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Structure of a Norbornane-Fused Pentacyclic Isoxazoline*

Pál Sohár† and István Kövesdi
Spectroscopic Department, EGIS Pharmaceuticals, P.O.B. 100, H-1475 Budapest, Hungary

Samuel Frimpong-Manso, Géza Stájer and Gábor Bernáth
Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, P.O.B. 121, H-6701 Szeged, Hungary

The steric structure of a pentacyclic adduct formed as a by-product in a retro-Diels–Alder reaction was elucidated by ^{1}H and ^{13}C NMR spectroscopy, making use of double resonance and differential nuclear Overhauser effect measurements.

KEY WORDS Pentacyclic isoxazoline fused with norbornane–norbornene skeleton Synthesis by double cycloaddition Stereostructure by NMR ^{1}H and ^{13}C NMR spectra DNOE DEPT

INTRODUCTION

A versatile general method was recently developed for the preparation of six-membered heteromonocycles, such as 1,3-oxazin-6-ones,[2] pyrimidinones,[3–5] uracils[6] and thiouracils,[7] which were previously available only via tedious methods or were even impossible to obtain by other routes. The new process involved a retro-Diels–Alder reaction taking place under unexpectedly mild conditions. Five-membered heterocycles had previously been prepared by cycloaddition, by the formation of fused tricyclic adducts from norbornadiene followed by the removal of cyclopentadiene.[8,9] In our methods the heterocycles are synthesized in several steps, starting with cyclopentadiene, through norborneneazetidinone or norbornene-β-amino acids and followed by splitting-off of the cyclopentadiene.

On attempting to prepare 3-phenylisoxazole by heating the norbornene-fused isoxazoline **1**, we observed the formation of another compound in addition to the expected[8] product **2**; this proved to be the pentacyclic isoxazoline **3**. The formation of **3** could be rationalized by the addition of cyclopentadiene to the double bond of the starting material **1**. Similar adducts had not been found in our earlier studies.

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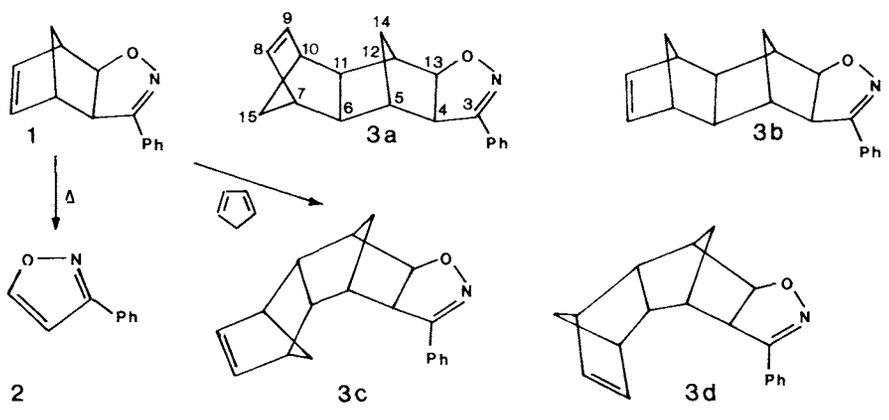
† Author to whom correspondence should be addressed.

STRUCTURE

The carbon numbering used in the text is not identical with the IUPAC nomenclature (see Experimental). The pentacyclic structure is obvious from the spectral data (see Experimental).

The presence of the phenyl-substituted isoxazoline ring follows unambiguously from the ^{1}H NMR signals of the aromatic hydrogens and the ^{13}C NMR absorptions of the phenyl ring. Saturation of the C=N bond can be excluded on the basis of the downfield-shifted signal of this carbon (156.0 ppm) and of the signal of the *o*-aryl hydrogens (the latter also proves the conjugation).

The doublet splitting of the heterocyclic H-4,13 signals shows an unchanged isoxazoline–norbornane di-*exo* annelation in the starting substances and the new



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compounds. We have previously found[10] that the signal of the annelated hydrogens is to a first approximation a doublet for di-*exo*-oxazines, while double doublets are characteristic for the di-*endo* analogues. In both cases the 7–11 Hz splitting is a consequence of the H-4, H-13 coupling, while the second splitting of 4.3 ± 0.3 Hz arises only for the di-*endo* derivatives, due to H-4, H-5 coupling. The corresponding dihedral angles are *ca.* 30° and *ca.* 90° for the di-*endo* and di-*exo* pairs, respectively. No appreciable splitting is therefore observable for di-*exo* compounds, in accordance with the Karplus relationship.[11] This interaction gives rise to a well observable, although small (1.3 Hz), splitting in **3**, which clearly demonstrates that the magnitude of the interaction depends on the size of the heterocycle. The low value of the analogous *J*(H-12, H-13) splitting decreases even further owing to the electron-withdrawing effect of the vicinal heteroatom,[12a] and cannot be observed.

