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# *rel*-(1*R*,6*S*,7*S*,8*R*,9*S*)-9-Methyl-8-phenyl-6-[(1*S*,2*R*)-(2-phenylcyclohexyl)oxy]-4-aza-3,5-dioxatricyclo[5.2.1.$0^{4,9}$]decane

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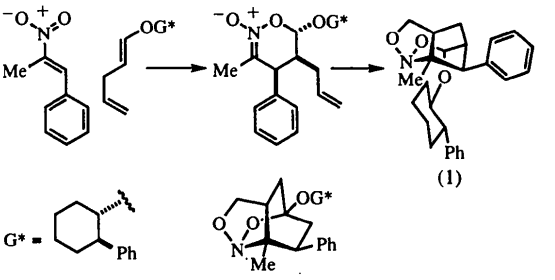
## Abstract

The structure of the title compound, $C_{26}H_{31}NO_3$, was determined by X-ray crystallography. It was found to be a unique bridged tricyclic nitroso acetal. Notable features include a chair conformation of the tetrahydro-1,2-oxazine ring and a highly pyramidalized N atom [$\Sigma_{angles}$ = 314.2 (6)°]. The configurations of the five contiguous stereogenic centers in the nitroso acetal establish that the tandem cycloaddition sequence proceeded *via* an *exo*-[4 + 2]/*endo*-[3 + 2] pathway.

## Comment

Although nitroso acetals are rather uncommon and labile molecules, their preparation and potential for organic synthesis has attracted considerable attention in recent years (Denmark & Thorarensen 1996; Rudchenko, 1993). Of the known nitroso acetals, only a small subset has been characterized by X-ray crystallography. The details of their molecular structure are valuable because of the unique O—N—O linkage, the diversity of the skeletons in which they have been made and their synthetic utility. The title compound, (1), was prepared as a part of our methodological program on the scope and limitations of our tandem nitroalkene [4 + 2]/[3 + 2] cycloaddition process. We have documented four different modes of inter[4 + 2]/intra[3 + 2] reactions. Compound (1) represents the first reported example of a bridged-mode tandem cycloaddition that forms an imbedded cyclopentane skeleton. An analogous process leading to an imbedded cyclohexane skeleton was reported recently (Denmark, Stolle, Dixon & Guagnano, 1995). The chiral auxiliary used in this




sequence was again (±)-(1*R*,2*S*)-2-phenylcyclohexanol (Denmark, Schnute & Senanayake, 1993).

The primary structural information provided by the X-ray analysis is the verification of the tricyclo[5.2.1.$0^{4,9}$] core structure. The relative configurations of the five contiguous stereogenic centers, C3, C1, C6, C5, and C7, are singularly established by an *exo*-mode [4 + 2] cycloaddition followed by an *endo*-mode [3 + 2] cycloaddition. Furthermore, the existence of a five- rather than a six-membered carbocycle confirms the regiochemical preference in the dipolar cycloaddition expected on the basis of tether length and strain.

Other structural details of note are revealed by comparison of (1) with a related [4.3.1.$0^{3,7}$] bridged nitroso acetal, (2), which has also been prepared and crystallographically defined (Denmark, Stolle, Dixon & Guagnano, 1995). The boat conformation of the tetrahydro-1,2-oxazine ring is required by the core structure of (2). However, in (1), a chair conformation is found, presumably to allow for anomeric stabilization involving the axially oriented auxiliary *via* the C7—O3 bond. Furthermore, in (2) the N—O bond in the 1,2-oxazine is 0.051 Å longer than the N—O bond in the isoxazolidine while in compound (1), the N—O bond in the 1,2-oxazine is 0.102 Å longer than the corresponding N—O bond in the isoxazolidine. As in all nitroso acetals,

