Synthesis of α-Substituted 1,2-Benzenedimethanamines

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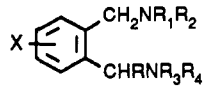
Our initial interest in the synthesis of 1,2-benzenedimethanamines was created because of their potential utility as intermediates in the synthesis of novel heterocycles for biological testing. A general route to these compounds was desired that would allow introduction of α-substituents and would have the versatility to differentiate between the two amino groups. Only two examples, **2**[1] and **3**,[2] of α-substituted 1,2-benzenedimethanamines **1**



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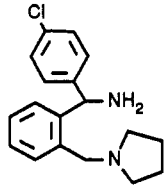

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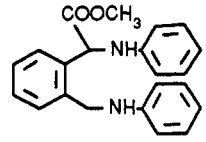

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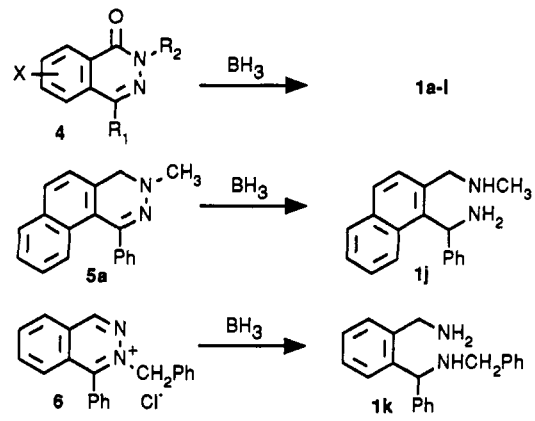
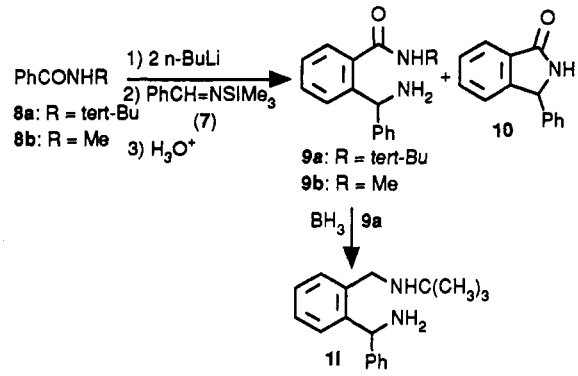
have been reported. The synthetic routes to **2** and **3** were neither general nor efficient and were not applicable to the synthesis of compounds with more diverse α-substituents and/or different substituents on the two amino groups. Consequently, new synthetic strategies to prepare **1** were desired. In this report we describe two general methods that have been developed for preparing these useful compounds (Table I). The first method utilizes borane to reduce 2,4-disubstituted phthalazinones **4**, 1,3-disubstituted 3,4-dihydrophthalazines **5**, and 1,2-disubstituted phthalazinium compounds **6** (Scheme I). Common to all three reductions is an unprecedented reductive cleavage of N–N bond by borane.[3] In the second method, silylated benzaldehyde imine **7**[4] was reacted with the dianion of benzamide **8a** to yield amine **9a**, which was then reduced to diamine **1l** using borane (Scheme II).

The ease of formation and the availability of starting materials made **4** attractive precursors to **1**. Routinely, **4** were prepared by azeotroping water from a boiling mixture of monosubstituted hydrazine and 2-aroyl- or 2-alkanoylbenzoic acid in toluene.[1] The first compound prepared in this manner was **4a**, the reaction product of methylhydrazine and 2-benzoylbenzoic acid.[5] Initial attempts to reduce **4a** with LAH in boiling dioxane gave only a 53% yield of impure **1a**. When borane in THF was substituted for the LAH and dioxane, and the reaction

Scheme I



Scheme II



mixture was treated with methanolic HCl, **1a** was isolated directly from the reaction mixture as the hydrochloride salt in 63% yield. This reduction of **4a** with excess borane in THF proceeds stepwise and can be followed by TLC. Total reaction time can often be shortened by the addition of sodium borohydride and enough diglyme to solubilize the sodium borohydride. Imine reduction appears to be rate limiting if borane is used alone, and therefore sodium borohydride can be added to provide nucleophilic borohydride, which increases the rate at which the imine reduces. The addition of sodium borohydride may also increase the rate of N–N bond cleavage.