It is not clear whether the empirical relationship between the annelation and the multiplicity is also valid for the alicycles, i.e. whether or not double doublet splitting observed for the H-6 and H-11 signals can be regarded as evidence of a di-*endo* annelation of the norbornene moiety to the norbornane skeleton (see Experimental). Both di-*exo* and di-*endo* annelations must therefore be considered. In addition, two further structures are possible for both annelation types depending on the relative stereoposition of the norbornene moiety, i.e. the mutual *cis* or *trans* position of the bridged 14- and 15-methylene groups. Hence, a decision has to be made between structures **3a–d**.

Compounds **3a** and **b** have the norbornene moiety di-*exo* annelated to the skeleton, while **3c** and **d** are their di-*endo* counterparts. At the same time this skeleton is in a di-*endo* position in **3a** and **d** to the norbornene moiety and di-*exo* in isomers **3b** and **c**. Consequently, a double doublet splitting is expected for **3a** and **3c** due to interactions 6,11 + 6,7/10,11 and 6,11 + 5,6/11,12 (Fig. 1). Hence, the di-*exo*–di-*exo* (**3b**) and di-*endo*–di-*endo* (**3d**) structures are improbable in advance. (A doublet would be expected for the H-6,11 signal of **3b** originating from the *AB*-type interaction of H-6 and H-11, while all four lines of this *AB* spectrum would split to further triplets by *ca.* 4 Hz in **3d**, where the 5,6- and 6,7-, in addition to the 10,11- and 11,12-couplings would result in splittings of this magnitude.)

According to molecular models the di-*endo* structures **3c** and **3d** are sterically unfavourable, and DNOE measurements provided data that definitely excluded these structures. A distinction between **3a** and **3b** was also made on the basis of DNOE measurements, which simultaneously allowed the unambiguous assignment of closely absorbing signal pairs with similar fine structures. Double resonance (DR) experiments were also used for this purpose (Table 1).

The response of the olefinic signals on irradiation of the broadened singlet at 2.92 ppm confirmed the presumed assignment of the latter to H-7,10. This experiment also allowed the assignments of the H-6,11 and the two H-15 signals. The triplet fine structure of the 1.25 and 1.42 ppm doublets, due to the H-7, H-15 and H-10, H-15 couplings, was not present in this DR spectrum, showing that these doublets originate from the 15-methylene hydrogens. Further DR measurements revealed that the overlapping double triplet and double doublet at about 2.15 ppm originate from H-6 or H-11 and one of the H-14 atoms, respectively.

The results of the DNOE experiments are given in Table 2. On saturation of the H-14 doublet at 0.93 ppm, the signal of the aromatic *ortho*-hydrogens becomes slightly stronger, suggesting the *exo* position of the irradiated H-14 atom. This assignment is obvious in

