Chemistry of Functionalized Benzazepines. 5 [1]. Synthesis and Chemical Transformation of the 1,2,4,5-Tetrahydrospiro-[3*H*-2-benzazepine-3,1'-cycloalkanes]

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The synthesis of new spiro derivatives of tetrahydro-2-benzazepine was accomplished and their nitration, bromination, allylation, acetylation, formylation and oxidation reactions were studied. Nitration and bromination of 5-methyl(1,5-dimethyl)-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloalkane] took place regioselectively on position C-8 of the phenyl ring. A nitrone was obtained for the first time in the title series. The structures of the compounds were established by ir and nmr spectroscopy.

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Introduction.

Nitrogen-containing saturated heterocycles occupy a special place among the large number of organic compounds. Many of these heterocycles have been found to play fundamental roles in biological processes or have exhibited important pharmacological activity. Benzazepine- and dibenzazepine-derivatives are currently under intense scrutiny due to their physiological activity. For example, a group of tetrahydrobenzazepines with high neuroleptic and neurotropic activity have been proposed for the treatment of depression and psychosis [2]. Another group of related substances has shown antiviral activity [3]. Other substances have shown potential application in the treatment of hypertonic conditions, and of cardiovascular and central nervous system illnesses [4].

Many molecules of natural origin, especially alkaloids, contain di- or tetrahydrobenzazepine fragments. *Bulgaramine* and *Cephalotaxine* are examples of alkaloids that contain the 3-benzazepine ring. Esters of *Cephalotaxine* have been recommended for the treatment of leukemia [5-8]. Alkaloids from the *Amaryllidaceae* family, such as *Galanthamine*, *Lycoramine* and *Narwedine* are 2-benzazepine derivatives [9-11]. These three natural products possess the spiro[5*H*-2-benzazepine-5,1'-cyclohexane] fragment. *Galanthamine* is the experimental drug most often studied clinically in the treatment of Alzheimer's disease due to the potent acetylcholinesterase inhibitory activity [12]. This compound and its analogues have also been shown to have analgesic activity similar to that of morphine [13].

The phytotoxins *Aurantioclavine* and *Clavicipitic acid*, isolated from *Claviceps* bacteria, possess the tetrahydro-2-benzazepine ring and are very promising antibacterial agents for the chemotherapy of various illnesses [14-16].

These few examples and the recent work by Myers and Hutching [17,18] illustrate the importance to study the isomeric benzazepines and the need for the development of new and more effective methods for the synthesis of these interesting nitrogen heterocycles.

This paper describes a new method for the preparation of spiro-derivatives of tetrahydro-2-benzazepine and their behavior in reactions such as aromatic electrophilic substitution, alkylation, acylation, and oxidation of the benzylamine fragment.

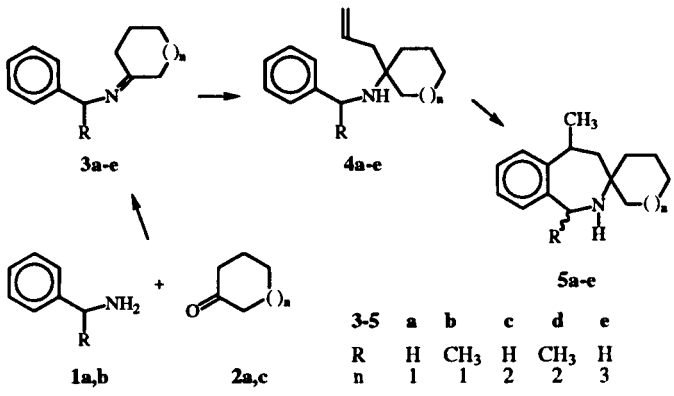
Results and Discussion.

