Chemistry of 7-Azabicyclo[2.2.1]hepta-2,5-dienes, 7-Azabicyclo[2.2.1]hept-2-enes, and 7-Azabicyclo[2.2.1]heptanes

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Received December 18, 1995 (Revised Manuscript Received February 26, 1996)

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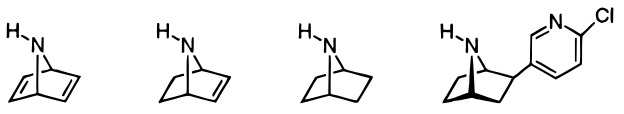
I. Introduction

The synthesis of the 7-azabicyclo[2.2.1]hepta-2,5-diene (**1**), 7-azabicyclo[2.2.1]hept-2-ene (**2**), and 7-azabicyclo[2.2.1]heptane (**3**) systems has been the



1 **2** **3** **4** (-)-epibatidine

subject of numerous synthetic studies which have resulted in the development of several methods for the construction of these novel azabicyclic systems.[1] Until recently these syntheses were only a matter of academic interest since no naturally occurring compound was known at the time to contain these ring systems.[1] However, in 1992 Daly et al. reported the discovery and structural elucidation of (−)-epibatidine (**4**), a new alkaloid isolated from Ecuadorian poison frog, *Epipedobates tricolor*.[2] Subsequent studies have shown that the absolute configuration of this structurally unique natural compound which features the 7-azabicyclo[2.2.1]heptane ring system with an exo-oriented 5-(2-chloropyridyl) substituent, is 1*R*, 2*R*, 4*S*.[3−6] As the free base, the natural material **4** exhibits a levorotatory optical rotation, while the salts of **4** (hydrochloride, hydrogen oxalate) were found to possess dextrorotatory optical rotations.[5] Preliminary biological assays have shown that epibatidine (**4**) is a very potent analgesic (200−500-fold more potent than morphine) with a non-opioid mechanism of action.[7−11] Due to the novel biological activity associated with epibatidine (**4**) and its paucity in nature (1 mg isolated from 750 frogs) the total synthesis of **4** has aroused the interests of organic chemists around the world.[12−16] In addition, a large number of 7-azabicyclo[2.2.1]heptane and 7-azabicyclo-[2.2.1]hept-2-ene derivatives have been recently synthesized and protected by patents.[17,18]

The renewed interest in these ring systems as important biomolecular substructures has prompted the writing of this review. The synthetic approaches employed to construct the 7-azabicyclo[2.2.1]hepta-2,5-diene (**1**), 7-azabicyclo[2.2.1]hept-2-ene (**2**), and 7-azabicyclo[2.2.1]heptane (**3**) systems are the primary focus of this review. In addition, the chemical, physical and biological properties associated with these and related compounds will be discussed.

II. Preparation of 7-Azabicyclo[2.2.1]hepta-2,5-dienes and 7-Azabicyclo[2.2.1]hept-2-enes by the [4+2] Cycloaddition Reaction

The [4+2] cycloaddition reaction between pyrroles and dienophiles has been shown to be a general method for the synthesis of the 7-azabicyclo[2.2.1]-hepta-2,5-diene and 7-azabicyclo[2.2.1]hept-2-ene derivatives. However, pyrrole (**5a**) is a poor diene for the [4+2] cycloaddition reaction and usually reacts with alkenyl and acetylenic dicarboxylic acid derivatives to give Michael addition products (Scheme 1).[19] Similarly, *N*-alkylpyrroles react with acetylene dicarboxylic acid derivatives to give the corresponding 2-substituted pyrrolyl derivatives.[20,21] In their paper

0009-2665/96/0796-1179$25.00/0

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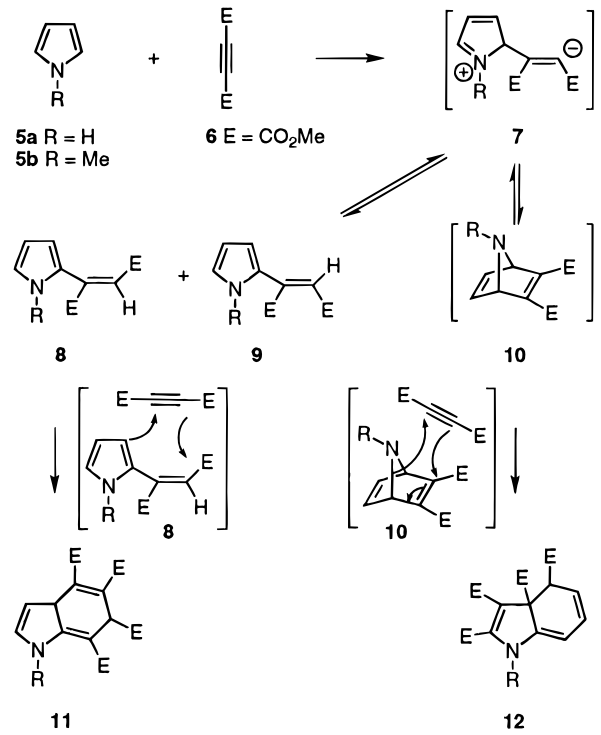
Mark L. Trudell was born in Pontiac, MI, in 1961 and was raised in Birmingham, MI. He received his undergraduate education at Hope College, Holland, MI, completing a degree in Chemistry (B.S.) in 1983. He then continued his studies at the University of Wisconsin—Milwaukee and received his Ph.D. in Organic Chemistry in 1989. After postdoctoral studies in the area of Natural Product Synthesis at the Imperial College of Science, Technology and Medicine, London, U.K. (1989–1991), he accepted a position at the University of New Orleans as Assistant Professor of Chemistry (1991). While at UNO, Dr. Trudell has established an active research group which has been internationally recognized for contributions in the areas of synthetic organic chemistry and medicinal chemistry. In addition, Dr. Trudell recently was awarded the 1994 UNO Alumni Association Early Career Achievement Award for Excellence in Research. A major aspect of Dr. Trudell's research program involves the design and synthesis of novel high-density energetic materials as potential explosives, propellants, and fuels. This work is supported by the Office of Naval Research and the Ballistic Missile Defense Organization. The thrust of the research in medicinal chemistry is aimed at the synthesis of novel cocaine analogues for the elucidation of the structure–activity relationships of cocaine and the development of new treatments and medications for cocaine addiction and overdose. This work is supported by the National Institute on Drug Abuse. Other areas of interests include design and synthesis of new laser dyes (Army Research Office) and synthesis of natural products.

exploring the reaction of dienophiles with pyrroles, Diels and Alder reported the isolation of a 1:2 adduct, which they formulated as the dihydroindole **11** (Scheme 1), from the reaction of 1-methylpyrrole (**5b**) with dimethyl acetylenedicarboxylate (DMAD, **6**).[22] The structure of **11** was compatible with a [4+2] cycloaddition of a second molecule of DMAD (**6**) to

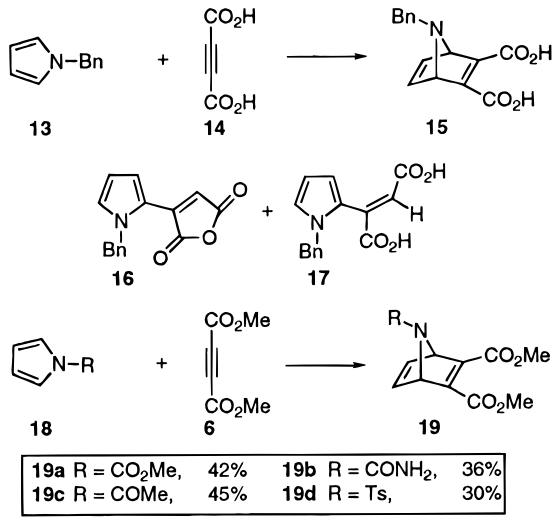
Scheme 1



the initially formed Michael addition product **8**. However, it was later shown that the actual structure of the 1:2 adduct was that of the isomeric compound **12** (Scheme 1).[23,24] The formation of **12** was rationalized by the initial formation of the [4+2] cycloadduct **10** which then reacted with a second molecule of DMAD (**6**). A similar product has been reported to be formed from the reaction of DMAD (**6**) with pyrrole (**5a**).[25] It has been suggested that the mechanism of the reaction involves electrophilic addition of the acetylene at the C(2) position of the pyrrole ring to form the zwitterionic intermediate **7**. In the case of pyrrole (**5a**), the zwitterion **7** may be quenched by migration of a proton from the acidic NH to give Michael addition products **8** and **9**. However, in the absence of an acidic proton (**5b**), it is believed that the zwitterionic intermediate **7** undergoes an intramolecular cyclization reaction to form the bicyclic adduct **10**, which then further reacts with a second equivalent of **6** to furnish **12**.[26,27]

The first derivative of a 7-azabicyclo[2.2.1]hepta-2,5-diene to be isolated and characterized was the [4+2] cycloaddition adduct **15**, obtained as a minor product (8%) from the reaction of *N*-benzylpyrrole (**13**) and acetylenedicarboxylic acid (**14**) together with the Michael addition products **16** and **17** (Scheme 2).[28−30] When an electron-withdrawing group was placed on the nitrogen atom of pyrrole, the aromatic ring was found to be more reactive as a diene toward acetylenic dienophiles.[31] The yields of the cycloadducts **19a**−**d** were found to be in the range 30−45% from the reaction of pyrroles **18** with **6** when the pyrrole was substituted at the N(1) position by electron-withdrawing groups [CO_2Me, $CONH_2$, COMe, and $SO_2C_6H_4Me$ (Ts)]. However, the Michael addition products were still found to be the major products of these reactions.

