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Synthesis of the Parent Compound and *N*-Substituted Derivatives of 1*H*-Benz[*de*]isoquinoline and Benz[*de*]isoquinolinium-1-ide

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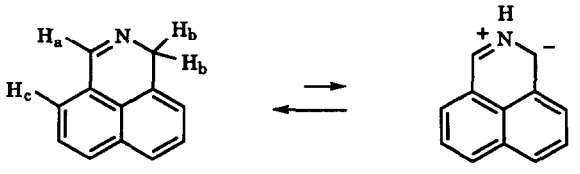
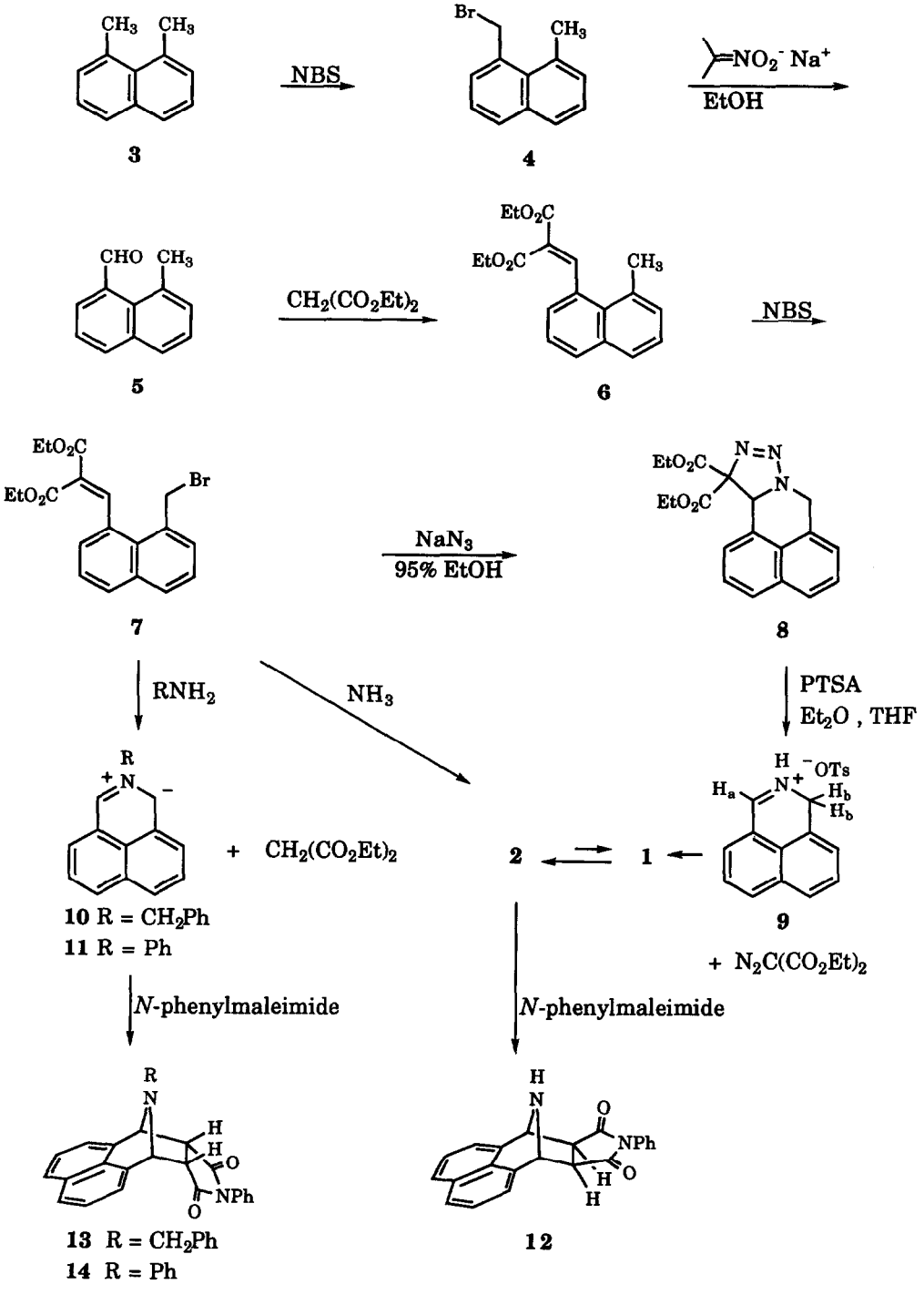
Abstract: The parent system 1*H*-benz[*de*]isoquinoline **1** was synthesized by the 1,3-dipolar cycloaddition and cycloreversion method, or by direct reaction of bromo-alkylidene **7** with ammonia. *N*-Substituted derivatives **10** and **11** were also prepared from **7** by treatment with benzylamine and phenylamine, respectively. 1*H*-Benz[*de*]isoquinoline **1** tautomerizes to benz[*de*]isoquinolinium-1-ide **2**. Compounds **2**,**10**,and **11** were not isolable, but trapped with *N*-phenylmaleimide to give cycloadducts **12-14**.

