

Acta Cryst. (1993). C49, 2177–2179

Annellated Carbazoles as Nucleic Acid Binding Drugs: Structure of [6-Ethyl-6,11-dihydro-5-(4-phenoxybutyl)-5*H*-6,11-*o*-benzenobenzo[*b*]carbazole

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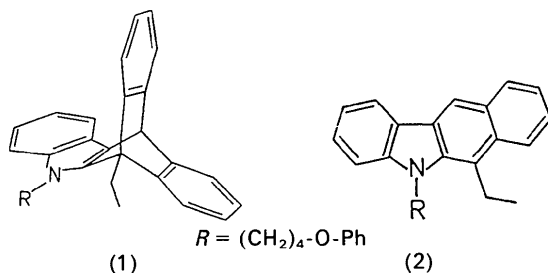
(Received 22 January 1993; accepted 9 June 1993)

Abstract

The title compound, C₃₄H₃₁NO, which has not been characterized before by any other analytical method, was provided from a double Diels–Alder reaction. The resulting structure shows the typical barrelene geometry.

Comment

Benzo- and pyrido-annellated carbazoles, among them the ellipticine group, are interesting lead structures for the development of antitumour-active drugs (Gribble, 1990; Pindur, 1987; Kansal & Poitier, 1986; Poitier, 1992). The principle of the action is intercalation in human B-DNA or an alternative interaction, e.g. groove binding with this biopolymer. Thus, these compounds lead to inhibition of DNA enzymes, such as topoisomerase II (Gribble, 1990). In this context, we have synthesized a variety of annellated carbazole derivatives (Pindur, 1993; Pindur, Haber & Erfanian-Abdoust, 1992; Pindur, Pfeuffer, Eitel, Rogge & Haber 1991). From these investigations the Diels–Alder reaction of 1-ethylpyrano[3,4-*b*]indole-3-one with aryne in tetrahydrofuran as solvent gave rise to the new *N*-substituted carbazoles (1) and (2) (Pindur, Haber & Erfanian-Abdoust, 1992).



The results of the X-ray analyses of the title compound (1) and compound (2) gave valuable detailed geometric information for our current molecular modelling studies about B-DNA–carbazole interactions (Pindur, Haber & Erfanian-Abdoust, 1992; Dräger, Haber, Erfanian-Abdoust, Pindur & Sattler, 1993; Pindur, Pfeuffer, Eitel, Rogge & Haber 1991; Pindur, Haber & Sattler, 1992) which will be used to design antitumour-active drugs.

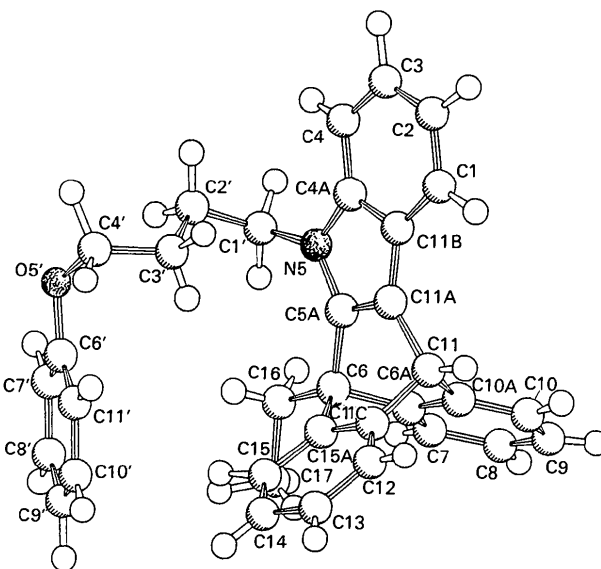


Fig. 1. SCHAKAL (Keller, 1986) plot of (1)

Experimental

Crystal data

C₃₄H₃₁NO
M_r = 469.3
 Monoclinic
C2/c
a = 28.0154 (6) Å
b = 9.8541 (2) Å
c = 21.8502 (3) Å
 β = 123.375 (1)°
V = 5037.4 (2) Å³
Z = 8
D_x = 1.24 Mg m⁻³
D_m = 1.23 Mg m⁻³
 Density measured by flotation in an aq. polytungstate solution

Cu *K*α radiation
 λ = 1.5418 Å
 Cell parameters from 75 reflections
 θ = 66–70°
 μ = 0.49 mm⁻¹
T = 298 K
 Rectangular
 0.8 × 0.3 × 0.2 mm
 Reddish
 Crystal source: slow diffusion of *n*-hexane into a solution of (1) in ethyl acetate

