

NEW DITERPENE ISOCYANIDES FROM A SPONGE

R. Kazlauskas, P.T. Murphy and R.J. Wells*

Roche Research Institute of Marine Pharmacology,
P.O. Box 255, Dee Why, N.S.W. 2099, Australia

and

J.F. Blount

Research Division, Hoffmann-La Roche Inc.,
Nutley, New Jersey 07110, U.S.A.

Summary: Six new diterpene isocyanides have been isolated from a sponge (*Adocia* sp.). Their structures support the biosynthetic suggestion for the formation of diisocyanoadociene reported from the same sponge.

We have previously reported the isolation of diisocyanoadociene (1) from a species of the sponge genus *Adocia*¹ and suggested that this unique tetracyclic diterpene could be formally derived from a suitable 'regular' diterpene precursor by means of a single methyl shift as shown in (2). The recent isolation of 8,15-diisocyno-11(20)-amphilectene (3) from the sponge *Hymeniacidon amphilecta*^{2,3} supported this biosynthetic suggestion and prompts us to report the structures of six new tri- and tetracyclic isocyanides which co-occur with (1).

The mother liquors from the direct crystallisation of (1) from the petroleum ether extract of the freeze-dried sponge constituted one third of the 3% extract but was a highly complex mixture of mono- and diisocyanides which were separated by exhaustive HPLC on silica gel⁴. Most compounds were not obtained in quantity sufficient to allow chemical correlation but several were highly crystalline. The structures of three compounds (4) - (6) were suggested by spectroscopic data and confirmed by single crystal X-ray structures whilst the structures of (7) - (9) are proposed on the basis of spectral comparison with (1) and (4) - (6).

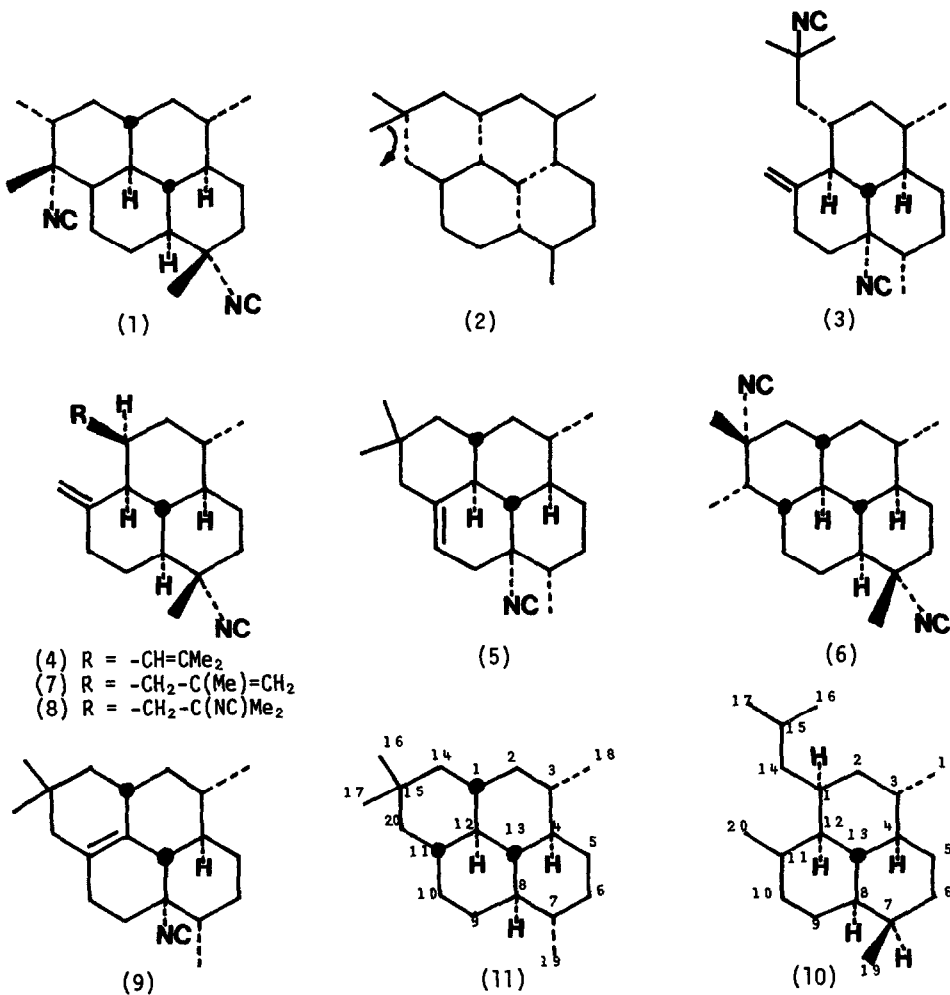
7-Isocyno-11(20),14-epiamphilectadiene (4)⁵ gave spectroscopic data⁶ indicating a tricyclic diterpene with one isocyanide group, an exocyclic methylene group, a Me₂C=CH-CH functionality, a secondary methyl group and a tertiary methyl group which is attached to the same carbon as the isocyanide group. These data, taken in conjunction with the known structure of (1) suggested structure (4) for this compound. This was confirmed by a single crystal X-ray structure determination⁷ which also gave the relative stereochemistry. Rather surprisingly the stereochemistry at C1 for (4) is epimeric with that in both (1) and (3).

