Conophylline and Conophyllidine: New Dimeric Alkaloids from Tabernaemontana divaricata

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CONOPHYLLINE AND CONOPHYLLIDINE: NEW DIMERIC ALKALOIDS FROM *TABERNAEMONTANA DIVARICATA*

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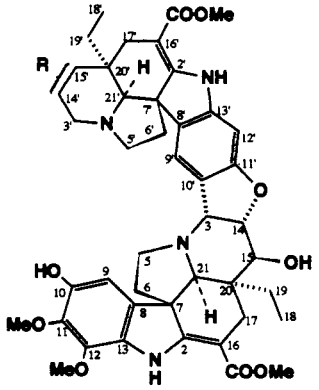
ABSTRACT.—The EtOH extract of the leaves of *Tabernaemontana divaricata* (single flower variety) provides, in addition to voacangine, voacristine, voacristine-7-hydroxyindolenine, apparicine, and 19-*epi*-voacristine, two new dimeric alkaloids: conophylline [**1**] and conophyllidine [**2**]. The structures of the dimeric alkaloids were established by spectral methods and subsequently confirmed by X-ray analysis.

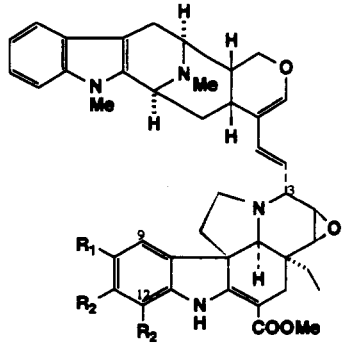
Tabernaemontana divaricata (L.) R.Br. ex Roem. & Schult. (Apocynaceae), although originally a native of India, is now widely cultivated as a popular garden plant in southeast Asia and other tropical countries. There are two distinct varieties, the single flower variety and the double flower variety (1–4), and both forms are widely cultivated in Malaysia where the flowers of the single flower variety are used by the local Indian community in religious rites. There seems to be considerable variation in the alkaloidal composition in this species depending on the geographical location (3–8), and because biological activities have also been reported in a number of instances (9,10), we undertook an investigation of the Malaysian species for which there has been no previous chemical study (11).

RESULTS AND DISCUSSION

The EtOH extract of the leaves furnished a number of known alkaloids including voacangine, voacristine, voacristine-7-hydroxyindolenine, apparicine, and 19-*epi*-voacristine which were readily identified based on their spectral data. Voacristine-7-hydroxyindolenine is an artifact derived by oxidation of voacristine; this was readily demonstrated as the conversion could be monitored by ^{1}H nmr over several days in a sample in $CDCl_3$ kept in an nmr tube at ca. 15°. In addition to these alkaloids, two new dimeric alkaloids were also isolated: conophylline [**1**] and conophyllidine [**2**]. The major alkaloid, conophylline [**1**], crystallized from EtOAc as light yellow prisms and was shown to be a dimeric indole by its mass spectrum (fabms $[MH]^+$ 795). The uv spectrum was characteristic of alkaloids with β-anilinoacrylate chromophores, and the ir spectrum of **1** showed the presence of NH, OH, and conjugated carbonyl functions.



1 R=β-O
2 R=$\Delta^{14',15'}$



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The ^{1}H- and ^{13}C-nmr spectral data (Tables 1 and 2) of conophylline [**1**] indicated a novel dimeric alkaloid constituted from highly oxygenated vincardiffformine-tabersonine epoxide moieties. The ^{1}H-nmr spectrum showed the presence of two indole NH, three isolated aromatic hydrogens one of which was significantly shielded (δ 5.55), an OH function (δ 5.19, singlet, exchanged with D_2O), four MeO groups of which two are associated with the presence of two ester carbomethoxy functions (δ_C 168.8, 168.7), and two ethyl groups. The presence of only three aromatic singlets indicated highly substituted indole rings where one indole ring is substituted at the 10, 11, and 12 positions while the other is substituted at the 10′ and 11′ positions. This was confirmed by the nOe interactions observed between one of the indole NH (δ 8.79) and the aromatic MeO at C-12 (δ 3.86) and between the other indole N′H (δ 9.01) and the aromatic H-12′ (δ 6.34). The unusually low field aromatic MeO carbon absorptions (δ_C 60.5, 61.0) suggested that they are in an ortho arrangement (12) and indicated that the other aromatic MeO group is at C-11 with C-10 substituted by an OH group (δ_C 138.7). Such arrangement is reminiscent of that in the dimer, pandicine [**3**] (13), and in fact, when compared with pandicine [**3**], there was generally good agreement of the aromatic ^{13}C shifts in particular, as well as those of the non-aromatic carbons with the exception of the ring E carbons. The other unit of the dimer was clearly shown to be a 10-alkyl-11-oxytabersonine-β-epoxide by the excellent correlation of the non-aromatic ^{13}C shifts with those of tabersonine-β-epoxide (14) and the aromatic ^{13}C shifts with those of vandrikine (15) and the dimeric alkaloid vincarubine (16) (Table 2).

