Synthesis of Tetrahydrobenzophenanthridinones. V [1]

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The preparation of tetrahydrobenzophenanthridinones **4** and **5**, potential useful intermediates for the synthesis of Dynemicin A models, is described. The structure of all products was corroborated by ir, ^{1}H-nmr, ms and X-ray spectroscopy.

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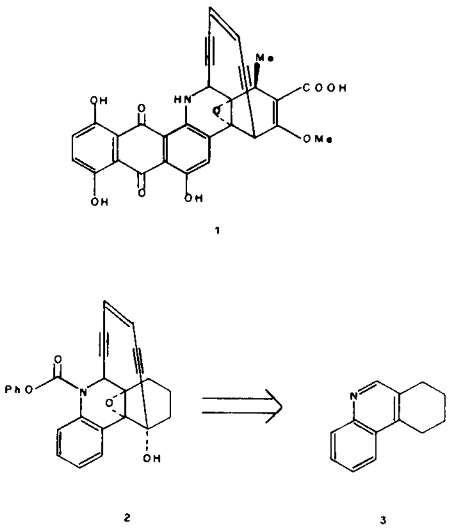
Esperamicins, calicheamicins and Dynemicin A, **1**, are the only naturally ocurring antibiotics known that possess a 1,5-diyn-3-ene bridging ring [4]. In view of the demonstrated effectiveness of **1**, at low concentration, against a number of human cell lines [5] and its low toxicity there has been renowed interest in the synthesis of Dynemicin A itself and models to clearly define the structural requirements necessary for its antitumor efficacy [6]. As a result of these efforts recently was reported the synthesis of the model system **2** starting from 7,8,9,10-tetrahydrophenanthridine **3** [7] (Scheme 1).

Scheme 1

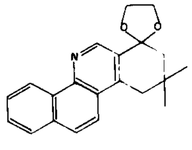


1

2

3

The present work describes a convenient route from 1- and 2-naphthylamines to benzophenanthridinones **4** and **5** (Scheme 2) which can be used for the synthesis of novel Dynemicin A models. Our reading of the extensive literature dealing with the synthesis of benzophenanthridines [8] encouraged us to explore the strategy depicted in Scheme 2 for the synthesis of **4** and **5** [9].



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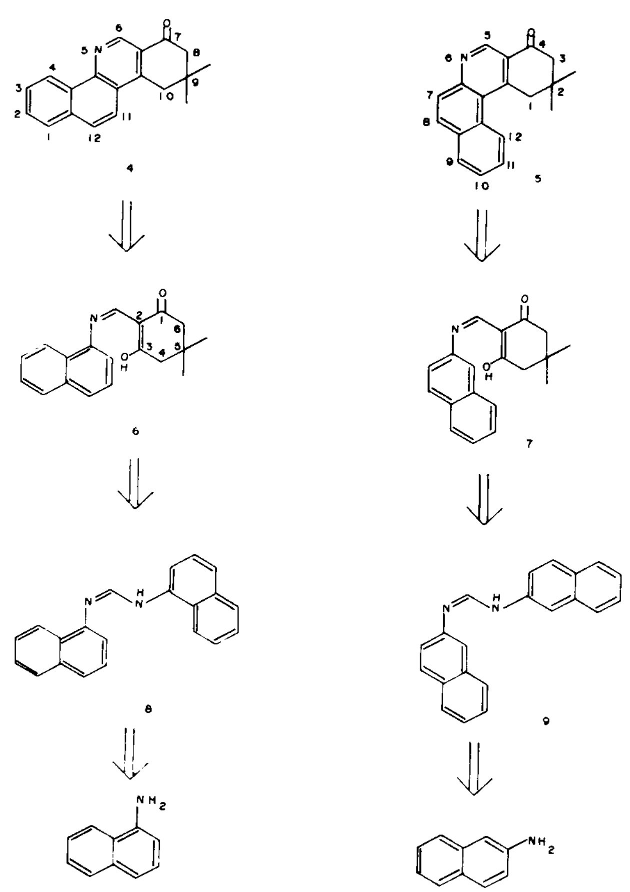
Thus, we reasoned that ring closure of iminoenolketones **6** and **7** represents a logical final step in the synthetic process. The precursors were analyzed as dimedone and the formamidines **8** and **9** from which the aromatic and aliphatic moieties were separated into 1- and 2-naphthylamine and methyl orthoformate. Accordingly, the formamidine **8** was prepared in high yield from 1-naphthylamine on treatment in methanol with methyl orthoformate. The infrared spectrum of **8** displayed absorption at 1661 cm^{-1} (C = N). The presence of ions at m/z 296 ($M^{+\cdot}$) and 153, 168, 143, 127 and 115 in the mass spectrum of **8** was consistent with its structure.

