2)	−137·9 (3)
C(3)—C(2)—O(2)—C(2‴)	−5	7	2	6	−2	4	0	−12·7 (3)	−0·9 (4)
C(3)—C(2)—C(1)—O(1)	−176	−175	178	168	178	175	176	−172·3 (2)	179·2 (3)
O(2)—C(2)—C(1)—O(1)	4	4	−2	−9	−2	−4	−6	6·8 (3)	0·2 (3)

(1): Colchicine (Lessinger & Margulis, 1978*a*); (1*a*): isocolchicine (Lessinger & Margulis, 1978*b*); (2): 2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (Rossi, Link & Lee, 1984; Mackay, Sands, Lacey & Burden, unpublished results); (6): 2-methoxy-5-(2′,4′-dimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (Banwell *et al.*, 1990).
The signs of the angles are consistent with those of the absolute structure of naturally occurring colchicine.

* The numerical values were calculated from coordinates for (2) derived by Mackay, Sands, Lacey & Burden (unpublished results) who at that time were unaware of the analysis of Rossi, Link & Lee (1984).

(see Table 3). Whilst the value of 55·1 (3)° for (4) lies within this range, the value of 43·0 (3)° for (5) is significantly smaller.

In the solid-state structures of colchicinoids which retain the three methoxy groups of the *A* ring, those at C(2′) and C(3′) are roughly orthogonal to the ring whereas the methoxy substituent at C(4′) lies close to the ring plane [see torsion angles C(3′)—C(2′)—O(2′)—C(2″), C(4′)—C(3′)—O(3′)—C(3″) and C(5′)—C(4′)—O(4′)—C(4″) in Table 3]. However, in the dimethoxy analogues, (4)–(6), all the *A*-ring methoxyls lie close to their ring planes apart from the one at C(3′) in (4) which is roughly orthogonal to it. Although the methoxyl and O(1) are coplanar with the *C* ring in (5) a significant deviation of this group and atom from the *C* ring is noted in (4) [torsion angles C(3)—C(2)—O(2)—C(2‴) −12·7 (3)°, C(3)—C(2)—C(1)—O(1) −172·3 (2)° and O(2)—C(2)—C(1)—O(1) −6·8 (3)°].

The crystal packings of (4) and (5) are illustrated in Fig. 2. As only hydrogen-bond acceptors are present in the molecules and the crystals are not solvated, hydrogen-bond formation is precluded. Consequently, the molecules are held together by van der Waals interactions. The shortest intermolecular contacts are O(1)···C(4′) ($1+x$, $1+y$, z) 3·312 (3) Å and O(1)···C(2″) ($\frac{1}{2}+x$, $1\frac{1}{2}-y$, $-z$) 3·289 (5) Å in (4) and O(1)···C(2′) ($1-x$, $-y$, $1-z$) 3·295 (3) Å and O(1)···C(6′) ($1-x$, $-1+y$, $\frac{1}{2}-z$) 3·315 (3) Å in (5). In the crystal of the latter the molecules are present as mirror image conformers whereas in (4) molecules of only one conformer are present.

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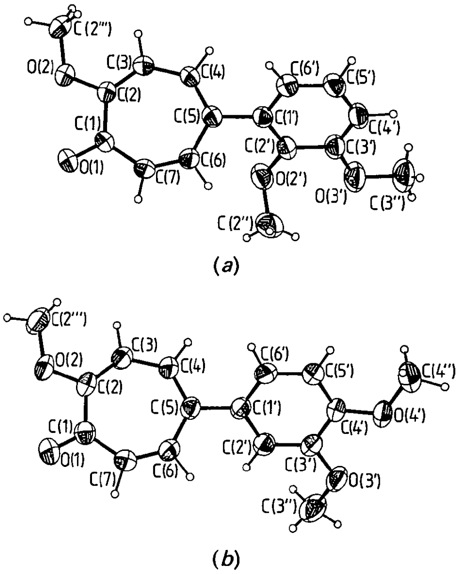
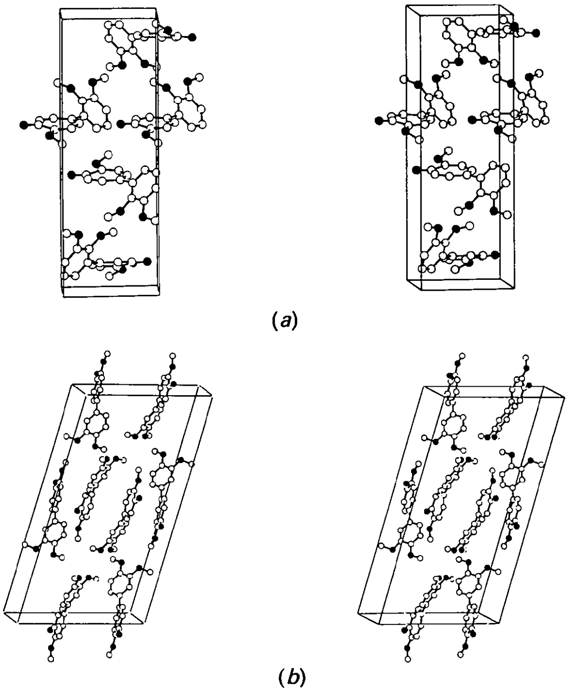