Similar reductions of phthalazinones **4b–g** gave benzenedimethanamines **1b–g** (Table I). An alternative procedure of phthalazinone synthesis was used for **4e** and **4f** and involved the alkylation of **4h**.[7]

An example of an α,α′-disubstituted 1,2-benzenedimethanamine was also prepared from **4a**. Treatment of **4a** at −65 °C with phenyllithium for 0.5 h, followed by the addition of excess borane in THF, resulted in an 87% yield of **1i**. Both ^{1}H NMR and TLC indicate that **1i** is a single pair of enantiomers. Further investigation will be necessary to determine which pair is present.

In some instances, when 2-benzoylbenzoic acids were difficult to prepare, we found that (2-benzoylaryl)methyl bromides could be utilized in their place. Thus, treatment of the appropriate (2-benzoylaryl)methyl bromide with methylhydrazine gave the intermediate 2,4-disubstituted 1,2-dihydrophthalazine **5a**, which underwent borane reduction to the expected **1j** (Scheme I).

This new synthetic method is not limited to α-substituted diamines that have the α-substituent on the carbon bearing the primary amine. In order to prepare the di-

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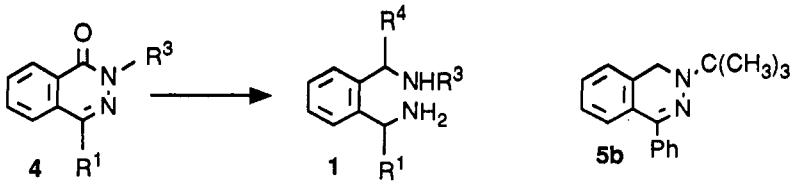
Table I. Reduction Products of 1-Phthalazinones



4[a]	R^1	R^3	yield[b], %	mp,[c] °C	product	R^4	yield,[b] %	mp,[c] °C (salt)	reaction time	equiv of BH_3
a[d]	Ph	Me	93	155–9	1a	H	63	166–8 (HCl)	5 days	4
b[e]	4-ClPh	Me	94	148–50	1b	H	59	259–61 (2HCl)	4 days	6[f]
c	1-naphthyl	Me	79	200–4	1c	H	61	224–6 (2HCl·$2H_2O$)	5 days	9[f]
d	$PhCH_2$	Me	75	146–8	1d	H	68	294–5 (2HCl)	7 days	7[f]
e	Ph	$CH(Me)_2$	97	137.0–8.5	1e	H	63	258–9 (2HCl)	2 days	5
f[g]	Ph	$PhCH_2$	96	175–8	1f	H	70	275.5–6.5 (2HCl)	4 days	4
g	4-OMePh	Me	86	198.5–200.5	1g	H	62	245–7 (2HCl)	3 days	6
h[h]	Ph	H	99	238–9	1h[i]	H	60	278–9 (2HCl)		
a	Ph	Me			1l[j]	Ph	87	301 (2HCl·$^1/_2H_2O$)	1 day	5[f]
i	Ph	$C(Me)_3$	67	139–41	5b		92	90–6	45 min	*k*

[a] Satisfactory C, H, N analyses have been obtained on all new compounds. [b] Isolated yield, unoptimized. [c] All melting points are uncorrected. [d] Reference 5, mp 165–6 °C. [e] Reference 1, mp 152–4 °C. [f] $NaBH_4$ (0.10 equiv) added. [g] Reference 7, mp 176–9 °C. [h] Reference 12, mp 236 °C. [i] Yield based upon three reduction steps: LAH; 10% Pd/C, H_2; RaNi, H_2. [j] Initial reaction with 1.05 equiv of PhLi followed by BH_3 reduction. [k] Reduced with LAH rather than BH_3.

amines with the α-substituent on the carbon bearing the secondary amine, a replacement for 2-benzoylbenzoic acid had to be devised that would react with monosubstituted hydrazines in the reverse mode. The known 2-benzoylbenzaldehyde fits this requirement and was prepared in two steps from 2-benzoylbenzoic acid in good yield.[8] Reduction of **6**, prepared from 2-benzoylbenzaldehyde and benzylhydrazine dihydrochloride, with borane in THF gave **1k** (Scheme I).

