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An Intercalating Isoxazole

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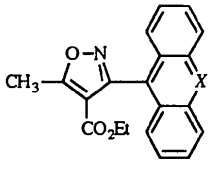
Abstract

The title compound, ethyl 3-(9-anthryl)-5-methyl-4-isoxazolecarboxylate, $C_{21}H_{17}NO_3$, possesses two planar ring systems that lie at 80° from coplanarity. The bond linking the two ring systems is 1.489 (3) Å, indicating only partial conjugation between the two ring systems. The resulting distortion causes large upfield NMR chemical shifts in the ethyl ester which lies directly underneath the anthracene ring.

Comment

Our work on the preparation of DNA-intercalating lexitropsins has recently included exploring the ability of an intercalator-tether lexitropsin to adopt a conformation conducive to both intercalation and minor-groove binding events (Mosher & Natale, 1995*a*,*b*). We have designed an acridinylisoxazolyl-polyamidopyrrole to meet the needs of both DNA-intercalation and minor-groove binding. The role of the tethering isoxazole in our model is to serve not only as a linkage between the major biologically active portions of the molecule, but also to position the intercalator and minor-groove binder at angles conducive to optimum DNA interactions.

The minor-groove binding lexitropsins (polyamidopyrroles) can be prepared by existing methodology (Bialer, Yagen & Mechoulam, 1978; Turchin, Grokhovskii, Zhuze & Gottikh, 1978; Nishiwaki *et al.*, 1990). These compounds could be linked to isoxazole tethers *via* existing methodology (Niou & Natale, 1986). The present work has centered on the construction of an isoxazole tether containing an intercalating molecule. Recently, the isolation of the title compound ethyl 3-(9-anthryl)-5-methyl-4-isoxazolecarboxylate, (1), and also ethyl 3-(9-acridinyl)-5-methyl-4-isoxazolecarboxylate, (2), was accomplished (Mosher & Natale, 1995*a*). Recent examination of the dihedral angle between the isoxazole and intercalator rings in these structures following X-ray crystallographic analysis of the title compound, (1), sheds light on the proposed ability of these molecules to interact with DNA.



(1) X = CH
(2) X = N

Fig. 1 shows the displacement ellipsoids with the atomic numbering scheme for (1). Analysis of this data indicates that the anthracene ring in (1) is slightly distorted from planarity. The r.m.s. deviation from the best plane is 0.038 Å.

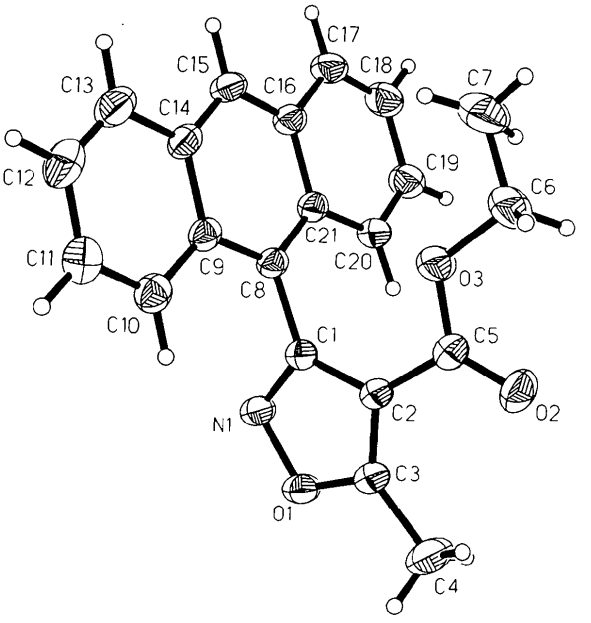


Fig. 1. View of $C_{21}H_{17}NO_3$ showing the labeling of the non-H atoms. Displacement ellipsoids are drawn at the 30% probability level; H atoms are shown as small circles of arbitrary radius.