Heating **8** and dimedone at 110-120° afforded the naphthyliminomethylcyclohexanodione **6**. The structure of this compound followed from spectroscopic data. Of particular note, a one-proton singlet at δ 8.8 in the ^{1}H-nmr spectrum of **6** could be assigned to the imino-proton while the two C-5 methyl group gives rise to a singlet at δ 1.15 and the enolic proton gives rise to a broad singlet at δ 11.36.

The iminomethylketone **6** was converted to the phenanthridinone **4** by heating in the presence of polyphosphoric acid in 74% yield. In agreement with the suggested structure the ir spectra (chloroform) of compound **4** exhibited a strong ketone carbonyl band at 1685 cm^{-1}. Its ^{1}H-nmr spectrum showed a singlet at δ 1.75 for the methyl protons of C-9 as well two singlets of the methylene protons joined to C-8 and C-10 at δ 2.56 and δ 3.21, respectively. Two one-proton signal at δ 9.46 (singlet) and δ 9.3 (multiplet) was assigned to the methine protons joined to C-6 and C-4. The remaining aromatic protons in compound **4** appeared as

Scheme 2



unresolved multiplet at δ 9.25-9.45. The structure of benzophenanthridinone **4** was confirmed by X-ray crystallographic analysis of the 7-(1,3-dioxolanyl) derivative **10** (Figure 1).

Table 1

Intramolecular Distances Involving the Nonhydrgen Atoms

atom	atom	distance	atom	atom	distance
O1A	C15A	1.421(5)	C11A	C12A	1.358(6)
O1A	C7A	1.423(4)	C15A	C16A	1.489(6)
O2A	C16A	1.410(5)	O1B	C16B	1.408(5)
O2A	C7A	1.441(4)	O1B	C7B	1.432(5)
C1A	C2A	1.368(6)	O2B	C15B	1.406(5)
C1A	C1AA	1.408(6)	O2B	C7B	1.432(4)
C1AA	C4AA	1.406(5)	C1B	C2B	1.366(6)
C1AA	C12A	1.434(5)	C1B	C1BA	1.414(6)
C2A	C3A	1.395(6)	C1BA	C4BA	1.400(5)
C3A	C4A	1.396(6)	C1BA	C12B	1.428(6)
C4A	C4AA	1.419(5)	C2B	C3B	1.378(7)
C4AA	C4AB	1.449(6)	C3B	C4B	1.376(6)
C4AB	N5A	1.355(4)	C4B	C4BA	1.416(6)
C4AB	C10AB	1.412(5)	C4BA	C4BB	1.450(6)
N5A	C6A	1.317(5)	C4BB	N5B	1.366(5)
C6A	C6AA	1.412(5)	C4BB	C10BB	1.414(5)
C6AA	C10AA	1.376(5)	N5B	C6B	1.321(5)
C6AA	C7A	1.511(5)	C6B	C6BA	1.409(5)
C7A	C8A	1.507(5)	C6BA	C10BA	1.374(5)
C8A	C9A	1.540(5)	C6BA	C7B	1.500(5)
C9A	C14A	1.524(6)	C7B	C8B	1.524(6)
C9A	C10A	1.525(6)	C8B	C9B	1.536(5)
C9A	C13A	1.527(6)	C9B	C13B	1.519(6)
C10A	C10AA	1.512(5)	C9B	C14B	1.526(6)
C10AA	C10AB	1.425(5)	C9B	C10B	1.528(5)
C10AB	C11A	1.424(5)	C10B	C10BA	1.517(5)
C10BA	C10BB	1.418(5)			
C10BB	C11B	1.435(5)			
C11B	C12B	1.343(6)			
C15B	C16B	1.485(7)			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

