Products from Furans. XXI [1a]. Synthesis of Novel Oxygen Containing Heterocyclic Isosteres of Tyrosine Derivatives

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Novel oxygen containing heterocyclic isosteres of tyrosine and tyramine derivatives were synthesized. All new compounds contain the pyran ring as a consequence of their common route of preparation. Furthermore several methyl, ethyl, diethyl and isopropyl derivatives of the prepared amines were synthesized.

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Introduction.

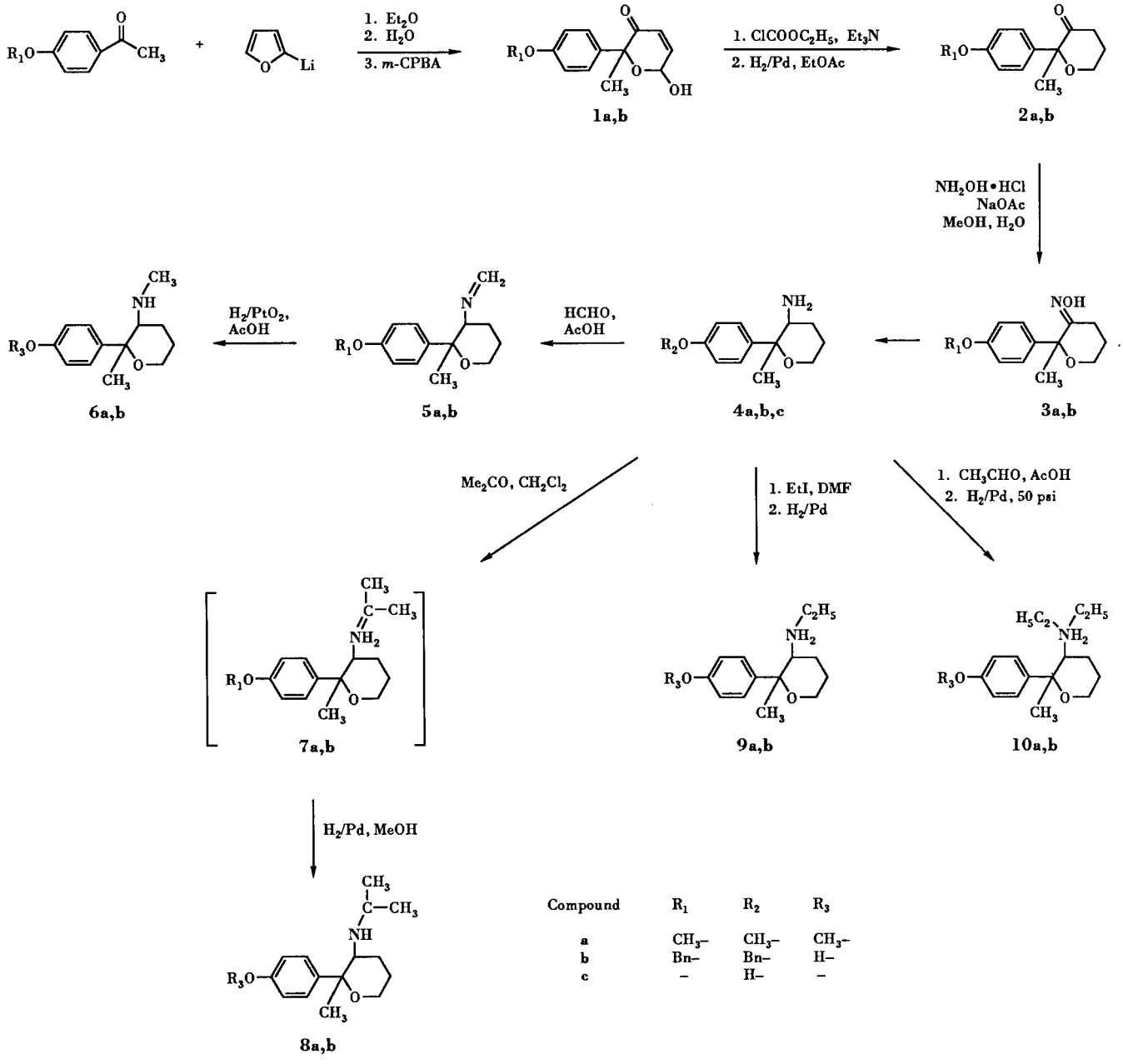
Aromatic amino acids and amines represented by sympathomimetic amines have received considerable attention from synthetic organic chemists due to their important role in biological systems [2]. They have been found to be of importance in such fields as the treatment of Parkinson's disease [3], the growth inhibition of certain tumors [4], the control of blood pressure [5], the treatment of several mental disorders [6] *etc.* Furthermore these amines have been subjected to extensive structure-activity studies and virtually almost every part of these molecules have been modified in an attempt to rationalize their structure-activity relationship [7,8]. The fact that all naturally occuring sympathomimetic amines are flexible molecules and can exist in several conformations (since their energy differences are not high enough), has prompted earlier researchers to prepare cyclic compounds in which certain portions of sympathomimetic amines are inserted into rigid or semirigid structures [8,9] and study their interactions with dopamine receptors. Thus there is a considerable recent interest for the synthesis of cyclic derivatives of the sympathomimetic amines and especially of their oxygen containing isosteres [10].

In continuation of our research work concerning the synthesis of heterocyclic compounds with potential biological activity [11,12], we have prepared several novel oxygen containing heterocyclic isosteres of tyrosine and tyramine which are being considered as the precursors of the biosynthesis of catecholamines (the most important sympathomimetic amines). These new compounds have semirigid structures and were designed to fulfill earlier considerations on the minimal structural requirements in order to attain sympathomimetic activity [13]. Furthermore since they have been substituted on α-carbon, they are expected to act as false neurotransmitters in the same manner as α-methyltyrosine and α-methyldopa [14], by blocking the biosynthesis of norepinephrine and replacing it in the adrenergic terminals [15]. On the other hand since it is well established that alkyl substitution on the amino group has enormous effect on their receptor and metabolic activity [15] which depends from the size of the alkyl group, we have prepared the methyl, ethyl, diethyl and isopropyl derivatives of the new amines aiming to investigate their differences in activity.

Results and Discussion.