Bond lengths, angles and torsion angles not reported in Table 2 are within expected values. The anthracene aromatic C—C bond lengths range from 1.341 (4) to 1.439 (3) Å. C—H bond lengths range from 0.84 (5) (C7—H7*C*) to 1.20 (4) Å (C7—H7*A*).

Steric effects associated with the two adjacent ring systems are apparently similar to those observed in other systems. For instance, the C1—C1′ bond length in biphenyl is 1.49 Å. However, the torsion angle between the two ring systems in (1) [80.2 (5)°; see Table 2] is significantly larger than that of biphenyl (~45°). The perpendicular nature of the two rings in (1) compares favorably with that seen in the O-*exo* conformation of 4-(dihydropyridin-4′-yl)-5-methyl-3-phenylisoxazole (83.5°; McKenna *et al.*, 1988), but not with the torsion angle observed in secondary carboxylates or carboxamides of 3-phenyl-4-substituted isoxazoles whose values range from 31.2 to 34.9° (Smith, Mirzaei, Natale, Scott & Willett, 1991; Verner, Oliver, Schlicksupp &

Natale, 1990; Schauer, Anderson, Natale & Quincy, 1986).

Evidence that the solution-state structure is similar to the crystal form observed can be found in the NMR spectra of (1) and the acridine derivative (2). Strong upfield chemical shifts were observed for the ethyl esters of both molecules (in anthracene: $COOCH_2CH_3$, δ 3.68; $COOCH_2CH_3$, δ 0.29), most likely the result of magnetic anisotropy from the neighboring tricylic aromatic ring system. The crystal structure indicates that the ester adopts a conformation such that the ethyl group is directly under the anthracene ring. The corresponding torsion angle (C1—C2—C5—O3) is 2.4 (3)°, in direct contrast to the carboxylates and carboxamides previously mentioned (values of the torsion angle in those molecules range from 47.2 to 53.7°). This indicates the carboxylate of (1) is in conjugation with the isoxazole and thus directs the ethyl group under the anthracene ring (resulting in the upfield shifts in the NMR).

The structure of the anthracenylisoxazole elucidated above (Fig. 1) indicates that the molecule may in fact be able to attain both intercalation events and minor-groove binding events at the same time. Replacement of the ester with the amine of a polyamidopyrrole should direct the lexitropsin down and underneath the intercalating ring system, and along the backbone of DNA. Application of the information obtained for (1) to the acridinylisoxazole (2) is satisfied by similar upfield chemical shifts in the NMR, and will be used to prepare the desired acridinylisoxazolyl-polyamidopyrroles.

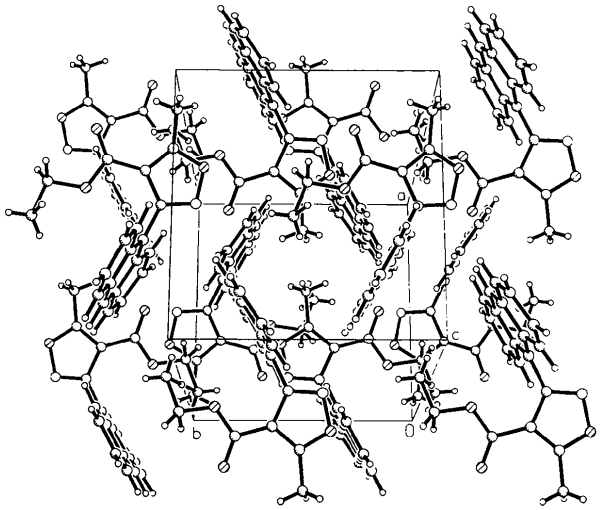


Fig 2. Packing diagram showing the lack of coplanarity between the two ring systems.

