G. Evan Boswell* [a], David L. Musso [a], Ann O. Davis [a], James L. Kelley [a], Francis E. Soroko [b] and Barret R. Cooper [b]

Division of Organic Chemistry [a] and Division of Pharmacology [a], Burroughs Wellcome Co., Research Triangle Park, NC 27709

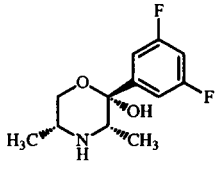
Received August 15, 1995
Revised August 28, 1997

A series of bicyclo analogues of several 2-phenylmorpholines were synthesized and tested for anti-tetrabenazine activity in mice. Most of the target compounds were prepared by reaction of 2-bromopropiophenone (**22**) with the appropriate amino alcohol to form 2-phenylmorpholinols. Reduction of the 2-phenylmorpholinols with sodium borohydride gave amino diols, which were cyclized to morpholines with acid. Alternatively, oxazines **17** and **18** were synthesized by alkylation of phenyl-(2-pyrrolo)carbinol (**32a**) and phenyl-(2-piperidyl)carbinol (**32b**) with 2-bromoethanol, followed by cyclization of the resulting amino diols with acid. Only the spirocyclic compounds **8** and **9** had i.p. anti-tetrabenazine activity comparable to the non-cyclic compounds **2a-3b**, but **8** and **9** were less active by the oral route of administration.

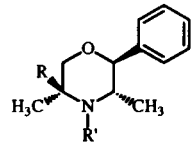
J. Heterocyclic Chem., **34**, 1813 (1997).

Introduction.

Agents of diverse structure and mechanism have been used in the treatment of clinical depression [2]. Bupropion, an aminoketone, is a clinically efficacious, antidepressant drug whose main human metabolite is a 2-phenylmorpholinol [3-11]. Structure-activity relationship studies with 2-phenylmorpholines and 2-phenylmorpholinols led to the discovery of 2-(3,5-difluorophenyl)morpholinol **1** (1555U88), a potent, selective norepinephrine uptake inhibitor, which is active in animal behavioral models that respond to clinically effective antidepressant drugs [12]. During the development of **1**, the di- and trimethyl-2-phenylmorpholines **2a-3b** were found to exhibit good activity in preventing tetrabenazine-induced sedation in mice and rats [13]. To gain further insight into the structure activity relationship of these 2-phenylmorpholines, we prepared several analogues of **2a-3b** that have the methyl substituents encompassed into a third ring. These analogues consist of (1) 5,5-spiroalkanes **8-10**, (2) C-5 to N-4 linked morpholines **12-16**, (3) C-3 to N-4 linked morpholines **17** and **18**, and (4) C-6 to N-4 linked bicyclononanes **19** and **20**. The synthesis, stereochemical assignments, and anti-tetrabenazine activity of these heterocycles are reported herein.



1; (1555U88)



2a; R = H, R' = H
2b; R = H, R' = CH_3
3a; R = CH_3, R' = H
3b; R = CH_3, R' = CH_3

Figure 1

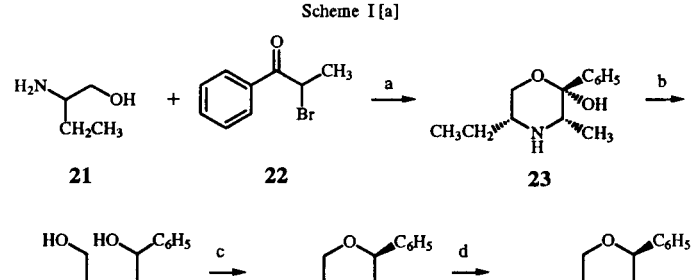
Chemistry.

The compounds in Table I were synthesized by the routes presented in Schemes I-V. Compounds **2-12** and **17-20** are racemic, and the depicted structures represent the relative stereochemistry of each compound. Morpholines **13** and **14** are single enantiomers with the absolute stereochemistry depicted in Scheme III. Isomers **15** and **16** are single enantiomers with the opposite absolute stereochemistry depicted in the scheme.

5-Ethylmorpholine.

The 5-ethylmorpholine **4** was synthesized in three steps from racemic 2-aminobutanol (**21**) and 2-bromopropiophenone (**22**) (Scheme I). Reaction of **21** with **22** by a modified literature procedure [14] provided 2-phenylmorpholinol **23**. The latter was reduced with sodium borohydride to give the amino diol **24**, which was of the erythro configuration. The *threo* and *erythro* diastereomers are identified by the chemical shift of the benzylic methine and its coupling constant with the adjacent methine in the nmr spectrum. The methine doublet of the *erythro* isomer is downfield of the

Scheme I [a]



21 **22** **23** **24** **4** **5**

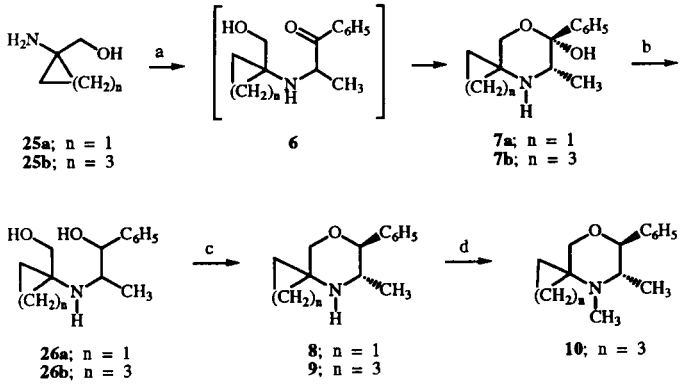
[a] (a) CH_3CN; (b) $NaBH_4$, $EtOH/H_2O$; (c) H_2SO_4, CH_2Cl_2; (d) $HCHO/HCO_2H$

doublet for the threo isomer and has a smaller J value [15, 16]. Diol **24** was cyclized with sulfuric acid in dichloromethane [17] to form morpholine **4**. The *N*-methyl derivative **5** was prepared from **4** using the Escheweiler-Clark reaction [18].

5, 5-Spiroalkanes.

Compounds **8-10** were synthesized from the amino-cycloalkylmethanols **25a** and **25b** as outlined in Scheme II. Reaction of **25a** and **25b** with **22** by a modified literature procedure [14] provided 2-phenylmorpholinols **7a** and **7b**, which were reduced to the corresponding amino diols **26a** and **26b** with sodium borohydride in ethanol/water. The amino diols **26a** and **26b** were cyclized with sulfuric acid in dichloromethane [17] to give morpholines **8** and **9**. The *N*-methyl derivative **10** was prepared from **9** by reductive formylation [18].

