Synthesis and Stereochemistry of Tetrahydro-4-aryl-3-[(dimethylamino)methyl]-2*H*-pyranols as Potential Analgesics

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Diastereomeric *cis*- and *trans*-tetrahydro-4-aryl-3-[(dimethylamino)methyl]-2*H*-pyranols derived from 3-[(dimethylamino)methyl]tetrahydro-4*H*-pyran-4-one (**5**), have been prepared and their configurations were established on the basis of ir data. The biologically more potent *trans* isomer **3** was resolved into its optical antipodes and the absolute stereochemistry of one of the enantiomers **14**, was determined by X-ray crystallography. Some of the compounds showed analgesic activity comparable to codeine.

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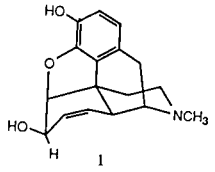
Studies [1-5] with "flexible" chiral 4-arylpiperidines indicate a significant dependence of analgesic activity on geometric isomerism.

The purpose of our investigation was to study conformational influences on analgesic activity using a novel group of substituted 4-aryltetrahydropyranol derivatives. These compounds were chosen for this study because, in addition to their conformational mobility, they contain basic structural elements of morphine (**1**). Since the substituted 4-phenyltetrahydropyranol possesses two asymmetric centers, two diastereomers are possible. The preferred conformations of these compounds are illustrated in structures **2** (*cis*) [6] and **3** (*trans*) [6].

In this report, we describe the preparation, stereochemistry and analgesic properties of several tetrahydro-4-aryl-3-[(dimethylamino)methyl]-2*H*-pyranols and their derivatives.

Compounds **2, 3, 5-14** were prepared in accordance with Scheme 1. The Mannich base **5** was prepared by condensation of tetrahydro-4*H*-pyran-4-one (**4**) with paraformaldehyde and dimethylamine hydrochloride. Reaction of **5** with *m*-methoxyphenylmagnesium bromide in anhydrous ether afforded a mixture of diastereomeric alcohols **6** in a ratio of 8:1 as determined by gas chromatography [7]. The major isomer was separated from the mixture by chromatography, however no effort was made to isolate the minor isomer in pure form. The major isomer in chloroform solution showed a broad absorption in the region at 3300-3100 cm^{-1} (bonded hydroxyl) which did not shift upon further dilution. The presence of intramolecular hydrogen bonding indicates that the hydroxyl and dimethylaminomethyl groups in this compound are *cis*. On the basis of its ir spectrum, the *trans* [6] configuration (structure **7**) was assigned to this isomer. Esterification of **7** was accomplished with acetic anhydride to give the acetate **8**. Since a phenolic hydroxyl group in the *meta* position on the aromatic ring might enhance the agonist potency of the substituted 4-aryltetrahydropyranols in a fashion similar to that of opiates [8], it was of interest to prepare and evaluate the phenolic analogs of **7**. As outlin-



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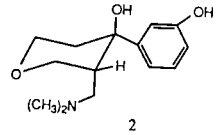

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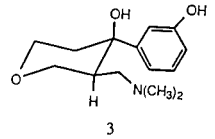

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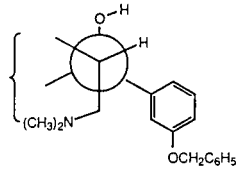
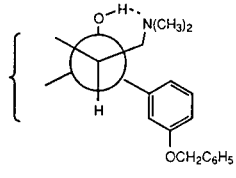


