Two-Step Synthesis of new 1,2,4,5-Tetrahydrospiro-[3*H*-2-benzazepine-3,4'-piperidines] from 4-Iminopiperidines

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New spiro[3*H*-2-benzazepine-3,4'-piperidines] and their precursors, *N*-substituted 4-allyl-4-*N*-benzylaminopiperidines, have been prepared as potential psychotic agents from readily available 4-iminopiperidines, by a sequence of reactions that included nucleophilic addition of Grignard reagents and Brönsted acid-mediated intramolecular cyclisation. Some of the compounds prepared have been tested in albine mice for spontaneous motor activity. All compounds prepared were characterized by ir and ^{1}H nmr spectroscopies and cg-ms spectrometry.

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Introduction.

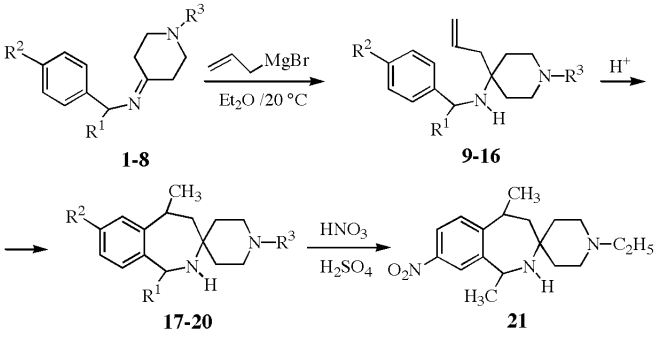
4-Iminopiperidines have received much attention owing to their obvious use in fine organic synthesis [1]. Specially, they are useful in design and subsequent synthesis of several medicinal agents, containing 4-substituted or 4,4'-disubstituted piperidine rings [2], such as the antihistaminic azatadine and cycloheptadine [3,4], or related fentanyl analgesics: carfentanyl and sufentanyl [5], alfentanyl [6], and ohmefentanyl [7-10]. The latter is an extremely potent analgesic agent with a high selectivity for the opiod μ-receptor. Its potency was estimated to be 20000-50000 times that of morphine [11]. Moreover, many piperidine derivatives spiroannulated at the C-4 position were also patented [2]. Some well-established representatives of this class of clinically useful compounds *e.g.*, spiperone and fluspiperone, are used as typical neuroleptics [12-14].

As a part of our continuing interest in developing biologically active compounds that may act as analgesics, which contain the piperidine ring with amine group at C-4, [15-17], we report herein the synthesis of new tetrahydrospiro[3*H*-2-benzazepine-3,4'-piperidines], *via* intramolecular cyclisation of 4-allyl-4-*N*-benzylaminopiperidines prepared by nucleophilic addition of Grignard reagents to 4-iminopiperidines. We also describe the preparation of the above mentioned 4-*N*-benzylaminopiperidines and the results of studies on some of their psychoactive properties.

Results and Discussion.

The starting imines **1-8** have been prepared in good yields by condensation of the corresponding commercially available benzylamines and *N*-substituted 4-piperidones as described in the literature [18]. These ketimines were used in the synthesis of tetrahydro-2-benzazepines C-3 spiroannulated with a piperidine moiety as shown in Scheme 1.

Scheme 1



1, **9,17** $R^1 = R^2 = H$, $R^3 = C_2H_5$; **2,10,18** $R^1 = CH_3$, $R^2 = H$, $R^3 = C_2H_5$; **3,11,19** $R^1 = H$, $R^2 = CH_3$, $R^3 = C_2H_5$; **4,12** $R^1 = H$, $R^2 = Cl$, $R^3 = C_2H_5$; **5,13,20** $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2C_6H_5$; **6,14** $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2C_6H_5$; **7,15** $R^1 = H$, $R^2 = Cl$, $R^3 = CH_2C_6H_5$; **8,16** $R^1 = R^2 = H$, $R^3 = CH_2C_6H_5$

Initially, *C*-allylation of the C=N bond of ketimines **1-8** was achieved immediately after their distillation with allylmagnesium bromide, prepared from allyl bromide and magnesium. From this reaction 4-allyl-4-*N*-benzylaminopiperidines **9-16** were obtained as viscous oils with high yields (Table 1). The simplicity of the procedure and accessibility of the starting materials allowed us to prepare these homoallylamines in large quantities.