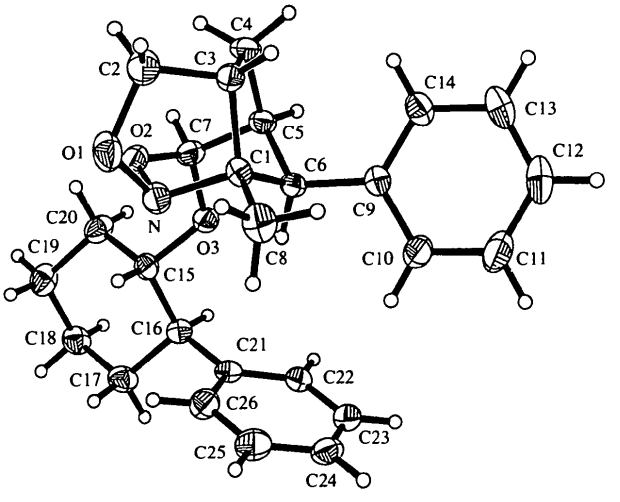



Fig. 1. *ORTEP*II (Johnson, 1971) plot showing 35% probability ellipsoids for non-H atoms and H atoms as circles of arbitrary size.

the N atom in (1) is extremely pyramidalized [$\Sigma_{angles}$ 312.4 (12)°], even more so than the N atom in (2) [$\Sigma_{angles}$ 316.7 (3)°].

## Experimental

The preparation of (1) will be described in full elsewhere. Single crystals of (1) (m.p. 414–415 K) were deposited from diethyl ether–pentane. The data crystal was mounted using oil (Paratone-N, Exxon) onto a thin glass fiber.

*Crystal data*

$C_{26}H_{31}NO_3$
$M_r$ = 405.52
Triclinic
$P\bar{1}$
$a$ = 9.8583 (3) Å
$b$ = 10.76310 (10) Å
$c$ = 11.3841 (3) Å
$\alpha$ = 64.636 (2)°
$\beta$ = 84.154 (2)°
$\gamma$ = 83.762 (2)°
$V$ = 1082.96 (4) Å$^3$
$Z$ = 2
$D_x$ = 1.244 Mg m$^{-3}$
$D_m$ not measured

Mo $K\alpha$ radiation
$\lambda$ = 0.71073 Å
Cell parameters from 2389 reflections
$\theta$ = 1.98–28.31°
$\mu$ = 0.080 mm$^{-1}$
$T$ = 198 (2) K
Prismatic
0.44 × 0.24 × 0.14 mm
Colorless

*Data collection*

Siemens CCD diffractometer
$\omega$–$\theta$ profile scans
Absorption correction: none
6949 measured reflections
4827 independent reflections
2905 observed reflections [$I > 2\sigma(I)$]
$R_{int}$ = 0.035

