Vinyl Azides in Heterocyclic Synthesis. Part 7.[1] Synthetic Studies on the Cytotoxic Marine Alkaloid Amphimedine

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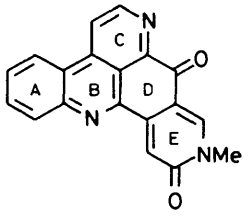
In an approach to the synthesis of the pentacyclic alkaloid amphimedine (**1**), a key tetracyclic structure (**6**) is readily constructed from 2-methoxyacridine-9-carbaldehyde in three steps. Condensation of the aldehyde (**2**) with methyl azidoacetate gives the vinyl azide (**3**) which on thermolysis in xylene gives the pyridoacridines (**4**) and (**5**) in high yield (78% and 19% respectively); this represents the first cyclisation of a vinyl nitrene to a *peri*-position. Oxidation of the major pyridoacridine (**4**), or of the mixed pyridoacridines (**4**) and (**5**), with manganese dioxide gives the pyridoacridone (**6**), but neither (**6**) nor the analogous isopropyl ester (**9**) undergoes Diels–Alder reaction with the azadiene (**7**).

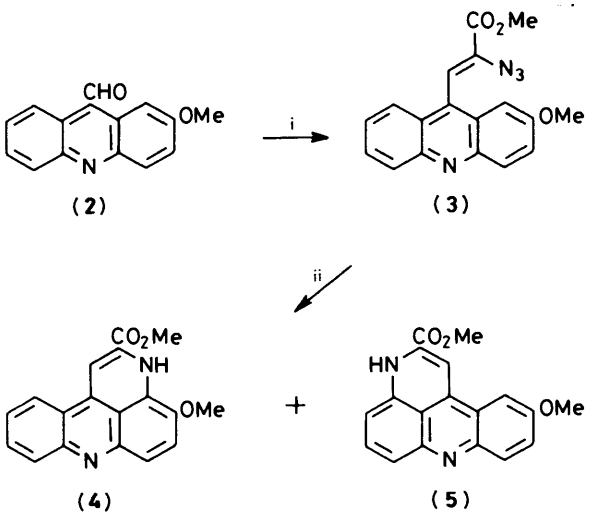
Marine organisms continue to provide a rich source of structurally diverse natural products, although to date relatively few alkaloids have been isolated from marine sources.[2,3] Recently, Schmitz and co-workers reported the isolation of a new pentacyclic aromatic alkaloid from an *Amphimedon* species of sponge collected off the Pacific island of Guam.[4] By a variety of spectroscopic techniques, they assigned structure (**1**) to the new alkaloid which they named amphimedine. As the first example of a new alkaloid skeleton, amphimedine is an interesting and challenging target for synthesis. In this paper we report an approach to the synthesis of amphimedine, based on vinyl azide chemistry,[1] which allows the simple and rapid construction of the tetracyclic A–B–C–D pyridoacridine fragment, together with our initial attempts at the fusion of the fifth E-ring.



(**1**)

Results and Discussion

At the outset it was envisaged that the pentacyclic system could be formed by the sequential fusion of the pyridine C-ring and the pyridone E-ring onto an acridine nucleus by means of a vinylnitrene cyclisation[5] and Diels–Alder reaction of an azadiene[6] respectively. Our chosen starting material was the known 2-methoxyacridine-9-carbaldehyde (**2**) which was easily prepared by the literature method[7] by oxidation of 2-methoxy-9-methylacridine obtained from 2-aminoacetophenone and 4-bromoanisole. Condensation of the aldehyde (**2**) with methyl azidoacetate gave the vinyl azide (**3**) in 48% yield. The relatively low yield in this condensation reflects the instability of the azide (**3**), which darkened rapidly with time and could not be obtained analytically pure. Thermolysis of the azide (**3**) in refluxing xylene gave a mixture of two products, both purple solids, in 97% yield in the ratio of *ca.* 4:1. These were easily separated by chromatography on silica gel, and were assigned the structures (**4**) (major product) and (**5**) (Scheme 1) on the basis of their ^{1}H n.m.r. spectra and n.O.e. difference experiments (see Experimental section).

