Synthesis and Anti-tetrabenazine Activity of C-3 Analogues of Dimethyl-2-phenylmorpholines

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A series of analogues of 2-phenylmorpholines with alkyl substituents at the C-3 position were synthesized for anti-tetrabenazine (anti-TBZ) testing in mice. The target compounds were prepared by reaction of (2-bromoalkyl) phenyl ketones **21a-h** with the appropriate aminoalcohol **20a-b** to form morpholinols **22a-h**. Hydride reduction of the morpholinols gave aminodiols **23a-h** which were cyclized to morpholines **6, 8, 10-12, 14-16, 18** and **19** by acid catalaysis. Compounds **7, 9, 13** and **17** were prepared by reductive formylation. The smaller straight chain substituents of **6, 8, 12** and **15**, and the *beta* branching of the *iso*-butyl group of **16** were well tolerated; anti-tetrabenazine $ED_{50's}$ were comparable to compounds **2-5**. The α-branched, *N*-methylated, and side chain aryl derivatives were less active.

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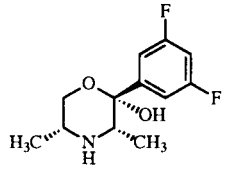
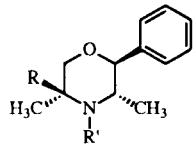
Introduction.

Structure-activity relationship (SAR) studies on 2-phenylmorpholines and 2-phenylmorpholinols led to the discovery of 2-(3,5-difluorophenyl)morpholinol **1** (1555U88) [1] and the methyl-2-phenylmorpholines **2-5** [2]. To gain further insight into the SAR of methyl-2-phenylmorpholines we prepared several analogues that have various alkyl substituents at the C-3 position of the morpholine ring. The synthesis and anti-tetrabenazine activity of these morpholines are reported herein.



1, (1555U88)



2, R = H, R' = H
3, R = H, R' = CH_3
4, R = CH_3, R' = H
5, R = CH_3, R' = CH_3

Figure 1

Chemistry.

The 2-phenylmorpholines in Table I were prepared in three or four steps from the appropriately substituted (2-bromoalkyl) phenyl ketones **21a-h** (Scheme 1). Compounds **6-9** and **12-19** are racemic, and the depicted structures represent the relative stereochemistry of these compounds. Compounds **10** and **11** are specific enantiomers with the absolute stereochemistry of **11** as depicted in Scheme I.

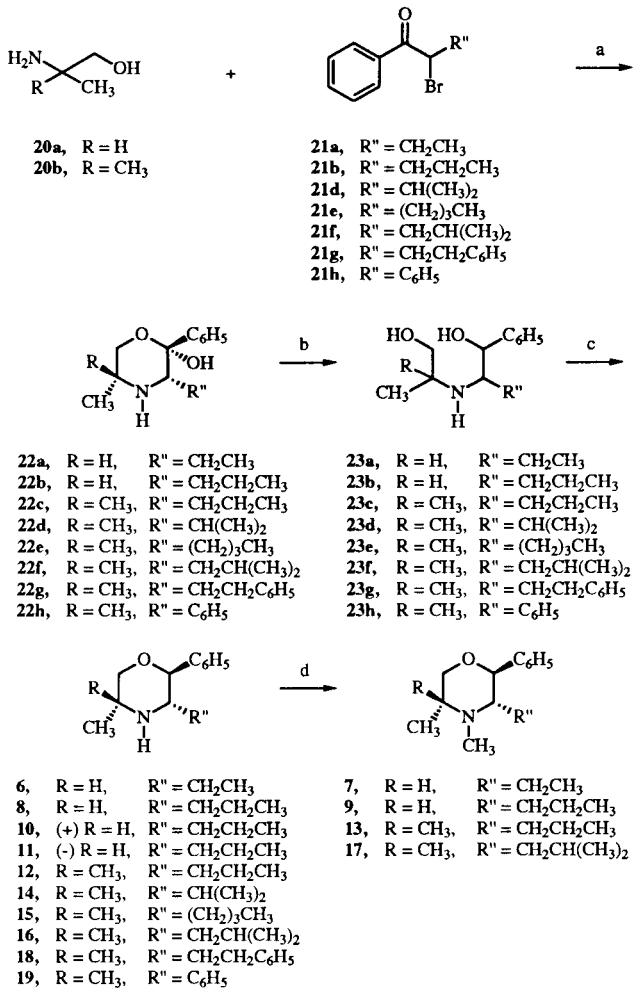
The (2-bromoalkyl) phenyl ketones **21b** and **21d-h** which were prepared from the appropriate alkyl phenyl ketones and dioxane dibromide [3], were reacted with 2-amino-2-methyl-1-propanol (**20b**) by a modified literature procedure [4] to provide the 2-phenyl-2-morpholinols **22c-22h**. Reaction of **21a-b** with racemic 2-amino-1-propanol (**20a**) yielded the C-5 monomethyl compounds **22a** and **22b** as the hydrobromide salts. Reduction of morpholinols **22c-22h** with sodium borohydride gave diastereomeric mixtures of the racemic (*R**,*S**)-erythro and (*R**,*R**)-threo aminodiols **23c-23h** in an erythro to threo ratio that varied with the C-3 substituent. The ratio could be established from the nmr spectrum [5,6]. The aminodiols were used without further purification in the next step.