1*H*-Benz[*de*]isoquinoline **1** and benz[*de*]isoquinolinium-1-ide **2** are tautomers. A 1,2-proton shift in **1** would generate the highly reactive azomethine ylide **2**. However, these parent heterocyclic systems are unknown. Only the *N*-alkyl and -aryl derivatives were synthesized by Ikeda[1] and Oehlschlager[2]. Recently, we developed a tandem 1,3-dipolar cycloaddition-cycloreversion method,[3] and a retro-malonate addition method[4] for the synthesis of iso-condensed heteroaromatic pyrroles. In the present work, we applied these methods to the synthesis of the parent compound **1** and its *N*-substituted derivatives **10** and **11**.



1 **2**

Bromination of 1,8-dimethylnaphthalene **3**[5] with *N*-bromosuccinimide (NBS) gave bromide **4**. Treatment of bromide **4** with the sodium salt of 2-nitropropane afforded


CH3 CH3
NBS
Br
CH3
=NO2- Na+
EtOH
3
4
CHO CH3
CH2(CO2Et)2
EtO2C
EtO2C
CH3
NBS
5
6
EtO2C
EtO2C
Br
NaN3
95% EtOH
N=N
N
EtO2C
EtO2C
7
8
RNH2
NH3
PTSA
Et2O , THF
R
+ N
-
+ CH2(CO2Et)2
2
1
H -OTs
Ha
N+
Hb
Hb
10 R = CH2Ph
11 R = Ph
9
+ N2C(CO2Et)2
N-phenylmaleimide
N-phenylmaleimide
R
N
H
H
O
NPh
O
H
N
O
NPh
O
H
H
13 R = CH2Ph
14 R = Ph
12

aldehyde **5**.[6] Knoevenagel condensation of **5** with diethyl malonate gave rise to alkylidenemalonate **6** which was subjected to bromination with NBS to give bromide **7**. S_N2 substitution of bromide **7** with sodium azide followed by 1,3-dipolar cycloaddition afforded triazoline **8**. Treatment of **8** with 1.1 equiv. of *p*-toluenesulfonic acid in ether yielded salt **9** and diethyl diazomalonate *via* a 1,3-dipolar cycloreversion reaction.[3] Salt **9** was isolated by filtration. When the ^1H NMR spectrum of **9** was recorded in D_2O, no hydrolysis of the iminium salt was observed. A triplet at δ 8.69 of H_a due to coupling with H_b clearly indicated the presence of the iminium moiety, as any aromatic aldehyde resulting from hydrolysis would have shown a proton signal above δ 9.0. The H_b of -NCH_2- appears as broad singlet due to the long-range coupling both with imine H_a and aromatic proton. Treatment of salt **9** in $CDCl_3$ with sodium bicarbonate in D_2O, in an NMR tube, afforded 1H-benz[*de*]isoquinoline **1**. The NMR spectrum of **1** was recorded immediately. Figure 1 shows the spectrum of salt **9**. Figure 2 shows the spectra of free base **1** with some decoupling experiments. Irradiation of peak at δ 5.45 (H_b) induces the collapse of the broad singlet at δ 8.58 (H_a) into a doublet. Irradiation of peak at δ 8.58 induces the collapse of the broad singlet at δ 6.97 (aromatic H_c) into a broad doublet. These decoupling experiments indicate the coupling between H_a and H_b, and between H_a and H_c in parent compound **1**. Benz[*de*]isoquinolinium-1-ide **2** was not detected by ^1H NMR. When salt **9** was treated with triethylamine and *N*-phenylmaleimide, *exo*-cycloadduct **12** was formed *via* 1,3-dipolar cycloaddition of **2** with *N*-phenylmaleimide.

