Products from Furans. XV [1a]. Synthesis of Novel Tyramine Derivatives *via* 6-Hydroxy-2*H*-Pyran-3(6*H*)-ones

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Furan chemistry was utilized for the synthesis of several novel tyramine derivatives. Thus 2*H*-pyran-3(6*H*)-ones were used as keystone intermediates for the preparation of novel α,β-disubstituted tyramine derivatives. Furthermore by the same approach tyramine was derivatized with a molecule of GABA.

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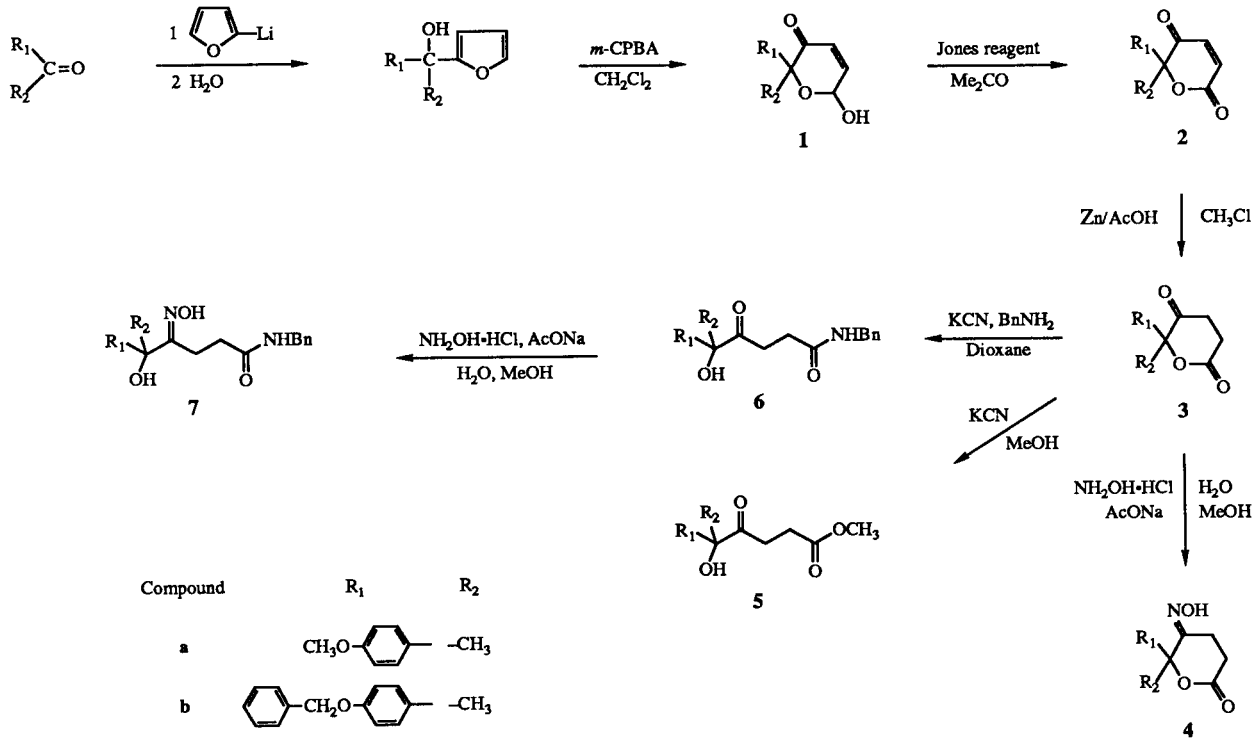
Introduction.

Catecholamine neurotransmission is of physiological importance in both the central nervous system and the periphery [2]. Out of this class of compounds dopamine receptors are the most important, since they not only mediate the actions of many psychotropic drugs, but also they play a role in several psychiatric and neurological illnesses as well as in vascular regulation. Thus ligands for dopamine receptors have been used either as basic research tools or as therapeutic agents [3] and numerous reviews outlining the structural requirements for agonist activity at dopamine receptors have been published [4]. On the other hand current studies on both D-1 and D-2 dopamine receptors have established that the catechol moiety is not required for activation of D-2 [5] receptors. Thus several non-catechol sympathomimetic amines and especially tyramine derivatives have been identified as selective D-2 receptor agonists [6].

In our search for the synthesis of new, more potent dopamine receptor agonists, we have used the furan chemistry approach *via* 6-hydroxy-2*H*-pyran-3(6*H*)-ones. An important feature inherent to the latter molecules is that they are admirably endowed with different functionalities suitable for further elaboration by reaction with selected nucleophiles and electrophiles. Thus a broad variety of biologically important compounds have been prepared from this molecule [7]. In the present work we described the synthesis of several novel α,β-disubstituted derivatives of tyramine *via* 6-hydroxy-2*H*-pyran-3(6*H*)-ones. These new compounds because of their α,β-substitution, are expected to act as false neurotransmitters by blocking the synthesis of norepinephrine and replacing it at the adrenergic terminals. Furthermore the substitution on α-carbon blocks their oxidation by monoamine oxidase

Scheme I



(MAO) thus greatly prolonging the duration of their action, while substitution on the β-carbon increases their α- and β-activity [2].

