Synthesis and Structural Determination of 5*H*-Benzocyclohepten-5,8-imines

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Treatment of 4-hydroxy-*N*-methylisoquinolinium iodide with triethylamine in tetrahydrofuran or acetonitrile forms 2-methyl-4-oxidoisoquinolinium (**2**) *in situ*. Once formed, **2** can be trapped with dipolarophiles possessing varying degrees of activation to form the 5*H*-benzocyclohepten-5,8-imine ring system. Various 2-D nmr experiments were used in the identification of the stereochemical and regiochemical assignments for the ring system.

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Introduction.

As part of a program directed toward the synthesis of ligands for PCP site 1 and site 2 [1], we were interested in preparing substituted analogs of the 5*H*-benzocyclohepten-5,8-imine ring system **1**. MK-801 which binds potently to PCP site 1 (NMDA coupled site) is a substituted analog of **1** (Figure 1). Dennis and Katritzky reported that the desired ring system could be formed by the 1,3-dipolar cyclo-

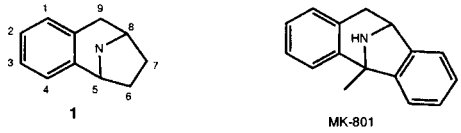


Figure 1. 5H-Benzocyclohepten-5,8-imine Ring System

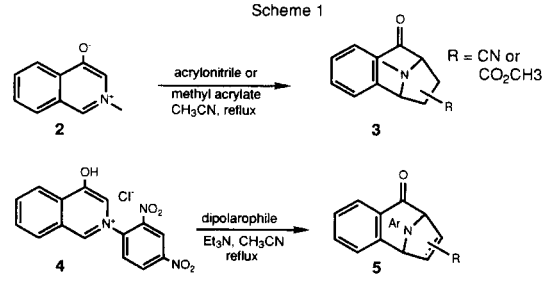
addition reaction of activated dipolarophiles with 2-methyl-4-oxidoisoquinolinium **2** [2]. These authors showed that preformed betaine **2** form cycloadducts **3** when treated with acrylonitrile and methyl acrylate but failed to give isolatable products when treated with acetylenic compounds such as dimethyl acetylenedicarboxylate (DMAD). In a latter study these authors reported that the replacement of *N*-methyl with *N*-Ar groups was required for the formation of betaines *in situ* by the addition of triethylamine to *N*-aryl-4-hydroxyisoquinolinium compounds such as **4** [3]. This modified procedure led to successful 1,3-dipolar cycloaddition reactions with activated as well as less reactive dipolarophiles to give the expected adducts **5** (Scheme 1) [4]. This study reports the results obtained from the cycloaddition reaction of *N*-methyl betaine **2** formed *in situ* with dipolarophiles possessing varying degrees of activation.

Synthesis.

In order to investigate whether the *N*-methyl betaine could be generated *in situ*, we treated isoquinolinium iodide **6** with triethylamine in the presence of acrylonitrile and found that all four possible cycloadducts were formed (Table 1). Preparative hplc was used to separate the four compound mixture into three fractions. The first fraction contained a mixture of compounds **7** and **10**, which could be separated by fractional recrystallization from methanol. The second and third hplc fractions contained compounds **9** and **8**, respectively. One of the adducts, **7**, was identical [5] to the compound characterized by Dennis and Katritzky [2].

Other activated dipolarophiles reacted with **6** and gave cycloadducts in good yields. For example the reaction with phenyl vinyl sulfone gave a 81% yield of the two regioisomers **11** and **12** in a 80:20 ratio (Table 1). Both products which were separated by hplc possessed the exo configuration. When 1,4-benzoquinone and 1,4-naphthoquinone were used as dipolarophiles the hydroquinones **13** and **14** were obtained (Scheme 2). In contrast to preformed betaine **2** in which cycloadducts were not isolatable [3], ace-

Scheme 1



Scheme 2

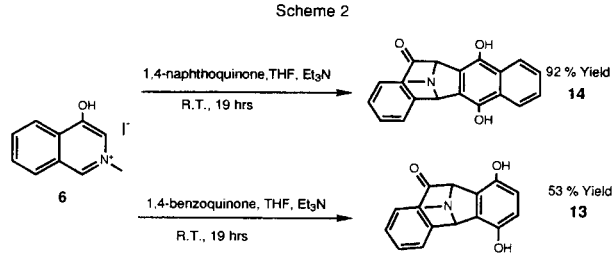
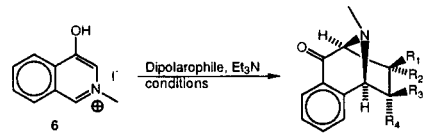


