The Synthesis of Octahydro-7-phenylpyrazino[2,1-*b*][3]benzazepines

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Octahydro-7-phenylpyrazino[2,1-*b*][3]benzazepine (**1a**) was prepared from 1-methyl-3-phenylmethylpiperazine **5a** by reaction with styrene oxide followed by sulfuric acid cyclization of the resulting alcohol **6a**. The diastereomeric mixture **1a** was further separated into the diastereomers **1a'** and **1a''**. Similarly 1-methyl-3-(3-chloro-4-methoxyphenyl)piperazine was reacted with styrene oxide to yield **6c** which on cyclization with 1.5 equivalents of sulfuric acid in trifluoroacetic acid gave a 3:7 mixture of phenolic, **1d**, and methoxy, **1c**, octahydropyrazino[2,1-*b*][3]benzazepines. The reaction of the 2,5-piperazinedione **4c** with sodium acetoxyborohydride gave a 49% yield of the 2-piperazinone **7** which was similarly carried on to the corresponding 1(2*H*)-oxohexahydropyrazino[2,1-*b*][3]benzazepine **9**.

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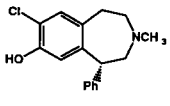
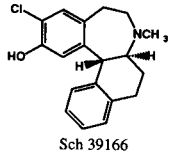
1-Aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines have received much attention as selective dopaminergic D-1 agonists and antagonists [1] and a SAR on the selective D-1 antagonist Sch 23390 has been published [2]. Whereas Sch 23390 has a short duration of activity, the fused ring analog Sch 39166 is a clinical candidate for trial in the treatment of schizophrenia [3].

In this paper we report our synthesis of 3,4-piperazine fused ring analogs of the 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines; the octahydro-7-phenylpyrazino[2,1-*b*][3]-benzazepines **1**.

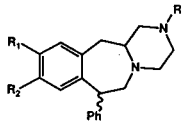
Structures #1



Sch 23390



Sch 39166

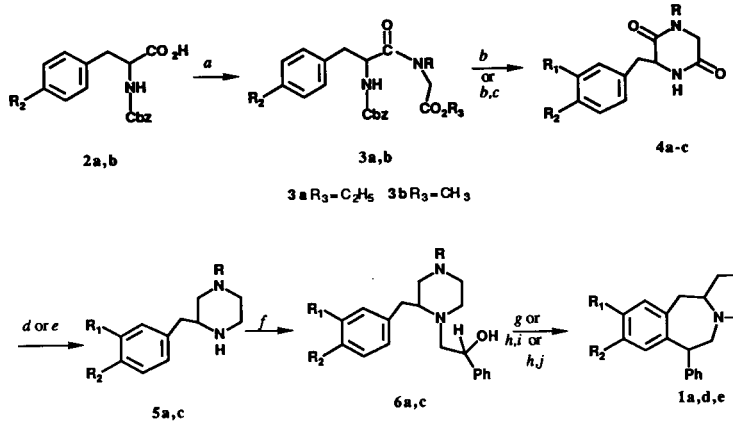


1

Synthesis.

The route used to synthesize **1** is shown in Scheme 1. Catalytic removal of the phenylmethoxycarbonyl (cbz)

Scheme 1



a) DCC, sarcosine ester *b)* H_2, Pd-C *c)* SO_2Cl_2 *d)* LAH
e) B_2H_6 *f)* Styrene oxide *g)* H_2SO_4 *h)* 1.5 equiv. H_2SO_4 / TFA
i) 48% HBr *j)* BBr_3