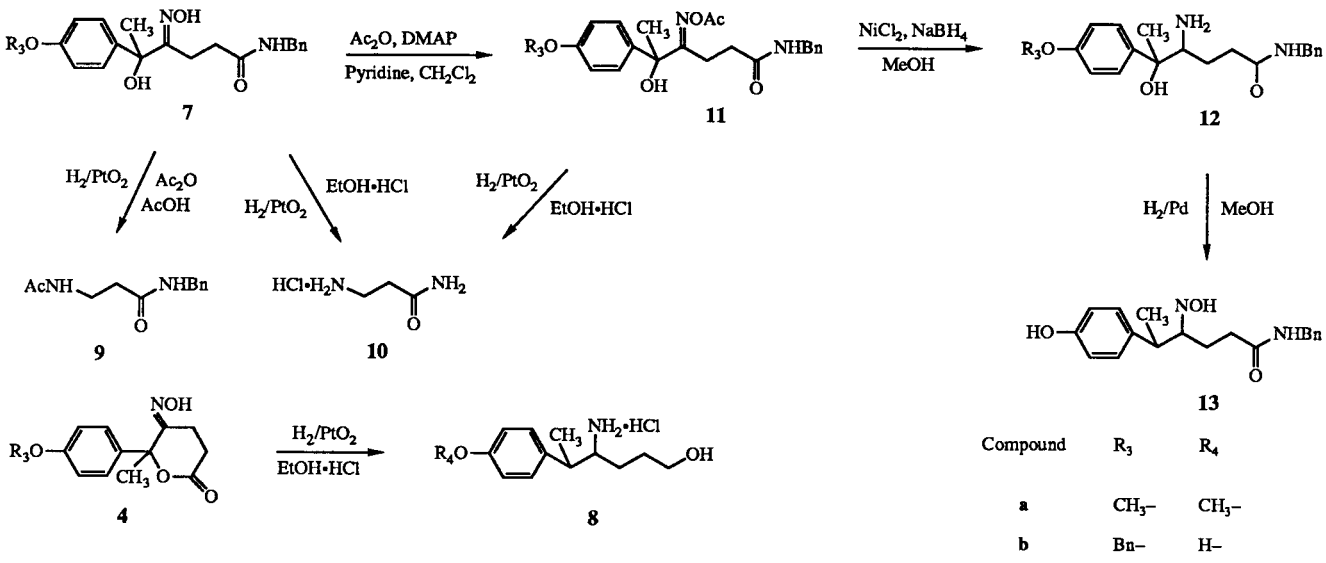
On the other hand having in mind that γ-aminobutyric acid (GABA) which is widely recognized as the principal inhibitory neurotransmitter in the brain [8], is not able to penetrate the blood brain barrier (BBB) [9], we have combined in a single molecule an active amide analogue of GABA with the prepared tyramine derivatives. The presence of GABA in these molecules is expected to enhance their neurotransmittive activity.

Results and Discussion.

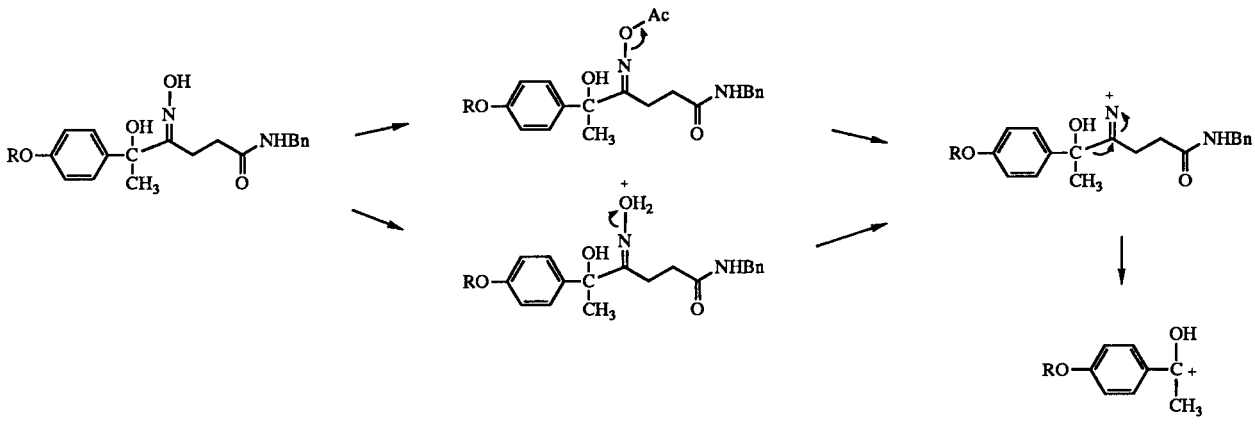
As substrates for our synthetic routes we have utilized the appropriately substituted (at 2-position) derivatives of 6-hydroxy-2*H*-pyran-3(6*H*)-ones **1a** and **1b**. These compounds were prepared, almost quantitatively, by reaction of furyllithium with *p*-methoxy(or *p*-benzyloxy)acetophenones and subsequent oxidation of the resulted 2-furylcarbinols [10]. Successively Jones oxidation and hydrogenation (with zinc/acetic acid) of these compounds afforded the corresponding δ-lactone derivatives **3a** and **3b**. Treatment of these compounds with a potassium cyanide solution caused the δ-lactone ring opening in two ways. More specifically in the presence of methanol as a protic solvent produced the corresponding methyl ester **5a** by solvolysis, while upon nuclophilic attack by benzylamine in dioxane as an aprotic solvent, it was converted to the corresponding benzyl amides **6a** and **6b**. It is evident that in both cases potassium cyanide acts as a soft base, facilitating thus the δ-lactone ring opening. It must also be noted that the addition of benzylamine in methanol did not lead to amide but rather to the methanolysis product.