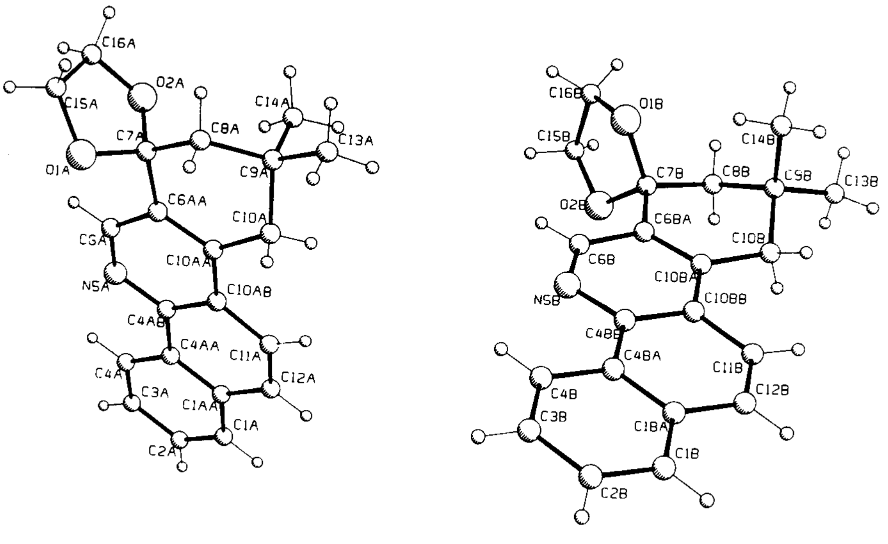


Figure 1

Table 2

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C15A	O1A	C7A	106.8(3)	C7A	C8A	C9A	115.0(3)
C16A	O2A	C7A	107.9(3)	C14A	C9A	C10A	110.8(4)
C2A	C1A	C1AA	120.8(4)	C14A	C9A	C13A	109.6(3)
C4AA	C1AA	C1A	119.6(4)	C14A	C9A	C8A	111.0(3)
C4AA	C1AA	C12A	118.7(4)	C10A	C9A	C13A	108.7(4)
C1A	C1AA	C12A	121.7(4)	C10A	C9A	C8A	107.6(3)
C1A	C2A	C3A	119.9(4)	C13A	C9A	C8A	109.1(3)
C4A	C3A	C2A	120.7(4)	C10AA	C10A	C9A	114.7(3)
C3A	C4A	C4AA	120.6(4)	C6AA	C10AA	C10AB	118.4(3)
C1AA	C4AA	C4A	118.4(4)	C6AA	C10AA	C10A	120.0(4)
C1AA	C4AA	C4A	120.1(4)	C10AB	C10AA	C10A	121.6(3)
C4A	C4AA	C4AB	121.6(4)	C4AB	C10AB	C11A	118.9(4)
N5A	C4AB	C10AB	123.4(4)	C4AB	C10AB	C10AA	117.8(3)
N5A	C4AB	C4AA	117.1(3)	C11A	C10AB	C10AA	123.4(3)
C10AB	C4AB	C4AA	119.5(4)	C12A	C11A	C10AB	121.7(4)
C6A	N5A	C4AB	116.8(3)	C11A	C12A	C1AA	121.1(4)
N5A	C6A	C6AA	125.0(3)	O1A	C15A	C16A	104.4(3)
C10AA	C6AA	C6A	118.4(4)	O2A	C16A	C15A	106.5(4)
C10AA	C6AA	C7A	123.6(3)	C16B	O1B	C7B	107.8(3)
C6A	C6AA	C7A	117.9(3)	C15B	O2B	C7B	107.7(3)
O1A	C7A	O2A	104.5(3)	C2B	C1B	C1BA	119.6(4)
O1A	C7A	C8A	111.0(3)	C4BA	C1BA	C1B	119.5(4)
O1A	C7A	C6AA	108.8(3)	C4BA	C1BA	C12B	119.3(4)
O2A	C7A	C8A	111.6(3)	C1B	C1BA	C12B	121.2(4)
O2A	C7A	C6AA	107.3(3)	C1B	C2B	C3B	121.2(5)
C8A	C7A	C6AA	113.3(3)	C4B	C3B	C2B	120.9(4)
C3B	C4B	C4BA	119.3(4)	C6BA	C10BA	C10BB	118.5(3)
C1BA	C4BA	C4B	119.5(4)	C6BA	C10BA	C10B	120.7(4)
C1BA	C4BA	C4BB	119.1(4)	C10BB	C10BA	C10B	120.8(3)
C4B	C4BA	C4BB	121.4(4)	C4BB	C10BB	C10BA	118.7(3)
N5B	C4BB	C10BB	122.1(4)	C4BB	C10BB	C11B	118.1(4)
N5B	C4BB	C4BA	117.7(4)	C10BA	C10BB	C11B	123.2(4)