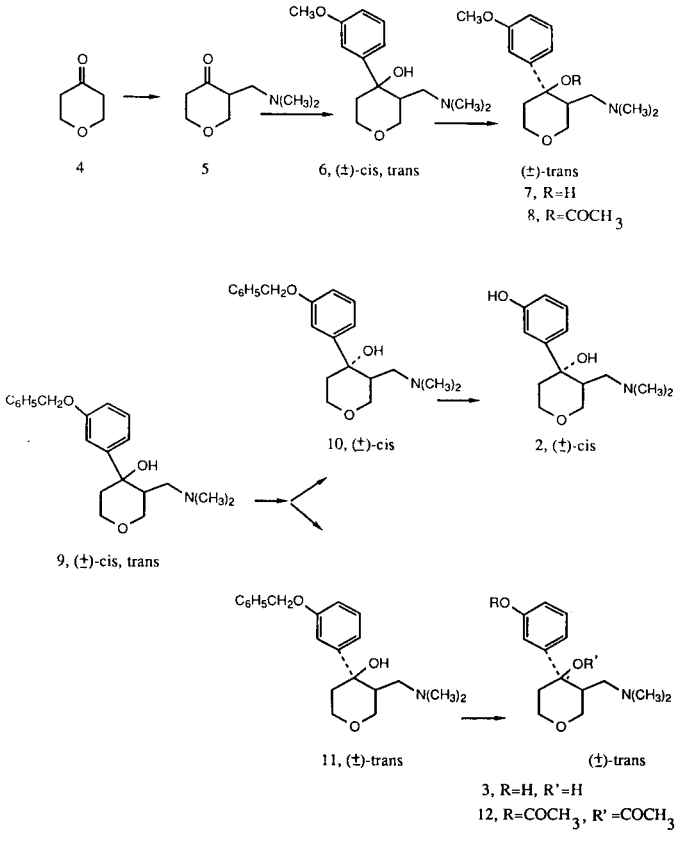
10 (Fig. A)

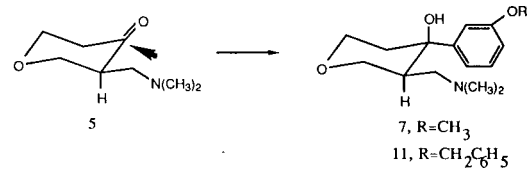


11 (Fig. B)

ed in Scheme 1, treatment of **5** with 3-benzyloxyphenylmagnesium bromide in dry tetrahydrofuran afforded a mixture of diastereomeric alcohols **9** in a ration of 6:1 [7]. The major isomer was separated from the mixture by crystallization of its hydrochloride salt (mp 246-248°) and the minor isomer was isolated from the recrystallization mother liquors as the free base (mp 133-134°). In the ir spectrum, the minor isomer in chloroform showed a sharp peak at 3600 cm^{-1} (free OH) corresponding to structure **10**, in which intramolecular hydrogen bonding is sterically impossible (Fig. A, OH is *trans* to the $CH_2N(CH_3)_2$ group), whereas the free base prepared from the major isomer showed an absorption in the region at 3260-3120 cm^{-1} with broad profile (bonded OH) and was assigned to structure **11** (Fig. B), in analogy to the assignment of **7**. The relative configurational assignments are also consistent from consideration of the stereochemistry of arylmagnesium reagents addition to cyclic ketones [9]. If isomer formation is considered from the likely steric course of addition of arylmagnesium reagents to **5**, attack from the least hindered side, giving the *trans* [6] isomer **7** or **11** is favored, provided the ketone **5** reacts in the chair conformation with the dimethylaminomethyl group equatorial. Finally, debenzylation of **10** and **11** was achieved by catalytic hydrogenation to give the corresponding phenols **2** and **3**, respectively.

Scheme 1





Since it is probable that one of the enantiomers might exhibit a higher degree of stereoselectivity toward the receptor than its mirror image, it was of interest: (a) to resolve the most active base **3** and (b) to determine the absolute configuration of a least one of the enantiomers. The resolution of the racemate **3** was carried out with *d*- and *l*-tartaric acid in methanol and the enantiomeric salts were converted by dilute ammonium hydroxide to the corresponding bases **13** and **14**, respectively. Finally, it remained to determine the absolute configuration of one of the enantiomers. The X-ray crystal structure of (+)-**14**·HCl [14] shown in Figure 1, revealed that the absolute configuration is (3*S*, 4*R*), and in the solid state the substituted 4-aryltetrahydropyranol ring has the chair conformation with the 4-aryl and the 3-dimethylaminomethyl groups in trans equatorial orientation. In addition, the X-ray structure of (+)-**14**·HCl confirmed the correctness of our previous relative configurational assignment based on ir data of the racemates, **2**, **3** and **7**.