Reaction of the prepared ketones **3a**, **3b**, **6a** and **6b** with hydroxylamine afforded the oximes **4a**, **4b**, **7a** and **7b**, which by catalytic hydrogenation and reduction yield-

Scheme II



Scheme III



ed the desired tyramine derivatives as outlined in Scheme II. More specifically, catalytic hydrogenation of oximes **4a** and **4b** over platinum oxide at 45 psi pressure led to the desired tyramine derivatives **8a** and **8b**, while the tertiary benzylic hydroxy group (which was formed when the δ-lactone ring opened) was removed. On the other hand, catalytic hydrogenation of oximes **7a** and **7b** caused hydrogenolytic cleavage of a C-C bond by removal of the aromatic moiety, leading to the undesired GABA derivatives **9** and **10**. This type of bond breaking presumably occurred *via* the proposed in Scheme III mechanism and is due to the great stability of the carbonium ion formed. The same hydrogenolysis products were also obtained at atmospheric pressure or when palladium was used as the catalyst. Furthermore since these oximes can not be reduced with metal hydrides, because reduction with lithium aluminum hydride leads to undesired aziridine by-products [11] and sodium borohydride is not able to reduce the oxime group, we have converted them to their corresponding acetoxyimino derivatives **11a** and **11b** by reaction with acetic anhydride and pyridine in the presence of *N,N*-dimethylaminopyridine (DMAP). These acetoxy derivatives are able to undergo reduction with a mixture of sodium borohydride and nickel chloride affording tyramine derivatives which were substituted with amidic GABA analogues, compounds **12a** and **12b**. Furthermore, catalytic hydrogenation of compound **12b** caused hydrogenolysis of the benzyl ether and tertiary hydroxyl groups, with the benzyl amide group remaining intact, leading to compound **13**.

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 [12] and the column packing was Merck 32-63 μm. The nmr spectra were recorded on Varian 360 EM (60 MHz) or on General Electric QE 300 (300 MHz) spectrometers in the indicated solvents. Chemical shifts are reported in part per million from tetramethylsilane as the internal standard (δ scale); multiplicities indicated by s (singlet), d (doublet), t (triplet), 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%). Microanalytical data were provided by the Microanalytical Service Laboratories of the University of Illinois, USA and University of Thessaloniki, Greece. *n*-Bytyllithium 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/Inc., Alfa (Ventron), Merck, Ferak, Fluka and BDH. All solvents were used as received.

Starting Materials.

6-Hydroxy-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-one (**1a**), 2-(*p*-benzyloxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-one (**1b**), δ-(*p*-methoxyphenyl)-δ-methyl-δ-(γ-oxo)crotonolactone (**2a**), δ-(*p*-methoxyphenyl)-δ-methyl-δ-(γ-oxo)valerolactone (**3a**) and γ-hydroxylimino-δ-(*p*-methoxyphenyl)-δ-methyl-δ-valerolactone (**4a**), have been prepared according to the literature [10]. The above compounds have been characterized by melting point, ir and ^1H nmr data.

δ-(*p*-Benzyloxyphenyl)-δ-methyl-δ-(γ-oxo)crotonolactone (**2b**).

To an ice cold stirred solution of **1b** (3 g, 9.8 mmoles) in 100 ml of acetone, Jones reagent [13] (3.5 ml) was added dropwise. After stirring for additional 15 minutes, tlc (7:3 ether/hexane, Rf 0.62) showed that the reaction was completed. Then the solid inorganic by-products were eliminated by decantation, the liquid layer was evaporated under reduced pressure and the resulted residue was partitioned in ethyl acetate (200 ml) and water (50 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to a yellowish oily residue, which was crystallized from ether to give 2.8 g (94%) of the pure δ-lactone as pale yellow needles, mp 83-84°; ir ν max 1730 s [conj. O-C=O], 1695 s [conj. C=O], 1630 w [C=C], 1250 s, 1095 s, 1020 s [C-O], 3020 w, 3010 w, 1605 s, 1510 s, 830 s, 750 s, 690 m [aromatic], 2980-2830 m (broad), 1475 w, 1455 w, 1370 m [CH_2, CH_3]; ^1H nmr (deuteriochloroform): 300 MHz δ 7.40 [s, 5H, H-Ar], 7.30 [d, J = 9.2, 2H, H(2,6)-Ar], 6.98 [d, J = 9.2, 2H, H(3,5)-Ar], 6.81 [d, J = 9.5, 1H, H-C(3)], 6.65 [d, J = 9.5, 1H, H-C(4)], 5.05 [s, 2H, CH_2O], 1.87 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{19}H_{16}O_4$ (308.32): C, 74.01; H, 5.23. Found: C, 74.53; H, 5.31.

δ-(*p*-Benzyloxyphenyl)-δ-methyl-δ-(γ-oxo)valerolactone (**3b**).