$\theta_{max}$ = 28.31°
$h = -12 \rightarrow 12$
$k = -5 \rightarrow 14$
$l = -14 \rightarrow 15$
136 frames standard reflections
frequency: 390 min
intensity decay: <0.1%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.126
$S$ = 1.03
4826 reflections
272 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0470P)^2 + 0.1452P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = -0.001$
$\Delta\rho_{max}$ = 0.15 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.20 e Å$^{-3}$
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å$^2$)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| N | −0.1928 (2) | −0.9614 (2) | −0.18496 (14) | 0.0389 (4) |
| O1 | −0.09332 (14) | −1.06328 (14) | −0.11524 (12) | 0.0505 (4) |
| O2 | −0.18825 (12) | −0.86268 (14) | −0.12362 (11) | 0.0392 (3) |
| O3 | −0.34653 (11) | −0.67515 (13) | −0.23103 (11) | 0.0350 (3) |
| C1 | −0.1260 (2) | −0.9053 (2) | −0.3214 (2) | 0.0334 (4) |
| C2 | 0.0428 (2) | −1.0128 (2) | −0.1654 (2) | 0.0540 (6) |
| C3 | 0.0220 (2) | −0.8936 (2) | −0.2978 (2) | 0.0393 (5) |
| C4 | 0.0213 (2) | −0.7475 (2) | −0.3035 (2) | 0.0429 (5) |
| C5 | −0.1262 (2) | −0.6825 (2) | −0.3331 (2) | 0.0338 (4) |
| C6 | −0.1849 (2) | −0.7582 (2) | −0.4017 (2) | 0.0297 (4) |
| C7 | −0.2086 (2) | −0.7209 (2) | −0.2039 (2) | 0.0367 (5) |
| C8 | −0.1478 (2) | −1.0105 (2) | −0.3721 (2) | 0.0483 (5) |
| C9 | −0.1498 (2) | −0.7084 (2) | −0.5469 (2) | 0.0330 (4) |
| C10 | −0.2441 (2) | −0.7189 (2) | −0.6238 (2) | 0.0469 (5) |
| C11 | −0.2158 (2) | −0.6794 (3) | −0.7557 (2) | 0.0603 (6) |
| C12 | −0.0936 (3) | −0.6268 (2) | −0.8147 (2) | 0.0586 (6) |
| C13 | 0.0007 (2) | −0.6132 (2) | −0.7413 (2) | 0.0537 (6) |
| C14 | −0.0272 (2) | −0.6538 (2) | −0.6086 (2) | 0.0434 (5) |
| C15 | −0.4478 (2) | −0.7309 (2) | −0.1256 (2) | 0.0343 (4) |
| C16 | −0.5853 (2) | −0.6788 (2) | −0.1869 (2) | 0.0332 (4) |
| C17 | −0.7023 (2) | −0.7240 (2) | −0.0812 (2) | 0.0434 (5) |
| C18 | −0.6873 (2) | −0.6818 (2) | 0.0287 (2) | 0.0453 (5) |
| C19 | −0.5507 (2) | −0.7362 (2) | 0.0877 (2) | 0.0498 (6) |
| C20 | −0.4333 (2) | −0.6884 (2) | −0.0168 (2) | 0.0443 (5) |
| C21 | −0.5993 (2) | −0.7238 (2) | −0.2942 (2) | 0.0326 (4) |
| C22 | −0.6178 (2) | −0.6277 (2) | −0.4212 (2) | 0.0366 (4) |
| C23 | −0.6299 (2) | −0.6678 (2) | −0.5198 (2) | 0.0454 (5) |
| C24 | −0.6237 (2) | −0.8054 (2) | −0.4934 (2) | 0.0487 (5) |
| C25 | −0.6062 (2) | −0.9034 (2) | −0.3676 (2) | 0.0515 (6) |
| C26 | −0.5944 (2) | −0.8622 (2) | −0.2693 (2) | 0.0441 (5) |

Table 2. *Selected geometric parameters (Å, °)*

The average length of aliphatic C—C bonds is 1.524 (8) Å and that of aromatic C—C bonds is 1.382 (6) Å.

| | | | |
|---|---|---|---|
| N—O1 | 1.405 (2) | C1—C6 | 1.532 (2) |
| N—O2 | 1.507 (2) | C1—C3 | 1.538 (2) |
| N—C1 | 1.512 (2) | C2—C3 | 1.520 (3) |
| O1—C2 | 1.469 (2) | C3—C4 | 1.545 (3) |
| O2—C7 | 1.407 (2) | C4—C5 | 1.548 (2) |
| O3—C7 | 1.413 (2) | C5—C7 | 1.518 (2) |
| O3—C15 | 1.437 (2) | C5—C6 | 1.532 (2) |
| C1—C8 | 1.516 (3) | C6—C9 | 1.518 (2) |
| O1—N—O2 | 99.59 (12) | C2—C3—C1 | 102.5 (2) |
| O1—N—C1 | 101.69 (12) | C2—C3—C4 | 116.1 (2) |
| O2—N—C1 | 111.15 (13) | C1—C3—C4 | 104.34 (14) |
| N—O1—C2 | 108.91 (13) | C3—C4—C5 | 105.64 (14) |
| C7—O2—N | 117.55 (12) | C7—C5—C6 | 106.03 (14) |
| C7—O3—C15 | 117.07 (13) | C7—C5—C4 | 107.62 (15) |
| N—C1—C8 | 104.54 (14) | C6—C5—C4 | 105.63 (14) |
| N—C1—C6 | 110.43 (14) | C9—C6—C1 | 113.27 (14) |
| C8—C1—C6 | 115.53 (15) | C5—C6—C1 | 99.79 (14) |
| N—C1—C3 | 102.32 (13) | O2—C7—O3 | 114.01 (14) |
| C8—C1—C3 | 116.7 (2) | O2—C7—C5 | 111.07 (15) |
| C6—C1—C3 | 106.49 (14) | O3—C7—C5 | 107.65 (14) |
| O1—C2—C3 | 105.53 (15) | | |

Methyl H-atom positions, C—$CH_3$, were optimized by rotation about $R$—C bonds with idealized C—H, C···H and H···H distances. Remaining H atoms were included as fixed idealized contributors. H atom $U$'s were assigned as 1.2 times $U_{eq}$ of the adjacent non-H atoms.

