Products from Furans. XVI [1]. Novel Synthetic Routes to Sympathomimetic Amine Analogues *via* 6-Hydroxy-2*H*-pyran-3(6*H*)-ones

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Novel heterocyclic analogues mimicking compounds with antipsychotic activity (sympathomimetic amines) were synthesized. These compounds contain the phenyl-substituted pyran ring system as a consequence of their common route of preparation. Furthermore an example of the synthetic route for preparing compounds having the features of both β-hydroxy-β-phenylethylamine and GABA is also presented.

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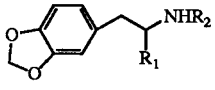
Introduction.

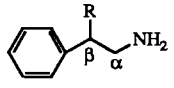
3,4-(Methylenedioxy)amphetamine (**1a**, MDA) and 3,4-(methylenedioxy)methamphetamine (**2a**, MDMA) are psychoactive agents which have become popular as recreational substances and are available on the illicit market as "love drug" and "ecstasy" [2]. They have gained their popularity due to their relatively mild effects and their ability to facilitate impersonal communication [3]. However, a number of psychiatrists have claimed that they possess unique properties in facilitating psychotherapy, by reducing the anxiety or fear which normally accompanies the discussion of emotionally painful events [4]. Furthermore current studies on α-ethyl homologues of these compounds **1b**, **2b** have established that they retain the useful therapeutic aspects of **1a** and **1b** while their hallucinogenic activity was completely abolished [5] and have considered them as representatives of a novel class of psychoactive drugs, known as entactogens [6]. In addition, as most antipsychotic agents [7], these compounds structurally are classified as sympathomimetic amines since they are considered derivatives of β-phenylethylamine (**3**), fulfilling thus the minimum structural requirements for sympathomimetic activity [8].