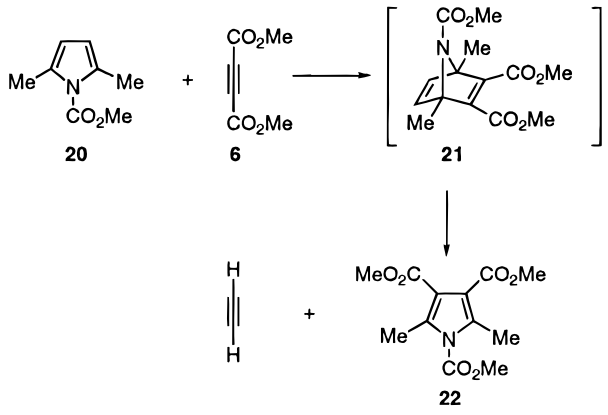
Scheme 2



19a R = CO_2Me,	42%	**19b** R = $CONH_2$,	36%
19c R = COMe,	45%	**19d** R = Ts,	30%

To prevent Michael addition at the C(2) position of the pyrrole, Acheson et al. and Gabel et al. independently attempted the reaction of 1,2,5-substituted pyrrole **20** with **6** at 150 °C.[24,32] The only product obtained from this reaction was the 1,2,3,4,5-pentasubstituted pyrrole **22** (Scheme 3). The formation of **22** can be explained by the formation and subsequent retrocycloaddition reaction of the adduct **21** with loss of acetylene. Actually, the failure to isolate many of the [4+2] cycloadducts of pyrrole derivatives has been attributed to their thermal instability and their susceptibility to rearrange in acidic or basic media and even when exposed to light.

Scheme 3

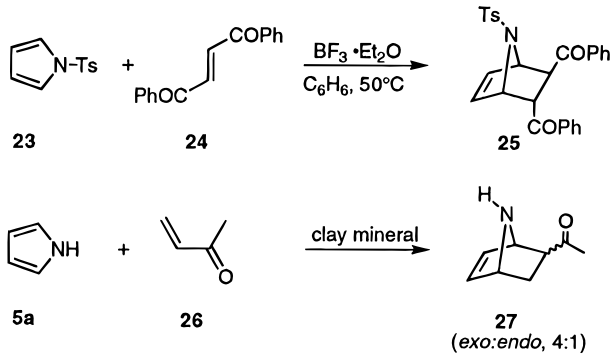


To stabilize the resultant adduct and accelerate the cycloaddition reaction, various physical and catalytic methods have been explored for the reaction between substituted pyrroles and various dienophiles. In most cases, these manipulations considerably extend the scope of the [4+2] cycloaddition reaction of pyrroles with dienophiles and enhance the synthetic utility of this reaction.

A. Lewis Acid Catalyzed Reactions

Lewis acids have been widely used to catalyze Diels–Alder reactions when the thermal conditions were not efficient.[33] The application of Lewis acids in the [4+2] cycloaddition reactions of pyrroles with dienophiles has led to improved yields of the desired cycloaddition adducts. Bansal et al. showed that aluminum trichloride increased the yield of the bicyclic triester **19a** to 90% from 42% (Scheme 2).[34,35] Rajakuman also has shown that boron trifluoride catalyzed the [4+2] cycloaddition reaction between *N*-*p*-toluenesulfonylpyrrole (**23**) and *trans*-1,4-diphenyl-2-butene-1,4-dione (**24**) to furnish the [4+2] cycloaddition adduct **25** in 80% yield (Scheme 4).[36] The role of the Lewis acid may not be as simple as to lower the energy differential between the HOMO and the LUMO of the dienophile and pyrrole. It is believed that the Lewis acids form a stabilized complex with the cycloaddition adduct. In addition, the Lewis acids may also complex with pyrrole and deactivate the pyrrole ring toward electrophiles while enhancing its reactivity as a diene by diminishing the aromaticity. Recently, Adams et al. used cation-exchanged clay minerals to catalyze the stereoselective cycloaddition reaction of pyrrole (**5a**) with methyl vinyl ketone (**26**) and obtained a 35% yield of the cycloaddition adduct **27** (Scheme 4).[37]

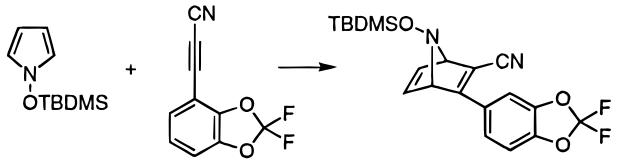
Scheme 4



It is important to note that the choice of Lewis acid, the quantity of the Lewis acid, and the reaction temperature were found to be key elements for the efficient catalysis of the [4+2] cycloaddition reaction of pyrroles and dienophiles. The optimum yield (65–90%) of the desired adducts **19** could be obtained from the reaction of acyl pyrroles **18** and **6** only when a 5-fold excess of aluminum trichloride was employed and the reaction temperature was maintained at 40 °C.[34,38] Variation of the reaction temperature and the ratio of aluminum trichloride to addends were found to lead to low yields of the desired cycloaddition adducts where the corresponding 2-substituted pyrroles **8** and **9** were obtained as the major products.

A limitation of the Lewis acid catalyzed [4+2] cycloaddition reaction has often been found to be the sensitivity of the substrates to the strongly acidic media. In a recent study of the [4+2] cycloaddition reaction of *N*-silyloxypyrrole **28** and phenylacetylene derivative **29**, it was found that Lewis acids ($AlCl_3$, BF_3, $TiCl_4$) led to decomposition of the starting materials while the thermal processes afforded only negligible amounts of the desired *N*-silyloxy-7-azabicyclo[2.2.1]heptadiene (**30**, Table 1).[39] The successful preparation of **30** was achieved with lithium perchlorate (5.0 M in diethyl ether) to furnish the cycloaddition adduct in 68–83% yield. The mechanism associated with the $LiClO_4$–diethyl ether catalyzed reactions may be due to a Lewis acid catalytic

Table 1. [4+2] Cycloaddition Reaction of Pyrrole 28 and 29



28 29 30

entry	temp (°C)	solvent	catalyst	time (h)	yield (%)
1	120	N/A	N/A	1.5	0
2	200	benzene	N/A	1.0	6
3	60	Et_2O	N/A	1.0	< 4
4	0	CH_2Cl_2	$AlCl_3$	0.3	0
5	60	Et_2O	$LiClO_4$	24	68
6	25	Et_2O	$LiClO_4$	1560	83

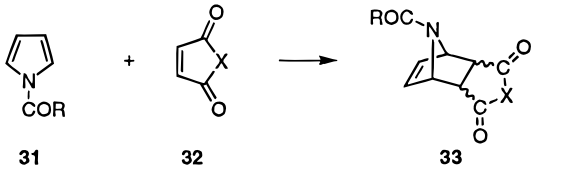
effect by the lithium cation or due to the inner pressure caused by changes in the solvent structure leading to a compression of the reactants. This compression is believed to be similar to the macroscopic application of external pressure.[40,41]

B. High-Pressure and Ultrasound Reactions

It is well-known that intermolecular [4+2] cycloaddition reactions generally have large negative activation volumes (about −25 to −45 $cm^3\ mol^{-1}$)[42] as well as large negative volumes of reaction and accordingly can be accelerated by the application of high pressure. This high-pressure approach certainly has served as a useful alternative for the synthesis of a number of 7-azabicyclo[2.2.1]hepta-2,5-diene and 7-azabicyclo[2.2.1]hept-2-ene derivatives. Pressures up to 1.4 GPa have been shown to accelerate the reaction between *N*-acylpyrroles **31** with N-substituted maleimides and maleic anhydride (**32**) to provide a variety of cycloaddition adducts **33** in yields ranging from 20 to 90% (Table 2).[43] In this system, the ratio of endo to exo products and the yields were case dependent. Different solvents were found to dramatically change the ratio of endo to exo products. The cycloaddition reaction of *N*-benzoylpyrrole and maleic anhydride in chloroform gave a 25% yield of exo adduct as a sole product; however, in ethyl acetate the cycloaddition reaction gave a 20% yield of endo adduct only. In general, polar solvents were preferred for these reactions. Benzene also exhibited a positive solvent effect. Under high pressure, attempted reactions between *N*-acylpyrroles and ethyl acrylate have failed to give the [4+2] cycloaddition adducts while acrylonitrile polymerized. This illustrated that dienophiles of quite high reactivity are still required in these systems. It was also found that the *N*-methyl- and *N*-benzylpyrrole failed to form cycloaddition adducts with *N*-phenylmaleimide (**32**) or DMAD (**6**).[44]

It is interesting to note that the introduction of alkylthio or arylthio groups as electron-donating substituents at the C(3) position of *N*-acylpyrroles enhanced the reactivity by raising the HOMO energy level.[45,46] 1-Methoxycarbonyl-3-phenylthiopyrrole (**34**) has been shown to react readily with the electron-

Table 2. High-Pressure [4+2] Cycloaddition Reactions of Pyrroles with Maleimides and Maleic Anhydride

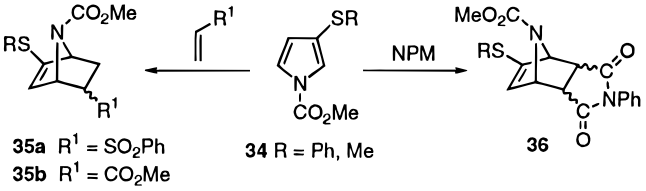


31 32 33

R	X	Solvent	Time (h)	Yield (endo)	Yield (exo)
Ph	NPh	AcOEt	90	45%	46%
Ph	NPh	CH_2Cl_2	150	34%	58%
Ph	NPh	C_6H_6	60	0	80%
Ph	O	$CHCl_3$	160	0	25%
Ph	O	AcOEt	300	20%	0
Me	O	$CHCl_3$	150	35%	0
Me	NPh	CH_2Cl_2	20	90%	0
Me	NMe	CH_2Cl_2	65	77%	0
OEt	NPh	CH_2Cl_2	70	0	46%
OEt	O	CH_2Cl_2	160	0	26%
OCH_2Ph	NPh	CH_2Cl_2	48	90%	0
p-C_6H_4Cl	NPh	CH_2Cl_2	24	90%	0

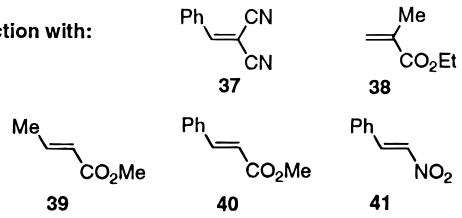
poor alkenes (methyl acrylate, phenyl vinyl sulfone, and *N*-phenylmaleimide) at 12 kbar to give 80% yields of the [4+2] cycloadducts (**35a**, **35b**, **36**, Scheme 5). However, the reaction with other dieno-

Scheme 5



35a $R^1 = SO_2Ph$
35b $R^1 = CO_2Me$
34 R = Ph, Me
36

No reaction with:

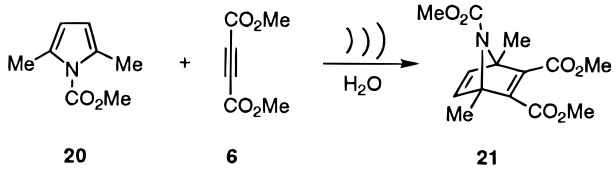


37 38 39 40 41

philes which are sterically more hindered (**37**, **39**−**41**) or less electron-deficient (**38**, **39**) resulted in only the recovery of the starting materials.