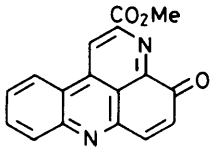


Scheme 1. *Reagents:* i, $MeO_2CCH_2N_3$, NaOMe, MeOH, −10 to 0 °C; ii, xylene, 140 °C

Thus the thermolysis of the azide (**3**) is both high yielding and regioselective to give the required pyridoacridine (**4**) (78% isolated). This type of cyclisation of a vinylnitrene intermediate to a *peri*-position is unprecedented, and it is noteworthy that the structurally similar vinyl azide derived from anthracene-9-carbaldehyde is reported to give a complex mixture on thermolysis from which none of the compound formed by cyclisation to the *peri*-position could be isolated.[8] In the present case, electron release from the methoxy group at C-2 probably facilitates cyclisation of the vinylnitrene to C-1, although the other *peri*-position, C-8, also benefits, albeit to a lesser extent, from the same effect.

Oxidation of the pyridoacridine (**4**) with manganese dioxide in 35% sulphuric acid gave the bright yellow pyridoacridone (**6**) in 75% yield. Interestingly, identical treatment of the isomeric pyridoacridine (**5**) resulted in its complete destruction. This result was convenient since it removed the need to separate the isomers (**4**) and (**5**), and simply oxidising the crude mixture from the thermolysis of the azide (**3**) gave (**6**) with no significant diminution of yield. Thus the key tetracyclic intermediate (**6**) is available in just three steps from the known 2-methoxyacridine-9-carbaldehyde in 34% overall yield.

It was intended at the outset that the E-ring of amphimedine would now be added by a Diels–Alder reaction of a suitable azadiene. Specifically, the 2-azadiene (**7**) introduced recently by



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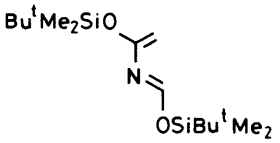
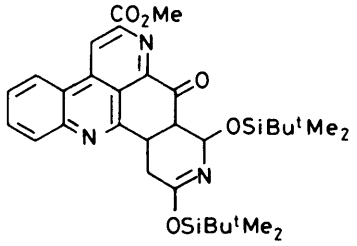


(7)

Ghosez and co-workers,[9] appeared to be the ideal candidate, since it is known to react with quinones to give fused pyridones in high yield after hydrolysis of the initial Diels–Alder adducts. Therefore, before turning our attention to the removal of the unwanted ester substituent, the Diels–Alder reaction of the enone (**6**) with the diene (**7**) was investigated. However, treatment of the enone (**6**) with the diene (**7**) in chloroform resulted in reisolation of starting materials, even after 16 h at reflux. Use of a large excess of the diene or more forcing conditions (sealed tube, 160 °C) resulted in decomposition. Adding Lewis acid catalysts such as boron trifluoride– diethyl ether, aluminium chloride, or zinc chloride also caused decomposition, with no evidence for the formation of the Diels–Alder adduct (**8**). Finally, the reactants were heated together at 40 °C under 12 kbar pressure for 40 h, but again no Diels–Alder reaction occurred.



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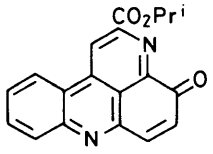

(9)

One possible reason for the failure of the Diels–Alder reaction was the poor solubility of the enone (**6**) in most organic solvents. Even in the best solvent, chloroform, a saturated solution contained only *ca.* 4—5 mg/ml at reflux, and therefore the attempted Diels–Alder reactions were necessarily carried out at high dilution. In a final effort to effect a Diels–Alder reaction, the corresponding isopropyl ester (**9**) of the enone was prepared by titanium tetraisopropoxide-mediated[10] transesterification. As had been hoped, the isopropyl ester (**9**) was much more soluble than the methyl ester (**6**), but unfortunately it too proved unreactive in Diels–Alder reactions with the azadiene (**7**). Alternative methods for the introduction of the fifth ring of amphimedine are currently being investigated.

Experimental

For general points see ref. 5.

2-*Methoxyacridine*-9-*carbaldehyde* (**2**).—This was prepared by the literature method, m.p. 145—148.5 °C (lit.,[7] 146.5—148 °C).