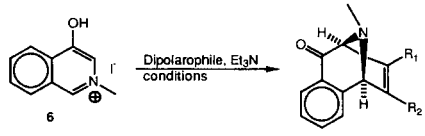
Table 1. Reaction of 6 with Olenifinic Dipolarophiles



	Dipolarophile	Conditions	No.	Product R1	R2	R3	R4	Ratio	Yield
(1)	acrylonitrile	THF, rt, 20 h	**7**	H	H	CN	H	32	63%
			8	H	H	H	CN	30	
			9	H	CN	H	H	18	
			10	CN	H	H	H	20	
(2)	C_6H_5–S(=O)(=O)–CH=CH$_2$	THF, rt, 18 h	**11**	H	H	$SO_2C_6H_5$	H	80	81%
			12	$SO_2C_6H_5$	H	H	H	20	
(3)	styrene	CH_3CN, reflux, 24 h	**20**	H	C_6H_5	H	H	83	79%
			21	H	H	H	C_6H_5	17	

tylenic dipolarophiles were shown to undergo the 1,3-dipolar cycloaddition reaction with compound **6**. When compound **6** was treated with triethylamine in the presence of DMAD, compound **15** was formed in a 92% isolated yield (Table 2).

Table 2. Reaction of 6 with Acetylinic Dipolarophiles



	Dipolarophile	Conditions	No.	Product R1	R2	Ratio	Yield
(1)	CH_3CO_2–≡–CO_2CH_3	THF, rt, 18 h	**15**	CO_2CH_3	CO_2CH_3	--	92%
(2)	⬭–≡–H phenylacetylene	CH_3CN, reflux 18 h	**18**	C_6H_5	H	66	77%
			19	H	C_6H_5	33	
(3)	⬭–≡–CH_3 1-phenyl-1-propyne	CH_3CN, 120°C. sealed tube 4 days	**17**	C_6H_5	CH_3	62	59%
			16	CH_3	C_6H_5	38	

Three less reactive dipolarophiles, styrene, phenyl acetylene and 1-phenylpropyne, were also treated with compound **6** in the presence of triethylamine. Since these dipolarophiles were unreactive at room temperature, it was necessary to change the reaction conditions to refluxing acetonitrile or in the case of 1-phenylpropyne, 120° in a sealed tube with acetonitrile as solvent. Under these more stringent conditions all three dipolarophiles gave cycloadducts. Styrene gave two of the four possible isomers, **20** and **21**, in a 83:17 ratio with a 79% isolated yield. Phenyl acetylene gave both possible regioisomers, **18** and **19**, in a 67:33 ratio with a 77% isolated yield. 1-Phenylpropyne gave two products, **16** and **17**, in a 38:62 ratio of regioisomers which were separated by hplc in a combined yield of 59%.

NMR Studies.

Various nmr methods including COSY, NOESY, inverse detected heteronuclear multiple quantum correlation (HMQC) [7] and inverse detected heteronuclear multiple bond correlation (HMBC) [6] were used for structural assignments.

Four possible compounds can form in cycloadditions with acrylonitrile, phenyl vinyl sulfone and styrene; two regioisomers as well as two stereoisomers. Stereochemical assignments can be made based on the multiplicity of the bridgehead protons. Since the dihedral angle between the endo protons and the bridgehead protons is approximately 90 degrees the vicinal coupling, $^3J_{HH}$, is nearly zero. Conversely, the dihedral angle between the exo protons and the bridgehead protons is approximately 20 degrees which induces a $^3J_{HH}$ of around 7 Hz giving rise to a doublet for the bridgehead proton. Regiochemical assignments could be made based on the proton adjacent to the nitrile, sulfone or phenyl substituent. The chemical shift of the proton indicated the adjacent functional group and the regiochemistry of the proton could be deduced from COSY and NOESY spectra.

In the 1,3-dipolar cycloaddition reactions with acrylonitrile all four possible products were formed. Compound **7** was assigned as having the exo-6-cyano configuration. The resonance at 4.48 ppm is correlated with the aromatic proton H-4 in the NOESY spectrum which identifies the resonance of 4.48 ppm as proton H-5. Furthermore, the resonance is a singlet which indicates an adjacent exo substituent. In compound **8**, endo-6-cyano, both bridgehead protons appear as doublets indicating the endo configuration. Bridgehead proton H-5 could again be identified by an interaction with aromatic proton H-4 in the NOESY spectrum. Proton H-6 could be identified by a correlation to H-5 in the COSY spectrum. The chemical shift of H-6 indicated that the nitrile was adjacent to H-6. The final two compounds **10** and **9** were assigned the 7-exo and 7-endo

configuration, respectively, based on the multiplicity of the bridge head resonances.