Treatment of bromide **7** with ammonia yielded compound **1** directly. Similar treatment of **7** with benzylamine and with phenylamine resulted in the formation of *N*-substituted benz[*de*]isoquinolinium-1-ides **10** and **11**, respectively. These unstable products, which were not isolable, were trapped with *N*-phenylmaleimide to give cycloadducts **12-14**.[1] A single crystal *X*-ray analysis confirmed the structure of **13**, Figure 3. Cycloadducts **13** and **14** were formed by *endo* addition presumbly due to the steric repulsion, in each case, between the *N*-substituents of the reactants.

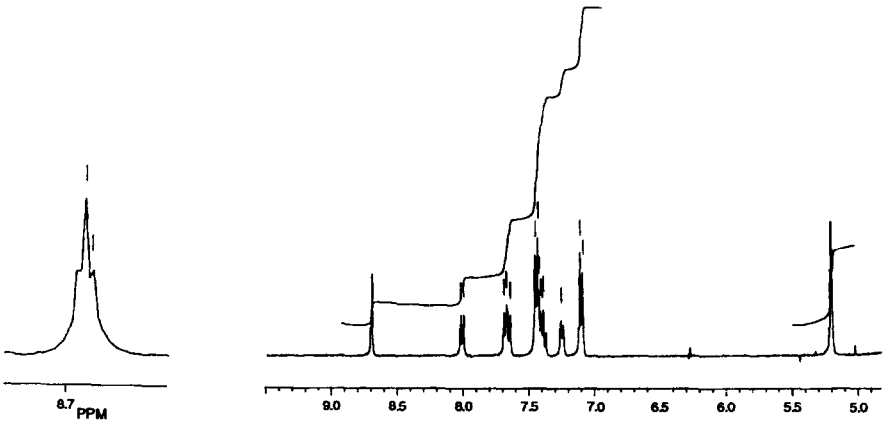


Figure 1. ^1H NMR Spectrum of Salt **9** in D_2O

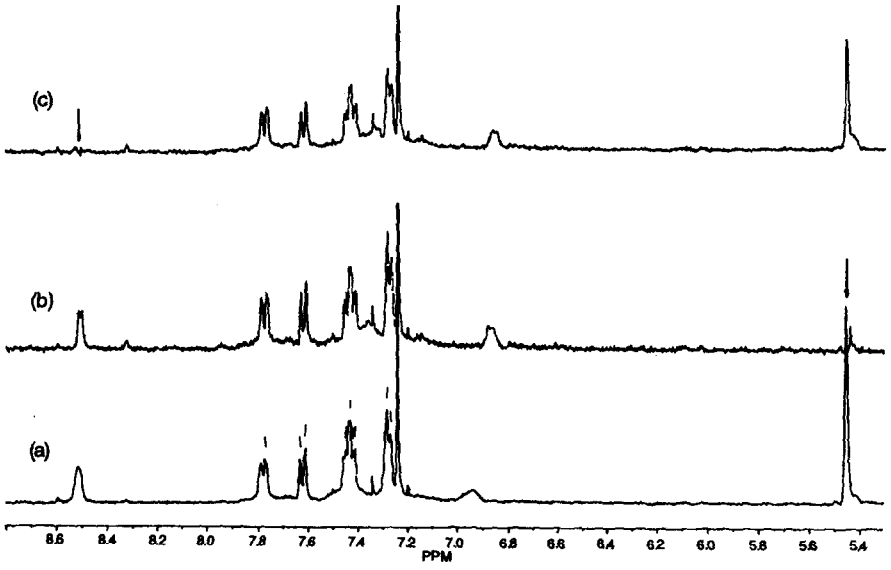


Figure 2. ^{1}H NMR Spectra of **1** with Decoupling Experiments (a) δ 5.4~8.8 expanded (b) irradiated at δ 5.45 (c) irradiated at δ 8.58

In summary, we report the first synthesis of parent compound **1**, and the alternative route leading to its derivatives. The structure of **1** was confirmed by ^{1}H NMR studies, and those of its tautomer **2** and derivatives **10**, and **11** were confirmed by trapping with *N*-phenylmaleimide.

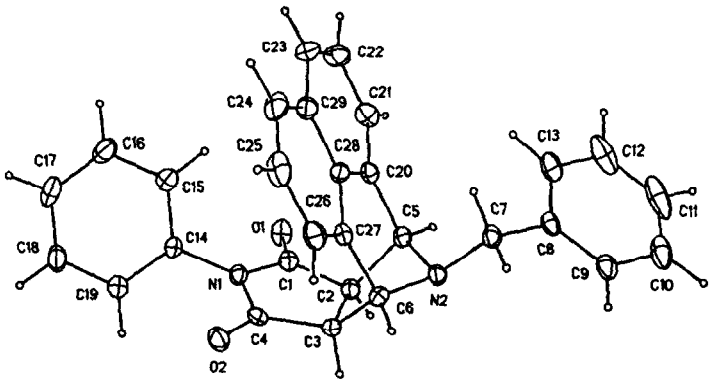


Figure 3. Crystal Structure of **13** Generated by SHELXTL PLUS

Experimental Section