To a stirred solution of **2b** (2 g, 6.5 mmoles) in 65 ml of chloroform and 40 ml of glacial acetic acid, maintained below 15°, well powdered zinc dust (2.5 g) was added portionwise. The reaction mixture was allowed to proceed at room temperature and stirring was continued for a total period of 3 hours. At that point tlc (3:2 ether/hexane, Rf 0.44) showed that the reaction had ended. The inorganic salts were removed by filtration and the filtrate was azeotroped with benzene under reduced pressure. The oily residue was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. Evaporation of the solvent yielded **3b** as a white solid which was recrystallized from ether/hexane to give 1.9 g (95%), melting at 90.5-92.5°; ir: ν max 1760 s [O-C=O], 1730 s [C=O], 1245 s, 1080 s, 1010 s [C-O], 3040 w, 3020 w, 1610 s, 1510 s, 840 s, 750 s, 700 s [aromatic], 2985 w, 2940 w, 2880 w, 1470 w, 1420 m, 1380 m, 1370 m [CH_2, CH_3]; ^1H nmr (deuteriochloroform): 300 MHz δ 7.19 [s, 5H, H-Ar], 7.13 [d, J = 9, 2H, H(2,6)-Ar], 6.78 [d, J = 9, 2H, H(3,5)-Ar], 4.94 [s, 2H, CH_2O], 2.53 [m, 3H, H-C(3) and H_{eq}-C(4)], 2.40 [m, 1H, H_{ax}-C(4)], 1.60 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{19}H_{18}O_4$ (310.33): C, 73.58; H, 5.85. Found: C, 73.46; H, 5.91.

δ-(*p*-Benzyloxyphenyl)-γ-hydroxylimino-δ-methylvalerolactone (**4b**).

To a solution of compound **3b** (2 g, 6.5 mmoles) in 40 ml of methanol, heated at 55°, a solution of hydroxylamine hydrochlo-

ride (1.6 g, 22 mmoles) and sodium acetate trihydrate (2.7 g, 20 mmoles) in 30 ml water was added under stirring in one pot. The stirring was continued at that temperature for 1 hour and at that point tlc (7:3 ether/hexane Rf 0.38) showed that the reaction was completed. Then the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (150 ml) and water (75 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure yielding a white solid, which was recrystallized from ethyl acetate/hexane to give 1.9 g (91%) of the title product **4b** (mp 110-112°); ir: ν max 3270 m (broad) [OH], 1765 s [O-C=O], 1675 m [C=N], 925 m [δ N-O], 1250 s, 1010 s [C-O], 3060 w, 3040 w, 1605 s, 1510 s, 840 s, 745 s, 700 m [aromatic], 3000-2830 w (broad), 1470 w, 1455 m, 1390 m [CH_2, CH_3]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 10.22 [s, disappeared on addition of deuterium oxide, 1H, OH], 7.32 [s, 5H, H-Ar], 7.19 [d, J = 8.9, 2H, H(2,6)-Ar], 6.84 [d, J = 8.9, 2H, H(3,5)-Ar], 5.00 [s, 2H, CH_2O], 2.78 [m, 2H, H-C(3)], 2.34 [m, 1H, H_{eq}-C(4)], 2.09 [m, 1H, H_{ax}-C(4)], 1.66 [s, 3H, angular CH_3].

Anal. Calcd. for $C_{19}H_{19}NO_4$ (325.35): C, 70.14; H, 5.89; N, 4.31. Found: C, 69.93; H, 5.82; N, 4.53.

5-Hydroxy-5-(*p*-methoxyphenyl)-4-oxohexanoic Acid Methyl Ester (**5a**).

To a solution of compound **3a** (2.3 g, 10 mmoles) in 20 ml of absolute methanol potassium cyanide (0.78 g, 12 mmoles) was added and the raction mixture was heated gradually with stirring at 55°. After 20 hours of stirring at that temperature, tlc (ether, Rf 0.57) showed that the reaction was completed. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in ethyl acetate (100 ml) and water (50 ml). The organic layer was separated, washed successively with a saturated solution of sodium bicarbonate and brine, dried over magnesium sulfate and the solvent was removed under reduced pressure yielding 2.14 g (82%) of the title product **5a** (mp 61-63°), which was recrystallized from diethyl ether ; ir: ν max 3380 m (broad) [OH], 1735 s [O-C=O], 1720 [C=O], 1250 s, 1145 m, 1035 s [C-O], 1030 w, 1610 s, 1510 s, 835 s [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.25 [d, J = 9.1, 2H, H(2,6)-Ar], 6.80 [d, J = 9.1, 2H, H(3,5)-Ar], 3.85 [s, 3H, $COOCH_3$], 3.70 [br, disappeared on addition of deuterium oxide, 1H, OH], 3.63 [s, 3H, CH_3O], 2.70 [s, 3H, CH_3], 2.55 [m, 4H, H-C(2,3)].

Anal. Calcd. for $C_{14}H_{18}O_5$ (266.28): C, 63.14; H, 6.81. Found: C, 63.22; H, 6.71.

5-Hydroxy-5-(*p*-methoxyphenyl)-4-oxohexanoic Acid Benzylamide (**6a**).