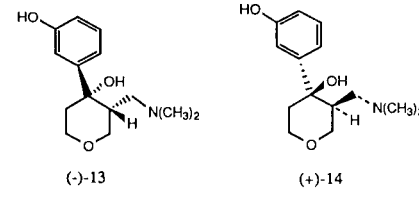


Table I

Algesic Activities

Compound	Route	Analgesic act.: [a] ED_{50}, mg/kg writhing test
2 [c]	sc	49.7 (39.8-58.0) [d]
	po	>200
3 [c]	sc	4.2 (3.0-5.3)
	po	4.3 (2.7-5.8)
7 [c]	sc	9.3 (7.7-11.0)
	po	24.8 (19.7-29.9)
13 [c]	sc	8.6 (7.1-10.0)
	po	18.0 (13.4-22.0)
14 [c]	sc	8.4 (5.8-10.0)
	po	15.0 (9.0-20.6)
codeine [b]	sc	2.3 (1.21-3.91)
	po	24.0 (13.71-42.00)

[a] The compounds were administered sc and po to the mice in distilled water for the writhing test [10,11]. [b] Phosphate. [c] Hydrochloride. [d] Numbers in parentheses are the 95% confidence limits obtained by the graphic [12] or regression [13] analysis.

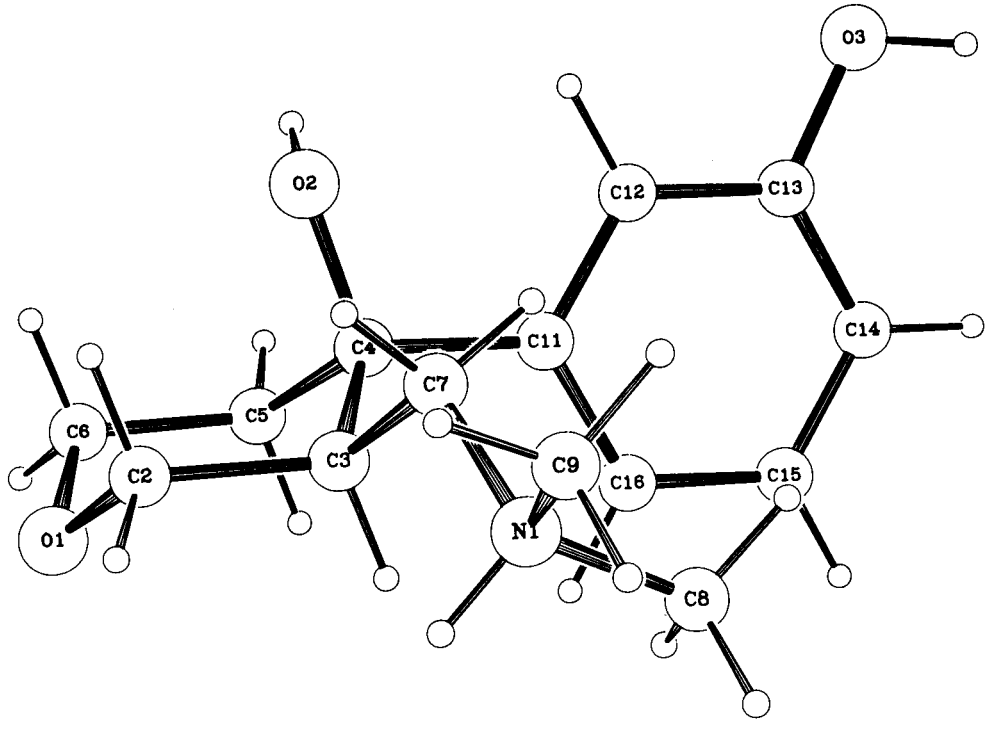


Figure 1. Conformation and absolute configuration of **14**.

Crystal Data and Structure Determination.

Compound **14**, $C_{14}H_{21}NO_3$·HCl, M = 287.79, crystal selected from a sample recrystallized from ethanol, of approximate dimensions 0.20 x 0.25 x 0.6 mm, space group $P2_12_12_1$, cell dimensions a = 8.990 (1), b = 10.848 (1), c = 15.622 (2) Å, Z = 4, d_{calcd} = 1.255 g cm^{-3}. Intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, 0-2-0 scans) and were corrected for absorption (μ = 22.7 cm^{-1}). Of the 1202 independent reflections for $0 < 57°$, 1176 were considered to be observed [$I > 2.5\ \sigma(I)$].

The structure was solved by a multiple solution procedure [15] and was refined by full-matrix least squares. Four reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The positions of the hydrogen atoms were calculated based on the local molecular geometry. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.026 and wR = 0.033 for the remaining 1172 observed reflections. The final difference map has no peaks greater than ± 0.2 e Å^{-3}.