General. ^{1}H NMR spectra were recorded on a Varian EM-390, a JEOL HX-100 or a Bruker AM-400 spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer. Mass spectra refer to the electron impact mass spectra and were recorded on a JEOL TMS-D-100 mass spectrometer. High-resolution mass spectra were recorded on a JEOL HX-110 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 781 spectrometer, and UV spectra on a Perkin-Elmer Lambda 5 UV-VIS spectrometer. Melting points determined with a Büchi 530 melting-point apparatus and are uncorrected. Flash-column chromatography was performed as follows: silica gel, Merck No. 7736 Kieselgel 60H, was placed in a sintered-glass column packed dry. Solvent was flushed through the silica gel under a water-aspirator vacuum. The compound was then deposited with a minimal amount of solvent and eluted with solvent under a water aspirator vacuum. Diethyl ether and tetrahydrofuran (THF) were distilled from potassium/sodium metal under a nitrogen atmosphere with benzophenone ketyl as the indicator. All reactions were conducted under a nitrogen atmosphere. Elemental analyses were performed by the Microanalytical Laboratory of the NSC Regional Instrumentation Center operated by Department of Chemistry, National Cheng Kung University, Tainan, Taiwan.

1-Bromomethyl-8-methylnaphthalene (4). To 1,8-dimethylnaphthalene **3** (647 mg, 4.15 mmol) in carbon tetrachloride (40 mL) was added *N*-bromosuccinimide (691 mg, 3.93 mmol) and dibenzoyl peroxide (3 mg). The mixture was heated to reflux for 6 h. After cooling to room temperature, filtration and concentration gave crude product **4** that was used for next step without further purification.

