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Smith, G., Wermuth, U. D., Young, D. J., and Healy, P. C., "Strychnine-8-Ammonio-2-naphthalenesulfonate-water (1/1/3.5): The First Structure of a Strychnine Compound with a Zwitterionic Species," *J. Chem. Crystallogr.*, 2006, **36**, 805-811

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Strychnine-8-ammonio-2-naphthalenesulfonate-water (1/1/3.5): The first structure of a strychnine or brucine compound with a zwitterionic species

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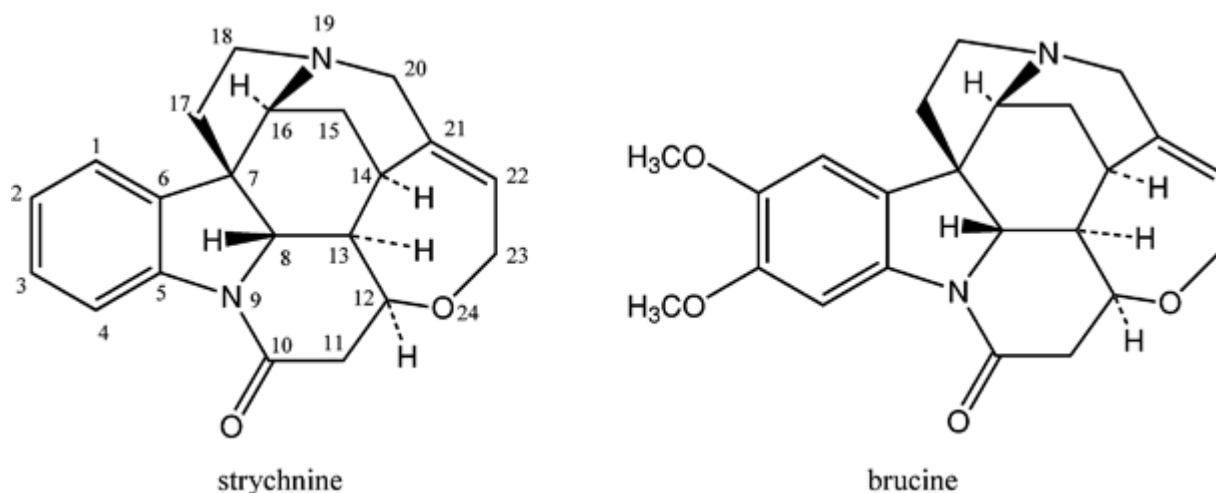
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Abstract: The crystal structure of the 1:1 adduct hydrate of strychnine with 1,7-Cleve's acid (8-amino-2-naphthalenesulfonic acid), namely strychnine-8-ammonio-2-naphthalenesulfonate-water (1/1/3.5) has been determined and provides a unique example of a neutral association involving strychnine and an achiral zwitterionic acid species, previously unobserved in the structures of either strychnine or brucine addition compounds. Crystals are orthorhombic, space group $P2_12_12_1$, with $Z=4$ in a cell with dimensions $a=10.4484(8)$, $b=30.850(3)$, $c=9.4998(11)$ Å. Hydrogen bonding involving all available proton-donor and acceptor sites on all species gives rise to a three-dimensional framework polymer structure. The crystallographic literature for strychnine and brucine and their compounds is also reviewed.

KEY WORDS: strychnine - 1,7-Cleve's acid - naphthylaminesulfonic acids - molecular adduct - hydrogen bonding

Introduction

The alkaloids strychnine (strychnidin-10-one) and brucine (2,3-dimethoxystrychnidin-10-one) were first used by Fischer¹ in 1899 for the separation of enantiomeric mixtures of optically active amino acids (as their *N*-benzoyl-protected derivatives). Since that time both of these alkaloids have been variously employed on a hit-or-miss basis for the resolution of chiral organic compounds, although of the two, brucine has proved to be the better one.