In the 1,3-dipolar cycloaddition reaction with phenyl vinyl sulfone only the two exo products were formed. The exo assignments were made based on the observation that each compound exhibited both a singlet and a doublet for the bridgehead protons. Compound **12** was assigned the exo-7-phenylsulfone configuration based on the bridgehead doublet which showed a correlation to the aromatic proton H-4 in the NOESY spectrum. Compound **11** was, therefore, the exo-6-phenylsulfone regioisomer.

In compounds where additional aromatic rings were present the assignment of bridgehead proton H-5 can be difficult. Therefore the adducts from the reactions of styrene, phenyl acetylene and 1-phenylpropyne were determined based on HMBC and HMQC analysis. In the 1,3-dipolar cycloaddition reaction with styrene only the two endo products were formed. The endo assignments were made based on the observation that each compound exhibited doublets for both bridgehead protons. Compound **20** was assigned the endo-7-phenyl configuration based on the bridgehead proton H-8 which showed a correlation to the carbonyl carbon (C-9, 196.8 ppm) *via* a two bond $^2J_{CH}$ coupling in the HMBC spectrum. The same proton, H-8, also showed a correlation to the H-7 exo proton in the HMQC spectrum. The H-7 exo proton was established based on its resonance of 4.15 ppm indicating an adjacent aromatic substituent. Compound **21** was assigned the endo-6-phenyl configuration in a similar manner. In this case the bridgehead proton that showed the correlation to the carbonyl carbon *via* a $^2J_{CH}$ coupling in the HMBC spectrum did not show a correlation to the proton with the adjacent aromatic substitutent in the HMQC.

In the reaction with phenyl acetylene, compound **18** was assigned the 7-phenyl configuration based on the observation that the bridgehead proton which showed a correlation to the carbonyl carbon *via* a $^2J_{CH}$ coupling in the HMBC sepctrum was a singlet. Likewise compound **19** was assigned the 6-phenyl configuration since the bridgehead proton which showed a correlation to the carbonyl carbon in the HMBC spectrum was a doublet.

In the 1,3-dipolar cycloaddition reaction with 1-phenylpropyne, compound **16** was established to have the 7-methyl-6-phenyl configuration based on HMBC and HMQC analysis. The bridgehead proton H-8 was established by its correlation to the carbonyl carbon (C-9, 191.9 ppm) *via* a two bond $^2J_{CH}$ coupling. The methyl protons H-11 were correlated *via* a three bond $^3J_{CH}$ coupling to the carbon at 83.8 ppm which was identified by HMQC as C-8. Compound **17** was assigned the 6-methyl-7-phenyl configuration in a similar manner. In this compound proton H-8 correlates to C-9 (carbonyl carbon) *via* a two bond coupling and the methyl protons H-11 correlate to C-5 *via* a three bond coupling. The HMQC analysis shows that in this compound proton H-8 correlates with C-8, not the same carbon the methyl protons are correlated with.

Conclusion.

Treatment of 4-hydroxy-*N*-methylisoquinolinium iodide with triethylamine in tetrahydrofuran or acetonitrile provides a convenient procedure for forming 2-methyl-4-oxidoisoquinolinium (**2**) *in situ*. Once formed, **2** can be trapped with dipolarophiles, including unactivated olefines and acetylenes, to form the 5*H*-benzocyclohepten-5,8-imine ring system of MK-801. Various 2-D nmr experiments were used in the identification of the stereochemical and regiochemical assignments for ring system. Previously lanthanide induced shifts were used to identify these cycloaddition products. In the present case this could cause difficulties in assignments especially with a small methyl substituent on nitrogen.

EXPERIMENTAL

The starting 4-hydroxy-*N*-methylisoquinolinium iodide was prepared according to the reported procedure [8]. The nmr spectra were recorded on a Bruker AMX-250 (^{1}H at 250.13 MHz, ^{13}C at 62.53 MHz) or on a Bruker AMX-500 (^{1}H at 500.13 MHz, ^{13}C at 125.77 MHz) spectrometer as indicated and their values were expressed in ppm in reference to tetramethylsilane.

Procedures for 2-D NMR Experiments.

All nmr spectra were recorded on a Bruker AMX-500 spectrometer operating at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C. All data were obtained using a 5 mm inverse detection broadband probe. Typical 90° pulses were 8.1 microseconds for ^{1}H and 8.8 microseconds for ^{13}C. The double quantum filtered phase sensitive COSY spectra were obtained using the pulse sequence of Shaka and Freeman [9] with the modified phase cycle of Derome and Williamson [10]. The data were acquired as 1024 x 512 points with a spectral width of 4761.9 Hz in both domains. The data were apodized with a squared sine function and zero filled to 2048 x 2048 points prior to Fourier transformation. NOESY spectra were acquired with a mixing time of 1.2 seconds and a recycle delay of 10 seconds. NOESY data were processed in a manner similar to the COSY data.