Methyl 2-*Azido*-3-(2-*methoxyacridin*-9-*yl*)*propenoate* (**3**).—A mixture of the aldehyde (**2**) (5.38 g, 0.023 mol) and methyl azidoacetate (11.6 g, 0.1 mol) in methanol (180 ml) was added dropwise to a stirred solution of sodium methoxide [from sodium (2.3 g, 0.1 mol)] in methanol (130 ml) the temperature being maintained at −5 °C. The reaction mixture was stirred at 0—5 °C for 2 h, and then at 4 °C overnight. After warming to room temperature, the dark red solution was poured into saturated aqueous ammonium chloride (650 ml) and extracted with ethyl acetate (4 × 260 ml). The combined organic extracts were washed with water, dried, evaporated, and the residue chromatographed to give the *title compound* (**3**) (3.61 g, 48%) as a yellow–orange solid, m.p. 116—118 °C (decomp.); $\nu_{max.}$(CHCl$_3$) 2 120, 1 720, and 1 630 cm^{-1}; δ (90 MHz; CDCl$_3$) 3.91 (3 H, s), 4.05 (3 H, s), 6.90 (1 H, d, *J* 2 Hz), 7.32—7.85 (5 H, m), and 7.96—8.25 (2 H, m); *m/z* 334 (M^+), 308, 291, 267 (base), 247, 237, 223, 208, 180, 166, and 84.

Thermolysis of the Azide (**3**).—A solution of the azide (**3**) (285 mg) in xylene (150 ml) was heated under reflux for 1.5 h. Evaporation of the solvent gave a dark purple solid which was chromatographed to give (i) *methyl* 10-*methoxy*-3H-*pyrido*[4,3,2-mn]*acridine*-2-*carboxylate* (**5**) (49.3 mg, 19%) as a purple solid, m.p. 210—212.5 °C (Found: M^+, 306.1011. $C_{18}H_{14}N_2O_3$ requires *M*, 306.1004); $\nu_{max.}$(CHCl$_3$) 3 440, 1 720, 1 620, 1 600, and 1 580 cm^{-1}; δ (250 MHz; CDCl$_3$) 3.87 (3 H, s), 4.04 (3 H, s), 6.58 (1 H, dd, *J* 6.8, 2.3 Hz), 6.82 (1 H, d, *J* 8.3 Hz), 6.98 (1 H, dd, *J* 8.3, 2.7 Hz), 7.27 (1 H, d, *J* 2.7 Hz), 7.43 (2 H, m), and 7.85 (1 H, s), NH not observed; pre-irradiation of the singlet at δ 7.85 resulted in enhancement of the doublet at 7.27 (11-H), and pre-irradiation of the singlet at 3.87 (10-OMe) caused enhancement of both the signals for 9-H (6.98) and 11-H (7.27); *m/z* 306 (M^+, base), and (ii) *methyl* 4-*methoxy*-3H-*pyrido*[4,3,2-mn]*acridine*-2-*carboxylate* (**4**) (204 mg, 78%) as a purple solid, m.p. 225—227 °C (Found: M^+, 306.1011); $\nu_{max.}$(Nujol) 3 300, 1 720, and 1 630 cm^{-1}; δ (250 MHz; CDCl$_3$) 3.98 (3 H, s), 4.01 (3 H, s), 6.57 (1 H, d, *J* 8.3 Hz), 6.78 (1 H, br d, *J* 8.3 Hz), 6.98 (1 H, d, *J* 8.3 Hz), 7.25—7.35 (2 H, m), 7.92 (1 H, br d, *J* 8.3 Hz), and 8.07 (1 H, s), NH not observed; pre-irradiation of the singlet at δ 8.07 (1-H) resulted in enhancement of the broadened doublet at 7.92 (11-H), and pre-irradiation of the singlet at 3.98 (4-OMe) caused enhancement of the doublet at 6.98 (5-H); *m/z* 306 (M^+, base).