Structural elucidation of homoallylamines **9-16** was carried out by ir and ^{1}H nmr spectroscopies and mass spectrometry. The ir spectra of amines **9-16** exhibited a single sharp peak in the region 3322-3342 cm^{-1} due to N-H stretching vibrations (Table 1). The fragmentation pattern of 4,4-disubstituted *N*-ethylpiperidines **9-12** in the mass spectra is different from that of related *N*-benzylpiperidines **13-16**. However, the spectra of both series contain a low-intensity (<1%) molecular ion peak which agree with the expected molecular mass (Table 2).

Table 1

Yields and some Physical and Spectral properties of the Homoallylaminopiperidines **9-16** and *N*-substituted Tetrahydrospiro[3*H*-2-benzazepine-3,4'-piperidines] **17-21**

No	B.p., °C/mm Hg	n^{20}	Yield, (%)	IR, cm^{-1}; ν_{NH}
9	165-181/10	1.527	61	3322
10	171-175/10	1.525	60	3339
11	180-188/10	1.524	39	3325
12	196-207/10	1.536	47	3327
13	165-185/10	1.554	51	3342
14	195-208/10	1.543	32	3326
15	[a]	1.568	57	3325
16	[a]	1.562	89	3322
17	[a]	1.537	82	3306
18	[a]	1.541	90	3315
19	[a]	1.539	55	3320
20	[a]	1.568	54	3318
21	[a]	--	43	3446, 1521, 1344 (δ NO_2)

[a] These compounds were isolated by alumina column chromatography.

The ^{1}H nmr spectra of substituted piperidines **9-16**, showed that the piperidine protons generated two groups of multiplet signals: at 1.40-1.90 ppm for β-H and β'-H protons, and at 2.14-2.80 ppm for α-H and α'-H protons. The 4-allyl fragment gave rise to very characteristic groups of signals (Table 3).

Subsequent intramolecular cationic allyl cyclisation of the homoallylamines **9-11** and **13** was readily carried out using concentrated sulfuric acid according to described method of spirocyclisation [19-21]. This way, the *N*-substituted 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,4'-piperidines] **17-20** have been obtained in 54-90 % yield (Table 1). These new spiropiperidines were isolated by alumina column chromatography as maroon viscous oils.

Moreover, the nitration of benzazepine hydrochloride **18** was carried out with HNO_3 and H_2SO_4 at 0°. Under these reaction conditions the C-8-nitroderivative **21** was obtained in 43 % overall yield as the exclusive product, according to the orientation rules in aromatic rings. In the ir spectrum of this compound bands appearing in the region 1521 cm^{-1}