The general agreement of the carbon resonances with the exception of the ring E carbons in the pandicine-like 10-hydroxy-11,12-dimethoxyvincadiffformine unit sug-

TABLE 1. ^{1}H-Nmr Data of Conophylline [**1**] and Conophyllidine [**2**].

Proton	Compound		Proton	Compound	
	1	**2**		**1**	**2**
H-3	4.81, d (7.8)	4.80, d (7.8)	H-3′	2.99, d (13)	3.28, d (16)
	—	—		3.59, d (13)	3.48, d (16)
H-5	2.7–3.1, m	2.6–2.9, m	H-5′	2.7–3.1, m	2.6–2.9, m
	2.7–3.1, m	2.97, dd (8,6)		2.7–3.1, m	3.07, t (7)
H-6	1.68, dd (11,3.9)	1.67, dd (11,4)	H-6′	1.68, dd (11,3.9)	1.80, dd (11,4)
	1.9–2.2, m	1.9–2.2, m		1.9–2.2, m	1.9–2.2, m
H-9	5.55, s	5.53, s	H-9′	7.14, s	7.21, s
	—	—	H-12′	6.34, s	6.35, s
H-14	5.06, dd (7.8,3.7)	5.06, dd (7.8,3.5)	H-14′	3.25, d (3.9)	5.7–5.8, m
H-15	4.16, dd (11,3.7)	4.15, d (3.5)	H-15′	3.11, d (3.9)	5.7–5.8, m
H-17	2.40, d (15.5)	2.39, d (15)	H-17′	2.52, d (15.5)	2.39, d (15)
	2.74, d (15.5)	2.74, dd (15,1.5)		2.74, d (15.5)	2.62, dd (15,1.5)
H-18	0.71, t (7)	0.70, t (7)	H-18′	0.79, t (7)	0.72, t (7)
H-19	0.7–0.9, m	0.7–1.0, m	H-19′	1.1–1.3, m	1.0–1.3, m
	1.1–1.3, m	1.0–1.3, m		1.1–1.3, m	1.0–1.3, m
H-21	2.60, s	2.78, d (1.5)	H-21′	2.55, s	2.61, d (1.5)
OMe	3.77, s	3.77, s	OMe	3.79, s	3.77, s
10-OH	5.19, s	5.10, s		—	—
11-OMe	3.82, s	3.81, s		—	—
12-OMe	3.86, s	3.85, s		—	—
NH	8.79, s	8.77, s	N′H	9.01, s	9.00, s

TABLE 2. ^{13}C-nmr Data of Conophylline [**1**], Conophyllidine [**2**], and Pandicine [**3**].