Reduction of morpholinols **22a** and **22b** with sodium borohydride gave pure erythro aminodiols **23a** and **23b** by nmr. Compound **23b** was fully characterized as the hydrochloride salt. In most cases the aminodiols **23** were cyclized to the corresponding morpholines with sulphuric acid in dichloromethane [7]. This method failed to give the desired product with aminodiol **23g**; however, heating **23g** with *p*-toluenesulphonic at 140° [8] provided morpholine **18**. *N*-Methyl derivatives **7, 9, 13** and **17** were prepared from **6, 8, 12** and **16**, respectively, by reductive formylation [9].

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 [10]. Phenylmorpholinol **1** (1555U88) was very active with i.p. and p.o. $ED_{50's}$ of 5.2 and 6.2 mg/kg. The 2-phenylmorpholines **2-5** also exhibited good potency with i.p. $ED_{50's}$ ranging from 3 to 6 mg/kg. The smaller straight chain substituents of ethyl (**6**), propyl (**8** and **12**) and butyl (**15**) were well tolerated with i.p. $ED_{50's}$ of 5 to 6 mg/kg. The alpha branching of the isopropyl group of **14** caused loss of activity, but the beta branching of the isobutyl group of **16** was tolerated. The larger phenethyl and phenyl groups of compounds **18** and **19** resulted in loss of activity. The *N*-methyl derivatives **7, 9** and **17**

Scheme 1 [a]



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

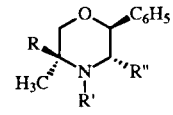
were less active than the parent NH compounds, but the *N*-methyl derivative **13** was as active as its NH analogue **12**. We previously determined that the active enantiomers of 3,5-dimethyl-2-(phenyl)morpholines have the absolute stereochemistry 2*S*, 3*S*, 5*R*, and that they can be synthesized enantioselectively from *R*-(-)-2-amino-1-propanol [1]. Their measured optical rotation is positive with one exception - compound **11**, which has a slight negative rotation. Therefore the activity of **11** (synthesized from R-(-)-2-amino-1-propanol) and inactivity of **10** is consistent with previous results.

Conclusion.

Straight chain alkyl groups (C1-C4) at the 3-position were well tolerated with anti-tetrabenazine ED_{50}'s comparable to compounds **2-5**. Introducing steric bulk β to the nitrogen with the isopropyl and phenyl groups essentially abolished activity. Steric bulk γ to the nitrogen was sensitive to the type of substituent: the isobutyl group

Table 1

Anti-tetrabenazine Activity in Mice [a]



No.	R	R'	R"	ED_{50}, mg/kg [b] i.p.	p.o.
1 [c]				5.2±0.7	6.2±0.3
2 [d]	H	H	CH_3	3.9±0.8	12.5±0.2
3 [d]	H	CH_3	CH_3	5.6±0.8	9.1±0.6
4 [d]	CH_3	H	CH_3	5	6.4±0.9
5 [d]	CH_3	CH_3	CH_3	3	8.9±0.5
6	H	H	CH_2CH_3	5±1	9.9±0.8
7	H	CH_3	CH_2CH_3	16±1	
8	H	H	$(CH_2)_2CH_3$	5	6.3±0.6
9	H	CH_3	$(CH_2)_2CH_3$	8	11.6±0.7
10 (+)	H	H	$(CH_2)_2CH_3$	>25	
11 (-)	H	H	$(CH_2)_2CH_3$	4.9±0.8	
12	CH_3	H	$(CH_2)_2CH_3$	6.0±0.9	7±1
13	CH_3	CH_3	$(CH_2)_2CH_3$	6	9
14	CH_3	H	$CH(CH_3)_2$	>25	
15	CH_3	H	$(CH_2)_3CH_3$	4.4±0.8	9±1
16	CH_3	H	$CH_2CH(CH_3)_2$	4.3±0.7	9±1
17	CH_3	CH_3	$CH_2CH(CH_3)_2$	12±2	12.5±0.7
18	CH_3	H	$CH_2CH_2C_6H_5$	>25	
19	CH_3	H	C_6H_5	25 [e]	

[a] The compounds were tested as described in reference 10. [b] Compounds were tested in mice by intraperitoneal (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 1 [d] Reference 2 [e] Anti-tetrabenazine ED_{50} determined in rat.

maintained activity while the phenethyl group did not. The effect of *N*-methylation was a modest diminishment of activity with one exception where activity was maintained.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian XL-200 and a Varian XL-300 and recorded in δ values with deuteriochloroform or dimethyl sulfoxide-d_6 as the solvent. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. High performance low pressure chromatography (Michael-Miller system) was performed on silica gel 60 (40-63 μM, E. Merck No. 9385) or preparative flash chromatography was performed on silica gel 60 (40-63 μM, E. Merck No. 9385). Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. Reduction of Morpholinols to Aminodiols. (rac)-(*R**,*S**)-2-[[(*R*,*S*)-2-Hydroxy-1-methylethyl]amino]-1-phenylpentanol Hydrochloride (**23b**).

Bromine (15.9 ml, 0.31 mole) was added dropwise to *p*-dioxane (200 ml). The resulting solution was added dropwise to a

solution of valerophenone (50.0 g, 0.31 mole) in *p*-dioxane (200 ml). The resulting mixture was stirred 16 hours. at 25°, diluted with water (500 ml), and extracted with diethyl ether. The ether extracts were washed with brine, dried (sodium sulfate) and concentrated *in vacuo* to yield 75.0 g (100%) of crude 2-bromovalerophenone (**21b**) as a clear oil.