The application of ultrasound to the reaction of the *N*-methoxycarbonyl-2,5-dimethylpyrrole (**20**) with **6** in an aqueous solution afforded the cycloaddition adduct **21** in 60% yield without the formation of Michael type products (Scheme 6).[47] It is believed

Scheme 6



20 6 21

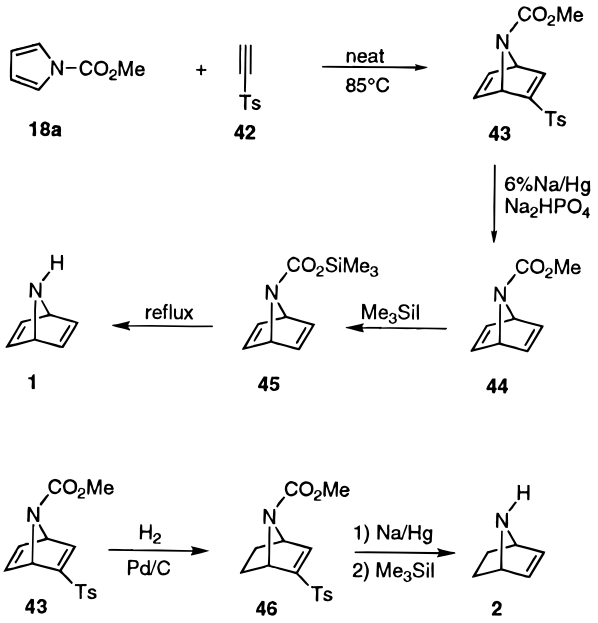
that ultrasound accelerated the cycloaddition reaction and the mild reaction conditions (room temper-

ature) helped to stabilize the cycloaddition adduct **21**, which was not isolated in the corresponding thermal reaction (Scheme 3).[24,32] Compound **21** was also obtained in yields of 85−90% from the reaction of **20** and **6** when Lewis acids (boron trifluoride or aluminum trichloride) were used.[35]

C. Reactions with Acetylene Equivalents

In recent years, a number of successful [4+2] cycloaddition reactions have employed acetylene equivalents as dienophiles.[48] Ethynyl *p*-tolyl sulfone (**42**) has been found to be one of the most synthetically useful acetylene equivalents because of its high reactivity toward dienes and ease of removal of the *p*-toluenesulfonyl moiety under reductive conditions.[49,50] It has been shown that **42** reacted with *N*-methoxycarbonylpyrrole (**18a**) to give the [4+2] cycloaddition adduct **43** in 68% yield (Scheme 7).[51]

Scheme 7

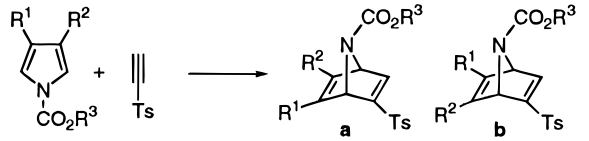


The simple reductive desulfonylation with sodium amalgam followed by the mild deprotection of *N*-methoxycarbonyl group with trimethylsilyl iodide afforded the 7-azabicyclo[2.2.1]hepta-2,5-diene (**1**). Compound **43** was also selectively hydrogenated to **46** with 1 equiv of hydrogen and 10% palladium on carbon.[52] The 7-azabicyclo[2.2.1]hept-2-ene (**2**) was then prepared in similar fashion from **46**.[52]

As an extension of this strategy, a few highly functionalized 7-azabicyclo[2.2.1]hepta-2,5-dienes have been prepared.[53] The [4+2] cycloaddition reaction between *N*-acylpyrroles **47** and **42** proceeded easily and in high yield to furnish the substituted 7-azabicyclo[2.2.1]heptadienes **48**−**54** (Table 3). In a typical reaction, the *N*-acylpyrrole **47** and **42** were combined and heated neat at the prescribed temperature (Table 3) for 24 h. In the case of compounds **51**, **52**, and **54**, a mixture of regioisomers (**a** and **b**) were obtained which could be separated by chromatography.

An acetylene equivalent was used in the total synthesis of (±)-epibatidine by Huang and Shen.[54]

Table 3. *N*-Acyl-2-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptadienes from the Thermal Reaction of 47 and 42

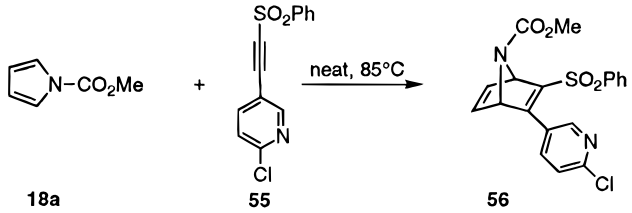


47 42 48-54

Product	R^1	R^2	R^3	Temp.(°C)	Yield (%)	a:b
48	H	H	Me	85	85	N/A
49	H	H	*t*-Bu	85	86	N/A
50	H	H	Bn	85	76	N/A
51	CO_2Me	Me	Me	85	86	2:3
52	CO_2Me	Ph	Me	110	90	1:1
53	CO_2Me	CO_2Me	Me	85	81	N/A
54	COMe	Ph	Me	85	87	1:1

This approach was further modified by Kotian and Carroll into a practical synthesis of (±)-epibatidine which was then resolved into (+)- and (−)-epibatidine.[55] The key step in this route was the facile [4+2] cycloaddition of the *N*-methoxycarbonylpyrrole (**18a**)- and benzenesulfonyl-6-chloro-3-pyridyl acetylene (**55**) to generate the 7-azabicyclo[2.2.1]heptadiene derivative **56** (Scheme 8). Further manipulation (hydrogenation, desulfonylation and decarbamoylation) provided useful quantities of (±)-epibatidine.

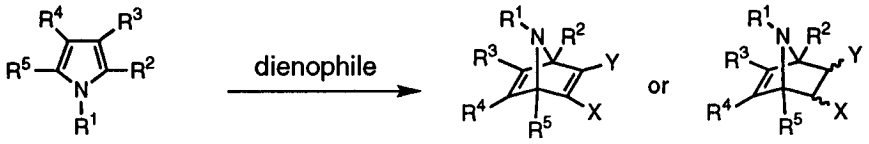
Scheme 8

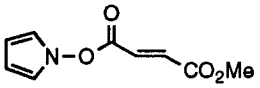
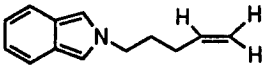
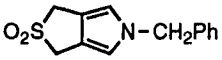
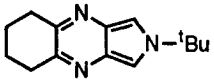
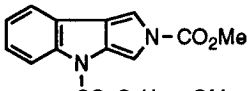
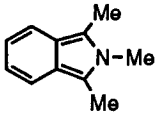
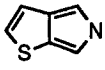


D. Miscellaneous Reactions

In addition to the three types of [4+2] cycloaddition reactions described above, a number of successful [4+2] cycloaddition reactions between various substituted pyrroles and highly reactive dienophiles have been reported over the past 20 years (Table 4). The reactions of highly strained dienophiles and pyrroles (entries 1, 2, 8−10, 23) furnished the corresponding cycloaddition products. The driving force of these reactions is believed to be the release of the ring strain of the dienophiles. Highly reactive arynes have also been successfully employed as dienophiles (entries 3−5, 13−15, 22). The *N*-oxy-substituted pyrroles have been shown to be more reactive in the [4+2] cycloaddition reactions than the *N*-acylpyrroles. Thus, *N*-hydroxypyrrole and *N*-benzoyl-oxypyrrole reacted with *N*-phenylmaleimide at room temperature to furnish [4+2] adducts in good yields (entries 11, 12). The intramolecular [4+2] cycloaddition reaction of the 1-pyrrolyl fumarate was also reported (entry 16) while the attempted intramolecular [4+2] reaction of *N*-acylpyrrole analogues failed.[64] Several 3,4-fused pyrroles and 3,4-disubstituted pyrroles have been reported to be reactive toward activated alkenes and alkynes (entries 17−24). It

Table 4. [4+2] Cycloaddition Reactions of Pyrroles with Highly Reactive Dienophiles