Experimental

The title compound (1) was prepared by nitrile oxide cycloaddition of the 9-anthryl nitrile oxide with the pyrrolidine enamine of ethyl acetoacetate. The product was obtained by extractive isolation and column chromatography (silica, 9:1 hexane:ethyl acetate). Recrystallization from hexane/acetone gave colorless crystals that emitted a blue–green fluorescence. ^{1}H NMR (Bruker AC-200 FT) ($CDCl_3$): δ 8.55 (*s*, 1 H, anthracene), 8.02 (*dd*, *J* = 2.2, 6.4 Hz, 2 H, anthracene), 7.64 (*dd*, *J* = 2.2, 6.4 Hz, 2 H, anthracene), 7.40 (*m*, 4 H, anthracene), 3.68 (*q*, *J* = 7.1 Hz, 2 H, OCH 2 CH 3), 2.89 (*s*, 3 H), 0.29 (*t*, *J* = 7.1 Hz, 3 H, OCH 2 CH 3); ^{13}C NMR ($CDCl_3$): δ 176.5, 161.5, 160.4, 138.1, 131.0, 130.8, 128.6, 128.4, 126.3, 125.4, 125.2, 120.6, 60.0, 13.4, 12.8. Analysis calculated for $C_{21}H_{17}O_3N$: C 76.12, H 5.17, N 4.23; found: C 76.31, H 5.01, N 4.10.

Crystal data

$C_{21}H_{17}NO_3$
M_r = 331.36
Monoclinic
$P2_1/n$
a = 10.27430 (10) Å
b = 9.6211 (2) Å
c = 17.3827 (4) Å
β = 94.9500 (10)°
V = 1711.87 (6) Å^3
Z = 4
D_x = 1.286 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
140 reflections from 60 frames
θ = 2.22–23.28°
μ = 0.086 mm^{-1}
T = 293 (2) K
Prismatic
0.80 × 0.25 × 0.25 mm
Colorless

Data collection

Siemens CCD diffractometer
ω scans (Campana, Shepard & Litchman, 1980)
Absorption correction: ψ scans refinement (raw data from reflection frames were used as the ψ-data file)
T_{min} = 0.713, T_{max} = 0.912
6529 measured reflections
2454 independent reflections
2314 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.038
θ_{max} = 23.28°
$h = -11 \rightarrow 11$
$k = -10 \rightarrow 6$
$l = -19 \rightarrow 19$
50 frames of standard reflections at beginning and end of data collection intensity decay: <2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.111
S = 1.20
2454 reflections
295 parameters
H atoms refined isotropically
$w = 1/[\sigma^2(F_o^2) + (0.0346P)^2 + 0.6031P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.003$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993*a*)
Extinction coefficient: 0.0174 (16)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

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}
O1	0.22814 (13)	0.5969 (2)	0.31699 (9)	0.0604 (4)
O2	0.34404 (14)	0.1845 (2)	0.37676 (10)	0.0719 (5)
O3	0.13194 (14)	0.14641 (15)	0.34434 (10)	0.0651 (5)
N1	0.0936 (2)	0.5666 (2)	0.29924 (10)	0.0544 (5)

C1	0.0829 (2)	0.4325 (2)	0.30851 (11)	0.0428 (5)
C2	0.2063 (2)	0.3707 (2)	0.33265 (11)	0.0445 (5)
C3	0.2916 (2)	0.4784 (2)	0.33683 (12)	0.0526 (5)
C4	0.4344 (3)	0.4912 (4)	0.3584 (3)	0.0853 (10)
C5	0.2378 (2)	0.2258 (2)	0.35330 (12)	0.0500 (5)
C6	0.1431 (3)	0.0036 (3)	0.3708 (2)	0.0839 (9)
C7	0.0101 (5)	−0.0499 (5)	0.3702 (5)	0.152 (3)
C8	−0.0474 (2)	0.3649 (2)	0.29457 (11)	0.0435 (5)
C9	−0.0960 (2)	0.3308 (2)	0.21868 (12)	0.0468 (5)
C10	−0.0335 (2)	0.3707 (2)	0.15184 (13)	0.0566 (6)
C11	−0.0842 (3)	0.3325 (3)	0.08003 (15)	0.0679 (7)
C12	−0.1978 (3)	0.2492 (3)	0.0703 (2)	0.0750 (8)
C13	−0.2604 (3)	0.2103 (3)	0.1314 (2)	0.0693 (7)
C14	−0.2149 (2)	0.2515 (2)	0.20774 (13)	0.0537 (6)
C15	−0.2826 (2)	0.2179 (2)	0.27087 (14)	0.0586 (6)
C16	−0.2382 (2)	0.2572 (2)	0.34538 (13)	0.0510 (5)
C17	−0.3089 (2)	0.2259 (3)	0.4109 (2)	0.0638 (7)
C18	−0.2626 (2)	0.2627 (3)	0.4829 (2)	0.0683 (7)
C19	−0.1416 (2)	0.3325 (3)	0.49531 (15)	0.0632 (6)
C20	−0.0712 (2)	0.3641 (2)	0.43541 (12)	0.0527 (5)
C21	−0.1166 (2)	0.3299 (2)	0.35788 (12)	0.0457 (5)