To a solution of **21b** (48.2 g, 0.20 mole) in acetonitrile (150 ml) was added dropwise a solution of 2-amino-1-propanol (**20a**) (16.5 g, 0.22 mole) and 2,6-lutidine (33 ml, 0.24 mole) in acetonitrile (50 ml) and the mixture was stirred at 25° under a nitrogen atmosphere for 72 hours. The resulting precipitate was filtered, washed with acetonitrile, and vacuum dried to yield 12.4 g (20%) of crude morpholinol **22b** as the hydrobromide salt.

The hydrobromide salt of **22b** (12.4 g, 0.039 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 (6.0 g, 0.158 mole) in water (60 ml) was added dropwise. The solution was then allowed to warm to room temperature while being stirred overnight. The solution was rechilled to 0° and concentrated hydrochloric acid (40 ml) was carefully added dropwise. The mixture was concentrated under reduced pressure to remove ethanol, then rediluted with water to dissolve solids. This solution was chilled with an ice bath, made basic by treating with 40% aqueous sodium hydroxide and extracted three times with diethyl ether. The combined ether extracts were washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to give 8.6 g (93%) of crude aminodiol **23b**. Treatment of 1.5 g with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 1.51 g of the hydrochloride salt **23b** as a white solid, mp 184-185°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 8.60 (broad, 1H, HCl), 8.10 (broad, 1H, NH), 7.45-7.23 (m, 5H, Ar-H's), 6.15 (d, 1H, OH), 5.47 (t, 1H, OH), 5.14 (broad s, 1H, C_2-H), 3.64 (t, 2H, CH_2), 3.40 (m, 2H, CH), 1.40 (m, 2H, CH_2), 1.28 (d, 3H, CH_3), 1.20 (m, 1H, CH_2), 0.80 (m, 1H, CH_2), 0.61 (t, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{24}ClNO_2$: C, 61.41; H, 8.84; N, 5.12. Found: C, 61.50; H, 8.85; N, 5.11

Method B. Cyclizaton of Aminodiols (rac)-(2*R**,3*R**,5*S**)-3-Ethyl-5-methyl-2-phenylmorpholine Hydrochloride (**6**).

Bromine (18.2 ml, 0.35 mole) was added dropwise to *p*-dioxane (400 ml). The resulting solution was added dropwise to a solution of butyrophenone (50.0 g, 0.34 mole) in *p*-dioxane (300 ml). The resulting mixture was stirred 16 hours at 25°, diluted with water (2500 ml), and extracted with chloroform. The chloroform extracts were washed with brine, dried (sodium sulfate) and concentrated *in vacuo* to yield 76.3 g (99%) of crude 2-bromobutyrophenone **21a** as a clear oil. To a solution of **21a** (45.4 g, 0.20 mole) in acetonitrile (300 ml) was added dropwise a solution of 2-amino-1-propanol (**20a**) (16.5 g, 0.22 mole) and 2,6-lutidine (33 ml, 0.28 mole) in acetonitrile (125 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 19.9 g (33%) of crude morpholinol **22a** as the hydrobromide salt, 14.75 g of which was reduced without further purification according to Method A to yield 9.4 g (88%) of crude aminodiol **23a**.

A solution of **23a** (9.4 g, 0.042 mole) in dichloromethane (200 ml) was added dropwise to concentrated sulfuric acid (35 ml) at 0° and let warm to room temperature while stirring overnight. The mixture was poured into ice water (300 ml) and the resulting layers were separated. The aqueous layer was chilled with an ice bath, made basic with 40% aqueous sodium hydroxide, and extracted three times with dichloromethane. The dichloromethane extracts were washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to give 7.0 g (81%) of the crude free base of **6** as a clear oil. Treatment of the free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 6.05 g of the hydrochloride salt **6** as a white solid, mp 183-184°. ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.40 (broad, 2H, NH, HCl), 7.26 (s, 5H, Ar-H's), 4.42 (d, 1H, J = 10.0, C_2-H), 3.99 (dd, 1H, J = 11.8, J = 4.0, C_6-H_{eq}), 3.59 (t, 1H, J = 11.1, C_6-H_{ax}), 3.50-3.25 (broad m, 2H, C_3-H, C_5-H), 1.55-1.30 (m, 2H, CH_2), 1.26 (d, 3H, CH_3), 0.69 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.32; N, 5.79. Found: C, 64.51; H, 8.35; N, 5.75.

Method C. Reductive Methylation of Morpholines. (rac)-(2*R**,3*R**,5*S**)-3-ethyl-4,5-dimethyl-2-phenylmorpholine *p*-Toluenesulphonate (**7**).