Scheme I



1a, $R_1 = CH_3$, $R_2 = H$
b, $R_1 = CH_2CH_3$, $R_2 = H$

2a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_2CH_3$, $R_2 = CH_3$



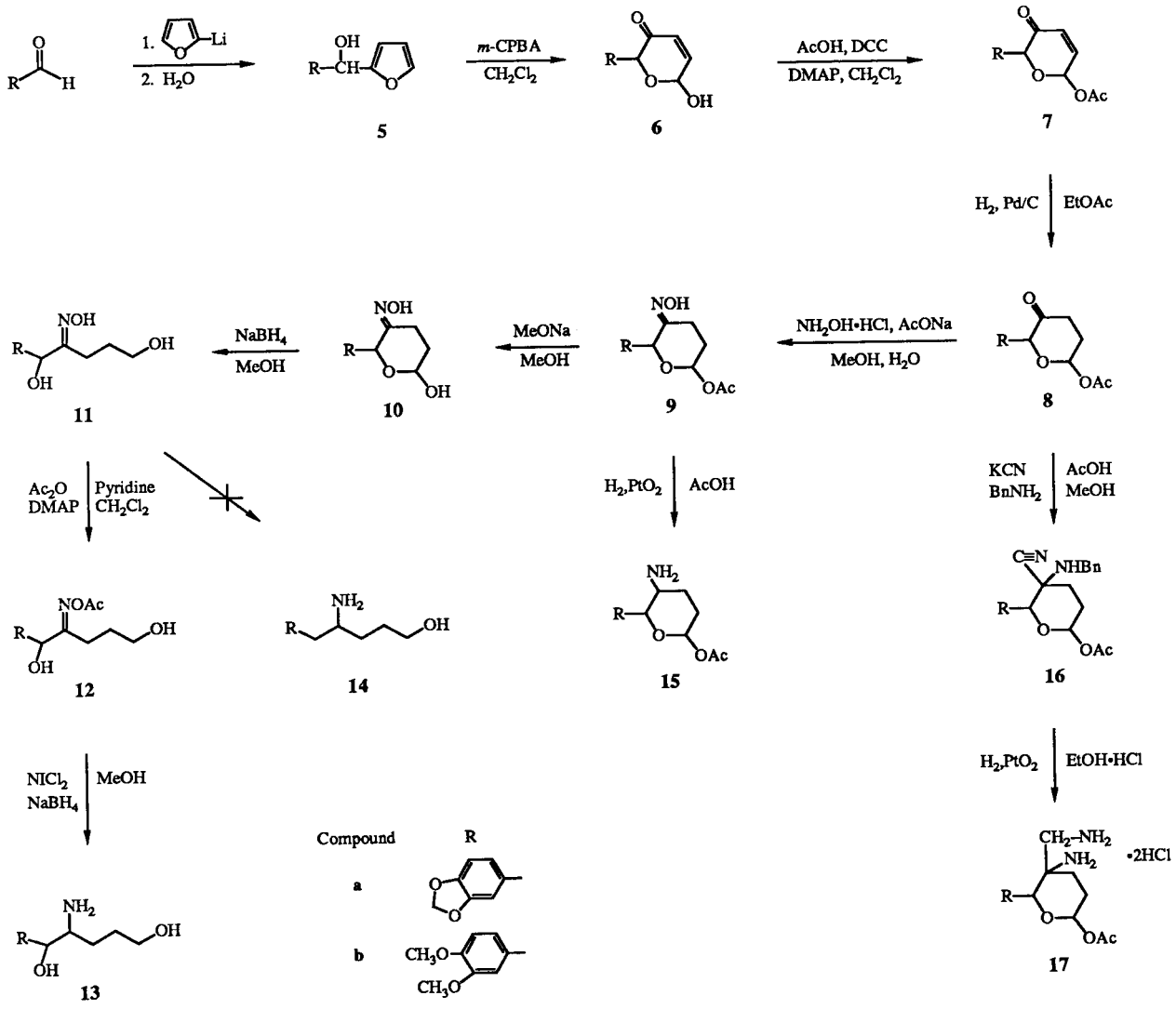
3 R = H
4 R = OH

The obvious need for new types of therapeutic substances for use in psychiatry [9], has stimulated us to investigate the potentials of this new class of psychiatric agents (entactogens) by preparing their novel heterocyclic analogues. Our working hypothesis was based on previous extensive work on the structural requirements for increased central nervous system (CNS) sympathomimetic (and antipsychotic) activity, which has underlined the importance of the existence of a hydroxy group (on the β-carbon) for high potency [10]. Thus we have prepared oxygen containing (on the β-position) heterocyclic analogues of these compounds. This synthetic goal was achieved by synthetic manipulations on appropriately substituted derivatives of 6-hydroxy-2*H*-pyran-3(6*H*)-ones. The prepared compounds because of their common route of preparation contain the β-phenylethylamine skeleton as part of a rigid phenyl-substituted pyran ring system. In addition, since replacement of the methyl substituent on the α-carbon of entactogens with an ethyl group causes drastic changes in their activity [5,6], we have opened the pyran ring and have obtained derivatives of known entactogens (on α-carbon) with a propanol structure, **13a** and **13b**. On the other hand the β-hydroxy-(as ether)-β-phenylethylamine moiety and the γ-aminobutyric acid (GABA-as lactone) are easily recognized in compound **20**. This existence of the GABA structure, which is widely recognized as a principal neurotransmitter in mammalian brain [11] is expected to enhance its neurotransmittive and sympathomimetic activity.