In a previous publication [19] we reported the synthesis of 1-methyl- and 1,5-dimethyl-1,2,4,5-tetrahydrospiro-[3*H*-2-benzazepine-3,1'-cyclopentane] and 1,5-dimethyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] from benzyl(α-phenylethyl)amines and cyclopentanone and/or cyclohexanone respectively. We established by high resolution ^{1}H nmr that the 1,5-dimethyl derivatives are formed as a mixture of *cis*/*trans* isomers. We have continued this research by synthesizing new spiroheterocyclic derivatives in order to study their chemical and biological properties.

The 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloalkanes] **5a-e** were obtained by the synthetic route depicted in Scheme 1. This route includes the formation of ketimines **3a-e**, their transformation to the corresponding benzylhomoallylamines **4a-e** and the cyclization of the latter in the presence of concentrated sulfuric acid.

The starting imines **3a-e** were obtained in good yield by refluxing equimolar amounts of the amines **1a,b** and ketones **2a-c** in anhydrous benzene. Upon reaction with excess allylmagnesium bromide in dry ether the imines **3a-e** were transformed into the corresponding 1-allyl-1-*N*-benzyl(α-phenylethyl)aminocycloalkanes **4a-e**. Heating these derivatives in concentrated sulfuric acid yielded the spiro compounds **5a-e** in moderate yields. Substances **3-5** are slightly viscous pale-yellow liquids that are easily oxidized upon exposure to light or air. Compounds **3a,b-5a,b** had been synthesized previously [19,20].

Scheme 1

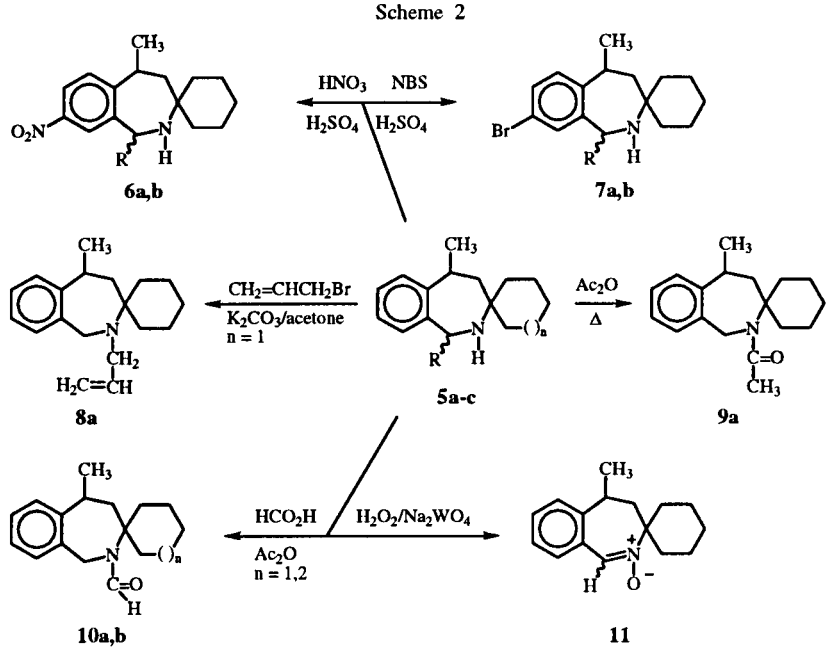


The structure of the new spiro heterocycles **5c-e** and their precursors **4c-e** was confirmed by ir and nmr spectroscopy. The ^{1}H nmr spectra of 1-allyl-1-*N*-aralkylaminocycloalkanes **4a-e** featured a very distinctive signal from the olefinic protons of the allylic fragment. The ^{1}H nmr spectra of spiro compounds **5c,e** indicated that they were obtained as a single isomer while compound **5d** was obtained as a mixture of two stereoisomers with *cis* and *trans* configuration of 1- and 5-Me groups. The equatorial orientation of the 5-CH_3 group was based on the value of the $J_{4H,5H}$ coupling constant. The dependence of the $J_{C,H}$ coupling constant on the orientation of the free electronic pair on the nitrogen was used to assign the orientation of the 1-CH_3 group [21]. These stereochemical aspects were described in detail during the structural elucidation of the spiro compounds **5a,b** [19].