Entry	R^1	R^2	R^3	R^4	R^5	Dienophile	Yield (%)	endo:exo	Ref.
1	H	H	H	H	H	Hexakis(trifluoro-methyl)benzvalene	12	0:100	56
2	H	H	H	H	H	Tetrakis(trifluoro-methyl)Dewar thiophen	70	0:100	57
3	Me	H	H	H	H	[Difluorobenzyne]	44	N/A	58
4	Me	H	H	H	H	$F_3C{-}{\equiv}{-}CF_3$	30	N/A	59
5	^{t}Bu	H	H	H	H	[Naphthyne]	78	N/A	60
6	CO_2Me	H	H	H	H	$EtO_2CHC{=}C{=}CHCO_2Et$	60	N/A	61
7	CO_2Me	Me	H	H	Me	$EtO_2CHC{=}C{=}CHCO_2Et$	66	N/A	61
8	CO_2Me	H	H	H	H		27.6	0:100	62
9	COPh	H	H	H	H		10	0:100	62
10	Ph	H	H	H	H		13	0:100	62
11	OH	H	H	H	H	NPM[a]	55	100:0	63
12	OCOPh	H	H	H	H	NPM[a]	75	100:0	63
13	Me	$-(CH_2)_2-$	$CH_2C(Me)_2$	H	H	[Difluorobenzyne]	12	N/A	58
14	Me	Me	H	H	Me	[Benzyne]	22-23	N/A	58
15	Me	Me	Me	Me	Me	[Fluorochlorobenzynes]	20	N/A	58
16						[intramolecular]	70	N/A	64
17						[intramolecular]	80	0:100	65
18						DMAD[b]	28	N/A	66
19						NMM[c]	87-91	N/A	67
20						DMAD[b]	94	N/A	67
21						NPM[a]	76	3:1	68
22						[Benzyne]	75	N/A	68
23						Tricyclo[3.1.1.0^{6,7}] hept-6(7)-ene	53	N/A	69
24						NMP[a]	43	10:1	70

[a]NPM = *N*-Phenylmaleimide; [b]DMAD = dimethyl acetylenedicarboxylate; [c]NMM = *N*-methylmaleimide.

was suggested that 3,4-disubstitution lowered the aromaticity of the pyrrole ring, making it more reactive as a diene.[45] An extreme example of this was the intramolecular cycloaddition of isoindole (entry 17). This is the only reaction which has been reported to take place between a pyrrole with a nonactivated alkene. An 80% yield of the [4+2] cycloaddition adduct was achieved by the distillation of the reaction mixture (entry 17).

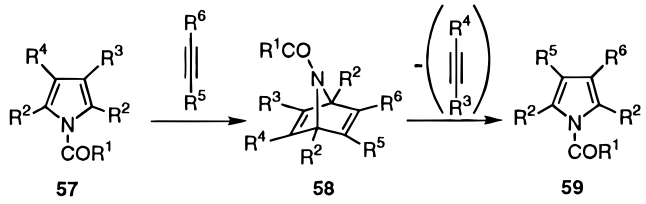
III. Chemistry of the 7-Azabicyclo[2.2.1]hepta-2,5-dienes and 7-Azabicyclo[2.2.1]hept-2-enes

A. Synthesis of Substituted Pyrroles

The instability of the 7-azabicyclo[2.2.1]heptadiene and 7-azabicyclo[2.2.1]heptene ring systems have been exploited as synthetic approaches for the preparation of a variety of substituted pyrroles. The

thermolysis of the 7-azabicyclo[2.2.1]heptadienes **58** have been reported to undergo a retrocycloaddition reaction with loss of acetylene to furnish the pyrroles **59** (Scheme 9). Further decarbonylation of **59** afforded 3,4-disubstituted pyrroles which are difficult to prepare by the conventional methods.[71−74] High temperatures were often required for the retrocycloaddition reaction of the 7-azabicycloheptadienes **58**. As a result, the decomposition of the diene has been a competitive pathway which has limited the scope of this method.

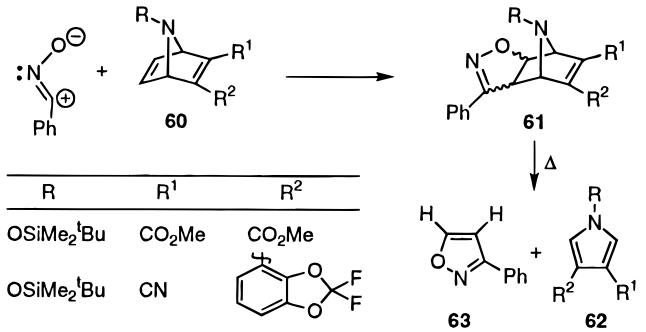
Scheme 9



R^1	R^2	R^3	R^4	R^5	R^6	Ref.
OMe	H	H	H	CO_2Me	CO_2Me	71
Ph	H	H	H	CO_2Me	CO_2Me	71
Ph	H	H	H	CO_2Et	CO_2Et	71
Ph	H	H	H	CF_3	CF_3	72
Ph	Me	H	H	CF_3	CF_3	72
^{t}Bu	H	H	H	CF_3	CF_3	73
OMe	H	H	H	*m*-$NO_2C_6H_4$	CO_2Me	74
Ph	H	H	H	*m*-$NO_2C_6H_4$	CO_2Me	74
OMe	H	CO_2Me	Ph	H	Ts	53

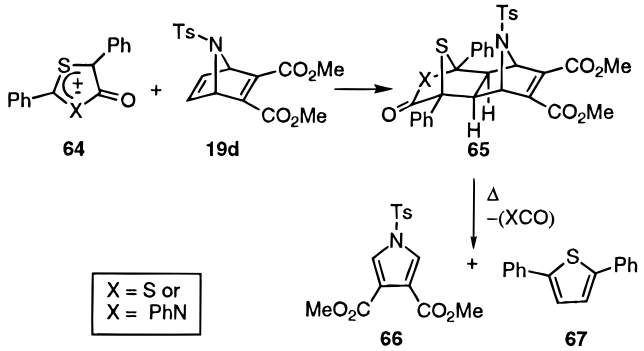
Subsequent studies have found that if the extruded acetylene unit was incorporated into an aromatic system, the retrocycloaddition reaction became more facile. It is believed that the aromatic system may help to stabilize the transition state of the retrocycloaddition reaction.[75] Thus 1,3-dipolar addition of the benzonitrile oxide provided endo and exo cycloadducts **61** and gentle heating of the cycloadducts **61** furnished the pyrrole **62** and isoxazole **63** (Scheme 10).[76,39] Pyrroles **62** were readily deprotected during reverse phase chromatography (YMC gel, methanol: water, 3:2) to give *N*-hydroxypyrroles which are difficult to prepare via other synthetic methods. The five-membered mesoionic compound, 2,5-diphenyl-1,3-dithio-4-one (**64**), has also been shown to add to the unsubstituted double bond of the dimethyl 7-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**19d**). Pyrolysis of the cycloadducts resulted in a double fragmentation reaction to give the substituted pyrrole **66** with 2,5-diphenylthiophene **67** (Scheme 11).[77]

Scheme 10



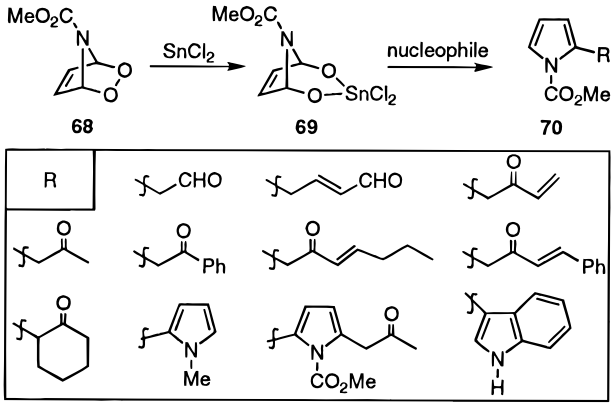
R	R^1	R^2
$OSiMe_2{}^tBu$	CO_2Me	CO_2Me
$OSiMe_2{}^tBu$	CN	

Scheme 11



The [4+2] cycloaddition adduct **68** generated from *N*-methoxycarbonylpyrrole (**18a**) with singlet oxygen was condensed with nucleophiles, such as trimethylsilyl enol ethers, vinyl ethers, *N*-methylpyrrole and indole catalyzed by $SnCl_2$ to afford 2-substituted pyrrole derivatives **70** (Scheme 12).[78] The reaction is thought to proceed through the stannic complex **69**, in which the reactive C−O bond is cleaved by the attack of a nucleophile, followed by the subsequent aromatization to afford **70** in moderate to good yields (50−70%).

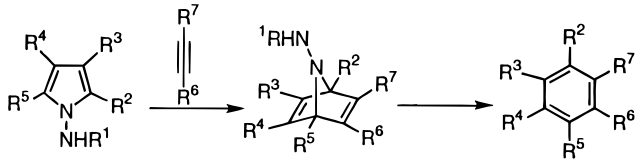
Scheme 12



B. Synthesis of Substituted Arene Derivatives

The [4+2] cycloaddition reaction of the 1-(alkylamino)pyrroles or 1-(alkoxycarbonylamino)pyrroles with electron-deficient alkynes has been shown to follow a predictable pathway and provide a remarkably simple route for the preparation of substituted benzenes. Upon heating **71** with 3 equiv of DMAD (**6**) or ethyl *β*-phenylsulfonylpropiolate in a solution of refluxing chloroform, benzene derivatives **73** were obtained in good yields (50−90%, Scheme 13).[79−81] The reaction was proposed to proceed through the formation of intermediate cycloadducts **72** followed by facile extrusion of aminonitrenes. However, the cycloaddition failed when both R^3 and R^4 were electron-withdrawing groups; only one electron-withdrawing group was tolerated in this reaction. When unsymmetrical dienophiles were employed, the reaction proceeded with little regiochemical control and mixtures of both isomers were obtained.