Earlier researchers have already defined that a minimal structural requirement, in order that sympathomimetic amines attain high affinity with the dopamine receptor, is to have a distance of 5-6 Å on a vector directed from the center of the aromatic ring to the basic N-atom [13]. Moreover, our previous findings on sympathomimetic amines which contain the structural framework of the pyran ring have indicated that only a diaxial orientation of both phenyl and amino groups is structurally suitable to insure a distance Ar–N within the required range [12]. Thus our synthetic pathway begins from appropriately substituted perhydropyran-3-one derivatives **2a** and **2b** which have the aromatic group on an axial position [16] and were prepared by known procedures [17]. These compounds were transformed to their corresponding axial perhydropyran-3-yl primary amines **4a** and **4c** with high stereoselectivity by oximation and subsequent catalytic hydrogenation. Since this treatment with hydrogen causes hydrogenolysis of the benzyl protective group and alternative methods of reduction with metal hydrides lead to products with the amino group at equatorial position, we have utilized diisobutylaluminum hydride (DIBALH) as the reductive agent, the bulky nature of which in connection with the stereochemical hinderence on C-2 insured the axial orientation of the amino group of the product **4b**. The exact configuration of the prepared amines was established by ^{1}H nmr studies of their derivatives. More specifically for spectra recorded on the same instrument, temperature, concentration and solvent, the chemical shifts of protons on C-4 and of the axial proton on C-5 are affected by the conversion of the diamagnetically anisotropic C=N bond of imine **5** to the C-N bond of amine **6** (Table I). This effect and the fact that no such influence was observed for the angular methyl group unequivocally confirm the stereochemistry

Scheme I



Compound	R_1	R_2	R_3
a	CH_3–	CH_3–	CH_3–
b	Bn–	Bn–	H–
c	–	H–	–

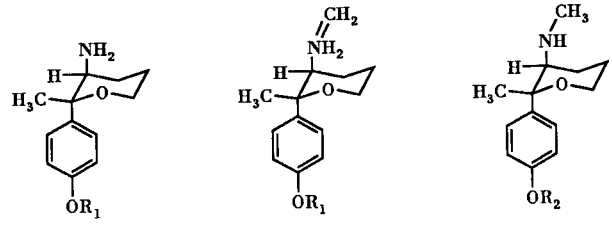
Table I

^{1}H NMR Chemical Shifts of Compounds 5,6

(300 MHz, deuteriochloroform)

Compound	H-C (4)	H_{eq}-C (5)	H_{ax}-C (5)	CH_3
5a	2.35	1.96	1.61	1.57
6a	1.93	1.93	1.93	1.54
5b	2.31	2.01	1.63	1.51
6b	1.99	1.99	1.99	1.49