The semi-empirical quantum mechanics program MOPAC was used with the AM1 field to calculate the most stable geometry of the two optical isomers of 1,3,3-trimethyl-1,2,4,5-tetrahydro-3*H*-2-benzazepine, which were taken as model compounds for the spiro compounds **5.** In both cases the calculations predicted a semi-chair conformation for the tetrahydrobenzazepine ring.

Despite the large number of reports that can be found for the synthesis of benzazepines, information on the synthesis and reactivity of tetrahydro-2-benzazepines is small. The only review article devoted to benzazepines [20] does not address the chemical transformations of tetrahydro-2-benzazepines. Thus, we have focused our research on a systematic study of the chemical properties of the spiro derivatives of tetrahydro-2-benzazepine starting with electrophilic substitution such as nitration and bromination on the aromatic ring of this molecule. Both nitration and bromination of the spirobenzazepines **5a,b** took place regioselectively on the position C-8 with formation of the corresponding 8-nitro **6a,b** and 8-bromo **7a,b** derivatives (Scheme 2). These results agree with published reports [23,24]. Nitration was accomplished with the nitrating mixture at 50-55°. Bromination was accomplished with *N*-bromosuccinimide and sulfuric acid. These derivatives were isolated by column chromatography and their structures were determined by ^{1}H nmr spectroscopy. The ^{1}H spectrum of nitro derivative **6b** exhibits methyl signals at 1.38 ppm (5-CH_3) and 1.56 ppm (1-CH_3). The aromatic region contains a doublet at 7.33 ppm (8.48 Hz), a double doublet at 8.04 ppm (2.2 Hz, 8.5 Hz) and another doublet at 8.09 ppm (2.16 Hz). A NOESY experiment with a mixing time of 600 ms featured cross peaks at 7.33, 1.38 ppm and at 8.1, 1.6 ppm, which established the identity of the aromatic protons as: H-9 = 8.09 ppm and H-6 = 7.33

Scheme 2



ppm. The assignment H-7 = 8.04 ppm follows and is the only one consistent with the chemical shifts and splittings observed.

Seeking substances with potential physiological activity, we performed alkylation and acylation of the spiro compounds **5** (Scheme 2), obtaining the corresponding *N*-substituted 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloalkanes] **8-10.**

Allylation of **5a** with allyl bromide in the presence of potassium carbonate afforded the 2-allyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] **8a**, white crystals, mp 75-78° in 68% yield. The olefinic protons are observed at 4.87-5.17 ($=CH_2$) and 5.60-6.10 (-CH=) ppm.

The *N*-acetyl derivative **9a** was obtained by refluxing **5a** in acetic anhydride. The formylation (formic acid/acetic anhydride) of the spiro compounds **5a,c** gave the *N*-formyl-substituted benzazepines **10a,b** in 63-64% yield.

Amidation was confirmed *via* ir. The *N*-acetyl derivative **9a** exhibited an intense absorption band at 1644 cm^{-1}, indicative of a CO group. This band appears at 1675 and 1653 cm^{-1} in the *N*-formyl derivatives **10a,b**.

Nitrones of the pyrrole and piperdine series are widely used in the synthesis of natural products. In the 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloalkane] series there has been no report of this type of radical. We report the formation of nitrone **11** in 60% yield from the oxidation of **5a** with hydrogen peroxide in the presence of sodium tungstate (Scheme 2). The ^1H nmr spectrum of this new nitrone shows no signal in the region corresponding to the 1-CH_2 protons but exhibits a singlet at 7.97 ppm, corresponding to the imine proton. These nitrones can be used as versatile synthons for the production of new polyheterocycles and potential radical traps [25].