C10BB	C4BB	C4BA	120.2(4)	C12B	C11B	C10BB	121.5(4)
C6B	N5B	C4BB	117.4(3)	C11B	C12B	C1BA	121.7(4)
N5B	C6B	C6BA	124.7(3)	O2B	C15B	C16B	106.1(4)
C10BA	C6BA	C6B	118.6(4)	O1B	C16B	C15B	105.9(4)
C10BA	C6BA	C7B	123.4(3)				
C6B	C6BA	C7B	118.0(3)				
O2B	C7B	O1B	104.3(3)				
O2B	C7B	C6BA	109.0(3)				
O2B	C7B	C8B	109.3(3)				
O1B	C7B	C6BA	108.4(3)				
O1B	C7B	C8B	111.8(3)				
C6BA	C7B	C8B	113.7(3)				
C7B	C8B	C9B	114.6(4)				
C13B	C9B	C14B	110.0(3)				
C13B	C9B	C10B	107.6(4)				
C13B	C9B	C8B	109.1(4)				
C14B	C9B	C10B	110.7(4)				
C14B	C9B	C8B	111.2(4)				
C10B	C9B	C8B	108.2(3)				
C10BA	C10B	C9B	114.3(3)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Compounds **9**, **7** and **5** have been prepared following similar procedures starting with 2-naphthylamine and their structures were supported by ir, ^{1}H-nmr and mass spectral data.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian FT-80 spectrometer operating at 80 MHz, in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Hewlett Packard 59854-A quadropole mass spectrometer.

Crystallography.

X-Ray Analysis for 9,9-Dimethyl-7,8,9,10-tetrahydrobenz[*c*]phenanthridin-7-one Ethylene Ketal, **10**.

On the two crystallographic independent molecules, the tetrahydro ring of the phenanthridine moiety adopts a sofa conformation with C-9 out of the mean plane and the 1,3-dioxolane ring lying perpendicular to it. The differences between both molecules arise from the different orientation of C-9 (towards the α and β faces of molecules A and B respectively) and the conformation of the 1,3-dioxolane ring (half-chair and envelop, respectively) moieties (Tables 1 and 2).