A solution of compound **3a** (2.34 g, 10 mmoles) in 20 ml of anhydrous dioxane was treated with potassium cyanide (0.78 g, 12 mmoles) and benzylamine (1.4 ml, 12.8 mmoles). The reaction mixture was treated as for compound **5** and the product was purified by flash chromatography (1:1 ether/hexane as eluant) giving 2.6 g (76%) of the title product **6a** (mp 70-71.5°; tlc ether 0.29); ir: ν max 3400 s (broad) [OH], 3300 s [NH], 1715 s [C=O], 1660 s [NHC=O], 1255 s, 1110 m, 1035 m [C-O], 3030 w, 1610 m, 1510 s, 825 s, 735 s, 695 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.30 [d, J = 9, 2H, H(2,6)-Ar], 7.25 [s, 5H, Ar], 6.80 [d, J = 9, 2H, H(3,5)-Ar], 6.30 [t, J = 5.8, disappeared on addition of deuterium oxide, 1H, CONH], 4.75 [br, disappeared on addition of deuterium oxide, 1H, OH], 4.36 [d, J = 5.8, 2H, CH_2N], 3.75 [s, 3H, CH_3O], 2.70 [m, 2H, H-C(3)], 2.40 [m, 2H, H-C(2)], 1.70 [s, 3H, CH_3].

Anal. Calcd. for $C_{20}H_{23}NO_4$ (341.39): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.28; H, 6.68; N, 4.03.

5-(*p*-Benzyloxyphenyl)-5-hydroxy-4-oxohexanoic Acid Benzylamide **6b**.

δ-(*p*-Benzyloxyphenyl)-δ-methyl-δ-(γ-oxo)valerolactone (**3b**) (1.4 g, 4.5 mmoles) was treated with potassium cyanide (0.38 g, 5.7 mmoles) and benzylamine (0.65 ml, 5.7 mmoles) in 20 ml of absolute methanol as described for compound **6a** yielding 1.54 g (82%) of the title product (mp 90-92°; tlc ether, Rf 0.27); ir: ν max 3380 m [NH], 3310 m (broad) [OH], 1710 s [C=O], 1650 s [NHC=O], 1245 s, 1110 m, 1010 s [C-O], 3030 w, 1605 s, 1510 s, 830 s, 740 s, 690 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.37 [s, 5H, H-Ar], 7.30 [d, J = 9, 2H, H(2,6)-Ar], 7.18 [s, 5H, H-Ar], 6.90 [d, J = 9, 2H, H(3,5)-Ar], 6.25 [t, J = 5.8, disappeared on addition of deuterium oxide, 1H, CONH], 5.00 [s, 2H, CH_2O], 4.65 [br, disappeared on addition of deuterium oxide, 1H, OH], 4.25 [d, J = 5.8, 2H, CH_2N], 2.55 [m, 4H, H-C(2,3)], 1.70 [s, 3H, CH_3].

Anal. Calcd. for $C_{26}H_{27}NO_4$ (417.49): C, 74.70; H, 6.52; N, 3.36. Found: C, 74.67; H, 6.66; N, 3.28.

5-Hydroxy-4-hydroxylimino-5-(*p*-methoxyphenyl)hexanoic Acid Benzylamide **7a**.

To a stirred solution of compound **6a** (4.1 g, 12 mmoles) in 70 ml of methanol, heated at 55°, a solution of hydroxylamine hydrochloride (7.2 g, 100 mmoles) and sodium acetate trihydrate (13.1 g, 97 mmoles) in 40 ml of water was added in one pot and the stirring was continued for 1 hour. At that point tlc (ether, Rf 0.49) showed that the reaction was completed. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (150 ml) and water (40 ml). The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure yielding a white solid which was recrystallized from ether/hexane to give 3.8 g (91%) of the desired product (mp 111-113°); ir: ν max 3340 s [NH], 3240 s (broad) [OH] 1640 s [NHC=O], 1250 s, 1150 m, 1030 m [C-O], 3020 w, 1600 s, 1505 s, 835 s, 750 s, 695 s [aromatic]; ^{1}H nmr (deuterioacetone): 60 MHz δ 9.95 [br, disappeared on addition of deuterium oxide, 1H, NOH], 7.35 [d, J = 9, 2H, H(2,6)-Ar], 7.28 [s, 5H, H-Ar], 6.85 [d, J = 9, 2H, H(3,5)-Ar], 6.30 [br, disappeared on addition of deuterium oxide, 1H, CONH], 5.55 [s, disappeared on addition of deuterium oxide, 1H, OH], 4.40 [d, J = 6, 2H, CH_2N], 3.80 [s, 3H, CH_3O], 2.65 [m, 2H, H-C(2)], 2.25 [m, 2H, H-C(3)], 1.65 [s, 3H, H-C(6)].

Anal. Calcd. for $C_{20}H_{24}N_2O_4$ (356.41): C, 67.39; H, 6.79; N, 7.86. Found: C, 67.19; H, 6.81; N, 7.91.

5-(*p*-Benzyloxyphenyl)-5-hydroxy-4-hydroxyliminohexanoic Acid Benzylamide **7b**.