Table 2

Elemental Analysis and Mass Spectrometric Data of Compounds **9-21**

No	Molecular Formula	% Found / Calculated C	H	N	MS, m/z (%)
9	$C_{17}H_{26}N_2$	79.15	10.13	10.73	258 ($M^{+\cdot}$ <1), 217 (27), 160 (33), 153 (14), 138 (8), 125 (12), 110 (100), 91 (70),
		79.07	10.08	10.85	84 (32), 72 (23), 65 (13), 58 (27)
10	$C_{18}H_{28}N_2$	79.29	10.32	10.23	272 ($M^{+\cdot}$ <1), 231 (32), 174 (8), 153 (13), 127 (15), 110 (100), 105 (60),
		79.41	10.29	10.29	103 (9), 84 (29), 79 (15), 70 (19)
11	$C_{18}H_{28}N_2$	79.29	10.13	10.40	272 ($M^{+\cdot}$ <1), 231 (27), 174 (25), 153 (21), 138 (10), 125 (14), 110 (100),
		79.41	10.29	10.29	105 (80), 84 (35), 72 (21)
12 [a]	$C_{17}H_{25}ClN_2$	69.53	8.37	9.49	292 ($M^{+\cdot}$ <1), 251 (17), 194 (19), 153 (15), 138 (11), 125 (61), 110 (100),
		69.74	8.55	9.57	84 (30), 72 (20)
13	$C_{23}H_{30}N_2$	82.45	8.87	8.29	334 ($M^{+\cdot}$ <1), 293 (31), 172 (71), 105 (59), 91 (100), 65 (11)
		82.63	8.98	8.38	
14	$C_{23}H_{30}N_2$	82.42	8.81	8.27	334 ($M^{+\cdot}$ <1), 293 (23), 172 (64), 105 (69), 91 (100), 65 (11)
		82.63	8.98	8.38	
15 [a]	$C_{22}H_{27}ClN_2$	74.29	7.51	7.78	354 ($M^{+\cdot}$ <1), 313 (13), 172 (58), 125 (38), 91 (100), 65 (10)
		74.47	7.62	7.90	
16	$C_{22}H_{28}N_2$	82.63	8.49	8.59	320 ($M^{+\cdot}$ <1), 279 (15), 172 (39), 91 (100), 65 (10)
		82.50	8.75	8.75	
17	$C_{17}H_{26}N_2$	79.23	9.93	10.79	258 ($M^{+\cdot}$, 35), 240 (28), 226 (21), 186 (23), 172 (9), 158 (14), 124 (100),
		79.07	10.08	10.85	117 (30), 110 (50), 91 (25), 84 (30), 72 (36)
18	$C_{18}H_{28}N_2$	79.60	10.06	10.18	Data for isomer with t_R=26.59 min.: 272 ($M^{+\cdot}$, 35), 254 (48), 240 (25), 228 (9),
		79.41	10.29	10.29	200 (28), 186 (10), 172 (20), 131 (36), 124 (100), 117 (21), 110 (46), 91 (28),
					84 (51), 72 (43), 56 (40)
					Data for isomer with t_R=27.63 min.: 272 ($M^{+\cdot}$, 33), 254 (48), 240 (26), 228 (10),
					200 (32), 186 (10), 172 (18), 131 (32), 124 (100), 117 (20), 110 (45), 91 (29),
					84 (55), 72 (45), 56 (40)
19	$C_{18}H_{28}N_2$	79.31	10.28	10.20	272 ($M^{+\cdot}$, 33), 254 (36), 240 (22), 200 (26), 186 (11), 172 (12), 131 (20),
		79.41	10.29	10.29	124 (100), 110 (45), 91 (12), 84 (36), 72 (39)
20	$C_{23}H_{30}N_2$	82.70	8.79	8.44	Data for isomer with t_R=37.53 min.: 334 ($M^{+\cdot}$, 11), 316 (9), 243 (9), 226 (7),
		82.63	8.98	8.38	200 (9), 186 (27), 172 (18), 146 (20), 131 (15), 117 (9), 91 (100), 65 (10)
					Data for isomer with t_R=38.42 min.: 334 ($M^{+\cdot}$, 9), 316 (10), 243 (12), 226 (6),
					200 (10), 186 (28), 172 (18), 146 (19), 131 (14), 117 (10), 91 (100), 65 (10)
21	$C_{18}H_{27}N_3O_2$	68.07	8.33	13.15	Data for isomer with t_R=37.10 min.: 317 ($M^{+\cdot}$, 9), 299 (15), 285 (6),
		68.14	8.52	13.25	273 (10), 124 (100), 110 (32), 84 (25), 72 (18), 56 (23)
					Data for isomer with t_R=38.0 min.: 317 ($M^{+\cdot}$, 12), 299 (15), 285 (6), 273 (11),
					124 (100), 110 (32), 84 (32), 72 (21), 56 (23)

[a] Relative to ^{35}Cl.