Although the reduction of 1-alkylpyrazolines to 1,3-diamines has been reported using LAH in refluxing toluene,[9] it has also been reported that 4-methyl-1-phthalazinone can be reduced with LAH to give only 1-methyl-3,4-dihydrophthalazine or 1-methyl-1,2,3,4-tetrahydrophthalazine.[10] No mention is made in this latter instance of the N–N cleaved product. We have encountered similar results using borane in THF or LAH when the 2-position of our phthalazinones was unsubstituted or substituted with a *tert*-butyl group. When the 4-phenylphthalazinone **4h** was reduced with LAH, only the amide carbonyl reduces at a rate fast enough to be useful. Diborane gave less satisfactory results than LAH. Following LAH reduction of **4h**, further reduction can be carried out catalytically with first Pd/C/H_2 and then with Ra-Ni/H_2 to give **1h** in 60% overall yield. In a similar manner, LAH, or less satisfactorily borane in THF, reduction of the 2-*tert*-butylphthalazinone **4i** gave only **5b**. In this case, however, catalytic reduction did not reduce **5b** further.

We have been unable to find reduction conditions that will reduce **4i** beyond **5b**. The expected diamine **1l** was of particular interest, and therefore a new approach to the synthesis of this material was attempted. Since difficulty was encountered in reducing the imine and the N–N bond of **5b**, a method that avoided these steps was investigated. Hart[4] has reported that the additions of alkyllithiums to silylated benzaldehyde imine **7** give primary amines. We reasoned that if the dianion of *N*-*tert*-butylbenzamide **8a** would undergo a similar reaction with **7**, **9a** would be the resultant product and it could be reduced with borane THF to give the desired diamine **1l**. Following this route (Scheme II), **1l** was obtained in 48% overall yield. To test the generality of this methodology, *N*-methylbenzamide **8b** was converted to **9b**; however, the yield of **9b** was lower due to the formation of byproduct **10**.[11] This byproduct **10** was not observed in the reaction of **8a** and suggests that this method will be more useful when there are bulky substituents on the amide nitrogen.

In conclusion, two complementary methods for the preparation of α-substituted 1,2-benzenedimethanamines have been described. The N-substituted benzamide approach can be useful when the N-substituent on the phthalazinone is large; however, it does not have the versatility of the phthalazinone approach. In reducing the phthalazines with borane, a novel cleavage of a N–N bond has been encountered. The extent to which this cleavage may be applied to other systems will be a direction for our future research.

Experimental Section

Reactions involving organometallic reagents, borane (BH_3), or lithium aluminum hydride (LAH) were run under a N_2 atmosphere. Solvents and reagents from commercial sources were used without further purification. Melting points (Pyrex capillary) are uncorrected. For ^1H NMR spectra, multiplicity is denoted by s (singlet), d (doublet), t (triplet), q (quartet), qin (quintet), sep (septet), m (multiplet), and br (broad). Coupling constants are in Hz. ^1H NMR spectra were run on either a 200-, 270-, or 300-MHz instrument, and ^{13}C NMR spectra were run on a 75-MHz instrument. Infrared spectra (IR) were measured as KBr pellets. High-resolution mass spectra were obtained by fast atom bombardment analysis on a M-Scan VG Analytical ZAB δ-SE high-field mass spectrometer operating at V_{acc} = 8 kV using a cesium ion gun to generate ions for the acquired mass spectra, which were recorded using a PDP 11-250J data system and are reported as MH^+. Mass calibration was performed using cesium iodide or cesium iodide/glycerol, and PEG 200 in MNBA was the matrix.

General Procedure for the Preparation of Phthalazinones 4a–d and 4g–i. The requisite hydrazine and 2-carbonylbenzoic acid were combined in toluene, and the mixture was heated under reflux using a Dean-Stark water trap until the evolution of water ceased (2–4 h). The reaction mixture was cooled to 0 ± 5 °C, and

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the product was collected, washed with cold toluene, and dried in vacuo to afford the desired phthalazinone.

General Procedure for the Preparation of α-Substituted 1,2-Benzenedimethanamines 1a–g and 1j–l. A solution of the appropriate compound to be reduced, **4a–g**, **5a**, **6**, and **8a** in 1 M BH_3·THF complex (4–9 equiv), was heated at the reflux temperature for 3–9 days. Usually, the 4–9 equiv of BH_3 were added in two or three portions over the course of the reaction. In some cases 0.1 equiv of $NaBH_4$ and 2-methoxyethyl ether were added to the reaction mixture to increase the reaction rate. After the reduction was complete, as determined by TLC analysis on silica gel, the cooled solution was quenched by the careful addition of MeOH and methanolic HCl (usually at least 4 equiv of HCl) and then heated at the reflux temperature 1 h. Concentration of the resulting solution on a rotary evaporator gave an oil that was dissolved in H_2O, washed with Et_2O, made basic with 10% NaOH, and extracted with Et_2O or EtOAc. This extract was dried (Na_2SO_4) and concentrated to give an oil that was transformed into an appropriate salt of the product.