Spectral comparison of (4) and (1) with 7-isocyno-11(20),15-epiamphilectadiene (7) and 7,15-diisocyno-11(20)-epiamphilectene (8) showed (7) to be a double bond isomer of (4) while (8) had an extra isocyanide group which had to be at C15. The stereochemistry especially at C1, of (7) and (8) has not been determined.

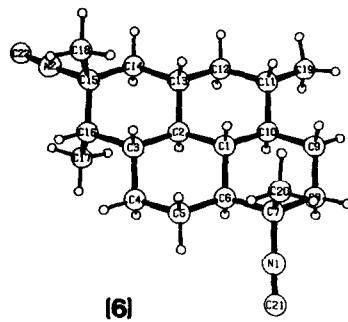
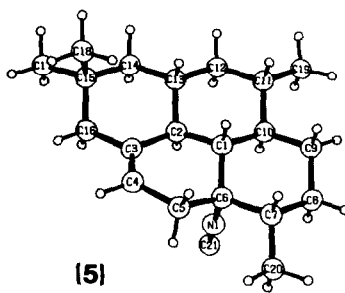
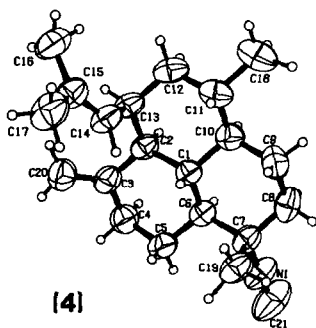
Spectral data for 8-isocyno-10-cycloamphilectene (5)⁸ demanded a tetracyclic skeleton, one isocyanide group and a trisubstituted double bond. The structure was obtained by single crystal X-ray analysis⁷ which only gave the relative stereochemistry. Compound (9)⁸ was a double bond isomer of (5) as shown by spectral comparison with the tetrasubstituted double bond most probably Δ 11(12). Again the limited amount available precluded chemical correlation.

The structure and relative stereochemistry of 7,15-diisocyanoadociene (6)⁹ was obtained by an X-ray study⁷ which showed it to be an isomer of (1).

Compound (1) and the isocyanide mixture giving compounds (4) - (9) displayed marked *in vitro* antimicrobial activity particularly against gram positive bacteria¹⁰, but showed no *in vivo* activity other than marked toxicity.



Perspective drawings of X-ray structures



Crystal Data

Compound	(4)	(5)	(6)
Molecular Weight	297.49	297.49	324.51
Space group	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2 ₁
a (Å)	9.020 (2)	6.761 (2)	10.226 (1)
b (Å)	10.065 (2)	16.000 (3)	11.569 (1)
c (Å)	20.710 (3)	17.023 (3)	16.461 (1)
Z	4	4	4
d _{calcd} (g cm ⁻³)	1.050	1.072	1.106
μ (Cu Kα) (cm ⁻¹)		4.6	4.9