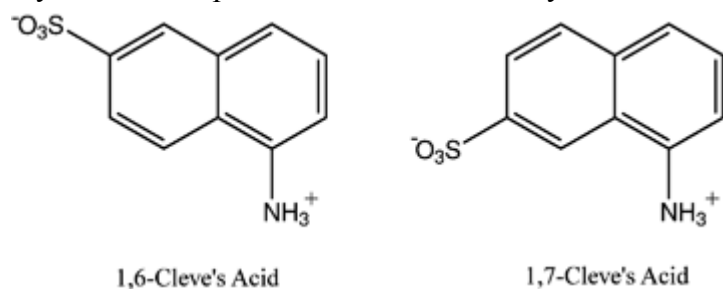


The Robinson and Woodward molecular structure^{2, 3} of strychnine was confirmed in an X-ray determination by Robertson and Beevers in 1951⁴ (on strychninium bromide), while the structures of a number of other inorganic strychninium salts are now known.⁵ The structures of anhydrous strychnine and brucine, strychnine variants, substituted strychnines, as well as a number of brucine solvates [brucine-H₂O (1/4) and (1/5.25), brucine-EtOH-H₂O (1/1/2), brucine-PrⁱOH-H₂O (1/1/2) and brucine-Me₂CO (1/1)] have been reported.⁶

The structures of the compounds of strychnine and brucine with organic molecular species are numerous and these may be placed into four separate categories: (a) those with chiral acidic species, giving mostly 1:1 proton-transfer compounds [for both strychnine and brucine, pK_{a2} (N19)=11.7]; (b) those with chiral organic species, giving neutral molecular adducts; (c) those with achiral acidic species, this category containing occasional 2:1 proton-transfer compounds with strong diprotic acids, e.g. H₂SO₄; (d) those with achiral neutral organic species. Of the four categories, (a) contains a large bulk of the examples since these compounds are more often the types giving good crystalline materials with strychnine and brucine in enantiomorph resolution. Examples include the strychninium and brucinium salts of both the Fischer-type *N*-benzoyl-protected alanines, the *N*-phthaloyl-protected alanines, the brucinium salt of *N*-acetyl-*L*-tryptophane, as well as those of the *N*-phthaloyl- β -hydroxy-*D*- and *L*-leucines.⁷ Other chiral acid types include hydroxy acids: glucuronic and galacturonic acids (both with brucine), tartaric acids (with strychnine and brucine); a disaccharide acid (with brucine), and other miscellaneous acid types (all with brucine), as well as a phosphodithiol salt with methylstrychnine.⁸ In category (b), the types of compound giving neutral adducts are fewer, including those with chiral alcohols and cyanohydrins,⁹ while those with achiral neutral organic molecules [category (d)] are limited to the previously considered brucine solvates with Me₂CO, EtOH and PrⁱOH.⁶ The achiral proton-transfer compounds again comprise the larger category (c) group^{10, 11} with all but two of the examples being brucinium salts. One of these, brucinium 3-nitrobenzoate¹⁰ demonstrated the selectivity of brucine for *m*-nitro, chloro- and bromo-substituted benzoic acids, giving no crystalline products with the *o*- or *p*-isomers. On this theme, we subsequently synthesized and characterized the 1:1 brucinium salts of 3,5-dinitrosalicylic acid (DNSA) (a monohydrate), 5-nitrosalicylic acid (5-NSA) (an anhydrate) and 5-sulfosalicylic acid (5-SSA) (a monohydrate),¹² 3-nitrophthalic acid (3-NPA) (a trihydrate),¹³ toluene-4-sulfonic acid (PTSA) (a trihydrate)¹⁴ as well as the 1:1

strychninium salts of DNSA (an anhydrate) and 5-NSA [an unusual bis(5-NSA acid) adduct].¹⁵

It was also of particular interest that there had been no reported examples of crystallographically characterized strychnine or brucine compounds with zwitterionic organic species, chiral or achiral. Therefore, it was unusual that large pale brown prismatic crystals of **1** were readily obtained from the reaction of strychnine with the achiral zwitterionic acid, 8-amino-2-naphthalenesulfonic acid (1,7-Cleve's acid) in 50% ethanol/water. This also represented another example of the hit-or-miss crystallizations peculiar to brucine and strychnine.



No equivalent crystalline product was obtained with brucine nor were any crystalline adduct materials formed in similar preparations using either strychnine or brucine with other known zwitterionic aromatic sulfonic acids, e.g. the isomeric 1,6-Cleve's acid (5-amino-2-naphthalenesulfonic acid)¹⁶ or the *meta*-substituted benzoic acid, metanilic acid.