Scheme II [a]



25a; n = 1
25b; n = 3

6

7a; n = 1
7b; n = 3

26a; n = 1
26b; n = 3

8; n = 1
9; n = 3

10; n = 3

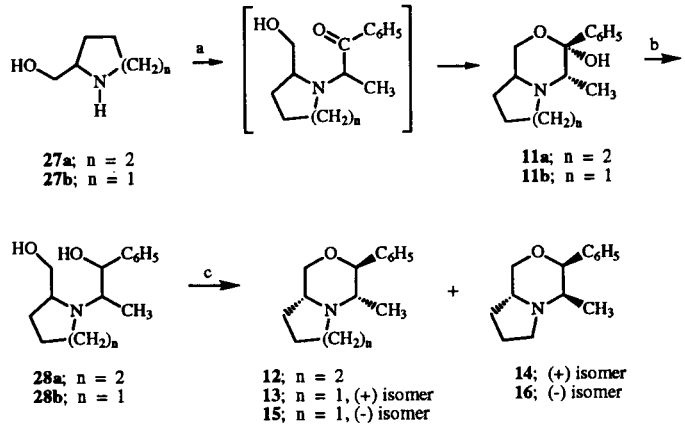
[a] (a) CH_3CN, $PhC(O)CHBrCH_3$ (**22**); (b) $NaBH_4$, $EtOH/H_2O$; (c) H_2SO_4, CH_2Cl_2; (d) $HCHO/HCO_2H$

C-5 to N-4 Linked Morpholines.

Compound **12** was synthesized in three steps from 2-piperidinemethanol (**27a**). Morpholines **13** and **14** were synthesized from (*R*)-(-)-prolinol (**27b**), and **15** and **16** were synthesized from (*S*)-(+)-prolinol (**27b**). In each case the synthetic sequence consisted of reaction of the appropriate amino alcohol with **22**, reduction of the resulting morpholinols **11a** and **11b** with sodium borohydride, and cyclization of the amino diols **28a** and **28b** with sulfuric acid in dichloromethane (Scheme III). Cyclization of **28a** yielded a single product, the *trans* fused morpholine **12**, as expected for acid-catalyzed cyclization [19]. This relative stereochemistry is assigned by the coupling constant of $J_{Ha}J_{Hb}$, which is typically 9-11 Hz for an axial-axial arrangement of the geminal protons in a conformationally locked 6-membered ring [20]. Acid catalyzed cyclization of **28b** yielded both *trans*-**13** and **15** and *cis*-**14** and **16** isomers in a ratio of 9:1.

The *cis* compounds **14** and **16** had $J_{Ha}J_{Hb}$ values of 2.8 Hz and 2.2 Hz respectively, whereas the *trans* compounds **13** and **15** had $J_{Ha}J_{Hb}$ values of 8.9 Hz and 8.8 Hz. The conformation of the *cis*-fused compounds was determined to be non-equilibrating with the methyl group locked into an axial position and the phenyl in an equatorial position. Comparison of the C-13 nmr of the *cis* and *trans* compounds showed marked upfield shift of the methyl group of the *cis* compound **14** (δ = 4.1 ppm) versus the *trans* compound **13** (δ = 15.6 ppm). This upfield shift is due to the steric compression of the methyl group held in a 1,3-diaxial relationship with the axial methines of the morpholine ring. The nOe spectra resulting from irradiation of the methyl group corroborated the spatial assignment.

Scheme III [a]



27a; n = 2
27b; n = 1

11a; n = 2
11b; n = 1

28a; n = 2
28b; n = 1

12; n = 2
13; n = 1, (+) isomer
15; n = 1, (-) isomer

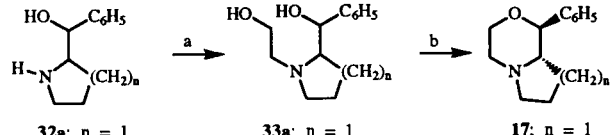
14; (+) isomer
16; (-) isomer

[a] (a) CH_3CN, $PhC(O)CHBrCH_3$ (**22**); (b) $NaBH_4$, $EtOH/H_2O$; (c) H_2SO_4, CH_2Cl_2

C-3 to N-4 Linked Morpholines.

The oxazines **17** and **18** were prepared by alkylation of phenyl-2-pyrrolylmethanol (**32a**) [21] and phenyl-2-piperidylmethanol (**32b**) [22] with 2-bromoethanol to give amino diols **33a** and **33b**. The latter were cyclized with sulfuric acid in dichloromethane to give **17** and **18** (Scheme IV).

Scheme IV [a]



32a; n = 1
32b; n = 2

33a; n = 1
33b; n = 2

17; n = 1
18; n = 2

[a] (a) $BrCH_2CH_2OH$, CH_3CN, Et_3N (b) H_2SO_4, CH_2Cl_2

C-6 to N-4 Linked Bicyclononanes.

Compounds **19** and **20** were synthesized in three steps from 3-hydroxypiperidine (**34**) (Scheme V). Reaction of **34** with **22** yielded the non-cyclic hydroxyketone **35**,

which was reduced with sodium borohydride to the amino diol **36**. Diol **36** was resistant to sulfuric acid catalyzed cyclization and also the effects of p-toluene-sulphonic acid at 140° [24]. However, low yields of **19** and **20** were obtained by heating the neat amino diol with *p*-toluenesulphonic acid at 180° for 72 hours.

The relative stereochemistry and conformation of **19** and **20** were determined by 2-D NOESY nmr and coupling constant analysis. The structure of **19** was assigned as (rac)-(2*R**,3*R**,5*R**)-2-methyl-3-phenyl-4-oxa-1-azabicyclo-[3.3.1]nonane with a *cis*-fused chair-chair conformation. In the 2D NOESY experiment a correlation between H_3 (δ 4.8 ppm) and H_7 (δ 2.2 ppm) is observed, which assigns the relative stereochemistry. An additional correlation is observed between the methyl (δ 0.75 ppm) and H_8 (δ 3.2 ppm). This correlation supports the conformation as chair-chair. Analysis of the coupling constants shows two large couplings for the axial H_8 of 12.8 Hz and 14.3 Hz. One of the couplings is the geminal, and the other is the coupling to one of the H_7's, which can only arise from an axial-axial interaction. This observation, in turn, supports a dominant chair conformation for the ring containing these protons because a significant boat conformer population would depress the H_7-H_8 vicinal coupling.

