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2-Ethylthio-5-methyl-6,7,8,9,10,11,12,13,14,15-decahydrocyclododeca[*b*]indole: an Unexpected Product from the Demethylation of an Indole Using Fujita's Reagent

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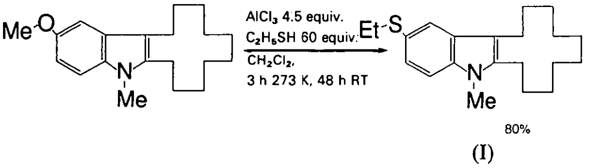
Abstract

Crystal structure analysis of the title compound, $C_{21}H_{31}NS$, showed that demethylation resulted in a thioalkyl group at the 2 position rather than the loss of the methyl group at the 5 position. The structural and conformational features of the molecule are discussed and compared with the results of molecular-mechanics calculations.

Comment

The crystal structure analysis of the title compound, (I), was considered in connection with the problem of demethylation of 5-methoxyindoles and was undertaken as part of a general research program on the synthesis of heterocycles.



(I)

The reagents BX_3 (Niwa, Hida & Yamada, 1981; Simon, Hosztafi, Makleit & Berenyi, 1991) and AlX_3 (Bhatt & Kulkarny, 1993; Akiyama, Hirofuji & Ozaki, 1992; von Asero, Colo, Erspamer & Vercellone, 1952) are used routinely to perform demethylation reactions on indoles, but in this case gave disappointing results. We therefore performed Fujita's demethylation reaction with AlX_3–*R*SH (Node, Nishide, Fuji & Fujita, 1980; Node, Nishide, Sai, Ichikawa, Fuji & Fujita, 1979) which gave the expected reaction. However, when substrates were reacted with a large excess of Fujita's reagent for a long reaction time, the completely unexpected reaction depicted in the scheme above was observed. The mechanism of such a reaction is unknown and the position of the thioalkyl group on the aromatic ring had to be determined by X-ray diffraction analysis as conventional spectroscopic methods were unable to give an unambiguous solution.

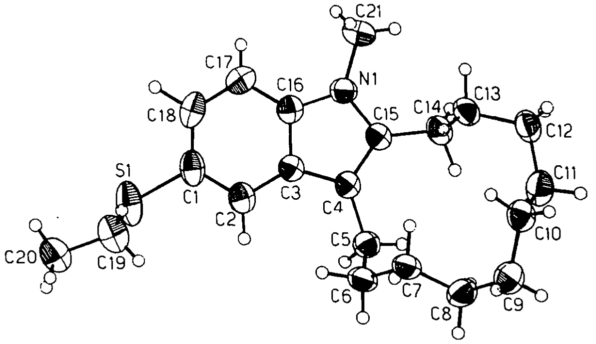


Fig. 1. *ORTEP* (Johnson, 1965) drawing of the title molecule with ellipsoids drawn at the 50% probability level.

The *ORTEP* (Johnson, 1965) projection (Fig. 1) shows that the structure is built of a cyclododecene ring fused to the 2,3-side of an *N*-methylindole nucleus which has an ethylthio substituent at the 5 position. In Table 2, selected bond distances and angles are compared with those calculated for the isolated molecule by *MMX* (*PCMODEL*; Serena Software, 1989) and *MM+* (*HYPERCHEM*; Autodesk, 1992) force fields. In both cases, the optimization process was started from the observed crystal geometry using the default input parameters. The most important differences between the observed and calculated values are for the ethylthio group:

(1) The S—C(alkyl) distance obtained experimentally [1.767 (6) Å] is marginally shorter than S—C(aromatic) [1.779 (4) Å]; this difference is not consistent with the calculated values. It may be a consequence of thermal motion since the S atom shows the largest ellipsoid anisotropy ($r_{\max}/r_{\min} = 3.29$ compared with an average value of 1.83 for the other atoms).

(2) The C(aromatic)—S—C(alkyl) bond angle of 104.1 (2)° agrees with the average value [103.2 (19)°] calculated for 44 structures retrieved from the 1993

release of the Cambridge Structural Database (CSD; Allen *et al.*, 1991) but is larger than that calculated by *MMX* (95.8°) and smaller than that calculated by *MM+* (120.5°). A possible explanation for this is that the default parameters used for the theoretical calculations require some improvement.

(3) The C2—C1—S1—C19 torsion angle (which defines the orientation of the ethylthio group with respect to the benzene plane) is 80.1 (4)° for the molecule in the crystal and 90.4° for the isolated molecule calculated by *MMX*, but *MM+* gives a value of only 0.1°. However, analysis of the 44 structures retrieved from the CSD shows that values of this angle range 0–90°, which is consistent with the lack of π conjugation between the alkylthio group and the benzene ring. The energy barriers to rotation about the C(aromatic)—S bond are relatively low (8–14 kJ mol^{-1}) and so they can easily be overcome by packing forces in the crystal.