Table 3

Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) of Protons in ^{1}H nmr Spectra of Homoallylamines **9-16**

No	Piperidine protons		N-R^3		Allylic protons			Arom. protons	Benzylic protons, CHR^1	
	α-H, α'-H	β-H, β'-H	-CH_2-	-CH_3	=CH_2	CH=	-CH_2-		H	CH_3
9	2.38-2.48 (m)	1.40-1.55 (m)	2.42 (q, J = 7.3)	1.08 (t, J = 7.3)	5.09 (m)	5.83 (m)	2.24 (d, J = 7.7)	7.18-7.34 (m)	3.60 (s)	--
10	2.14-2.29 (m)	1.45-1.53 (m)	2.23 (q, J = 7.3)	0.92 (t, J = 7.3)	4.94 (m)	5.65 (m)	2.16 (d, J = 7.7)	7.04-7.28 (m)	3.83 (q, J = 6.8)	1.19 (d, J = 6.9)
11 [a]	2.26-2.38 (m)	1.53-1.58 (m)	2.32 (q, J = 7.3)	0.99 (t, J = 7.3)	5.01 (m)	5.76 (m)	2.16 (d, J = 7.7)	7.02 -7.15 (m)	3.50 (s)	--
12	2.37-2.53 (m)	1.54-1.62 (m)	2.33 (q, J = 7.3)	0.98 (t, J = 7.3)	5.02 (m)	5.73 (m)	2.15 (d, J = 7.7)	7.14-7.22 (m)	3.58 (s)	--
13	2.22-2.32 (m)	1.44-1.58 (m)	3.43 (s)	--	5.02 (m)	5.75 (m)	2.25 (d, J = 7.7)	7.15-7.37 (m)	3.85, 3.95 (q, J = 6.8)	1.29 (d, J = 6.8)
14 [a]	2.40-2.55 (m)	1.56-1.64 (m)	3.52 (s)	--	5.11 (m)	5.86 (m)	2.26 (d, J = 7.7)	7.11-7.34 (m)	3.59 (s)	--
15	2.35-2.53 (m)	1.52-1.63 (m)	3.55 (s)	--	5.14 (m)	5.87 (m)	2.27 (d, J = 7.7)	7.26-7.36 (m)	3.62 (s)	--
16	2.55-2.80 (m)	1.70-1.90 (m)	3.71 (s)	--	5.30 (m)	6.05 (m)	2.24 (d, J = 7.7)	7.35-7.65 (m)	3.81 (s)	--

[a] 2.23 ppm (3H, s, *p*-CH_3).

and 1344 cm^{-1} are attributed to NO_2 asymmetric and symmetric vibrations, respectively. The ^{1}H nmr spectrum of **21** is very similar to that of **18**, except for the multiplicity of the aromatic protons, which resonated at 7.36 (J = 8.2 Hz) and 7.98 (J = 2.4 Hz) ppm as doublets and at 8.04 (J = 2.4 and 8.2 Hz) ppm as double doublet. A NOESY experiment with a mixing time of 600 ms featured cross peaks at 7.36, 1.36 ppm and at 7.98, 1.50 ppm, which established the unambiguously identity of H-6 and H-9, respectively. Consequently, the double doublet at 8.04 ppm corresponds to H-7. These results are in agreement with those of related heterocycles investigated previously [19,21].

Table 4

Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) of Protons in ^{1}H nmr Spectra of Spirobenzazepines **17-21**