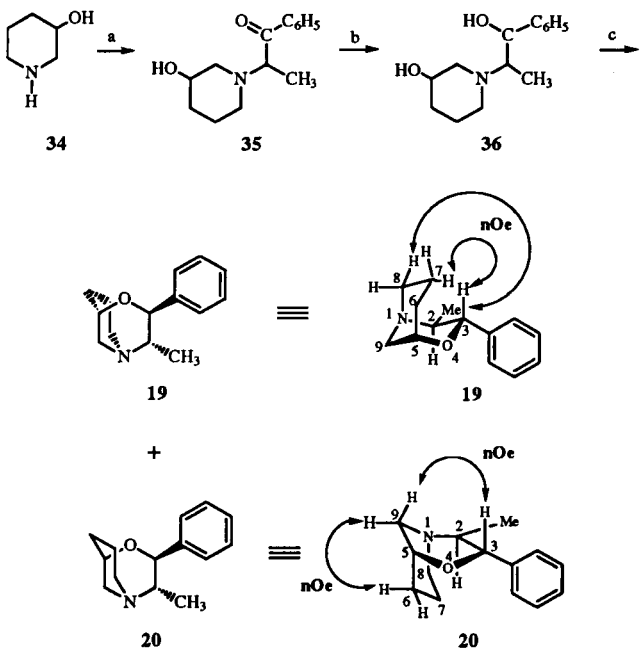
The structure of **20** was assigned as (rac)-(2*R**,3*R**,5*S**)-2-methyl-3-phenyl-4-oxa-1-azabicyclo[3.3.1]nonane with a *cis*-fused boat-chair conformation. The relative stereochemistry and boat conformation were confirmed by the presence of a strong nOe between H_3 (δ 4.19 ppm) and the equatorial H_9 (δ 3.3 ppm). The boat-chair conformation of **20** is due to the steric repulsion of the phenyl ring: it would be in a 1,3-diaxial relationship with the second ring if the chair-chair conformation were adopted. The chair conformation of the second ring is supported by a correlation from the axial H_9 (δ 2.46 ppm) to the axial H_6 (δ 1.54 ppm). Analysis of the coupling constants for the axial H_6 and the axial H_8 (δ 2.8 ppm) shows that both have 2 large coupling constants of approximately 13 Hz each, one for the geminal and one for the axial-axial coupling with axial H_7. If the boat conformer population were significant, the coupling constant would be depressed.

Biological Results and Discussion.

The compounds in Table I were evaluated in the anti-tetrabenazine test, an animal model that has been predictive for agents with antidepressant activity in humans [26]. Phenylmorpholinol **1** (1555U88) prevented tetrabenazine-induced sedation in mice and rats with oral ED_{50}'s of 6.2 and 1.4 mg/kg, respectively [12]. The 2-phenylmorpholines **2a-3b** also exhibited good activity with oral and i.p. ED_{50}'s in mice ranging from 7 to 13 mg/kg and 3 to 6 mg/kg, respectively. If the 5-methyl of **2a** was extended to the 5-ethyl of **4**, the compound was 4-fold less active i.p., and the *N*-methyl derivative **5** was even less active with an ED_{50} >25 mg/kg.

The 5,5-spiroalkanes **8** and **9** retained good i.p. activity in the anti-tetrabenazine test but were 2- to 3-fold less active than **2a-3b** by the oral route of administration. The *N*-methyl derivative of **9**, morpholine **10**, was more than

Scheme V [a]



[a] (a) CH_3CN, PhC(O)CHBrCH$_3$ (22); (b) $NaBH_4$, EtOH/H_2O; (c) p-TsOH, 180 °C

Table I

Anti-tetrabenazine Activity in Mice of 2-Phenylmorpholines[a]

Compound	ED_{50}, mg/kg [b] i.p.	p.o.
1 [c]	5.2 ±0.7	6.2 ±0.3
2a [d]	3.9 ±0.8	12.5 ±0.2
2b [d]	5.6 ±0.8	9.1 ±0.6
3a [d]	5	6.4 ±0.9
3b [d]	3	8.9 ±0.5
4	15 ± 1	
5	>25	
8	7.6 ±0.8	22.8 ±0.6
9	5.4 ±0.9	20.3 ±0.5
10	>25	
12	>25	
13	>25	
14	>25	
15	>25	
16	>25	
17	>25	
18	>25	
19	>25	
20	11.6 ±0.6	>25

[a] The compounds were tested as described in reference 26. [b] Compounds were tested by introperitoneal (i.p.) or oral (p.o.) administration as solutions or fine suspensions in water or 5% methylcellulose. ED_{50} >25 means no significant activity at 25 mg/kg. [c] Reference 11. [d] Reference 12.

4-fold less active than **9**. The deleterious effect of an *N*-methyl substituent on the activity of **4** and **9** is in contrast with the innocuous effect of an *N*-methyl group with compounds **2a-3b**. Compounds like **2b** and **3b** were found to be *N*-demethylated when administered to rats or mice [23] and may not be active in the absence of metabolic demethylation. Compounds **5** and **10** may be less susceptible to metabolic demethylation.

The three types of carbon to nitrogen linked analogues **12-20** were evaluated in the anti-tetrabenazine test but only **20** exhibited significant activity with an i.p. ED_{50} of 12 mg/kg.

Conclusion.

Several bicyclo analogues of the methyl-2-phenylmorpholines **2a-3b** were synthesized and tested for anti-tetrabenazine activity. Only the 5,5-spiroalkanes **8** and **9** retained good i.p. activity that was comparable to the di- and trimethyl-2-phenylmorpholines **2a-3b**, but **8** and **9** were 2- to 3-fold less active by the oral route of administration.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. The nmr spectra were recorded on Varian XL-200, Varian XL-300, and Unity 400 instruments and recorded in δ values with deuteriochloroform or dimethyl sulfoxide-d_6 as the solvent. The NOESY experiments for compounds **19** and **20** were acquired on a Varian Unity 400 MHz NMR; dimethyl sulfoxide-d_6 was used as a solvent. The experimental parameters used for the acquisition of the NOESY are relaxation delay = 1.7 sec, mixing time = 0.66 sec, pulse width = 11.4 μsec and number of repetitions = 64. The data for compound **19**, acquired with 2048x(150x2) hypercomplex files, were zero-filled and processed with a Guassian weighting function. The data for compound **20**, acquired with 2112x(200x2) hypercomplex files, were also zero-filled and processed with a Gaussian weighting function. The uv absorbtion spectra were measured on a Cary 118 UV-vis spectophotometer. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. High performance low pressure chromatography (Michael-Miller system) or preparative flash chromatography was performed on silica gel 60 (40-63 μ*M*, E. Merck No. 9385). Elemental analyses were performed by Atlantic Microlab, Inc.

Method A.

Preparation of Morpholinols. (rac)-*cis*-7-Methyl-8-phenyl-9-oxa-6-azaspiro[4.5]decan-8-ol Hydrochloride (**7b**).