A mixture of **6** (4.0 g, 19.5 mmoles), 97% formic acid (2.0 ml, 54 mmoles) and 37% aqueous formaldeyhde (1.8 ml, 23 mmoles) 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 and extracted with ether . The ether extract was washed with brine, dried (potassium carbonate) and concentrated under reduced pressure to yield 3.5 (82%) g of crude free base as a green oil. To a stirred solution of the crude free base (2.8 g, 12.8 mmoles) in acetone (50 ml) was added *p*-toluenesulphonic acid monohydrate (2.41 g, 12.7 mmoles). The resulting solution was diluted with ethyl acetate (500 ml) and diethyl ether (500 ml) then stirred overnight at room temperature to give 2.0 g of crude *p*-toluenesulfonate salt. Recrystallization with ethanol/ether yielded 920 mg of the *p*-toluenesulphonic acid salt **7** as a white solid, mp 107-109°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 7.80 (d, 2H, Ar-H's), 7.36 (s, 5H, Ar-H's), 7.23 (d, 2H, Ar-H's), 4.85 (d, 1H, J = 10.3, C_2-H), 4.16 (t, 1H, J = 12.5, C_6-H_{ax}), 3.92 (dd, 1H, J = 12.9, J = 3.5, C_6-H_{eq}), 3.50 (broad m, 1H, C_3-H), 2.94 (s, 3H, N-CH_3), 2.82 (broad m, 1H, C_5-H), 2.36 (s, 3H, CH_3), 1.70 (broad, 2H, CH_2), 1.49 (d, 3H, CH_3), 0.66 (t, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.49; H, 7.51; N, 3.58.

(rac)-(2*R**,3*R**,5*S**)-5-Methyl-2-phenyl-3-propylmorpholine Hydrochloride (**8**).

Compound **23b** (7.1 g, 0.03 mole) was cyclized according to Method B to yield 5.8 g (88%) of the crude free base of **8** as a yellow oil. Treatment of 2.0 g free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 2.32 g of the hydrochloride salt **8** as a white solid, mp 197-199°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.42 (broad, 2H, NH, HCl), 7.38 (s, 5H, Ar-H's), 4.40 (d, 1H, J = 10.0, C_2-H), 3.98 (dd, 1H, J = 11.7, J = 4.0, C_6-H_{eq}), 3.62 (t, 1H, J = 11.0, C_6-H_{ax}), 3.50-3.30 (broad m, 2H, C_3-H, C_5-H), 1.42 (m, 2H, CH_2), 1.24 (d, 3H, CH_3), 1.2 (m, 1H, CH_2), 0.98 (m, 1H, CH_2), 0.63 (t, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.82; H, 8.71; N, 5.44.

(rac)-(2*R**,3*R**,5*S**)-4,5-Dimethyl-2-phenyl-3-propylmorpholine Hydrochloride (**9**).

Compound **8** (3.8 g, 17.3 mmoles) was methylated with 97% formic aad (2.3 ml, 62 mmoles) and 37% aqueous formaldehyde (2.0 ml, 25.6 mmoles) according to method C to yield 4.1 g (100%) of the crude free base of **9** as a colorless oil. Treatment with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 3.86 g of the hydrochloride salt **9** as a white solid, mp 170-171°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 10.96 (broad, 1H, HCl), 7.40 (s, 5H, Ar-H's), 4.60 (d, 1H, J = 10.0, C_2-H), 3.99 (dd, 1H, J = 12.5, J = 3.7, C_6-H_{eq}), 3.78 (t, 1H, J = 11.0, C_6-H_{ax}), 3.50 (broad m, 2H, C_3-H, C_5-H), 2.82 (d, 3H, NCH_3), 1.60-0.60 (m, 4H, CH_2), 1.32 (d, 3H, CH_3), 0.53 (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.82; H, 9.02; N, 5.19.

(+)-(2*R*,3*R*,5*S*)-5-Methyl-2-phenyl-3-propylmorpholine Hydrochloride (**10**).

To a solution of 2-bromovalerophenone (**21b**) (29.0 g, 0.12 mole) in acetonitrile (60 ml) was added dropwise a solution of *S*-(+)-2-amino-1-propanol (**20a**) (10.0 g, 0.133 mole) and 2,6-lutidine (17 ml, 0.144 mole) in acetonitrile (40 ml), the mixture was stirred at room temperature under a nitrogen atmosphere for 72 hours. The resulting precipitate was filtered, washed with diethyl ether, and vacuum dried to yield 8.2 g of crude morpholinol **22b** as the hydrobromide salt. The mother liquors were diluted with diethyl ether to precipitate a second crop of 6.86 g to give a combined yield of 15.06 g (40%) which was reduced without further purification according to Method A to yield 5.8 g (51%) of crude aminodiol **23b** which was cyclized according to Method B to yield 4.1 g (77%) of the crude free base of **10** as a clear yellow oil. Treatment of 1.5 g free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 1.63 g of the hydrochloride salt **10** as a white solid, mp 241-243°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.44 (broad, 2H, NH, HCl), 7.38 (s, 5H, Ar-H's), 4.42 (d, 1H, J = 9.9, C_2-H), 3.99 (dd, 1H, J = 11.8, J = 3.1, C_6-H_{eq}), 3.63 (t, 1H, J = 11.0, C_6-H_{ax}), 3.50 (broad m, 2H, C_3-H, C_5-H), 1.40 (m, 2H, CH_2), 1.25 (d, 3H, CH_3), 1.10 (m, 1H, CH_2), 0.92 (m, 1H, CH_2), 0.63 (t, 3H, CH_3); $[a]_D^{20}$ = +0.96° (c = 0.656, absolute ethanol).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.82; H, 8.69; N, 5.42

(-)-(2*S*,3*S*,5*R*)-5-Methyl-2-phenyl-3-propylmorpholine Hydrochloride (**11**)