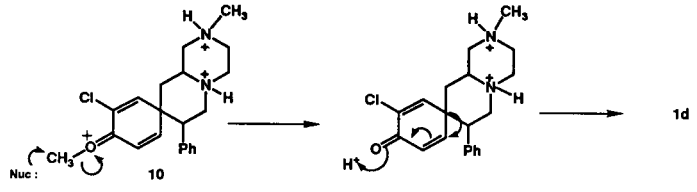
	R	R_1	R_2
a	CH_3	H	H
b	CH_3	H	CH_3O
c	CH_3	Cl	CH_3O
d	CH_3	Cl	HO
e	H	Cl	HO

group of **3a** and **3b** and concomitant cyclization of the aminoester gave the piperazinediones **4a** and **4b**. Compound **4b** was reacted with sulfuryl chloride in acetic acid at room temperature to yield **4c**. Reduction of the piperazinediones **4a** and **4c** with lithium aluminum hydride and borane, respectively, gave the corresponding piperazines which were reacted with styrene oxide to yield **6a** and **6c**. Compounds **6a** and **6c** were obtained as diastereomeric pairs, distinguishable by nmr, which could be separated by repeated column chromatography if desired. Ring closure of the diastereomeric pair **6a** was carried out in cold concentrated sulfuric acid to yield after column chromatography 19% of **1a'**, the less polar diastereomer of **1a** [4] and 13% of **1a''**, more polar diastereomer of **1a**. The absolute stereochemistry of these diastereomers was not determined. Compound **1d**, which has the benzene ring substitution pattern of Sch 23390 and Sch 39166, was obtained by a similar route as shown in Scheme 1. The ring closure of **6c** was carried out using 1.5 equivalents of sulfuric acid in trifluoroacetic acid [5] which has experimental advantages over the concentrated sulfuric acid method. The product from the ring closure consisted of a 3:7 mixture of the phenolic:methoxy, **1d**:**1c**, diastereomers. Resubmitting the mixture to the reaction conditions returned the same 3:7 mixture. The phenolic product most likely arises from the cyclic intermediate **10** [6] as shown below. Further treatment of the 3:7 mixture with 48% hydrobromic acid and column chromatography gave the pure phenolic diastereomers in 9%, (**1d'** less polar diastereomer) and 12% (**1d''** more polar diastereomer) yields. The corresponding *N*-desmethylpiperazines **1e'** and **1e''** were prepared by treatment of **1d'** and **1d''** with 2.3 equivalents of vinyl chloroformate, followed by treatment with hydrogen chloride in methanol.

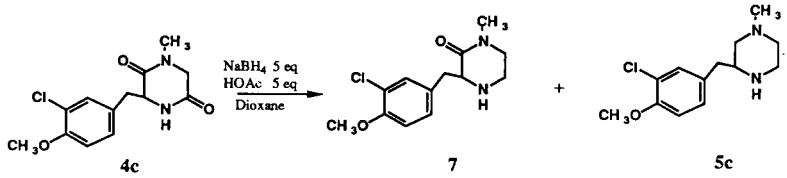
Umino *et al* [7] reported that sodium acetoxyborohydride in refluxing dioxane reduces primary and secondary amides rapidly while tertiary amides gave only poor results. We decided to see if this selectivity would allow the reduction of the secondary amide of **4c** while leaving the tertiary amide intact. Indeed, reduction of **4c** gives, after chromatography, 49% of **7** and 31% **5c**. The structure of **7** was confirmed using COSY nmr.

The piperazinone **7** was converted to the lactam **9** as shown in Scheme 2. The ring closure step in this case also gave a mixture of phenolic and methoxy products. The isolated lactam **9** was one diastereomer; we expect due to epimerization in the ring closure step. The nmr chemical shift of the aromatic proton in the 8 position appears to be diagnostic for the diastereomers. The less polar diastereomers (silica gel chromatography) was shifted to higher field (see Table 2). The H_8 chemical shift for **9** corresponds to the more polar diastereomer. Crude **9** contained a small amount of an impurity with a nmr peak at 6.18 δ which was probably the other diastereomer.