A mixture of 2-bromopropiophenone (**22**) (4.62 g, 0.022 mole) and 1-amino-1-cyclopentanemethanol (**25b**) (5.0 g, 0.043 mole) was heated to reflux in acetonitrile (100 ml) for 16 hours. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water . The organic phase was extracted three times with 1 *N* hydrochloric acid. The acidic extracts were combined, chilled with an ice bath, treated with 40% aqueous sodium hydroxide solution to adjust the *p*H to 12, and extracted three times with dichloromethane. The combined dichloromethane extracts were dried (sodium sulfate) and concentrated under reduced pressure to give 5.4 g (100%) of the crude free base of **7b** as a tan solid.

Treatment of 900 mg of the free base with ethereal hydrogen chloride followed by recrystallization with ethanol/ether mixtures yielded 680 mg of the hydrochloride salt **7b** as a white solid, mp 202-203° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.90 (broad d, 1H, HCl), 9.00 (broad t, 1H, NH), 7.60-7.38 (m, 6H, Ar-H's and OH), 4.05 (d, 1H, J = 12.2, C_{10}-H), 3.50 (d, 1H, J = 12.0, C_{10}-H); 3.31 (broad m, 1H, C_7-H); 2.41-1.45 (m, 8H, spiro methylenes); 0.98 (d, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.53; H, 7.84; N, 4.93.

Method B.

Reduction of Morpholinols to Amino Diols. (rac)-(2*RS*) -2-[(1*R**, 2*S**)-(2-hydroxy-1-methyl-2-phenylethyl)amino]butanol Hydrochloride (**24**).

To a solution of 2-bromopropiophenone (**22**) (85.2 g, 0.4 mole) in acetonitrile (400 ml) was added dropwise a solution of 2-amino-1-butanol (**21**) (37.5 g, 0.42 mole) and 2,6-lutidine (56 ml, 0.48 mole) in acetonitrile (250 ml), and the mixture was stirred at room temperature under a nitrogen atmosphere for 72 hours. The resulting precipitate was filtered, washed with acetonitrile, and vacuum dried to yield 41.5 g (34%) of crude morpholinol **23** as the hydrobromide salt. This was used without further purification for the reduction to the amino diol **24**.

The hydrobromide salt of compound **23** (36.3 g, 0.12 mole) was dissolved in a 50:50 mixture of ethanol/water (300 ml) and chilled to 0° while stirring under a nitrogen atmosphere. A solution of sodium borohydride (18.2 g, 0.48 mole) in water (200 ml) was added dropwise. After addition the solution was allowed to warm to room temperature while stirring overnight. The solution was rechilled to 0° and concentrated hydrogen chloride (175 ml) was carefully added dropwise. The mixture was concentrated under reduced pressure to remove ethanol, then rediluted with water to bring the total volume to 600 ml. This solution was chilled with an ice bath, made basic by treating with 40% aqueous sodium hydroxide solution and extracted three times with dichloromethane. The combined dichloromethane extracts were dried (sodium sulfate) and concentrated under reduced pressure to give 26.3 g (98%) of the crude free base of **24** as a white solid.

Treatment of 4.0 g of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 4.06 g of the hydrochloride salt **24** as a white solid, mp 148-150°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 8.50 (broad d, 2H, NH, HCl), 7.38-7.27 (m, 5H, Ar-H's), 6.08 (d, 1H, OH), 5.38 (t, 1H, OH), 5.14 (broad s, 1H, C_2-H), 3.80-3.10 (m, 4H), 1.75 (m, 2H, CH_2), 1.05 (m, 6H, CH_3). This nmr pattern is consistent with the amino on C_1 and the alcohol on C_2 having an erythro relationship [15].

Anal. Calcd. for $C_{13}H_{22}ClNO_2$: C, 60.10; H, 8.54; N, 5.39. Found: C, 60.19; H, 8.58; N, 5.34.

Method C.

Cyclizaton of Amino Diols. (rac)-(2*R**, 3*R**, 5*S**)-5-Ethyl-3-methyl-2-phenylmorpholine Hydrochloride (**4**).

A solution of **24** (22.3 g, 0.1 mole) in dichloromethane (200 ml) was added dropwise to concentrated sulfuric acid (100 ml) at 0° and warmed to room temperature while stirring overnight. The mixture was poured into ice water (1000 ml) and the resulting

layers were separated. The aqueous layer was chilled with an ice bath, made basic with 40% aqueous sodium hydroxide solution, and extracted three times with dichloromethane. The dichloromethane extracts were dried (potassium carbonate) and concentrated under reduced pressure to give 19.9 g (97%) of the crude free base of **4** as a clear oil.

Treatment of 9.6 g of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 10.41 g of the hydrochloride salt **4** as a white solid, mp 208-210°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.60 (broad d, 2H, NH, HCl), 7.37(s, 5H, Ar-H's), 4.41 (d, 1H, J = 10.0, C_2-H), 4.12 (dd, 1H, J = 12.3, J = 3.5, C_6-H_{eq}), 3.64 (t, 1H, J = 11.1, C_6-H_{ax}), 3.35 (broad m, 2H, C_3-H, C_5-H), 1.80-1.50 (m, 2H, CH_2), 0.97 (m, 6H, CH_3).

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.32; N, 5.79. Found: C, 64.65; H, 8.39; N, 5.74.

(rac)-(2*R**, 3*R**, 5*S**)-5-Ethyl-3,4-dimethyl-2-phenylmorpholine *p*-Toluenesulphonate (**5**).

A mixture of compound **4** (10.3 g, 0.05 mole), 97% formic acid (5.7 ml, 0.156 mole) and 37% aq. formaldehyde (5.2 ml, 0.066 mole) was heated to reflux on a steam bath for 16 hours. The resulting mixture was dissolved in 1 *N* hydrochloric acid (100 ml) and concentrated under reduced pressure. The residue was dissolved in water and washed with ether. The aqueous phase was made basic with 40% aqueous sodium hydroxide solution and extracted with ether. The ether extract was washed with brine, dried (potassium carbonate) and concentrated under reduced pressure to yield 9.85 g (90%) of the crude free base as a clear oil. To a stirred solution of the crude free base in acetone (60 ml) was added p-toluenesulphonic acid monohydrate (8.1 g, 0.043 mole). The solution was then diluted with ethyl acetate (350 ml) and stirred overnight at room temperature. The resulting crystals were filtered and dried to give 14.3 g of the *p*-toluenesulphonic acid salt of **5** as a white solid, mp 137-139°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.40 (broad , 1H, SO_3H), 7.48-7.39 (m, 7H, Ar-H's), 7.09 (d, 2H, Ar-H's) 4.38 (d, 1H, J = 10.2, C_2-H), 4.12 (dd, 1H, J = 12.3, J = 3.5, C_6-H_{eq}), 4.00-3.45 (m, 3H, C_3-H, C_5-H, C_6-H_{ax}), 2.90 (s, 3H, NCH_3), 2.05 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 0.88 (m, 6H, CH_3).