HMQC spectra were obtained using the pulse sequence of Bax and Subramanian [7]. The data were acquired as 1024 x 256 points with a spectral width of 4761.9 in F2 and 26315.8 in F1. $\frac{1}{2}J_{CH}$ delays were optimized for an average coupling of 145 Hz. The data were apodized with a squared sine function and zero filled to 2048 x 512 points prior to Fourier transformation. HMBC were obtained using the pulse sequence of Bax and Summers [6] the data were obtained as 1024 x 256 points with a spectral width of 4761.9 Hz in F2 and 26315.8 in F1. For evolution of long range couplings, $\frac{1}{2}J$ delays were optimized for a coupling of 8 Hz. The data were apodized with a gaussian function and zero filled to 2048 x 512 points prior to Fourier transformation.

General Procedure for Formation of Amine Hydrochloride Salts.

A 0.05 molar solution of amine in dry ether was treated with 1.1 equivalents of hydrogen chloride (1*M* solution in ether). The resulting precipitate was filtered and washed with dry ether to yield the hydrochloride salt.

(exo-6-Cyano), (endo-6-cyano), (endo-7-cyano) and (exo-7-cyano)-*N*-methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imines **7**, **8**, **9** and **10** Respectively.

To a stirred solultion of 4-hydroxy-*N*-methylisoquinolinium iodide (0.7331 g, 2.53 mmoles) and acrylonitrile (0.20 ml, 3.04 mmoles) in dry tetrahydrofuran (15 ml) under nitrogen was added triethylamine (0.42 ml, 3.02 mmoles). The solution was allowed to stir at room temperature for 20 hours. The mixture was diluted with ether (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a yellow solid. The solid was purified by flash column chromatography (silica gel, chloroform) to yield a yellow solid (0.340 g, 63%) consisting of four compounds in a ratio of 32 (6-exo): 20 (7-exo): 30 (6-endo): 18 (7-endo). The solid was further separated by preparative hplc (silica gel, 10% to 50% 2-propanol in hexane) to yield three fractions. The first fraction consisted of the 6-exo and the 7-exo compounds. The second fraction consisted of the 6-endo compound, **8**; ^{1}H nmr (250 MHz, deuteriochloroform): δ 2.18 (1H, dd, J = 4.6, 9.4 Hz), 2.51 (3H, s), 2.75-2.86 (1H, m), 2.98 (1H, dd, J = 3.8, 9.4 Hz), 3.87 (1H, d, J = 8.0 Hz), 4.48 (1H, s), 7.31 (1H, d, J = 8.6 Hz), 7.45 (1H, t, J = 8.3 Hz), 7.63 (1H, t, J = 7.5 Hz), 7.98 (1H, d, J = 9.0 Hz). The third fraction consisted of the 7-endo compound, **9**; partial ^{1}H nmr (250 MHz, deuteriochloroform): δ 2.11 (1H, dd, J = 4.4, 12.8 Hz), 3.95 (1H, d, J = 7.4 Hz), 4.22 (1H, d, J = 6.4 Hz). The 6-exo and 7-exo compounds were separated by fractional crystallization from methanol. The 6-exo, **7**, crystallized first; ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.94 (1H, dd, J = 6.2, 13.0 Hz), 2.43 (3H, s), 2.86-2.99 (1H, m), 3.56-3.65 (1H, m), 3.77 (1H, d, J = 8.0 Hz), 4.37 (1H, d, J = 5.8 Hz), 7.37 (1H, d, J = 7.6 Hz), 7.50 (1H, t, J = 7.1 Hz), 7.68 (1H, t, J = 8.2 Hz), 8.05 (1H, d, J = 7.7 Hz); and the 7-exo compound, **10**, followed; partial ^{1}H nmr (250 MHz, deuteriochloroform): δ 4.03 (1H, s), 4.33 (1H, d, J = 6.3 Hz).

Compound **7** was converted to its hydrochloride salt and appeared as a pale yellow solid, mp = 184° dec; ^{1}H nmr (250 MHz, methanol-d_4): δ 2.63 (1H, dd, J = 10.2, 14.9 Hz), 3.08 (3H, s), 3.00-3.18 (1H, m), 3.72 (1H, dd, J = 5.0, 10.4 Hz), 4.63 (1H, d, J = 8.2 Hz), 5.52 (1H, s), 7.64-7.70 (2H, m), 7.80-7.86 (1H, m), 8.10 (1H, d, J = 8.4 Hz).

