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Anti-Cancer Agents. I. *N,N,N′,N′*-Tetraacetylhexamethylenediamine

S.-W. Zhang, Q. Liu, Y. G. Wei and M.-C. Shao

Department of Chemistry, Peking University, Beijing 100871, People's Republic of China

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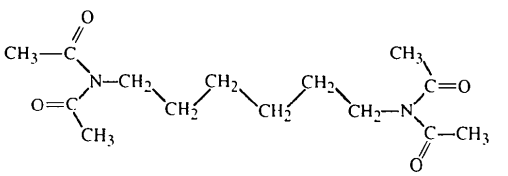
Abstract

The centrosymmetric molecule *N,N,N′,N′*-tetraacetylhexamethylenediamine, $C_{14}H_{24}N_2O_4$, occupies a special position, with only half of the molecule in the asymmetric unit. Each terminal *N,N*-bisacetylamine group is planar but not twofold symmetric.

Comment

Since the discovery that dimethyl sulfoxide (DMSO) induces erythroid differentiation in murine virus-induced erythroleukemic cells (Friend, Scher, Holland & Sato, 1971), numerous chemical compounds such as butyric acid (Leder & Leder, 1975), *N,N*-dimethylacetamide, hexamethylenebisacetamide (HMBA) (Reuben, Wife, Breslow, Rifkind & Marks, 1976) and retinoic acid (Strickland & Mahdavi, 1978) have been demonstrated to have this type of activity. HMBA, as an effective differentiating agent, is used in Phase II clinical trials (Andreeff *et al.*, 1992). The title compound, (I), is slightly more potent and somewhat more effective than HMBA. As a step towards understanding the molecular mechanism by which this compound initiates cell differentiation, identifying the structure–activity relationship and providing structural data for drug design, its crystal structure has been determined.



(I)

Each acetyl group can assume one of the two possible conformations with respect to the central hydrocarbon chain: one with the carbonyl O atom *cis* to the chain and the other with the methyl group *cis* to the chain. In the observed structure (Fig. 1), the two acetyl groups at each end have different conformations. The molecule is centrosymmetric and the asymmetric unit of the crystal contains only half the molecule. The *N,N*-bisacetylamine group is planar, but the possibility of twofold symmetry about the N—C(3) bond is not realised.

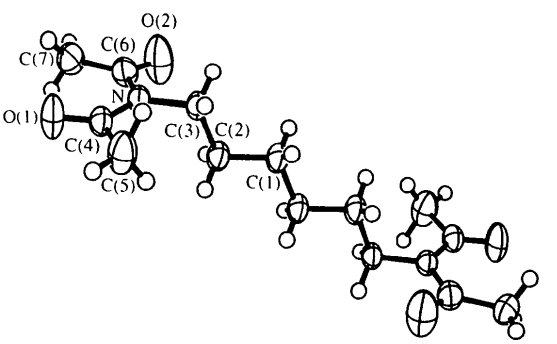


Fig. 1. Molecular structure showing 50% probability displacement ellipsoids for non-H atoms.

Experimental

The title compound was synthesized by the reaction of HMBA with excess acetic anhydride (Haces, Breitman & Driscoll, 1987). The product was recrystallized in ether.

Crystal data

$C_{14}H_{24}N_2O_4$
M_r = 284.4
Monoclinic
$P2_1/n$
a = 8.978 (2) Å
b = 8.689 (2) Å
c = 10.702 (2) Å
β = 106.98 (3)°

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 20 reflections
θ = 6–10°
μ = 0.081 mm^{-1}
T = 295 K
Block

V = 798.5 (3) Å^3
Z = 2
D_x = 1.183 Mg m^{-3}
0.25 × 0.20 × 0.20 mm
Colourless

Data collection

Rigaku AFC-6*S* diffractometer
2θ scans
Absorption correction: ψ scan (Coppens, Leiserowitz & Rabinovich, 1965)
T_{min} = 0.953, T_{max} = 1.000
1513 measured reflections
1407 independent reflections
1213 observed reflections [$F \geq 4\sigma(F)$]
$R_{int} < 0.001$
$\theta_{max} = 25°$
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 10$
$l = -12 \rightarrow 11$
3 standard reflections monitored every 150 reflections
intensity decay: <3%

Refinement

Refinement on F
R = 0.0563
wR = 0.0534
S = 0.5
1213 reflections
139 parameters
All H-atom parameters refined
Unit weights applied
$(\Delta/\sigma)_{max} = 0.012$
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

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

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

	x	y	z	U_{eq}
O(1)	0.8080 (3)	−0.1612 (2)	0.6447 (2)	0.075 (1)
O(2)	0.6246 (3)	0.1100 (3)	0.3325 (2)	0.106 (1)
N	0.7549 (2)	0.0715 (2)	0.5420 (2)	0.039 (1)
C(1)	0.9253 (3)	0.4701 (3)	0.5111 (3)	0.048 (1)
C(2)	0.9186 (3)	0.2947 (3)	0.5145 (3)	0.048 (1)
C(3)	0.7773 (3)	0.2408 (3)	0.5523 (3)	0.043 (1)
C(4)	0.8221 (3)	−0.0235 (3)	0.6494 (2)	0.045 (1)
C(5)	0.9132 (5)	0.0517 (4)	0.7731 (3)	0.075 (1)
C(6)	0.6668 (3)	0.0173 (3)	0.4192 (3)	0.055 (1)
C(7)	0.6250 (4)	−0.1486 (3)	0.3977 (4)	0.068 (1)

Table 2. *Selected torsion angles (°)*

C(1^i)—C(1)—C(2)—C(3)	173.4 (3)	C(3)—N—C(6)—O(2)	3.7 (4)
C(1)—C(2)—C(3)—N	173.3 (2)	C(3)—N—C(4)—O(1)	−179.3 (3)
C(4)—N—C(3)—C(2)	90.6 (3)		

Symmetry code: (i) $2-x, 1-y, 1-z$.

The structure was refined by full-matrix least squares using *SHELXTL-Plus* (Sheldrick, 1990). Data collection, all calculations and graphics were carried out using *SHELXTL-Plus*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: VJ1033). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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[3-(4-Chlorophenyl)-5-methylthio-4,5-dihydro-5-isoxazolyl]acetonitrile

NARESH KUMAR,[a] ARCHANA VATS,[a] VIRINDER S. PARMAR[a] AND WILLIAM ERRINGTON[b]*

[a]*Department of Chemistry, University of Delhi, Delhi 110 007, India, and* [b]*Department of Chemistry, University of Warwick, Coventry CV4 7AL, England. E-mail: msrpq@csv.warwick.ac.uk*

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Abstract

The title compound, $C_{12}H_{11}ClN_2OS$, is formed by the reaction between 6-(4-chlorophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile and hydroxylamine hydrochloride in pyridine solution. The best plane through the five atoms of the isoxazole ring makes an angle of 10.48 (8)° with the plane of the aromatic ring.

Comment

The high antispasmodic activity of isoxazoles (Naruto *et al.*, 1982, 1983) has prompted us to synthesize different types of isoxazoles and their derivatives for structure–activity studies. The reaction of 6-(4-chlorophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile, (I), with hydroxylamine hydrochloride in pyridine has recently been reported to give three compounds, (II), (III) and (IV), each containing an isoxazole moiety (Ram, Hussaini, Singh & Shoeb, 1993); compound (III) was obtained only as a gummy mass. We now report a modified preparative procedure which gives (III) as a crystalline solid. The X-ray structure of (III) was determined in order to obtain an unambiguous characterization.