Data collection

CAD-4 diffractometer
 $\omega/2\theta$ scans
 Absorption correction: none

θ_{\max} = 70°
h = 0 → 35
k = -13 → 0
l = -27 → 27

5174 measured reflections
 4525 independent reflections
 4143 observed reflections
 $[F/\sigma(F) > 3.92]$
 $R_{\text{int}} = 0.014$

3 standard reflections
 frequency: 66.67 min
 intensity variation: 5%
 drop off

Refinement

Refinement on F

$R = 0.042$

$wR = 0.042$

4143 reflections

336 parameters

Only H-atom U 's refined

Unit weights applied

$(\Delta/\sigma)_{\text{max}} = 0.001$

$\Delta\rho_{\text{max}} = 0.205 \text{ e } \text{\AA}^{-3}$

$\Delta\rho_{\text{min}} = -0.204 \text{ e } \text{\AA}^{-3}$

Extinction correction: none

Atomic scattering factors from *SHELX76* (Sheldrick, 1976)

C5A—C6	1.541 (2)	C16—C17	1.553 (3)
C5A—C11A	1.360 (3)	C1'—C2'	1.524 (3)
C6—C6A	1.557 (3)	C2'—C3'	1.524 (3)
C6—C15A	1.552 (2)	C3'—C4'	1.514 (4)
C6—C16	1.535 (3)	C4'—O5'	1.443 (3)
C6A—C7	1.381 (2)	O5'—C6'	1.376 (2)
C6A—C10A	1.403 (3)	C6'—C7'	1.386 (3)
C7—C8	1.395 (3)	C6'—C11'	1.377 (3)
C8—C9	1.378 (4)	C7'—C8'	1.382 (4)
C9—C10	1.388 (3)	C8'—C9'	1.383 (4)
C10—C10A	1.381 (3)	C9'—C10'	1.365 (4)
C10A—C11	1.528 (2)	C10'—C11'	1.391 (3)
C11B—C1—C2	118.5 (2)	C11B—C11A—C11	136.3 (2)
C3—C2—C1	121.4 (2)	C11A—C11B—C1	135.4 (2)
C4—C3—C2	121.5 (2)	C11A—C11B—C4A	105.4 (2)
C4A—C4—C3	117.5 (2)	C15A—C11C—C11	113.6 (2)
C11B—C4A—C4	122.3 (2)	C15A—C11C—C12	120.6 (2)
C11B—C4A—N5	109.2 (2)	C13—C12—C11C	119.6 (2)
C1'—N5—C4A	123.1 (2)	C14—C13—C12	120.0 (2)
C1'—N5—C5A	129.9 (1)	C15—C14—C13	120.8 (2)
C11A—C5A—N5	110.1 (2)	C15A—C15—C14	119.6 (2)
C11A—C5A—C6	115.5 (2)	C15—C15A—C6	125.9 (2)
C16—C6—C5A	118.0 (1)	C15—C15A—C11C	119.3 (2)
C16—C6—C6A	113.8 (2)	C17—C16—C6	115.2 (2)
C16—C6—C15A	113.9 (2)	C2'—C1'—N5	113.7 (2)
C10A—C6A—C6	114.4 (2)	C3'—C2'—C1'	114.9 (2)
C10A—C6A—C7	119.3 (2)	C4'—C3'—C2'	112.6 (2)
C8—C7—C6A	119.7 (2)	O5'—C4'—C3'	110.4 (2)
C9—C8—C7	120.6 (2)	C6'—O5'—C4'	118.3 (2)
C10—C9—C8	120.0 (2)	C11'—C6'—O5'	124.2 (2)
C10A—C10—C9	119.5 (2)	C11'—C6'—C7'	120.3 (2)
C11—C10A—C6A	113.7 (2)	C8'—C7'—C6'	119.5 (2)
C11—C10A—C10	125.6 (2)	C9'—C8'—C7'	120.6 (2)
C11C—C11—C10A	104.5 (1)	C10'—C9'—C8'	119.2 (2)
C11C—C11—C11A	106.0 (1)	C11'—C10'—C9'	121.2 (2)
C11B—C11A—C5A	108.4 (2)	C10'—C11'—C6'	119.2 (2)
C11B—C4A—N5—C1'	176.6 (2)		
C4A—N5—C1'—C2'	-72.7 (2)		
N5—C1'—C2'—C3'	-41.8 (2)		
C1'—C2'—C3'—C4'	-157.6 (2)		
C2'—C3'—C4'—O5'	65.6 (2)		
C3'—C4'—O5'—C6'	70.7 (2)		
C4'—O5'—C6'—C7'	-155.1 (2)		
C6A—C6—C16—C17	60.6 (2)		
C5A—C6—C15A—C11C	-55.2 (2)		
C6A—C6—C15A—C15	-128.4 (2)		
C10A—C11—C11C—C12	121.2 (2)		
C10—C10A—C11—C11A	124.5 (2)		
C5A—C6—C6A—C7	-122.6 (2)		
C11—C11C—C15A—C6	3.6 (2)		
C11C—C11—C11A—C11B	134.6 (2)		
C15A—C6—C16—C17	-59.3 (2)		