A solution of 5-(*p*-benzyloxyphenyl)-5-hydroxy-4-oxohexanoic acid benzylamide **6b** (1 g, 2.4 mmoles) in 35 ml of methanol was treated with a solution of hydroxylamine hydrochloride (2.9 g, 40 mmoles) and sodium acetate trihydrate (5.2 g, 38 mmoles) in 20 ml of water as described for compound **7b**, yielding 0.96 g (94%) of the desired product (mp 145-146.5°; tlc ether, Rf 0.31); ir: ν max 3430 s [NH], 3300 s (broad) [OH], 1645 [NHC=O], 1240 s, 1140 m, 1020 m [C-O] 945 m [δ N-O], 3020 w, 1600 m, 1505 s, 835 s, 740 s, 690 s [aromatic]; ^{1}H nmr (deuteriochloroform): 300 MHz δ 9.88 [s, disappeared on addition of deuterium oxide, 1H, NOH], 7.37 [d, J = 8.9, 2H, H(2,6)-Ar], 7.30 [s, 5H, H-Ar], 7.20 [s, 5H, H-Ar], 6.90 [d, J = 8.9, 2H, H(3,5)-Ar], 6.10 [t, J = 6, disappeared on addition of deuterium oxide, 1H, CONH], 5.55 [br, dis-

appeared on addition of deuterium oxide, 1H, OH], 5.10 [s, 2H, CH_2O], 4.35 [d, J = 6, 2H, CH_2N], 2.90 [m, 2H, H-C(2)], 2.20 [m, 2H, H-C(3)], 1.60 [s, 3H, CH_3].

Anal. Calcd. for $C_{26}H_{28}N_2O_4$ (432.50): C, 72.20; H, 6.52; N, 6.48. Found: C, 72.38; H, 6.67; N, 6.57.

1-(*p*-Methoxymethylbenzyl)propan-4-olamine Hydrochloride **8a**.

To a solution of compound **4a** (1.25 g, 5 mmoles) in 100 ml of absolute ethanol, 4 ml of ethanolic hydrogen chloride (2*N*) was added and the mixture was hydrogenated over platinum oxide (0.12 g, 0.5 mmoles). The hydrogenation was run under 45 psi pressure for 4 hours. At that time tlc (2:8:1 methanol/chloroform/-ammonia, Rf 0.4) showed that the reaction was completed. The catalyst was removed by filtration and the solvent was removed under reduced pressure, yielding the title product as hydrochloride salt which was purified by washing with anhydrous ether and acetone giving 1 g (92%) of analytically pure material mp 234-235° dec; ir: ν max 3350 m [OH], 2970-2820 s (broad) [NH_3^+], 1580 m [δ as NH_3^+], 1520 m [δ s NH_3^+], 1250 s, 1105 s, 1030 s [C-O], 1610 m, 1500 s, 830 s [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): 60 MHz δ 8.55 [br, disappeared on addition of deuterium oxide, 3H, NH_3^+], 7.33 [d, J = 8.7, 2H, H(2,6)-Ar], 6.92 [d, J = 8.7, 2H, H(3,5)-Ar], 4.12 [m, disappeared on addition of deuterium oxide, 1H, OH], 3.81 [s, 3H, CH_3O], 3.65 [m, 3H, H-C(4) and CH], 3.32 [m, 1H, H-C(1)], 1.85 [m, 2H, H-C(2)], 1.38 [m, 5H, H-C(3) and CH_3].

Anal. Calcd. for $C_{13}H_{22}ClNO_2$ (259.78): C, 60.10; H, 8.54; N, 5.39. Found: C, 60.22; H, 8.31; N, 5.31.

1-(*p*-Hydroxymethylbenzyl)propan-4-olamine Hydrochloride **8b**.

δ-(*p*-Benzyloxyphenyl)-γ-hydroxylimino-δ-methylvalerolactone (**4b**) (1.63 g, 5 mmoles) was hydrogenated over platinum oxide (0.12 g, 5 mmoles) as described before for compound **8a** yielding 1.1 g (89%) of amine hydrochloride, mp 220-222° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.3; ir: ν max 3400 s (broad) [OH], 3000-2820 s (broad) [NH_3^+], 1590 m [δ as NH_3^+], 1515 s [δ s NH_3^+], 1245 s, 1100 m, 1020 m [C-O], 1610 s, 1500 s, 835 m [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): 60 MHz δ 8.45 (br, disappeared on additon of deuterium oxide, 4H, OH and NH_3^+], 7.23 [d, J = 9.6, 2H, H(2,6)-Ar], 6.71 [d, J = 9.6, 2H, H(3,5)-Ar], 3.98 [br, disappeared on addition of deuterium oxide, 1H, OH], 3.59 [m, 3H, H-C(4) and CH], 3.18 [m, 1H, H-C(1)], 1.75 [m, 4H, H-C(2,3)], 1.41 [d, J = 6.9, 3H, CH_3].

Anal. Calcd. for $C_{12}H_{20}ClNO_2$ (245.75): C, 58.64; H, 8.20; N, 5.70. Found: C, 58.77; H, 8.01; N, 5.62.

4-Amino-5-hydroxy-5-(*p*-methoxyphenyl)hexanoic Acid Benzylamide **12a**.