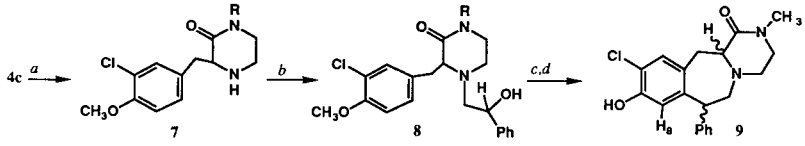
Equation #1



Equation #2



Scheme 2



a) $NaBH_3OAc$, Dioxane b) Styrene Oxide c) TFA-H_2SO_4 d) BBr_3

Table 1 lists the compounds prepared in this work.

Table 1

Compound	R [a]	R_1 [a]	R_2 [a]	Yield (%)	Method prep	MP (°C) or BP (°C/torr)	Formula	Analysis % Calcd./found C	H	N
3a	CH_3	H	H	97	a [a]	93-94 [b]				
3b	CH_3	H	CH_3O	[c]	a [a]	oil				
4a	CH_3	H	H	89	b [a]	170-172 [d]				
4b	CH_3	H	CH_3O	61 [e]	b [a]	158-159.5	$C_{13}H_{16}N_2O_3$	62.89	6.50	11.28
								62.59	6.55	11.16
4c	CH_3	Cl	CH_3O	98	c [a]	168-172	$C_{13}H_{15}ClN_2O_3$	55.23	5.35	9.91
								54.95	5.23	10.28
7				47	a [f]	60-62	$C_{13}H_{17}N_2O_2Cl \cdot HCl$	51.16	5.94	9.18
								50.93	5.93	8.98
5a	CH_3	H	H	90	d [a]	97-98/0.5	$C_{12}H_{18}N_2 \cdot 0.25H_2O$	73.99	9.57	14.38
								74.20	9.47	15.09
5c	CH_3	Cl	CH_3O	66	e [a]	115 dec [g]	$C_{13}H_{19}ClN_2O \cdot 2HCl \cdot 0.5H_2O$	46.37	6.59	8.32
								46.08	6.46	7.83
6a' [h]	CH_3	H	H	19	f [a]	74-77	$C_{20}H_{26}N_2O$	77.38	8.44	9.02
				85 [i]				77.45	8.44	9.01
6a" [j]	CH_3	H	H	16	f [a]	119-122	$C_{20}H_{26}N_2O$	77.38	8.44	9.02
								77.38	8.48	8.97
6c	CH_3	Cl	CH_3O	85 [i]	f [a]	oil	$C_{21}H_{27}ClN_2O_2$			
8				74	b [f]	oil	$C_{21}H_{25}ClN_2O_3$			
1a' [h]	CH_3	H	H	19	g [a]	246-249 dec	$C_{20}H_{24}N_2 \cdot 2HCl \cdot H_2O$	62.66	7.36	7.31
								62.83	7.18	7.12
1a" [j]	CH_3	H	H	13	g [a]	249-252 dec	$C_{20}H_{24}N_2 \cdot 2HCl \cdot H_2O$	62.66	7.36	7.31
								63.10	7.03	7.29
1d' [h]	CH_3	Cl	HO	9	h,i [a]	260-263 dec	$C_{20}H_{23}ClN_2O \cdot 2HBrH_2O$	45.96	5.21	5.36
								46.01	5.15	5.13
1d" [j]	CH_3	Cl	HO	11	h,i [a]	220-230 dec	$C_{20}H_{23}ClN_2O \cdot 2HCl \cdot 0.25H_2O$	57.16	6.12	6.67
								57.05	6.13	6.73
1e' [h]	H	Cl	HO	65	[k]	238-242 dec	$C_{19}H_{21}ClN_2O \cdot 2HCl \cdot 1.5H_2O$	53.24	6.07	6.54
								53.40	5.87	6.49
1e" [j]	H	Cl	HO	89	[k]	206-212 dec	$C_{19}H_{21}ClN_2O \cdot 2HCl$	56.80	5.77	6.97
								57.18	5.81	6.66
9				33	c,d [f]	253-256 dec	$C_{20}H_{21}ClN_2O_2 \cdot HCl \cdot 0.25H_2O$	60.38	5.70	7.04
								60.22	5.59	6.86

[a] See Scheme 1. [b] ref 8, oil (for S(+)isomer). [c] Used crude. [d] Ref 8, 180-181° (for S(+)isomer). [e] Yield for steps a and b. [f] See Scheme 2. [g] Free base 143-147/0.025. [h] Less polar diastereomer. [i] Yield of diastereomeric mixture. [j] More polar diastereomer. [k] See text.