α,α′-Diphenyl-*N*-methylbenzenedimethanamine (1i). A solution of 18.9 g (80 mmol) of **5a** in 450 mL of THF was cooled to −65 °C at which point a precipitate formed. The reaction mixture was stirred magnetically and treated with 42 mL (84 mmol) of 2 M phenyllithium in cyclohexane over 15 min. The resulting solution was stirred an additional 15 min at −65 °C followed by the addition of 400 mL (400 mmol) of 1 M BH_3·THF complex over 30 min at −65 °C, and the mixture was allowed to come to rt over 45 min. The reaction mixture was then heated at the reflux temperature for 1 h and cooled, and 185 mL of 2-methoxyethyl ether and 0.30 g (8 mmol) of $NaBH_4$ were added. After being heated at the reflux temperature for 22 h, the mixture was cooled, and 130 mL of MeOH was carefully added. The mixture was again heated at the reflux temperature for 1 h, and then 110 mL of 3.5 M HCl in MeOH was added and heating was continued for an additional 1 h. The resulting mixture was concd on a rotary evaporator, and the solids were collected and washed with $CHCl_3$. The filtrate was concd, and the residual solid was treated sequentially with Et_2O, 40 mL of MeCN, and 120 mL of Et_2O. The resultant precipitate, 35 g, was collected and combined with the original solid and treated with 2 M NaOH and extracted 3× with Et_2O. The Et_2O extract was washed with saturated NaCl containing 1 mL of 2 M NaOH, dried (Na_2SO_4), and concd on a rotary evaporator to give 30 g of an oil. The HCl salt was precipitated with HCl from MeCN/Et_2O and collected to give 26.7 g (87%) of **1i** as the dihydro chloride hemihydrate: mp 202–16 °C partially melts, resolidifies, and remelts at 301 °C; IR 3520, 2920 br, 1600, 1500, 1460 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.61 (s, 3), 6.15 (s, 1), 6.19 (s, 1), 7.10–7.70 (m, 13), 8.00 (d, 1, J = 7), 9.00–10.20 (s br, 5). Anal. Calcd for $C_{21}H_{22}N_2$·HCl·$^1/_2H_2O$: C, 65.63; H, 6.56; N, 7.29. Found: C, 66.08; H, 6.73; N, 7.09.

3,4-Dihydro-3-methyl-1-phenylbenzo[*d*]phthalazine (5a). To a mixture of 4.37 g (17.7 mmol) of (2-methyl-1-naphthalenyl)phenylmethanone[12] in 75 mL of CCl_4 was added 5.4 g (30.3 mmol) of NBS and 0.25 g of benzoyl peroxide. After the mixture was heated at the reflux temperature for 90 min, an additional 1.0 g of NBS and 0.10 g of benzoyl peroxide were added, and heating was continued overnight. Another 1.0 g of NBS and 0.25 g of benzoyl peroxide were added, and the mixture was heated at the reflux temperature for an additional 2 h. The cooled reaction mixture was placed on a silica gel flash column and eluted with 5% EtOAc in hexane to give 3.07 g (53%) of an oil that was dissolved in 50 mL of $CHCl_3$ and treated dropwise with 0.50 mL (0.43 g, 9.4 mmol) of methylhydrazine in 2.0 mL of Et_3N. After stirring for 30 min, the mixture was washed with 20 mL of 10% $KHCO_3$. Chromatography of the organic solution on a silica gel column that was eluted with increasing increments of from 5 to 10% EtOAc in hexane afforded 1.73 g (68%) of **5a** as a yellow solid: mp 124–6 °C; IR 1330, 1140, 1115, 1010, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (s, 3), 4.01 (s, 2), 7.05–7.17 (m, 1), 7.22–7.52 (m, 8), 7.80 (d, 1 J = 8), 7.90 (d, 1, J = 8). Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92, N, 10.29. Found: C, 83.46; H, 5.93; N, 10.12.