To a stirred solution of compound **7a** (1.85 g, 5.2 mmoles) in 40 ml of methylene chloride were added acetic anhydride (0.64 g, 6.3 mmoles), pyridine (0.49, 6.3 mmoles) and several crystals of DMAP. The reaction was run at room temperature under stirring for 30 minutes. At that point tlc (ether, Rf 0.4) showed that the reaction was completed. Then the reaction mixture was quenched with 5 ml hydrochloric acid (0.01 *N*), washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the remaining yellowish residue was chromatographed (1:1 ethyl acetate/hexane as eluant) yielding the 4-acetoxyimino-5-hydroxy-5-(*p*-methoxyphenyl)hexanoic acid benzylamide **11a** as a colorless liquid (1.7 g, 83%) which was used without further purification; ir (thin film): ν max 3320 (broad) [OH], 3280 s [NH], 1760 s [C=O], 1655 s [NHC=O], 920 m [δ N-O], 1250 s, 1110 m, 1040 s [C-O], 3040 w, 1605 m, 1510 s, 830 s, 735 s, 695 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.35 [d, J = 9, 2H, H(2,6)-Ar], 7.25 [s, 5H, H-Ar], 6.85 [d, J = 9, 2H, H(3,5)-Ar], 6.45 [t, J = 5.7, disappeared on addition of deuterium oxide, 1H, CONH], 5.00 [br, disappeared on additon of deuterium oxide, 1H, OH], 4.40 [d, J = 5.7, 2H, CH_2N], 3.75 [s, 3H, CH_3O], 2.50 [m, 4H, H-C(2,3)], 2.15 [s, 3H, $COCH_3$], 1.76 [s, 3H, CH_3]. In a mixture of compound **11a** (0.8 g, 2 mmoles) and nickel chloride hexahydrate (1.19 g, 5 mmoles) in 30 ml of absolute methanol, cooled at −10°, sodium borohydride (0.76 g, 20 mmoles) was added in portions under stirring. The reaction was allowed to reach room temperature and continued for 5 hours. At that point tlc (1:6:1 methanol/-ethyl acetate/hexane Rf 0.13) showed that the reaction was complete. The reaction was quenched with 50 ml of saturated solution of sodium chloride and 150 ml of ethyl acetate. The organic layer was separated and extracted with 50 ml hydrochloric acid (1*N*). Thus the product was in the aqueous layer as the hydrochloride while the organic by-products remained in the organic layer. The aqueous layer was separated, neutralized with the addition of alkaline solution (sodium hydroxide 2*N*) and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to dryness yielding a slurry which was solidified upon addition of diethyl ether. Recrystallization from methanol/ether afforded 0.48 g (69%) of the desired amine as the free base (mp 120-121°); ir: ν max 3330 s [NH], 3220 s (broad) [OH], 1660 s [NHC=O], 1260 s, 1170 m, 1030 m [C-O], 3020 w, 1605 s, 1515 s, 840 s, 745 s, 700 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.35 [d, J = 9.2, 2H, H(2,6)-Ar], 7.25 [s, 5H, H-Ar], 6.80 [d, J = 9.2, 2H, H(3,5)-Ar], 6.32 [br, disappeared on addition of deuterium oxide, 1H, CONH], 4.46 [d, J = 6, 2H, CH_2N], 3.80 [s, 3H, CH_3O], 3.75 [s, disappeared on addition of deuterium oxide, 1H, OH], 2.88 [m, 1H, H-C(4)], 2.40 [m, 4H, H-C(2,3)], 2.00 [br, disappeared on addition of deuterium oxide, 2H, NH_2], 1.50 [s, 3H, CH_3].

Anal. Calcd. for $C_{20}H_{26}N_2O_3$ (342.43): C, 70.14; H, 7.65; N, 8.18. Found: C, 70.32; H, 7.86; N, 7.90.

4-Amino-5-(*p*-benzyloxyphenyl)-5-hydroxyhexanoic Acid Benzylamide **12b**.

5-(*p*-Benzyloxyphenyl)-5-hydroxy-4-hydroxyliminohexanoic acid benzylamide (**7b**) (2 g, 4.6 mmoles) was reacted with acetic anhydride (0.58 g, 5.7 mmoles), pyridine (0.45 g, 5.7 mmoles) and several crystals of DMAP in 40 ml of methylene chloride as described for compound **11a**, yielding 2.08 g (95%) of 4-acetoxyimino-5-(*p*-benzyloxyphenyl)-5-hydroxyhexanoic acid benzylamide (**11b**), melting at 109-111° (tlc ether, Rf 0.27); ir (thin film): ν max 3300 s (broad) [NH, OH], 1755 s [C=O], 1650 s [NHC=O], 1245 s, 1110 m, 1020 s [C-O], 3040 w, 1610 m, 1510 s, 845 s, 735 s, 690 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.35 [d, J = 9, 2H, H(2,6)-Ar], 7.30 [s, 5H, H-Ar], 7.25 [s, 5H, H-Ar], 6.90 [d, J = 9, 2H, H(3,5)-A], 6.05 [br, disappeared on addition of deuterium oxide, 1H, CONH], 5.00 [br, disappeared on addition of deuterium oxide, 1H, OH], 4.95 [s, 2H, CH_2O], 4.35 [d, J = 5.8, 2H, CH_2N], 2.50 [m, 4H, H-C(2,3)], 2.18 [s, 3H, $COCH_3$], 1.72 [s, 3H, CH_3]. A solution of compound **11b** (2.2 g, 4.6 mmoles) in 100 ml of methanol was treated with nickel chloride hexahydrate (2.65 g, 11 mmoles) and sodium borohydride (1.75 g, 46 mmoles) as described for compound **11a** affording 1.2 g (62%) of the title product (mp 129-131°; tlc 6:1 ethyl acetate/hexane, Rf 0.11); ir: ν max 3360 s (sharp) [NH], 3280 s (broad) [OH], 1665 s [NHC=O], 1250 s, 1095 m, 1035 m [C-O], 3060 w, 3030 w, 1600 s, 1510 s, 835

s, 745 s, 690 s [aromatic]; ^{1}H nmr (deuteriochloroform): 60 MHz δ 7.35 [s, 5H, H-Ar], 7.32 [d, J = 9, H(2,6)-Ar], 7.20 [s, 5H, H-Ar], 6.93 [d, J = 9, 2H, H(3,5)-Ar], 6.65 [br, disappeared on addition of deuterium oxide, 1H, CONH], 4.98 [s, 2H, CH_2O], 4.26 [m, 3H, (one disappeared on addition of deuterium oxide), CH_2N, OH], 3.20 [m, 1H, H-C(4)], 2.42 [m, 4H, H-C(2,3)], 1.89 [br, disappeared on addition of deuterium oxide, 2H, NH_2], 1.55 [s, 3H, CH_3].