Results and discussion

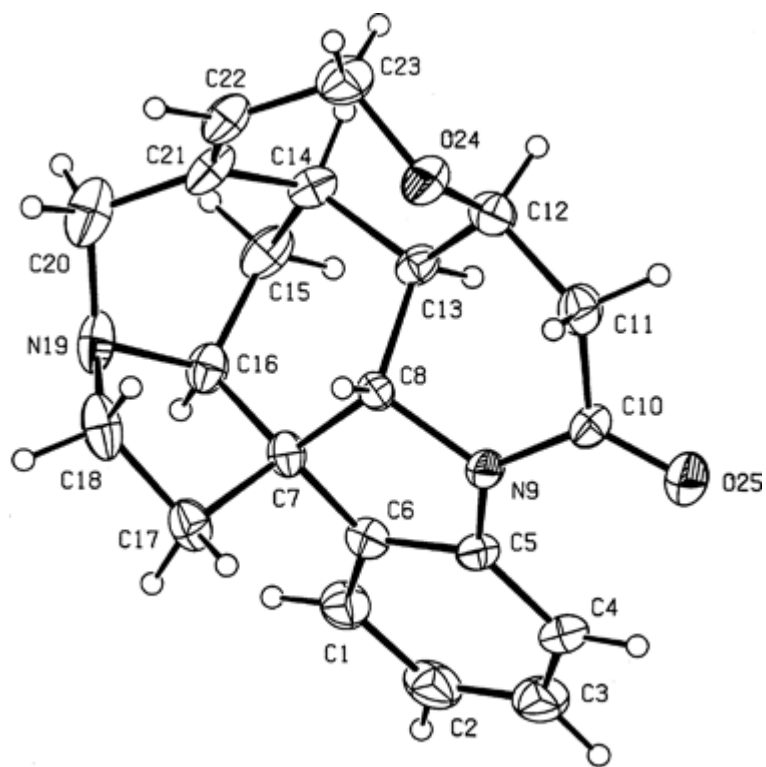
The crystal structure determination identified **1** as the hydrated adduct of strychnine with the zwitterionic form of 1,7-Cleve's acid, strychnine-8-ammonio-2-naphthalenesulfonate-water (1/1/3.5). Crystal data are given in Table 1 while the two organic molecular species (less the water molecules) are shown in Fig. 1a and 1b, the atom numbering scheme for the strychnine ring system following the convention of Robinson.^{2, 3}