Anal. Calcd. for $C_{13}H_{13}ClN_2O \cdot 0.25H_2O$: C, 61.66; H, 5.37; N, 11.06. Found: C, 61.73; H, 5.21; N, 11.08.

Compound **10** was converted to its hydrochloride salt and appeared as a white solid, mp 181° dec; ^{1}H nmr (250 MHz, methanol-d_4): δ 2.26 (1H, dd, J = 5.7, 14.9 Hz), 2.94 (3H, s), 3.20-3.34 (1H, m), 4.36 (1H, dd, J = 5.8, 11.2 Hz), 4.55 (1H, d, J = 8.1 Hz), 5.35 (1H, d, J = 6.4 Hz), 7.65-7.76 (2H, m), 7.85-7.91 (1H, m), 8.18 (1H, d, J = 7.7 Hz).

Anal. Calcd. for $C_{13}H_{13}ClN_2O \cdot 0.25H_2O$: C, 61.66; H, 5.37; N, 11.06. Found: C, 61.80; H, 5.31; N, 11.04.

(exo-6-Phenylsulfone) and (exo-7-phenylsulfone)-*N*-methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imines **11** and **12**.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.600 g, 2.08 mmoles) and phenyl vinyl sulfone (0.420 g, 2.50 mmoles) in dry tetrahydrofuran (15 ml) under nitrogen was added triethylamine (0.35 ml, 2.50 mmoles). The solution was allowed to stir at room temperature for 18 hours. The mixture was diluted with ether (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a yellow solid. The solid was purified by flash column chromatography (silica gel, chloroform) to yield a yellow solid consisting of starting sulfone and the desired products in a ratio of 80:20 (6-endo:7-exo). The solid was washed with ether to remove the phenyl vinyl sulfone and then further separated by preparative hplc (silica gel, 10% 2-propanol/hexane) to yield two products with the 6-exo compound, **11**, eluting first; ^{1}H nmr (250 MHz, deuteriochloroform): δ 1.98 (1H, dd, J = 9.3, 14.5 Hz), 2.80-2.91 (1H, m), 3.57 (1H, dd, J = 5.5, 9.2 Hz), 3.78 (1H, d, J = 7.7 Hz), 4.66 (1H, s), 7.17 (1H, d, 8.0 Hz), 7.34-7.96 (8H, m); and the 7-exo compound, **12**, second; ^{1}H nmr (250 MHz, deuteriochloroform): δ 2.06 (1H, dd, J = 8.9, 12.9 Hz), 2.48 (3H, s), 2.92 (1H, q, J = 6.6 Hz), 3.45 (1H, t, J = 8.4 Hz), 4.07 (1H, s), 4.31 (1H, d, J = 5.8 Hz), 7.15 (1H, d, J = 7.6 Hz), 7.3 (1H, dt, J = 1.0, 7.7 Hz), 7.47-7.53 (3H, m), 7.60-7.63 (1H, m), 7.85-7.88 (3H, m).

Compound **11** was converted to its hydrochloride salt and appeared as a white solid, mp 199°; ^{1}H nmr (250 MHz, methanol-d_4): δ 2.42 (1H, dd, J = 9.7, 14.9 Hz), 3.07-3.19 (1H, m), 3.10 (3H, s), 4.32 (1H, t, J = 9.17 Hz), 4.64 (1H, d, J = 7.6 Hz), 5.57 (1H, s), 7.23 (1H, d, J = 7.5 Hz), 7.63-7.83 (5H, m), 8.01-8.10 (3H, m).

Anal. Calcd. for $C_{18}H_{18}ClNO_3S$: C, 59.42; H, 4.99; N, 3.85. Found: C, 59.49; H, 4.96; N, 3.89.

12,13-Dihydro-6,11-dihydroxy-13-oxo-5*H*-benzo[4,5]cyclohepta-[1,2-*b*]naphthalen-5,12-imine **14**.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.500 g, 1.73 mmoles) and 1,4-naphthoquinone (0.320 g, 2.04 mmoles) in dry tetrahydrofuran (20 ml) under nitrogen was added triethylamine (0.28 ml, 2.04 mmoles). The solution was allowed to stir at room temperature for 19 hours. The mixture was diluted with chloroform (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a dark brown solid. The solid was purified by flash column chromatography (silica gel, chloroform) to yield a light brown solid (0.505 g, 92%); ^{1}H nmr (250 MHz, deuteriochloroform): δ 2.62 (3H, s), 4.75 (1H, s), 5.06 (1H, s), 7.35-7.50 (3H, m), 7.70-7.76 (2H, m), 7.91 (1H, d, J = 7.0 Hz), 8.03-8.11 (2H, m).