Carbon	Compound			Carbon	Compound		
	1	**2**	**3**		**1**	**2**	—[a]
2	164.3[b]	164.6[i]	164.8	2′	165.2[b]	166.5[i]	164.9
3	59.5	59.5	55.1	3′	49.4	50.2	49.4
5	46.0	45.9	48.4	5′	51.1	50.9	51.0
6	41.8	41.8	42.2	6′	44.4	44.9	43.9
7	54.4[c]	54.7[j]	54.0	7′	54.8[c]	54.8[j]	54.7
8	133.5	133.5	134.0	8′	131.0	131.3	130.6
9	103.9	104.1	104.2	9′	119.3	119.4	122.8
10	138.7	138.6	138.7	10′	113.8	113.7	116.7
11	136.8	136.7	137.0	11′	161.1	161.0	157.7
12	143.5	143.6	143.8	12′	93.1	93.1	93.5
13	128.8	128.7	126.6	13′	145.0	145.0	148.9
14	85.1	85.1	56.4	14′	52.2	124.3	52.0
15	69.5	69.5	54.4	15′	56.4	133.1	56.2
16	90.7[d]	90.6[k]	90.4	16′	91.4[d]	92.2[k]	90.4
17	22.2[e]	22.1	42.3	17′	23.3[e]	28.2	23.5
18	7.4	7.4[l]	7.3	18.′	7.4	7.6[l]	7.1
19	26.4[f]	26.3[m]	27.3	19′	26.7[f]	27.3[m]	26.5
20	44.8	44.8	36.0	20′	37.1	40.8	37.0
21	65.3	65.2	62.5	21′	71.8	71.0	70.9
CO_2Me	168.8[g]	168.9[n]	168.8	CO_2Me	168.7[g]	168.8[n]	168.6
$CO_2\mathit{Me}$	51.1[h]	51.0[p]	50.9	$CO_2\mathit{Me}$	50.9[h]	50.9[p]	50.8
11-OMe	61.0	60.9	61.0		—	—	—
12-OMe	60.5	60.4	60.5		—	—	—

[a]δ values of non-aromatic carbons are for tabersonine-β-epoxide,while values for aromatic carbons are for vincarubine.

[b–p]These assignments may be interchanged.

gested an essentially similar structure but differing in the mode of attachment of the monomer units. The mode of attachment of the monomer units was deduced from examination of the ring E H-3, -14, and -15 resonances which were clear and well resolved in the region from ca. δ 4 to 5. Analysis of the H-H and H-C COSY nmr data revealed the partial structure for ring E of the vincadifformine unit as follows:

$$\begin{array}{l} N_4-C_3H-C_{14}H-C_{15}H-C_{20} \\ \quad\quad\;\; | \quad\quad\;\; | \quad\quad\;\; | \\ \quad\quad\;\; R \quad\quad OR \quad\quad OH \end{array}$$

The OH function was placed on C-15, since on exchange with deuterium the H-15 doublet of doublets (J=11.0, 3.7 Hz) collapsed to a doublet (J=3.7 Hz). The mode of attachment of the monomeric units is, thus, via C-3 and C-14 of the vincadifformine unit to C-10′ and C-11′ of the tabersonine-epoxide unit, the C-14 to C-11′ connection being mediated by an ether oxygen. The substitution at C-3 and C-14 has to be cis, this being dictated by the fact the C-3 and C-14 form part of a dihydrofuran unit. The similarity of the C-3 shift (δ 59.5) to those in the dimers criophylline (δ 58.1) (17) and pandicine [**3**] (δ 55.1) (13) suggested that conophylline [**1**] also has C-3α substitution. This was further confirmed by the observation that H-9 of conophylline [**1**] (δ 5.55) is significantly shielded compared to H-9 of pandicine [**3**] (δ 6.34) in the ^{1}H nmr, which is due to its being affected by the anisotropy of the aromatic ring of the tabersonine epoxide unit, a feature which is only possible if the tabersonine epoxide unit is attached on the α face at C-3 and C-14. The configuration of the remaining stereocenter, that of the 15-OH, is readily deduced to be β from the nOe interaction observed between H-15 and the C-18 hydrogens of the α-ethyl substituent.

Based on the foregoing arguments the structure of conophylline [**1**] is as shown. Since conophylline [**1**] furnished well formed crystals, we carried out X-ray diffraction analysis which confirmed the structure we proposed (11) based on analysis of the spectral data as shown in the perspective diagram of Figure 1. The crystals of conophylline [**1**] are monoclinic, belonging to the space group $P2_1$, with $a=12.1877(9)$ Å, $b=13.808(2)$ Å, $c=12.667(1)$ Å, $\alpha=\gamma=90°$, $\beta=107.475(8)°$, $V=2033.3(4)$ Å^3; $D_x=1.298$ mg·m^{-3} and $Z=2$. The structure was solved by the direct method DIRDIF (18) and refined by the full-matrix least squares method. One H_2O molecule is located at 2.97 (1) Å from O-16 and 2.90 (1) Å from O-15 with the O-15–O_W–O-16 angle at 109.0 (4)°. There are two more intermolecular hydrogen-bonds between O-12 and N-1′ at 2.93 (1) Å and between O-14′ and O-15 at 2.74 (1) Å.