The absolute configuration is based on the anomalous scattering of the chlorine atom and was established by refining both enantiomers. The final weighted R values are 0.033 for the configuration shown in the Figure and 0.059 for its antipode. Thus, by Hamilton's test [16], the configuration shown corresponds to the absolute configuration.

Table II

Final Atomic Parameters for **14** with Standard Deviations in Parentheses

Atom	x	y	z	Beqv
Cl	0.64765(7)	0.55757(8)	0.77696(4)	4.56(1)
O(1)	0.2793(2)	0.3473(2)	0.1708(1)	4.52(4)
O(2)	0.5186(2)	0.5175(2)	0.2947(1)	3.29(3)
O(3)	0.7145(2)	0.5141(2)	0.5857(1)	5.53(4)
N(1)	0.0799(2)	0.5798(2)	0.3886(1)	3.86(4)
C(2)	0.2454(3)	0.4595(3)	0.2133(2)	3.85(5)
C(3)	0.2718(3)	0.4525(2)	0.3102(2)	3.14(4)
C(4)	0.4349(2)	0.4160(2)	0.3270(2)	2.96(4)
C(5)	0.4695(3)	0.2992(2)	0.2756(2)	3.57(5)
C(6)	0.4325(3)	0.3152(3)	0.1822(2)	4.11(5)
C(7)	0.2339(3)	0.5769(3)	0.3510(2)	3.60(5)
C(8)	0.0718(4)	0.5152(3)	0.4720(2)	5.45(7)
C(9)	0.0242(4)	0.7092(3)	0.3963(3)	6.56(8)
C(11)	0.4655(3)	0.3959(2)	0.4217(2)	3.02(4)
C(12)	0.5725(3)	0.4642(3)	0.4639(2)	3.36(5)
C(13)	0.6026(3)	0.4449(3)	0.5500(2)	3.86(5)
C(14)	0.5248(4)	0.3566(3)	0.5951(2)	4.25(6)
C(15)	0.4163(4)	0.2885(3)	0.5539(2)	4.31(6)
C(16)	0.3879(3)	0.3069(2)	0.4679(2)	4.04(5)

The final atomic coordinates and equivalent isotropic temperature factors for the nonhydrogen atoms are given in Table II. Bond lengths and bond angles are presented in Tables III and IV.

Compounds were screened for analgesic activity in mice using the phenylquinone writhing assay [10,11]. The results are presented in Table I and comparative data for codeine is also given. In general, the 4-aryltetrahydropyranols represent a new class of analgesics having agonist activity in the range of codeine. The analgesic activity resided mostly in the *trans* [6] diastereomers (compounds **3** and **7**) while the *cis* [6] racemate **2** was almost inactive.

Table III
Bond Lengths (Å) in **14** with Standard Deviations in Parentheses

O(1)- C(2)	1.419(3)	C(4)- C(5)	1.531(3)
O(1)- C(6)	1.431(4)	C(4)-C(11)	1.520(3)
O(2)- C(4)	1.426(3)	C(5)- C(6)	1.507(4)
O(3)-C(13)	1.374(4)	C(11)-C(12)	1.382(4)
N(1)- C(7)	1.504(3)	C(11)-C(16)	1.392(4)
N(1)- C(8)	1.480(4)	C(12)-C(13)	1.387(4)
N(1)- C(9)	1.495(4)	C(13)-C(14)	1.380(4)
C(2)- C(3)	1.535(4)	C(14)-C(15)	1.382(4)
C(3)- C(4)	1.541(3)	C(15)-C(16)	1.382(4)
C(3)- C(7)	1.531(4)		