1-Phenyl-2-(phenylmethyl)phthalazinium Chloride (6). A solution of 5.00 g (23.8 mmol) of 2-benzoylbenzaldehyde[8] in 35 mL of THF was cooled in an ice bath and stirred while 16.5 g (119 mmol) of K_2CO_3 and then 5.16 g (26.2 mmol) of benzylhydrazine dihydrochloride was added. After the mixture was stirred for 10 min, the ice bath was removed, and after 45 min, 10 mL of CH_2Cl_2 was added. After a total reaction time of 1.5 h, the reaction mixture was filtered through Solca Floc and the residue washed well with CH_2Cl_2. Concentration of the filtrate gave a gum, which, after several recrystallizations from CH_2Cl_2/EtOAc, yielded 4.05 g (49%) of **6** as the monohydrate: mp 176.0–7.5 °C; IR 3435 br, 3015, 1575, 1450, 1325, 1030, 990, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (s, 2), 5.96 (s, 2), 7.08 (m, 2), 7.25 (m, 3), 7.72 (m, 4), 7.83 (m, 2), 8.06 (t, 1, J = 7.7), 8.28 (t, 1, J = 7.5), 8.88 (d, 1, J = 8.0), 10.37 (s, 1). Anal. Calcd for $C_{21}H_{17}ClN_2$·H_2O: C, 71.89; H, 5.46; N, 7.99. Found: C, 71.67; H, 5.34; N, 7.87. Anhydrous **6** was prepared but due to its hygroscopic nature, an acceptable elemental analysis could not be obtained. The ^1H NMR of the anhydrous **6** was identical with the hydrated **6** except that there was no signal at 1.97 (H_2O).

α-Phenylbenzenedimethanamine (1h). A slurry of 5.7 g (150 mmol) of LAH in 180 mL of THF was stirred while 16.7 g (75 mmol) of **4h** was added in portions during a 5-min period. The reaction mixture was heated at the reflux temperature 1 h, cooled in ice, and treated sequentially with 150 mL of Et_2O, 5.7 mL of H_2O, 5.7 mL of 15% NaOH, and 17.1 mL of H_2O. The resulting mixture was stirred 30 min, filtered, dried (Na_2SO_4), and concd on a rotary evaporator to give 17.6 g of a crude oil. This crude oil was dissolved in 200 mL of EtOH and 30 mL of ethanolic HCl (5.8 mmol/mL) added. This solution was hydrogenated over 2.0 g of 10% Pd–C at 45–53 °C on a Parr apparatus until hydrogen uptake ceased (4 h). The catalyst was removed by filtration and washed with 300 mL of hot MeOH. The combined alcoholic solutions were concd to 150 mL and diluted with 300 mL of Et_2O to give product in three crops. The combined solids were recrystallized from 200 mL of MeOH and 400 mL of Et_2O to give 14.1 g (67%) of 1-phenyl-1,2,3,4-tetrahydrophthalazine as the monohydrochloride: mp 258–60 °C; IR 3200, 2790, 1600, 1500 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.42 (s br, 2), 4.30 (d, 1, J = 16), 4.55 (d, 1, J = 16), 5.58 (s, 1), 6.73 (d, 1, J = 10), 7.15–7.55 (m, 8), 11.10 (s br, 1). Anal. Calcd for $C_{14}H_{14}N_2$·HCl: C, 68.15; H, 6.13; N, 11.35. Found: C, 68.03; H, 6.20; N, 11.41. To a solution of 10.0 g (41 mmol) of the above diamine monohydrochloride in 200 mL of warm MeOH was added 4 g of Raney nickel (Aldrich) active catalyst that had been washed with H_2O and MeOH. Hydrogenation of this mixture on a Parr apparatus at 49 °C for 6 h was followed by cooling to rt. The catalyst was removed by filtration, 10 mL of 6 M HCl in EtOH was added, and the solution was concd on a rotary evaporator. The residue was crystallized from MeOH/MeCN/Et_2O to give 11.1 g (89%) of **1h** as the dihydro chloride: mp 278–9 °C; IR 2850 br, 2065, 1610, 1515 cm^{-1}; ^1H NMR (D_2O) δ 3.98 (d, 1, J = 15), 4.25 (d, 1, J = 15), 4.78 (s, 6), 6.00 (s, 1), 7.32–7.78 (m, 9). Anal. Calcd for $C_{14}H_{16}N_2$·2HCl: C, 58.96; H, 6.36; N, 9.82. Found: C, 58.83; H, 6.46; N, 9.78.