Table 2. *Selected geometric parameters (Å, °)*

O1—N1	1.421 (2)	C1—C8	1.489 (3)
O2—C5	1.199 (2)	C2—C5	1.469 (3)
O3—C5	1.327 (2)	C3—C4	1.487 (3)
O3—C6	1.451 (3)	C6—C7	1.459 (5)
N1—C1	1.306 (3)		
C5—O3—C6	117.8 (2)	O3—C5—C2	110.8 (2)
C2—C1—C8	128.9 (2)	O3—C6—C7	106.5 (3)
C3—C2—C5	125.8 (2)	C21—C8—C1	119.1 (2)
C1—C2—C5	129.6 (2)	C9—C8—C1	119.7 (2)
O2—C5—C2	125.0 (2)		
C6—O3—C5—O2	5.5 (4)	C5—O3—C6—C7	167.7 (4)
C6—O3—C5—C2	−172.9 (2)	N1—C1—C8—C21	−101.2 (2)
C3—C2—C5—O2	0.1 (3)	C2—C1—C8—C21	78.2 (3)
C1—C2—C5—O2	−176.1 (2)	N1—C1—C8—C9	82.1 (2)
C3—C2—C5—O3	178.6 (2)	C2—C1—C8—C9	−98.5 (2)
C1—C2—C5—O3	2.4 (3)		

The raw data file obtained from the reflection frames contains directional cosines and was used as the ψ-data file for the absorption correction. The measured intensities were corrected for Lorentz and polarization effects.

Data collection: *SMART* (Siemens, 1995). Cell refinement: *SMART*. Data reduction: *SAINT* (Siemens, 1995). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993*a*). Molecular graphics: *SHELXTL-Plus* (Sheldrick, 1993*b*). Software used to prepare material for publication: *SHELXTL-Plus*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1222). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Monospiroaryloxyphosphazenes: *p*-Fluorophenoxy Derivatives Containing the 1,2-Phenylenedioxy and 2,3-Naphthalenedioxy Groups

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Abstract

The reactions of p-$FC_6H_4OSiMe_3$ with $N_3P_3F_4X$ [where X is either 1,2-$O_2C_6H_4$ or 2,3-$O_2C_{10}H_6$] provide a convenient route to fully substituted phosphazenes, $N_3P_3(p\text{-}FC_6H_4O)_4X$. The X-ray structures of the monospiro phosphazene derivatives of 1,2-benzenediol [4,4,6,6-tetrakis(4-fluorophenoxy)-2,2-(1,2-phenylenedioxy)-1,3,5,2,4,6-cyclophosphazene, (1), $C_{30}H_{20}F_4N_3O_6P_3$] and 2,3-naphthalenediol [4,4,6,6-tetrakis(4-fluorophenoxy)-2,2-(1,2-naphthalenedioxy)-1,3,5,2,4,6-cyclophosphazene, (2), $C_{34}H_{22}F_4N_3O_6P_3$] contain an almost planar N_3P_3 core which lies perpendicular to the planar five-membered spiro group. The F atoms of the phenoxy groups are involved in the for-