Experimental

Crystal size (mm)	0.25 x 0.3 x 0.5	0.20 x 0.30 x 0.65	0.20 x 0.30 x 0.60
Maximum θ (°)	76	57	57
No. of reflections	2206	1466	1521
No. of observed reflections	1869	1383	1404
Absorption corrections	No	No	No
Least squares refinement	full matrix	full matrix	full matrix
Heavier atoms	anisotropic	anisotropic	anisotropic
Hydrogen atoms	iso (fixed)	iso (fixed)	iso (fixed)
Final R	0.048	0.033	0.038
Final wR	0.054	0.043	0.048
Final difference map- largest peak (e Å ⁻³)	< ± 0.2	< ± 0.1	< ± 0.1

8. 8-Isocyano-10-cycloamphilectene (5), mp 88-89°, $[\alpha]_D^{20} = -21.7$ (c=2, CHCl₃), ν_{\max} (KBr) 2245 cm⁻¹; ¹H n.m.r. spectrum: δ (CDCl₃) 5.20 (1H, bd, J 4 Hz); ¹³C [¹H] n.m.r. spectrum: (CDCl₃) 154.4 (bs), 137.5 (s), 115.2 (d), 62.8 (t, J 4 Hz), 49.0, 47.6, 46.2, 44.0, 43.1, 42.7, 40.6, 38.0, 37.7, 32.2, 31.6, 29.8, 29.5, 25.1 (q), 19.5 (q), 15.2 (q) ppm; mass spectrum: m/e 297 (5), 282 (10), 272 (3), 271 (24), 270 (100), 256 (21), 255 (97), 241 (8), 228 (9), 227 (6), 215 (10), 214 (42), 213 (56), 201 (7), 200 (6), 199 (26), 185 (16), 172 (16), 171 (11), 159 (15), 157 (19), 145 (12), 143 (17), 105 (15), 91 (17).
- 8-Isocyano-11-cycloamphilectene (9), colourless gum, $[\alpha]_D^{20} = +39.6$ (c=0.6, CHCl₃), ν_{\max} (KBr) 2130 cm⁻¹; ¹H n.m.r. spectrum: (CDCl₃) 0.92 (apparent singlet 12H); ¹³C [¹H] n.m.r. spectrum: 154.8 (bs), 128.5 (s), 127.5 (s), 62.9 (t, J 4 Hz), 46.7 (d), 44.6, 43.6, 42.7, 40.0, 39.8, 35.8, 34.1, 32.2, 30.0, 29.8, 29.5, 28.7, 26.4, 26.1, 19.1 (q), 15.0 (q) ppm; mass spectrum: m/e 297 (2), 282 (3), 272 (3), 271 (19), 270 (83), 256 (21), 255 (100), 241 (5), 215 (7), 214 (33), 213 (51), 200 (5), 199 (25), 185 (25).
9. 7,15-Diisocyanoadociane (6), mp 123.4°; $[\alpha]_D^{20} = +45.8$ (c=0.7, CHCl₃), ν_{\max} (KBr) 2140 cm⁻¹; ¹H n.m.r. spectrum: δ (CDCl₃) 1.60 (3H, t, J 2 Hz), 1.30 (3H, t, J 2 Hz), 1.07 (3H, d, J 7 Hz), 0.88 (3H, d, J 5 Hz), mass spectrum: m/e 324 (3), 309 (5), 297 (13), 282 (10), 271 (25), 270 (100), 256 (20), 255 (85), 241 (28), 228 (23), 215 (19), 213 (18), 201 (52), 199 (21), 185 (16), 159 (19), 145 (36), 143 (17), 131 (24), 119 (22), 117 (18), 107 (21), 105 (38), 95 (17), 93 (28), 91 (52), 81 (27), 78 (37), 77 (29), 67 (28), 55 (49), 53 (23).