Table 2

R	R_1	R_2	Compoud	δH_8	Compound	δH_8
CH_3	H	H	**1a'**	6.47, d, J = 6.0	**1a"**	7.10, d, J = 6.0
CH_3	Cl	CH_3O	**1c'**	6.07	**1c"**	6.69
CH_3	Cl	HO	**1d'**	6.15	**1d"**	6.76
H	Cl	HO	**1e' [a]**	6.12	**1e" [a]**	6.74
					9	6.77

[a] Compound 1e' and 1e" spectra were on the hydrochloride salts in DMSO-d_6. All other spectra were on the free base in deuteriochloroform.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Brucker WM 250 (250 MHz) or a Brucker AM 300 (300 MHz) instrument and chemical shifts are reported in δ units with tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS-80 instrument. Combustion analysis were performed on a Perkin-Elmer 241 instrument by ICI Americas Analytical Department. Flash chromatography was conducted on Keiselgel 60 (230-400 mesh) supplied by E. Merck.

N-Methyl-*N*-[*N*-[(phenylmethoxy)carbonyl]-D,L-phenylalanyl]glycine Ethyl Ester (**3a**).

To a stirred solution of 50.0 g (0.325 mole) of sarcosine ethyl ester hydrochloride in 300 ml of methylene chloride was added 32.9 g (0.325 mole) of triethylamine. The thick mixture was vigorously stirred for 10 minutes, then filtered and the salt cake washed well with methylene chloride. The filtrate was added to a stirred cooled (−5°, ice-bath) slurry of *N*-phenylmethyloxycarbonyl-D,L-phenylalanine in 300 ml of methylene chloride. The stirred clear −5° solution was treated with 80.5 g (0.39 mole) of dicyclohexylcarbodiimide portionwise over 5 minutes. The temperature rose to 18° during the addition. After an additional 15 minutes stirring, the ice-bath was removed and the mixture stirred at room temperature for 2.5 hours. The reaction mixture was filtered and the solvent removed *in vacuo*. The residual material was treated with ethyl acetate, filtered and the organic phase washed with 3*N* hydrochloric acid (a precipitate filtered off), water and sodium bicarbonate solution. The dried (magnesium sulfate) solution was filtered and the solvent removed *in vacuo*. The resulting solid was taken up in the minimum of hot ethyl acetate and refrigerated. The resulting white **3a** weighed 111.0 g (88%), mp 93-94° (lit [8] oil). Two additional crops totalling 11.25 g (9%), mp 92-95° were obtained from the liquors.

1-Methyl-3-phenylmethyl-2,5-piperazinedione (**4a**).

A mixture of 30 g (0.075 mole) of **3a**, 2 g of 10% Pd-C and 300 ml of acetic acid was hydrogenated in a Parr apparatus at 50 psi for 6 hours. The catalyst was removed by filtration through a Celite pad and the solvent removed *in vacuo*. Recrystallization from ethyl acetate yielded two crops totalling 14.63 g (89%), mp 170-172° (lit [8] mp 180-181° for the S(+) isomer).

1-Methyl-3-phenylmethylpiperazine (**5a**).