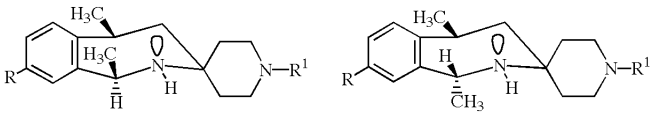
No	Piperidine protons		N-R^3		Azepine protons [a]			Arom. Protons	Substituents	
	α-H, α'-H	β-H, β'-H	-CH_2-	-CH_3	1-H	4-H_{ax}	5-H_{ax}	6H-9H/others	1-CH_3	5-CH_3
17	2.15-2.60 (m)	1.56-1.82 (m)	2.45 (q) J = 7.2	1.10 (t) J = 7.2	3.67 (d, H_A), 4.09 (d, H_B) J = 15.5	1.27(dd) J = 10.9, 12.8	3.26 (m)	7.10-7.33 (m)	-- J = 7.2	1.36 (d)
18a	2.20-2.56 (m)	1.53-1.74 (m)	2.41 (q) J = 7.2	1.07 (t) J = 7.2	4.21 (q) J = 6.8	1.22 (dd) J = 10.9, 13.6	3.33 (m)	7.11-7.26 (m)	1.50 (d) J = 6.8	1.36 (d) J = 7.2
18b	2.20-2.56 (m)	1.53-1.74 (m)	2.44 (q) J = 7.2	1.11 (t) J = 7.2	4.35 (q) J = 6.8	1.50 (dd) J = 10.2, 14.0	3.50 (m)	7.11-7.26 (m)	1.48 (d) J = 6.8	1.35 (d) J = 7.2
19	2.40-2.63 (m)	1.54-1.79 (m)	2.43 (q) J = 7.1	1.17 (t) J = 7.1	3.59 (d, H_A), 3.62 (d, H_B) J = 15.3	1.25 (dd) J = 10.6, 14.1	3.22 (m)	6.90-7.20 (m)	--	1.30 (d) J = 7.0
20a	2.30-2.60 (m)	1.55-1.74 (m)	3.46 (s)	--	4.20 (q) J = 6.8	1.26 (dd) J = 10.9, 13.6	3.31 (m)	7.07-7.35 (m)	1.49 (d) J = 6.9	1.34 (d) J = 7.1
20b	2.30-2.60 (m)	1.55-1.74 (m)	3.51 (s)	--	4.34 (q) J = 6.8	1.52 (dd) J = 10.8, 14.0	3.42 (m)	7.07-7.35 (m)	1.46 (d) J = 6.9	1.32 (d) J = 7.1
21a	2.33-2.66 (m)	1.51-1.62 (m)	2.41 (q) J = 7.2	1.07 (t) J = 7.2	4.21 (q) J = 6.8	1.22 (dd) J = 10.9, 13.6	3.33 (m)	7.36 (d, H-6) 7.98 (d, H-9) 8.04 (dd,H-7)	1.50 (d) J = 6.8	1.36 (d) J = 6.8
21b	2.33-2.66 (m)	1.51-1.62 (m)	2.44 (q) J = 7.2	1.11 (t) J = 7.2	4.35 (q) J = 6.8	1.49 (dd) J = 10.7, 13.9	3.50 (m)	7.36 (d, H-6) 7.98 (d, H-9) 8.04 (dd,H-7)	1.48 (d) J = 6.8	1.35 (d) J = 6.8

[a] Signal of the 4-H_{eq} proton overlapped with signals of piperidine β,β' protons.

The structural assignments proposed for the spiro[3*H*-2-benzazepine-3,4'-piperidines] **17-21** were also consistent with their ^{1}H and ^{13}C nmr spectra (Tables 4 and 5) and were supported by mass spectrometric data.