EXPERIMENTAL

The purity of the substances obtained and the composition of the reaction mixtures was monitored by tlc over Alufol 60 and Silufol uv_{254} plates. Final products were isolated by column chromatography over aluminum oxide (Brockmann activity 2) eluting with ethyl ether:heptane mixtures of progressive polarity (1:10, 1:6, 1:2). ir spectra were obtained from potassium bromide pellets on a Perkin Elmer 599B-FT spectrophotometer. The nmr data were acquired in deuteriochloroform solutions on a WM-400 and an AMX-600 Bruker spectrometers. Mass spectra were obtained on an LKB-9000 spectrometer with 70 eV electron impact ionization. Elemental analyses were performed on Leco CHN-600 analyzer. Refractive indices were measured with a Schmidt Haesch 17452 refractometer. Melting points were determined on a Thomas Hoover melting point apparatus using 1.1 mm capillary tubes.

1-Allyl-1-*N*-benzylaminocycloalkanes **4a-e**. General Procedure A.

Imines **3a-e** (0.05 mole) dissolved in 15 ml of absolute ether were added slowly to a magnetically stirred solution of 0.16 mole (19.2 g) of allyl bromide and 0.32 mole (7.7 g) of magnesium in 100 ml of ethyl ether, at 10°. The mixture was heated to 30-35° during 4 hours, cooled to 0° and treated with a saturated ammonium chloride solution to a *p*H of between 8 and 9. Two liquid-liquid extractions with ethyl ether (50 ml each) were performed. The organic layers were combined and dried over anhydrous magnesium sulfate. The residue from ether evaporation was fractionated at reduced pressure.

1-Allyl-1-*N*-benzylaminocycloheptane (**4c**).

General procedure A applied on imine **3c** afforded a compound with the following properties in 80% yield: bp 146-150°/10 mm Hg, n^{20} 1.5407; ir: ν NH 3324, 1605, ν C=C 1640 cm^{-1}; ^1H nmr: δ 1.45-1.73 (m, 12H, cycloheptyl protons), 2.28 (d, 2H, -CH_2-), 2.49 (br s, 1H, NH), 3.65 (s, 2H, $PhCH_2$-), 4.95-5.18 (m, 2H, $=CH_2$), 5.66-6.10 (m, 1H, -CH=), 7.28 ppm (br s, 5H, phenyl protons); ms: m/z 243 (M^+).

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.95; H, 10,29; N, 5.76. Found: C, 83.88; H, 10.21; N, 5.70.

1-Allyl-1-*N*-(α-phenylethyl)aminocycloheptane (**4d**).

Application of the general procedure A to imine **3d** led to an 85% yield of a compound with the following properties: bp 145-147°/10 mm Hg, n^{20} 1.5366; ir: ν NH 3350, 1602, ν C=C 1639 cm^{-1}; ^1H nmr: δ 1.23-1.66 (m, 12 H, cycloheptyl protons), 1.28 (d, 3H, CH_3), 2.17 (d, 2H, -CH_2-), 2.49 (br s, 1H, NH), 4.05 (m, 1H, PhCH), 4.89-5.13 (m, 2H, $=CH_2$), 5.62-5.98 (m, 1H, -CH=), 7.20-7.39 ppm (m, 5H, phenyl protons); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{18}H_{27}N$: C, 84.05; H, 10.51; N, 5.45. Found: C, 84.05; H, 10.51; N, 5.45.

1-Allyl-1-*N*-benzylaminocyclooctane (**4e**).