Table 1. Crystal Data for **1**

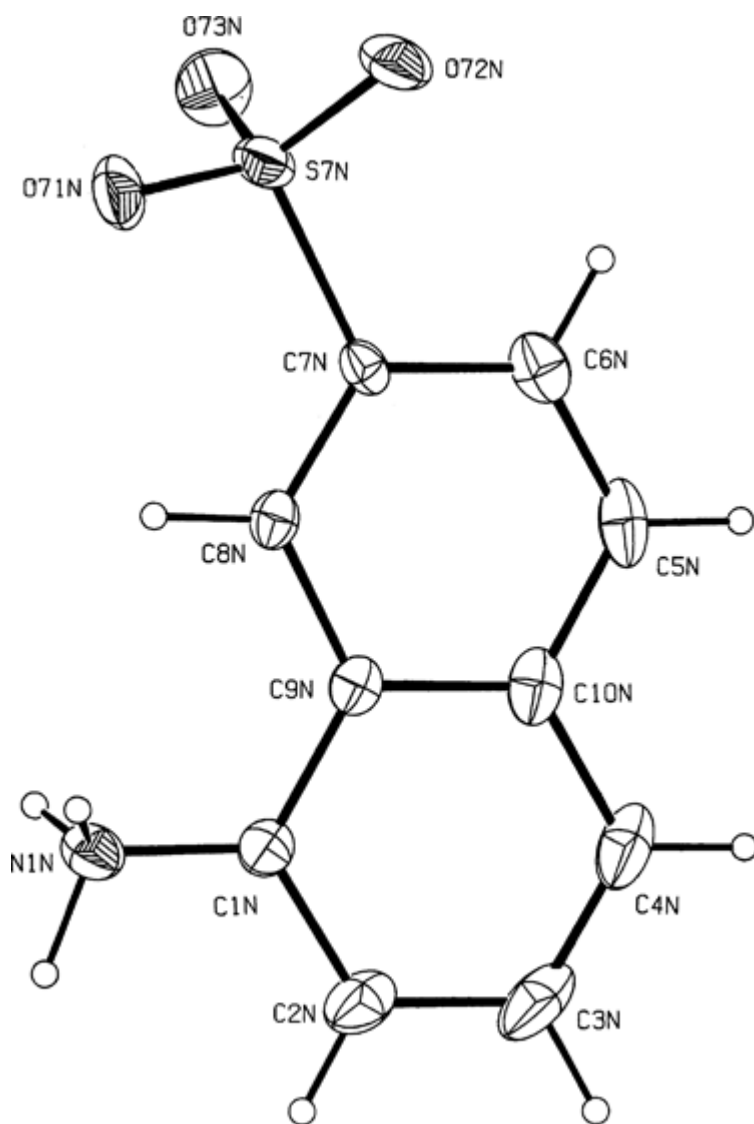
Compound	(1)
Melting point (°C)	103.7–105.6
Molecular formula	C ₃₁ H ₃₈ N ₂ O _{8.5} S
<i>M</i> _r	620.70
Temperature (K)	298(2)
Wavelength (λ)	0.71069
Crystal system	orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> (Å)	10.4484(8)
<i>b</i> (Å)	30.850(3)
<i>c</i> (Å)	9.4998(11)
<i>V</i> (Å ³)	3062.1(5)

Compound	(1)
Z	4
D_c (g cm ⁻³)	1.346
μ (mm ⁻¹)	1.63
$F(000)$	1316
Instrument	Rigaku AFC7 R
Reflections total, θ_{\max} (°)	3719, 27.5
Crystal size (mm)	0.34×0.20×0.18
Collection range	
h	-12 to 5
k	0 to 36
l	-5 to 11
Reflections independent	3242
Reflections [$I > 2.0 \sigma(I)$]	2096
R_{int}	0.020
$T_{\text{max/min}}$	0.97/0.95
R_1^* [$I > 2.0 \sigma(I)$]	0.053
wR_2^* (all data)	0.176
S^*	1.035
n_p	399
Flack parameter ²⁵	0.2(2)(160 Friedel pairs)
Residuals: $\Delta_{\text{max./min}}$ (eÅ ⁻³)	0.507/-0.437

$$R_1 = (\Sigma|F_o| - |F_c|)/\Sigma|F_o|; wR_2 = \{\Sigma w[(F_o^2 - F_c^2)]^2 / \Sigma w(F_o^2)\}^{1/2}; S = \{\Sigma[w(F_o^2 - F_c^2)]^2 / (n_p)\}^{1/2}$$



(a)



(b)

Fig. 1. Molecular configuration and atom numbering scheme for the individual strychnine (1a) and the 8-ammonio-2-naphthalenesulfonate species (1b) in compound **1**. For strychnine, the scheme follows that of Robinson.^{2, 3} Non-hydrogen atoms are shown as 30% probability displacement ellipsoids.²³

Compound **1** is particularly unusual because of the absence of proton transfer, probably because of the presence of the amine-sulfonic acid zwitterion in 1,7-Cleve's acid. The historic Fischer technique for the resolution of chiral amino acids using brucine and strychnine⁴ requires that these inherently zwitterionic acids are *N*-protected, the reason being the destruction of the amine-carboxylic acid zwitterion. However, the resolution of certain unprotected amino acids has been achieved by using other resolving agents, e.g. zwitterionic glutamic acid may be resolved using a number of optically active amino compounds,¹⁷ including 2-aminobutanol. Although the structures of many chiral zwitterionic amino acids with common achiral carboxylic acids are known,¹⁸ there is no reported structure of a neutral strychnine or brucine adduct with a zwitterionic molecular species, chiral or achiral. Compound **1** therefore represents the first example of such an adduct.