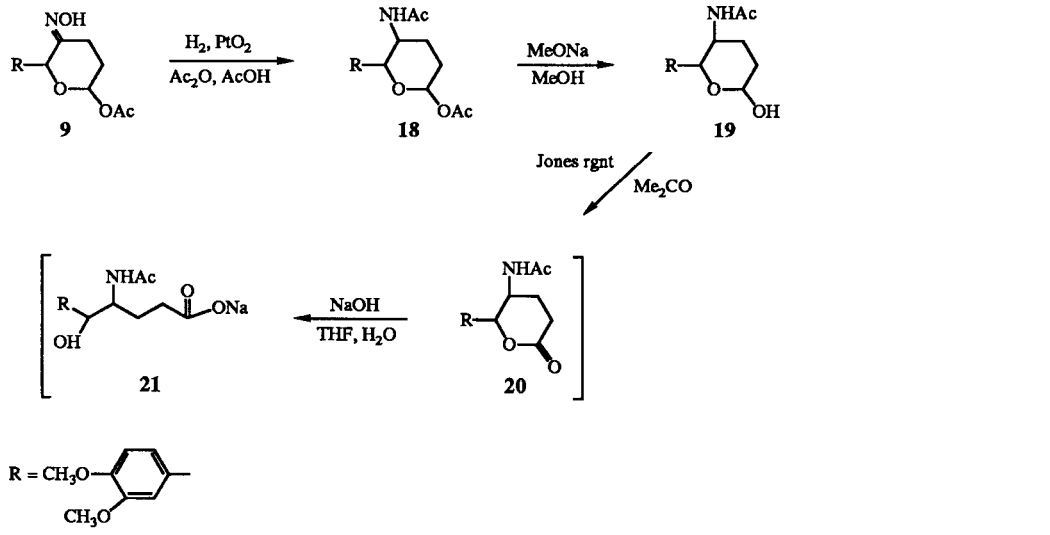
Results and Discussion.

Since our synthetic goal was to prepare compounds containing the structural framework of β-phenylethanolamine (**4**), our synthetic sequence (Scheme II) was designed so as to generate key intermediates, compounds **9a** and **9b**, which contain the desired aromatic moiety (3,4-methylenedioxyphenyl or 3,4-dimethoxyphenyl) along with a hetero-

Scheme II



Scheme III



cyclic moiety (the pyran ring) derivatized on the β-position by a nitrogen-containing group. This was achieved by transforming the appropriate benzaldehydes to 6-hydroxy-2*H*-pyran-3(6*H*)-ones **6a** and **6b** by reaction with furyllithium, subsequent oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) and further manipulations on the molecule. More specifically the 6-hydroxy group was converted to an acetoxyl group by reaction with acetic acid and 1,3-dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP). This method was preferred to the literature procedure [12] which involves reaction in basic media and leads to byproducts by reaction with the acidic proton on C-2. Hydrogenation of the double bond was carried out quantitatively in 15 minutes at atmospheric pressure using Palladium as catalyst. Oximation of the ketone group afforded the desired compounds **9a** and **9b**.

Reaction of the oximes **9a** and **9b** with sodium methoxide and subsequent reduction with sodium borohydride resulted in the removal of the acetyl group and the opening of the pyran ring, (compounds **11a** and **11b**). Treatment of the latter compounds with hydrogen at 45 psi pressure in ethanolic hydrogen chloride with platinum oxide as catalyst resulted in hydrogenolysis of the benzylic C-C bond, leading to undesired aliphatic products instead of compounds **14a** and **14b**. The amines **13a** and **13b** were prepared by transforming the oximes **11a** and **11b** to their corresponding acetoxyimino derivatives and reduction with sodium borohydride and nickel dichloride. On the other hand heterocyclic entactogen analogues were obtained by catalytic hydrogenation of the oximes **9a** and **9b** in acetic acid, (compounds **15a, 15b**). Furthermore Strecker reaction and subsequent hydrogenation of 2*H*-pyran-3-ones **8a** and **8b** led to novel heterocyclic diamino derivatives of entactogens **17a** and **17b**.

Catalytic hydrogenation of oxime **9b** in the presence of acetic anhydride/acetic acid led to the corresponding amide **18**, which by reaction with sodium methoxide and subsequent treatment with Jones reagent afforded the desired entactogen-GABA heterocyclic derivative **20**. This compound in the presence of alkaline media may be transformed to its corresponding acyclic derivative **21**.