General procedure A applied to imine **3e** gave an 88% yield of a compound with the following properties: bp 148-150°/10 mm Hg, n^{20} 1.5435; ir: ν NH 3362, 1602, ν C=C 1640 cm^{-1}; ^1H nmr: δ 1.25-1.87 (m, 14H, cyclooctyl protons), 2.24 (d, 2H, -CH_2-), 3.63 (s, 2H, $PhCH_2$), 5.00-5.18 (m, 2H, $=CH_2$), 5.74-6.05 (m, 1H, -CH=), 7.20-7.39 ppm (m, 5H, phenyl protons); ^{13}C nmr: δ 149 (aromatic, unprotonated), 126.0, 126.4, 126.5, 128 (aromatic, protonated), 135.1 (=CH), 117.3 ($=CH_2$), 58.5 (quaternary C), 51.2 (CH), 41.2 (CH_2) 22.4 (CH_3), 34.1, 33.3, 29.0, 27.8, 27.3, 25.2, 21.9 (CH_2 in ring); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{18}H_{27}N$: C, 84.05; H, 10.51; N, 5.45. Found: C, 84.00; H, 10.42; N, 5.38.

5-Methyl(1,5-dimethyl)-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloalkanes] **5a-e**. General Procedure B.

Concentrated sulfuric acid (2.0 ml) was added to 1.0 g of the allylamine **4a-e** and the mixture was heated to 90° for 6-8 hours while stirring vigorously. The reaction progress was monitored *via* tlc. At the end of the reaction the mixture was cooled down to room temperature and a concentrated ammonium hydroxide solution was added to pH between 8 and 9. Two 50 ml extractions with ether were performed. The organic layers were combined and dried with anhydrous sodium sulfate. The residue after ether evaporation was purified by column chromatography over alumina. Products **5a-e** were obtained as yellow oils.

5-Methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloheptane] (**5c**).

A 30% yield was obtained with general procedure B on allylamine **4c**, of a compound with the following properties: n^{20} 1.5523; ir: ν NH 3323, 1603 cm^{-1}; ^1H nmr: δ 1.39-2.00 (m, 12H, cycloheptyl protons), 1.27 (m, 1H, 4a-H), 1.79 (m, 1H, 4e-H),

1.31 (d, 3H, 5-CH_3), 3.22 (m, 1H, 5a-H), 3.68 and 4.11(dd, 2H, 1-CH_2), 7.10-7.35 ppm (m, 4H, phenyl protons); ^{13}C nmr: δ 21.0, 22.0, 22.4, 30.0, 30.3, 30.4, 34.4, 44.6, 47.1, 49.1, 57.9, 124.1, 125.4, 126.7, 127.8, 142.0, 145.7; ms: m/z 243 (M^+).

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.95; H, 10.29; N, 5.76. Found: C, 83.80; H, 10.14; N, 5.65.

1,5-Dimethyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloheptane] (**5d**).

General procedure B used on allylamine **4d** led to a compound with the following properties in 35% yield: n^{20} 1.5432; ir: ν NH 3317, 1601 cm^{-1}; ^1H nmr: δ 1.09-1.72 (m, 12H, cycloheptyl protons), 1.19 (m, 1H, 4a-H), 1.62 (m, 1H, 4e-H), 1.31 (d, 3H, 5-CH_3), 1.47 (d, 3H, 1-CH_3), 3.45 (m, 1H, 5a-H), 4.49 (m, 1H, 1-CH), 7.08-7.22 ppm (m, 4H, phenyl protons); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{18}H_{27}N$: C, 84.05; H, 10.51; N, 5.45. Found: C, 84.10; H, 10.40; N, 5.37.

5-Methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclooctane] (**5e**).

General procedure B on allylamine **4e** afforded a compound with the following properties in 38% yield: n^{20} 1.5428; ir: ν NH 3324, 1604 cm^{-1}; ^1H nmr: δ 0.89-1.85 (m, 14H, cyclooctyl protons), 1.24 (m, 1H, 4a-H), 1.30 (d, 3H, 5-CH_3), 3.53 (m, 1H, 5a-H), 3.79 and 4.15(dd, 2H, 1-CH_2), 7.10-7.30 ppm (m, 4H, phenyl protons); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{18}H_{27}N$ M, 257: C, 84.05; H, 10.51; N, 5.45. Found: C, 83.97; H, 10.40; N, 5.33.

5-Methyl-8-nitro-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**6a**).