Also, because 1,6-Cleve's acid does not give any obvious reaction product with strychnine, **1** represents an example of strychnine molecular recognition. The importance of molecular recognition in the hit-or-miss resolution using the Strychnos alkaloids, especially brucine has previously been described.⁷ With brucine, undulating host substructures such as are found in the brucine-EtOH-H₂O and brucine-PrⁱOH-H₂O solvate crystals⁶ are also found in a significant number of brucine structures.^{6, 7} These host structures are commonly generated by a 2₁ screw operation in the unit cell and have an identifiable dimer repeat period of *ca.* 12.5 Å. The guest molecule/s are accommodated between the layers, interacting with the host substructure through hydrogen-bonding associations. However, strychnine does not usually form into this type of periodic host structure, presumably because of the absence of the two methoxy groups and as a consequence there is a smaller incidence of molecular recognition involving strychnine compared to brucine. This is consistent with the structure of **1** where there is a absence in the solid-state packing of any inter-strychnine interactions, the primary structure comprising discrete strychnine molecules and zwitterionic aminonaphthalene sulfonic acid species. These, together with the four water molecules (O1W-O4W; O3W has half-occupancy) form hydrogen-bonded layers (Table 2) lying perpendicular to the *b* axis in the unit cell (Fig. 2). These layers are linked to the discrete strychnine molecules through single water-strychnine-N interactions. [OW4 ··· N19^c, 2.783(8) Å; symmetry code: ^c-1+x, y, z] while the strychnine carbonyl oxygen (O25) is not involved in hydrogen bonding. The result is a three-dimensional hydrogen-bonded framework structure. The strychnine molecules have the C7(*R*), C8(*S*), C12(*S*), C13(*R*), C14(*R*), C16(*S*) absolute configuration expected for neutral strychnine.¹⁵

Table 2. Hydrogen-bonding Interactions (Å/deg.)

D-H···A	D-H	H···A	D···A	DHA
O1W-H1A···O71N	0.96	1.92	2.830(7)	160
O1W-H1B···O4W ^a	0.86	1.95	2.750(7)	153
O2W-H2A···O1W	0.80	2.21	2.982(7)	161
O2W-H2B···O1W ^a	1.01	1.80	2.761(8)	157
O3W-H3A···O71N	0.93	1.86	2.788(9)	179
O3W-H3B···O73N ^b	0.93	1.87	2.796(10)	178
O4W-H4A···O72N	0.84	2.00	2.784(8)	154
O4W-H4B···N19 ^c	0.92	1.86	2.783(8)	180
N1N-H11N···O73N ^b	0.80	2.19	2.969(8)	162
N1N-H12N···O72N ^d	1.00	2.14	3.091(7)	159
N1N-H13N···O2W	0.93	1.94	2.858(9)	172

Symmetry codes: ^a 0.5-x, -y, 0.5+z; ^b 1.5-x, -y, 0.5+z; ^c -1+x, y, z; ^d x, y, 1+z.