Anal. Calcd. for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.48; H, 7.51; N, 3.52.

(rac)-*Trans*-5-Methyl-6-phenyl-7-oxa-4-azaspiro[2.5]octane (**8**).

A mixture of 2-bromopropiophenone (**22**) (6.4 g, 0.03 mole), 1-amino-cyclopropylmethanol hydrochloride (**25a**) [25] (3.7 g, 0.03 mole) and triethylamine (6.1 g, 0.06 mole) was reacted together according to Method **A** to yield 5.2 g of **7a** as the crude free base. Treatment of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixture yielded 1.1 g of the hydrochloride salt of **7a** which was reduced according to Method **B**. The resulting amino diol, **26a** was heated to 140° with *p*-toluenesulphonic acid monohydrate (1.9 g, 0.01 mole) for 16 hours. The mixture was dissolved in water, made basic with 40% aqueous sodium hydroxide solution, and extracted with ether. The ether extract was washed with brine, dried (potassium carbonate) and concentrated under reduced pressure to yield 800 mg of the crude free base as a brown oil. The crude free base was chromatographed over silica gel eluting with ethyl acetate (0.1% triethylamine) to yield 630 mg (4.9% calculated from 2-bromopropiophenone) of the purified free base. Treatment of the free base with ethereal hydrogen chloride, followed by tritruation with acetonitrile yielded 300 mg of the hydrochloride salt **8** as an off-white solid, mp 187-189° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 10.0 (broad d, 2H, NH, HCl), 7.39 (s, 5H, Ar-H's), 4.45 (d, 1H, J = 9.8, C_6-H), 4.24 (d, 1H, J = 12.4, C_8-H), 3.45 (broad m, 1H, C_5-H), 3.41 (d, 1H, J = 12.5, C_8-H), 1.35-0.88 (m, 4H, spiro methylenes), 0.96 (d, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.84. Found: C, 65.01; H, 7.62; N, 5.82.

(rac)-*trans*-7-Methyl-8-phenyl-9-oxa-6-azaspiro[4.5]decane Hydrochloride (**9**).

Compound **7b** (4.5 g of free base, 0.018 mole) was reduced according to Method **B** to yield 3.8 g of the crude amino diol **26b** as a yellow oil. This was cyclized according to Method **C** to yield 2.9 g (69% from **7b**) of the crude free base of **9**. Treatment of 1.1 g of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 900 mg of the hydrochloride salt **9** as a white solid, mp 205-206°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.70 (broad m, 2H, NH, HCl), 7.38 (s, 5H, Ar-H's), 4.35 (d, 1H, J = 10.0, C_8-H), 3.72 (s, 2H,C_{10}-H's), 3.40 (broad m, 1H, C_7-H), 1.50-1.30 (m, 8H, spiro methylenes), 0.98 (m, 6H, CH_3).

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.28; H, 8.34; N, 5.18.

(rac) -*trans*-6, 7-Dimethyl-8-phenyl-9-oxa-6-azaspiro[4.5]decane *p*-Toluenesulphonate (**10**).

A mixture of **9** (1.8 g, 7.8 mmoles), 97% formic acid (0.8 ml, 21 mmoles) and 37% aqueous formaldehyde (0.7 ml, 8.6 mmoles) was heated to reflux on a steam bath for 16 hours. The resulting mixture was dissolved in 1 *N* hydrochloric acid (30 ml) and concentrated under reduced pressure. The residue was dissolved in water, made basic with 40% aqueous sodium hydroxide solution and extracted with ether. The ether extract was washed with brine, dried (potassium carbonate) and concentrated under reduced pressure to yield 1.6 g (84%) of the crude free base as an orange oil which crystallized upon standing. To a stirred solution of the crude free base (1.3 g, 5.3 mmoles) in ethyl acetate (80 ml) was added *p*-toluenesulphonic acid monohydrate (0.96 g, 5.0 mmoles). The solution was stirred overnight at room temperature and the resulting crystals were filtered and dried to give 1.48 g of the *p*-toluenesulphonic acid salt of **10** as a white solid : mp 142-144°. The nmr of the *p*-toluenesulphonate salt is complex due to broading and multiplicities arising from slow conformational inversion so a sample was converted back to the free base for the nmr; ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 7.35-7.25 (m, 5H, Ar-H's), 4.13 (d, 1H, J = 9.4, C_8-H), 3.57 (3, 2H, C_{10}-H's), 2.52 (m, 1H, C_7-H) 3.28 (m, 1H, C_6-H), 2.1-1.18 (m, 8H, spiro methylenes), 0.82 (d, 3H, CH_3).

Anal. Calcd. for $C_{23}H_{31}NO_4S$: C, 66.15; H, 7.48; N, 3.35. Found: C, 66.20; H, 7.55; N, 3.32.

(rac)-(3*R**, 4*R**, 9A*S**)-Octahydro-4-methyl-3-phenylpyrido-[2,1-*c*][1,4]oxazin-3-ol (**11a**).

This compound was obtained in 99% yield as the crude free base from 2-bromopropiophenone (**22**) (21.3 g, 0.10 mole) and 2-piperidinemethanol (**27a**) (25 g, 0.20 mole) according to Method A. Treatment of 4.5 g of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 3.15 g of the hydrochloride salt **11a** as a white solid, mp 204-205° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.75 (broad, 1H, HCl), 7.61-7.35 (m, 6H, Ar-H's and OH), 4.04 (t, 1H, J = 12.3,

C_1-H_{ax}), 3.81 (dd, 1H, J = 12.6, J = 3.51, C_1-H_{eq}), 3.60-3.40 (broad m, 3H, C_4-H, C_{9a}-H, C_6-H_{ax}), 2.83 (m, 1H, C_6-H_{eq}), 1.90-1.35 (m, 6H, CH_2), 0.99 (d, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.55; H, 7.84; N, 4.92.

(rac)-(3*R**, 4*R**, 9A*S**)-Octahydro-4-methyl-3-phenylpyrido-[2,1-*c*][1,4]oxazine (**12**).