Table IV
Bond Angles (°) in **14** with Standard Deviations in Parentheses

C(2)- O(1)- C(6)	110.9(2)
C(7)- N(1)- C(8)	112.3(2)
C(7)- N(1)- C(9)	111.0(2)
C(8)- N(1)- C(9)	110.9(2)
O(1)- C(2)- C(3)	112.6(2)
C(2)- C(3)- C(4)	109.1(2)
C(2)- C(3)- C(7)	109.4(2)
C(4)- C(3)- C(7)	111.6(2)
O(2)- C(4)- C(3)	104.1(2)
O(2)- C(4)- C(5)	110.3(2)
O(2)- C(4)-C(11)	111.1(2)
C(3)- C(4)- C(5)	108.5(2)
C(3)- C(4)-C(11)	112.0(2)
C(5)- C(4)-C(11)	110.8(2)
C(4)- C(5)- C(6)	111.6(2)
O(1)- C(6)- C(5)	111.1(2)
N(1)- C(7)- C(3)	112.7(2)
C(4)-C(11)-C(12)	120.9(2)
C(4)-C(11)-C(16)	120.9(2)
C(12)-C(11)-C(16)	118.2(2)
C(11)-C(12)-C(13)	121.2(2)
O(3)-C(13)-C(12)	117.1(2)
O(3)-C(13)-C(14)	122.8(2)
C(12)-C(13)-C(14)	120.1(3)
C(13)-C(14)-C(15)	119.4(3)
C(14)-C(15)-C(16)	120.3(3)
C(11)-C(16)-C(15)	120.8(3)

Because of its favorable analgesic activity, the racemate **3** was resolved into its enantiomers. In contrast to classical narcotic analgesics, the analgesic potency of the enantiomers (**13** and **14**) was not significantly different. While different distribution and metabolism of the enantiomers cannot be excluded as a possibility, it seems unlikely that this can account for the nearly identical potency. It is therefore tempting to ascribe the less enantioselective action of these compounds to their greater degree of conformational mobility and to the fact that the various functional groups may not be held in their optimal orientation for receptor interaction as in the opiates.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Carey Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR-9 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60 or HA-100 spectrometer and recorded δ values with deuteriochloroform as the solvent and tetramethylsilane as an internal reference. The proton signals are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (70 eV, direct inlet system) were determined with a CEC type 21-110 spectrometer. Crystallographic data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, 0-2-0 scans, pulse-height discrimination).

3[(Dimethylamino)methyl]tetrahydro-4*H*-pyran-4-one (**5**).

A mixture of 2.0 g (0.02 mole) of tetrahydro-4H-pyran-4-one (**4**), 0.7 g (0.023 mole) of paraformaldehyde, 1.7 g (0.02 mole) of dimethylamine hydrochloride, and three drops of concentrated hydrochloric acid in 10 ml of dimethylformamide was heated at 70° for 2 hours. Evaporation of the dimethylformamide under reduced pressure and recrystallization of the residue from ethanol-ethyl acetate gave 3.5 g (92%) of **5**·HCl as a pale yellow solid. The above hydrochloride was partitioned between methylene chloride and dilute ammonium hydroxide. The methylene chloride solution was washed with brine, dried (magnesium sulfate) and concentrated under reduced pressure to give 2.2 g (80%) of **5** as a colorless oil, bp 60° (0.08 mm).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.94; H, 9.61; N, 9.14.

(±)-*trans*-Tetrahydro-4-(3-methoxyphenyl)-3-[(dimethylamino)-methyl]-2*H*-pyran-4-ol (**7**).

To a mixture of 0.7 g (0.018 g-atom) of magnesium turnings in 14 ml of anhydrous ether containing 0.2 g of iodomethane was added dropwise 5.6 g (0.03 mole) of *m*-bromoanisole under nitrogen at a rate sufficient to cause the mixture to reflux. After the addition was completed, the mixture was heated at reflux for one hour and then cooled to room temperature. A solution of 2.0 g (0.013 mole) of **5** in 25 ml of ether (anhydrous) was added dropwise to the above mixture and stirred at 25° overnight. The reaction mixture was poured onto a mixture of ice-hydrochloric acid and the aqueous mixture was washed with ether (3 x 30 ml). The

ether solutions were extracted with 2*N* hydrochloric acid (2 x 30 ml), then the combined acid solutions were basified with concentrated ammonium hydroxide. The aqueous suspension was extracted with ether (3 x 30 ml). The combined ether solutions were washed with brine, dried (magnesium sulfate) and evaporated to give 3.2 g of mixture of diastereomeric alcohols **6** in a ratio of 8:1 [7], which was chromatographed on silica gel (300 g). Elution with methanol-methylene chloride (10:2, v/v) afforded, after removal of the solvent and distillation of the residue, 2.3 g (68%) of **7** as a pale yellow oil, bp 155-160° (0.08 mm); ir (chloroform): 3300-3110 (bonded OH), 2790, 1602, 1584, 1255 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.06 (m, 4H, ArH), 4.00 (m, 4H, CH_2OCH_2), 3.82 (s, 3H, OCH_3), 2.09 [s, 6H, $N(CH_3)_2$]; ms: (70 eV) m/e 265 (M^+).