Scheme 13

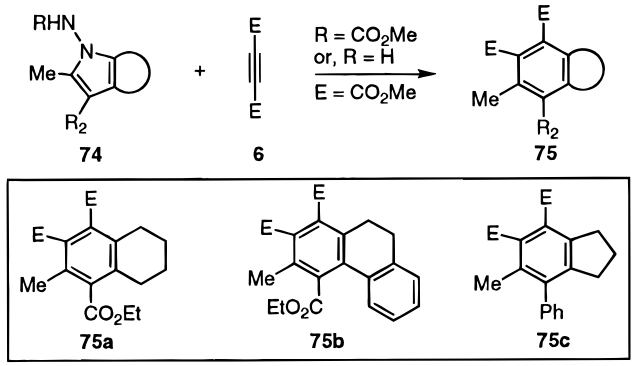


71 72 73

R^1	R^2	R^3	R^4	R^5	R^6	R^7
H	Me	H	H	Me	CO_2Me	CO_2Me
H	Me	Me	Me	Me	CO_2Me	CO_2Me
Me	Me	Me	Me	Me	CO_2Me	CO_2Me
Me_2	Me	Me	Me	Me	CO_2Me	CO_2Me
CO_2Me	Me	CO_2Et	Me	Et	CO_2Me	CO_2Me
CO_2Me	Me	CO_2Et	Et	Me	CO_2Me	CO_2Me
CO_2Me	Me	H	H	Me	$PhSO_2$	CO_2Et

The cycloaddition reaction of 2,3-fused 1-alkoxycarbonylaminopyrroles **74** (R = CO_2Me) with DMAD (**6**) required rather vigorous conditions (refluxing in toluene for 48 h), and the yields of benzene derivatives **75a**−**c** (Scheme 14) were generally low (13−

Scheme 14

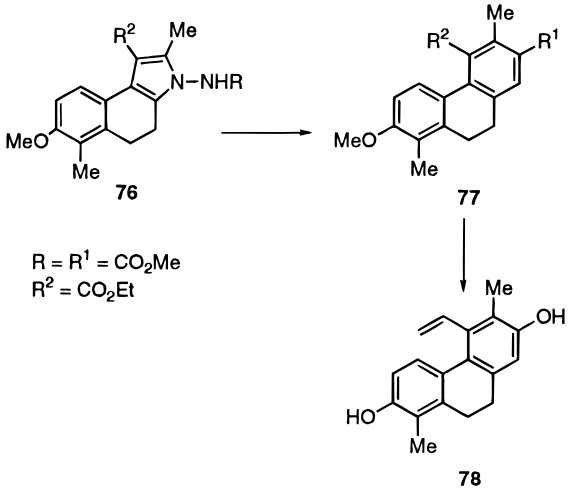


74 6 75

75a 75b 75c

50%).[79] However, the unsubstituted 1-aminopyrroles **74** (R = H) were found to react at room temperature to give **75a**−**c** in high yields (90%). This benzene ring construction method has been utilized in the total synthesis of the highly active antineoplastic agent juncusol (**78**).[82] The cycloaddition reaction of the 1-(alkoxycarbonylamino)pyrrole (**76**) with methyl propiolate provided the key intermediate **77** which was further converted into juncusol (**78**, Scheme 15).[83]

Scheme 15

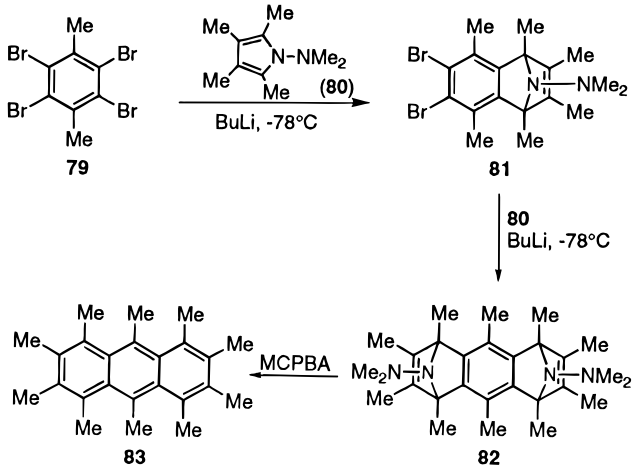


76 77 78

R = R^1 = CO_2Me
R^2 = CO_2Et

The cycloaddition of tetrabromoarene **79** (bisaryne equivalent) with two molecules of 1-aminopyrrole (**80**) in the presence of butyllithium gave the bis-adduct **82**. Treatment of **82** with *m*-chloroperbenzoic acid (MCPBA) afforded decamethylanthracene **83** in 54% overall yield (Scheme 16).[84] The same sequence was

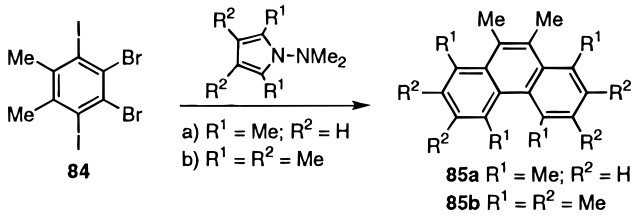
Scheme 16



79 (80) 81 83 82

used to synthesize permethylnaphthalene.[85] The analogous reaction of 1,2-dibromo-3,6-diiodo-4,5-dimethylbenzene (**84**) with 1-(dimethylamino)pyrroles followed by pyrolysis of the resultant bisadduct at 150 °C under vacuum, provided a novel synthetic route to the phenanthrene derivative **85** (Scheme 17).[86] This reaction has also been shown to be useful

Scheme 17



84

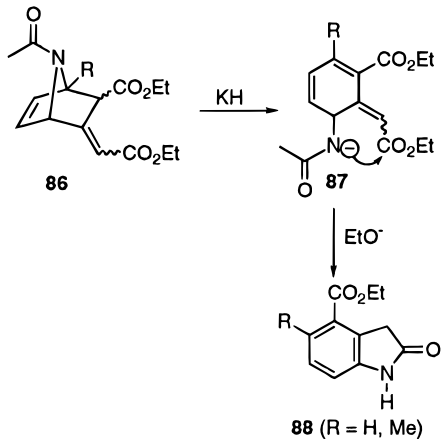
a) R^1 = Me; R^2 = H
b) R^1 = R^2 = Me

85a R^1 = Me; R^2 = H
85b R^1 = R^2 = Me

with furan as the diene instead of aminopyrroles. The same nitrene-extrusion strategy has been utilized by Gribble et al. for the convenient preparation of naphthalene and anthracene derivatives via the cycloaddition of pyrrole or isoindole with benzyne or naphthyne followed by the extrusion of the heteroatom bridge.[60,87−89]

The 7-azabicyclo[2.2.1]heptene (**86**) generated from *N*-acylpyrrole and 1,3-diethoxycarbonylallene underwent base-induced rearrangement to afford the oxindole **88** in 60−75% yield (Scheme 18).[90] The mechanism of the rearrangement is believed to proceed through a ring opening at the bridge to generate intermediate **87**, which was followed by lactamization and aromatization to give **88**. The same ring-opening methodology has recently been employed for the synthesis of the (±)-conduramine alkaloids.[91]

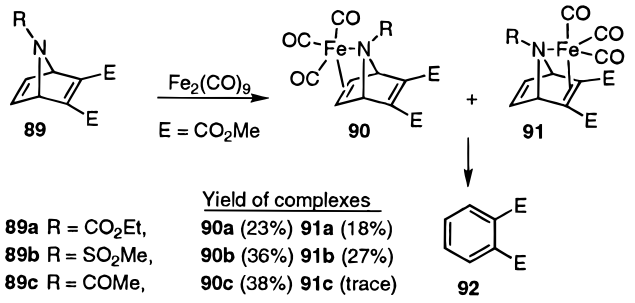
Scheme 18



C. Synthesis of the Organometallic Complexes

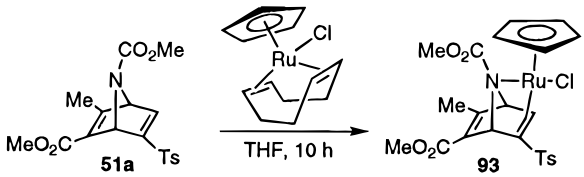
The 7-azabicyclo[2.2.1]hepta-2,5-dienes were recently found to coordinate with transition metals to form organometalic complexes.[92−95] The tricarbonyliron complexes of 7-azabicyclo[2.2.1]heptadiene derivatives were prepared from the reaction of the 7-azabicyclo[2.2.1]heptadiene derivatives **89** with $Fe_2(CO)_9$ in tetrahydrofuran (THF) at room temperature (Scheme 19).[92] Careful separation by column chromatography gave the two exo complexes **90** and **91** in moderate yield. Heating the purified samples of **90a**−**c** or **91b** in acetonitrile at 60 °C produced dimethyl phthalate (**92**) in over 80% yield. This deamination approach is different than the classical deamination methods mentioned above by the fact that the reaction takes place despite the presence of an electron-withdrawing group at the N(7) position of the 7-azabicyclo[2.2.1]hepta-2,5-dienes **89**.

Scheme 19



The 7-azabicyclo[2.2.1]heptadiene derivative **51a** was found to coordinate with ruthenium to form organometallic complexes. The only product isolated after chromatography was **93** in 65% yield (Scheme 20).[96] In contrast to other CpRu(II) complexes, the complex **93**, was not air sensitive or moisture sensitive. After 6 months exposed to the air, the sample was found by NMR spectroscopy to be unaltered.

Scheme 20



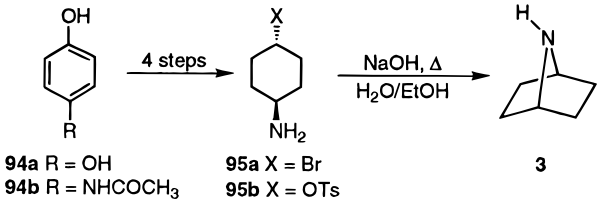
IV. Synthetic Approaches to the 7-Azabicyclo[2.2.1]heptanes

The synthesis of the 7-azabicyclo[2.2.1]heptane system has been the subject of numerous synthetic studies which have resulted in the development of several methods for the construction of the azabicyclic system.