In contrast with mass spectra of compounds **9-16**, intensities of molecular ion peaks ($M^{+\cdot}$) in the mass spectra of spirotetrahydro-2-benzazepines **17-20** varied between 7 and 42%. The mass spectra of benzazepines spirocondensed with the *N*-ethylpiperidine moiety **17-19** and benzazepine spiroannulated with the *N*-benzyl-piperidine moiety **20** show base peaks at m/z 124 and m/z 91, respectively. The chemical shifts of the methyl (doublet at 1.30-1.36 ppm) and methyne (multiplet at 3.22-3.50 ppm) protons at the C-5 position in the ^{1}H nmr provide the best evidence that the cyclisation of **9-11**, and **13** take place. We assume, that these tetrahydro-2-benzazepine derivatives, as well as in the parent tetrahydrospiro[3*H*-2-benzazepine-3,1'-cycloalkanes] adopts the semi-chair conformation [19,21]. Moreover, the equatorial orientation of the 5-CH_3 group for all spiranes **17-20** was established based on the value of *trans* $^3J_{4H,5H}$ coupling constant (Table 4). By ^{1}H nmr and cg-ms data it was determined that spirocompounds **17** and **19** are present as a unique conformer. The chemical shifts of the benzylic 1-H protons in the above mentioned compounds appeared in the range of 3.59-4.09 ppm as double doublets with geminal coupling constants of J_{AB} = 15.3-15.5 Hz, indicating that these protons are nonequivalent. According to chromatographic and mass-spectral data, the spiro-tetrahydro-2-benzazepines **18** and **20** obtained by our route from racemic α-phenyl-ethylamine and 4-piperidones are formed as a 1:1 mixture of geometric isomers. The benzazepine **18** isomers eluted from an HP-5 [5%-phenyl-poly(dimethylsiloxane)] capillary column at 26.59 and 27.63 minutes, using an oven temperature programmed from 120 to 280°, at 5°/minute, while the benzazepine **20** isomers emerged from the column at 37.53 and 38.42 minutes under the same chromatographic conditions. For these compounds with two methyl groups at the 1-C and 5-C positions, the ^{1}H nmr spectra showed the presence of two pairs of doublets at 1.48/1.50 and 1.35/1.36 ppm (2-benzazepine **18**), as well as at 1.46/1.49 and 1.32/1.33 ppm (2-benzazepine **20**). Decoupling experiments gave additional support for the structural assignment of both 1-CH_3 (1'-CH_3) and 5-CH_3 (5'-CH_3) protons in the spectra of **18** and **20**. Thus, it was established that the protons of the 1-CH_3 (1'-CH_3) group resonate at lower fields than the 5-CH_3 (5'-CH_3) protons. The dependence of the $^1J_{C,H}$ coupling constant on the orientation of the free electronic pair on the nitrogen atom was used to established the spatial orientation of the 1-CH_3 group. Thus, the larger coupling constant observed for the isomers **18b**,**20b** ($J_{C,H}$ = 134 Hz) in comparison with the coupling constant for the isomers **18a,20a** ($J_{C,H}$ = 130 Hz) indicates that the free electron pair on the nitrogen and C-H bond in **18b**,**20b** have a *cis* configuration relative to one another. The chemical shifts of the benzylic 1-H protons appeared in the range of 4.20-4.35 ppm as two different quartets for the spirobenzazepines **18** and **20**. The second quartet observed at lower fields also demonstrates the pseudoequatorial orientation of 1-H in these molecules. From these results it was inferred that the products obtained existed as diastereoisomers mixture, which were represented in figure 1 as the *cis*-e,e and *trans*-a,e forms. We have previously made this observation for related compounds [18].

The ^{1}H nmr spectrum of compound **21**, which was obtained from the diastereomeric mixture of spirane **18**, is very similar to that of the above described compounds. The cg-ms analysis of nitrobenzazepine **21** showed that two diastereoisomers (**21a** and **21b**) eluted from the column at 37.14 and 38.01 minutes under the same chromatographic conditions and both exhibit molecular ion peaks of low intensity (9 and 11%) which agree with the expected molecular mass. Unfortunately, all attempts to separate these diastereoisomers by conventional column chromatography were unsuccessful.



***Cis*-e,e-18a,20a,21a** ***Trans*-a,e-18b,20b,21b**

18: R = H, $R^1 = C_2H_5$; **20:** R = H, $R^1 = CH_2C_6H_5$; **21:** R = NO_2, $R^1 = C_2H_5$

Figure 1. Configurational isomers of the spiro-3*H*-2-benzazepines **18, 20**, **21**

The spontaneous motor activity assay showed significant differences ($p<0.001$) between the vehicle effect (distilled water, 1 ml/100 g, IP) and that of 4-allyl-4-*N*-benzyl-aminopiperidines **9**,**11**,**12** and **16** at a dose of 10 mg/kg. None of these compounds was active at lower doses. In the subsequent assay of the amphetamine-induced hyperactivity antagonism the molecule **9** with representative structure of the compounds tested did not show any activity at a dose of 10 mg/kg (Figure 2). No deaths were produced by any of these compounds, at any doses tested (10, 5 and 2 mg/kg).