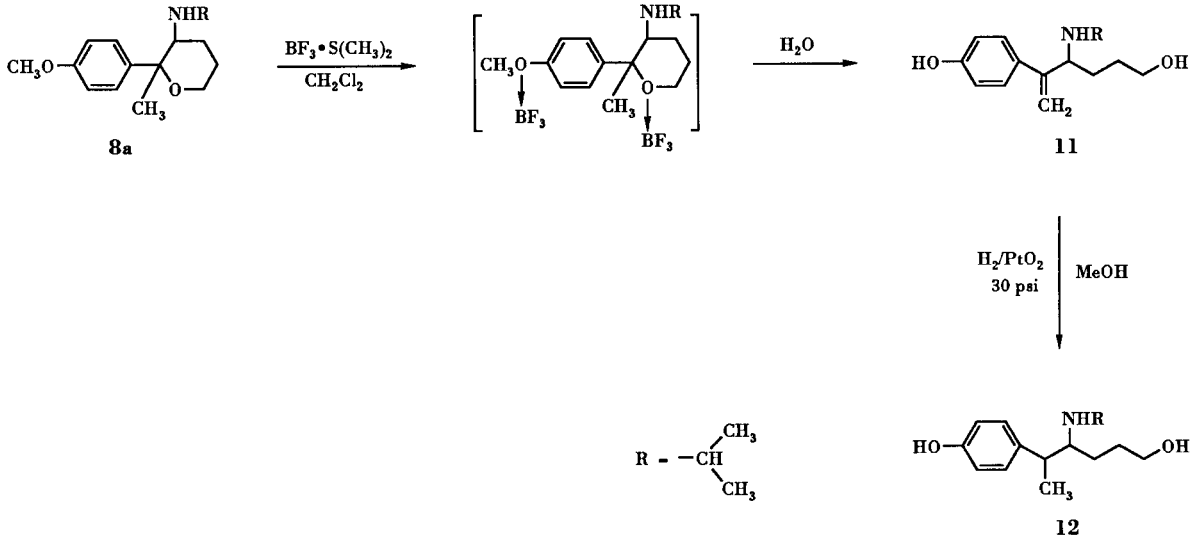
Scheme II



4 5 6

Compound	R_1	R_2
a	CH_3–	CH_3–
b	Bn–	H–

Scheme III



Scheme IV

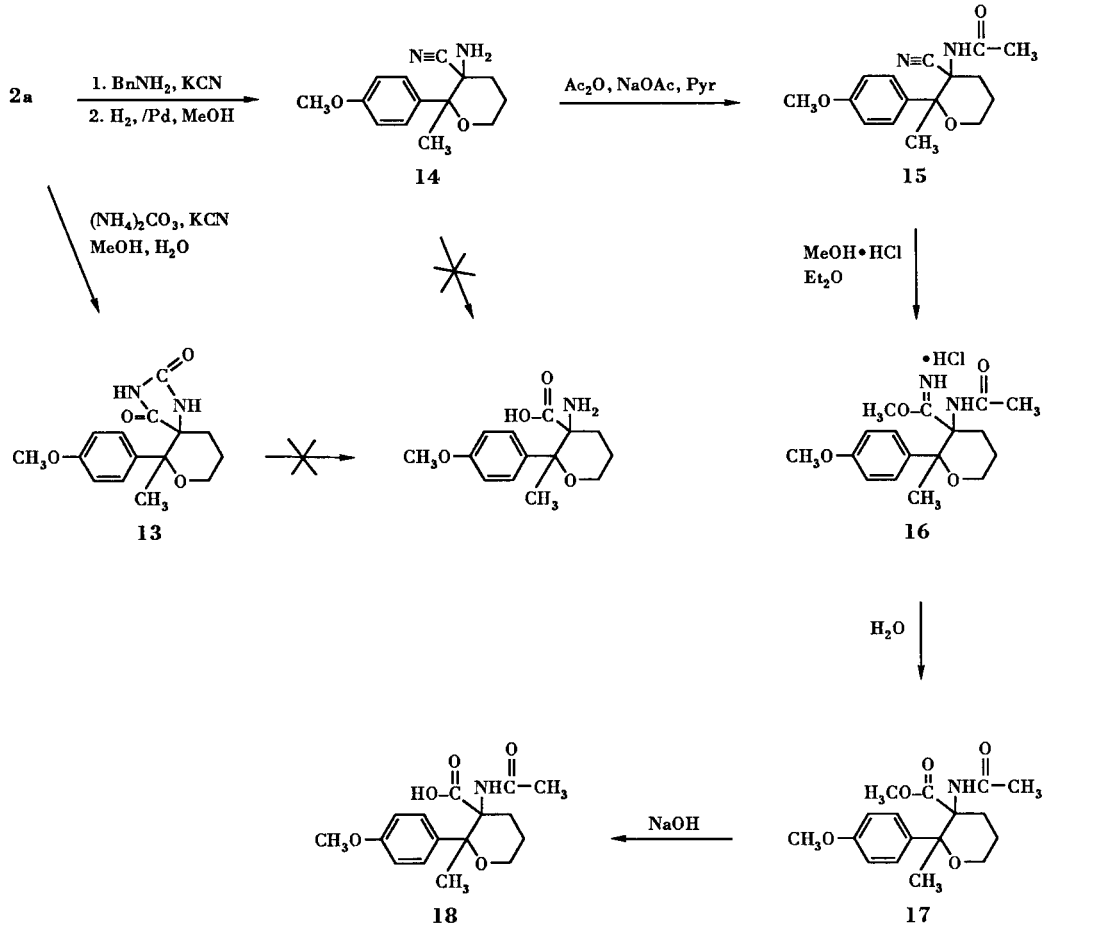


Table II

^{13}C NMR Chemical Shifts of Compound **11** (75 MHz, deuteriomethanol)

Straight Chain Carbons						Aromatic Carbons				Other Carbons		
C-1	C-2	C-3	C-4	C-5	C-6	C'-2 C'-6	C'-3 C'-5	C'-1	C'-4	CH_3	CH_3	CH
62.64	34.04	30.71	60.16	132.73	112.70	128.58	115.80	150.45	157.39	21.27	23.39	45.83

of compound **4** (Scheme II). Furthermore for compound **4** the distance between the center of the aromatic ring and the N-atom was determined by molecular mechanics calculations to be 5.180 Å, thus confirming our working hypothesis.

For the preparation of a series of *N*-substituted derivatives of compounds **4** the sequence outlined in Scheme I was employed and 2-*p*-benzyloxy(or 2-*p*-methoxy)phenyl derivatives of (2-methylperhydropyran-3-yl)amines **4a** and **4b** have been used as starting materials. These were converted to Schiff bases **5a**, **5b**, **7a** and **7b** and subsequently hydrogenated to their corresponding *N*-methyl, **6a** and **6b**, or *N*-isopropyl derivatives **8a** and **8b**. On the other hand the *N*-ethyl or *N*-diethyl derivatives were prepared in high yields from compounds **4a** and **4b** by alkylation with ethyl iodide or reductive ethylation (reaction with acetaldehyde and subsequent hydrogenation) respectively. Treatment of compound **8a** with boron trifluoride-dimethyl sulfide complex in methylene chloride and subsequent hydrolysis caused the deprotection of the methoxyphenyl group and the simultanous opening of the pyran ring, yielding the compound **11**. The formation of this product can be rationalized on the basis of the high electronegativity of the oxygen atom, which forms a complex with boron trifluoride (Scheme III). Hydrolysis of this intermediate complex from the less hindered, more electrophilic site caused the pyran ring opening. It is further noticeable that at these conditions (acidic) the tertiary benzylic hydroxy group was also removed. The structure of compound **11** was confirmed by spectral data (see experimental) and ^{13}C nmr spectra (Table II). Furthermore catalytic hydrogenation of alkene **11** afforded an α,β-disubstituted *N*-isopropyl derivative of tyramine (**12**).

The synthesis of an α-amino acid on a pyran ring (especially the oxygen containing isoster of tyramine) has been a synthetic challange in our laboratory for sometime. All previous attempts to hydrolize its corresponding hydantoin **13** (Bucherer synthesis) have failed, because under the required drastic acidic or basic conditions [18] the pyran ring is not stable. Moreover, we were not able to obtain the α-amino acid even with a two phase hydrolysis (acidic or basic) of the hydantoin, using various phase transfer catalysts. On the other hand hydrolysis of the cyano group of α-aminonitriles **14** (Strecker synthesis) can not be achieved either with basic conditions since the α-aminonitriles undergo a retro Strecker reaction, or with strongly acidic conditions [19] because the pyran ring is not stable enough. Furthermore mild acidic hydrolysis of the α-aminonitriles is not possible, presumably because the amino group is first protonated thus preventing the protonation (under these mild conditions) of the cyano group. The latter is a prerequisite for its hydrolysis. In order to prevent this protonation of the amino group we have converted it to amide **15** and by reaction with anhydrous methanolic hydrogen chloride obtained the intermediate methyl imidate hydrochloride **16**, which was easily hydrolized in water yielding the corresponding methyl ester **17**. The latter compound by saponification afforded the target tyrosine derivative **18**.

EXPERIMENTAL

General Procedures.

All melting points are in degrees Centigrade and were determined in open capillary tubes with a Büchi melting point apparatus and are uncorrected. Analytical thin-layer chromatography (tlc) was performed with 0.2 mm silica gel coated plastic sheets with fluorescent indicator UV_{254} (Merck). All column chromatography was done by the flash chromatography technique and the column packing was Merck 32-63 μm. The nmr spectra were recorded on General Electric QE 300 (300 MHz) or on Varian EM 360 (60 MHz) spectrometers in the indicated solvents. Chemical shifts are reported in part per million from tetramethylsilane as internal standard (δ scale); multiplicities indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) or br (broadened). Infrared (ir) spectra were obtained on a Perkin Elmer Model 283 B (4,000-200 cm^{-1}) spectrophotometer, from samples prepared in accordance with the potassium bromide disk technique, unless otherwise stated. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67-100%), m (medium, 34-66%) and w (weak, 0-33%). Low resolution mass spectra were obtained on a Varian Associates MAT CH-5 mass spectrometer (ionization by electron impact at 70 eV). Data are presented in the form m/z (intensity relative to base peak = 100) only for selected compounds. High-resolution mass spectra were obtained on a Varian 731 high-resolution mass spectrometer. Microanalytical data were provided by the Microanalytical Service Laboratories of the University of Illinois, USA and NRC "Democritos", Greece. Acetic anhydride and pyridine were distilled immediately prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Methylene chloride was dried over 4-Å molecular sieves. Other reagents and catalysts were purchased as analytical reagent grade. Commercial sources included: Aldrich Chemical Co., Mallinckrodt Inc., Alfa (Ventron), Merck and BDH. All solvents were used as received.

Molecular Mechanics.