The molecular formula is $C_{21}H_{21}NO_2$, Mw 0 319.4, monoclinic, space group P21/n, Z = 8, a = 16.260 (2), D = 11.420 (2), C = 19.299 (3) Å, β = 113.53 (1)°, V = 3286 (2) Å^3, Dx = 1.29 g cm^{-3}, μ(CuKα) = 6.17 cm^{-1}; crystal size *ca.* 0.08 x 0.2 x 0.32 mm (colorless).

The cell dimensions and intensities were measured on a Nicolet P3F automatic four-circle diffractometer with Ni-filtered CuKα radiation (λ = 1.54178 Å). A total of 4580 reflections were collected up to 110° on 2θ of which 2356 independent reflections corrected by Lorentz and polarization effects with $I > 3\ \sigma(I)$ were used for structure solution and refinement.

The structure was solved by direct methods and refined by full matrix least-squares based on F with anisotropic temperature factors for non-H atoms. The final R was 0.051. Atomic scattering factors from International Tables for X-ray Crystallography [10]. All calculations performed on a VAXSTATION II using the TEXSAN-TEXRAY program package [11].

1-Naphthylformamidine, **8**.

A mixture of 0.1 mole (15 g) of 1-naphthylamine and 0.08 mole (8.6 ml) of methyl orthoformate in methanol (30 ml) was stirred under reflux overnight. Then 0.07 mole (8 ml) of methyl orthoformate was added and the mixture heated for 1 hour at 50°. The precipitated product was filtered off and washed with methanol to yield 13.5 g (87%) of **8**, mp 202-205°; ir (neat): ν cm^{-1} 1661; ms: m/z 296 ($M^{+\cdot}$), 143, 127, 115.

Anal. Calcd. for $C_{21}H_{15}N_2$: C, 85.1; H, 5.44. Found: C, 84.97; H, 5.41.

2-Naphthylformamidine, **9**.

2-Naphthylamine (0.09 mole, 12.5 g) and 8.2 ml (0.07 mole) of methyl orthoformate were allowed to react according to the procedure described above for the preparation of **8**. The desired product was formed in 77% yield (9.9 g), mp 181-182°; ir (neat): ν cm^{-1} 1668; ms: m/z 296 ($M^{+\cdot}$), 143, 127, 115.

5,5-Dimethyl-2-(1-naphthyliminemethyl)-1,3-cyclohexanedione, **6**.

A mixture of **8** (0.046 mole, 13 g) and dimedone (0.046 mole, 6.4 g) was heated to 110-120° for 2 hours. The reaction mixture was then allowed to cool. It was treated with ethyl acetate and the precipitated solid was filtered off. The organic layer was washed with water (3 x 20 ml), a 10% solution of hydrochloric acid (3 x 75 ml), a 20% solution of sodium bicarbonate (5 x 20 ml), water (3 x 20 ml), dried over anhydrous sodium sulfate and concentrated (rotatory evaporator) to afford a slightly yellow solid. Crystallization of this material from dichloromethane-hexane gave 11.8 g (88%) of **6**, mp 135-137°; ir (neat): ν cm^{-1} 1665 (C=N), 1596 (ketone-CO); ^{1}H-nmr (deuteriochloroform): δ ppm 1.15 (s, 6H, 2CH$_3$), 2.45 (s, 2H, C$_4$-H), 2.15 (s, 2H, C$_6$-H), 7.42-8.11 (m, 6H, Ar), 8.58 (s, 1H, Ar, C$_8$-H), 8.8 (s, 1H, N=CH), 11.3 (bs, 1H, -O*H*); ms: m/z 293 ($M^{+\cdot}$), 292.

5,5-Dimethyl-2-(2-naphthyliminemethyl)-1,3-cyclohexanedione, **7**.