The second dimeric alkaloid, conophyllidine [**2**], was isolated in relatively minor amounts when compared to conophylline [**1**]. The fabms showed an $[MH]^+$ at *m/z* 779 corresponding to the formula $C_{44}H_{50}N_4O_9$, i.e., with one oxygen less when compared with conophylline [**1**]. The ^{1}H- and ^{13}C-nmr spectra are very similar to that of conophylline [**1**] except for one telling difference, the replacement of the epoxide function at positions 14′ and 15′ of the tabersonine epoxide unit by a double bond, which is clearly evident from both the ^{1}H- and ^{13}C-nmr spectra [δH 5.7–5.8 (H-14′, -15′), m; δC 124.3 (C-14′), 133.1 (C-15′)]. The structure of conophyllidine [**2**] is, therefore, as shown.

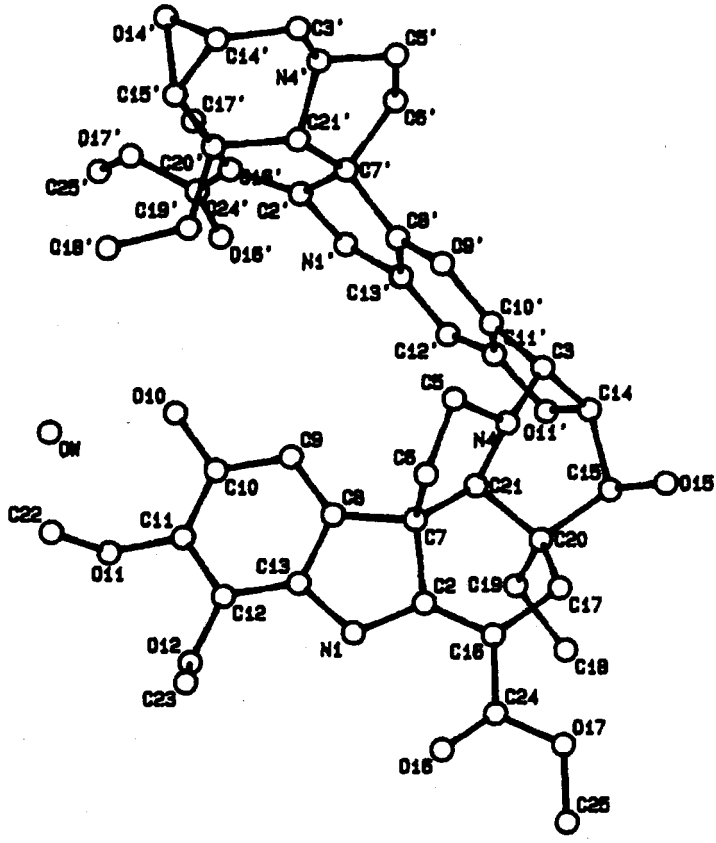

FIGURE 1. Perspective diagram of conophylline [**1**].

TABLE 3. Atomic Coordinates and Isotropic Displacement Parameters.[a]