Compound **4a** (15.46 g, 0.071 mole) was added portionwise to a stirred slurry of 10.78 g (0.284 mole) of lithium aluminum hydride and 600 ml of tetrahydrofuran and the mixture refluxed for 18 hours. The mixture was cooled, treated cautiously with 11 ml of water, 11 ml of 15% sodium hydroxide solution and 30 ml of water, stirred for an additional hour and filtered. The solvent was removed *in vacuo* and the residual light yellow oil was distilled through a 4 inch Vigreux column to yield 12.14 g (90%) of **5a**, bp 97-98°/0.5 torr.

1-Methyl-3-(4-methoxy-3-chlorophenylmethyl)-2-piperazinone (**7**).

To a stirred, cooled (10°, ice-bath) slurry of 0.95 g of sodium borohydride and 1.41 g (0.005 mole) of **4c** in 10 ml of dioxane was added 1.5 g (0.025 mole) of acetic acid over 6 minutes. The foaming reaction mixture was allowed to warm to room temperature then placed in a 120° oil bath and refluxed for 2.5 hours. The cooled reaction mixture was then poured into water and extracted with methylene chloride. The combined extracts was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel using methylene chloride, then 5%, 10%, 20% and 40% methanol-methylene chloride as elutent. Concentration of the proper fractions yielded 0.66 g (49%) of **7** and 0.39 g (31%) of **5c**; ^{1}H nmr (deuteriochloroform): 2.24-2.38 (m, 3H, piperazine CH_2), 2.65 (s, 3H, NCH_3) 2.71-2.78 (m, 1H, piperazine CH_2), 2.87 (q, 1H, piperazine CH), 2.90 (s, 3H, OCH_3), 3.36 (q, 1H, benzylic H), 3.45 (q, 1H, benzylic H), 6.43 (d, 1H, aromatic H, J = 8.4), 6.99 (q, 1H, aromatic H), 7.34 (d, 1H, aromatic H, J = 2.0).

N-[2-(4-Methoxypheny)-1-[[(phenylmethoxy)carbonyl]amino]ethyl-*N*-methylglycine Methyl Ester (**3b**).

Sarcosine methyl ester hydrochloride (37.42 g, 0.319 mole) and 113.6 g (0.345 mole) of *N*-phenylmethoxycarbonyl-4-methoxy-D,L-phenylalanine [9] reacted as described for the synthesis of **3a** yielded **3b** in quantitative crude yield as a gold oil. The crude material was used in the synthesis of **4b** without further purification.

1-Methyl-3-(4-methoxyphenylmethyl)-2,5-piperazinedione (**4b**).

The crude **3b** was hydrogenated at 50 psi in two 68.4 g portions using 550 ml of acetic acid and 4.5 g of 10% Pd-C in each run. After removal of the catalyst the runs were combined, the solvent removed *in vacuo* and the resulting off-white solid recrystallized from ethyl acetate to yield 48.8 g (61%) of white **4b**, mp 158-159.5.

1-Methyl-3-(3-chloro-4-methoxyphenylmethyl)-2,5-piperazinedione (**4c**).

To a stirred solution of 48.60 g (0.196 mole) of **4b** and 500 ml of glacial acetic acid was added dropwise 29.07 g (0.215 mole) of sulfuryl chloride at such a rate that the temperature was maintained at 26°. After stirring at room temperature overnight an aliquot (solvent removed *in vacuo*) was taken and nmr analysis indicated that *ca.* 6.5% of **4b** remained unreacted. An additional 2.43 g (0.018 mole) of sulfuryl chloride was added and the reaction stirred an additional 18 hours at room temperature. Removal of the solvent yielded an oil which solidified on trituration with hexane containing a small amount of methylene chloride. The methylene chloride was distilled off, the solution cooled then filtered to give a near quantitative yield of **4c** which was used in the next step without further purification. Recrystallization of a sample from ethyl acetate gave an analytical sample, mp 168-172°.

1-Methyl-3-(3-chloro-4-methoxyphenylmethyl)piperazine (**5c**).