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_{245} (Merck). All column chromatography was done by the flash chromatography technique [13] and the column packing was Merck 32-63 μm. The nmr spectra were recorded on Varian 360 EM (60 MHz) spectrometer in the solvents indicated. 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. 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*-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. All other solvents were used as received.

Starting Materials.

α-(3,4-Methylenedioxyphenyl)furfuryl alcohol (**5a**) and 6-hydroxy-2-(3,4-methylenedioxyphenyl)-2*H*-pyran-3(6*H*)-one (**6a**), have been prepared according to the literature [14]. The above compounds have been characterized by melting point, ir and ^1H nmr data.

2-(3,4-Dimethoxyphenyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one (**6b**).

To a solution of freshly distilled furan (64 ml) in anhydrous ether (200 ml), *n*-butyllithium in hexane (15%, 250 ml) was added dropwise under nitrogen and with temperature maintained below -5°. After being stirred for 1 hour at 20°, the mixture was cooled to 0° and a solution of 3,4-dimethoxybenzaldehyde (41.5 g, 250 mmoles) in 200 ml of anhydrous THF was added dropwise. The reaction was allowed to reach room temperature and continued for 3 hours. At that point tlc (ether, Rf 0.54) showed that the reaction was completed. Cold water (300 ml) was added slowly under stirring and the product was taken by extraction with ether (3 x 150 ml). The organic layers were pooled together, washed with water, dried over magnesium sulfate and evaporated under reduced pressure yielding 57.3 g (93%) of α-(3,4-dimethoxyphenyl)furfuryl alcohol (**5b**) as a yellowish solid (mp 60.5-62°); ir: ν max 3440 br [OH], 1015 m, 882 m (sharp), 745 m [furan], 1260 s, 1025 s [C-O], 3020 w, 1600 m, 1510 s, 810 m [aromatic]; ^1H nmr (deuteriochloroform): δ 7.40 [m, 1H, H-C(5)], 7.05 [s, H-Ar], 6.90 [m, 2H, H-Ar], 6.30 [m, 1H, H-C(4)], 6.10 [m, 2H, H-C(4)], 5.85 [s, 1H, CH], 3.88 [s, 6H, CH_3O], 3.75 [br, disappeared on addition of deuterium oxide, 1H, OH]. The furfuryl alcohol (10 g, 42.7 mmoles) was dissolved in methylene chloride (150 ml) and *m*-chloroperbenzoic acid (80%, 15 g) 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 (ether, Rf 0.31) 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 dryness. The remaining slurry was crystallized from ether giving 8.4 g (79%) of the title product, melting at 108-110°; ir: ν max 3380 s [OH], 1690 s [conj C=O], 1640 m [C=C], 1270 s, 1145 m,

1040 s [C-O], 3030 w, 1600 s, 1520 s, 810 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.95 [dd, J = 10, 3.2, 1H, H-C(5)], 6.85 [s, 3H, H-Ar], 6.20 [d, J = 10, 1H, H-C(4)], 5.70 [d, J = 3.2, 1H, H-C(6)], 5.50 [s, 1H, H-C(2)], 4.25 [br, disappeared on addition of deuterium oxide, 1H, OH], 3.88 [s, 6H, CH_3O].

Anal. Calcd. for $C_{13}H_{14}O_5$ (250.24): C, 62.39; H, 5.64. Found: C, 62.50; H, 5.53.

6-Acetoxy-2-(3,4-methylenedioxyphenyl)-2*H*-pyran-3(6*H*)-one **7a**.