Anal. Calcd. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.67; H, 8.89; N, 5.51.

The base **7** on treatment with hydrogen chloride (anhydrous) in ethyl acetate, gave after recrystallization from ethanol-ethyl acetate, 2.4 g (92%) of **7**·HCl as a white solid, mp 196-197°.

Anal. Calcd. for $C_{15}H_{23}NO_3$·HCl: C, 59.69; H, 8.02; N, 4.64. Found: C, 59.32; H, 8.01; N, 4.80.

(±)-*trans*-Tetrahydro-4-(3-methoxyphenyl)-3-[(dimethylamino)-methyl]-2*H*-pyran-4-ol Acetate **8** Hydrochloride.

A mixture of 1.0 g (0.0033 mole) of **7**·HCl and acetic anhydride (12 ml) was heated at reflux for 2 hours and the excess of reagent was removed under reduced pressure. The crude product was recrystallized from ethanol-methanol to give 0.56 g (50%) of **8**·HCl as a white solid, mp 201-203°.

Anal. Calcd. for $C_{17}H_{25}NO_4$·HCl: C, 59.38; H, 7.62; N, 4.07. Found: C, 59.21; H, 7.81; N, 4.26.

(±)-*cis*- and *trans*-Tetrahydro-3-[(dimethylamino)methyl]-4-[3-(phenylmethoxy)phenyl]-2*H*-pyran-4-ol (**10** and **11**).

A few drops of iodoethane and *m*-bromophenol benzyl ether were added under nitrogen to a mixture of 0.81 g (0.02 g-atom) of magnesium turnings and 20 ml of dry tetrahydrofuran. The mixture was warmed to start the reaction, then the remaining *m*-bromophenyl benzyl ether (a total of 9.0 g, 0.034 mole) in 30 ml of dry tetrahydrofuran was added at such a rate to cause the mixture to reflux. After the addition, the mixture was heated at reflux for one hour. The flask was cooled in an ice-bath and 4.3 g (0.027 mole) of **5** in 30 ml of dry tetrahydrofuran was added dropwise and stirred at room temperature overnight. It was then cooled in an ice-bath and decomposed with a solution of 4.6 g ammonium chloride in 15 ml of water. The organic layer was separated and the aqueous solution was extracted with methylene chloride (3 x 75 ml). The combined organic solutions were dried (magnesium sulfate) and removal of the solvent gave 9.2 g of a mixture of diastereomeric alcohols **9** in a ration of 6:1 [7]. The mixture in ethyl acetate (100 ml) was treated with hydrogen chloride (anhydrous) to give the crude **11**·HCl, which after recrystallization from ethanol afforded 4.9 g (47%) of **11**·HCl as a slight yellow solid, mp 246-248°.

Anal. Calcd. for $C_{21}H_{27}NO_3$·HCl: C, 66.74; H, 7.47; N, 3.71. Found: C, 66.62; H, 7.48; N, 3.92.

The above salt was converted to the free base **11** using diluted ammonium hydroxide as base and methylene chloride for extraction. The methylene chloride solutions were washed with water, dried (magnesium sulfate) and evaporated to give after recrystallization from methanol 3.78 g (86%) of **11**, mp 61-62°; ir (chloroform): 3260-3120 (bonded OH), 2790, 1600, 1583, 1498 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.1 (m, 9H, ArH), 6.63 (broad, 1H, OH), 5.04 (s, 2H, CH_2Ar), 4.00 (m, 4H, CH_2OCH_2), 2.05 [s, 6H, $N(CH_3)_2$]; ms: (70 eV): m/e 341 (M^+).

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.92; H, 7.81; N, 3.93.