8-Methyl-1-naphthaldehyde (5). To a solution of the sodium salt of 2-nitropropane (654 mg, 5.89 mmol) in absolute ethanol (50 mL) was added a solution of crude **4** from the above experiment in absolute ethanol (15 mL) dropwise. The reaction mixture was stirred at room temperature for 4 h. Concentration gave an oily crude product that was triturated with dichloromethane. The unwanted solid salt was removed by filtration. Concentration of the filtrate and silica gel chromatography (ethyl acetate: hexane, 1:6) gave brown solid **5** (388 mg, 55%, 2 steps from **3**): mp 69-70°C; IR (KBr) 1655 cm^{-1} ; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.72 (s, 3 H), 7.18-8.10 (m, 6 H), 10.81 (s, 1 H); MS *m*/*z* (relative intensity) 170 (M^+, 100), 169 (27), 141 (14).

Diethyl [(8-Methyl-1-naphthyl)ethylene]malonate (6). To a solution of **5** (388 mg, 2.28 mmol) in benzene (70 mL) was added diethyl malonate (754 mg, 4.71 mmol), piperidine (0.10 mL, 1.01 mmol), and acetic acid (0.06 mL, 1.05 mmol). The reaction mixture was heated to reflux with a Dean-Stark water separator for 24 h. Concentration and silica gel chromatography (ethyl acetate: hexane, 1:19) gave **6** as a yellow oil (631 mg, 89%): IR (neat) 1730, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.86 (t, 3 H, *J* = 6.1 Hz), 1.31 (t, 3 H, *J* = 6.1 Hz), 2.78 (s, 3 H), 4.01 (q, 2 H, *J* = 6.1 Hz), 4.29 (q, 2 H, *J* = 6.1 Hz), 7.27-7.88 (m, 6 H), 8.53 (s, 1 H).

MS *m/z* (relative intensity) 312 (M^+, 73), 267 (41), 266 (100), 220 (96), 152 (23). HRMS Calcd for $C_{19}H_{20}O_4$ 312.1361, found 312.1362.

Diethyl [(8-Bromomethyl-1-naphthyl)ethylene]malonate (7). To a solution of **6** (52 mg, 0.17 mmol) in carbon tetrachloride (10 mL) was added *N*-bromosuccinimide (36 mg, 0.20 mmol) and dibenzoyl peroxide (2 mg). The reaction mixture was heated to reflux for 10 h. After cooling to room temperature, the mixture was diluted with dichloromethane (10 mL), and washed with water and then with brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography (ethyl acetate: hexane, 1:16) gave **7** as a yellow oil (60 mg, 90%) : IR (KBr) 1765, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.84 (t, 3 H, *J* = 8.1 Hz), 1.32 (t, 3 H, *J* = 6.3 Hz), 3.99 (q, 2 H, *J* = 6.3 Hz), 4.32 (q, 2 H, *J* = 8.1 Hz), 4.89 (s, 2 H), 7.34-7.84 (m, 6 H), 8.91 (s, 1 H). MS *m/z* (relative intensity) 392 (M+2, 27), 390 (M^+, 27). 311 (20), 265 (100), 264 (80). HRMS Calcd for $C_{19}H_{19}BrO_4$ 390.0467, found 390.0475.

3,3-Bis-(ethoxycarbonyl)-3,3a-dihydro[1.2.3]triazolo[1',5':1,2]-10*H*-benz[*de*]isoquinoline (8). To a solution of **7** (33 mg, 0.084 mmol) in 95% ethanol (3 mL) was added sodium azide (16 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 3 h. Concentration and silica gel chromatography (ethyl acetate: hexane, 1:6) gave colorless solid **8** (27 mg, 90%): mp 110-112°C; IR (KBr) 1740, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.60 (t, 3 H, *J* = 7.2 Hz), 1.40 (t, 3 H, *J* = 7.0 Hz), 3.62-3.76 (m, 2 H), 4.35-4.53 (m, 2 H), 4.95 (d, 1 H, *J* = 16.3 Hz), 5.65 (d,1 H, *J* = 16.3 Hz), 5.97 (s, 1 H), 7.24-7.46 (m, 4 H), 7.73 (t, 2 H, *J* = 7.7 Hz); MS *m/z* (relative intensity) 354 (M^++1, 6), 353 (M^+, 3), 325 (M^+-28, 29), 280 (100), 252 (37), 167 (100). HRMS Calcd for $C_{19}H_{19}N_3O_4$ 353.1375, found 353.1377.