To a solution of **6a** (1.87 g, 8 mmoles), glacial acetic acid (0.58 g, 10 mmoles) and DMAP (0.1 g, 0.8 mmoles) in methylene chloride (35 ml) cooled to 0°, a solution of DCC (1.82 g, 8.8 mmoles) in methylene chloride (7 ml) 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 (3:7 ethyl acetate/hexane, Rf 0.83) showed that the reaction was completed. The reaction mixture was filtered, in order to remove the formed byproduct (dicyclohexylurea), washed successively with a saturated solution of sodium bicarbonate and brine, dried over magnesium sulfate and evaporated to a residue which was crystallized from ether/hexane yielding 1.96 g (89%) of the title product (mp 99-101°); ir: ν max 1735 s [O-C=O], 1700 s [conj C=O], 1635 m [C=C], 1245 s, 1095 m, 1030 s [C-O], 3080 w, 1610 m, 1500 s, 810 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.85 [dd, J = 10, 3, 1H, H-C(5)], 6.72 [m, 3H, H-Ar], 6.52 [d, J = 3, 1H, H-C(6)], 6.20 [d, J = 10, 1H, H-C(4)], 5.98 [s, 2H, CH_2O], 5.33 [s, 1H, H-C(2)], 2.08 [s, 3H, CH_3].

Anal. Calcd. for $C_{14}H_{12}O_6$ (276.24): C, 60.86; H, 4.39. Found: C, 60.59; H, 4.14.

6-Acetoxy-2-(3,4-dimethoxyphenyl)-2*H*-pyran-3(6*H*)-one **7b**.

A solution of compound **6b** (2.5 g, 10 mmoles), glacial acetic acid (0.6 g, 10 mmoles), DMAP (0.12 g, 1 mmole) in methylene chloride (40 ml) was reacted with a solution of DCC (2.27 g, 11 mmoles) in methylene chloride (10 ml) as described for compound **7a**, yielding 2.7 g (93%) of title product **7b** (mp 94-95°; tlc ether, Rf 0.47); ir: ν max 1740 s [C=O], 1695 s [conj C=O], 1620 w [C=C], 1230 s, 1140 m, 1025 s [C-O], 3090 w, 1600 s, 1510 s, 810 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.95 [dd, J = 10, 3, 1H, H-C(5)], 6.90 [m, 3H, H-Ar], 6.65 [d, J = 3, 1H, H-C(6)], 6.30 [d, J = 10, 1H, H-C(4)], 5.45 [s, 1H, H-C(2)], 3.88 [s, 6H, CH_3O], 2.12, [s, 3H, CH_3].

Anal. Calcd. for $C_{15}H_{16}O_6$ (292.28): C, 61.64; H, 5.52. Found: C, 61.38; H, 5.38.

6-Acetoxy-2-(3,4-methylenedioxyphenyl)-tetrahydro-2*H*-pyran-3-one **8a**.

A solution of **7a** (1.38 g, 5 mmoles) in ethyl acetate (80 ml), containing 0.14 g of 10% Pd/C was hydrogenated at atmospheric pressure and room temperature for 15 minutes. At that point tlc (1:2 ethyl acetate/hexane, Rf 0.53) showed that the reaction was completed. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to a residue which was crystallized from ether to give 1.31 (94%) melting at 86-87°; ir: ν max 1745 s [O-C=O], 1720 s [C=O], 1265 s, 1095 s, 1040 s [C-O], 3040 w, 1615 s, 1500 s, 815 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.73 [m, 3H, H-Ar], 6.42 [m, 1H, H-C(6)], 5.91 [s, 2H, CH_2O], 5.09 [s, 1H, H-C(2)], 2.55 [m, 4H, H-C(4,5)], 2.10 [s, 3H, CH_3].

Anal. Calcd. for $C_{14}H_{14}O_6$ (278.25): C, 60.43; H, 5.07. Found: C, 60.12; H, 5.15.

6-Acetoxy-2-(3,4-dimethoxyphenyl)-tetrahydro-2*H*-pyran-3-one **8b**.