The crystallization mother liquors of **11**·HCl were combined and the solvent was removed under reduced pressure. The residue, in 75 ml of water, was made basic with concentrated ammonium hydroxide and the aqueous suspension was extracted with methylene chloride (3 x 75 ml). The combined methylene chloride solutions were washed with water (30 ml) and dried (magnesium sulfate). Removal of the solvent and recrystallization of the residue from ethyl acetate--ether gave 0.9 g (10%) of **10** as a white solid, mp 133-134°; ir (chloroform): 3600 (free OH), 2785, 1265, 1240, 703 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.2 (m, 9H, ArH), 5.05 (s, 2H, CH_2Ar), 2.85 (m, 4H, CH_2OCH_2), 2.00 [s, 6H, $N(CH_3)_2$]; ms (70 eV): m/e 341 (M^+).

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.03; H, 7.77; N, 4.12.

(±)-*trans*-Tetrahydro-4-(3-hydroxyphenyl)-3-[(dimethylamino)-methyl]-2*H*-pyran-4-ol (**3**) Hydrochloride.

A mixture of 2.00 g (0.053 mole) of **11**·HCl in ethanol-methanol (50 ml:25 ml) and 2 ml of concentrated hydrochloric acid was hydrogenated over 0.65 g of palladium on carbon (10%) at room temperature and at 50 psi for 1.5 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give the crude **3**·HCl, which afforded after recrystallization from methanol 1.3 g (87%) of pure **3**·HCl as a white solid, mp 264-266°.

Anal. Calcd. for $C_{14}H_{21}NO_3$·HCl: C, 58.42; H, 7.70; N, 4.86. Found: C, 58.21; H, 7.80; N, 4.96.

A sample of the above salt was converted to the base **3** using ammonium hydroxide as base and methylene chloride for extraction, mp 173-174°; ir (chloroform): 3245, 2660, 2560, 1612, 1585 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.65 (broad, 1H, OH), 7.10 (m, 4H, ArH), 3.80 (m, 4H, CH_2OCH_2), 2.04 [s, 6H, $N(CH_3)_2$]; ms: (70 eV) m/e 251 (M^+).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.51; H, 8.46; N, 5.54.

(±)-*cis*-Tetrahydro-4-(3-hydroxyphenyl)-3-[(dimethylamino)-methyl]-2*H*-pyran-4-ol (**2**) Hydrochloride.

This compound was prepared following the procedure given for **3**, starting from 1.6 g (0.0047 mole) of **10**·HCl, 10 ml of methanol, 2 ml of concentrated hydrochloride acid and 0.6 g of 10% of palladium on carbon. The isolated crude **2** on treatment with hydrogen chloride (anhydrous) in ethyl acetate afforded after recrystallization from ethanol-ether, 1.0 g (83%) of **2**·HCl as a white solid, mp 193-194°.

Anal. Calcd. for $C_{14}H_{21}NO_3$·HCl: C, 58.42; H, 7.70; N, 4.86. Found: C, 58.74; H, 7.87; N, 4.87.

A sample of the above salt was converted to the free base **2** using ammonium hydroxide as base and methylene chloride for extraction, mp 165-166°; ir (potassium bromide): 3350, 2660, 2580, 1587, 1487, 1250; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.04 (broad, 1H, OH), 6.76 (m, 4H, ArH), 4.80 (broad, 1H, OH), 3.75 (m, 4H, CH_2OCH_2), 2.04 [s, 6H, $N(CH_3)_2$]; ms: (70 eV) 251 (M^+).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.69; H, 8.26; N, 5.59.

(±)-*trans*-Tetrahydro-4-(3-acetyloxyphenyl)-3-[(dimethylamino)-methyl]-2*H*-pyran-4-ol Acetate (**12**) Hydrochloride.

A mixture of 0.6 g (0.0021 mole) of **3**·HCl and acetic anhydride (8 ml) was heated at 120° for 2 hours and then concentrated at reduced pressure. The residue was partitioned between dilute ammonium hydroxide and methylene chloride. The methylene chloride solution was washed with water, dried (magnesium sulfate) and removal of the solvent *in vacuo* gave the crude base **12**. The base, on treatment with hydrogen chloride (anhydrous) in ethyl acetate afforded after recrystallization from ethanol, 0.5 g (73%) of **12**·HCl as a white solid, mp 224-225°.

Anal. Calcd. for $C_{18}H_{25}NO_5$·HCl: C, 58.13; H, 7.04; N, 3.79. Found: C, 57.94; H, 7.06; N, 3.72.

Resolution of (±)-*trans*-Tetrahydro-4-(3-hydroxyphenyl)-3-[(dimethylamino)methyl]-2*H*-pyran-4-ol (**3**).