(*a*)

(*b*)

Fig. 1. Perspective views of the molecules with thermal ellipsoids scaled to 50% probability, H atoms are denoted by spheres of arbitrary radius. (*a*) Compound (4) and (*b*) compound (5).



(*a*)

(*b*)

Fig. 2. Stereoviews of the crystal packings. (*a*) Compound (4), direction of projection **b**, *a* axis is horizontal, (*b*) compound (5), direction of projection **b**, *c* axis is horizontal.

Table 4. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

	(4)	(5)
C(1)—C(2)	1·477 (3)	1·468 (3)
C(1)—C(7)	1·443 (4)	1·455 (4)
C(1)—O(1)	1·229 (3)	1·228 (3)
C(2)—C(3)	1·363 (3)	1·351 (4)
C(2)—O(2)	1·358 (3)	1·370 (4)
C(3)—C(4)	1·416 (4)	1·424 (4)
C(4)—C(5)	1·361 (4)	1·368 (4)
C(5)—C(6)	1·437 (3)	1·414 (3)
C(5)—C(1′)	1·492 (3)	1·491 (4)
C(6)—C(7)	1·348 (3)	1·357 (3)
C(1′)—C(2′)	1·386 (3)	1·406 (4)
C(1′)—C(6′)	1·397 (3)	1·384 (3)
C(2′)—C(3′)	1·407 (4)	1·386 (4)
C(2′)—O(2′)	1·379 (3)	
O(2′)—C(2″)	1·433 (4)	
C(3′)—C(4′)	1·382 (3)	1·393 (4)
C(3′)—O(3′)	1·363 (3)	1·378 (4)
O(3′)—C(3″)	1·423 (5)	1·420 (5)
C(4′)—C(5′)	1·382 (3)	1·389 (4)
C(4′)—O(4′)		1·369 (3)
O(4′)—C(4″)		1·412 (5)
C(5′)—C(6′)	1·377 (4)	1·385 (4)
O(2)—C(2‴)	1·431 (4)	1·425 (4)
C(2)—C(1)—C(7)	121·5 (2)	121·0 (2)
C(2)—C(1)—O(1)	119·1 (2)	120·4 (2)
C(7)—C(1)—O(1)	119·3 (2)	118·6 (2)
C(1)—C(2)—C(3)	128·1 (2)	129·2 (2)
C(1)—C(2)—O(2)	109·1 (2)	108·6 (2)
C(3)—C(2)—O(2)	122·8 (2)	122·2 (2)
C(2)—C(3)—C(4)	130·9 (2)	131·3 (2)
C(3)—C(4)—C(5)	131·1 (2)	130·0 (2)
C(4)—C(5)—C(6)	123·9 (2)	124·3 (2)
C(4)—C(5)—C(1′)	119·0 (2)	118·8 (2)
C(6)—C(5)—C(1′)	117·1 (2)	116·9 (2)
C(5)—C(6)—C(7)	130·6 (2)	131·3 (2)
C(1)—C(7)—C(6)	133·1 (2)	132·6 (2)
C(5)—C(1′)—C(2′)	121·4 (2)	120·0 (2)
C(5)—C(1′)—C(6′)	119·6 (2)	121·7 (2)
C(2′)—C(1′)—C(6′)	119·0 (2)	118·3 (2)
C(1′)—C(2′)—C(3′)	120·4 (2)	120·6 (2)
C(1′)—C(2′)—O(2′)	118·5 (2)	
C(3′)—C(2′)—O(2′)	120·9 (2)	
C(2′)—C(3′)—C(4′)	119·6 (2)	120·3 (2)
C(2′)—C(3′)—O(3′)	115·9 (2)	123·7 (2)
C(4′)—C(3′)—O(3′)	124·5 (2)	115·9 (2)
C(3′)—C(4′)—C(5′)	119·8 (2)	119·3 (2)
C(3′)—C(4′)—O(4′)		115·6 (2)
C(5′)—C(4′)—O(4′)		125·1 (2)
C(4′)—C(5′)—C(6′)	120·8 (2)	120·2 (2)
C(1′)—C(6′)—C(5′)	120·4 (2)	121·4 (2)
C(2)—O(2)—C(2‴)	118·3 (2)	119·2 (2)
C(3′)—O(3′)—C(3″)	118·2 (2)	116·3 (2)
C(2′)—O(2′)—C(2″)	116·5 (2)	
C(4′)—O(4′)—C(4″)		117·7 (2)