A. Intramolecular Cyclization of Cyclohexylamine Derivatives

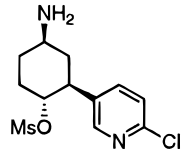
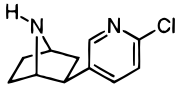
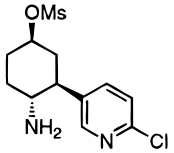
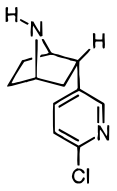
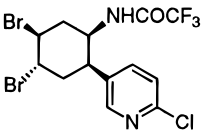
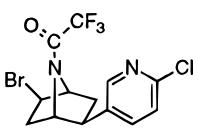
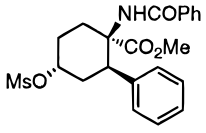
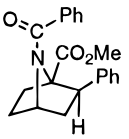
The first synthesis of 7-azabicyclo[2.2.1]heptane (**3**) was reported by von Braun and Schwarz in 1929.[97] The synthesis started with hydroquinone **94a**, which was converted into *cis*- and *trans*-4-bromocyclohexylamine **95a** (four steps). Intramolecular cyclization of **95a** under hot alkaline conditions resulted in the SN_2 displacement of bromide by the amino group to give **3** in less than 1% overall yield (Scheme 21). An improved synthesis of **3** was later reported by Fraser and Swingle in 1970.[98] The modified approach used the tosylate **95b** (from **94b**) in the intramolecular cyclization reaction which increased the overall yield of **3** to 18−36% (Scheme 21).

Scheme 21



Recently, several ring-closure reactions from cyclohexylamine derivatives have been employed for the synthesis of epibatidine or constrained proline analogues (Table 5). An interesting stereochemical

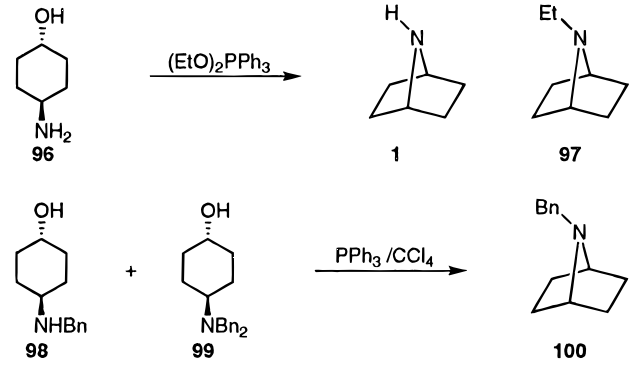
Table 5. Ring-Closure Reactions from Cyclohexylamine Derivatives

Cyclohexylamine	Product	Conditions	Yield(%)	Ref.
		$CHCl_3$ 55°C 4 days	84	3 13 16
		toluene reflux 24 h	46	99
		KO*t*-Bu THF -78°C	75	6
		KO*t*-Bu THF -78° to 4°C,18 h	N/A	100

feature of these ring closure reactions is that all substituents cis to the amino group have an exo orientation in the resultant 7-azabicyclo[2.2.1]heptanes and trans groups have an endo orientation.

Diethoxytriphenylphosphorane is a mild, regioselective cyclodehydrating reagent for the conversion of diols or β-amino alcohols to cyclic ethers or aziridines.[101,102] Recently, this methodology has been applied to the cyclodehydration of *trans*-4-hydroxycyclohexylamine. Nelsen et al. showed that *trans*-4-hydroxycyclohexylamine (**96**) could be directly converted into the 7-azabicyclo[2.2.1]heptane (**1**, 26%) and 7-ethyl-7-azabicyclo[2.2.1]heptane (**97**, 18%) with diethoxytriphenylphosphorane (Scheme 22).[103] Hass-

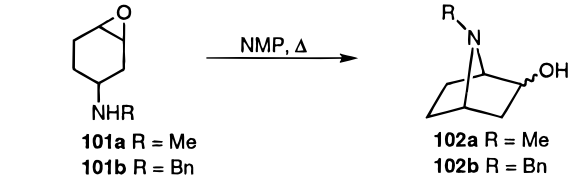
Scheme 22



ner also showed that *trans*-4-alkylaminocyclohexanols **98** and **99** could be directly converted into 7-benzyl-7-azabicyclo[2.2.1]heptane (**100**) by reaction with triphenylphosphine−carbon tetrachloride.[104] The triphenylphosphine−DEAD system was employed in the total synthesis of epibatidine.[105]

The 4-amino-1,2-epoxycyclohexanes **101** have also been shown to cyclize in dry *N*-methylpyrrolidone (NMP) upon heating to yield 2-hydroxy-7-azabicyclo-[2.2.1]heptane derivatives **102** (Scheme 23).[4,5,106−108]

Scheme 23

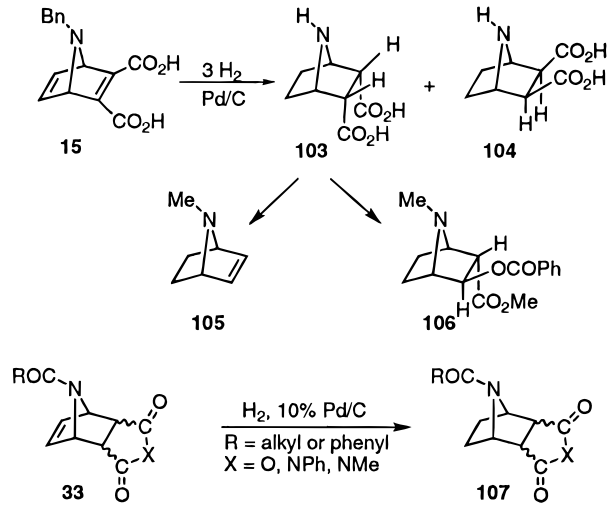


Here, the amino group is thought to attack at the C(4) position and open the epoxide ring to generate the desired bicyclic ring system. It is noteworthy that both the cis and trans isomers of epoxide **101b** were readily converted into ***exo*-102b** and ***endo*-102b**, respectively.[5]

B. Reduction of 7-Azabicyclo[2.2.1]hepta-2,5-dienes and 7-Azabicyclo[2.2.1]hept-2-enes

Catalytic hydrogenation of 7-azabicyclo[2.2.1]-heptadienes has been reported to be a straightforward method for the preparation of 7-azabicyclo-[2.2.1]heptanes. Hydrogenation of **15** resulted in the saturation of both carbon−carbon double bonds and cleavage of the *N*-benzyl group,[30,109] giving a mixture of diastereomeric diacids **103** and **104** (Scheme 24).

Scheme 24

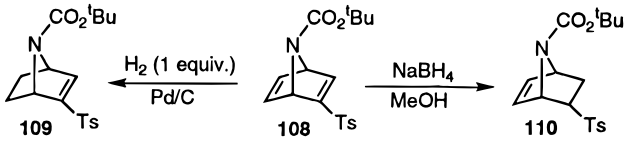


The cis,endo compound **103** was converted into the 7-methyl-7-azabicyclo[2.2.1]heptene (**105**).[110] In addition, **103** was converted into the *pseudo*-norcocaine analogue **106**.[109]

The 7-azabicyclo[2.2.1]heptene derivatives **33** obtained from high-pressure [4+2] cycloaddition reactions (Table 2) have also been reduced to the corresponding 7-azabicyclo[2.2.1]heptanes **107**, which have been suggested to be useful precursors for a variety of compounds of potential pharmacological interest (Scheme 24).[43]

Regioselective hydrogenation of the carbon−carbon double bonds of symmetrically substituted 7-azabicyclo[2.2.1]heptadienes has also been developed. An interesting example of this was the selective hydrogenation of the diene **108** (Scheme 25). Catalytic

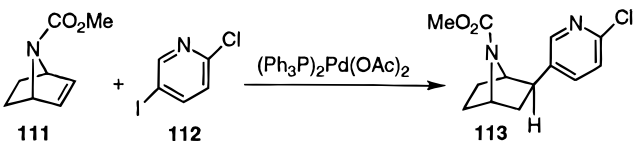
Scheme 25



hydrogenation with one equivalent of hydrogen over palladium on carbon reduced the 5,6-double bond while the hydride reduction furnished **110**.[91,111] The 5,6-double bond of 7-azabicyclo[2.2.1]heptadiene **56** (Scheme 8) has also been selectively reduced with nickel boride which was found to be a key step in the practical synthesis of epibatidine.[55]

Substituted norbornanes have been prepared by palladium-catalyzed coupling reactions of vinyl halides or aryl halides with norbornenes.[112−115] This chemistry has also been applied to the 7-azabicyclo-[2.2.1]heptene derivatives for the synthesis of epibatidine (Scheme 26).[116] Compounds **111** and **112** were

Scheme 26



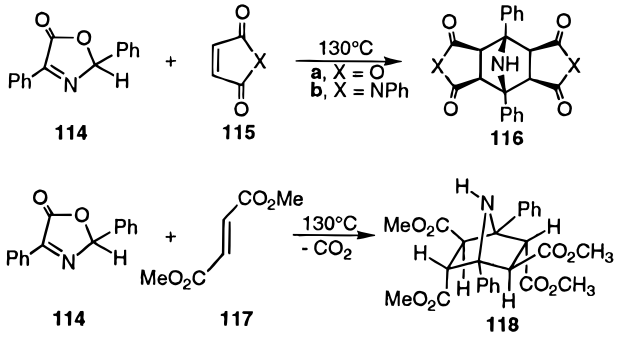
heated together at 70 °C in a solution of DMF containing piperidine, formic acid, and 8 mol % of Pd-

$(Ph_3P)_2(OAc)_2$. The coupling reaction proceeded to give the exo isomer **113** in 35% yield.

C. [3+2] Cycloaddition Reactions

Huisgen et al. have described 1,3-dipolar cycloaddition reactions of azalactones which led to the formation of polysubstituted 7-azabicyclo[2.2.1]heptane derivatives (Scheme 27).[117,118] The mechanism of

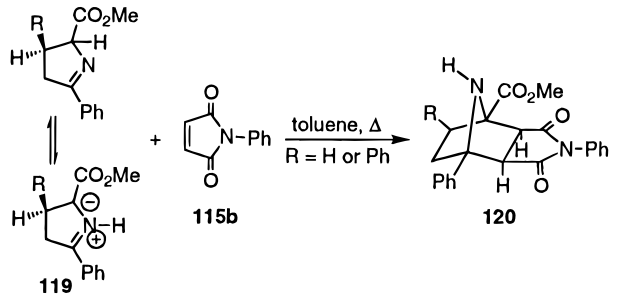
Scheme 27



these reactions involves tautomerization of the azalactone into a mesoionic oxazolium 5-oxide which sequentially reacts with two molecules of an olefinic dipolarophile with concomitant decarboxylation.[119] Thus, from the 2,4-diphenyloxazolin-5-one **114**, the adducts **116** were obtained with maleic anhydride and *N*-phenylmaleimide. The reaction of azalactone **114** and dimethyl fumarate (**117**) at 130 °C gave the 1:2 adduct **118**.