Atom	x	y	z	B(Å^2)
OW	0.3064 (7)	−0.1726 (7)	−0.3126 (7)	7.1 (2)
O-10	0.2862 (5)	−0.115	−0.1164 (5)	4.0 (2)
O-11′	0.4206 (5)	−0.3181 (5)	0.3875 (5)	2.7 (1)
O-11	0.4608 (5)	−0.0161 (6)	−0.1718 (5)	3.4 (2)
O-12	0.6220 (5)	0.0860 (5)	−0.0106 (5)	3.8 (2)
O-14′	−0.3083 (6)	−0.2123 (5)	−0.2158 (6)	4.4 (2)
O-15	0.5085 (5)	−0.1468 (5)	0.6151 (5)	3.0 (2)
O-16′	0.1325 (6)	−0.5036 (7)	−0.1641 (6)	5.7 (2)
O-16	0.7965 (6)	0.1346 (6)	0.3877 (6)	4.4 (2)
O-17	0.8378 (6)	0.0549 (6)	0.5495 (6)	4.8 (2)
O-17′	−0.0224 (6)	−0.4700 (6)	−0.3025 (5)	4.7 (2)
N-1′	0.1491 (6)	−0.4274 (6)	0.0395 (7)	3.4 (2)
N-1	0.6137 (6)	0.0676 (6)	0.2226 (6)	2.9 (2)
N-4′	−0.1900 (6)	−0.2697 (6)	0.0053 (7)	3.4 (2)
N-4	0.3636 (5)	−0.0905 (5)	0.3820 (5)	2.1 (2)
C-2′	0.0474 (8)	−0.3837 (7)	−0.0259 (7)	2.8 (2)
C-2	0.5935 (7)	0.0272 (8)	0.3143 (7)	2.7 (2)
C-3	0.3100 (7)	−0.1804 (7)	0.4059 (7)	2.5 (2)
C-3′	−0.2694 (8)	−0.1896 (9)	−0.0128 (9)	4.4 (3)
C-5	0.2923 (7)	−0.0145 (8)	0.3162 (7)	2.7 (2)
C-5′	−0.1680 (8)	−0.3207 (9)	0.1077 (8)	4.3 (3)
C-6	0.3851 (8)	0.0543 (7)	0.3022 (8)	3.0 (2)
C-6′	−0.0763 (9)	−0.3888 (8)	0.0984 (9)	3.9 (3)
C-7	0.4736 (7)	−0.0160 (7)	0.2778 (7)	2.4 (2)
C-7′	0.0023 (7)	−0.3242 (7)	0.0509 (7)	2.5 (2)
C-8′	0.1120 (7)	−0.3014 (7)	0.1432 (7)	2.1 (2)
C-8	0.4512 (8)	−0.0256 (7)	0.1522 (7)	2.7 (2)
C-9′	0.1409 (7)	−0.2340 (7)	0.2283 (7)	2.2 (2)
C-9	0.3660 (7)	−0.0714 (8)	0.0715 (7)	2.8 (2)
C-10	0.3690 (8)	−0.0663 (8)	−0.0370 (8)	3.2 (2)
C-10′	0.2483 (7)	−0.2425 (7)	0.3089 (7)	2.3 (2)
C-11′	0.3196 (7)	−0.3169 (7)	0.3016 (6)	2.1 (2)
C-11	0.4522 (7)	−0.0127 (7)	−0.0633 (7)	2.4 (2)
C-12′	0.2979 (8)	−0.3834 (8)	0.2157 (7)	2.9 (2)
C-12	0.5372 (7)	0.0361 (7)	0.0167 (7)	2.8 (2)
C-13′	0.1926 (7)	−0.3716 (7)	0.1385 (7)	2.5 (2)
C-13	0.5354 (7)	0.0287 (7)	0.1253 (7)	2.7 (2)
C-14′	−0.2828 (9)	−0.1466 (9)	−0.1226 (9)	4.3 (3)
C-14	0.4068 (8)	−0.2482 (8)	0.4675 (7)	2.8 (2)
C-15′	−0.1981 (8)	−0.1642 (8)	−0.1798 (8)	3.7 (2)
C-15	0.5227 (7)	−0.1981 (7)	0.5221 (7)	2.4 (2)
C-16′	−0.0029 (8)	−0.3928 (7)	−0.1358 (8)	2.9 (2)
C-16	0.6603 (7)	0.0230 (7)	0.4202 (7)	2.6 (2)
C-17′	−0.1051 (8)	−0.3271 (8)	−0.1845 (8)	3.4 (2)
C-17	0.6187 (7)	−0.0417 (7)	0.4976 (7)	2.5 (2)
C-18	0.7688 (8)	−0.213 (1)	0.4781 (9)	4.6 (3)
C-18′	0.026 (1)	−0.165 (1)	−0.255 (1)	7.6 (4)
C-19	0.6505 (8)	−0.1938 (8)	0.3981 (7)	2.9 (2)
C-19′	0.0142 (9)	−0.1708 (9)	−0.1398 (9)	4.5 (3)
C-20′	−0.0906 (8)	−0.2272 (7)	−0.1275 (7)	2.8 (2)
C-20	0.5655 (7)	−0.1350 (7)	0.4402 (7)	2.3 (2)
C-21	0.4610 (7)	−0.1098 (6)	0.3409 (6)	2.0 (2)
C-21′	−0.0796 (8)	−0.2414 (8)	−0.0071 (8)	3.3 (2)
C-22	0.395 (1)	0.056 (1)	−0.245 (1)	6.6 (4)
C-23	0.622 (1)	0.187 (1)	0.008 (1)	7.8 (4)
C-24	0.7681 (8)	0.0765 (8)	0.4477 (8)	3.4 (2)
C-24′	0.0441 (9)	−0.4589 (9)	−0.1964 (9)	4.2 (3)
C-25	0.945 (1)	0.112 (1)	0.579 (1)	8.2 (4)
C-25′	0.017 (1)	−0.544 (1)	−0.3634 (9)	6.0 (3)