Concentrated nitric acid (0.78 ml) was combined with 1.8 ml of concentrated sulfuric acid to form a nitrating mixture that was slowly added at 0-5° to a stirred solution of 1.12 g (4.8 mmoles) of **5a** in 1.0 ml of concentrated sulfuric acid. The reaction mixture was stirred and heated to 50-55° for 4-5 hours. The reaction progress was monitored *via* tlc. Upon completion of the reaction, the mixture was poured on ice and concentrated ammonium hydroxide was added to obtain a *p*H between 10 and 11. Two 50-ml extractions with ether were performed. The organic fractions were combined, dried with anhydrous magnesium sulfate and the ether allowed to evaporate. The residue was purified on a chromatographic column over alumina. Compound **6a** (0.68 g, 51% yield) was obtained as red crystals, with the following properties: mp 78-80° (heptane); ir: ν NH 3345, 1604, NO_2 1525, 1354 cm^{-1}; ^1H nmr: δ 1.30-2.00 (m, 10H, cyclohexyl protons), 1.25 (m, 1H, 4a-H), 1.73 (m, 1H, 4e-H), 1.40 (d, 3H, 5-CH_3), 3.34 (m, 1H, 5a-H), 3.76 and 4.18 (dd, 2H, 1-CH_2), 7.35 (s, 1H, 9-H), 7.97 (d, 1H, 6-H), 8.06 (d, 1H, 7-H); ms: m/z 274 (M^+).

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.22. Found: C, 70.32; H, 8.30; N, 10.51.

1,5-Dimethyl-8-nitro-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**6b**).

The same procedure used for **6a** was applied, starting with 1.2 g (4.9 mmoles) of **5b**; 0.78 g (55% yield) of **6b** was obtained as red crystals with the following properties: mp 108-109° (heptane); ir: ν NH 3339, 1602, NO_2 1520, 1353 cm^{-1}; ^1H nmr: δ 1.05-1.60 (m, 10H, cyclohexyl protons), 1.25 (m, 1H, 4a-H), 1.63 (m, 1H, 4e-H), 1.38 (d, 3H, 5-CH_3), 1.56 (d, 3H, 1-CH_3), 3.35 (m, 1H, 5a-H), 4.25 (m, 1H, 1-CH), 7.33 (d, 1H, 6-H), 8.04 (dd, 1H, 7-H), 8.09 (d, 1H, 9-H); ^{13}C nmr: δ 154.0, 147.19, 146.1 (aromatic, unprotonated), 124.7, 121.8, 118.3 (aromatic, protonated), 53.8 (1-CH), 47.5 (quaternary), 45.3 (5-CH), 41.6 (4-CH_2), 21.5, (1-CH_3), 21.4 (5-CH_3), 32.2, 30.3, 26.3 (CH_2 in ring); ms: m/z 288 (M^+).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.83; H, 8.33; N, 9.72. Found: C, 70.79; H, 8.21; N, 9.67.

8-Bromo-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**7a**).

N-Bromosuccinimide (1.2 g, 6.7 mmoles) was added in small portions to a solution of 1.35 g (5.9 mmoles) of **5a** in 10 ml of dichloromethane and 1.5 ml of sulfuric acid. The reaction mixture was kept at 40-45° during 8-10 hours. Reaction progress was monitored *via* tlc. Upon completion of the reaction, the mixture was poured on ice and concentrated ammonium hydroxide was added to pH between 10 and 11. Two 50-ml extractions with ether were performed. The organic fractions were combined, dried with anhydrous magnesium sulfate and the ether allowed to evaporate. The residue was purified on a chromatographic column over alumina. Compound **7a** (1.07 g, 59% yield) was obtained as a brown viscous liquid with the following properties: ir: ν NH 3314, 1606, δ C=C 1499,1456, ν C-Br 695 cm^{-1}; ^1H nmr: δ 1.30-2.00 (m, 10H, cyclohexyl protons), 1.31 (m, 1H, 4a-H), 1.72 (m, 1H, 4e-H), 1.33 (d, 3H, 5-CH_3), 3.19 (m, 1H, 5a-H), 3.63 and 4.09 (dd, 2H, 1-CH_2), 7.06 (s, 1H, 9-H), 7.23 (d, 1H, 6-H), 7.33 (d, 1H, 7-H); ms: m/z 308 (M^+).