To a solution of 2-bromovalerophenone (**21b**) (29.0 g, 0.12 mole) in acetonitrile (60 ml) was added dropwise a solution of R-(-)-2-amino-1-propanol (**20a**) (10.0 g, 0.133 mole) and 2,6-lutidine (17 ml, 0.144 mole) in acetonitrile (40 ml); the mixture was stirred at room temperature under a nitrogen atmosphere for 72 hours. The resulting precipitate was filtered, washed with diethyl ether, and vacuum dried to yield 7.75 g of crude morpholinol **22b** as the hydrobromide salt. The mother liquors were diluted with diethyl ether to precipitate a second crop of 5.50 g to give a combined yield of 13.25 g (35%) which was reduced without further purification according to Method A to yield 5.9 g (59%) of crude aminodiol **23b** which was cyclized according to Method B to yield 5.1 g (93%) of the crude free base of **11** as a clear yellow oil. Treatment of 1.5 g free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 1.62 g of the hydrochloride salt **11** as a white solid, mp 242-243°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.47 (broad, 2H, NH, HCl), 7.38 (s, 5H, Ar-H's), 4.42 (d, 1H, J = 10.0, C_2-H), 3.98 (dd, 1H, J = 11.7, J = 3.0, C_6-H_{eq}), 3.63 (t, 1H, J = 11.1, C_6-H_{ax}), 3.50 (broad m, 2H, C_3-H, C_5-H), 1.42 (m, 2H, CH_2), 1.25 (d, 3H, CH_3), 1.18 (m, 1H, CH_2), 0.98 (m, 1H, CH_2), 0.63 (t, 3H, CH_3); $[a]_D^{20}$ = -1.0° (c = 0.700, absolute ethanol).

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.80; H, 8.72; N, 5.42.

(rac)-*trans*-5,5-Dimethyl-2-phenyl-3-propylmorpholine Hydrochloride (**12**).

Compound **22c** (12.0 g, 0.048 mole) was reduced according to Method A to yield 12.1 g (100%) of crude aminodiol **23c** which was cyclized accordiog to Method B to yield 6.8 g (61%) of the crude free base of **12** as a clear yellow oil. Treatment of 2.5 g free base with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 1.94 g of the hydrochloride salt **12** as a white solid, mp 174-176° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6 , 200 MHz): δ 9.40 (broad, 2H, NH, HCl), 7.46-7.36 (m, 5H, Ar-H's), 4.37 (d, 1H, J = 10.0, C_2-H), 3.69 (s, 2H, C_6-H's), 3.40 (broad m, 1H, C_3-H), 1.53 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.30-0.80 (m, 4H, CH_2), 0.63 (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.83; H, 8.99; N, 5.19

(rac)-*trans*-4,5,5-Trimethyl-2-phenyl-3-propylmorpholine Hydrochloride (**13**).

Compound **12** (4.3 g, 18.4 mmoles) was methylated with 97% formic acid (2.3 ml, 62 mmoles) and 37% aqueous formaldehyde (2.0 ml, 25.6 mmoles) accordiog to Method C to yield 4.1 (90%) g of the crude free base of **13** as a yellow oil. Treatment with ethereal hydrogen chloride, followed by recrystallization with acetonitrile/ether yielded 2.80 g of the hydrochloride salt **13** as a white solid, mp 187-189°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 7.46-7.38 (m, 5H, Ar-H's), 4.58 (d, 1H, J = 10.4, C_2-H), 3.94 (d, 1H, J = 12.7, C_6-H), 3.74 (d, 1H, J = 12.5, C_6-H), 3.40 (broad m, 1H, C_3-H), 2.74 (d, 3H, NCH_3), 1.65 (m, 1H, CH_2), 1.47 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.40-1.00 (m, 2H, CH_2), 0.75 (m, 1H, CH_2), 0.52 (t, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67.70; H, 9.23; N, 4.94. Found: C, 67.80; H, 9.25; N, 4.93.

(rac)-*trans*-3-Isopropyl-5,5-dimethyl-2-phenylmorpholine Hydrochloride (**14**).

Bromine (3.2 ml, 0.062 mole) was added dropwise to *p*-dioxane (250 ml). The resulting solution was added dropwise to isovalerophenone (10.0 g, 0.062 mole). The resulting mixture was stirred 16 hours at room temperature, diluted with water (1400 ml), and extracted with dichloromethane. The dichloromethane extracts were washed with brine, dried (sodium sulfate) and concentrated *in vacuo* to yield 16.9 g (100%) of crude **21d** as a clear oil.

To a solution of crude **21d** (14.95 g, 0.062 mole) in acetonitrile (150 ml) was added dropwise a solution of 2-amino-2-methyl-1-propanol, (**20b**) (13.8 g, 0.155 mole) in acetonitrile (200 ml). The resulting mixture was refluxed for 12 days, cooled to room temperature, filtered and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and

water. The ethyl acetate was extracted with 1 *N* hydrochloric acid. The acid extract was chilled in an ice bath, treated with 40% aqueous sodium hydroxide, and extracted with ethyl ether. The ethyl ether extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to yield 2.90 g (19%) of the crude morpholinol **22d** as a yellow oil, which was reduced according to Method A to yield 2.5 g (86%) of crude aminodiol **23d** which was cyclized according to Method B to yield 2.3 g of the crude free base of **14** as a clear yellow oil. The crude morpholine was chromatographed over silica gel eluting with ethyl acetate:methanol/98:2 to yield 1.8 g (77%) of the purified free base of **14**. Treatment with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 520 mg of the hydrochloride salt **14** as a white solid, mp 241-243° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.25 (broad, 1H, HCl), 8.64 (broad, 1H, NH), 7.50-7.35 (m, 5H, Ar-H's), 4.50 (d, 1H, J = 10.4, C_2-H), 3.69 (q, 2H, J = 12.3, C6-H's), 3.57 (broad m, 1H, C_3-H), 1.68 (m, 1H, CH), 1.56 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 0.90 (d, 3H, CH_3), 0.70 (d, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.80; H, 8.98; N, 5.19.