[a]Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a^2*B(1,1)+b^2*B(2,2)+c^2*B(3,3)+ab(cos gamma)*B(1,2)+ac(cos beta)*B(1,3)+bc(cos alpha)*B(2,3)].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mp's were uncorrected. Uv spectra were recorded on a Shimadzu UV-160A spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded in $CDCl_3$ using TMS as internal standard on a Jeol JNM-GSX 270 spectrometer at 270 and 67.8 MHz, respectively.

PLANT MATERIAL.—Plant material was collected in Petaling Jaya, Malaysia, in April 1990 and identified by D. Jones, Department of Botany, University of Malaya. Voucher specimens (GK 492) are deposited at the Herbarium, Forest Research Institute of Malaysia.

EXTRACTION AND ISOLATION.—Extraction of the ground leaves (2 kg) was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid which has been described in detail elsewhere (19,20) to give a total crude alkaloid yield of ca. 3.5 $g \cdot kg^{-1}$. The alkaloids were isolated by initial cc on Si gel using $CHCl_3$ with increasing MeOH gradient followed by rechromatography of appropriate partially resolved fractions (solvent systems: $CHCl_3$ with increasing MeOH gradient, Et_2O and Et_2O with increasing EtOAc gradient) and finally preparative tlc on Si gel [solvent system hexane-EtOAc (3:7)]. The yields ($g \cdot kg^{-1}$) of the alkaloids isolated were as follows: voacangine (0.13), voacristine (0.87), voacristine-7-hydroxyindolenine (0.013), apparicine (0.0043), 19-*epi*-voacristine (0.087), conophylline [**1**] (0.65), and conophyllidine [**2**] (0.043).

Conophylline [**1**].—Light yellow prisms from EtOAc: mp ca. 200° (dec); fabms (glycerol) *m/z* $[MH]^+$ 795.4; uv (EtOH) λ max (log ε) 206 (4.59), 240 (4.45), 310 (4.48) sh, 334 (4.59) nm; ir ($CHCl_3$) ν max 3350, 1680, 1605 cm^{-1}; ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

Conophyllidine [**2**].—Amorphous: fabms (glycerol) *m/z* $[MH]^+$ 779.2; uv (EtOH) λ max (log ε) 202 (4.28), 230 (4.09) sh, 311 (4.02), 335 (4.09) nm; ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

X-RAY DIFFRACTION ANALYSIS.[1]—A total of 4358 reflections were collected up to θ max of 26° on a CAD4 diffractometer at 27° using MoK_α (λ=0.71073 Å). The data were collected by the ω–2θ method, 1813 observed reflections with $I>3\sigma(I)$, and were corrected for Lorentz-polarization effect but not for absorption. The structure was solved by using the direct method DIRDIF (18). All non-hydrogen atoms were refined anisotropically by full-matrix least squares refinement on a microvax II minicomputer to R=0.052, wR=0.057 for the observed reflections, $w=[\sigma^2(F)+0.0004F^2+1]^{-1}$. Hydrogen atoms were generated geometrically at C-H 0.95 Å and were allowed to ride on their respective parent atoms with B fixed at 1.3 times that of the parent atom. Atomic coordinates for the non-hydrogen atoms and their equivalent isotropic displacement parameters are given in Table 3.

ACKNOWLEDGMENTS

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[1]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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