A stirred solution of 30.00 g (0.106 mole) of **4c** in 315 ml of dry tetrahydrofuran was treated dropwise at 0° with 496 ml of 1*M* borane in tetrahydrofuran. No exotherm was noted during addition. After an additional 15 minutes the bath was removed and the mixture stirred at reflux overnight. The cooled (10°) stirred mixture was treated successively with 8 ml of methanol and 40 ml of saturated hydrogen chloride in methanol. The solvent was then removed *in vacuo*, 650 ml of saturated hydrogen chloride in methanol added and the mixture refluxed for 1.5 hours. Removal of the solvent gave a white solid which was partitioned between 250 ml of water and 350 ml of ethyl acetate. The aqueous phase was basified to *p*H = 12 with saturated sodium bicarbonate solution and the phases separated. The aqueous phase was addition-

ally extracted with five 300 ml portions of methylene chloride. The combined organics was dried over magnesium sulfate, filtered and the solvent removed to yield a brown oil. Distillation through a 4 inch Vigreaux column returned 17.75 g (66%) of **5c**, bp 143-147°/0.025 torr.

1-(2-Hydroxy-2-phenylethyl)-2-phenylmethyl-4-methylpiperazine (**6a**).

A stirred solution of 3.76 g (0.020 mole) of **5a** and 2.37 g (0.020 mole) of styrene oxide was stirred at 110° for 18 hours. The resulting oil was chromatographed on silica gel using 10% methylene chloride in ethyl ether as eluent. The yield of recovered pure **6a** was 5.21 g (85%).

Isolation of **6a'** and **6a''**.

A stirred solution of 3.00 g (0.016 mole) of **5a** and 2.04 g (0.017 mole) of styrene oxide was stirred at 110° for 18 hours. Trituration of the resulting oil with ethyl ether gave 0.86 g of solid and, after removal of the solvent, 4.12 g of oil. The oil was chromatographed on silica gel using ethyl ether as eluent. The proper fractions were combined, the solvent removed and the residues recrystallized from hexane to give 0.42 g (8%) of **6a'**, mp 76-78° and 0.79 g (16%) of **6a''**, mp 118-121°. The 0.86 g of material from ether was similarly chromatographed to yield, after recrystallization, an additional 0.55 g (11%) of **6a''**, mp 118-121°; **6a'**; ^{1}H nmr (deuteriochloroform): 2.22 (s, 3H, NCH_3), 2.1-3.1 (m, 11H, aliphatic H), 4.1 (broad s, 1H, OH), 4.65 (q, 1H, CHO), 7.1-7.4 (m, 10H, aromatic H); **6a''**; ^{1}H nmr (deuteriochloroform): 2.20 (s, 3H, NCH_3), 2.1-3.2 (m, 11H), 3.9 (broad s, 1H, OH), 4.81 (q, 1H, CHO), 7.1-7.4 (m, 10H).

1-(2-Hydroxy-2-phenylethyl)-2-(3-chloro-4-methoxyphenylmethyl)-4-methylpiperazine (**6c**).

A mixture of 17.45 g (0.0685 mole) of **5c** and 8.25 g (0.69 mole) of styrene oxide was stirred at 105° for 18 hours. The resulting material was chromatographed on silica gel using ethyl acetate as eluent. The proper fractions were combined and the solvent removed *in vacuo* to yield 21.68 g (85%) of oil; diastereomeric mixture **6c**; ^{1}H nmr (DMSO-d_6): 4.67 (broad, 0.5H, CHO), 4.96 (broad, 0.5H, CHO).

1,2,3,4,6,7,12,12a-Octahydro-2-methyl-7-phenylpyrazino[2,1-*b*][3]-benzazepine (**1a**) and Separation into **1a'** and **1a''**.