10. B. Kinsela and J. Reichelt - unpublished results.

References and Notes

1. J.T. Baker, R.J. Wells, W.E. Oberhänsli and G.B. Hawes, *J. Amer. Chem. Soc.*, **98**, 4010 (1976).
2. S.F. Wratten, D.J. Faulkner, K. Hirotsu and J. Clardy, *Tetrahedron Lett.*, 4345 (1978).
3. For comparative purposes and because the absolute configuration of both (1) and (3) is unknown, we have drawn (3) as the mirror image of the structure drawn in ref. 2 to conform to our original drawing of (1).
4. Mono- and diisocyanides were separated by silica gel chromatography. Monoisocyanides were then processed (25 mg per injection) on a Whatman Magnum 9 (10 μ silica gel) column using dichloromethane. Unresolved mixtures from this procedure were completely separated using hexane-diisopropyl ether (4:1) on the same column. Diisocyanides were separated using hexane-diisopropyl ether (3:2) as eluting solvent.
5. The name 8,15-diisocyno-11(20)-amphilectene has been coined for (3) based on a hypothetical hydrocarbon amphilectane. We coin the name epiamphilectane for the hypothetical hydrocarbon (10). This hydrocarbon is epimeric with amphilectane at both C1 and C7. We name compounds (5) and (9) as derivatives of the hypothetical tetracyclic hydrocarbon cycloamphilectane (11), which, for the sake of convenience, retains the same numbering system.
6. 7-Isocyno-11(20),14-epiamphilectadiene (4), mp 113-115; $[\alpha]_D^{20} + 116.8^\circ$ (c=1, CHCl₃); ¹H n.m.r. spectrum: δ (CDCl₃) 5.20 (1H, bd, J 8 Hz), 4.68 (1H, bs), 4.48 (1H, bs), 2.86 (1H, m), 1.70 (3H, bs), 1.64 (3H, bs), 1.36 (3H, t, J 1.5 Hz), 0.82 (3H, distorted d, J \sim 5 Hz); [Irradiation at δ 2.86 collapsed the δ 5.20 doublet to a broad singlet]; ¹³C [¹H] n.m.r. spectrum: (CDCl₃) 152.1 (bs), 148.5 (s), 130.3 (s), 126.4 (d), 108.1 (t), 60.8 (t, J 4.5 Hz), 49.9, 49.7, 48.2, 42.4, 40.9 (2C), 35.9, 34.5, 31.7, 27.4, 26.0 (2C), 20.6, 20.0, 17.7 ppm; mass spectrum (70 ev): m/e 297 (20, M), 282 (47), 270 (18), 254 (77), 228 (39), 227 (41), 201 (76), 158 (21), 145 (39), 109 (43), 91 (53), 43 (30) and 41 (100%).

7-Isocyno-11(20) 15-epiamphilectadiene (7) mass spectrum: m/e 297 (13), 282 (15), 270 (15), 255 (19), 242 (7), 241 (10), 240 (5), 215 (7), 214 (10), 213 (5), 202 (9), 201 (7), 199 (10), 187 (11), 159 (11), 145 (10), 131 (15), 105 (18), 93 (15), 91 (22), 81 (17), 79 (19), 77 (12), 69 (13), 67 (16), 55 (27), 41 (100), 40 (40%); ¹H n.m.r. spectrum: δ (CDCl₃) 4.80 (1H, bs), 4.70 (1H, bs), 4.62 (1H, bs), 4.58 (1H, bs), 1.72 (3H, bs), 1.28 (3H, t, J \sim 2 Hz), 0.82 (3H, d, J 6 Hz).
7. 7,15-Diisocyno-11(20)-epiamphilectene (8) oil, $[\alpha]_D^{20} + 3.6^\circ$ (c=1.6, CHCl₃); ¹H n.m.r. spectrum: δ (CDCl₃) 4.84 (1H, s), 4.57 (1H, s), 1.44 (6H, bs), 1.26 (3H t, J \sim 2 Hz), 0.88 (3H, d, J 6 Hz); ¹³C [¹H] n.m.r. spectrum: (CDCl₃) 150.6 (s), 106.0 (t), 60.5 (bs), 56.4 (bs), 51.4, 49.3, 48.0 (2C), 46.0, 41.8, 40.8, 37.4, 35.3, 33.5, 32.2, 30.4, 29.6, 25.5, 20.8, 20.0 ppm; mass spectrum: m/e 324 (38), 309 (43), 297 (13), 283 (40), 242 (57), 241 (46), 228 (37), 201 (60), 159 (36), 145 (50), 109 (100), 105 (64), 91 (92%).
7. Intensity data for all crystallographic analyses were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K α radiation, θ -2 θ scans, pulse height discrimination). A multiple solution procedure [G. Germain, P. Main and M.M. Woolfson, *Acta Cryst.* **A27**, 368 (1971)] was used to solve all structures. Crystal data and experimental details as summarised below. More detailed data available on request from Dr. J.F. Blount.

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