Compound **14** was converted to its hydrochloride salt and appeared as a pale yellow solid, mp 164° dec; ^{1}H nmr (250 MHz, methanol-d_4): δ 3.15 (3H, s), 5.48 (1H, s), 5.98 (1H, s), 7.60-8.15 (8H, m).

Anal. Calcd. for $C_{20}H_{16}ClNO_3 \cdot 0.25H_2O$: C, 67.04; H, 4.64; N, 3.91. Found: C, 67.26; H, 4.14; N, 3.88.

10,11-Dihydro-6,9-dihydroxy-*N*-methyl-11-oxo-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine **13**.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.500 g, 1.73 mmoles) and 1,4-benzoquinone (0.220 g, 2.04 mmoles) in dry tetrahydrofuran (20 ml) under nitrogen was added triethylamine (0.28 ml, 2.04 mmoles). The solution was allowed to stir at room temperature for 19 hours. The mixture was diluted with chloroform (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a dark brown solid. The solid was purified by preparative hplc (silica, chloroform:hexane, 95:5) to yield a yellow

solid, **13**, (0.2450 g, 53%); ^{1}H nmr (250 MHz, chloroform-d_1-dimethyl sulfoxide-d_6): δ 2.51 (3H, s), 4.69 (1H, s), 5.04 (1H, s), 6.50 (2H, s), 7.23-7.30 (3H, m), 7.83 (1H, d, J = 7.5 Hz), 8.33 (1H, s), 8.47 (1H, s).

Compound **13** was converted to its hydrochloride salt and appeared as a pale yellow solid, mp 190° dec; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 2.92 (3H, s), 5.45 (1H, s), 6.04 (1H, s), 6.67 (2H, s), 7.54-7.76 (2H, m), 7.71 (1H, t, 7.5 Hz), 7.86 (1H, d, J = 7.5 Hz), 9.70 (1H, br s), 9.78 (1H, s).

Anal. Calcd. for $C_{16}H_{14}ClNO_3 \cdot 0.75H_2O$: C, 60.57; H, 4.92; N, 4.41. Found: C, 60.34; H, 5.29; N, 4.13.

6,7-Dicarbomethoxy-8,9-dihydro-*N*-methyl-9-oxo-5*H*-benzocyclohepten-5,8-imine **15**.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.400 g, 1.38 mmoles) and dimethyl acetylenedicarboxylate (0.20 ml, 1.63 mmoles) in dry tetrahydrofuran (15 ml) under nitrogen was added triethylamine (0.23 ml, 1.63 mmoles). The solution was allowed to stir at room temperature for 16 hours. The mixture was diluted with diethyl ether (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a yellow oil. The oil was purified by flash column chromatography (silica gel, 9:1 hexane:2-propanol) to yield a yellow oil (0.3818 g, 92%); ^{1}H nmr (250 MHz, chloroform-d_1): δ 2.59 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 4.39 (1H, s), 4.71 (1H, s), 7.25 (1H, d, J = 7.1 Hz), 7.36-7.48 (2H, m), 7.94 (1H, d, J = 7.1 Hz).

Compound **15** was converted to its hydrochloride salt and appeared as a white solid, mp 176° dec; ^{1}H nmr (250 MHz, methanol-d_4): δ 3.14 (3H, s), 3.83 (3H, s), 3.84 (3H, s), 5.24 (1H, s), 5.71 (1H, s), 7.56 (1H, d, J = 6.9 Hz), 7.60-7.78 (2H, m), 8.06 (1H, d, J = 7.4 Hz).

Anal. Calcd. for $C_{16}H_{16}ClNO_5$: C, 56.90; H, 4.77; N, 4.15. Found: C, 56.89; H, 4.72; N, 4.07.

8,9-Dihydro-*N*-methyl-7-methyl-9-oxo-6-phenyl-5*H*-benzocyclohepten-5,8-imine **16** and 8,9-Dihydro-*N*-methyl-6-methyl-9-oxo-7-phenyl-5*H*-benzocyclohepten-5,8-imine **17**.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.500 g, 1.73 mmoles) and 1-phenyl propyne (0.26 ml, 2.08 mmoles) in dry acetonitrile (15 ml) under nitrogen was added triethylamine (0.30 ml, 2.12 mmoles) in a sealed tube at 120°. The solution was allowed to stir for 4 days. The mixture was diluted with diethyl ether (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a yellow oil. The oil was purified by preparative hplc (silica, 95:5 chloroform:hexane) to yield a brown oil, **17**, (0.160 g, 33%); ^{1}H nmr (500 MHz, chloroform-d_1): δ 2.04 (3H, s), 2.60 (3H, s), 4.23 (1H, s), 4.37 (1H, s), 7.17-7.43 (8H, m), 7.97 (1H, d, J = 7.0 Hz); ^{13}C nmr (500 MHz, chloroform-d_1): δ 13.8, 39.2, 77.0, 81.4, 124.1, 127.1, 127.5, 128.0, 128.1, 128.4, 129.0, 131.9, 132.7, 134.7, 143.7, 144.9, 192.5; and a brown solid, **16**, (0.120 g, 25%); ^{1}H nmr (500 MHz, chloroform-d_1): δ 2.00 (3H, s), 2.59 (3H, s), 4.00 (1H, s), 4.62 (1H, s), 7.20-7.40 (8H, m), 7.95 (1H, d, J = 7.0 Hz); ^{13}C nmr (500 MHz, chloroform-d_1): δ 12.7, 39.2, 75.3, 83.8, 124.4, 127.0, 127.6, 127.8, 128.4, 129.1, 131.8, 132.7, 134.9, 144.9, 145.9, 191.9.