In recent years, three new types of [3+2] reactions which yield highly substituted 7-azabicyclo[2.2.1]-heptanes have been developed. The 5-phenyl-2-methoxycarbonyl-3,4-dihydro-2*H*-pyrrole derivatives **119** have been shown to tautomerize in refluxing toluene to afford cyclic azomethine ylides, which react with *N*-phenylmaleimide **115b** to give the [3+2] cycloadducts **120**.[120,121] The stereochemistry of the reaction was established by X-ray crystallography of the adduct **120** (Scheme 28).[121] This stereochemistry

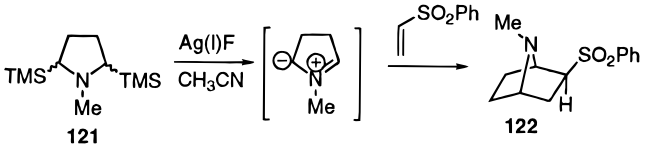
Scheme 28



was rationalized to be the result of an endo transition state.[122]

A one-pot reaction of the pyrollidine **121** with a mixture of AgF and phenyl vinyl sulfone in dry acetonitrile under an argon atmosphere at room temperature gave cycloadduct **122** in 90% yield (Scheme 29).[123] This reaction proceeded via [3+2] cycloaddition of the transient cyclic azomethine ylide with the dipolarophile. The exo stereochemistry of the benzenesulfonyl group was elucidated by exten-

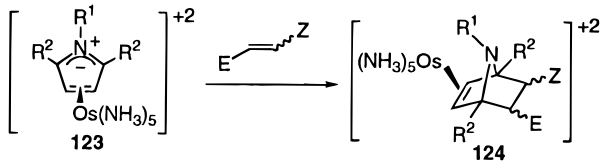
Scheme 29



sive proton decoupling experiments.[123] This strategy was recently used for the total synthesis of epibatidine.[15]

Reaction of pyrrole with $[Os(NH_3)_5OTf](OTf)_2/Mg^0$ in DME/DMAc has been shown to give $Os(NH_3)_5(\eta^2$-pyrrole$)(OTf)_2$ complex **123**. Addition of the pentaammineosmium(II) moiety across C(3) and C(4) was found to transform the aromatic pyrrole into an azomethine ylide, which readily reacted with a variety of diplolarophiles.[124−126] The η^2-pyrrole complex **123** was combined with Michael acceptors in the absence of a Lewis acid to give the dipolar cycloaddition products **124** (Scheme 30). The metal served

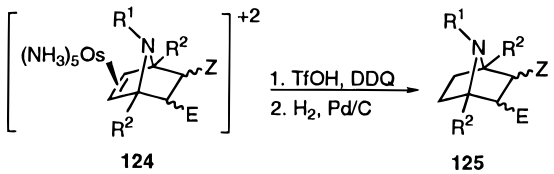
Scheme 30



R^1	R^2	*cis/trans*	E	Z	*exo/endo*	yield (%)
H	Me	*cis*	CO_2Me	CO_2Me	2:1	82
H	Me	*cis*	CO_2Me	3-pyridyl	9:1	83
H	H	*trans*	CO_2Me	CO_2Me	-	78
H	Me	*trans*	CO_2Me	CO_2Me	-	86
H	Me	*trans*	CO_2Me	3-pyridyl	16:1	93
H	Me	-	CO_2Me	H	12:1	97
H	Me	-	CN	H	5:1	83
Me	H	-	CO_2Me	H	1:1	84
Me	H	-	CN	H	1:1	98

not only to activate the pyrrole toward the formation of an exo cycloaddition product but also stabilized the resultant 7-azabicyclo[2.2.1]hept-2-ene, which would have otherwise spontaneously undergone a retrocycloaddition reaction at ambient conditions. Treatment of the adduct **124** with excess of triflic acid, followed by hydrogenation over palladium on carbon provided the corresponding 7-azabicyclo[2.2.1]heptane derivatives **125** (Scheme 31).[126]

Scheme 31

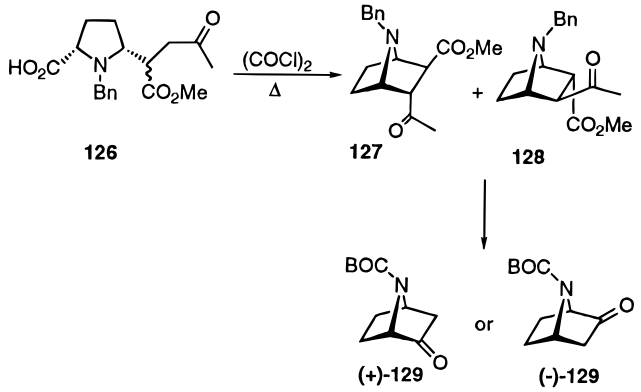


D. Intramolecular Cyclization of Substituted Proline Derivatives

N-benzyl-5-(1′-methoxycarbonyl-3′-oxobutyl)proline (**126**) has been converted into *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes **127** and **128** (3:1) via a decarbonylation/iminium ion cyclization

process (Scheme 32).[127] The mixture of **127** and **128**

Scheme 32

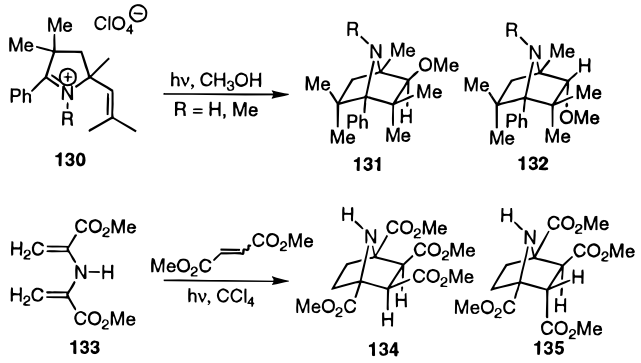


was selectively converted into (+)- or (−)-*N*-Boc-7-azabicyclo[2.2.1]heptane-2-one (**129**). This asymmetric methodology has been suggested to have potential for the enantiospecific synthesis of (+)- and (−)-epibatidine.[127]

E. Miscellaneous Reactions

Mariano et al. have described photocyclization reactions of 5-vinyl-1-pyrrolinium perchlorates **130** upon irradiation in methanol to furnish the intramolecular cycloaddition adduct **131** with a trace amount of the *endo*-methoxy isomer **132** (Scheme 33).[128] The

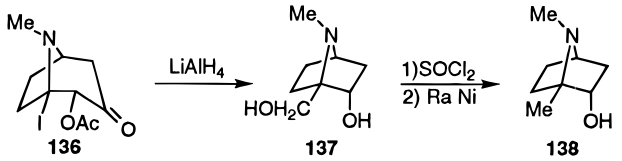
Scheme 33



photoinitiated reaction of 1,1′-bis(methoxycarbonyl)-divinylamine (**133**) with dimethyl maleate and dimethyl fumarate was also reported to afford 7-azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylates **134** and **135**, respectively (Scheme 33).[129] This reaction was found to proceed stereoselectively, retaining the original configuration of the dipolarophiles. Compound **133** was also found to react with dialkyl acetylenedicarboxylates to give tetraalkyl 7-azabicyclo[2.2.1]hept-2-ene-1,2,3,4-carboxylates.[130]

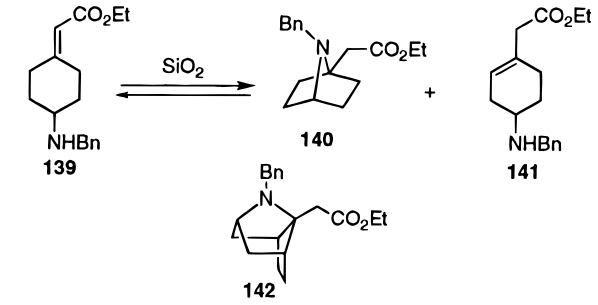
1-Iodo-2-acetoxy-8-methyl-8-azabicyclo[3.2.1]octan-3-one (**136**) was reductively transformed into 7-azabicyclo[2.2.1]heptane (**137**) with lithium aluminum hydride.[131] The structural assignment of the 1-(hydroxymethyl)-2α-hydroxy-7-methyl-7-azabicyclo-[2.2.1]heptane (**137**) was determined spectroscopically (IR, NMR, and mass spectrometry) and by chemical transformation into 1-methyl-2α-hydroxy-7-methyl-7-azabicyclo[2.2.1]heptane **138** (Scheme 34).[131]

Scheme 34



7-Benzyl-7-azabicyclo[2.2.1]heptane-1-acetic acid ethyl ester (**140**) was recently prepared by a silica gel catalyzed transannular cyclization reaction (Scheme 35).[132] The intramolecular conjugate addi-

Scheme 35

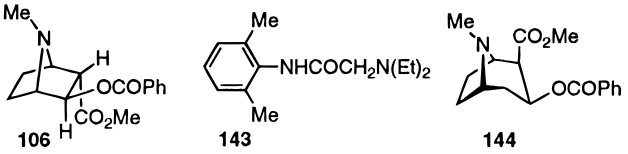


tion reaction of **139** was found to be an equilibrium process. However, the equilibrium could be shifted toward **140** by performing the reaction in a nonpolar solvent. When **139** was refluxed in heptane with silica gel (10%) equilibrium was achieved in 14 h (**139**:**140**, 34:66). Workup with acetic anhydride to acetylate any secondary amines (**139** and **141**) present in the reaction mixture furnished **140** in 61% isolated yield. This methodology has also been employed for the synthesis of the tricyclic analogue **142**.[132]