Strain Energies of the prepared amines were determined by minimizing the energy of the molecules using Maximin, a Molecular Mechanics program contained in the SYBYL package. The program was run on a VAX 750 computer. In each case 10 iterations were made and up to 2 flexible bonds were specified for each molecule. When the conformation corresponding to minimum Strain Energy was obtained, the distance between the center of the aromatic ring and the N-atom was calculated using the same program.

Starting Materials.

2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-one (**2a**) [17], 2-(*p*-benzyloxyphenyl)-2-methylperhydropyran-3-one (**2b**) [12], 6-(*p*-methoxyphenyl)-6-methyl-7-oxa-1,3-diazaspiro[4,5]decane-2,4-dione (**13**) [17] and [3-amino-2-(*p*-methoxyphenyl)-2-methylperhydropyran-3-yl]carbonitrile hydrochloride (**14**) [20] were prepared according to the literature procedures and have been characterized by melting point, ir and ^{1}H nmr data.

2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-one Oxime (**3a**).

To a solution of compound **2a** (4 g, 18 mmoles) in 50 ml of methanol, heated at 55°, a solution of hydroxylamine hydrochloride (2.8 g, 40 mmoles) and sodium acetate trihydrate (5.16 g, 38 mmoles) in 50 ml of water was added under stirring in one pot. The reaction was run at that temperature for 1 hour and tlc (3:2 ether/hexane, Rf 0.67) showed that the reaction was completed. The mixture was cooled at 0° yielding an oily precipitate, which was separated from the liquid by decantation and treated with petroleum ether to give 3.98 g (93%) of the oxime as white crystals, melting at 115-116.5°; ir: ν max 3280 s (broad) [OH], 1675 w [C=N], 945 s [ν N-O], 1250 s, 1075 s, 1030 s [C-O], 1020 w, 1610 m, 1510 s, 830 s [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 9.41 [br, disappeared on addition of deuterium oxide, 1H, OH], 7.26 [d, J = 8.7, 2H, H-Ar], 6.91 [d, J = 8.7, 2H, H-Ar], 3.82 [s, 3H, CH_3O], 3.77 [m, 2H, H-C(6)], 1.89 [m, 3H, H-C(4) and H_{eq}-C(5)], 1.68 [m, 1H, H_{ax}-C(5)], 1.58 [s, 3H, angular CH_3]; ms: m/z (relative intensity) 236 [M^+ + 1, 1], 235 [M^+, 6], 220 [73], 218 [56], 151 [36], 135 [70], 92 [15], 91 [12], 77 [30], 43 [100].

Anal. Calcd. for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.10; H, 7.32; N, 5.98.

2-(*p*-Benzyloxyphenyl)-2-methylperhydropyran-3-one Oxime (**3b**).

A solution of compound **2b** (0.4 g, 1.35 mmoles) in 15 ml of methanol was treated with a solution of hydroxylamine hydrochloride (0.21 g, 3 mmoles) and sodium acetate trihydrate (0.39 g, 2.8 mmoles) in 8 ml of water as described for compound **3a** yielding 0.4 g (95%) of the title product (mp 159-160°; tlc 3:2 ether/hexane Rf 0.69); ir: ν max 3280 m (broad) [OH], 1660 w [C=N], 1240 s, 1080 s, 1010 s [C-O], 3025 w, 3010 w, 1610 m, 1505 s, 835 m, 750 m, 690 m [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 9.05 [br, disappeared on addition of deuterium oxide, 1H, OH], 7.28 [s, 5H, H-Ar], 7.12 [d, J = 9.2, 2H, H-Ar], 6.85 [d, J = 9.2, 2H, H-Ar], 4.95 [s, 2H, CH_2O], 3.66 [m, 2H, H-C(6)], 1.83 [m, 4H, H-C(4,5)], 1.55 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{19}H_{21}NO_3$ (311.37): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.22; H, 6.74; N, 4.44.

[2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-yl]amine Hydrochloride (**4a**).

A solution of compound **3a** (0.3 g, 1.3 mmoles) in 40 ml ethanolic hydrogen chloride (0.5 *N*) containing 0.08 g of platinum oxide was shaken in a Parr apparatus at 45 psi of hydrogen. After shaking for 6 hours, tlc (2:8:1 methanol/chloroform/ammonia, Rf 0.8) showed that the reaction was completed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The remaining residue was dissolved in 20 ml of water and extracted with chloroform in order to remove the organic byproducts. The *p*H of the water layer was adjusted to 10 (by addition of a solution of sodium hydroxide) and then extracted with chloroform. The organic layer was separated, dried over magnesium sulfate and evaporated to dryness. The resulted oily residue was treated with etherial hydrogen chloride yielding 0.29 g (89%) of the title product, mp 155° (turned ivory), 166.5-168° dec; ir: ν max 2980-2820 s (broad) [NH_3^+], 1567 m [δ NH], 1245 s, 1080 m, 1030 m [C-O], 1610 m, 1510 s, 820 s [aromatic]; ^{1}H nmr of the free base (deuteriochloroform): 300 MHz δ 7.31 [d, J = 8.8, 2H, H-Ar], 6.86 [d, J = 8.8, 2H, H-Ar], 3.86 [m, 2H, H-C(6)], 3.78 [s, 3H, CH_3O], 2.97 [m, 1H, H-C(3)], 2.09 [m, 1H, H_{eq}-C(4)], 1.83 [m, 3H, H_{ax}-C(4), H-C(5)], 1.56 [s, 3H, angular CH_3], 1.43 [m, disappeared on addition of deuterium oxide, 2H, NH_2]; ms of the free base: m/z (relative intensity) 223 [M^+ + 2, 1], 222 [M^+ + 1, 5], 221 [M^+, 22], 193 [37], 151 [27], 135 [100], 88 [10], 71 [42], 56 [20]; hrms: m/z 221.1417 (M^+, Calcd. for $C_{13}H_{19}NO_2$: 221.1419).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.48; H, 8.39; N, 6.55.

[2-(*p*-Benzyloxyphenyl)-2-methylperhydropyran-3-yl]amine Hydrochloride (**4b**).