Data collection: *SMART* (Siemens, 1994*a*). Cell refinement: *SAINT* (Siemens, 1994*b*). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1971). Software used to prepare material for publication: *CIFTAB SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1243). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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# A [3.1.0]-Fused 2′,3′-Modified β-D-Pyrazolo[3,4-*d*]pyrimidine Nucleoside†


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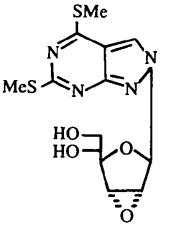
## Abstract

The furanose ring in 4,6-bis(methylthio)-2-(2,3-anhydro-1-deoxy-β-D-allofuranosyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{13}H_{16}N_4O_4S_2$, is almost planar with the epoxide ring in an *exo* orientation.


## Comment

3′-Deoxy and 2′,3′-dideoxy nucleosides are important in the treatment of AIDS (Connolly & Hammer, 1992; Huryn & Okabe, 1992). The potent antileishmanial activity of allopurinol riboside has generated considerable interest in pyrazolo[3,4-*d*]pyrimidine nucleosides (Hupe, 1986). Other pyrazolo[3,4-*d*]-pyrimidine nucleosides with important biological properties have been reported (Rideout *et al.*, 1983; Cottam, 1994). Our continued interest in pyrazolo[3,4-*d*]-pyrimidines (Garg, Avasthi & Bhakuni, 1989; Avasthi *et al.*, 1993; Biswas, Chandra, Avasthi & Maulik, 1995) and their nucleosides (Misra, Jain, Avasthi & Bhakuni, 1990) has led us to report the first synthesis of 'hexofuranosyl nucleosides' of pyrazolo[3,4-*d*]-pyrimidines (Avasthi, Dev, Garg & Bhakuni, 1991). Some 2′,3′-modified nucleosides effectively inhibit the action of several DNA polymerases including virus reverse transcriptase (Kraevskii *et al.*, 1988; Chiggeavadze *et al.*, 1989). This, together with the X-ray crystallographic studies on several [3.1.0]-fused 2′,3′-modified β-D nucleosides of various natural bases (Koole *et al.*, 1991), has prompted us to report the synthesis and X-ray structure of the [3.1.0]-fused 2′,3′-modified nucleoside of pyrazolo[3,4-*d*]pyrimidine, (2). To the best of our knowledge this is the first report describing the synthesis and X-ray study of a novel [3.1.0]-fused 2′,3′-modified nucleoside comprising a six-carbon furanose sugar and a pyrazolo[3,4-*d*]pyrimidine ring system, which is isomeric with the biologically important purine system.




(2)

The X-ray diffraction study of the nucleoside (2) showed three molecules (*A*, *B* and *C*) of similar conformation in one asymmetric unit, connected by intermolecular hydrogen bonding (Fig. 1). The pyrazolo-[3,4-*d*]pyrimidine bases together with the exocyclic methylthio groups attached at the 4 and 6 positions are planar. The furanose ring of the six-carbon sugar moiety of each molecule is flattened compared with 2′-deoxy-nucleosides, presumably due to fusion of the epoxide ring with the C(2′)—C(3′) bond. This result is similar to that observed in many [3.1.0]-fused 2′,3′-modified nucleosides where the furanose ring is derived from a five-carbon sugar (Koole *et al.*, 1991).

The C(2′) and C(3′) atoms deviate [average value of −0.49 (2) Å in each case] in the same direction from the planes through atoms C(1′), O(1′) and C(4′). The epoxy O(23) atoms are further away from these planes [by −1.74 (2), −1.72 (2) and −1.72 (2) Å for *A*, *B* and *C*, respectively], while atoms O(5′) and O(6′) of the ethylene glycol moiety deviate in the opposite direction.

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