Anal. Calcd. for $C_{16}H_{22}BrN$: C, 62.34; H, 7.14; N, 4.54. Found: C, 62.51; H, 7.21; N, 4.26.

8-Bromo-1,5-dimethyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**7b**).

The procedure followed for **7a** was used, starting with 1.5 g (6.2 mmoles) of **5b** to 1.23 g (62%) of **7b**, a brown viscous liquid with the following properties: ir: ν NH 3320, 1604, δ C=C 1499, 1456, ν C-Br 696 cm^{-1}; ^1H nmr: δ 1.35-1.75 (m, 10H, cyclohexyl protons), 1.28 (m, 1H, 4a-H), 1.75 (m, 1H, 4e-H), 1.27 (d, 3H, 5-CH_3), 1.47 (d, 3H, 1-CH_3), 3.27 (m, 1H, 5a-H), 4.20 (m, 1H, 1-CH), 7.00 (s, 1H, 9-H), 7.20 (d, 1H, 6-H), 7.32 (d, 1H, 7-H); ms: m/z 321.5 (M^+).

Anal. Calcd. for $C_{17}H_{24}BrN$: C, 63.45; H, 7.47; N, 4.35. Found: C, 63.39; H, 7.42; N, 4.27.

2-Allyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**8a**).

A solution prepared from 3.5 g (15 mmoles) of **5a**, 2.0 g (16 mmoles) of allyl bromide, 2.5 g of potassium carbonate, 10 ml of acetonitrile and 1.0 ml of water was heated to 40-45° for 6 hours. The reaction was monitored by tlc. At the end of the reaction 18% hydrochloric acid was used to bring the *p*H to 2-3. The solution was extracted with ether, neutralized with 3*N* sodium hydroxide and extracted with ether again. The ether extract was dried (magnesium sulfate) and distilled. The residue was purified by column chromatography (alumina) affording 2.37 g (68%) of compound **8** as white crystals, mp 75-78° (hexane). ir: ν C=C 1656, ν CH= 908 cm^{-1}; ^1H nmr: δ 1.30-2.00 (m, 10H, cyclohexyl protons), 1.26 (m, 1H, 4a-H), 1.73 (m, 1H, 4e-H), 1.32 (d, 3H, 5-CH_3), 3.20 (m, 1H, 5a-H), 3.65 and 4.37 (dd, 2H, 1-CH_2), 4.87-5.17 (m, 2H, =CH_2), 5.60-6.10 (m, 1H, -CH=), 7.00-7.30 (m, 4H, phenyl protons); ms: m/z 269 (M^+).

Anal. Calcd. for $C_{19}H_{27}N$: C, 84.76; H, 10.04; N, 5.20. Found: C, 84.58; H, 9.95; N, 5.11.

2-Acetyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**9a**).

Spiro compound **5a** (2.0 g,8.7 mmoles) was dissolved in 7.0 ml of acetic anhydride and refluxed for 5 hours. The reaction progress was monitored *via* tlc. At the end of the reaction the *p*H was brought to 10-11 with a saturated solution of sodium carbonate. The solution was extracted with ether. The ether extract was dried (magnesium sulfate) and distilled. The residue was purified by column chromatography (alumina). The acetamide **9a** was obtained as a viscous brown liquid in 62% (1.46 g) yield; ir: ν CO 1644 cm^{-1}; ^1H nmr: δ 1.30-2.40 (m, 10H, cyclohexyl protons), 1.28 (m, 1H, 4a-H), 1.76 (m, 1H, 4e-H), 1.32 (d, 3H, 5-CH_3), 2.15 (s, 3H, CH_3CO), 3.17 (m, 1H, 5a-H), 4.21 and 4.81 (dd, 2H, 1-CH_2), 7.15-7.65 (m, 4H, phenyl protons); ms: m/z 271 (M^+).