To 6.01 g (0.0194 mole) of **6a**, cooled in an ice bath, was added 165 ml of precooled (0-5°) sulfuric acid and the mixture stirred 2 hours in the bath and then allowed to warm to room temperature over a 1 hour period during which time all the material dissolved. The reaction mixture was poured onto ice and basified with concentrated sodium hydroxide solution. The mixture was then extracted with methylene chloride (4 x 300 ml) and the combined organic phase was washed with saline, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to yield 4.15 g of brown solid. The solid was chromatographed on silica gel using 2% methanol/chloroform as elutent. The mixed fraction from the chromatography were combined and rechromatographed to give a total of 1.63 g (29%) of **1a'** and 1.37 g (24%) of **1a''**. The diastereomers were additionally recrystallized from hexane and converted to the hydrochloride salts. The yield of **1a'**·2HCl·H_2O was 1.44 g (19%) and **1a''**·2HCl·H_2O was 0.95 g (13%).

1,2,3,4,6,7,12,12a-Octahydro-2-methyl-7-phenyl-9-hydroxy-10-chloropyrazino[2,1-*b*][3]benzazepine (**1d**) and Separation into **1d'** and **1d''**.

To a stirred solution of 21.68 g (0.0578 mole) of **6c** and 220 ml of trifluoroacetic acid was added 7.5 ml of concentrated sulfuric acid and the mixture stirred at reflux for 2 hours. The trifluoroacetic acid was removed *in vacuo* and ice water was added to the residual brown oil. The mixture was basified to *p*H = 12 with sodium hydroxide solution and extracted with methylene chloride (8 x 75 ml). The combined extracts were dried (magnesium sulfate), filtered and the solvent removed *in vacuo* to yield 19.5 g of brown oil. Chromatography on silica gel using 2% methanol/chloroform as elutent returned 15.69 g of a mixture **1c'**, **1c''**, **1d'** and **1d''**. A solution of 14.74 g of the mixture and 250 ml of 48% hydrobromic acid was stirred at reflux for 2.5 hours and the solvent removed *in vacuo*. The residue was dissolved in water, basified to *p*H = 12 with sodium bicarbonate solution and extracted several times with ethyl acetate. The extracts were dried over magnesium sulfate, filtered and the solvent removed. Column chromatography on silica gel (5% methanol in chloroform as elutent) followed by a second chromatography of the combined mixed fractions gave 1.63 g (9%) of **1d'** and 2.23 g (12%) of **1d''**. A sample of **1d'** free base, mp 224-225°, in ethyl ether was treated with hydrogen bromide gas to yield **1d'**·HBr·H_2O, mp 260-263° dec. Similarly a sample of **1d''** free base, mp 96-112°, was converted to **1d''**·HCl·0.25 H_2O, mp 220-230° dec.

The Less Polar Diastereomer of 1,2,3,4,6,7,12,12a-Octahydro-7-phenyl-9-hydroxy-10-chloropyrazino[2,1-*b*][3]benzazepine (**1e'**).

A stirred, cooled (0°, ice bath) solution of 0.76 g (0.0023 mole) of **1d'** and 1.11 g (0.0052 mole) of 1,8-bis(diamino)naphthalene in 15 ml of 1,2-dichloroethane was treated dropwise with 0.55 g (0.0052 mole) of vinyl chloroformate. The mixture was stirred an additional 10 minutes at 0° and then at reflux for 1.5 hours. The cooled solution was treated with water and the organic layer separated, washed with saturated sodium chloride solution and dried over magnesium sulfate. Filtration, removal of the solvent *in vacuo* and column chromatography (chloroform) of the resulting oil returned 0.98 g (91%) of the intermediate carbamate-carbonate as a gold oil. The oil was treated with 75 ml of 5% hydrogen chloride in methanol and the solution refluxed for 6 hours. Removal of the solvent and recrystallization of the resulting solid from ethanol returned 0.66 g (65%) of **1e'**·2HCl·1.5 H_2O, mp 238-242° dec.

Compound **1e''** was prepared essentially by the method described for **1e'** with the exception that the intermediate carbamate-carbonate was used without purification.