(rac)-*trans*-3-Butyl-5,5-dimethyl-2-phenylmorpholine Hydrochloride (**15**).

Bromine (14.6 ml, 0.284 mole) was added dropwise to *p*-dioxane (200 ml). The resulting solution was added dropwise to a solution of hexanophenone (50 g, 0.284 mole) in *p*-dioxane (150 ml). The resulting mixture was stirred 1 hour at 25°, diluted with water (300 ml), and extracted with diethyl ether. The diethyl ether extracts were washed with brine, dried (sodium sulfate) and concentrated *in vacuo* to yield 78.3 g (100%) of crude 2-bromohexanophenone (**21e**) as a clear oil. To a solution of the crude **21e** (32.4 g, 0.127 mole) in acetonitrile (100 ml) was added dropwise a solution of 2-amino-2-methyl-1-propanol (**20b**) (22.6 g, 0.254 mole) in acetonitrile (200 ml). The resulting mixture was refluxed for 16 hours, cooled to room temperature, filtered and concentrared *in vacuo*. The residue was partitioned between ethyl ether and water. The ethyl ether was extracted with 1 *N* hydrochloric acid. The acid extract was chilled in an ice bath, treated with 40% aqueous sodium hydroxide, and extracted with ethyl ether. The ethyl ether extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to yield 22.6 g (68%) of the crude morpholinol **22e** as a yellow oil, which was reduced according to Method A to yield 17.1 g (98%) of crude aminodiol **23e** which was cyclized according to Method B to yield 12.3 g (77%) of the crude free base of **15** as a clear yellow oil. Treatment with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 11.06 g of the hydrochloride salt **15** as a white solid, mp 142-144°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.30 (broad, 2H, NH, HCl), 7.44-7.36 (m, 5H, Ar-H's), 4.37 (d, 1H, J = 10.1, C_2-H), 3.69 (s, 2H, C_6-H's), 3.40 (broad m, 1H, C_3-H), 1.53 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.40-0.80 (m, 6H, CH_2), 0.66 (t, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67.71; H, 9.23; N, 4.93. Found: C, 67.66; H, 9.23; N, 4.92.

(rac)-*trans*-3-Isobutyl-5,5-dimethyl-2-phenylmorpholine Hydrochloride (**16**).

Compound **22f** (18.7 g, 0.071 mole) was reduced according to Method A to yield 16.0 g (85%) of crude aminodiol **23f**. The crude aminodiol (10.0 g, 0.038 mole) was cyclized according to Method B to yield 7.8 g (84%) of the crude free base of **16** as a clear yellow oil. Treatment of 3.0 g with ethereal hydrogen chloride, followed by recrystallization from ether yielded 2.7 g of the hydrochloride salt **16** as a white solid, mp 150-154°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.50 (broad, 1H, HCl), 9.27 (m, 1H, NH), 7.47-7.38 (m, 5H, Ar-H's), 4.35 (d, 1H, J = 10.0, C_2-H), 3.70 (s, 2H, C_6-H's), 3.40 (broad m, 1H, C_3-H), 1.55 (s, 3H, CH_3), 1.50-1.35 (m, 2H, CH_2), 1.45 (s, 3H, CH_3), 1.00 (m, 1H, CH), 0.66 (d, 3H, CH_3), 0.53 (d, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{26}ClNO$: C, 67.70; H, 9.23; N, 4.94. Found: C, 67.55; H, 9.25; N, 4.92.

(rac)-*trans*-3-Isobutyl-4,5,5-trimethyl-2-phenylmorpholine Hydrochloride (**17**).

Compound **16** (4.8 g, 19.4 mmoles) was methylated with 97% formic acid (6.0 ml, 162 mmoles) and 37% aqueous formaldeyhde (6.0 ml, 78 mmoles) according to method C to yield 4.7 (93%) g of the crude free base of **17** as an orange oil. Treatment with ethereal hydrogen chloride, followed by recrystallization with ethanol/ether yielded 4.1 g of the hydrochloride salt **17** as a white solid, mp 184-186°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 10.55 (broad, 1H, HCl), 7.48-7.36 (m, 5H, Ar-H's), 4.52 (d, 1H, J = 10.0, C_2-H), 3.93 (d, 1H, J = 12.5, C_6-H), 3.76 (d, 1H, J = 12.4, C_6-H), 3.20 (broad m, 1H, C_3-H), 2.70 (d, 3H, NCH_3), 1.7 (m, 1H, CH), 1.49 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 0.80-1.25 (m, 2H, CH_2), 0.68 (d, 3H, CH_3), 0.20 (d, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{28}ClNO$: C, 68.55; H, 9.48; N, 4.70. Found: C, 68.51; H, 9.51; N, 4.74.

(rac)-*trans*-5,5-Dimethyl-3-phenethyl-2-phenylmorpholine Hydrochloride (**18**).