Oxidation of the Pyridoacridine (**4**).—Activated manganese dioxide (268 mg, 3.27 mmol) was added to a stirred solution of the pyridoacridine (**4**) (250 mg, 0.82 mmol) in sulphuric acid (35%; 35 ml) at 0 °C. The resulting suspension was stirred at 0 °C for 40 min, diluted with chloroform (100 ml), neutralised with solid sodium hydrogen carbonate, and filtered through Celite. The filtrate was separated into two layers, and the aqueous layer was extracted with chloroform (30 ml). The combined organic layers were dried, and evaporated to give *methyl* 4-*oxo*-4H-*pyrido*[4,3,2-mn]*acridine*-2-*carboxylate* (**6**) (179 mg, 75%) as a bright yellow solid, m.p. 288—291 °C (decomp.) (from chloroform–methanol) (Found: M^+, 290.0695. $C_{17}H_{10}N_2O_3$ requires *M*, 290.0691); $\nu_{max.}$(Nujol) 1 720, 1 670, and 1 585 cm^{-1}; δ (250 MHz; CDCl$_3$) 4.16 (3 H, s), 7.14 (1 H, d, *J* 11 Hz, 5-H), 7.96 (1 H, d, *J* 11 Hz, 6-H), 7.87—8.10 (2 H, m, 9-H and 10-H), 8.32 (1 H, dd, 11-H), 8.71 (1 H, dd, 8-H), and 9.47 (1 H, s, 1-H); *m/z* 292 (M^+ + 2), 290 (M^+), 232 (base), 204, and 176.

Transesterification of the Pyridoacridine (**6**).—A mixture of the pyridoacridine (**6**) (116 mg, 0.4 mmol) and titanium tetraisopropoxide (71 mg, 0.25 mmol) in isopropyl alcohol (80 ml) was heated under reflux for 16 h. The solution was concentrated to *ca.* 30 ml, diluted with hydrochloric acid (1M; 30 ml), and extracted with chloroform (5 × 20 ml). The combined organic extracts were washed with water, dried, and evaporated, and the residue purified by chromatography to give *isopropyl* 4-*oxo*-4H-*pyrido*[4,3,2-mn]*acridine*-2-*carboxylate* (**9**) (92 mg, 72%) as a bright yellow solid, m.p. 263—265 °C (Found: C, 71.8; H, 4.4; N, 8.8. $C_{19}H_{14}N_2O_3$ requires C, 71.7; H, 4.4; N, 8.8%); $\nu_{max.}$(CHCl$_3$) 1 720, 1 670, 1 600, and 1 580 cm^{-1}; δ (250 MHz; CDCl$_3$) 1.55 (6 H, d, *J* 7 Hz), 5.46 (1 H, septet, *J* 7 Hz), 7.12 (1 H, d, *J* 11 Hz), 7.92 (1 H, d, *J* 11 Hz), 7.86—8.20 (2 H, m), 8.33 (1 H,

m), 8.71 (1 H, m), and 9.41 (1 H, s); *m/z* 320 (M^+ + 2), 318 (M^+), 303, 278, 260, 233, 232 (base), 231, and 204.

Attempted Diels–Alder Reactions.—(*a*) A mixture of the enone (**6**) (20 mg, 0.07 mmol) and the diene[9] (**7**) (24 mg, 0.08 mmol) in dry acid-free chloroform (2 ml) was heated under reflux under nitrogen for 16 h. Evaporation of the solvent left the unchanged enone (**6**) as a bright yellow solid.

(*b*) A mixture of the enone (**6**) (1 equiv.) and the diene (**7**) (20 equiv.) in chloroform was heated under reflux for 20 h. Evaporation of the solvent left a dark oil which was chromatographed to give a dark red oil, the ^{1}H n.m.r. spectrum of which contained no aromatic protons.

(*c*) Experiment (*a*) was repeated heating the reactants in a sealed tube at 160 °C for 14 h. Evaporation of the solvent left an intractable black tar.

(*d*) A mixture of the enone (**6**) (20 mg) and the diene (**7**) (44 mg) in chloroform was maintained at 40 °C and 12 kbar for 40 h. Evaporation of the solvent left unchanged enone (**6**) as a bright yellow solid.

(*e*) Experiments (*a*) and (*c*) were repeated using the isopropyl enone (**9**) in place of (**6**) but with similar results.

Acknowledgements

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