With regard to the indole nucleus, it appears that there is a systematic tendency for the observed bond distances to be longer than the calculated ones (by 0.025–0.091 Å). The largest difference is observed for C3—C4 but the length found experimentally [1.431 (4) Å] is consistent with the average value [1.434 (11) Å] calculated for indoles in the CSD (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). Better agreement is observed for the bond angles in the indole nucleus, the largest difference being 3.6° for C15—N1—C16. In general, a substantially good agreement is also observed for the torsion angles, except for those involving the N1—C21 bond which show differences of as much as 10° between the values obtained experimentally and those calculated for the molecule optimized by the *MM+* force field. This is a consequence of the fact that this treatment gives a pyramidal N atom with the methyl C atom (C21) 0.282 Å outside the plane of the pyrrole moiety; this displacement is 0.081 (6) Å for the experimental structure and 0.012 Å for that calculated by the *MMX* force field.

The fusion with the indole imposes a *cis* configuration at the double bond joining the cyclododecene ring to that nucleus. Fig. 2 gives the relevant conformational parameters of this ring. The presence of the double bond causes a small reduction of the total ring-puckering amplitude (Cremer & Pople, 1975) to Q_T = 1.500 (4) Å (Q_T = 1.550 Å for an isolated cyclododecane ring). The values of the displacement asymmetry parameters (Nardelli, 1983*a*) show that there are two local pseudo-twofold axes running along C9···C15 and C6···C12. This conformation is maintained essentially in the calculated molecules; differences in the torsion-angle values range from 0.1 to 8.8 with an average of 4.0°. It is interesting that the structural and conformational parameters (*b*) (see below) for the only *cis*-cyclododecene ring determined structurally whose atomic coordinates were available from the CSD [15-phenylbicyclo[10.3.0]pentadec-1(12)-en-13-one (Xiao-Lan, Jie-You, Zhong, Shi-Xiong & Ru-Ji, 1990)] are remarkably close to those (*a*) found by the present analysis, indicating that the observed conformation is particularly suitable for crystal packing:

	(*a*)	(*b*)
q_2 (Å)	0.425 (4)	0.398 (2)
q_3 (Å)	0.288 (3)	0.295 (2)
q_4 (Å)	1.394 (4)	1.413 (3)
q_5 (Å)	0.183 (4)	0.189 (3)
q_6 (Å)	0.100 (4)	0.092 (3)
Q_T (Å)	1.500 (4)	1.512 (3)
φ_2 (°)	−38.4 (5)	−24.3 (4)
φ_3 (°)	−29.7 (8)	−30.4 (5)
φ_4 (°)	−142.8 (2)	−141.6 (1)
φ_5 (°)	−37.3 (12)	−37.7 (8)
θ_2 (°)	55.9 (1)	53.4 (3)
θ_3 (°)	11.7 (4)	11.8 (1)
θ_4 (°)	82.5 (4)	82.4 (1)
θ_5 (°)	61.4 (11)	64.0 (7)
Δ_2(C6)	0.0723 (7)	0.0812 (5)
Δ_2(C9)	0.0639 (6)	0.0784 (5)

The analysis of 'thermal' motion, carried out in terms of the Schomaker & Trueblood (1968) **TLS** rigid-body approximation using the *THMV* program (Trueblood, 1984), gave an overall residual error index R_{wU} of 0.112. Only a small improvement (R_{wU} = 0.101) is obtained if the internal motions of the ethylthio and methyl groups are considered according to Dunitz & White (1973).

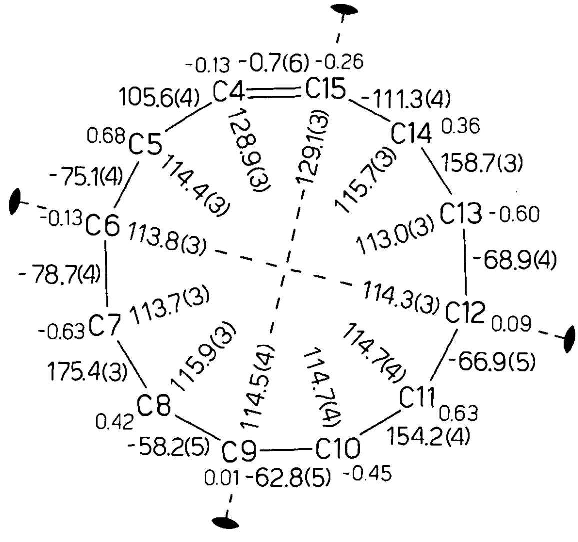


Fig. 2. Bond angles (°), torsion angles (°) and displacements (Å) of the atoms from the mean plane through the cyclododecene ring.