The hydrochloride salt of **22g** (37.7 g, 0.108 mole) was reduced according to Method A to yield 33.0 g (98%) of crude aminodiol **23g**. The crude aminodiol **23g** (10.3 g, 0.033 mole) was cyclized by heating neat with *p*-toluenesulphonic acid monohydrate (13.8 g, 0.072 mole) at 150° for 16 hours. The resulting mixture was diluted with water, made basic with 40% aqueous sodium hydroxide, and extracted with dichloromethane. The dichloromethane extracts were combined, washed with brine, and dried (sodium sulfate) to yield 9.5 g of the crude free base of **18** as a dark oil. The crude morpholine was chromatographed over silica gel eluting with ethyl acetate:hexane/50:50 (0.1% triethylamine) to yield 6.1 g (63%) of **18** as the purified free base. Treatment with ethereal hydrogen chloride, followed by recrystallization from ether yielded 3.8 g of the hydrochloride salt **18** as a white solid, mp 160-161°; ^{1}H-nmr (dimethyl sulfoxide-d_6 200 MHz): δ 9.53 (broad, 2H, NH, HCl), 7.39 (s, 5H, Ar-H's), 7.26-6.89 (m, 5H, Ar-H's), 4.43 (d, 1H, J = 10.2, C_2-H), 3.71 (s, 2H, C_6-H's), 3.45 (broad m, 1H, C_3-H), 2.62 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 1.90 (m, 1H, CH_2), 1.53 (s, 3H, CH_3), 1.48 (m, 1H, CH_2), 1.39 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{26}ClNO$: C, 72.38; H, 7.90; N, 4.22. Found: C, 72.16; H, 7.98; N, 4.18.

(rac)-*trans*-5,5-Dimethyl-2,3-diphenylmorpholine Hydrochloride (**19**).

The hydrochloride salt **22h** (10.1 g, 0.032 mole) was reduced according to Method A to yield 10.1 g (100%) of

crude aminodiol **23h**. Compound **23h** (6.1 g, 0.021 mole) was cyclized according to Method B to yield 4.8 g (85%) of the crude free base of **19** as a white solid. Treatment with ethereal hydrogen chloride, followed by recrystallization from ethanol/ether yielded 4.4 g of the hydrochloride salt **19** as a white solid, mp 296-298°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.78 (broad, 1H, HCl), 9.56 (broad, 1H, NH), 7.58 (m, 2H, Ar-H's), 7.28-7.16 (m, 8H, Ar-H's), 4.97 (d, 1H, J = 10.1, C_2-H), 4.70 (t, 1H, J = 10.5, C_3-H), 4.06 (d, 1H, J = 12.1, C_6-H), 3.80 (d, 1H, J = 12.3, C_6-H) 1.64 (s, 3H, CH_3), 1.42 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30; N, 4.61. Found: C, 71.22; H, 7.32; N, 4.58.

(rac)-*cis*-5,5-Dimethyl-2-phenyl-3-propylmorpholinol Hydrochloride (**22c**).

To a solution of 2-bromovalerophenone, (**21b**) (16.9 g, 0.07 mole) in acetonitrile (150 ml) was added dropwise a solution of 2-amino-2-methyl-1-propanol (**20b**) (18.7 g, 0.21 mole) in acetonitrile (50 ml). The resulting mixture was refluxed for 16 hours, cooled to room temperature, filtered and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The ethyl acetate was extracted with 1 *N* hydrochloric acid. The acid extract was chilled in an ice bath, treated with 40% aqueous sodium hydroxide, and extracted with ethyl ether. The ethyl ether extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to yield 14.0 g (80%) of the free base of **22c** as a yellow oil. Treatment of 2.0 g free base with ethereal hydrogen chlonde, followed by recrystallization with ethanol/ether yielded 2.16 g of the hydrochloride salt **22c** as a white solid, mp 197-198° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6 , 200 MHz): δ 9.33 (broad d 1H, HCl); 8.82 (broad t, 1H, NH), 7.80-7.55 (m, 6H, Ar-H's, OH), 4.05 (d, 1H, J = 12.3, C_6-H), 3.48 (d, 1H, C_6-H), 3.31 (broad m, 1H, C_3-H), 1.80 (s, 3H, CH_3), 1.50-0.80 (m, 4H, CH_2), 1.58 (s, 3H, CH_3), 0.68 (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{24}ClNO_2$: C, 63.03; H, 8.46; N, 4.90. Found: C, 63.11; H, 8.49; N, 4.87

(rac)-*cis*-3-Isobutyl-5,5-dimethyl-2-phenylmorpholinol Hydrochloride (**22f**).

Bromine (6.2 ml, 0.12 mole) was added dropwise to *p*-dioxane (150 ml). The resulting solution was added dropwise to a solution of 4-methylpentanophenone (21.2 g, 0.12 mole) in *p*-dioxane (50 ml). The resulting mixture was diluted with water (200 ml), and extracted with dichloromethane. The dichloromethane extracts were washed with brine, dried (potassium carbonate) and concentrated *in vacuo* to yield 30.6 g (100%) of crude 2-bromo4-methyl-pentanophenone (**21f**) as a clear oil. To a solution of the crude **21f** (30.6 g, 0.12 mole) in acetonitrile (100 ml) was added dropwise a solution of 2-amino-2-methyl-1-propanol (**20b**) (26.8 g, 0.30 mole) in acetonitrile (100 ml). The resulting mixture was refluxed for 16 hours, cooled to room temperature, filtered and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The ethyl acetate was extracted with 1 *N* hydrochloric acid. The acid extract was chilled in an ice bath, treated with 40% aqueous sodium hydroxide, and extracted with ethyl ether. The ethyl ether extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to yield 29.0 g (93%) of the crude morpholinol **22f** as a yellow oil. Treatment of 2.5 g with ethereal hydrogen chloride, followed by recrystallization from ethanol/ether yielded 1.85 g of the hydrochloride salt **22f** as a white solid, mp 206-207° dec; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.25 (broad d, 1H, HCl), 8.83 (m, 1H, NH), 7.60-7.42 (m, 6H, Ar-H's, OH), 3.99 (d, 1H, J = 12.3, C_6-H), 3.49 (d, 1H, J = 12.2, C_6-H), 3.20 (broad m, 1H, C_3-H), 1.57 (s, 3H, CH_3), 1.50-1.10 (m, 3H, CH_2, CH), 1.34 (s, 3H, CH_3), 0.67 (d, 3H, CH_3), 0.38 (d, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; N, 4.67. Found: C, 64.17; H, 8.76; N, 4.66.