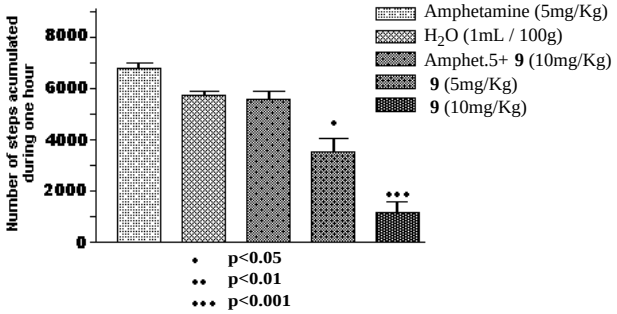


Figure 2. Study of spontaneous motor activity of compound **9**.

Table 5

^{13}C NMR Data for Isomers **18a**, **18b**, **20a** and **20b**

No	^{13}C NMR Resonances
18a	δ 145.60 (9a-C), 145.15 (5a-C), 122.46-126.02 (6-C-9-C), 53.24 (3-C), 52.53 (N-1'-C), 49.14 (2'/6'-C), 48.26 (4-C), 45.00 (1-C), 35.20 (3'/5'-C), 29.27 (5-C), 21.39 (1-CH_3), 21.09 (5-CH_3), 12.20 (N-2'-C).
18b	δ 143.64 (5a-C), 143.56 (9a-C), 122.46-126.02 (6-C-9-C), 52.85 (3-C), 52.51 (N-1'-C), 51.08 (1-C), 49.45 (2'/6'-C), 47.66 (4-C), 38.92 (3'/5'-C), 32.07 (5-C), 24.34 (1-CH_3), 21.09 (5-CH_3), 12.20 (N-2'-C).
20a	δ 145.63 (9a-C), 145.18 (5a-C), 138.07 (quaternary), 126.86-129.43 (*o*,*m*,*p*-$C_{Ar.}$), 122.46-126.10 (6-C-9-C), 63.24 (N-1'-C), 53.26 (3-C), 49.34 (2'/6'-C), 48.22 (4-C), 45.03 (1-C), 35.19 (3'/5'-C), 29.26 (5-C), 21.40 (1-CH_3), 21.12 (5-CH_3).
20b	δ 143.65 (5a-C), 143.54 (9a-C), 138.05 (quaternary), 126.86-129.43 (*o*,*m*,*p*-$C_{Ar.}$), 122.46-126.02 (6-C-9-C), 63.20 (N-1'-C), 52.85 (3-C), 51.03 (1-C), 49.45 (2'/6'-C), 47.61 (4-C), 38.88 (3'/5'-C), 32.04 (5-C), 24.32 (1-CH_3), 21.06 (5-CH_3).

EXPERIMENTAL

1. Chemistry.

The purity of the obtained substances and the composition of the reaction mixtures were monitored by tlc over Alufol 60 and Silufol UV_{254} plates. The final spiranes were isolated by column chromatography over aluminium oxide (Brockmann activity 2) eluting with heptane. The ir spectra were obtained from potassium bromide pellets on a Perkin Elmer 599B-FTIR spectrophotometer. The ^{1}H and ^{13}C nmr spectra were recorded on Bruker AC-200 and AC-300 spectrometers, and are reported in ppm on the δ scale in $CDCl_3$ solvent with TMS as internal standard. Data are reported as follows: chemical shift (integral intensity, multiplicity, coupling constants in Hz and group). A Hewlett-Packard (HP) 5890A Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS ChemStation Data system was used for MS identification. The electron beam energy was 70 eV. Mass spectra and reconstructed chromatograms were obtained by automatic scanning in the mass range m/z 50-400 a.m.u.'s at 2.2 scan/s. Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer. Refractive indices were measured with a Schmidt Haesch 17452 refractometer.

General Procedure for Reaction of Ketimines **1-8** with Allylmagnesium Bromide.