V. Properties of 7-Azabicyclo[2.2.1]heptane Derivatives

A. 7-Azabicyclo[2.2.1]heptane and 7-Azabicyclo[2.2.1]heptene Derivatives as Potential Chemotherapeutic Drugs

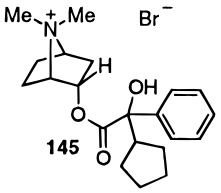
The 7-azabicyclo[2.2.1]heptane ring as a conformationally rigid, nitrogen-containing ring system has been employed as a representative substructure in a number of biological studies to differentiate the biological responses induced by conformationally mobile analogues. 2-*exo*-(Benzoyloxy)-3-*endo*-carbomethoxy-7-methyl-7-azabicyclo[2.2.1]heptane (**106**, *pseudo*-norcocaine) was the first 7-azabicyclo[2.2.1]-



heptane derivative designed and synthesized as a potential biological agent.[109] The cocaine analogue **106** was prepared to investigate the structure−activity relationships (SAR) of local anesthetics. The anesthetic activity of **106** was found to be equipotent with lidocaine (**143**) and half as potent as (−)-cocaine (**144**).[133]

A number of ester derivatives of *endo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol (**102a**) and the corresponding quaternary salts have been described in

patents as potential anticholinergic bronchodilators.[134,135] The *endo*-2-(2-cyclopentyl-2-hydroxy-2-phenyl)acetoxy-7-methyl-7-azabicyclo[2.2.1]heptane methobromide (**145**) was found to be a potent, long-acting anticholinergic bronchodilator.[108]



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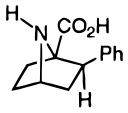
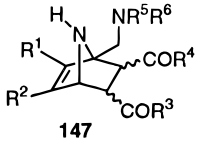


146

2-*exo*-Phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid (**146**) was recently synthesized as a conformationally constrained proline analogue.[100] The amino acid **146** will be employed for the synthesis of structurally defined peptides to be used as biological probes and pharmacological agents.

A number of unsaturated analogues of 7-azabicyclo[2.2.1]heptane have also been developed as pharmacological agents. One example of these is the 1-(aminomethyl)-7-azabicyclo[2.2.1]heptene-2,3-dicarboxylates (**147**) which were recently patented as neoplasm inhibitors.[17]

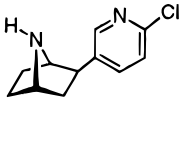


147

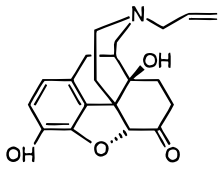
$R^1 = R^2$ = alkyl, cycloalkyl
$R^3 = R^4$ = OH, amino acid
R^5 = carbonyl, sulfonyl
R^6 = alkyl, OPh

B. Biological Activity of Epibatidine

Epibatidine (**4**) has been shown to possess potent analgesic activity.[2] The analgesic effects of epibatidine were not blocked by administration of the potent opiate receptor antagonist naloxone (**148**).[2,7−11] However, the analgesic activity was antagonized by the neuronal nicotinic acetylcholine receptor channel blocker, mecamylamine (**149**) but was not affected by the nicotinic acetylcholine receptor antagonist, hexamethonium (**150**). Since hexamethonium has been shown to be incapable of crossing the blood−brain barrier, it is believed that the primary mechanism of action of epibatidine is mediated through occupation of nicotinic acetylcholine receptors in the brain.[7,8,136]



4 (-)-epibatidine



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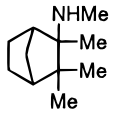

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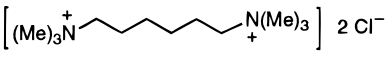

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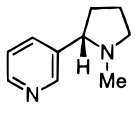


151

Limited SAR studies have demonstrated that both the (+) and (−) enantiomers of **4** exhibit equipotent analgesic activity. Both enantiomers also equally displaced bound [^{3}H]nicotine (**151**) from rat brain (K_i = 55 pM), making epibatidine one of the most potent nicotinic acetylcholine receptor ligands known to date.[7,10,136] In addition, it was found that removal of the chlorine atom had little effect on the binding affinity.[6] More recently it has been shown that (±)-[^{3}H]epibatidine binds to two sites in rat brain with affinities of 15 and 360 pM (IC_{50}).[137,138] (±)-[^{3}H]-Epibatidine was also found to bind to two sites in human brain with affinities less than 1 pM (IC_{50}).[138]

Studies with epibatidine (**4**) in vivo have further demonstrated that the pharmacological activity of this novel alkaloid is mediated by nicotinic acetylcholine receptors in the central and autonomic nervous systems.[7,10,136−140] In addition to analgesic activity, **4** elicited similar effects to those of other nicotinic acetylcholine receptor ligands, albeit with much greater potency. Moreover, epibatidine has been shown to be an extremely potent toxin producing convulsions and death at doses of 40−86 μg/kg in mice.[141,142]

With the availability of synthetic (±)-, (+)-, and (−)-epibatidine, a number of useful nicotinic acetylcholine receptor probes have been developed. [^{3}H]Epibatidine has been employed as chemical probe for the study of nicotinic receptors in chick retina and in rodent and human brains.[137,138,143] The high affinity of epibatidine and noncompliance with current nicotine receptor pharmacophore models suggests that a new nicotine receptor pharmacophore needs to be developed.[144,145] In addition, the 4′-substituted ^{18}F and ^{123}I analogues are currently being developed as useful imaging agents for emission tomography.[146]

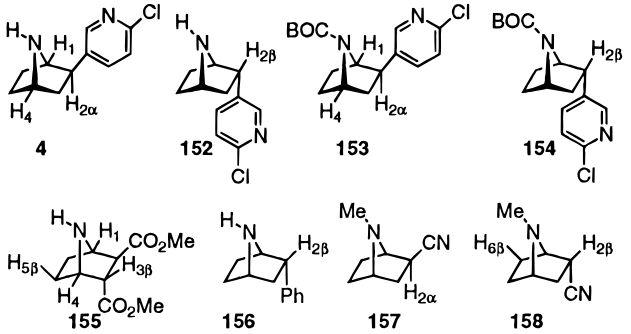
C. Physical and Spectroscopic Characteristics

The stereochemistry of a number of 7-azabicyclo[2.2.1]heptane derivatives has been determined by the magnitude of ^{1}H NMR coupling constants (Table 6). A coupling constant of ∼0 Hz for $H_{bridgehead}-H_{endo}$ and ∼3.5−5 Hz for $H_{bridgehead}-H_{exo}$ were diagnostic for exo and endo substitution, respectively. It has been found that the H(2)−H(3) vicinal coupling constants are smaller in exo isomers (6 Hz < $^3J_{2\alpha,3\alpha}$ < 10 Hz) than in endo isomers (10 Hz < $^3J_{2\beta,3\beta}$ < 13 Hz). In addition, the presence of long-range *W*-coupling between exo ring protons has been shown to be useful in cases where the bridgehead positions are substituted.[126] The values of $^4J_{2\beta,6\beta}$ and $^4J_{3\beta,5\beta}$ coupling constants are usually in the range of 1−3 Hz. For compound **154**, the $^4J_{3\beta,5\beta}$ was reported to be 5.4 Hz.[5]

A study of mass spectral fragmentation of 7-azabicyclo[2.2.1]heptane derivatives has revealed that the general fragmentation mode is the loss of the C(2), C(3) moiety from the molecular ion. The driving force for this fragmentation process has been assumed to be the ease of formation of the substituted pyrrolidinyl ion.[147] The mass spectral fragmentation pattern was instrumental for the structural identification of epibatidine.[2]

The 7-azabicyclo[2.2.1]heptane derivatives have been shown to posses an especially high nitrogen inversion barrier which is on the order of ∼3.5 kcal/mol relative to an α-unbranched monocyclic compound of the same pyramidal geometry at nitrogen.[103] This has been referred to as the "bicyclic effect".[148−152]

Table 6. Coupling Constants of Selected 7-Azabicyclo[2.2.1]heptanes



cmpd	$J_{1,2\alpha}$	$J_{1,2\beta}$	$J_{2\alpha,3\beta}$	$J_{2\alpha,3\alpha}$	$J_{2\beta,3\beta}$	$J_{2\beta,3\alpha}$	$J_{3\alpha,3\beta}$	$J_{2\beta,6\beta}$	$J_{3\beta,5\beta}$
4[a]	<1	N/A	5.1	9.0	N/A	N/A	12.2	N/A	N/A
152[a]	N/A	4.4	N/A	N/A	12	5.6	12.5	<1	N/A
153[b]	<1	N/A	4.9	9.0	N/A	N/A	12.4	N/A	N/A
154[b]	N/A	5.4	N/A	N/A	11.3	5.4	11.3	N/A	5.4
155[c]	0	N/A	4.8	N/A	N/A	N/A	N/A	N/A	1.8
156[d]	N/A	5	N/A	N/A	12.5	5.5	13	N/A	3
157[c]	0	N/A	5.1	9.3	N/A	N/A	12.6	N/A	N/A
158[c]	N/A	4.5	N/A	N/A	12.0	4.8	12.3	1.8	N/A

a: The coupling constants of compounds **4** and **152** are from ref. 99, the values published in ref.5 are slightly different;
b: ref. 5; c: ref. 126; d: ref. 46.

Restricted nitrogen inversion in 7-azabicyclo[2.2.1]-hepta-2,5-diene derivatives has also been studied.[153−161] A similar bicyclic effect has been found to exist.

VI. Conclusions

In the past 20 years, the development of special physical methods, catalysts and new acetylene equivalents has led to facile synthesis of 7-azabicyclo[2.2.1]-hepta-2,5-dienes. The 7-azabicyclo[2.2.1]hepta-2,5-dienes have been shown to be important precursors for numerous syntheses. In addition, several new synthetic routes have been developed for the preparation of the 7-azabicyclo[2.2.1]heptane derivatives. Much of this chemistry has been recently used in the syntheses of epibatidine and other 7-azabicyclo[2.2.1]-heptanes of biological and pharmacological interests.

VII. References

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