Compound **7b** (2.92 g, 10 mmoles) was hydrogenated in 150 ml of ethyl acetate with 0.29 g 10% of Pd/C catalyst as described for compound **8a** yielding 2.79 g (95%) of the desired product (mp 90-92°; tlc ether, Rf 0.48); ir: ν max 1740 s [O-C=O], 1725 s [C=O], 1260 s, 1140 m, 1025 s [C-O], 3020 w, 1600 m, 1515 s, 815 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.92 [m, 3H, H-Ar], 6.50 [m, 1H, H-C(6)], 5.25 [s, 1H, H-C(2)], 3.90 [s, 6H, CH_3O], 2.59 [m, 4H, H-C(4,5)], 2.13 [s, 3H, CH_3].

Anal. Calcd. for $C_{15}H_{18}O_6$ (294.29): C, 61.22; H, 6.16. Found: C, 61.29; H, 6.02.

6-Acetoxy-3-hydroxyimino-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-one **9a**.

To a solution of compound **8a** (2.78 g, 10 mmoles) in 40 ml of methanol, heated at 55°, a solution of hydroxylamine hydrochloride (1.39 g, 20 mmoles) and sodium acetate trihydrate (2.58 g, 19 mmoles) in 30 ml of water was added under stirring in one pot. After 30 minutes stirring at that temperature a white precipitate appeared, but the reaction was run for an additional 30 minutes. At that point tlc (2:3 ethyl acetate/hexane, Rf 0.48) showed that the reaction was completed. The reaction mixture was cooled in order for the precipitation to be complete and the product was isolated by filtration. Crystallization from ether afforded 2.6 g (89%) of analytically pure material, mp 144-145°; ir: ν max 3250 s (broad) [OH], 1745 s [C=O], 1655 w [C=N], 1250 s, 1040 s [C-O], 3020 w, 1610 m, 1500 s, 805 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 8.35 [s, disappeared on addition of deuterium oxide, 1H, OH], 6.78 [m, 3H, H-Ar], 6.34 [t, J = 3.5, 1H, H-C(6)], 5.95 [s, 2H, CH_2O], 5.23 [s, 1H, H-C(2)], 2.72 [m, 2H, H-C(5)], 2.11 [s, 3H, CH_3], 1.96 [m, 2H, H-C(4)].

Anal. Calcd. for $C_{14}H_{15}NO_6$ (293.26): C, 57.34; H, 5.15; N, 4.77. Found: C, 57.49; H, 5.13; N, 4.82.

6-Acetoxy-2-(3,4-dimethoxyphenyl)-6-hydroxyiminotetrahydro-2*H*-pyran-3-one **9b**.

A solution of compound **8b** (2.35 g, 8 mmoles) in 30 ml of methanol was reacted with a solution of hydroxylamine hydrochloride (1.11 g, 16 mmoles) and sodium acetate trihydrate (2.04 g, 15 mmoles) in 25 ml of water as described for compound **9a** yielding 2.1 g (85%) of the title product (mp 163-165°; tlc ether, Rf 0.51); ir: ν max 3280 s (broad) [OH], 1750 s [C=O], 1240 s, 1140 m, 1015 s [C-O], 3010 w, 1600 m, 1520 s, 805 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 9.90 [br, disappeared on addition of deuterium oxide, 1H, OH], 6.90 [m, 3H, H-Ar], 6.31 [t, J = 4.2, 1H, H-C(6)], 5.41 [s, 1H, H-C(2)], 3.90 [s, 6H, CH_3O], 2.80 [m, 2H, H-C(5)], 2.15 [s, 3H, CH_3], 2.04 [m, 2H, H-C(4)].

Anal. Calcd. for $C_{15}H_{19}NO_6$ (309.31): C, 58.24; H, 6.19; N, 4.53. Found: C, 58.11; H, 6.07; N, 4.83.

2-Hydroxyimino-1-(3,4-methylenedioxyphenyl)-1,5-pentanodiol **11a**.