Anal. Calcd. for $C_{18}H_{25}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.49; H, 7.60; N, 5.09.

2-Formyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] (**10a**).

Spiro compound **5a** (0.95 g, 4 mmoles) dissolved in 2 ml of formic acid and 2 ml of acetic anhydride (3 hours, rt) afforded 0.68 g (64%) of amide **10a**, a viscous brown liquid; ir: ν CO 1675 cm^{-1}; ^1H nmr: δ 1.38-2.01 (m, 10H, cyclohexyl protons), 1.26 (m, 1H, 4a-H), 1.73 (m, 1H, 4e-H), 1.29 (d, 3H, 5-CH_3), 3.28 (m, 1H, 5a-H), 4.33 (dd, 2H, 1-CH_2), 6.78-7.08 (m, 4H, phenyl protons), 8.23 (s, 1H, H-CO); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.38; H, 8.95; N, 5.45. Found: C, 79.23, H, 8.83, N, 5.32.

2-Formyl-5-methyl-1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloheptane] (**10b**).

Following the procedure used for **9a** 0.10 g (0.4 mmole) of **5c** and 1 ml of a mixture of formic acid and acetic anhydride (1:1) yielded 0.07 g (63%) of amide **10b**, a viscous brown liquid; ir: ν CO 1653 cm^{-1}; ^1H nmr: δ 1.28-1.95 (m, 12H, cycloheptyl protons and 2H, 4-H), 1.45 (d, 3H, 5-CH_3), 3.37 (m, 1H, 5a-H), 4.45 (dd, 2H, 1-CH_2), 7.10-7.45 (m, 4H, phenyl protons), 8.32 (s, 1H, H-CO); ^{13}C nmr: δ 21.6, 22.1, 23.0, 29.5, 29.8, 31.3, 35.1, 39.8, 42.6, 48.7, 63.2, 125.0, 125.9, 127.7, 129.7, 137.0, 144.0, 160.8; ms: m/z 271 (M^+).

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.70; H, 9.22; N, 5.16. Found: C, 79.38, H, 9.46, N, 5.08.

5-Methyl-4,5-dihydrospiro[3*H*-2-benzazepine-3,1'-cyclohexane] 2-oxide (**11**).

To a solution of 1.0 g (3 mmoles) of sodium tungstate dihydrate and 1.5 g (6.5 mmoles) of the spiro compound **5a** in 5.0 ml of water, 15 mmoles of hydrogen peroxide (30%) were added slowly with cooling. The reaction mixture was stirred at room temperature for 5 hours, monitoring progress *via* tlc. At the end of the reaction the mixture was treated with sodium acid sulfate followed by sodium chloride and was finally extracted with ether (2 x 50 ml). The ether was dried (magnesium sulfate) and evaporated. The residue was purified by column chromatography (alumina) to yield 0.90 g (60%) of compound **11**, white crystals, mp 131-132° (heptane); ir: ν N-O 1230, 920 cm^{-1}; ^1H nmr: δ 1.30-2.50 (m, 10H, cyclohexyl protons), 1.29 (m, 1H, 4a-H), 1.70 (m, 1H, 4e-H), 1.43 (d, 3H, 5-CH_3), 3.12 (m, 1H, 5a-H), 7.14-7.26 (m, 4H, phenyl protons), 7.97 (s, 1H, 1-CH); ms: m/z 243 (M^+).

Anal. Calcd. for $C_{16}H_{21}NO$: C, 79.01; H, 8.64; N, 5.76. Found: C, 78,96; H, 8.50; N, 5.64.

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