Compound **16** was converted to its hydrochloride salt and appeared as a white solid, mp 252°; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 2.00 (3H, s), 3.04 (3H, s), 4.97 (1H, s), 5.91 (1H, s), 7.35-7.63 (8H, m), 7.90 (1H, d, J = 7.8 Hz).

Anal. Calcd. for $C_{19}H_{18}ClNO \cdot 0.125H_2O$: C, 72.66; H, 5.86; N, 4.46. Found: C, 72.61; H, 5.84; N, 4.44.

Compound **17** was converted to its hydrochloride salt and appeared as a white solid, mp 241° dec; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 2.05 (3H, s), 3.04 (3H, s), 5.32 (1H, s), 5.40 (1H, s), 7.25-7.54 (5H, m), 7.56-7.80 (3H, m), 7.91 (1H, d, J = 6.8 Hz).

Anal. Calcd. for $C_{19}H_{18}ClNO \cdot 0.33H_2O$: C, 71.81; H, 5.92; N, 4.41. Found: C, 71.89; H, 5.88; N, 4.41.

8,9-Dihydro-*N*-methyl-9-oxo-7-phenyl-5*H*-benzocyclohepten-5,8-imine **18** and 8,9-Dihydro-*N*-methyl-9-oxo-6-phenyl-5*H*-benzocyclohepten-5,8-imine **19**.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.500 g, 1.73 mmoles) and phenyl acetylene (0.28 ml, 2.55 mmoles) in dry acetonitrile (5 ml) under nitrogen was added triethylamine (0.30 ml, 2.12 mmoles). The solution was allowed to stir at reflux for 18 hours. The mixture was diluted with diethyl ether (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a dark brown oil. The oil consisted of two regioisomers **18** and **19** in a 66:33 ratio as determined by ^{1}H nmr. The oil was purified by flash column chromatography (silica gel, chloroform) to yield **18** and **19** (0.350 g, 77% yield) as a tan oil. The regioisomers were separated by preparative hplc (silica, 90:10 chloroform:hexane) to yield a brown oil, **18**, (0.170 g); ^{1}H nmr (500 MHz, chloroform-d_1): δ 2.61 (3H, s), 4.52 (1H, s), 4.54 (1H, d, J = 2.5 Hz), 6.95 (1H, d, J = 2.5 Hz), 7.14 (1H, d, J = 7.5 Hz), 7.24-7.41 (5H, m), 7.54-7.56 (2H, m), 7.89 (1H, d, J = 9.0 Hz); ^{13}C nmr (500 MHz, chloroform-d_1): δ 39.5, 72.1, 78.9, 123.6, 126.3, 127.6, 127.9, 128.2, 128.3, 128.5, 132.9, 133.0, 133.8, 140.9, 144.7, 192.1; and a tan solid, **19**, (0.096 g); ^{1}H nmr (500 MHz, chloroform-d_1): δ 2.58 (3H, s), 4.22 (1H, d, J = 2.5 Hz), 4.81 (1H, s), 6.42 (1H, d, J = 2.5 Hz), 7.26-7.40 (6H, m), 7.51-7.53 (2H, m), 7.94 (1H, d, J = 8.5 Hz); ^{13}C nmr (500 MHz, chloroform-d_1): δ 39.4, 72.0, 78.7, 120.2, 124.4, 125.9, 128.0, 128.1, 128.6, 128.7, 129.1, 132.6, 133.0, 143.7, 154.1, 191.4.

Compound **18** was converted to its hydrochloride salt and appeared as a pale yellow solid, mp 158° dec; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d_6): δ 3.01 (3H, s), 5.60 (2H, s), 7.31-7.75 (9H, m), 7.86 (1H, d, J = 7.6 Hz).

Anal. Calcd. for $C_{18}H_{16}ClNO \cdot 0.5H_2O$: C, 70.47; H, 5.59; N, 4.57. Found: C, 70.84; H, 5.57; N, 4.60.