A mixture of 6.2 g (0.025 mole) of **3** and 3.75 g (0.025 mole) of *d*-tartaric acid in 100 ml of methanol was heated at reflux until solution occurred. The salt, which crystallized on standing at room temperature for 2.5 hours, was collected and washed with a mixture of acetonitrile-ether (1:1, v/v) to afford 2.6 g (53%) of **13**·$C_4H_6O_6$ as a white solid, mp 160-162°, $[\alpha]_D^{25}$ + 3.39° (*c* 1.15, methanol).

Anal. Calcd. for $C_{14}H_{21}NO_3$·$C_4H_6O_6$: C, 53.86; H, 6.78; N, 3.49. Found: C, 53.73; H, 6.68; N, 3.63.

The free base **13** was prepared by adding dilute ammonium hydroxide to a sample of the above salt and extracting the aqueous suspension with ethyl acetate. The ethyl acetate extracts were dried (magnesium sulfate) and the solvent was removed *in vacuo* to give the crude base (-)-**13**, which after recrystallization from ethyl acetate afforded 1.4 g (90%) of (-)-**13**, mp 190-192°, $[\alpha]_D^{25}$ - 44.09° (*c* 1.01, methanol); ir (chloroform): 3450, 2500-2340, 788, 698 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.58 (broad, ^1H, OH), 7.00 (m, 4H, ArH), 3.85 (m, 4H, CH_2OCH_2), 2.10 [s, 6H, $N(CH_3)_2$]; ms: (70 eV) m/e 251 (M^+).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.63; H, 8.28; N, 5.62.

The above base on treatment with hydrogen chloride (anhydrous) in ethyl acetate gave after recrystallization from ethanol 1.25 g (75%) of (-)-**13**·HCl as a white solid, mp 253-254°, $[\alpha]_D^{25}$ -20.4° (*c* 1.00, methanol).

Anal. Calcd. for $C_{14}H_{21}NO_3$·HCl: C, 58.42; H, 7.70; N, 4.86. Found: C, 58.37; H, 7.74; N, 4.89.

The partially resolved (+)-**14** was recovered from the resolution mother liquors by evaporation of the solvent, then addition of dilute ammonium hydroxide to the residue and extracting the aqueous suspension with ethyl acetate. The isolated 1.9 g (0.008 mole) of crude (+)-**14** was combined with 1.2 g (0.0079 mole) of *l*-tartaric acid in 50 ml of hot methanol and allowed to crystallize at room temperature for 17 hours. The crystals were separated by filtration and washed with a mixture of acetonitrile-ether (1:1, v/v) to afford 2.3 g (46%) of (+)-**14**·$C_4H_4O_6$, mp 166-168°, $[\alpha]_D^{25}$ + 1.63° (*c* 1.04, methanol).

Anal. Calcd. for $C_{14}H_{21}NO_3$·$C_4H_6O_6$: C, 53.86; H, 6.78; N, 3.49. Found: C, 53.71; H, 6.78; N, 3.63.

The free base **14** was prepared by adding dilute ammonium hydroxide to a portion of the above salt and extracting the aqueous suspension with ethyl acetate. The combined ethyl acetate extracts were dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the crude **14**, which after recrystallization from ethyl acetate afforded pure **14**, mp 191-193°, $[\alpha]_D^{25}$ + 48.08° (*c* 1.07, methanol); ir (chloroform): 3440, 2500-2340, 788, 698 cm^{-1}, ^1H nmr (deuteriochloroform): δ 8.65 (broad, 1H, OH), 7.00 (m, 4H, ArH), 3.85 (m, 4H, CH_2OCH_2), 2.06 [s, 6H, $N(CH_3)_2$]; ms: (70 eV) m/e 251 (M^+).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.66; H, 8.22; N, 5.53.

A sample of the above base **14**, on treatment with hydrogen chloride (anhydrous) in ethyl acetate afforded after recrystallization from ethanol (+)-**14**·HCl [14], as a white solid, mp 253-254°, $[\alpha]_D^{25}$ + 23.69° (*c* 1.03, methanol).

Anal. Calcd. for $C_{14}H_{21}NO_3$·HCl: C, 58.42; H, 7.70; N, 4.86. Found: C, 58.45; H, 7.73; N, 4.86.

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