Experimental

Crystal data

$C_{21}H_{31}NS$
M_r = 329.54

Cu $K\alpha$ radiation
λ = 1.5418 Å

Monoclinic
$P2_1$
$a = 13.183$ (5) Å
$b = 7.831$ (2) Å
$c = 9.213$ (4) Å
$\beta = 95.11$ (2)°
$V = 947.3$ (6) Å^3
$Z = 2$
$D_x = 1.155$ Mg m^{-3}

Cell parameters from 29 reflections
$\theta = 19–39°$
$\mu = 1.452$ mm^{-1}
$T = 293$ (2) K
Small prism
0.48 × 0.34 × 0.29 mm
Colourless

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}
S1	0.15738 (7)	0.1232 (2)	0.5724 (1)	0.0769 (4)
N1	0.4803 (2)	0.5903 (4)	0.8176 (3)	0.0470 (9)
C1	0.2535 (3)	0.2575 (5)	0.6587 (4)	0.0547 (11)
C2	0.3548 (3)	0.2393 (5)	0.6297 (4)	0.0500 (11)
C3	0.4276 (2)	0.3555 (4)	0.6900 (3)	0.0413 (9)
C4	0.5335 (2)	0.3805 (4)	0.6733 (3)	0.0408 (10)
C5	0.5944 (3)	0.2678 (5)	0.5820 (4)	0.0472 (11)
C6	0.6241 (3)	0.0969 (5)	0.6513 (4)	0.0543 (12)
C7	0.7100 (2)	0.1085 (6)	0.7730 (4)	0.0498 (11)
C8	0.8149 (3)	0.1243 (8)	0.7186 (4)	0.0621 (15)
C9	0.9031 (3)	0.1505 (6)	0.8357 (6)	0.0685 (16)
C10	0.8931 (3)	0.3087 (6)	0.9308 (4)	0.0584 (14)
C11	0.8922 (3)	0.4790 (6)	0.8484 (5)	0.0633 (16)
C12	0.8379 (3)	0.6226 (7)	0.9190 (5)	0.0603 (12)
C13	0.7225 (3)	0.5967 (6)	0.9200 (4)	0.0532 (11)
C14	0.6657 (3)	0.6075 (6)	0.7678 (4)	0.0485 (11)
C15	0.5637 (2)	0.5239 (4)	0.7509 (3)	0.0419 (10)
C16	0.3963 (2)	0.4896 (5)	0.7781 (3)	0.0460 (10)
C17	0.2957 (3)	0.5070 (6)	0.8102 (4)	0.0551 (12)
C18	0.2256 (3)	0.3906 (6)	0.7488 (4)	0.0618 (14)
C19	0.1683 (4)	−0.0681 (7)	0.6743 (6)	0.0750 (16)
C20	0.0791 (4)	−0.1836 (9)	0.6374 (8)	0.0896 (24)
C21	0.4773 (4)	0.7468 (7)	0.9015 (7)	0.0703 (18)

Data collection

Siemens AED diffractometer
θ–2θ scans
Absorption correction: none
2047 measured reflections
1943 independent reflections
1394 observed reflections [$I > 2\sigma(I)$]
$R_{int} = 0.0452$

$\theta_{max} = 70.1°$
$h = -16 \rightarrow 16$
$k = -9 \rightarrow 8$
$l = -5 \rightarrow 11$
1 standard reflection monitored every 50 reflections
intensity variation: within statistical fluctuation

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0326$
$wR(F^2) = 0.0716$
$S = 1.013$
1941 reflections
333 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0388P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.033$
$\Delta\rho_{max} = 0.168$ e Å^{-3}
$\Delta\rho_{min} = -0.187$ e Å^{-3}

Extinction correction: $F_c^* = kF_c[1 + (0.001\chi \times F_c^2\lambda^3/\sin2\theta)]^{-1/4}$
Extinction coefficient: 0.0081 (7)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

The integrated intensities were obtained by a modified version (Belletti, Ugozzoli, Cantoni & Pasquinelli, 1979) of the Lehmann & Larsen (1974) peak-profile analysis procedure. All reflections were corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by anisotropic full-matrix least squares on F using *SHELX*76 and on F^2 using *SHELXL*93. The conventional residual error indices for the F refinement were $R = 0.0372$ and $wR = 0.0525$

Table 2. *Comparison of selected bond distances* (Å), *bond angles* (°) *and torsion angles* (°)

Δ represents the difference between the observed and calculated values.