Compound **19** was converted to its hydrochloride salt and appeared as a tan solid, mp 142° dec; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d_6): 2.93 (3H, s), 5.05 (1H, br s), 5.96 (1H, br s), 6.93 (1H, s), 7.10-7.95 (9H, m).

Anal. Calcd. for $C_{18}H_{16}ClNO \cdot 0.75H_2O$: C, 69.45; H, 5.67; N, 4.50. Found: C, 69.57; H, 5.47; N, 4.56.

(endo-7-Phenyl) and (endo-6-phenyl)-*N*-methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5,8-imines **20** and **21** Respectively.

To a stirred solution of 4-hydroxy-*N*-methylisoquinolinium iodide (0.600 g, 2.09 mmoles) and styrene (0.36 ml, 3.14 mmoles) in dry acetonitrile (6 ml) under nitrogen was added triethylamine (0.36 ml, 3.59 mmoles). The solution was allowed to stir at reflux for 24 hours. The mixture was diluted with diethyl ether (200 ml) and washed with water (20 ml), brine (20 ml), dried (sodium sulfate) and concentrated under reduced pressure to yield a dark brown oil. The oil consisted of two regioisomers **20** and **21** in a 83:17 ratio as determined by ^{1}H nmr. The oil was purified by flash column chromatography (silica gel, 90:10 hexane:isopropyl

alcohol) to yield two oils **21** (0.055 g, 10% yield); ^{1}H nmr (500 MHz, chloroform-d$_1$): δ 1.89 (1H, dd, J = 14.3, 7.0 Hz), 2.49 (3H, s), 2.90-2.97 (1H, m), 3.85 (1H, d, J = 8.2 Hz), 4.08 -4.13 (1H, m), 4.20 (1H, d, J = 6.0 Hz), 6.51 (1H, d, J = 7.4 Hz), 6.65-6.68 (2H, m), 7.02-7.07 (3H, m), 7.21-7.31 (2H, m), 8.03 (1H, d, J = 7.6 Hz); ^{13}C nmr (500 MHz, chloroform-d$_1$): δ 31.0, 36.5, 48.4, 70.6, 125.8, 126.4, 127.5, 127.8, 128.1, 128.5, 130.2, 133.6, 138.9, 140.6, 198.7, and **20**, (0.380 g, 69% yield); ^{1}H nmr (500 MHz, chloroform-d$_1$): δ 2.11 (1H, dd, J = 13.0, 5.5 Hz), 2.47 (3H, s), 3.00-3.06 (1H, m), 3.92 (1H, d, J = 7.5 Hz), 4.13-4.18 (1H, m), 4.29 (1H, d, J = 7.0 Hz), 6.81-6.82 (2H, m), 7.09-7.15 (3H, m), 7.26-7.37 (2H, m), 7.58-7.61 (1H, m), 7.83 (1H, d, J = 7.5 Hz); ^{13}C nmr (500 MHz, chloroform-d$_1$): δ 36.5, 37.3, 44.7, 64.6, 77.0, 125.9, 126.0, 126.7, 127.5, 128.2, 130.8, 134.5, 138.2, 145.6, 195.8.

Compound **21** was converted to its hydrochloride salt and appeared as a pale yellow solid, mp 210° dec; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d$_6$): 2.12 (1H, dd, J = 14.9, 6.7 Hz), 2.95 (3H, br s), 3.00-3.20 (1H, m), 4.50-4.70 (2H, m), 5.30 (1H, d, J = 5.8 Hz), 6.70-6.82 (3H, m), 7.05-7.20 (3H, m), 7.35-7.58 (2H, m), 8.02 (1H, d, J = 7.5 Hz).

Anal. Calcd. for $C_{18}H_{18}ClNO \cdot 0.25H_2O$: C, 71.05; H, 6.13; N, 4.60. Found: C, 71.14; H, 6.04; N, 4.55.

Compound **20** was converted to its hydrochloride salt and appeared as a pale yellow solid, mp 203° dec; ^{1}H nmr (250 MHz, dimethyl sulfoxide-d$_6$): 2.25 (1H, dd, J = 13.9, 6.5 Hz), 2.93 (3H, br s), 3.12-3.30 (1H, m), 4.40-4.56 (1H, m), 4.70 (1H, d, J = 8.5 Hz), 5.25 (1H, d, J = 5.9 Hz), 6.83 (2H, br s), 7.17 (3H, br s), 7.51-7.98 (4H, m).

Anal. Calcd. for $C_{18}H_{16}ClNO \cdot 0.25H_2O$: C, 71.05; H, 6.13; N, 4.60. Found: C, 71.20; H, 6.16; N, 4.59.

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