***3H*-Benz[*de*]isoquinolinium *p*-Toluenesulfonate (9).** To a solution of *p*-toluenesulfonic acid (12 mg, 0.071 mmol) in anhydrous tetrahydrofuran (3 mL) and ether (2 mL) was added a solution of **8** (21 mg, 0.059 mmol) in anhydrous ether (3 mL). The reaction mixture was stirred at room temperature for 3 h. A solid precipitated after standing. The ether was removed with a syringe. The solid was washed three times with anhydrous ether. Removal of residual solvent under vacuum gave yellowish salt **9** (19 mg, 93%): IR (KBr) 3650-3300, 1665 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 2.14 (s, 3 H), 5.20 (s, 2 H), 7.10 (d, 2 H, *J* = 8.1 Hz), 7.24(d, 1 H, *J* = 7.9 Hz). 7.40-7.45 (m, 4 H), 7.64-7.68 (m, 2 H), 8.00 (d, 1 H, *J* = 8.4 Hz), 8.69 (t, 1 H, *J* = 1.5 Hz); UV (H_2O) λ_{max} (log ε) 252.0 (3.43). 347.2 (1.05), 370.0 (2.20), 391 (2.27); MS *m/z* (relative intensity) 172 (M^+-167, 100), 167(M^+-172, 70).

^1H NMR Spectrum of 3*H*-Benz[*de*]isoquinoline (1). To a small sample of salt **9** in $CDCl_3$ (0.3 mL) was added a solution of sodium bicarbonate (1M) in D_2O (0.5 mL) in an NMR tube. After vigorous shaking, the ^1H NMR spectrum of free base **1** was recorded immediately : ^1H NMR (400 MHz) δ 5.45 (s, 2 H), 6.97 (br s, 1 H), 7.27 (d, *J* = 12 Hz, 1 H), 7.40-7.45 (m, 2 H), 7.64 (d, *J* = 12 Hz, 1 H), 7.80 (d, *J* = 12 Hz, 1 H), 8.58 (br s, 1 H).

***exo*-7,8,9,10-Tetrahydro-7,10-iminocyclohepta[*de*]naphthalene-8,9-*N*-phenyldicarboximide (12). Method A:** To a solution of **8** (100 mg, 0.31 mmol) in dichloromethane was added a solution of *p*-toluenesulfonic acid (64 mg, 0.37 mmol) in dichloromethane (30 mL), and a solution of *N*-phenylmaleimide (108 mg, 0.62 mmol) and triethylamine (0.05 mL, 0.39 mmol) in dichloromethane (2 mL) dropwise. After stirring for 36 h, the reaction mixture was diluted with dichloromethane (20 mL), washed with water, and dried ($MgSO_4$). Concentration and silica gel chromatography (ethyl acetate: hexane: CH_2Cl_2, 1:5:5) gave pale yellow solid **12** (75 mg, 71%): mp 238-240°C. **Method B:** To a solution of **7** (20 mg, 0.051 mmol) in 95% ethanol (1.5 mL) was added a solution of aqueous ammonia (25%, 0.07 mL, 1.02 mmol) in 95% ethanol (5 mL) dropwise. After stirring for 6 h, ammonia and solvent were removed under vacuum. *N*-Phenylmaleimide (44 mg, 0.26 mmol) in dichloromethane (7 mL) was added. The reaction mixture was stirred at room temperature for 24 h. Concentration and silica gel chromatography (ethyl acetate: hexane, 1:6) gave **12** (5.3 mg, 31%): IR (KBr) 3310, 1775, 1695, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.42 (s, 2 H), 5.00 (s, 2 H), 7.24-7.76 (m, 11 H); UV (CH_2Cl_2) λ_{max} (log ε) 234.0 (3.75), 288.0 (2.97); MS *m*/*z* (relative intensity) 340 (M^+, 4), 167 (100); HRMS Calcd for $C_{22}H_{16}N_2O_2$ 340.1212, found 340.1204.