To a stirred solution of compound **9a** (1.46 g, 5 mmoles) in 100 ml of absolute methanol cooled to 0°, sodium methoxide (0.11 g) was added. The reaction was run at that temperature for 1 hour, then tlc (1:1 ethyl acetate/hexane, Rf 0.29) showed that the reaction was completed. The *p*H of the solution was adjusted to 7 by addition of acetic acid and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform,

filtered (in order to remove the sodium acetate which was formed) and the filtrate was evaporated to dryness yielding 1.14 g (91%) of 6-hydroxy-3-hydroxyimino-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-one **10a**; ir: ν max 3460 m [OH], 3200 m (broad) [OH], 1640 w [C=C], 1255 s, 1100 m, 1040 s [C-O], 3030 w, 1605 w, 1500 s, 795 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.73 [m, 3H, H-Ar], 5.88 [s, 2H, CH_2O], 5.22 [d, J = 4, 1H, H-C(6)], 5.13 [s, 1H, H-C(2)], 4.74 [br, disappeared on addition of deuterium oxide, OH], 1.95 [m, 4H, H-C(4,5)]. To a solution of compound **10a** (2.51 g, 10 mmoles) in 70 ml of absolute methanol, sodium borohydride (0.53 g, 14 mmoles) was added portionwise. The reaction was run under stirring for 3 hours and tlc (3:1 ethyl acetate/hexane, Rf 0.35) showed that the reaction was completed. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted with methylene chloride. The organic layer was separated, washed with water, brine, dried over magnesium sulfate and evaporated to dryness. The residue was crystallized from methanol/petroleum ether yielding 2.2 g (87%) of the title product (mp 111-113°); ir: ν max 3450-3150 s (broad) [OH], 1645 m [C=C], 1245 s, 1110 m, 1040 s [C-O], 1610 s, 1510 s, 810 m, [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.71 [m, 3H, H-Ar], 5.87 [s, 2H, CH_2O], 5.43 [br, disappeared on addition of deuterium oxide, OH], 5.13 [s, 1H, H-C(1)], 3.43 [m, 2H, H-C(5)], 2.23 [m, 2H, H-C(3)], 1.87 [m, 2H, H-C(4)].

Anal. Calcd. for $C_{12}H_{15}NO_5$ (253.25): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.78; H, 6.06; N, 5.71.

1-(3,4-Dimethoxyphenyl)-2-hydroxyimino-1,5-pentanodiol **11b**.

Compound **9b** (1.55 g, 5 mmoles) was treated with sodium methoxide (0.11 g) as described for the compound **10a**, yielding 1.18 g (88%) of 2-(3,4-dimethoxyphenyl)-6-hydroxy-3-hydroxyiminotetrahydro-2*H*-pyran-3-one **10b**; tlc ether, Rf 0.23; ir: ν max 3250 s (broad) [OH], 1245 s, 1135 s, 1030 s [C-O], 3010 w, 1595 s, 1510 s, 795 s [aromatic]; ^{1}H nmr (deuterioacetone): δ 8.77 [br, disappeared on addition of deuterium oxide, 1H, NOH], 6.94 [m, 3H, H-Ar], 6.37 [m, 1H, H-C(6)], 5.43 [s, 1H, H-C(2)], 4.33 [br, disappeared on addition of deuterium oxide, 1H, OH], 3.91 [s, 6H, CH_3O], 2.71 [m, 4H, H-C(4,5)]. A solution of compound **10b** (1.34 g, 5 mmoles) in 50 ml of absolute methanol was treated with sodium borohydride (0.27 g, 7 mmoles) as described for compound **11a**, yielding 1.16 g (86%) of the title product, (mp 127-128°, tlc 3:1 ethyl acetate/hexane 0.26); ir: ν max 3500-3150 s (broad) [OH], 1260 s, 1135 s, 1020 s [C-O], 1605 m, 1510 s, 810 m [aromatic]; ^{1}H nmr (per deuterioacetone): δ 6.98 [m, 3H, H-Ar], 5.33 [s, 1H, H-C(1)], 4.30 [br, disappeared on addition of deuterium oxide, OH], 3.89 [s, 6H, CH_3O], 3.51 [m, 2H, H-C(5)], 2.30 [m, 2H, H-C(3)], 1.85 [m, 2H, H-C(4)].