1-Methyl-3-(3-chloro-4-methoxyphenylmethyl)-4-(2-hydroxy-2-phenylethyl)-2-piperazinone (**8**).

A mixture of 6.62 g (0.0185 mole) of **7** and 2.21 g (0.0185 mole) of styrene oxide was stirred at 105° for 7 hours. The resulting oil was chromatographed on silica gel (chloroform as elutent) to yield 5.31 g (74%) of **8** as an oil; diastereomeric pair; ^{1}H nmr (deuteriochloroform): 2.4-3.5 (m, 9H), 2.96 (s, 3H, OCH_3), 3.86 (s, 1.5H, NCH_3), 3.88 (s, 1.5H, NCH_3), 4.27 (q, 0.5H, CHO), 4.66 (q, 0.5H, CHO), 6.65-7.4 (m, 8H).

1(2*H*)-Oxo-2-methyl-3,4,6,7,12,12a-hexahydro-7-phenyl-9-hydroxy-10-chloropyrazino[2,1-*b*][3]benzazepine (**9**).

A mixture of 1.65 g (0.0042 mole) of **8**, 17 ml of trifluoroacetic acid and 0.6 ml of concentrated sulfuric acid was stirred at reflux for 2 hours. The solvent was removed *in vacuo* and the resulting brown oil treated with ice water and 10% sodium hydroxide solution until the *p*H = 12. The mixture was extracted with ethyl ether and then methylene chloride. The combined extracts were dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to yield 0.66 g of a brown oil. The aqueous phase was acidified to *p*H = 1 with concentrated hydrochloric acid then basified to *p*H = 12 with saturated sodium bicarbonate solution. The precipitated brown solid was isolated by filtration and chromatographed on silica gel (2% methanol/chloroform as elutent) to yield 0.22 g of slightly impure **9**. The 0.66 g of oil was treated with 2.32 g (0.0093 mole) of boron tribromide in 25 ml of methylene chloride to yield after aqueous work up 0.53 g impure **9**. The combined 0.75 g of crude **9** was chromatographed on silica gel (chloroform elutent) to yield 0.50 g of pure **9** free base which was converted to **9**·HCl, mp 253-256° dec.

REFERENCES AND NOTES

[1] I. Pettersson, T. Liljefors and K. Bøgesø, *J. Med. Chem.*, **33**, 2197 (1990).

[2] L. C. Iorio, A. Barnett, W. Billard and E. H. Gold in Neurobiology of central D1-Dopamine Receptors, G. R. Breese and I. Creese, eds, Plenum Press, New York, NY, 1986, p 1.

[3] R. E. Chipkin, L. C. Iorio, V. L. Coffin, R. D. McQuade, J. G. Berger and A. Barnett, *J. Pharmacol. Exp. Ther.*, **247**, 1093 (1988).

[4] The less polar diastereomer is the diastereomer with the higher Rf on silica gel thin layer chromatography (Silica Gel GHLF, Analtech Inc., Newark, DE) using methanol in chloroform as elutent.

[5] S. T. Ross, R. G. Franz, J. W. Wilson, R. A. Hahn and H. M. Sarau, *J. Heterocyclic Chem.*, **23**, 1805 (1986).

[6] S. J. Coote, S. G. Davies, D. Middlemiss and A. Naylor, *J. Chem. Soc., Perkin Trans. I*, 2223 (1989).

[7] N. Umino, T. Iwakuma and N. Itoh, *Tetrahedron Letters*, 763 (1976).

[8] Netherlands Appl. 6,412,779; *Chem. Abstr.*, **63**, P13268f (1965).

[9] Mp 108-116°; *Anal.* Calcd. $C_{18}H_{19}NO_5$: C, 65.76; H, 5.82; N, 4.25. Found: C, 65.60; H, 5.85; N, 4.39. Prepared in 73% yield by the reaction of phenylmethylchloroformate and 4-methoxy-DL-phenylalanine.