***endo*-7,8,9,10-Tetrahydro-11-benzyl-7,10-iminocyclohepta[*de*]naphthalene-8,9-*N*-phenyldicarboximide (13).** To a solution of **7** (20 mg, 0.051 mmol) and *N*-phenylmaleimide (23 mg, 0.13 mmol) in dichloromethane (2.5 mL) was added a solution of benzylamine (0.01 mL, 0.1 mmol) in dichloromethane (10 mL) dropwise. After stirring at room temperature for 40 h, the reaction mixture was diluted with dichloromethane, washed with dilute HCl (10%), saturated sodium bicarbonate, brine, and then dried ($MgSO_4$). Concentration and silica gel chromatography (ethyl acetate: hexane: CH_2Cl_2, 1:2:10) gave **13** (16 mg, 72%) as a white solid: IR (KBr) 1770, 1715, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.52 (s, 2 H), 4.13 (m, 2 H), 4.73 (m, 2 H), 5.98 (d, J = 7.3 Hz, 2 H), 7.09-7.48 (m, 12 H), 7.79 (d, 2 H, J = 8.5 Hz); MS *m*/*z* (relative intensity) 430 (M^+, 6), 258 (28), 257 (100); HRMS Calcd for $C_{29}H_{22}N_2O_2$ 430.1681, found 430.1682. Anal. Calcd for $C_{29}H_{22}N_2O_2$: C, 71.09; H, 6.70; N, 10.36. Found: C, 71.21; H, 6.67; N, 10.38.

***endo*-7,8,9,10-Tetrahydro-11-phenyl-7,10-iminocyclohepta[*de*]naphthalene-8,9-*N*-phenyldicarboximide (14).** To a solution of **7** (20 mg, 0.051 mmol) and *N*-phenylmaleimide (23 mg, 0.13 mmol) in dichloromethane (2 mL) was added a solution of phenylamine (0.01 mL, 0.11 mmol) in dichloromethane (10 mL). After stirring at room temperature for 48 h, the reaction mixture was diluted with dichloromethane (10 mL), washed with water, brine, and then dried ($MgSO_4$). Concentration and silica gel chromatography (ethyl acetate: hexane, 1:6) gave yellow solid **14** (13 mg, 62%): mp 260-262°C; IR (KBr) 1780, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.26-4.28 (m, 2 H), 5.65-5.67 (m, 2 H), 6.01-6.03 (m, 2 H), 6.68 (t, J = 7.2 Hz, 1 H), 6.68 (d, J = 8.5 Hz, 2 H), 7.05-7.44 (m, 9 H), 7.64 (d, J = 7.9 Hz, 2 H); MS *m*/*z* (relative intensity) 416 (M^+, 53), 243 (100).

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7. Crystal data of **13** : $C_{29}H_{22}N_2O_2$: M = 430.5, monoclinic, space group $P2_1/c$, a = 10.161(2), b = 15.473(3), c = 14.566(2) Å, b = 108.08(2)°, Z = 4, D_c = 1.313 g/cm^3. 3680 Independent reflections were measured of which 1943 were considerated observed [$I > 3.0\sigma(I)$]. The structure was solved by direct methods to an R value of 0.0407. All calculations were performed on a MicroVax II based Nocolet SHELXTL PLUS system. Atomic co-ordinates, bond lengths and angels, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center.

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