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Structure of 3,4-Dihydro-3-methyl-1′-phenyl-3′,4′-di-*p*-tolylspiro[naphthalene-2,5′-[2]pyrazoline]-1(2*H*)one

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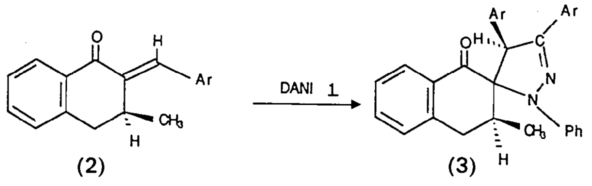
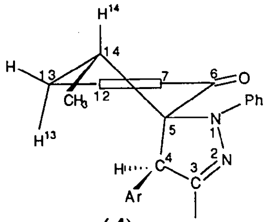
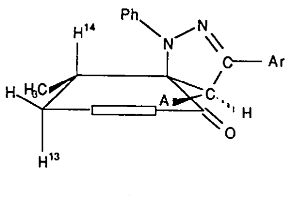
Abstract. $C_{33}H_{30}N_2O$, $M_r = 470{\cdot}6$, orthorhombic, $Pbca$, $a = 10{\cdot}199$ (3), $b = 15{\cdot}518$ (3), $c = 32{\cdot}625$ (8) Å, $V = 5163$ (4) Å^3, $Z = 8$, $D_x = 1{\cdot}211$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, μ = 0·0679 mm^{-1}, $F(000) = 2000$, $T = 293$ K, $R = 0{\cdot}053$ for 1313 unique reflections. The conformation of the title compound shows that the approach of the dipole (diarylnitrilimine) occurs towards the less hindered side of the dipolarophile. Furthermore the ketonic ring of the cycloadduct is in a 1,3-diplanar conformation.

Introduction. In a previous work (Kerbal, Tshiamala, Vebrel & Laude, 1988) on the cycloaddition of diarylnitrilimines [DANI, (1)] to 2-arylidene-1-indanones, the diastereochemistry of the dipole–dipolarophile approach has been studied. We wished to extend this investigation to the behaviour of more pliable dipolarophiles, *i.e.* the 3-methyl-2-arylidene-1-tetralones (2). NMR (^{1}H, ^{13}C) results threw some light on the regiochemistry of the reaction but gave little information about the stereochemistry of the (sole) cycloaddition product (3). In particular they proved unable to show whether the actual conformation of (3) is (*A*) or (*B*). To solve this ambiguity, the crystal structure of one of the cycloadducts (3) (Ar = *p*-tolyl) is determined in the present paper.







Experimental. Parallelepiped shaped crystal from an ethanol solution, 0·05 × 0·18 × 0·32 mm. CAD-4 Enraf–Nonius diffractometer, cell parameters determined from 25 reflections having 4·57 ≤ θ ≤

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