SYNTHESIS OF AMPHIMEDINE, A NEW FUSED AROMATIC ALKALOID FROM A PACIFIC SPONGE, *Amphimedon* sp.

Akinori Kubo* and Shinsuke Nakahara
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

*Abstract*—Synthesis of the cytotoxic fused pentacyclic aromatic alkaloid, amphimedine 1, is described.

Although marine organisms have been a rich source of structurally diverse natural products, relatively few alkaloids have been isolated from marine sources.\(^1\)

In 1983 Schmitz and co-workers reported the isolation of a novel cytotoxic fused aromatic alkaloid, named amphimedine 1, from an *Amphimedon* sp. of sponge found near Guam island.\(^2\) The structure 1 was assigned on the basis of an extensive long-range heterocorrelation and carbon-carbon correlation analyses.

To date, the structurally related fused aromatic alkaloids include calliactine 2,\(^3\) 2-bromo-leptoclinidinone 3,\(^4\) ascldldemin 4,\(^5\) petrosamine 5,\(^6\) and cystodytins A, B, and C.\(^6,7\)

Their highly fused structures have proven not only to be challenging structural elucidation problems but also to be challenging targets for synthesis.

Although a few synthetic studies\(^8\) toward them have been reported recently, no total synthesis has yet been accomplished. In this paper, we report the first synthesis of amphimedine 1.

Our starting material was the o-nitrobenzoylacetonilide 7 [ mp 93.5-95°C; ms m/z 344 (M\(^+\)) ], which was prepared in quantitative yield by heating 2,5-dimethoxyaniline with ethyl o-nitrobenzoylacetate in toluene and a slight amount of pyridine at 140°C for 6 h. Cyclization of 7 in 80% H\(_2\)SO\(_4\) at 75°C for 30 min gave in 53% yield the quinolone 8 [ mp 208-209°C; ms m/z 326 (M\(^+\)) ], which was converted to the 2-chloroquinoline 9 [ mp 225-226°C; ms m/z 346 (M\(^+2\)) ] in 66% yield using PCl\(_5\)/POCl\(_3\) at 70°C for 45 min. Oxidative demethylation of 9 with ceric ammonium nitrate (CAN)\(^9\) in aqueous CH\(_3\)CN at 0°C for 15 min afforded the quinolinequinone 10 [ mp 188-190°C (decomp); ms m/z 316 (M\(^+2\)) ] in 77% yield.
The crucial step, formation of an isoquinolone ring, was performed according to the procedure of Ghosez and co-workers.\textsuperscript{10} The Diels-Alder reaction of 10 with 2-aza-1,3-bis(tert-butyldimethylsilyloxy)-1,3-butadiene \textsuperscript{11} in CHCl\textsubscript{3} at 35°C for 8 h gave a mixture of crude adducts after acidic workup; which was methylated with CH\textsubscript{3}I/K\textsubscript{2}CO\textsubscript{3}/tris[2-(2-methoxyethoxy)ethyl]amine\textsuperscript{11} in DMF at room temperature for 1 h to provide two N-methylisoquinolones \{12 (7%) and 13 (8\%)\} after silica gel chromatography \{12: mp 286-288°C; ms m/z 397 (M\textsuperscript{+}+2, 4), 395 (M\textsuperscript{+}, 11), 351 (34), 349 (100); \textsuperscript{1}H-nmr (400MHz, CDCl\textsubscript{3}) \( \delta \) 3.73 (3H, s), 7.03 (1H, s), 7.26 (1H, dd, \( J = 1.2, 7.3 \) Hz), 7.48 (1H, s), 7.72 (1H, ddd, \( J = 1.2, 7.6, 8.2 \) Hz), 7.80 (1H, ddd, \( J = 1.2, 7.3, 7.6 \) Hz), 8.38 (1H, dd, \( J = 1.2, 8.2 \) Hz), 8.67 (1H, s). 13: mp > 300°C; ms m/z 397 (M\textsuperscript{+}+2, 1), 395 (M\textsuperscript{+}, 3), 351 (37), 349 (100); \textsuperscript{1}H-nmr (400MHz, CDCl\textsubscript{3}) \( \delta \) 3.64 (3H, s), 7.29 (1H, dd, \( J = 1.2, 7.3 \) Hz), 7.35 (1H, s), 7.51 (1H, s), 7.70 (1H, ddd, \( J = 1.2, 7.6, 8.2 \) Hz), 7.79 (1H, ddd, \( J = 1.2, 7.3, 7.6 \) Hz), 8.32 (1H, s), 8.35 (1H, dd, \( J = 1.2, 8.2 \) Hz)\}. Finally, catalytic hydrogenation of 12 with 10% Pd-C/Et\textsubscript{3}N in MeOH at room temperature for 20 h afforded in 13\% yield amphimedine 1 \{mp > 300°C; high-resolution ms Calcd for C\textsubscript{19}H\textsubscript{11}N\textsubscript{3}O\textsubscript{2}: 313.0852, Found 313.0857; \textit{uv} (EtOH): \( \lambda_{\text{max}} \) nm (\( e \)) 235 (38,000), 281 (10,000), 340 (7,000); ms}
Synthetic amphiedine had spectral properties (\(^{1}\text{H}-, {^{13}}\text{C-nmr, HRms, uv)}\) and HPLC mobility identical with those of a natural specimen.

In a similar manner the regio isomer 13 afforded an isomer 14 of amphiedine in 11% yield (mp > 300°C; ms m/z 313 (M\(^{+}, 100\)), 298 (69), 285 (23); \(^{1}\text{H-nmr (400MHz, 2:1 CF}_{3}\text{COOD:CDCl}_{3})}\)
δ 4.10 (3H, s), 7.92 (1H, s), 8.15 (1H, t like), 8.34 (1H, t like), 8.53 (1H, d, J = 8.5 Hz), 8.91 (1H, d, J = 8.1 Hz), 9.45 (2H, s like), 9.68 (1H, s).

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REFERENCES

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