To a solution of diisobutylaluminum hydride (DIBH, 3 mmoles) in dry THF (5 ml) cooled to -20°, a solution of compound **3b** (0.32 g, 1 mmole) in 15 ml of dry THF was added portionwise under nitrogen. The mixture was stirred for 4 hours, the cold bath was removed and the stirring was continued for additional 20 hours. Then the reaction mixture was quenched by cautious addition of 3 ml of a saturated solution of ammonium chloride, stirred for 15 minutes, added to ice water and extracted with ethyl acetate. The organic layer was separated, washed with brine and dried over magnesium sulfate. The solvent was evaporated yielding an oil, which was converted to its hydrochloride salt and purified by washing with anhydrous ether and acetone yielding 0.28 g (82%) of analytically pure material mp 181-182° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.71; ir (neat, of free base): ν max 3350 m (broad) [NH_2], 1245 s, 1105 m, 1005 s [C-O], 3030 w, 3010 m, 1605 s, 1500 s, 830 s, 750 s, 700 s [aromatic]; ^{1}H nmr of the free base (deuteriochloroform): 300 MHz δ 7.36 [s, 5H, H-Ar], 7.23 [d, J = 9, 2H, H-Ar], 6.88 [d, J = 9, 2H, H-Ar], 4.95 [s, 2H, CH_2O], 3.73 [m, 2H, H-C(6)], 2.93 [m, 1H, H-C(3)], 2.12 [m, 1H, H_{eq}-C(4)], 1.87 [m, 3H, H_{ax}-C(4), H-C(5)], 1.48 [s, 3H, angular CH_3], 1.39 [br, disappeared on addition of deuterium oxide, NH_2].

Anal. Calcd. for $C_{19}H_{24}NO_2Cl$ (333.85): C, 68.35; H, 7.25; N, 4.20. Found: C, 68.53; H, 7.06; N, 4.33.

[2-(*p*-Hydroxyphenyl)-2-methylperhydropyran-3-yl]amine Hydrochloride (**4c**).

Compound **3b** (0.25 g, 0.8 mmole) was hydrogenated over platinum oxide (0.05 g, 0.22 mmole) as described for compound **4a** yielding 0.17 g (86%) of amine hydrochloride, which was recrystallized from absolute methanol/ether, mp 118° (turned grey), 129-131° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.77; ir: ν max 3400 s (broad) [OH], 2980-2850 s (broad) [NH_3^+], 1250 s, 1075 m, 1040 m [C-O], 1610 m, 1510 m, 835 s [aromatic]; ^{1}H nmr

(deuteriodimethyl sulfoxide): 60 MHz δ 8.40 [br, disappeared on addition of deuterium oxide, OH, NH_2^+], 7.19 [d, J = 8.6, 2H, H-Ar], 6.72 [d, J = 8.6, 2H, H-Ar], 3.78 [m, 2H, H-C(6)], 3.34 [m, 1H, H-C(3)], 1.99 [m, 4H, H-C(4,5)], 1.59 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{12}H_{18}NO_2Cl$ (243.73): C, 59.13; H, 7.44; N, 5.75; Cl, 14.55. Found: C, 59.34; H, 7.28; N, 5.68; Cl, 14.48.

[2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-yl]methylimine (**5a**).

A solution of compound **4a** (0.4 g, 1.8 mmoles) in 35% formaldehyde (0.96 g) and glacial acetic acid (1.6 g) was heated gradually under stirring and refluxed for 6 hours. At that point tlc (1:1 methanol/ether, Rf 0.54) showed that the reaction was completed, the reaction mixture was treated with a solution of sodium hydroxide (2*N*) and extracted with benzene (3 x 50 ml). The combined extracts were dried over magnesium sulfate and evaporated under reduced pressure, yielding the title product as a white solid which was crystallized from ethyl acetate, yield 0.33 g (78%), mp 137-139°; ir: ν max 1670 m [C=N], 1240 s, 1080 m, 1030 s [C-O], 3040 w, 1610 s, 1515 s, 830 s [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.37 [d, J = 8.8, 2H, H-Ar], 6.87 [d, J = 8.8, 2H, H-Ar], 6.56 [d, J = 7.6, 1H, NCH_2], 6.38 [d, J = 7.6, 1H, NCH_2], 4.31 [tr, J = 3.5, 1H, H-C(3)], 3.97 [m, 2H, H-C(6)], 3.79 [s, 3H, CH_3O], 2.35 [m, 2H, H-C(4)], 1.96 [m, 1H, H_{eq}-C(5)], 1.61 [m, 1H, H_{ax}-C(5)], 1.57 [s, 3H, angular CH_3]; ms: m/z (relative intensity) 233 [M^+, 1], 219 [M^+-CH_2, 2], 135 [15], 121 [100], 98 [14], 91 [15], 83 [11], 77 [10], 55 [14], 43 [19].

Anal. Calcd. for $C_{14}H_{19}NO_2$ (233.30): C, 72.08; H, 8.20; N, 6.13. Found: C, 71.88; H, 8.12; N, 6.31.

[2-(*p*-Benzyloxyphenyl)-2-methylperhydropyran-3-yl]methylimine (**5b**).

Compound **4b** (1 g, 3 mmoles) was reacted with formaldehyde as described for compound **5a**, yielding 0.75 g (81%) of the title compound **5b** (mp 151-153°; tlc 1:1 chloroform/ether, Rf 0.33); ir: ν max 1665 m (C=N), 1250 s, 1095 m, 1020 s [C-O], 3035 w, 3010 s, 1610 s, 1505 s, 840 m, 745 m, 690 s [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.31 [s, 5H, H-Ar], 7.22 [d, J = 8.8, 2H, H-Ar], 6.89 [d, J = 8.8, 2H, H-Ar], 6.49 [d, J = 7.2, 1H, NCH_2], 6.34 [d, J = 7.2, NCH_2], 4.99 [s, 2H, CH_2O], 4.30 [m, 1H, H-C(3)], 3.85 [m, 2H, H-C(6)], 2.31 [m, 2H, C(4)], 2.01 [m, 1H, H_{eq}-C(5)], 1.63 [m, 1H, H_{ax}-C(5)], 1.51 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{20}H_{23}NO_2$ (309.39): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.55; H, 7.78; N, 4.61.

[2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-yl]methylamine (**6a**).

A solution of compound **5a** (0.062 g, 0.27 mmole) in 11 ml of glacial acetic acid, containing 0.03 g of platinum oxide was treated with hydrogen at atmospheric pressure until tlc (1:1 methanol/ether, Rf 0.85) indicated that the reaction was completed. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in chloroform and extracted with saturated solution of sodium carbonate, washed with brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure yielding a colorless oil which was solidified in high vacuum to give 0.054 g (86%) of the desired amine (mp 76-78°); ir: ν max 3350 m (broad) [NH], 1250 s, 1085 s, 1020 s [C-O], 3060 w, 1610 m, 1505 s, 840 s [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.46 [d, J = 8.8, 2H, H-Ar], 6.87 [d, J = 8.8, 2H, H-Ar], 3.89 [m, 2H, H-C(6)], 3.86 [s, 3H, CH_3O], 2.69 [m, 1H, H-C(3)], 2.25 [s, 3H, NCH_3], 1.93 [m, 4H, H-C(4,5)], 1.54 [s, 3H, angular CH_3], 1.26 [m, 1H, disappeared on addition of deuterium oxide, NH]; ms: m/z (relative intensity) 235 [M^+, 5], 135 [35], 85 [48], 84 [18], 77 [10], 70 [48], 58 [20], 57 [100], 56 [24], 43 [33], 42 [35].