(rac)-*cis*-5,5-Dimethyl-3-phenethyl-2-phenylmorpholinol Hydrochloride (**22g**).

Bromine (22.8 ml, 0.315 mole) was added dropwise to *p*-dioxane (300 ml). The resulting solution was added dropwise to a solution of 4-phenylbutyrophenone [11] (70.6 g, 0.315 mole) in *p*-dioxane (300 ml). The resulting mixture was diluted with water (400 ml), and extracted with ethyl ether. The ether extracts wae washed with brine, dried (sodium sulfate) and concentrated *in vacuo* to yield 112.7 g (100%) of crude 2-bromo-4-phenylbutyrophenone **21g** as a dark oil (nmr shows 15% *p*-dioxane). To a solution of crude **21g** (50.0 g, 0.14 mole) in acetonitrile (100 ml) was added dropwise a solution of 2-amino-2-methyl-1-propanol (**20b**) (25.0 g, 0.28 mole) in acetonitrile (100 ml). The resulting mixture was refluxed for 16 hours, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The ethyl acetate was extracted with 1 *N* hydrochloric acid. The acid extract was chilled in an ice bath, treated with 40% aqueous sodium hydroxide, and extracted with ethyl ether. The ethyl ether extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to yield the crude morpholinol **22g** as a yellow oil. Treatment with ethereal hydrogen chloride, followed by recrystallization from ethanol/ether yielded 25.3 (52%) g of the hydrochloride salt **22g** as a white solid, mp 201-202°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.55 (broad d, 1H, HCl), 8.85 (broad t, 1H, NH), 7.80-6.89 (m, 11H, Ar-H's, OH), 4.03 (d, 1H, J = 12.3, C_6-H), 3.49 (d, 1H, C_6-H), 3.30 (broad m, 1H, C_3-H), 2.62 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 1.70 (m, 2H, CH_2), 1.55 (s, 3H, CH_3), 1.38 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03. Found: C, 68.99; H, 7.55; N, 4.02.

(rac)-*cis*-5,5-Dimethyl-2,3-diphenylmorpholinol Hydrochloride (**22h**).

Bromine (13.1 ml, 0.26 mole) was added dropwise to *p*-dioxane (200 ml). The resulting solution was added dropwise to a solution of deoxybenzoin (50.0 g, 0.26 mole) in *p*-dioxane (200 ml). The resulting mixture was stirred at room temperature for 16 hours, then diluted with water (300 ml), and extracted with ethyl ether. The ether extracts were washed with brine, dried (potassium carbonate) and concentrated *in vacuo* to yield 75.9 g (100%) of crude α-bromodeoxybenzoin **21h** as a yellow oil (nmr shows 8% *p*-dioxane). To a solution of crude **21h** (27.5 g, 0.14 mole) in acetonitrile (200 ml) was added dropwise a solution of 2-amino-2-methyl-1-propanol (**20b**) (17.8 g, 0.20 mole) in acetonitrile (200 ml). The resulting mixture was refluxed for 16 hours, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The ethyl acetate was extracted with 1 *N* hydrochloric acid. The acid extract was chilled in an ice bath, treated with 40% aqueous sodium hydroxide, and extracted with ethyl ether.

The ethyl ether extracts were washed with brine, dried (sodium sulfate), and concentrated *in vacuo* to yield 23.9 g (84%) the crude morpholinol **22h** as a yellow oil. Treatment with ethereal hydrogen chloride, followed by recrystallization from ethanol/ether yielded 13.3 g of the hydrochloride salt **22h** as a white solid, mp 200-201°; ^{1}H-nmr (dimethyl sulfoxide-d_6, 200 MHz): δ 9.82 (broad, 1H, HCl), 9.05 (broad, 1H, NH), 7.62 (s, 1H, OH), 7.36-7.09 (m, 10H, Ar-H's), 4.50 (d, 1H, J = 11.3, C_3-H), 4.25 (d, 1H, J = 12.2, C_6-H), 3.63 (d, 1H, J = 12.1, C_6-H), 1.65 (s, 3H, CH_3), 1.42 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.93; N, 4.38. Found: C, 67.64; H, 6.94; N, 4.31.

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REFERENCES AND NOTES

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

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

[3] S. J. Pasaribu and L. R. Williams, *Aust. J. Chem.*, **26**, 1327 (1973).

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

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

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

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

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

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

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

[11] W. Borsche and F. Sinn, *Liebigs Ann. Chem.*, **553**, 260 (1942).