A mixture of **9** (7 x 10^{-3} mole, 2 g) and dimedone (6.4 x 10^{-3} mole, 0.76 g) was allowed to react according to the procedure described above for the preparation of **6**. The desired product was formed in 88% yield (0.175 g), mp 160-162°; ir (neat): ν cm^{-1} 1665 (-C=N), 1596 (ketone-CO); ^{1}H-nmr (deuteriochloroform): δ ppm 1.12 (s, 6H, 2CH$_3$), 2.55 (s, 2H, C$_4$-H), 2.45 (s, 2H, C$_6$-H), 7.23-7.9 (m, 6H, Ar), 8.6 (s, 1H, Ar, C$_1$-H), 8.76 (s, 1H, N=CH), 11.0 (bs, 1H, -O*H*); ms: m/z 293 ($M^{+\cdot}$), 237, 264, 167.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.68; H, 6.20.

9,9-Dimethyl-7,8,9,10-tetrahydrobenz[*c*]phenanthridin-7-one, **4**.

Compound **6** (7.2 x 10^{-3} mole, 2 g) was added to a mixture of phosphorus pentoxide (2.8 x 10^{-1} mole, 40 g) and phosphoric acid (2 x 10^{-1} mole, 20 g). The reaction mixture was mechanically stirred at 120-135° overnight. It was treated with ice and the precipitated product was filtered off and recrystallized from dichloromethane-hexane to yield 1.6 g (74%) of **4**, mp 197°; ir (neat): ν cm^{-1} 1685, 1575; ^{1}H-nmr (deuteriochloroform): δ ppm 1.75 (s, 6H, 2CH$_3$), 2.56 (s, 2H, C$_8$-H), 3.21 (s, 2H, C$_{10}$-H), 7.65-7.95 (m, 5H, Ar), 9.25-9.45 (m, 1H, C$_4$-H), 9.46 (s, 1H, C$_6$-H); ms: m/z 275 ($M^{+\cdot}$), 219, 191.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.87; H, 6.23. Found: C, 82.83; H, 6.20.

2,2-Dimethyl-1,2,3,4-tetrahydrobenz[*a*]phenanthridin-4-one, **5**.

A mixture of **7** (3.6 x 10^{-3} mole, 1 g), phosphorus pentoxide (1.4 x 10^{-1} mole, 20 g) and phosphoric acid (1 x 10^{-1} mole, 10 g) was allowed to react according to the procedure described above. The desired product was formed in 60% yield (0.57 g), mp 178-180°; ir (neat): ν cm^{-1} 1683, 1568; ^{1}H-nmr (deuteriochloroform): δ ppm 1.1 (s, 6H, 2CH$_3$), 2.16 (s, 2H, C$_3$-H), 3.63 (s, 2H, C$_1$-H), 7.61-89.15 (m, 5H, Ar), 8.51-8.65 (m, 1H, C$_7$-H), 9.48 (s, 1H, C$_5$-H); ms: m/z 275 ($M^{+\cdot}$).

9,9-Dimethyl-7,8,9,10-tetrahydrobenz[*c*]phenanthridin-7-one Ethylene Ketal, **10**.

A mixture of **4** (1.8 x 10^{-3} mole, 0.5 g), ethylene glycol (60 x 10^{-3} mole, 4.2 g) and boron trifluoride etherate (6.6 x 10^{-3} mole, 0.95 g) in dichloromethane (30 ml) was allowed to react according to reported procedure [12]. The desired product was formed in 72% yield (0.42 g), mp 140°; ir (neat): ν cm^{-1} 1665; ^{1}H-nmr (deuteriochloroform): δ ppm 1.75 (s, 6H, 2CH$_3$), 2.56 (s, 2H, C$_8$-H), 3.21 (s, 2H, C$_{10}$-H), 7.65-7.95 (m, 5H, Ar), 9.25-9.45 (m, 1H, C$_4$-H), 9.46 (s, 1H, C$_6$-H); ms: m/z 275 ($M^{+\cdot}$), 219, 191.

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