Anal. Calcd. for $C_{26}H_{30}N_2O_3$ (418.52): C, 74.61; H, 7.22; N, 6.70. Found: C, 74.31; H, 7.38; N, 6.85.

4-Amino-5-(*p*-hydroxyphenyl)hexenoic Acid Benzylamide **13**.

A solution of **12b** (1 g, 2.4 mmoles) in 130 ml of methanol containing 0.1 g of 10% Pd/barium sulfate was hydrogenolysed by treatment with hydrogen at 45 psi pressure and at room temperature. Hydrogenolysis was completed within 4 hours, (tlc 1:6:1 methanol/ethyl acetate/hexane, Rf 0.11). The catalyst was filtered and the filtrate was evaporated under reduced pressure. The residue was crystallized from ether to give 0.66 g (89%) melting at 147-149° dec; ir: ν max 3410 s (broad) [OH], 3300 s (broad) [NH], 1660 s [NHC=O], 1235 s 1100 m, 1020 s [C-O], 3030 w, 1605 s, 1510 s, 830 s, 750 s, 695 s [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): 60 MHz δ 7.95 [br, disappeared on addition of deuterium oxide, 1H, OH], 7.33 [d, J = 9.5, 2H, H(2,6)-Ar], 7.25 [s, 5H, H-Ar], 6.83 [d, J = 9.5, 2H, H(3,5)-Ar], 6.38 [br, disappeared on addition of deuterium oxide, 1H, NHCO], 4.49 [d, J = 6, 2H, CH_2N], 2.93 [m, 1H, H-C(4)], 2.68 [m, 1H, H-C(5)], 2.35 [m, 4H, H-C(2,3)], 1.97 [br, disappeared on addition of deuterium oxide; 2H, NH_2], 1.42 [d, J = 7, 3H, CH_3].

Anal. Calcd. for $C_{19}H_{24}N_2O_2$ (312.40): C, 73.04; H, 7.74; N, 8.97. Found: C, 72.88; H, 7.71; N, 9.11.

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REFERENCES AND NOTES

[1a] For previous publications in the series see reference 7; [b] Taken in part from the Ph.D. Thesis of C. D. A., Agricultural University of Athens, Greece.

[2] I. R. Innes and M. Nickerson in The Pharmacological Basis of Therapeutics, 4th Ed, L. S. Goodman and A. Gilman eds, McMillan, New York, 1975, p 478.

[3] W. K. Brewster, D. E. Nichols, R. M. Riggs, D. M. Mottola, T. W. Lovenberg, M. H. Lewis and R. B. Mailman, *J. Med. Chem.*, **33**, 1756 (1990).

[4a] C. Kaiser and T. Jain, *Med. Res. Rev.*, **5**, 145 (1985); [b] J. G. Cannon, *Prog. Drug Res.*, **29**, 303 (1985).

[5a] J. W. Kebabian and D. B. Calne, *Nature*, **277**, 93 (1979); [b] L. I. Goldberg and J. D. Kohli in Advances in the Biosciences, Vol **37**, M. Kohsaka, T. Shohmori, Y. Tsukada and G. N. Woodruff eds, Pergamon Press, Oxford, England, 1982, p 41.

[6] C. Kaiser, P. A. Dandridge, E. Garvey, K. E. Flaim, R. L. Zeid and J. P. Hieble, *J. Med. Chem.*, **28**, 1803 (1985) and references within.

[7] M. P. Georgiadis in Trends in Medicinal Chemistry 88, Vol **12**, H. Van Der Goot, G. Domany, L. Pallos and H. Timmerman, eds, Elsevier Science Publishers, Amsterdam, The Netherlands, 1989, p 197.

[8] S. M. Nanvati and R. B. Silverman, *J. Med. Chem.*, **32**, 2413 (1989).

[9] P. Krogsgaard-Larsen, E. Falsch and H. Hjeds in Progress in Medicinal Chemistry 22, G. P. Ellis and G. B. West, eds, Elsevier Science Publishers Amsterdam, The Netherlands, 1985, p 68.

[10a] M. P. Georgiadis, S. A. Haroutounian and J. C. Bailar Jr., *J. Heterocyclic Chem.*, **25**, 995 (1988); [b] M. P. Georgiadis, S. A. Haroutounian and C. D. Apostolopoulos, *Synthesis*, in press.

[11] H. O. House Modern Synthetic Reactions, 2nd Ed, W. A. Benjamin Inc., London, 1972, p 76.

[12] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

[13] Jones reagent was prepared by dissolving 26.72 g of chromic trioxide in 23 ml of concentrated sulfuric acid and diluted with water to a volume of 100 ml.