Anal. Calcd. for $C_{14}H_{21}NO_2$ (235.32): C, 71.45; H, 9.00; N, 5.95. Found: C, 71.31; H, 8.87; N, 5.91.

[2-(*p*-Hydroxyphenyl)-2-methylperhydropyran-3-yl]methylamine (**6b**).

Compound **5b** (0.5 g, 1.6 mmoles) was hydrogenated-hydrogenolysed as described for compound **6a**, yielding 0.61 g (85%) of **6b**, mp 61-63° dec; tlc 1:1 methanol/ether, Rf 0.58; ir: ν max 3450-3300 s (broad) [OH, NH_2], 1245 m, 1180 m, 1100 m, 1020 m [C-O], 3040 m, 1610 s, 1510 s, 830 m [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 8.61 [br, disappeared on addition of deuterium oxide, OH], 7.33 [d, J = 9.7, 1H, H-Ar], 7.25 [d, J = 9.7, 1H, H-Ar], 6.90 [d, J = 9.7, 1H, H-Ar], 6.76 [d, J = 9.7, 1H, H-Ar], 3.78 [m, 2H, H-C(6)], 2.65 [m, 1H, H-C(3)], 2.24 [s, 3H, NCH_3], 1.99 [m, 4H, H-C(4,5)], 1.49 [s, 3H, angular CH_3], 1.37 [br, disappeared on addition of deuterium oxide, NH_2].

Anal. Calcd. for $C_{13}H_{19}NO_2$ (221.29): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.73; H, 8.43; N, 6.39.

[2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-yl]isopropylamine (**8a**).

A solution of compound **4a** (free base, 2.2 g, 10 mmoles) in methylene chloride (40 ml) and anhydrous acetone (15 ml) was refluxed with a Dean-Stark trap for 20 hours. Then 80 ml of absolute methanol and 0.25 g of Pd/C (10%) were added and the mixture was hydrogenated at room temperature and atmospheric pressure for 4 hours (tlc 1:4 methanol/ether, Rf 0.79). The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The remaining residue was crystallized from ether to give 2.1 g (81%), mp (of hydrochloride) 211-213°; ir: ν max 3340 m (broad) [NH], 3070 w, 1610 s, 1510 s, 835 s [aromatic], 1250 s, 1040 m [C-O]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.48 [d, J = 8.8, 2H, H-Ar], 6.86 [d, J = 8.8, 2H, H-Ar], 3.79 [s, 3H, CH_3O], 3.74 [m, 2H, H-C(6)], 2.83 [m, 1H, H-C(3)], 2.55 [m, 1H, CH], 1.92 [m, 2H, H-C(4)], 1.74 [m, 2H, H-C(5)], 1.54 [s, 3H, angular CH_3], 1.45 [s, disappeared on addition of deuterium oxide, NH], 0.94 [d, J = 6.2, 3H, CH_3], 0.82 [d, J = 6.2, 3H, CH_3]; ms: m/z (relative intensity) 264 [M^+ + 1, 0.7], 263 [M^+, 2], 227 [6], 135 [42], 113 [23], 85 [100], 70 [20]; hrms: m/z 263.1889 (M^+, Calcd. for $C_{16}H_{25}NO_2$: 263.1894).

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.73; H, 9.66; N, 5.40.

[2-(*p*-Hydroxyphenyl)-2-methylperhydropyran-3-yl]isopropylamine (**8b**).

Compound **4b** (free base, 1.8 g) was reacted with acetone and subsequently hydrogenated-hydrogenolysed by a method similar with that described for compound **8a**, yielding 1.12 g (74%) of the title product (mp 147-149°; tlc 1:4 methanol/ether, Rf 0.63); ir: ν max 3450-3300 (broad) [OH, NH], 3050 m, 1600 m, 1510 s, 835 m [aromatic], 1245 s, 1100 m, 1025 s [C-O]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.29 [d, J = 9, 2H, H-Ar], 6.82 [d, J = 9, 2H, H-Ar], 3.82 [m, 2H, H-C(6)], 2.78 [m, 1H, H-C(3)], 2.39 [m, 1H, CH], 1.87 [m, 4H, H-C(4,5)], 1.55 [s, 3H, angular CH_3], 1.40 [br, disappeared on addition of deuterium oxide, NH], 0.88 [d, J = 6, 3H, CH_3], 0.79 [d, J = 6, 3H, CH_3]; hrms: m/z 249.3383 (M^+, Calcd. for $C_{15}H_{23}NO_2$: 249.3376).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.33; H, 9.41; N, 5.57.

[2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-yl]ethylamine Hydrochloride (**9a**).

Anhydrous sodium carbonate (0.86 g, 8 mmoles) and ethyl iodide (0.94 g, 6 mmoles) were added to a solution of compound **4a** hydrochloride (1 g, 4 mmoles) in 20 ml of dry DMF. The mixture was stirred for 20 hours at 55° and then poured into 100 ml of water and extracted with ether (2 x 100 ml). The combined organic layers were washed successively with a 10% ammonium chloride solution and brine, dried over magnesium sulfate and evaporated to dryness. The resulting oil was converted to the hydrochloride salt and recrystallized from anhydrous methanol/ether to give 1.05 g (95%) of the title product **9a** (mp 197-199°; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.77); ir: ν max 3100-2900 (broad) [NH_2^+], 1250 s, 1080 m, 1030 s [C-O], 1605 m, 1510 s, 835 m [aromatic]; ^{1}H nmr of the free base (deuteriochloroform): 60 MHz δ 7.38 [d, J = 9, H-Ar], 6.92 [d, J = 9, 2H, H-Ar], 4.87 [br, disappeared on addition of deuterium oxide, NH], 3.87 [s, 3H, CH_3O], 3.78 [m, 2H, H-C(6)], 3.13 [m, 1H, H-C(3)], 2.90 [m, 2H, NCH_2], 1.89 [m, 4H, H-C(4,5)], 1.57 [s, 3H, angular CH_3], 1.08 [t, J = 6.5, 3H, CH_3].

Anal. Calcd. for $C_{15}H_{24}NO_2Cl$ (285.81): C, 63.03; H, 8.46; N, 4.90. Found: C, 62.91; H, 8.63; N, 4.81.

[2-(*p*-Hydroxyphenyl)-2-methylperhydropyran-3-yl]ethylamine Hydrochloride (**9b**).