Compound **11a** (20.0 g of free base, 0.081 mole) was reduced according to Method B to yield 21.3 g of the crude amino diol, **28a** as a yellow oil, 9.7 g of which was cyclized according to Method C to yield 7.4 g (82% from **11a**) of the crude free base. Treatment with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures and a second recrystallization in acetonitrile yielded 3.38 g of the hydrochloride salt **12** as a white solid, mp 249-252°; ^{1}H-nmr (dimethyl sulfoxide-d_6 , 200 MHz): δ 7.38 (s, 5H, Ar-H's), 4.65 (d, 1H, J = 9.9, C_3-H), 3.96 (dd, 1H, J = 12.6, J = 4.1, C_1-H_{eq}), 3.86 (t, 1H, J = 10.1, C_1-H_{ax}), 3.70 (m, 1H), 3.45 (m, 1H), 2.80 (m, 1H), 1.90-1.40 (m, 6H, C_7-H's, C_8-H's, C_9-H's), 1.12 (d, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found; C, 67.28; H, 8.30; N, 5.22.

(+)-(3*S*, 4*S*, 8a*R*)-Hexahydro-4-methyl-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine 4-toluenesulphonate (**13**) and (+)-(3*S*, 4*R*, 8a*R*)-Hexahydro-4-methyl-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine 4-toluenesulphonate (**14**).

A mixture of 2-bromopropiophenone (**22**) (21.2 g, 0.10 mole) and *R*-(-)-2-pyrrolidinemethanol (20.0 g, 0.20 mole) was allowed to react in acetonitrile (500 ml) according to Method A to yield 21.8 g of the crude morpholinol, **11b**. Compound **11b** (18.3 g) was reduced, without further purification according to Method B to yield 16.5 g of the crude amino diol **28b**, which was cyclized according to Method C to yield 13.1 g of **13** and **14** as a mixture. The mixture was chromatographed over silica gel eluting with ethyl acetate, to yield, in order of elution, 9.7 g of **13** (64% from 2-bromopropiophenone) and 1.3 g of **14** (8.5% from 2-bromopropiophenone).

To a stirred solution of compound **13** in ethyl acetate (200 ml) was added *p*-toluenesulphonic acid monohydrate (7.65 g, 0.40 mole). The solution was stirred overnight at room temperature and the resulting crystals were filtered and dried to give 14.89 g of the *p*-toluenesulphonic acid salt of **13** as a white solid, mp 159-161°. The nmr of the *p*-toluenesulphonate salt is complex due to broading and multiplicities arising from slow conformational inversion so a sample was converted back to the free base for the nmr; ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 7.32 (s, 5H, Ar-H's), 4.12 (dd, 1H, J = 10.8, J = 3.1, C_1-H_{eq}), 4.03 (d, 1H, J = 8.9, C_3-H), 3.50 (t, 1H, J = 10.6, C_1-H_{ax}) 3.27 (m, 1H, C_6-H), 2.38 (m, 2H, C_4-H, C_{8a}-H), 2.12 (q, 1H, J = 8.4, C_6-H), 1.90-1.70 (m, 3H, C_7-H's, C_8-H), 1.45 (m, 1H, C_8-H), 0.85 (d, 3H, CH_3); $[\alpha]_D^{20}$ = +20.5° (c = 0.727, 95% ethanol).

Anal. Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.85; H, 7.02: N, 3.58.

To a stirred solution of compound **14** in ethyl acetate (40 ml) was added *p*-toluenesulphonic acid monohydrate (1.08 g, 5.7 mmole). The solution was stirred overnight at room temperature and the resulting crystals were filtered and dried to give 1.12 g of the *p*-toluenesulphonic acid salt of **14** as a white solid, mp 136-137°. The nmr of the *p*-toluenesulphonate salt is complex due to broading and multiplicities arising from slow conformational inversion so a sample was converted back to the free base for the nmr. ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 7.36-7.21 (m, 5H, Ar-H's), 4.78 (d, 1H, J = 2.8, C_3-H), 4.13 (dd, 1H, J = 10.7, J = 3.5, C_1-H_{eq}), 3.42 (t, 1H, J = 10.5, C_1-H_{ax}) 3.34 (qd, 1H, J = 6.6, J = 2.9, C_4-H), 2.95 (m, 1H, C_6-H), 2.80 (m, 1H, C_{8a}-H), 2.65 (q, 1H, J = 8.2, C_6-H), 2.05-1.70 (m, 3H, C_7-H's, C_8-H), 1.30 (m, 1H, C_8-H), 0.70 (d, 3H, CH_3); $[\alpha]_D^{20}$ = +26.2 °C (c = 0.727, 95% ethanol).

Anal. Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.48; H, 7.04: N, 3.54.

(-)-(3*R*, 4*R*, 8a*S*)-Hexahydro-4-methyl-3-phenyl-1*H*-pyrrolo-[2,1-*c*][1,4]oxazine 4-Toluenesulphonate (**15**) and 4(-)-(3*R*, 4*S*, 8a*S*)-Hexahydro-4-methyl-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine 4-Toluenesulphonate (**16**).

A mixture of 2-bromopropiophenone (**22**) (22.5 g, 0.105 mole) and *S*(+) -2-pyrrolidinemethanol (21.4 g, 0.21 mole) was allowed to react in acetonitrile (650 ml) according to Method A to yield 20.7 g of the crude morpholinol, **11b** which was reduced without further purification according to Method B to yield 20.2 g of the crude amino diol **28b**. Compound **28b** (15.2 g) was cyclized according to Method C to yield 10.5 g of **15** and **16** as a mixture. The mixture was chromatographed on silica gel, eluting with ethyl acetate, to yield, in order of elution, 11.5 g of **15** (82%), and 1.35 g of **16** (9.6%).

To a stirred solution of compound **15** in ethyl acetate/acetone (200 ml/25 ml) was added *p*-toluenesulphonic acid monohydrate (9.5 g, 0.40 mole). The solution was stirred overnight at room temperature and the resulting crystals were filtered and dried to give 17.77 g of the *p*-toluenesulphonic acid salt of **15** as a white solid, mp 159-161°. The nmr of the *p*-toluenesulphonate salt is complex due to broading and multiplicities arising from slow conformational inversion so a sample was converted back to the free base for the nmr; ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 7.33 (s, 5H, Ar-H's), 4.12 (dd, 1H, J = 10.8, J = 2.93, C_1-H_{eq}), 4.05 (d, 1H, J = 8.8, C_3-H), 3.51 (t, 1H, J = 10.4, C_1-H_{ax}) 3.28 (m, 1H, C_6-H), 2.40 (m, 2H, C_4-H, C_{8a}-H), 2.12 (q, 1H, J = 8.6, C_6-H), 1.90-1.70 (m, 3H, C_7-H's, C_8-H), 1.45 (m, 1H, C_8-H), 0.88 (d, 3H, CH_3); $[\alpha]_D^{20}$ = -20.4 ° (c = 0.714, 95% ethanol).