Table 1. Fractional atomic coordinates and equivalent isotropic thermal parameters (\AA^2)

$$U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	U_{eq}
C1	0.28412 (8)	0.0620 (2)	0.6136 (1)	0.0478 (10)
C2	0.34312 (9)	0.0743 (2)	0.6548 (1)	0.057 (1)
C3	0.37228 (8)	0.1394 (2)	0.7230 (1)	0.055 (1)
C4	0.34373 (7)	0.1915 (2)	0.7527 (1)	0.0469 (9)
C4A	0.28420 (7)	0.1795 (2)	0.71143 (9)	0.0379 (8)
N5	0.24573 (6)	0.2272 (2)	0.72754 (7)	0.0363 (6)
C5A	0.19149 (7)	0.1930 (2)	0.66875 (9)	0.0350 (7)
C6	0.13046 (7)	0.2273 (2)	0.64725 (9)	0.0350 (7)
C6A	0.10635 (7)	0.3063 (2)	0.57423 (9)	0.0354 (7)
C7	0.08467 (7)	0.4366 (2)	0.5596 (1)	0.0417 (8)
C8	0.06456 (8)	0.4945 (2)	0.4912 (1)	0.0497 (10)
C9	0.06670 (8)	0.4234 (2)	0.4385 (1)	0.0495 (9)
C10	0.08993 (7)	0.2938 (2)	0.45350 (9)	0.0427 (8)
C10A	0.10982 (7)	0.2360 (2)	0.52100 (9)	0.0362 (7)
C11	0.13815 (7)	0.0967 (2)	0.54642 (9)	0.0369 (8)
C11A	0.19509 (7)	0.1259 (2)	0.61701 (9)	0.0358 (7)
C11B	0.25372 (7)	0.1155 (2)	0.64192 (9)	0.0367 (8)
C11C	0.10242 (7)	0.0217 (2)	0.56862 (9)	0.0363 (7)
C12	0.07383 (7)	-0.0996 (2)	0.5392 (1)	0.0433 (8)
C13	0.04286 (8)	-0.1572 (2)	0.5651 (1)	0.0493 (9)
C14	0.04213 (8)	-0.0957 (2)	0.6211 (1)	0.0490 (9)
C15	0.07088 (7)	0.0265 (2)	0.6511 (1)	0.0425 (8)
C15A	0.09985 (7)	0.0876 (2)	0.62351 (9)	0.0360 (7)
C16	0.12349 (7)	0.3023 (2)	0.70343 (9)	0.0417 (8)
C17	0.06081 (8)	0.3337 (2)	0.6779 (1)	0.053 (1)
C1'	0.26348 (8)	0.2924 (2)	0.79724 (9)	0.0434 (8)
C2'	0.28851 (8)	0.1940 (2)	0.8616 (1)	0.0504 (9)
C3'	0.25693 (8)	0.0593 (2)	0.8449 (1)	0.0479 (9)
C4'	0.26767 (9)	-0.0097 (2)	0.9132 (1)	0.055 (1)
O5'	0.24340 (6)	0.0697 (2)	0.94546 (7)	0.0551 (7)
C6'	0.18487 (8)	0.0760 (2)	0.9095 (1)	0.0462 (9)
C7'	0.1638 (1)	0.1899 (2)	0.9242 (1)	0.062 (1)
C8'	0.1056 (1)	0.2023 (3)	0.8928 (2)	0.076 (2)
C9'	0.0684 (1)	0.1028 (3)	0.8464 (1)	0.074 (1)
C10'	0.0897 (1)	-0.0083 (3)	0.8320 (1)	0.067 (1)
C11'	0.14812 (9)	-0.0235 (2)	0.8633 (1)	0.057 (1)

Table 2. Geometric parameters (\AA , $^\circ$)