The reaction was carried out as described above for compound **9a** yielding [2-(*p*-benzyloxyphenyl)-2-methylperhydropyran-3-yl]-ethylamine. The latter compound was subsequently hydrogenolysed in methanol with 10% Pd/Barium carbonate catalyst and 30 psi hydrogen pressure to give an oil which was converted to hydrochloride salt and recrystallized from anhydrous methanol/ether, yield 83%, mp 171-173°; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.68; ir: ν max 3400 (broad) [OH], 3100-2900 (broad) [NH_2^+], 1240 s, 1110 m, 1035 s [C-O], 1605 s, 1510 s, 835 s [aromatic]; ^{1}H nmr of the free base (deuteriochloroform): 60 MHz δ 8.32 [br, disappeared on addition of deuterium oxide, OH], 7.28 [d, J = 9, 2H, H-Ar], 6.83 [d, J = 9, 2H, H-Ar], 4.51 [br, disappeared on addition of deuterium oxide, NH], 3.76 [m, 2H, H-C(6)], 3.21 [m, 1H, H-C(3)], 2.86 [m, 2H, NCH_2], 1.90 [m, 4H, H-C(4,5)], 1.61 [s, 3H, angular CH_3], 1.12 [t, J = 6, 3H, CH_3].

Anal. Calcd. for $C_{14}H_{22}NO_2Cl$ (271.79): C, 61.87; H, 8.16; N, 5.15. Found: C, 62.03; H, 8.01; N, 5.24.

[2-(*p*-Methoxyphenyl)-2-methylperhydropyran-3-yl]diethylamine Hydrochloride (**10a**).

A mixture of compound **4a** (1 g, 4 mmoles), acetaldehyde (5 ml) and 0.55 g of 10% Pd/C in 70 ml of glacial acetic acid was hydrogenated in a Parr apparatus at room temperature and an initial pressure of 50 psi for 4 hours. Then the catalyst was removed by filtration, the filtrate was evaporated to dryness and the resulting residue was partitioned between methylene chloride and saturated solution of sodium bicarbonate. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to dryness giving an oil which was converted to the hydrochloride salt of the amine. Recrystallization from anhydrous methanol/ether yielded 0.96 g (79%) of pure product, mp 206-208°; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.87; ir: ν max 2900-2800 (broad) [NH^+], 1250 s, 1100 m, 1040 s [C-O], 1600 s, 1505 s, 835 m [aromatic]; ^{1}H nmr of free base (deuteriochloroform): 60 MHz δ 7.38 [d, J = 9.5, 2H, H-Ar], 6.94 [d, J = 9.5, 2H, H-Ar], 3.88 [s, 3H, CH_3O], 3.79 [m, 2H, H-C(6)], 2.92 [m, 1H, H-C(3)], 2.63 [q, J = 6.5, 4H, NCH_2], 1.88 [m, 4H, H-C(4,5)], 1.62 [s, 3H, angular CH_3], 0.95 [t, J = 6.5, 6H, CH_3].

Anal. Calcd. for $C_{17}H_{28}NO_2Cl$ (313.86): C, 65.05; H, 8.99; N, 4.46. Found: C, 65.31; H, 8.81; N, 4.51.

[2-(*p*-Hydroxyphenyl)-2-methylperhydropyran-3-yl]diethylamine Hydrochloride (**10b**).

Compound **10b** was prepared by the same procedure as described for the preparation of the methoxy analogue, compound **10a**. The yield of **10b** was 70% and the pure material has the following properties: mp 181-183° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.69; ir: ν max 3400 (broad) [OH], 2950-2800 (broad) [NH^+], 1240 s, 1110 m, 1010 s [C-O], 1600 m, 1505 s, 840 m [aromatic]; ^{1}H nmr of free base (deuteriochloroform): 60 MHz δ 8.28 [br, disappeared on addition of deuterium oxide, OH], 7.34 [d, J = 9, 2H, H-Ar], 6.82 [d, J = 9, 2H, H-Ar], 3.80 [m, 2H, H-C(6)], 2.98 [m, 1H, H-C(3)], 2.59 [q, J = 6, 4H, NCH_2], 1.94 [m, 4H, H-C(4,5)], 1.55 [s, 3H, angular CH_3], 0.91 [t, J = 6, 6H, CH_3].

Anal. Calcd. for $C_{16}H_{26}NO_2Cl$ (299.84): C, 64.09; H, 8.74; N, 4.67. Found: C, 63.93; H, 8.55; N, 4.51.

5-(*p*-Hydroxyphenyl)-4-*N*-isopropylamino-5-hexen-1-ol (**11**).

To a solution of compound **8a** (1 g, 4 mmoles) in dry methylene chloride (30 ml), cooled at 0° in a nitrogen atmosphere, was added dropwise under stirring 11 ml of boron trifluoride-dimethyl sulfide complex. The reaction was allowed to reach the room temperature and stirred for 24 hours. At that point tlc (1:4 methanol/ether, Rf 0.33) showed that the reaction was completed and the resulting precipitate was separated by decantation and dissolved in water (15 ml). Then a saturated solution of sodium carbonate was added (*p*H 8) and the product was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The resulting yellow solid was washed with hexane and ether, recrystallized from methanol/ether to give 0.89 g (94%) of pure product as off-white solid, mp 231-233° dec; ir: ν max 3500-3250 s (broad) [OH, NH], 1635 w [C=N], 1260 s, 1120 s, 1040 s [C-O], 3015 w, 1610 s, 1505 s, 835 s [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): 300 MHz δ 9.36 [br, disappeared on addition of deuterium oxide, HO-Ar], 7.23 [d, J = 8.5, 2H, H-Ar], 6.72 [d, J = 8.5, 2H, H-Ar], 5.15 [s, 1H, H-C(6)], 5.09 [s, 1H, H-C(6)], 3.45 [m, 1H, H-C(4)], 3.32 [m, 2H, H-C(1)], 2.78 [m, 1H, CH], 1.43 [m, 4H, H-C(2,3)], 1.31 [br, disappeared on addition of deuterium oxide, NH], 1.02 [d, J = 6, 3H, CH_3], 0.97 [d, J = 6, 3H, CH_3]; ms: m/z (relative intensity) 192 [M^+ + 1-C_3H_6O, 36], 191 [M^+-C_3H_6O, 57], 190 [24], 149 [21], 132 [64], 131 [100], 130 [46], 112 [20], 86 [16], 85 [17], 71 [55], 61 [15]; hrms (Measured on 191 peak, because molecular ion peak is unstable and 192 corresponds to C-13 isotope peak): m/z 191.1281 (M^+-C_3H_6O, Calcd. for $C_{12}H_{17}NO$: 191.1272).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.98; H, 9.11; N, 5.46.

5-(*p*-Hydroxyphenyl)-4-*N*-isopropylaminohexan-1-ol (**12**).

A solution of **11** (2 g, 8 mmoles) in 100 ml of methanol containing 0.05 g of platinum oxide was hydrogenated in a Parr apparatus at 30 psi pressure for 2 hours. The catalyst was filtered and the filtrate was evaporated under reduced pressure. The remain-

ing residue was crystallized from methanol/ether to give 1.83 g (91%) melting at 193-194°; tlc 1:4 methanol/ether, Rf 0.55; ir: ν max 3450-3300 (broad) [OH, NH], 1250 s, 1100 m [C-O], 3030 w, 1600 m, 1505 s, 830 m [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.01 [d, J = 9, 2H, H-Ar], 6.62 [d, J = 9, 2H, H-Ar], 3.22 [m, 3H, H-C(1,4)], 2.95 [m, 2H, H-C(5), CH], 1.57 [s, 3H, H-C(6)], 1.35 [m, 4H, H-C(2,3)], 0.98 [m, 6H, CH_3].

Anal. Calcd. for $C_{15}H_{25}NO_2$ (251.36): C, 71.67; H, 10.03; N, 5.57. Found: C, 71.50; H, 10.15; N, 5.43.

N-[3-Cyano-2-(*p*-methoxyphenyl)-2-methylperhydropyran-3-yl]acetamide (**15**).

[2-(*p*-Methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]carbonitrile hydrochloride (0.7 g, 2.5 mmoles) was reacted with anhydrous sodium acetate (0.6 g) and 3 ml of anhydrous pyridine in 25 ml of anhydrous acetic anhydride. After stirring at room temperature for 2 days, tlc (1:1 ether/ethyl acetate, Rf 0.29) showed that the reaction was completed. Then ice water (20 ml) was added and stirring was continued for 0.5 hour. A solution of sodium hydroxide (2*N*) was added to neutralize the solution and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated to dryness to give a solid. Recrystallization from acetone/petroleum ether furnished the analytically pure material as white crystals, yield 0.52 g (73%), mp 170-171°; ir: ν max 3360 s [NH], 1520 s [δ NH], 2250 w (sharp) [C≡N], 1695 s [NHC=O], 1250 s, 1095 s, 1020 s [C-O], 3015 w, 1610 m, 1505 s, 825 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.47 [d, J = 9, 2H, H-Ar], 6.82 [d, J = 9, 2H, H-Ar], 5.85 [br, disappeared on addition of deuterium oxide, NH], 3.76 [s, 3H, CH_3O], 3.69 [m, 2H, H-C(6)], 2.52 [m, 2H, H-C(4)], 1.93 [s, 3H, $COCH_3$], 1.83 [m, 2H, H-C(5)], 1.63 [s, 3H, angular CH_3]; ms: m/z (relative intensity) 288 [M^+, 7], 262 [M^+-C≡N, 2], 245 [M^+-$COCH_3$, 3], 218 [M^+-HCN and $COCH_3$, 4], 151 [20], 135 [35], 95 [10], 77 [10], 43 [100].

Anal. Calcd. for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.64; H, 6.99; N, 9.72. Found: C, 66.78; H, 7.03; N, 9.57.

[3-*N*-Acetamido-2-(*p*-methoxyphenyl)-2-methylperhydropyran-3-yl]-carboxylic Acid Methyl Ester (**17**).

In a solution of 100 ml dry and cooled tetrahydrofuran/methanol (3:1) mixture, previously saturated with dry hydrogen chloride (gas), 1 g (3.5 mmoles) of compound **15** was dissolved and the solution was kept below 5° overnight under stirring. Then ice water (5 ml) was added and the stirring was continued until the disappearence of the imidate intermediate **16** was detected by tlc (1:4 methanol/chloroform, Rf 0.37). The mixture was concentrated to 30 ml and partitioned between ethyl acetate/water (150:50 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to dryness. The oily residue was crystallized from ethyl acetate/ether yielding 1.14 g (84%) of the pure compound, mp 190-191°; ir: ν 3340 s [NH], 1740 s [O-C=O], 1685 s [NHC=O], 1250 s, 1160 m, 1090 m, 1035 s [C-O], 3025 w, 1610 m, 1510 s, 830 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.35 [d, J = 9, 2H, H-Ar], 6.89 [d, J = 9, 2H, H-Ar], 5.71 [br, disappeared on addition of deuterium oxide, NH], 3.79 [s, 3H, CH_3O], 3.70 [m, 2H, H-C(6)], 3.51 [s, 3H, OCH_3], 2.14 [m, 2H, H-C(4)], 1.96 [s, 3H, $COCH_3$], 1.90 [m, 2H, H-C(5)], 1.58 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{17}H_{23}NO_5$ (321.36): C, 63.53; H, 7.21; N, 4.36. Found: C, 63.31; H, 7.53; N, 4.22.

[3-*N*-Acetamido-2-(*p*-methoxyphenyl)-2-methylperhydropyran-3-yl]-carboxylic Acid (**18**).

To a solution of ethyl ester **17** (0.67 g, 2 mmoles) in a mixture of dioxane/water (15:15 ml), solid sodium hydroxide (0.12 g, 3 mmoles) was added and stirred at room temperature for 3 hours. Then the mixture was concentrated and partitioned between water/methylene chloride (70/40 ml). The aqueous layer was separated, acidified to *p*H 3 and extracted with methylene chloride (2 x 150 ml). The combined organic layers were extracted with brine, dried over magnesium sulfate and evaporated to dryness to give quantitatively the corresponding carboxylic acid **18**, mp 204-206°; ir: ν 3340 s [NH], 3000 m (broad) [OH], 1760 m and 1715 s [C=O], 1685 s [NHC=O], 1240 s, 1100 m, 1020 s [C-O], 1600 m, 1505 s, 830 s [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): 60 MHz δ 10.55 [br, disappeared on addition of deuterium oxide, OH], 7.45 [d, J = 9, H-Ar], 6.89 [d, J = 9, H-Ar], 5.78 [br, disappeared on addition of deuterium oxide, NH], 3.81 [s, 3H, CH_3O], 3.73 [m, 2H, H-C(6)], 2.11 [m, 2H, H-C(4)], 1.96 [s, 3H, $COCH_3$], 1.86 [m, 2H, H-C(5)], 1.60 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{16}H_{21}NO_5$ (307.34): C, 62.52; H, 6.89; N, 4.18. Found: C, 62.74; H, 6.71; N, 4.03.

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