3,4-Dihydro-1-phenyl-3-(1,1-dimethylethyl)phthalazine (5b). A slurry of 4.28 g (113 mmol) of LAH in 60 mL of THF was stirred and heated at the reflux temperature while a solution of 25.0 g (90 mmol) of **4i** in 240 mL of THF was added dropwise in 15 min. After 45 min at the reflux temperature, the reaction mixture was cooled in an ice bath and treated sequentially with 4.3 mL of H_2O, 4.3 mL of 15% NaOH, and 12.9 mL of H_2O. The resulting mixture was diluted with 150 mL of Et_2O, stirred 45 min, filtered through Solca Floc, and concd to give 21.8 g (92%) of **5b**: mp 90–6 °C; IR 2980, 2785, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9), 4.00 (s, 2), 7.18–7.49 (m, 7), 7.68 (d, 2, J = 8). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78, H, 7.63; N, 10.60. Found: C, 81.71; H, 7.60; N, 10.64.

2-(Aminophenylmethyl)-*N*-(1,1-dimethylethyl)benzamide (9a). A solution of 5.3 g (30 mmol) of *N*-(1,1-dimethylethyl)-benzamide[13] in 130 mL of THF was stirred at −20 °C while 26.4 mL (66 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes was added over 5 min. After the reaction mixture was stirred at −20 °C for 5 min, a heavy precipitate formed. This mixture was allowed to sit at 0 °C for 1 h and then stirred at −5 °C while 5.84 g (33 mmol) of *N*-(trimethylsilyl)benzalimine[4] was added over 5

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min. The resulting maroon solution was stirred at 0 °C for 1 h and at rt for 1 h. The solution was then poured into 150 mL of 1 M HCl, washed with Et_2O, made basic with 65 mL of 2 M NaOH, and extracted with Et_2O 2X. The Et_2O extracts were combined, dried (Na_2SO_4), and concd on a rotary evaporator to yield 8.0 g (94%) of **9a** as an oil that was pure by TLC (SiO_2 eluted with MeO–*t*-Bu:hexane:IPA = 30:67:3) and was converted to 4.75 g (50%) of **9a** as the monohydrochloride salt: mp 182.0–2.5 °C; IR 3240, 2960–2800 br, 2085, 1640, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.3 (s, 9), 5.95 (s, 1), 7.28–7.58 (m, 8), 7.71 (d, 1, J = 8), 8.05 (s, 1), 9.28 (s, 3). Anal. Calcd for $C_{18}H_{24}N_2O$·HCl: C, 67.80; H, 7.21; N, 8.79. Found: C, 67.80; H, 7.30; N, 8.72.

2-(Aminophenylmethyl)-*N*-methylbenzamide (9b) and 2,3-Dihydro-3-phenyl-1*H*-isoindol-1-one (10). A solution of 0.68 g (5.0 mmol) of *N*-methylbenzamide in 18 mL of THF was stirred at −10 °C while 4.4 mL (11 mmol) of 2.5 M *n*-butyllithium in hexanes was added in 5 min. The reaction mixture was stirred at 0 ± 2 °C for 1 h, and then 0.97 g (5.5 mmol) of *N*-(trimethylsilyl)benzalimine[4] was added in 3 min. After being stirred another 1 h at 0 °C and at rt for 1 h, the mixture was poured into ice–water containing 15 mL of 1 M HCl and washed with Et_2O 2X. The aqueous solution was then made basic with 2 M NaOH and extracted 2X with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and ethereal HCl was added. The resulting precipitate was crystallized from $CHCl_3$ and gave 0.50 g (36%) of **9b** as the HCl salt: mp 210–2 °C; IR 3250, 3150, 2900, 1625, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.72 (d, 3, J = 4), 6.02 (s, 1), 7.26–7.75 (m, 9), 8.52 (d, 1, J = 4), 9.25 (s, 3). Crystals formed in the aqueous basic solution and were collected to give 0.36 g (34%) of **10**: mp 222–4 °C (lit.[11] mp 218–20 °C).