A solution (0.10 mole) of the ketimines (**1-8**) dissolved in dry ether (30 ml) was added dropwise to a stirred solution of allylmagnesium bromide, prepared from allyl bromide (0.30 mole) and metallic magnesium (0.60 mole) in dry ether (100 ml). After the addition was complete, the reaction mixture was heated to 35° and vigorously stirred for four hours. Work-up of the reaction mixture with a cold saturated solution of ammonium chloride, extraction with ether (3x100 ml), and vacuum distillation of the dried extracts afforded the corresponding 4-allyl-4-*N*-benzylaminopiperidines as yellow or brown viscous oils. Yields and some physical and spectral properties of these compounds are given in Tables 1-3.

General Procedure for Cyclisation of Homoallylamines **9-11, 13** Under Acidic Conditions.

To a stirred and cooled (0°) solution of homoallylamines **9-11** and **13** (1.0 g) and chloroform (2.0 ml) was added concentrated sulfuric acid (2.0 ml) dropwise for five minutes. The reaction mixture was heated at 80° and vigorously shaken for three hours, and reaction progress was monitored by tlc. Neutralisation of the reaction mixture with a concentrated solution of ammonium hydroxide (pH≈ 9-10) in the cold, extraction with ether (2x50 ml), and purification by column chromatography of the dried extracts gave the corresponding spirobenzazepines **17-20** as brown viscous oils. Yields and some physical and spectral properties of these compounds are given in Tables 1, 2, 4 and 5.

Nitration of 1,2,4,5-Tetrahydrospiro[3*H*-2-benzazepine-3,4'-piperidine] Hydrochloride **18**.

To a stirred and cooled (0°) mixture of conc. H_2SO_4 and 65% HNO_3 (1.7 ml), 1.0 g (2.91 mmole) of benzazepine hydrochloride **18** was added by portions. After the addition was complete, the dark yellow suspension was stirred at room temperature for 18 hours. The reaction mixture was then neutralized with ammonium hydroxide (pH≈ 9) in the cold. The chloroform layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was then purified by column chromatography. The mononitroderivative **21** was obtained in 43% (0.4 g) as maroon viscous oil. Yield and spectral properties of this compound are given in tables 1, 2, and 4.

2. Pharmacology.

The spontaneous motor activity assay was always carried out at the same hour of the day in a thermostated (22 ± 1°) chamber with a twelve-hour (8 a.m-8 p.m.) light/darkness cycle. All experiments used albine male mice (Charles River CD1), 27 ± 3 g in weight. The animals were utilised only once in order to avoid tolerance, sensitisation and learning alteration effects on their response. For the adaptation of the mice to the chamber environment, they were maintained for at least 48 hours in groups of 20, in 52x28 cm cages, with free water and food access. All compounds, dissolved in distilled water, were administered intraperitoneally at 0.01 ml/g. Solutions were prepared immediately before the administration. Statistical analysis was performed by means of the Newman-Keuls test from the GradPhad Prism program.

Modification of Spontaneous Motor Activity.

The Panlab (Ref. 0603) activity boxes were used. Each one consists of a 34.5 cm x 34.5 cm plate, capable of electromagnetic field generation. A 27.5 cm x 27.5 cm cage with three mice, was placed over the plate. All the time the mice had free access to food and water. The electromagnetic field is affected by animal displacement, registering every movement as a step. These signals were detected by means of an automated Actisystem PanLab (DAS 16 V.1). Three batches of three mice each were used. The vehicle and/or new molecules **9**, **11**, **12** and **16** at a dose of 10 mg/kg *via* intraperitoneally were supplied to the animals. Those

molecules which showed some effect (activity) over mice, were employed in three additional batches, and depending upon results the doses of 2 and 5 mg/kg were used.

Hypermotility Antagonism Induced by Amphetamine.

Hyperactivity antagonism induced by amphetamine was evaluated by means of the same system described for the spontaneous motor activity assay. Compound **9** at concentration of 10 mg/kg was administered intraperitoneally to the animals, thirty minutes before the administration of dextroamphetamine sulfate (5 mg/kg). Then, the number of steps was registered at 10-minute-intervals during the next 60 minutes after amphetamine administration.

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