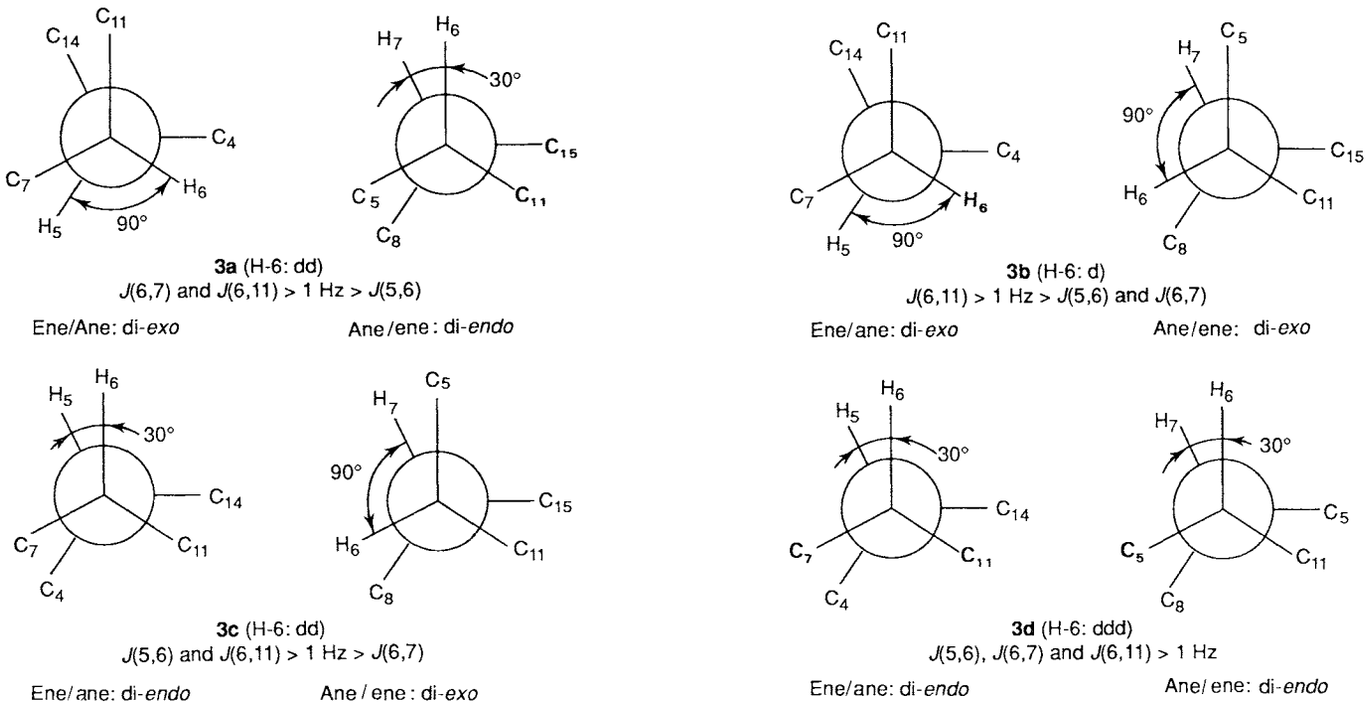

Figure 1. Newman projections around the C-5—C-6 and C-6—C-7 bonds with the dihedral angles H-5—C-5, C-6—H-6 and H-6—C-6, C-7—H-7 in compounds **3a–d**. Ane/ene: position of norbornane to norbornene. Ene/ane: position of norbornene to norbornane.

Table 1. Results of DR experiments on compound 3a

Saturated signal			Changed signal			
Assignment	Chemical shift (ppm)	Multiplicity	Chemical shift (ppm)	Multiplicity Original	Changed	Assignment
H-7,10	2.92	s	5.93	dd	d	H-8,9
			6.02	dd	d	
			1.96	dd	d	H-6,11
			2.18	dd	d	
			1.25	dt	d	H-15
			1.42	dt	d	
H-14 (*exo*)	0.93	d	2.15	dt	~s	H-14 (*endo*)
H-11	1.96	dd	2.18	dd	d	H-6

Table 2. Results of DNOE measurements on compound 3a

		Irradiated signal				
Signals in DNOE[a]		H-14 (*exo*) 0.93	H-15 (*exo*) 1.25	H-13 4.54	H-8[b] 5.93	H-9[b] 6.02
H-4	3.42			+		
H-5	2.38	+			++	+
H-6	2.18		+			
H-7,10	2.92		+		+	+
H-11	1.96		+	+		
H-12	2.47	+		+	+	++
H-14 (*endo*)	2.15	+			+	+
H-15 (*endo*)	1.42		+		+	+
H-*ortho*(Ph)	7.9	+				

[a] Signals with enhanced intensities (DNOE signals) are denoted by +.
[b] The higher intensity enhancement (stronger DNOE signal) for one of the H-5,12 signal pair is denoted by ++.

advance, because of the strong shielding of this signal as a consequence of the anisotropy of the nearby phenyl ring.[12b] The unchanged intensity of the olefinic H-8,9 signals and the response of the H-6,11 signal pair on saturation of the doublet at 1.25 ppm, which is the signal of one of the H-15 atoms, provide evidence of the *exo* position of this irradiated hydrogen. Saturation of the H-13 doublet allows the distinction of the H-5,12 and H-6,11 signal pairs (cf. Table 2).

The strong NOE measured for the *endo* H-14 signal on irradiation of both of the olefinic signals is further convincing evidence of their steric proximity, and hence of structure **3a**. A small intensity enhancement can also be observed for the H-5,12 singlet pair, which have opposite intensity ratios in the two olefinic DNOE spectra, and the firm assignment of the two olefinic signals to H-8 and H-9 is therefore possible on this basis. The assignment of the H-12 signal was proved by its appearance in the DNOE spectrum on irradiation of the H-13 doublet (see Table 2). Hence the higher intensity of the singlet at 2.47 ppm in the DNOE spectrum obtained on saturation of the downfield olefinic signal (and the higher relative intensity of the signal at 2.38 ppm when the upfield olefin hydrogen signal at 5.93 ppm was saturated) revealed the downfield position of the H-9 signal relative to that of H-8. Hence all the ^{1}H NMR signals were assigned unambiguously and the stereostructure was established as **3a**.

EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temperature on a Bruker WM-250 Fourier transform spectrometer controlled by an Aspect 2000 computer at 250.15 Hz (^{1}H) and 62.89 MHz (^{13}C), with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: sweep width, 5 and 18.5 kHz; pulse width 1 μs (^{1}H) and 7.0 μs (^{13}C) (*ca.* 20° and *ca.* 90° flip angle, respectively); acquisition time, 1.64 and 0.40 s; number of scans, 16 (^{1}H) and 512 (^{13}C); and computer memory, 16K. Lorentzian exponential multiplication was applied for signal-to-noise enhancement (line width 0.7 or 1.0 Hz), and complete proton noise decoupling (*ca.* 0.5 W) was applied for the ^{13}C NMR spectrum.

The DNOEMULT.AU standard Bruker microprogram to generate the NOE was used with a selective preirradiation time of 5 s and a decoupling power (CW mode) of *ca.* 30–40 mW; number of scans 64–256, dummy scans 4–8, pulse width 5.0 μs (90°) and 16K data points for *ca.* 2 kHz sweep width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

The HETCOR 2D spectra were obtained by using the standard Bruker pulse program XHCORRD.AU. The number of data points was 4K in the ^{13}C domain and 64–256 increments were used to give a better than 5 Hz per point digital resolution in the ^{1}H domain; 256 transients were obtained with a relaxation delay of 3 s. All C–H correlations were found by using a value of J(CH) = 135 Hz for the calculation of the delay.

Preparation of 4-phenyl-2-oxa-3-aza-*r*-1, *c*-5, *c*-6, *c*-7, *t*-8, *t*-11, *c*-12, *c*-13-pentacyclo [8.3.1^{8,11}.1^{6,13}.0^{7,12}.0] pentadeca-3, 9-diene (3a)

3-Phenylnorborneneisoxazoline[13] (**1**) (1.0 g) was heated in an oil-bath (170 °C, 20 min). After cooling the product was dissolved in ethyl acetate (30 ml), transferred to an aluminium oxide column (Alumina Woelm N, Akt. I) and then eluted with benzene and ethyl acetate. The latter was evaporated and the residue was crystallized from ethanol; colourless crystals, m.p. 201–203 °C; yield 30%.

^{1}H NMR ($\delta_{TMS} = 0$ ppm): H-14 (*exo*), 0.93 d (11.6 Hz); H-15 (*exo*), 1.25 d (7.8 Hz); H-15 (*endo*), 1.42 dt (7.9, 1.7, 1.7 Hz); H-11, 1.96 dd (8.0, 4.0 Hz); H-14 (*endo*),* 2.15 dt (11.6, 1.7, 1.7 Hz); H-6,* 2.18 dd (8.0, 4.0 Hz); H-5, 2.38 s;† H-12, 2.47 s;† H-7,10, ~2.92 s;† H-4, 3.42 dd (8.2, 1.3 Hz); H-13, 4.54 d (8.2 Hz); H-8, 5.93 dd (5.5, 3.4 Hz); H-9, 6.02 dd (5.5, 3.4 Hz); H-3′,4′,5′ (Ph), ~7.4 m (3H); H-2′6′(Ph), 7.70 dd (2H, ~8, ~2 Hz).

^{13}C NMR ($\delta_{TMS} = 0$ ppm):‡ C-14, 27.5; C-5, 41.3; C-11, 42.4; C-12, 45.0; C-7,10, 45.9; 46.3; C-6, 48.0; C-15, 53.0; C-4, 60.4; C-13, 89.5; C-1′,2′,6′ (Ph),§ 126.8; C-3′,5′, 128.6; C-4′, 129.6; C-8,9, 135.5, 135.7; C-3, 156.0.

Elemental analysis: $C_{19}H_{19}NO$ requires C 82.28, H 6.90, N 5.05; found, C 82.19, H 6.73, N 5.14%.

* Overlapping signals.

† Broadened signals with a half band width of 6–8 Hz.

‡ Assignments were also proved by DEPT and 2D-HSC measurements.

§ Two lines.

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