Anal. Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.48; H, 7.08: N, 3.51.

To a stirred solution of compound **16** in ethyl acetate (40 ml) was added *p*-toluenesulphonic acid monohydrate (1.1 g, 5.7 mmole). The solution was stirred overnight at room temperature and the resulting crystals were filtered and dried to give 1.16 g of the *p*-toluenesulphonic acid salt of **16** as a white solid, mp 135°. The nmr of the *p*-toluenesulphonate salt is complex due to broading and multiplicities arising from slow conformational inversion so a sample was converted back to the free base for the nmr; ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 7.34-7.21 (m, 5H, Ar-H's), 4.77 (d, 1H, J = 2.2, C_3-H), 4.13 (dd, 1H, J = 10.7, J = 3.5, C_1-H_{eq}), 3.40 (t, 1H, J = 10.4, C_1-H_{ax}) 3.34 (qd, 1H, J = 6.6, J = 2.9, C_4-H), 2.99 (m, 1H, C_6-H), 2.80 (m, 1H, C_{8a}-H), 2.65 (q, 1H, J = 8.2, C_6-H), 2.05-1.70 (m, 3H, C_7-H's, C_8-H), 1.26 (m, 1H, C_8-H), 0.70 (d, 3H, CH_3); $[\alpha]_D^{20}$ = -25.9° (c = 0.724, 95% ethanol).

Anal. Calcd. for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.51; H, 7.07: N, 3.53.

(rac)-(1*R**, 8a*R**)-Hexahydro-1-phenyl-1*H*-pyrrolo[1,2-*b*][1,4]-oxazine (**17**).

To a mixture of phenyl-2-pyrrolylmethyl **32a** [21] (6.23 g, 35 mmole) and triethylamine (3.88 g, 38.5 mmole) in acetonitrile (70

ml) was added 2-bromoethanol (4.84 g, 38.5 mmole) in acetonitrile (35 ml) at ambient temperature. The mixture was then heated to reflux for 16 hours. The mixture was concentrated under reduced pressure and partitioned between ether and water. The aqueous phase was made basic with 40% aqueous sodium hydroxide solution and extracted with ether. All ether extracts were combined and washed with brine, dried (potassium carbonate) and concentrated under reduced pressure to give 7.7 g of the crude product as a yellow oil. The crude free base was chromatographed on silica gel eluting with ethyl acetate:methanol/9:1(0.5% triethylamine) to yield 4.5 g (58%) of **33a**.

Compound **33a** (4.0 g, 18 mmoles) was cyclized according to Method C to give 2.3 g of the crude product as a yellow oil which was chromatographed on silica gel eluting with ethyl acetate: hexanes/1:1(0.25% triethylamine) to yield 1.12 g (31%) of **17** as a clear light red oil; ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 7.40-7.20 (m, 5H, Ar-H's), 4.25 (d,1H, J = 9.5, C_1-H), 4.06 (dd, 1H, J = 11.4, J = 2.87, C_3-H_{eq}), 4.14 (td, 1H, J = 10.5, J = 2.9, C_3-H_{ax}), 3.21 (td, 1H, J = 8.5, J = 1.9, C_6-H_a), 3.05 (d, 1H, J = 9.5, C_4-H_{eq}), 2.49 (td, 1H, J = 11.4, J = 3.8, C_4-H_{ax}), 2.67 (q, 1H, J = 9.6, C_6-H_b), 2.08 (q, 1H, J = 7.6, C_{8a}-H), 1.95-1.50 (m, 4H, CH_2).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.79; H, 8.45; N, 6.89.

(rac)-(1*R**, 9a*R**)-Octahydro-1-phenylpyrido[2, 1-*c*][1,4]oxazine (**18**).

To a mixture of phenyl-2-piperidylmethyl **32b** [18] (13.4 g, 0.07 mole) and triethylamine (9.6 g, 0.07 mole) in acetonitrile (300 ml) was added 2-bromoethanol (7.8 g, 0.07 mole) in acetonitrile (100 ml) at ambient temperature. Work up was the same as for **17** to give 15.8 g of the crude amino diol **33b** as a viscous yellow oil, which crystallized upon standing. Amino diol **33b** was recrystallized from hexane to yield 10.5 g as a white solid, 8.0 g of which was cyclized according to Method C to yield 5.8 g of crude **18** as a yellow oil which was chromatographed on silica gel eluting with ethyl acetate:hexanes/1:1(0.25% triethylamine) to yield 4.2 g (36% from **32b**) of **18** as a clear yellow oil. Treatment with ethereal hydrogen chloride, followed by recrystallization with ether gave 4.3 g of the hydrochloride salt of **18** as a white solid, mp 177-179°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 11.38 (broad, 1H, HCl), 7.38 (s, 5H, Ar-H's), 4.55 (d, 1H, J = 9.6, C_1-H), 4.07 (s, 2H, C_3-H's), 3.50-3.05 (broad m, 5H, C_4-H's, C_6-H's, C_{9a}-H), 1.89-1.05 (m, 6H, C_7-H's, C_8-H's, C_9-H's).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.23; H, 7.95; N, 5.47.

(rac) -(2*R**,3*R**, 5*R**)-2-Methyl-3-phenyl-4-oxa-1-azabicyclo-[3.3.1]nonane Hydrochloride (**19**) and
(rac) -(2*R**,3*R**, 5*S**)-2-Methyl-3-phenyl-4-oxa-1-azabicyclo-[3.3.1]nonane Hydrochloride (**20**).

Compound **35** (38.2 g of the free base, 0.164 mole) was reduced according to Method B to yield 39.0 g of the crude amino diol **36**, 14.8 g of which was heated to 180° with *p*-toluenesulphonic acid monohydrate (26.6 g, 0.14 mole) for 72 hours. The mixture was dissolved in water, made basic with 40% aqueous sodium hydroxide solution, and extracted with ether. The ether extract was washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to yield 7.3 g of a mixture of **19** and **20** as a dark brown oil. This was chromatographed over silica gel eluting with ethyl acetate (0.1% triethylamine) to yield 1.2 g of **19** (8.8%) and 1.7 g of **20** (12%).