C1—C2	1.386 (3)	C11—C11A	1.516 (3)
C1—C11B	1.402 (3)	C11—C11C	1.523 (3)
C2—C3	1.399 (4)	C11A—C11B	1.422 (2)
C3—C4	1.377 (3)	C11C—C12	1.384 (3)
C4—C4A	1.398 (2)	C11C—C15A	1.400 (3)
C4A—N5	1.387 (3)	C12—C13	1.392 (3)
C4A—C11B	1.417 (3)	C13—C14	1.375 (4)
N5—C5A	1.388 (2)	C14—C15	1.396 (3)
N5—C1'	1.465 (3)	C15—C15A	1.387 (3)

The data were corrected for Lorentz and polarization effects. The direct methods option from *SHELXS86* (Sheldrick, 1985) provided the locations of all non-H atoms. The structure was refined by full-matrix least squares (*SHELX76*; Sheldrick, 1976), including positional and anisotropic displacement parameters for non-H atoms. The H atoms were located in a difference Fourier map and refined with grouped isotropic displacement parameters.

We wish to thank the Deutsche Forschungsgemeinschaft, Bonn, for financial support.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71386 (38 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: SH1050]

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Acta Cryst. (1993). **C49**, 2179–2181

Structure of 1,3,9-Trimethylalloxazine

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(Received 15 February 1993; accepted 9 June 1993)

Abstract

The structure of 1,3,9-trimethylbenzo[*g*]pteridine-2,4(1*H*,3*H*)-dione (1,3,9-MALL) was solved by direct methods. The molecule is flat and the 14 atoms in the three rings are coplanar to within 0.052 (2) Å; the methyl C atoms deviate at most 0.11 (3) Å from the plane. The crystal packing of 1,3,9-MALL can be described as a 'herringbone' type.

Comment

The title compound was synthesized (Kozioł, Koziołowa, Konarski, Panek-Janc & Dawidowski, 1980) as part of a continuing study of a series of

9-methylalloxazines (9-MALL). Alloxazines are photolysis products of flavin (Ohkawa, Ohishi & Yagi, 1983) and can replace flavin in the bacterial bioluminescence reaction (Matheson, Lee & Müller, 1981). These compounds, when unsubstituted at N(1), show double fluorescence resulting from excited-state concerted double-proton transfer in the presence of compounds having proton donor and/or acceptor properties. Such substances are, for example, water, carboxylic and phosphoric acids, pyridine and other bases (Koziołowa, 1979; Szafran, Kozioł & Heelis, 1990). The aim of the crystal structure determination of 1,3,9-MALL was to provide more information on 9-methyl-substituted alloxazines and a comparison with earlier studies (Csöreg, Kierkegaard, Kozioł & Müller, 1987).

A perspective drawing of the molecule is shown in Fig. 1 (Motherwell & Clegg, 1978). Distances, bond angles, selected torsion angles (Klyne & Prelog, 1960; Stanford & Waser, 1972) and deviations from 120° for selected endocyclic angles are listed in Tables 2 and 3. The conformational features were computed using the program *PARST* (Nardelli, 1983). Fig. 2 is a stereoscopic packing illustration.

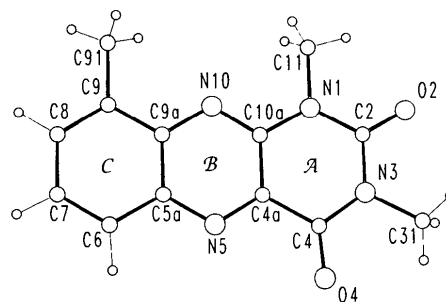


Fig. 1. A *PLUTO* (Motherwell & Clegg, 1978) illustration of 1,3,9-methylalloxazine showing the crystallographic atom numbering scheme. H atoms are unlabeled and the tricyclic rings are assigned labels *A*, *B* and *C*.

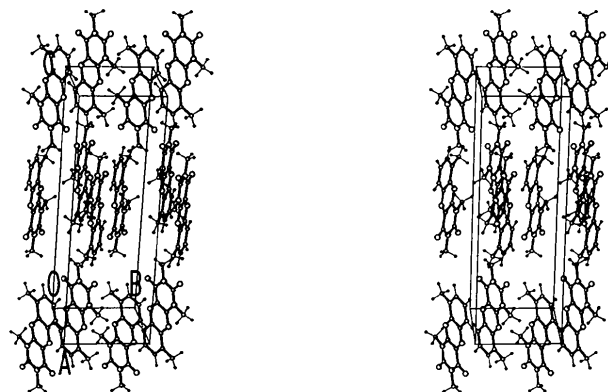


Fig. 2. A stereoscopic packing illustration viewed along the crystallographic *a* axis.