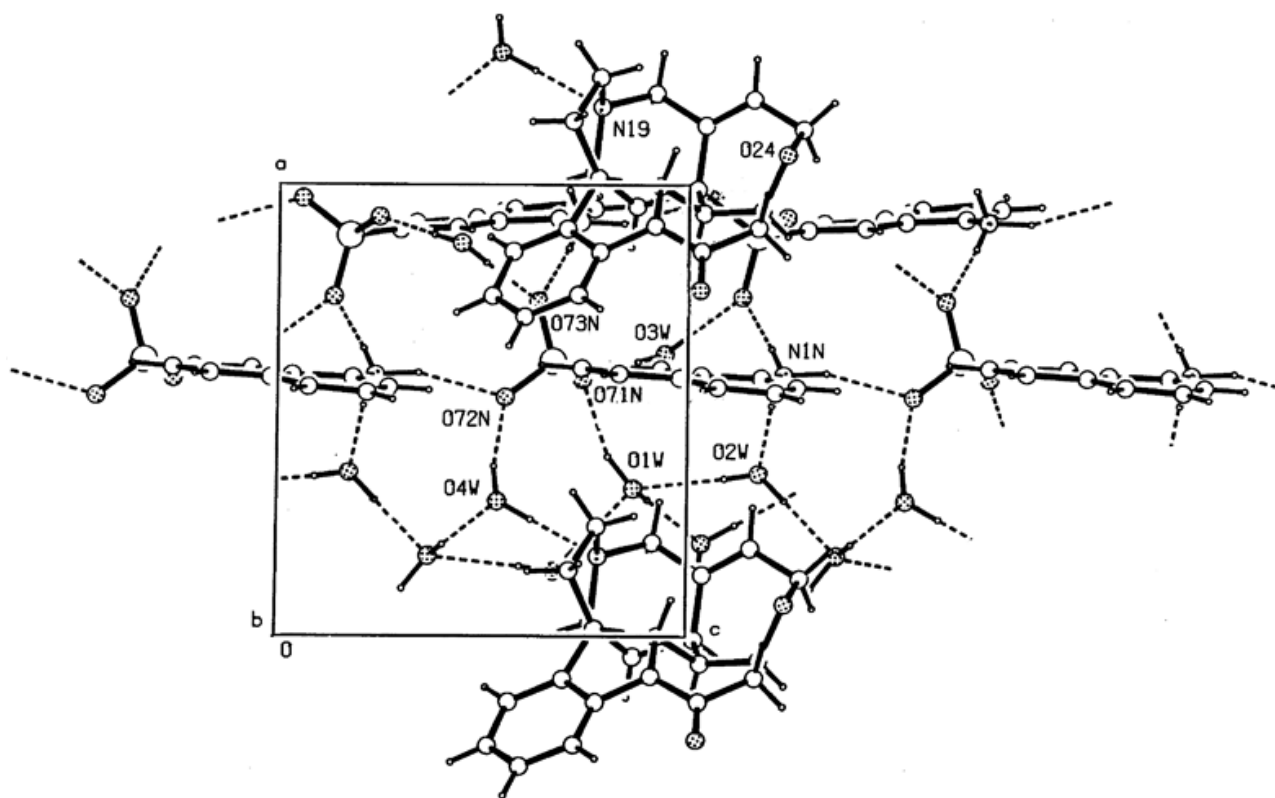


Fig. 2. The packing of **1** in the unit cell viewed down the *b* axis. Hydrogen-bonding associations (Å) are shown as broken lines.

Experimental Preparation

The title compound **1** was synthesized by heating 1 mmol quantities of strychnine and 8-amino-2-naphthalenesulfonic acid (1-naphth-ylamine-7-sulfonic acid: 1,7-Cleve's acid) in 50 mL of 50% ethanol/water under reflux for 10 min. After concentration to *ca.* 30 mL, partial room temperature evaporation of the hot-filtered solution gave large pale-brown crystal prisms of **1** (mp 103.7–105.6°C).

Crystallography

X-ray diffraction data for **1** were collected at room temperature on a Rigaku AFC 7R four-circle diffractometer using crystal monochromatised Mo-K α X-radiation ($\lambda=0.71069$ Å) from a 12 KV rotating anode source. Data were corrected for extinction and for absorption (psi scans). The structure was solved by direct methods using SIR-92¹⁹ and refined with anisotropic thermal parameters for all non-hydrogen atoms using SHELXL 97²⁰ operating within the TeXsan system.²¹ Hydrogen atoms attached to ring carbons of the strychnine and the substituted naphthalene molecules were included in the refinement at calculated positions as riding models while those potentially involved in hydrogen-bonding interactions (H11N, H12N, H13N and water protons) were located by difference methods and included with their positional and isotropic thermal parameters fixed. The atom numbering scheme employed for strychnine follows the convention of Robinson.^{2, 3} The absolute configuration determined by Peerdeman²² for the parent strychnine molecule was invoked giving in

neutral strychnine (or brucine) the following Cahn-Ingold-Prelog designations²³ for the six chiral centres of the molecule: C7(*R*), C8(*S*), C12(*S*), C13(*R*), C14(*R*), C16(*S*). It should be noted that protonation of the strychnine (or brucine) molecule subsequently generates another chiral centre in the cation [N19(*S*)].¹⁵

Acknowledgments The authors acknowledge financial support from the School of Physical and Chemical Sciences (Queensland University of Technology) and Griffith University.

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Supplementary material

CCDC 254727 contains supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif by emailing datarequest@ccdc.cam.ac.uk, or contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ.