Products from Furans. V [1a]. Synthesis of Oxygen Containing Isosteres of Sympathomimetic Amines *via* 6-Hydroxy-2*H*-pyran-3(6*H*)-ones and their *cis*-Platinum(II) Complexes

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Novel amino analogues of sympathomimetic amines, which contain the pyran ring as a consequence of their common route of preparation, were synthesized. A modified Strecker reaction on tetrahydro-2*H*-pyran-3-one derivatives yielded α-benzylamino nitriles, which upon subsequent hydrogenation and hydrogenolysis gave the target 1,2-diamines. The prepared diamines were indeed sympathomimetic on the basis of molecular mechanics studies, since they have been found to fulfill earlier considerations on the minimal structural requirements, necessary to attain high affinity to dopamine (DA) receptors. Furthermore the prepared 1,2-diamino compounds were used as ligands for the synthesis of *cis*-Platinum(II) complexes.

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Introduction.

Sympathomimetic amines comprise one of the most extensively studied groups of pharmacological agents [2]. They have been found to be of importance in such fields as blood pressure abnormalities, mental disorders, Parkinson's disease, tumors, control and maintenance of pregnancy and different metabolic disorders [3]. Much work has been carried out on the synthesis of sympathomimetic amines, that is potentiating, mimicking or inhibiting neurotransmitter action of catecholamines or blocking their biosynthetic pathways.

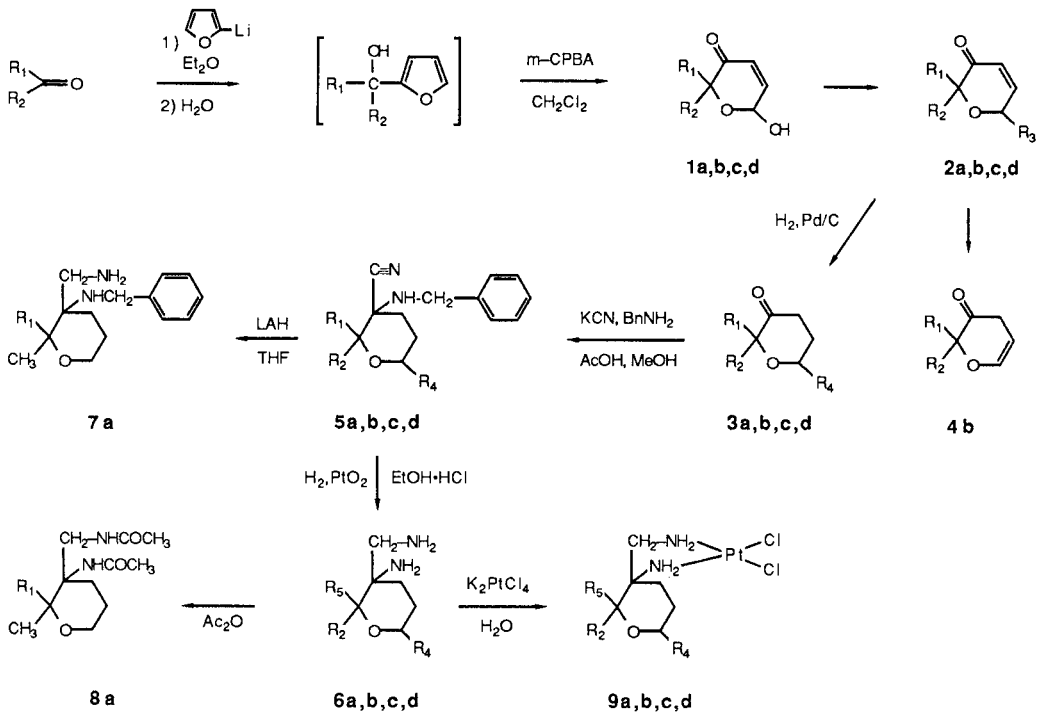
Since there is a considerable recent interest [4] in preparing oxygen-containing isosteres of sympathomimetic amines (especially of various dopamine agonists), we have synthesized novel amino isosteres of sympathomimetic amines, all of which contain the pyran ring as a consequence of the common route of their synthesis. In order to accomplish this goal we have utilized the 6-hydroxy-2*H*-pyran-3(6*H*)-ones, which can easily be prepared from furans and contain various functional groups, making them very useful for synthetic purposes [5]. Thus we have converted derivatives of 6-hydroxy-2*H*-pyran-3(6*H*)-ones to tetrahydro-2*H*-pyran-3-one derivatives, which subsequently gave the target 1,2-diamines *via* a modified Strecker reaction. Furthermore, since *cis*-diamminedichloroplatinum(II) which is in use against various tumors [6] has no selectivity [7], we have used the prepared 1,2-diamines as ligands for the synthesis of *cis*-platinum(II) complexes, hoping that they may show selectivity against certain tumors.

Results and Discussion.

In planning the synthesis of novel analogues of sympathomimetic amines, we relied on earlier considerations that β-phenylethylamine is the parent compound of the sympathomimetic amines [8] and that there are some minimal structural requirements, necessary for high affinity to DA(D_2) receptors [9]. Thus the amines should have the following structural features: a) the existence of an aromatic nucleus, usually a benzene ring and b) distance of 5-6.5 Å on a vector directed from its center to a basic *N*-atom. In order to achieve our goal which was the synthesis of novel, oxygen containing, isosteres of sympathomimetic amines, we have converted (Scheme I) 6-hydroxy-2*H*-pyran-3(6*H*)-ones, **1a**, **1b**, and **1c** to their carbonates **2a**, **2b**, and **2c**. These allylic carbonates upon treatment with hydrogen in the presence of Pd/C were hydrogenolysed in the same manner as the carbamates in the carbobenzoxy blocking group (peptide chemistry) and subsequently were hydrogenated, yielding the tetrahydro-2*H*-pyran-3-ones **3a**, **3b**, and **3c**. Thus the rate of this reaction could be controlled by the amount of the catalyst, time and solvent [12]. Consequently it is possible (see Experimental) according to the reaction conditions to obtain various products (**4a**) as well as analytically pure ketones **3a**, **3b** and **3c**. Methylation of the 6-hydroxy group of **1d** and subsequent reduction gave the 6-methoxy-tetrahydro-2*H*-pyran-3-one **3d**.

Since the original procedure for Strecker reaction [10] gives low yields and a considerable amount of cyanohydrin by-product [11], we attempted to perform the synthesis

Scheme I



Compound	R_1	R_2	R_3	R_4	R_5
a	CH_3O-Ph	$-CH_3$	$-O-C(=O)-OC_2H_5$	$-H$	CH_3O-Ph
b	CH_3O-Ph	$-CH_3$	$-O-C(=O)-OC_2H_5$	$-H$	HO-Ph
c	3,4-methylenedioxyphenyl	$-CH_3$	$-O-C(=O)-OC_2H_5$	$-H$	3,4-methylenedioxyphenyl
d	3,4-methylenedioxyphenyl	$-H$	$-OCH_3$	$-OCH_3$	3,4-methylenedioxyphenyl

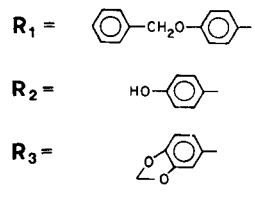
stepwise, that is, first to synthesize the benzylimino derivative of the appropriate ketone and by a subsequent treatment with hydrogen cyanide to form the corresponding α-benzylaminonitrile. We have found, however, that the one pot treatment of ketones with benzylamine, potassium cyanide and acetic acid in methanol at 60° overnight (18 hours), gives almost quantitative yields of the corresponding α-benzylaminonitriles **5a, 5b, 5c**, and **5d**. This modification has indeed remarkable advantages since it gives by far better yields, shorter reaction time and no by-products. Furthermore, α-benzylaminonitriles are more stable, easier to crystallize and have better properties in identifying them spectroscopically than the corresponding α-aminonitriles [12]. The α-benzylaminonitriles were easily identified in ir by the characteristic very sharp and rather strong absorption at 3320 cm^{-1} (NH of benzylamine derivative), in addition to the weak cyanide absorption at 2220 cm^{-1}. Furthermore α-benzylaminonitriles gave molecular ions in Mass Spectra, in contrast with the corresponding α-aminonitriles which were decomposed by losing HCN. It is noteworthy that this modified reaction has been applied to give comparable yields on a variety of ketones [8]. The most important feature of this modification of the Strecker reaction, however, is the maintenance of the remarkable stereospecificity of Strecker reaction [13]. Thus the axial or equatorial orientation of cyano (or benzylamino) group depends on the stereochemistry of the starting ketone (see Scheme II), as shown by the 2D nmr (NOESY experiment) spectroscopy [14] of α-benzylaminonitriles.

We have found that the α-benzylamino nitriles may be treated with hydrogen over platinum oxide at 50 psi

Scheme II

5b 5d

6b 6d



pressure and 40°, yielding 1,2-diamines **6a**, **6b**, **6c**, and **6d** as hydrogenation-hydrogenolysis products. On the other hand, the cyano group may be reduced by lithium aluminum hydride with the benzyl group intact. Thus, we have prepared the sympathomimetic amine analogue **7a** with a bulky *N*-substituent, which may be of pharmacological interest [9]. Finally we have decided to study the structural features of two (the most characteristic) of the prepared diamines by combining nmr data and minimum strain energy calculations. We have used a molecular mechanics program in order to determine which conformation corresponds to minimum strain energy and then calculated the distance between the center of the aromatic

Table I

Compound	Strain Energy (Kcal/mole)	Distance Ar-N (Å) N_1	N_2
6b	4.389	4.440	5.180
6d	7.368	5.165	3.926

N_1: Amino group derived from nitrile.

ring and the *N*-atoms (Table I). We thought that it is important to distinguish the difference between β-phenylethylamine (which may be considered as the parent compound of the sympathomimetic amines [8]) and its derivatives (acyclic carbon chain) from the prepared heterocyclic analogues where the structure is more rigid. In the first case, it has been found that the structural features of β-ethylamine derivatives of aromatic compounds are sufficient to insure a distance (Ar-N) within the required range, in order to satisfy the structural features of sympathomimetic amines [8,9]. In the case of the heterocyclic analogues, we have found that only a diaxial orientation on the pyran ring of both phenyl and amino group of heterocyclic β-phenylethylamine analogue (compound **6b**) is structurally suitable to insure a distance Ar-N within the required range (5-6.5 Å). Other possible orientations (diequatorial or axial-equatorial) of phenyl and amino group can not insure the required distance. However, we have noted that in the case of compound **6d** (where the phenyl group has equatorial orientation) the distance of the second amino group, which structurally may be considered as a heterocyclic analogue of γ-phenylpropylamine is indeed within the required range.

The complexation of 1,2-diamine hydrochlorides with Platinum was carried out in water and the rate of complexation was followed by monitoring the *p*H of the reaction [15], which was maintained at around 6.5. We have found that this maintenance of the *p*H is essential for good yields, short reaction time and avoidance of byproducts (dimers *etc.*). The formation of the *cis*-platinum(II) complexes **9a**, **9b**, **9c**, and **9d** was confirmed by elemental analysis, nmr spectra (the chemical shift of the protons of the amino group characteristically appear in the range 5-5.5 ppm), ms (molecular ions by FD technique) and ir (N-H stretching vibration near 3200 cm^{-1} and a weak absorption near 550 cm^{-1} for the Pt-N stretching vibration). The absorption bands near 320 cm^{-1} (due to Pt-Cl bond) were used as indicator of the configuration of the complexes. According to the literature [16] the *cis*-configuration shows two absorption bands near 320 cm^{-1}, while the *trans*-configuration only one, thus our spectral data were consistent with the *cis*-configuration.

We have found that the above described use of the Strecker reaction for the synthesis of 1,2-diamines and their *cis*-platinum(II) complexes may be considered as a general procedure, since it could be applied on a variety of molecules containing a carbonyl group [8,18].

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). The nmr spectra were recorded on Varian 360 EM (60 MHz) or Nicolet NT 360 (360 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%), w (weak 0-33%). Mass spectra were obtained on a Varian Associates MAT CH-5 spectrometer (ionization by electron impact) at 70 eV, the determination of the molecular ion of the complexes was done using the field desorption technique on a Varian MAT 731 spectrometer. Data are presented in the form m/e (intensity relative to base peak = 100) for selected compounds. Microanalytical data were provided by the Microanalytical Service Laboratory of the University of Illinois. *n*-Butyllithium was purchased from Merck and titrated prior to use. Furan, acetic anhydride and pyridine were distilled immediately prior to use. Other reagents and catalysts were purchased as analytical reagent grade. Commercial sources included: Aldrich Chemical Co., Mallinckrodt/nc., Alfa (Ventron), Merck, Ferak, Fluka and BDH. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Dimethylformamide (DMF) was dried over 4-Å molecular sieves. All other solvents were used as received.

Molecular Mechanics.

Strain Energies of the prepared diamines 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-atoms was calculated using the same program.

Starting Materials.

6-Hydroxy-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-one (**1a**), 2-(*p*-benzyloxyphenyl)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (**1b**), 5,6-dihydro-6-(*p*-methoxyphenyl)-6-methyl-5-oxo-2*H*-pyran-2-yl, ethyl carbonate (**2a**), 5,6-dihydro-6-(*p*-benzyloxyphenyl)-6-methyl-5-oxo-2*H*-pyran-2-yl, ethyl carbonate (**2b**) and 2-(*p*-methoxyphenyl)-2-methyltetrahydropyran-3-one (**3a**), have been prepared according to the literature [17]. The above compounds have been characterized by melting point, ir and ^1H nmr data.

6-Hydroxy-2-(3,4-methylenedioxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-one (**1c**).

To a solution of freshly distilled furan (25 ml) in anhydrous ether (100 ml), *n*-Butyllithium in hexane (15%, 100 ml) was added dropwise under nitrogen and with the temperature maintained below -5°. After being stirred for 1 hour at 20°, the mixture was cooled to 0° and a solution of 3,4-methylenedioxyacetophenone (16 g, 0.1 mole) in 100 ml anhydrous THF was added dropwise. The reaction was allowed to reach room temperature and continued for 5 hours. At that point tlc (1:1 ether/hexane, Rf 0.73) showed that the reaction was completed. Cold water was added slowly under stirring and the product was taken by extraction with ether (2 x 150 ml). The organic layers were pooled together, washed with water, dried over magnesium sulfate and evaporated under reduced pressure yielding the α-(3,4-methylenedioxyphenyl)-α-methylfurfuryl alcohol as a yellowish oily residue (21 g, 93%); ir (thin film): ν max 3430 br [OH], 1010 m, 883 w (sharp), 745 [furan], 3030 w, 1605 m, 1503 s, 812 m [aromatic], 1245 s, 1040 s [C-O], 2975 m, 2890 m, 2870 m, 1440 s, 1360 m [CH_2, CH_3]; nmr (60 MHz, carbon tetrachloride): δ 7.20 [m, 3H, H-Ar], 6.80 [m, 1H, furan, H-C(5)], 6.18 [m, 2H, furan], 5.67 [s, 2H, CH_2O], 3.88 [s, disappeared on addition of deuterium oxide, OH], 1.74 [s, 3H, CH_3]. The furfuryl alcohol was dissolved in methylene chloride (320 ml) and *m*-chloroperbenzoic acid (83%, 32 g, 0.21 mole) was added in portions under stirring, while the temperature was kept between 7 and 15°. After the mixture had been stirred for 3 hours, tlc (4:1 ether/hexane, Rf 0.59) showed that the reaction was finished. The mixture was cooled and the precipitated solid (*m*-chlorobenzoic acid) was filtered. The filtrate was washed successively with 20% potassium iodide, 30% sodium thiosulfate, concentrated bicarbonate and water, dried over magnesium sulfate and evaporated to a yellowish liquor which was crystallized from ether to give 17.7 g (73% total yield), melting at 113-114° dec; ir: ν max 3438 s [OH], 1680 s [conj C=O], 1625 m [C=C], 1250 s, 1172 m, 1110 m, 1090 m, 1040 s [C-O], 3000 m, 1608 m, 1502 s, 808 s [aromatic], 2950 w, 2920 m, 2900 m, 2830 w, 1482 s, 1448 s, 1370 s [CH_2, CH_3]; nmr (60 MHz, deuteriochloroform): δ 6.77 [m, 1H, H-C(5)], 6.62 [m, 3H, H-Ar], 6.05 [dd, J = 10.2, 1.7, 1H, H-C(4)], 5.85 [s, 2H, CH_2O], 5.33 [ddd, J = 8.2, 1.7, 1.7 1H, H-C(6)], 3.65 [d, J = 8.2, disappeared on addition of deuterium oxide OH], 1.61 [s, 3H, angular CH_3]; ms: m/e (relative intensity) 248 [M^+, 2], 165 [6], 131 [4], 113 [7], 85 [9], 57 [12], 43 [72], 32 [98], 28 [100].

Anal. Calcd. for $C_{13}H_{12}O_5$ (248.23): C, 62.90; H, 4.88. Found: C, 62.81; H, 4.95.

6-Hydroxy-2-(3,4-methylenedioxyphenyl)-2*H*-pyran-3(6*H*)-one (**1d**).

3,4-Methylenedioxybenzaldehyde (15 g, 0.1 mole) was treated with furan (25 ml) and *n*-Butyllithium (15%, 100 ml) as described for the compound **1c**, yielding 20.5 g (94%) α-(3,4-methylenedioxyphenyl)furfuryl alcohol; tlc 1:1 ether/hexane, Rf 0.69; ir (thin film): ν max 3450 br [OH], 1015 m, 885 m (sharp), 745 [furan], 1250 s, 1035 s [C-O], 3050 m, 1600 m, 1500 s, 815 s [aromatic], 2960 m, 2870 w, 1440 m [CH_2]; nmr (60 MHz, deuteriochloroform): δ 7.40 [m, 1H, H-C(5)], 6.90 [m, 3H, H-Ar], 6.31 [dd, J = 3, 1.1, 1H, H-C(4)], 6.20 [m, 1H, H-C(3)], 5.93 [s, 2H, CH_2O], 3.58 [br, disappeared on addition of deuterium oxide, OH]. The above alcohol was oxidized with *m*-chloroperbenzoic acid (83%, 30 g, 0.2 mole) by the same procedure as for compound **1c** yielding 16.8 g (72% total yield) of the title product mp 119-120° dec, tlc 4:1 ether/hexane Rf 0.44; ir: ν max 1702 s [conj C=O], 3455 s [OH], 1632 w [C=C], 1250 s, 1110 m, 1083 s, 1020 s [C-O], 3080 w, 1612 w, 1505 s, 825 s [aromatic], 2940 m, 2880 w, 1450 s [CH_2]; nmr (360 MHz, deuterioacetone): δ 7.15 [dd, J = 10.1, 3.4, 1H, H-C(5)], 6.86 [m, 3H, H-Ar], 6.12 [d, J = 10.1, 1H, H-C(4)], 6.01 [s, 2H, CH_2O], 5.76 [dd, J = 5.7, 3.4, 1H, H-C(6)], 5.50 [s, 1H, H-C(2)], 3.09 [br, disappeared on addition of deuterium oxide OH]; ms: m/e (relative intensity) 235 [M^+ + 1, 2], 234 [M^+, 15], 151 [100], 150 [11], 149 [33], 123 [10], 93 [49], 84 [92], 65 [31], 56 [35], 55 [46], 39 [14].

Anal. Calcd. for $C_{12}H_{10}O_5$ (234.20): C, 61.54; H, 4.30. Found: C, 61.38; H, 4.24.

5,6-Dihydro-6-methyl-6-(3,4-methylenedioxyphenyl)-5-oxo-2*H*-pyran-2-yl, Ethyl Carbonate (**2c**).

To a solution of **1c** (1.15 g, 4.6 mmoles), triethylamine (0.9 g, 9 mmoles) in methylene chloride (80 ml) cooled to -5°, ethyl chloroformate (1.16 g, 11 mmoles) was added under stirring in such a rate that the reaction temperature was maintained below 0°. The reaction was allowed to proceed at room temperature and after 2 hours of stirring, tlc (3:2 ether/hexane, Rf 0.61) showed that the reaction was completed. The reaction mixture was washed, dried over magnesium sulfate and evaporated to a residue which was crystallized from ether yielding 1.16 g (78%) of analytically pure material (mp 74-75°): ir: ν max 1698 s [conj C=O], 1754 s [O-C=O], 1640 w [C=C], 3065 w, 1610 w, 1503 s, 812 s [aromatic], 1260 s, 1230 s, 1170 m, 1150 m, 1110 m, 1070 m, 1020 s [C-O], 2975 m, 2940 m, 2870 w, 1480 s, 1440 m, 1370 s [CH_2, CH_3]; nmr (360 MHz, deuteriochloroform): δ 7.0 [s, 1H, H(2)-Ar], 6.89 [d, J = 8.5, 1H, H(6)-Ar], 6.86 [d, J = 8.5, 1H, H(5)-Ar], 6.81 [dd, J = 9.9, 1.8, 1H, H-C(5)], 6.33 [dd, J = 1.8, 1.7, 1H, H-C(6)], 6.26 [dd, J = 9.9, 1.7, 1H, H-C(4)], 5.97 [s, 2H, CH_2O], 4.32 [q, J = 7.2, 2H, CH_2OCO], 1.68 [s, 3H, angular CH_3], 1.37 [t, J = 7, 3H, CH_3]; ms: m/e (relative intensity) 321 [M^+ + 1, 2], 320 [M^+, 8], 231 [9], 164 [7], 156 [28], 149 [16], 84 [100], 55 [13], 44 [10], 43 [44].

Anal. Calcd. for $C_{16}H_{16}O_7$ (320.29): C, 60.00; H, 5.04. Found: C, 60.15; H, 4.94.

6-Methoxy-2-(3,4-methylenedioxyphenyl)-2*H*-pyran-3(6*H*)-one (**2d**).

To a solution of **1d** (4.5 g, 19 mmoles) and methyl iodide (6 ml) in acetone (80 ml) was added powdered silver oxide (6 g) portionwise. The reaction was run with stirring overnight and tlc (7:3 ether/hexane, Rf 0.57) showed that the reaction was completed. The mixture was refluxed with Norite, filtered on Celite and the filtrate was evaporated to a residue which was crystallized by the addition of ether yielding 3.44 g (81% yield) of the title product: ir (thin film): ν max 1690 s [conj C=O], 1652 m [C=C], 1257 s, 1085 s, 1020 s [C-O], 3070 w, 1600 m, 1490 m, 795 s [aromatic], 2960 s, 2920 s, 2845 m, 2820 w, 1445 m [CH_2, CH_3]; nmr (60

MHz, carbon tetrachloride): δ 6.73 [dd, J = 10, 1.5, 1H, H-C(5)], 6.55 [m, 3H, H-Ar], 6.0 [dd, J = 10, 1.5, 1H, H-C(4)], 5.76 [s, 2H, CH_2O], 5.08 [m, 1H, H-C(6)], 4.83 [s, 1H, H-C(2)], 3.31 [s, 3H, CH_3].

Anal. Calcd. for $C_{13}H_{12}O_5$ (248.23): C, 62.90; H, 4.87. Found: C, 62.86; H, 4.63.

2-Methyl-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-one (**3c**).

A solution of **2c** (2 g, 8.1 mmoles) in ethyl acetate (100 ml) and methanol (20 ml) containing 0.2 g of 10% Pd/C was hydrogenolysed by treatment with hydrogen at atmospheric pressure and room temperature. Hydrogenolysis was completed within 2.5 hours, (tlc, 7:3 ether/hexane, Rf 0.64). The catalyst was filtered and the filtrate was evaporated under reduced pressure. The residue was crystallized from ether-hexane to give 1.35 g (92%) melting at 86-88°; ir: ν max 1725 s [C=O], 1248 s, 1090 s, 1020 s [C-O], 3065 w, 1605 w, 1501 s, 811 s [aromatic], 2980 m, 2930 m, 2890 m, 1480 s, 1440 m, 1370 m [CH_2, CH_3]; nmr (360 MHz, deuteriochloroform): δ 6.99 [s, 1H, H(2)-Ar], 6.88 [d, J = 9, H(6)-Ar], 6.80 [d, J = 9, 1H, H(5)-Ar], 5.97 [s, 2H, CH_2O], 3.85 [m, 2H, H-C(6)], 2.30 [m, 4H, H-C(4,5)], 1.49 [s, 3H, angular CH_3]; ms: m/e (relative intensity) 236 [M^+ + 2, 1], 235 [M^+ + 1, 2], 234 [M^+, 11], 206 [9], 192 [12], 191 [99], 164 [10], 150 [9], 149 [100], 147 [7], 121 [14], 91 [8], 89 [11], 65 [17], 63 [16], 43 [52], 41 [12].

Anal. Calcd. for $C_{13}H_{14}O_4$ (234.24): C, 66.65; H, 6.02. Found: C, 66.72; H, 5.91.

2-(*p*-Benzyloxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-one (**3b**).

A solution of **2b** (4 g, 10 mmoles) was hydrogenolysed using as catalyst 0.3 g 10% Pd/C as described for compound **3c** but in order to prevent the hydrogenolysis of the benzyl group, methanol was not used and the reaction was stopped when a precalculated volume of hydrogen has been absorbed. By this procedure two products were obtained (tlc, 6:4 ether-hexane, Rf 0.82 and 0.71) which were separated by column chromatography (silica gel with 1:4 ether/hexane as eluant). The fractions with the lower Rf value gave 1.8 g (59% yield) of compound **3b**, mp 109°; ir: ν max 1712 s [C=O], 1245 s, 1172 m, 1105 m, 1080 m, 1005 s [C-O], 3030 w, 3010 m, 1608 s, 1505 s, 829 s, 750 s, 698 s [aromatic], 2935 m, 2875 m, 2830 w, 1475 m, 1455 w, 1380 s [CH_2, CH_3]; nmr (60 MHz, deuteriochloroform): δ 7.33 [s, 5H, H-Ar], 7.13 [d, J = 9, 2H, H(2,6)-Ar], 6.86 [d, J = 9, 2H, H(3,5)-Ar], 4.97 [s, 2H, CH_2O], 3.73 [m, 2H, H-C(6)], 2.37 [m, 2H, H-C(4)], 1.97 [m, 2H, H-C(5)], 1.40 [s, 3H, angular CH_3]; ms: m/e (relative intensity) 297 [M^+ + 1, 1], 296 [M^+, 1], 253 [22], 182 [87], 92 [25], 91 [100], 65 [55], 39 [37], 28 [91].

Anal. Calcd. for $C_{19}H_{20}O_3$ (296.35): C, 77.00; H, 6.80. Found: C, 77.22; H, 6.63.

Fractions with the higher Rf value yielded 0.69 g (22%) of 2-(*p*-benzyloxyphenyl)-2-methyl-3,4-dihydro-2*H*-pyran-3-one, **4b**, mp 87-88°; ir: ν max 1720 s [C=O], 1665 m [C=C], 1242 s, 1175 m, 1060 s, 1008 s [C-O], 3030 w, 3005 m, 1606 m, 1502 s, 834 s, 750 s, 699 s [aromatic], 2935 m, 2920 w, 2875 w, 1472 m, 1455 m, 1373 m [CH_2, CH_3]; nmr (60 MHz, deuteriochloroform): δ 7.38 [s, 5H, H-Ar]; 7.23 [d, J = 9, 2H, H(2,6)-Ar], 6.89 [d, J = 9, 2H, H(3,5)-Ar], 6.49 [m, 1H, H-C(6)], 5.05 [s, 2H, CH_2O], 4.75 [ddd, J = 3.1, 6.5, ≅0, 1H, H-C(5)], 2.82 [dd, J = 3.1, ≅0, 2H, H-C(4)], 1.65 [s, 3H, angular CH_3]; ms: m/e (relative intensity) 295 [M^+ + 1, 21], 294 [M^+, 77], 276 [M^+ - 18(OH), 5], 266 [98], 251 [10], 238 [24], 147 [21], 91 [100], 65 [24], 39 [8], 28 [18].

Anal. Calcd. for $C_{19}H_{18}O_3$ (294.33): C, 77.53; H, 6.16. Found: C, 77.81; H, 6.35.

6-Methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-one (**3d**).

A solution of **2d** (4 g, 16 mmoles) in 150 ml of ethyl acetate was hydrogenated over 0.4 g 10% Pd/C as described for compound **3b** yielding 3.85 g (95%) of the title product (mp 151.5-153.5°), which was recrystallized from ether (tlc 7:3 ether/hexane Rf 0.43); ir: ν max 1720 s [C=O], 1248 s, 1100 w, 1040 s [C-O], 3080 w, 1610 w, 1503 s, 810 m [aromatic], 2940 m, 2905 s, 1490 s, 1445 s, 1375 m [CH_2, CH_3]; nmr (60 MHz, deuterioacetonitrile): δ 6.4 [m, 3H, H-Ar], 5.65 [s, 2H, CH_2O], 4.71 [d, J = 4.1, 1H, H-C(6)], 4.53 [s, 1H, H-C(2)], 3.22 [s, 3H, CH_3], 2.13 [m, 4H, H-C(4,5)].

Anal. Calcd. for $C_{13}H_{14}O_5$ (250.24): C, 62.39; H, 5.64. Found: C, 62.11; H, 5.72.

3-*N*-Benzylamino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-ylcarbonitrile (**5a**).

A solution of **3a** (1.5 g, 6.8 mmoles), potassium cyanide (0.45 g, 6.9 mmoles) in 15 ml absolute methanol in a round bottom flask was treated with benzylamine (0.85 ml, 7.8 mmoles) and glacial acetic acid (0.9 ml). The reaction mixture was heated gradually with stirring at 60° and the reaction run for 20 hours. At that point tlc (6.5:3.5 ether/hexane, Rf 0.67) showed that the reaction was complete. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in water (20 ml) and ether (60 ml). The organic layer was separated, dried over magnesium sulfate and the solvent removed under reduced pressure yielding 2.1 g (93%) of the title product **5a** (mp 107-108°) which recrystallized from methanol; ir: ν max 2215 w (sharp) [C≡N], 3318 m (sharp) [NH], 1248 s, 1175 s, 1092 m, 1026 m [C-O], 3030 m, 1610 m, 1510 s, 828 s, 737 m, 697 m, [aromatic], 2960 w, 2925 m, 2880 m, 2838 w, 1460 m, 1362 m [CH_2, CH_3]; nmr (360 MHz, deuteriochloroform): δ 7.57 [d, J = 9, 2H, H(2,6)-Ar], 7.25 [m, 5H, H-Ar], 6.87 [d, J = 9, H(3,5)-Ar], 3.91 [m, 2H, CH_2N], 3.77 [s, 3H, CH_3O], 3.74 [m, 2H, H-C(6)], 2.19 [m, 2H, H-C(4)], 1.83 [m, 2H, H-C(5)], 1.72 [s, 3H, angular CH_3], 1.60 [s, disappeared on addition of deuterium oxide NH]; ms: m/e (relative intensity) 337 [M^+ + 1, 1], 336 [M^+, 3], 310 [M^+ + 1 - 27 (HCN), 6], 309 [M^+ - 27 (HCN), 23], 218 [65], 151 [37], 135 [20], 92 [11], 91 [100], 65 [11], 43 [71].

Anal. Calcd. for $C_{21}H_{24}O_2N_2$ (336.42): C, 74.97; H, 7.19; N, 8.33. Found: C, 74.85; H, 7.20; N, 8.12.

3-*N*-Benzylamino-2-(*p*-benzyloxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-ylcarbonitrile (**5b**).

2-(*p*-Benzyloxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-one (**3b**) (0.3 g, 1 mmole) was treated with potassium cyanide (0.1 g, 1.5 mmoles), benzylamine (0.25 ml, 2.2 mmoles) and glacial acetic acid (0.3 ml) in 25 ml absolute methanol as described for compound **5a** yielding 0.4 g (96%) of the title product **5b** (mp 146.5-147.5°; tlc 7:3 ether/hexane, Rf 0.74); ir: ν max 3320 s (sharp) [NH], 2210 w (sharp) [C≡N], 3065 m, 3030 m, 1610 s, 1511 s, 835 s, 741 s, 693 s [aromatic], 1242 s, 1185 s, 1110 m, 1005 s [C-O], 2958 s, 2940 m, 2896 m, 1460 s, 1385 s [CH_2, CH_3]; nmr (60 MHz, deuteriochloroform): δ 7.33 [d, J = 8.5, 2H, H(2,6)-Ar], 7.13 [s, 5H, H-Ar], 7.04 [s, 5H, H-Ar], 6.72 [d, J = 8.5, 2H, H(3,5)-Ar], 4.88 [s, 2H, CH_2O], 3.84 [m, 2H, CH_2N], 3.70 [m, 2H, H-C(6)], 2.0 [m, 4H, H-C(4,5)], 1.67 [s, 3H, angular CH_3]; 1.48 [s, disappeared on addition of deuterium oxide, NH]; ms: m/e (relative intensity) 413 [M^+ + 1, 1], 412 [M^+, 2], 386 [M^+ + 1 - 27 (HCN), 2], 385 [M^+ - 27 (HCN), 6], 295 [18], 227 [2], 201 [2], 121 [5], 92 [9], 91 [92], 77 [9], 65 [19], 43 [11], 28 [100].

Anal. Calcd. for $C_{27}H_{28}O_2N_2$ (412.51): C, 78.61; H, 6.84; N, 6.79. Found: C, 78.42; H, 6.91; N, 6.64.

3-*N*-Benzylamino-2-methyl(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-ylcarbonitrile Hydrochloride (**5c**).

2-Methyl(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-one (**3c**) (0.7 g, 3 mmoles) was reacted with potassium cyanide (0.22 g, 3.4 mmoles), benzylamine (0.4 ml, 3.6 mmoles) and glacial acetic acid (0.45 ml) in 15 ml absolute methanol as described for compound **5a**. The product (1.05 g, 91% yield mp 144-145) was taken as hydrochloride by treatment with ethereal hydrogen chloride; (tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.67); ir: ν max 3000-2800 s (broad) [NH_2^+], 1555 m [δ NH_2^+], 1255 s, 1170 m, 1100 s, 1040 s [C-O], 1608 w, 1498 s, 808 s, 750 m, 692 m [aromatic], 1470 m, 1450 m, 1358 s [CH_2, CH_3]; nmr (60 MHz, deuteriodimethyl sulfoxide): δ 7.22 [s, 5H, H-Ar], 7.08 [s, 1H, H(2)-Ar], 7.03 [d, J = 9, 1H, H(6)-Ar], 6.85 [br, disappeared on addition of deuterium oxide NH_2^+], 6.80 [d, J = 9, 1H, H(5)-Ar], 5.92 [s, 2H, CH_2O], 3.83 [m, 2H, CH_2N], 3.70 [m, 2H, H-C(6)], 1.97 [m, 4H, H-C(4,5)], 1.67 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{21}H_{23}ClO_3N_2$ (386.87): C, 65.19; H, 5.99; N, 7.24. Found: C, 64.98; H, 6.21; N, 7.12.

3-*N*-Benzylamino-6-methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-ylcarbonitrile (**5d**).

A solution of **3d** (2 g, 8 mmoles) in 20 ml absolute methanol was treated with potassium cyanide (0.6 g, 9.2 mmoles), benzylamine (1.1 ml, 10 mmoles) and glacial acetic acid (1.2 ml) as described for compound **5a**, except that the extraction was carried out with methylene chloride (80 ml). The product (2.6 g, 88%) turned brown at 165° and melted at 173-175° dec; tlc 7:3 ether/hexane, Rf 0.69; ir: ν max 3330 s (sharp) [NH], 2220 w (sharp) [C≡N], 1245 s, 1225 m, 1125 s, 1090 m, 1060 s [C-O], 3070 w, 3040 w, 1605 m, 1495 s, 815 m, 750 s, 710 s [aromatic]: 2950 m, 2920 m, 2860 m, 2840 w, 1450 s, 1375 s [CH_2, CH_3]; nmr (360 MHz, deuteriochloroform): δ 7.23 [s, 5H, H-Ar], 7.13 [s, 1H, H(2)-Ar], 6.95 [dd, J = 9, 2.7, 1H, H(6)-Ar], 6.76 [d, J = 9, 1H, H(5)-Ar], 5.95 [s, 2H, CH_2O], 4.93 [m, 1H, H-C(6)], 4.63 [s, 1H, H-C(2)], 3.82 [d, J = 12.5, 1H, CH_2N], 3.62 [d, J = 12.5, 1H, CH_2N], 3.34 [s, 3H, CH_3], 2.20 [m, 2H, H-C(4)], 2.06 [m, 2H, H-C(5)], 1.63 [br, disappeared on addition of deuterium oxide, NH]; ms: m/e (relative intensity) 366.3 [M⁺, 1], 340.3 [M⁺ + - 27 (HCN), 1], 339.2 [M⁺ - 27 (HCN), 2], 158 [24], 151 [11], 150 [20], 125 [23], 98.1 [16], 91 [100], 65 [11].

Anal. Calcd. for $C_{21}H_{22}O_4N_2$ (366.41): C, 68.83; H, 6.05; N, 7.65. Found: C, 68.71; H, 6.13; N, 7.77.

[3-Amino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride (**6a**).

To a solution of 3-*N*-benzylamino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-ylcarbonitrile hydrochloride (1.2 g, 3.2 mmoles) in ethanol-methanol (100:10 ml), 3 ml of ethanolic hydrogen chloride (2*N*) was added and the mixture was hydrogenated over platinum oxide (0.11 g, 0.48 mmole). The hydrogenation was run under 50 psi pressure and 40° temperature for 8 hours. At that time tlc (2:8:1 methanol/chloroform/ammonia, Rf 0.7) showed that the reaction was completed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure yielding the title product as dihydrochloride salt. This diamine dihydrochloride was purified by washing with anhydrous ether and acetone yielding 0.98 g (94%) of analytically pure material mp 170° (turns ivory), 186-188° dec; ir: ν max 2970-2820 (broad) [NH_3^+], 1582 m [δ as NH_3^+], 1520 m [δ s NH_3^+], 1610 m, 1510 s, 832 s [aromatic], 1254 s, 1182m, 1108 s, 1030 s [C-O], 1460 m, 1385 w [CH_2, CH_3]; nmr (360 MHz, deuteriodimethyl sulfoxide): δ 8.67 and 8.52 [br, disappeared on addition of deuterium oxide, NH_3^+], 7.39 [d, J = 8.7, 2H, H(2,6)-Ar], 6.94 [d, J = 8.7, 2H, H(3,5)-Ar], 3.82 [m, 2H, H-C(6)], 3.76 [s, 3H, CH_3O], 3.53 [d, J = 12.5, 1H, CH_2N], 2.25 [d, J = 12.5, 1H, CH_2N], 1.97 [m, 4H, H-C(4,5)], 1.72 [s, 3H, angular CH_3]; ms: of the free base m/e (relative intensity) 250 [M⁺, 2], 220 [M⁺ - 30 (CH_2NH_2), 3], 204 [M⁺ - 46 (CH_2NH_2, NH_2), 1], 150 [6], 135 [20], 100 [24], 72 [35], 44 [28], 37.5 [32], 35.4 [100].

Anal. Calcd. for $C_{14}H_{24}Cl_2O_2N_2$ (323.26): C, 52.01; H, 7.48; N, 8.67. Found: C, 52.33; H, 7.24; N, 8.71.

[3-Amino-2-(*p*-hydroxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride (**6b**).

3-*N*-Benzylamino-2-(*p*-benzyloxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-ylcarbonitrile hydrochloride (0.73 g, 1.6 mmoles) was hydrogenated over platinum oxide (0.07 g, 0.3 mmole) as described before (compound **6a**) yielding 0.44 g (92%) of diamine dihydrochloride, mp 163° (turned brown), melted at 178° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.35; ir: ν max 3420 m (broad) [OH], 2970-2850 s (broad) [NH_3^+], 1590 m [δ as NH_3^+], 1515 s [δ NH_3^+], 1610 s, 1510 s, 832 m [aromatic], 1245 m, 1180 m, 1100 m, 1020 m [C-O], 1450 m, 1382 m [CH_2, CH_3]; nmr (360 MHz, deuteriodimethyl sulfoxide): δ 8.61 [br, disappeared on addition of deuterium oxide, OH and NH_3^+], 7.36 [d, J = 10, 1H, H-Ar], 7.25 [d, J = 10, 1H, H-Ar], 6.92 [d, J = 10, 1H, H-Ar], 6.78 [d, J = 10, 1H, H-Ar], 3.80 [m, 2H, H-C(6)], 3.37 [d, J = 13.5, 1H, CH_2N], 2.31 [m, 1H, CH_2N], 1.84 [m, 4H, H-C(4,5)], 1.69 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{13}H_{22}ClO_2N_2$ (309.24): C, 50.49; H, 7.17; N, 9.06. Found: C, 50.72; H, 7.01; N, 9.31.

[3-Amino-2-methyl-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride (**6c**).

Compound **5c** (0.3 g, 0.78 mmole) was hydrogenated over platinum oxide (0.04 g, 0.18 mmole) as described for compound **6a**, yielding 0.235 g (90%) of the title product, mp 191° (turned orange), melted at 228-230° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.73; ir: ν max 2980-2850 s (broad) [NH_3^+], 1585 m [δ as NH_3^+], 1515 m [δ s NH_3^+], 1610 m, 1505 s, 815 m [aromatic], 1248 s, 1035 s [C-O], 1475 s, 1448 m, 1350 s [CH_2, CH_3]; nmr (60 MHz, deuteriodimethyl sulfoxide): δ 8.15 [br, disappeared on addition of deuterium oxide NH_3^+], 6.49 [m, 3H, H-Ar], 5.70 [s, 2H, CH_2O], 3.60 [m, 2H, H-C(6)], 3.21 [m, 1H, CH_2N], 2.31 [m, 1H, CH_2N], 2.00 [m, 4H, H-C(4,5)], 1.64 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{14}H_{22}Cl_2O_3N_2$ (337.25): C, 49.86; H, 6.58; N, 8.31; Cl, 21.03. Found: C, 49.63; H, 6.71; N, 8.19; Cl, 20.93.

[3-Amino-6-methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride (**6d**).

3-*N*-Benzylamino-6-methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-ylcarbonitrile hydrochloride (1.35 g, 3.4 mmoles) was hydrogenated over platinum oxide (0.13 g, 0.57 mmole) as described for compound **6a** yielding 1.04 g (91%) of the title product, mp 170° (turned ivory), 192-194° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.56; ir: ν max 2950-2840 s (broad) [NH_3^+], 1575 m [δ as NH_3^+], 1503 s [δ s NH_3^+], 1610 m, 1495 s, 820 m [aromatic], 1252 s, 1128 m, 1105 m, 1038 s [C-O]; nmr (360 MHz, deuteriodimethyl sulfoxide): δ 8.80 and 8.62 [br, disappeared on addition of deuterium oxide, NH_3^+], 6.96 [m, 3H, H-Ar], 6.05 [s, 2H, CH_2O], 5.05 [s, 1H, H-C(2)], 4.92 [m, 1H, H-C(6)], 3.70 [d, J = 13.9, 1H, CH_2N], 3.21 [s, 3H, OCH_3], 2.73 [d, J = 13.9, 1H, CH_2N], 2.14 [m, 4H, H-C(4,5)]; ms: of free diamine m/e (relative intensity) 280 [M⁺, 1], 264 [M⁺ - 16 (NH_2), 1], 250 [M⁺ - 30 (CH_2NH_2), 1] 213 [16], 201 [43], 149 [48], 122 [48], 72 [99], 45 [100], 32 [99].

Anal. Calcd. for $C_{14}H_{22}Cl_2O_4N_2$ (353.25): C, 47.60; H, 6.28; N, 7.93; Cl, 20.07. Found: C, 47.58; H, 6.14; N, 7.77; Cl, 19.98.

[3-*N*-Benzylamino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride (**7a**).

To a suspension of lithium aluminum hydride (0.12 g, 3.2 mmoles) in anhydrous THF (20 ml), placed in a two necked flask equipped with a dropping funnel and a condenser connected with a drying tube, a solution of aluminum chloride (0.43 g, 3 mmoles) in anhydrous THF (25 ml) was added rapidly under stirring. After five minutes a solution of **5a** (1 g, 3 mmoles) in anhydrous THF (40 ml) was added dropwise. The reaction mixture was stirred for 3.5 hours and at that point tlc (2:8:1 methanol/chloroform/ammonia, Rf 0.73) showed that the reaction was completed. A calculated amount of water was added dropwise and the mixture was filtered on Celite. The filtrate was evaporated yielding crude diamine which was converted to hydrochloride salt and purified in the usual manner (see compound **6a**) yielding 0.72 g (58%) of the title product, mp 145°; ir: ν max 3000-2800 s (broad) [NH_3^+, NH_2^+], 1578 m [δ as NH_3^+], 1510 s [δ s NH_3^+], 1258 s, 1181 s, 1100 m, 1070 s, 1030 m [C-O], 1611 m, 1500 m, 828 s, 740 m, 695 m [aromatic], 1450 s, 1385 m [CH_3, CH_2]; nmr (60 MHz, deuteriodimethyl sulfoxide): δ 9.90 [br, disappeared on addition of deuterium oxide, NH_2^+, NH_3^+], 7.46 [d, J = 9, 2H, H(2,6)-Ar], 7.23 [s, 5H, H-Ar], 7.13 [d, J = 9, 2H, H(3,5)-Ar], 4.23 [m, 4H, CH_2-Ar and H-C(6)], 4.08 [s, 3H, CH_3O], 3.50 [m, 1H, CH_2N], 2.35 [m, 1H, CH_2N], 1.88 [m, 4H, H-C(4,5)], 1.73 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{21}H_{30}Cl_2O_2N_2$ (413.38): C, 61.01; H, 7.32; N, 6.79; Cl, 17.15. Found: C, 60.74; H, 7.45; N, 6.94; Cl, 17.02.

N,N'-Diacetyl[3-amino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine (**8a**).

A solution of [3-amino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride (**6a**) (0.25 g, 0.77 mmole) and anhydrous sodium acetate (0.4 g, 4.7 mmoles) in anhydrous (by distillation) acetic anhydride (15 ml) and pyridine (2 ml) was placed in a round bottom flask equipped with a condenser and a drying tube. The reaction mixture was stirred for 72 hours and at that point tlc [3:2 ether/chloroform, Rf 0.2 (x 1), 0.34 (x 2)] showed that the reaction was complete. Then cold water (5 ml) was added and the mixture was stirred for 0.5 hour. The

solution was neutralized by addition of sodium carbonate and extracted with ether (3 x 80 ml). The organic layers were collected, dried over magnesium sulfate and evaporated to dryness yielding the title product which was recrystallized from acetone-petroleum ether to give 0.166 g (64%) of analytically pure material (mp 128°); ir: ν max 3385 m, 3285 m [NH], 1660 s, 1633 s [C=O], 1540 s, 1560 s [δ NH], 1298 m, 1305 m [ν C-N], 1258 s, 1181 m, 1098 s, 1030 m [C-O], 3005 w, 1610 m, 1510 s, 828 m [aromatic], 2965 w, 2940 w, 2880 w, 1455 m, 1380 m [CH_2, CH_3]; nmr (360 MHz, deuterioacetone): δ 7.46 [d, J = 9, 2H, H(2,6)-Ar], 6.86 [d, J = 9, 2H, H(3,5)-Ar], 3.78 [s, 3H, CH_3O], 3.72 [m, 2H, H-C(6)], 3.66 [d, J = 6.7, 1H, CH_2N], 3.59 [d, J = 6.7, 1H, CH_2N], 2.84 [s, disappeared on addition of deuterium oxide, CONH], 2.80 [t, disappeared on addition of deuterium oxide, CONH on N acetyl], 2.03 [m, 4H, H-C(4,5)], 1.86 [s, 3H, CH_3], 1.84 [s, 3H, CH_3 of N acetyl], 1.68 [s, 3H, angular CH_3]; ms: m/e (relative intensity) 334 [M⁺, 2], 303 [M⁺ - 31 (OCH_3), 1], 184 [32], 156 [20], 135 [30], 144 [43], 97 [30], 83 [24], 71 [26], 43 [100].

Anal. Calcd. for $C_{18}H_{26}O_4N_2$ (334.41): C, 64.65; H, 7.84; N, 8.38. Found: C, 64.83; H, 7.74; N, 8.45.

cis-[3-Amino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-ylmethylamine]dichloroplatinum(II) (**9a**).

To a solution of [3-amino-2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine dihydrochloride (**6a**) (0.15 g, 0.46 mmole) in 12 ml water, a solution of potassium tetrachloroplatinate (0.2 g, 0.48 mmole) in 10 ml water was added with stirring. The *p*H of the reaction was monitored (and maintained until the end of the reaction) at 6.5. After 1 hour a yellow precipitate appeared, but the reaction was run for an additional 21 hours. The precipitate was filtered (0.15 g) and the filtrate was evaporated to dryness under a stream of air. Anhydrous dimethylformamide (3 ml) was added to the residue, in order to dissolve the complex (in contrast to the inorganic byproducts), which was precipitated by the addition of anhydrous ether yielding additional 0.05 g of the title product (83% total yield). The complex at 240° turned gray and melted at 275° dec; ir: ν max 3205 s, 1535 m (bend) [NH_2], 552 m [Pt-N], 315 m, 322 m [Pt-Cl], 3010 w, 1610 m, 1510 m, 822 s [aromatic], 1250 s, 1185 m, 1100 s, 1030 m, [C-O], 2950 m, 2930 m, 2880 w, 1468 m, 1442 m, 1380 m [CH_2, CH_3]; nmr (360 MHz, deuteriodimethyl sulfoxide): δ 7.44 [d, J = 8.8, 2H, H(2,6)-Ar], 6.95 [d, J = 8.8, 2H, H(3,5)-Ar], 5.15 and 5.43 [br, NH_2], 3.78 [s, 3H, CH_3O], 3.74 [m, 2H, H-C(6)], 3.49 [d, J = 11.9, 1H, CH_2N], 2.08 [d, J = 11.9, 1H, CH_2N], 1.96 [m, 4H, H-C(4,5)], 1.59 [s, 3H, angular CH_3]; ms: (F. D. technique) 516.3 (M^+ ion), 443, 410, 408, 390, 279, 274, 256, 140.

Anal. Calcd. for $C_{14}H_{22}Cl_2O_2N_2Pt$ (516.34): C, 32.57; H, 4.29, N, 5.43; Cl, 13.73; Pt, 37.78. Found: C, 32.53; H, 4.25; N, 5.51; Cl, 13.63; Pt, 37.47.

cis-[3-Amino-2-(*p*-hydroxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-ylmethylamine]dichloroplatinum(II) (**9b**).

A solution of [3-amino-2-(*p*-hydroxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-yl]methylamine dihydrochloride (**6b**) (0.11 g, 0.36 mmole) was treated with potassium tetrachloroplatinate (0.15 g, 0.36 mmole) in water, as described for compound **9a**, yielding after 24 hours 0.105 g precipitate and 0.035 g from the solution (total yield 78%) of the pale yellow title product, mp 185° turned tan, melted at 220° dec; ir: ν max 3450 m (broad) [OH], 3220 s [NH_2], 550 w [Pt-N], 315 m, 328 w [Pt-Cl], 1610 m, 1510 s, 825 m [aromatic], 1240 s, 1180 m, 1096 s [C-O], 2940 s, 2930 s, 2900 m, 2858 m, 1465 m, 1450 m, 1380 m [CH_2, CH_3]; nmr (360 MHz, deuteriodimethyl sulfoxide): δ 9.50 [s, disappeared on addition of deuterium oxide, OH], 7.43 [d, J = 9, 1H, H-Ar], 7.30 [d, J = 9, 1H, H-Ar], 6.92 [d, J = 9, 1H, H-Ar], 6.78 [d, J = 9, 1H, H-Ar], 5.47 and 5.12 [m, NH_2], 3.77 [m, 2H, H-C(6)], 3.42 [d, J = 13.8, 1H, CH_2N], 2.08 [m, 1H, CH_2N], 1.90 [m, 4H, H-C(4,5)], 1.57 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{13}H_{20}Cl_2O_2N_2Pt$ (502.31): C, 31.08; H, 4.01; N, 5.58; Cl, 14.12; Pt, 38.84. Found: C, 31.08; H, 4.12; N, 5.75; Cl, 13.97; Pt, 38.57.

cis-[3-Amino-2-methyl-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-ylmethylamine]dichloroplatinum(II) (**9c**).

A solution of [3-amino-2-methyl-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]methylamine dihydrochloride (**6c**) (0.11 g, 0.33 mmole) was treated in water with 0.14 g (0.33 mmole) potassium tetrachloroplatinate, as described for the compound **9a**, yielding after 24 hours 0.14 g (81%) of the pale yellow complex mp 206-208°; ir: ν max 3210 s [NH_2], 1252 s, 1095 m, 1034 s [C-O], 3000 w, 1612 w, 1503 m, 810 m [aromatic], 2940 m, 2890 w, 1485 s, 1440 m [CH_2, CH_3], 568 w [Pt-N], 322 w, 314 m [Pt-Cl]; nmr (60 MHz, deuteriodimethyl sulfoxide): δ 6.84 [m, 3H, H-Ar], 5.85 [s, 2H, CH_2O], 5.08 [br, NH_2], 3.65 [m, 2H, H-C(6)], 3.60 [m, 1H, CH_2N], 2.39 [m, 1H, CH_2N], 1.99 [m, 2H, H-C(4,5)], 1.58 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{14}H_{20}Cl_2O_3N_2Pt$ (530.32): C, 31.71; H, 3.80; N, 5.28; Cl, 13.37; Pt, 36.79. Found: C, 31.64; H, 3.79; N, 5.33; Cl, 13.50; Pt, 36.51.

cis-[3-Amino-6-methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-ylmethylamine]dichloroplatinum(II) (**9d**).

Treatment of a solution of [3-amino-6-methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]methylamine dihydrochloride (**6d**) (0.17 g, 0.48 mmole) with potassium tetrachloroplatinate (0.2 g, 0.48 mmole) in water, as described for the compound **9a**, yielded 0.076 g precipitate and 0.115 g from the solution (total yield 72%) of the ivory complex, mp 244.5-246.5° dec; ir: ν max 3200 s, 1650 m (bend) [NH], 547 w [Pt-N], 312 m, 326 w [Pt-Cl], 1610 m, 1502 s, 812 m [aromatic], 1245 s, 1125 m, 1040 s [C-O], 2930 s, 2845 m, 1480 s, 1445 s [CH_2, CH_3]; nmr (360 MHz, deuteriodimethyl sulfoxide): δ 6.89 [d, J = 9, 1H, H-Ar]; 6.73 [s, 1H, H-Ar], 6.71 [d, J = 9, 1H, H-Ar], 5.99 [s, 2H, CH_2O], 5.28 [br, NH_2], 4.89 [s, 1H, H-C(2)], 4.78 [d, J = 4.6, 1H, H-C(6)], 3.61 [d, J = 12.5, 1H, CH_2N], 3.27 [s, 3H, CH_3O], 2.37 [d, J = 12.5, 1H, CH_2N], 2.10 [m, 4H, H-C(4,5)].

Anal. Calcd. for $C_{14}H_{20}Cl_2O_4N_2Pt$ (546.32): C, 30.78; H, 3.69; N, 5.13. Found: C, 30.55; H, 3.97; N, 5.25.

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