	X-ray data	*PCMODEL-MMX*		*HYPERCHEM-MM+*	
		calc.	Δ	calc.	Δ
S1—C1	1.779 (4)	1.773	0.006	1.727	0.052
S1—C19	1.767 (6)	1.824	−0.057	1.822	−0.055
N1—C15	1.406 (4)	1.376	0.030	1.356	0.050
N1—C16	1.381 (4)	1.367	0.014	1.346	0.035
N1—C21	1.452 (6)	1.455	−0.003	1.444	0.008
C3—C4	1.431 (4)	1.345	0.086	1.340	0.091
C3—C16	1.411 (5)	1.341	0.070	1.388	0.023
C4—C15	1.372 (4)	1.347	0.025	1.350	0.022
C1—S1—C19	104.1 (2)	95.8	8.3	120.5	−16.4
C16—N1—C21	124.3 (3)	125.7	−1.4	126.0	−1.7
C15—N1—C21	127.1 (3)	128.5	−1.4	128.5	−1.4
C15—N1—C16	108.3 (2)	105.7	2.6	104.7	3.6
C4—C3—C16	107.4 (3)	109.6	−2.2	107.0	0.4
C3—C4—C15	107.2 (3)	106.9	0.3	106.9	0.3
C3—C4—C5	123.8 (3)	125.1	−1.3	124.1	−0.3
N1—C15—C14	121.7 (3)	120.7	1.0	122.5	−0.8
N1—C15—C4	109.2 (3)	109.4	−0.2	111.5	−2.3
N1—C16—C3	107.9 (3)	108.3	−0.4	109.8	−1.9
C1—S1—C19—C20	167.9 (4)	174.0	−6.1	179.6	−11.7
C19—S1—C1—C18	−104.4 (4)	−90.4	−14.0	−179.5	75.1
C19—S1—C1—C2	80.1 (4)	90.4	−10.3	0.1	80.0
C21—N1—C16—C3	176.3 (3)	−178.9	−4.8	166.9	9.4
C21—N1—C15—C4	−175.6 (4)	179.2	5.2	−166.0	−9.6
C21—N1—C15—C14	3.8 (5)	−1.6	5.4	14.1	−10.3
C21—N1—C16—C17	−2.4 (6)	1.6	−4.0	−12.7	10.3

for 1394 observed [$I > 2\sigma(I)$] reflections and 331 refined parameters. All the structural parameters quoted in Table 2 and discussed in the *Comment* are from the F^2 refinement. The atomic coordinates of Table 1 correspond to the absolute structure assumed on the basis of the Flack (1983) index, $x = 0.04\,(3)$. Comparison of the results of the two refinements by means of half-normal probability plots (Abrahams & Keve, 1971) gave the following regression parameters:

	i	s	r	N	$(\Delta/\sigma)_{\max}$
d	0.019 (6)	0.680 (6)	0.996	125	1.92
U_{ij}	0.016 (5)	0.704 (5)	0.996	138	2.13
xyz	−0.119 (14)	0.909 (14)	0.992	69	2.47

where d represents all interatomic distances <4.65 Å, U_{ij} the atomic displacement parameters, xyz the positional coordinates and i is the intercept, s the slope, r the correlation coefficient and N the number of points in the plot defining the regression line. The values of i and s indicate that there are no relevant systematic errors and that the e.s.d.'s are overestimated by a factor of 1.4 for the d's and U_{ij}'s and by a factor of 1.1 for the coordinates.

Calculations were performed using the ENCORE91 and GOULD-POWERNODE 6040 computers of the Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma).

Cell refinement: *LQPARM* (Nardelli & Mangia, 1984). Program used to solve the structure: *SHELXS*86 (Sheldrick, 1985). Programs used to refine the structure: *SHELX*76 (Sheldrick, 1976) and *SHELXL*93 (Sheldrick, 1994). Molecular graphics: *ORTEP* (Johnson, 1965). Software used for geometric calculations: *PARST* (Nardelli, 1983*b*). Software used to prepare material for publication: *PARSTCIF* (Nardelli, 1991).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: LI1099). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1,2-Dihydro-8-methyl-4(3*H*)-carbazolone Prepared by a New Arynic Cyclization Reaction

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Abstract

Of the two possible keto–enol tautomeric species of the title compound, $C_{13}H_{13}NO$, it is the keto one that is found in the crystal; it involves an intermolecular N—H···O=C hydrogen bond between molecules, related