Treatment of the free base of **19** with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 700 mg of the hydrochloride salt **19** as a white solid, mp 213-214°. A sample was converted back to the free base for the nmr; ^{1}H-nmr (dimethyl sulfoxide-d_6, 400 MHz): δ 7.2-7.4 (m, 5H, Ar-H's), 4.83 (d, 1H, J = 10.4, C_3-H), 3.58 (m, 1H, J = 2.8, C_5-H), 3.15-3.25 (br m, 2H, C_8-H and C_9-H), 2.98 (d, 1H, J = 13.9 Hz, C_9-H), 2.9-3.0 (m, 2H, C_2-H and C_8-H), 2.0-2.1 (m, 2H, C_6-H and C_7-H), 1.88 (m, 1H, C_6-H), 1.49 (m, 1H, J = 6.4 Hz, J = 13.9 Hz, C_7-H), 0.84 (d, 1H, J = 6.9 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.20; H, 7.95; H, 5.50.

Treatment of the free base of **20** with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 1.13 g of the hydrochloride salt **20** as a white solid, mp 244-245°. A sample was converted back to the free base for the nmr; ^{1}H-nmr (dimethyl sulfoxide-d_6, 400 MHz): δ 7.2-7.45 (m, 5H, Ar-H's), 4.19 (d, 1H, J = 10.0, C_3-H), 3.92 (br m, 1H, J = 1.0 Hz, J = 4.0 Hz, C_5-H), 3.3 (1H, C_{9eq}-H), 2.89 (d of q, 1H, J = 6.2 Hz, J = 10.0 Hz, C_2-H), 2.7-2.85 (m, 2H, C_8-H's), 2.46, (d, 1H, J = 14.9 Hz, C_9-H), 2.3 (m, 1H, C_7-H), 1.86 (br m, 1H, C_6-H), 1.54 (m, 1H, J = 1.4 Hz, J = 4.9 Hz, J = 13.2 Hz, C_6-H), 1.22 (br m, 1H, C_7-H), 0.75 (d, 3H, J = 6.5 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.17; H, 7.97; H, 5.49.

2-(3-Hydroxypiperidino)propiophenone (**35**).

This compound was obtained in 74% yield as the crude free base from 2-bromopropiophenone (52.5 g, 0.246 mole) and 3-hydroxypiperidine (50.0 g, 0.492 mole) reacted in acetonitrile (900 ml) according to Method A. Treatment of 4.2 g of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether mixtures yielded 2.93 g of the hydrochloride salt **35** as a white solid, mp 194-196° dec; ir (nujol mull): 1684 cm^{-1}(ketone carbonyl): uv (absolute ethanol): λ max 241.0 nm (ketone carbonyl). A sample was converted to the free base for nmr; ^{1}H-nmr (deuteriochloroform, 200 MHz): δ 8.00 (d, 2H, Ar-H's), 7.61-7.42 (m, 3H, Ar-H's), 4.32 (m, 1H, CH), 3.78 (m, 1H, CH), 2.80 (m, 5H, CH_2, OH), 1.9 (m, 1H, CH_2), 1.58 (m, 3H, CH_2), 1.31 (d, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.15; H, 7.52; N, 5.08.

Acknowledgements.

We acknowledge the assistance of Mr. B. T. Kenney who performed the anti-tetrabenazine experiments. We thank Ms. D. T. Staton for the art work, and the Burroughs Wellcome Co. Research Document Center for assistance in preparation of the manuscript.

REFERENCES AND NOTES

[1] Presented, in part, at the 34th National Organic Symposium, Williamsburg, VA, June 11th, 1995.

[2] C. Kaiser and P. E. Setler, Antidepressant Agents, In Burger's Medicinal Chemistry, Part III, 4th Ed.; M. E. Wolff, ed.; John Wiley and Sons, New York, 1981, pp 997.

[3] F. E. Soroko, N. B. Mehta, R. A. Maxwell, R. M. Ferris, and D. H. Schroeder, *J. Pharm. Pharmacol.*, **29**, 767 (1977).

[4] B. R. Cooper, T. J. Hester, and R. A. Maxwell, *J. Pharmacol. Exp. Ther.*, **215**, 127 (1980).

[5] W. E. Fann, D. H. Schroeder, N. B. Mehta, F. E. Soroko, and R. A. Maxwell, *Curr. Ther. Res.*, **23**, 222 (1978).

[6] L. R. Fabre Jr., and D. M. McLendon, *Curr. Ther. Res.*, **23**, 393 (1978).

[7] J. Davidson, R. Miller, J. V. W. Fleet, R. Stickland, P. Manberg, S. Allen, and R. Parrott, *J. Clin Psychiatry*, **44**, 115 (1983).

[8] J. P. Feighner, C. H. Meredith, W. C. Stern, G. Hendrickson, and L. L. Miller, *Am. J. Psychiatry*, **141**, 525 (1984).

[9] S. G. Bryant, B. G. Guernsey and N. B. Ingrim, *Clin. Pharm.*, **2**, 525 (1983).

[10] S. H. Preskorn and S. C. Othmer, *Pharmacotherapy*, **4**, 20 (1984).

[11] R. M. Welch, A. A. Lai, and D. H. Schroeder, *Xenobiotica*, **17**, 287 (1987).

[12] J. L. Kelley, D. L. Musso, G. E. Boswell, and B. R. Cooper, US patent 5,104,870.

[13] F. E. Soroko, unpublished data (1988).

[14] N. H. Cromwell and K-C. Tsou, *J. Am. Chem. Soc.*, **71**, 993 (1949).

[15] D. L. Musso and N. B. Mehta, *J. Liquid Chromatog.*, **4**, 1417 (1981).

[16] H. Tucker, *J. Org. Chem.*, **44**, 2943 (1979).

[17] A. Balsamo, P. Crotti, B. Macchia, F. Macchia, M. del Tacca and L. Mazzanti, *J. Med. Chem.*, **16**, 224 (1973).

[18] H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem Soc.*, **55**, 4571 (1933).

[19] H. Nishimura, O. Yamauchi and H. Takamatsu, *Chem. Pharm. Bull.*, **12**, 1004 (1964).

[20] R. M. Silverstein, G. C. Bassler, and T. C. Morrill, Spectrometric Identification of Organic Compounds, 4th Ed, John Wiley and Sons, Ney York, 1981; p 206.

[21] A. I. Meyers, P. D. Edwards, W. F. Rieker, T. R. Bailey, *J. Am. Chem. Soc.*, **106**, 3270 (1984).

[22] K. Winterfeld and H. Geschonke, *Arch. Pharm.*, **296**, 38 (1963).

[23] Mr. R. N. Norton, personal communication (1993).

[24] F. Kurzen, H. Siemer and A. Doppstadt, German Patent 1, 137, 439 (1962); *Chem Abstr.*, **58**, 2458e (1963).

[25] J. S. Kiely, M. C. Schroeder and J. C. Sesnie, *J. Med. Chem.*, **31**, 2004 (1988).

[26] F. Sulser and F. Soroko, *Psychopharmacologia*, **8**, 191 (1965).