Registry No. **1a**, 134389-96-1; **1b**, 134389-97-2; **1c**, 134389-98-3; **1d**, 134389-99-4; **1e**, 134390-00-4; **1f**, 134390-01-5; **1g**, 134390-02-6; **1h**·HCl, 134390-03-7; **1i**·2HCl, 134390-04-8; **1j**, 134390-06-0; **1k**, 134390-07-1; **1l**, 134390-08-2; **4a**, 49572-99-8; **4b**, 4725-83-1; **4c**, 134389-93-8; **4d**, 51107-08-5; **4e**, 134389-94-9; **4f**, 3306-73-8; **4g**, 134389-95-0; **4h**, 5004-45-5; **4i**, 134418-61-4; **5a**, 134390-09-3; **5b**, 134390-05-9; **6**, 134390-10-6; **8a**, 5894-65-5; **9a**·HCl, 134390-12-8; **9b**·HCl, 134390-13-9; **10**, 835-18-7; phenyllithium, 591-51-5; (2-methyl-1-naphthalenyl)phenylmethanone, 4919-69-1; methylhydrazine, 60-34-4; 2-benzoylbenzaldehyde, 16780-82-8; benzylhydrazine dihydrochloride, 20570-96-1; 1-phenyl-1,2,3,4-tetrahydrophthalazine monohydrochloride, 134390-11-7; *N*-(trimethylsilyl)benzalimine, 17599-61-0; *N*-methylbenzamide, 613-93-4; 2-(1-naphthoyl)benzoic acid, 5018-87-1; 2-phenylacetylbenzoic acid, 33148-55-9; 2-(4-methoxybenzoyl)benzoic acid, 1151-15-1; 2-benzoylbenzoic acid, 85-52-9; *tert*-butylhydrazine hydrochloride, 7400-27-3.

Supplementary Material Available: Experimental details and spectroscopic and analytical data for compounds **4c–e**, **4g**, **4i**, **1a–g**, and **1j–l** (5 pages). Ordering information is given on any current masthead page.

Amphidinolides G and H: New Potent Cytotoxic Macrolides from the Cultured Symbiotic Dinoflagellate *Amphidinium* sp.

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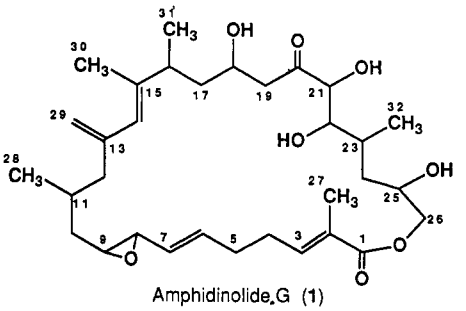
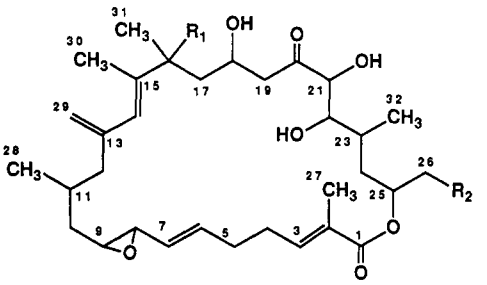
Marine microorganisms have proven to be a new valuable source of compounds with interesting pharmacological activities.[2] During our studies on bioactive substances from Okinawan marine organisms,[3] we have investigated symbiotic microalgae associated with marine invertebrates and previously isolated five novel cytotoxic macrolides, amphidinolides A–E, from the cultured dinoflagellates.[4] Our continuing search for more pharmacologically useful substances from cultured dinoflagellates of the genus *Amphidinium* has now led to the isolation of two new cytotoxic macrolides, amphidinolides G (1) and H (2), possessing extremely potent cytotoxic activity. This paper describes the isolation and structure elucidation of 1 and 2.



Amphidinolide G (1)



R_1=H, R_2=OH Amphidinolide H (2)
R_1=OH, R_2=H Amphidinolide B (3)

The dinoflagellate *Amphidinium* sp.[5] was isolated from the Okinawan flatworm *Amphiscolops breviviridis* and grown unialgally in a sea-water medium enriched with 1% Provasoli's ES supplement at 25 °C for 2 weeks.[4c] The harvested cells (70 g from ca. 160 L of culture) were extracted with methanol–toluene (3:1), and the extracts were partitioned between toluene and 1 M aqueous NaCl. The toluene-soluble fraction was chromatographed on a silica

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(5) This species of *Amphidinium* is different from those reported previously.[4]

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