Anal. Calcd. for $C_{13}H_{19}NO_5$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.71; H, 7.22; N, 5.34.

2-[1,5-Dihydroxy-1-(3,4-methylenedioxyphenyl)]pentanamine Hydrochloride **13a**.

To a stirred solution of compound **11a** (2.53 g, 10 mmoles) in 70 ml of methylene chloride were added acetic anhydride (1.22 g, 12 mmoles), pyridine (0.94 g, 12 mmoles) and several crystals of DMAP. The reaction was run at room temperature with stirring for 30 minutes. Then the reaction mixture was quenched with 10 ml of hydrochloric acid (0.01 *N*), washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the remaining residue was chromatographed (1:1 ethyl acetate/hexane as eluant) yielding 2.6 g (88%, 8.8 mmoles) of 2-acetoxyimino-1-(3,4-methylenedioxyphenyl)pentan-1,5-diol (**12a**). A solution of the latter compound and nickel dichloride hexahydrate (4.76 g, 20 mmoles) in 80 ml absolute methanol was cooled at -10° and sodium borohydride (3.04 g, 80 mmoles) was added portionwise under stirring. The reaction was allowed to reach room temperature and continued for 6 hours. At that point tlc (1:8:1 methanol/ethyl acetate/hexane, Rf 0.33) showed that the reaction was completed. The reaction was quenched with 60 ml of a saturated solution of sodium chloride and 200 ml of ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to dryness. The product was converted to the hydrochloride salt and purified by washing with anhydrous ether and acetone giving 1.6 g (66%) of the title product, mp 174° (turned ivory), 186-188° dec; ir: ν max 3380-3250 s (broad) [OH], 3010-2850 s (broad) [NH_3^+], 1250 s, 1110 m, 1040 s [C-O], 1610 s, 1510 s, 805 m [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.30 [br, disappeared on addition of deuterium oxide, NH_3^+], 6.97 [m, 3H, H-Ar], 5.93 [s, 2H, CH_2O], 4.87 [br, disappeared on addition of deuterium oxide, OH], 4.39 [br, Ar-CH], 3.43 [m, 3H, H-C(1,4)], 2.41 [m, 2H, H-C(2)], 2.05 [m, 2H, H-C(3)].

Anal. Calcd. for $C_{12}H_{18}ClNO_4$ (275.75): C, 52.26; H, 6.58; N, 5.08. Found: C, 52.01; H, 6.71; N, 6.39.

2-[1,5-Dihydroxy-1-(3,4-dimethoxyphenyl)pentanamine Hydrochloride **13b**.

In a procedure similar to that for compound **13a**, 2.69 g (10 mmoles) of oxime **11b** were converted to 1.7 g (58% total yield) of the amine hydrochloride, mp 192-194° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.3; ir: ν max 3400-3200 s (broad) [OH], 2970-2820 s (broad) [NH_3^+], 1230 s, 1140 m, 1020 s [C-O], 1600 m, 1500 m, 810 m [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.55 [br, disappeared on addition of deuterium oxide, NH_3^+], 7.03 [m, 3H, H-Ar], 4.66 [br, disappeared on addition of deuterium oxide, OH], 4.28 [m, Ar-CH], 3.89 [s, 6H, CH_3O], 3.39 [m, 3H, H-C(1,4)], 2.35 [m, 4H, H-C(2,3)].

Anal. Calcd. for $C_{13}H_{22}ClNO_4$ (291.81): C, 53.50; H, 7.60; N, 4.80. Found: C, 53.17; H, 7.82; N, 4.55.

[6-Acetoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]amine **15a**.

A solution of compound **9a** (2.93 g, 10 mmoles) in 100 ml glacial acetic acid containing 0.15 g of platinum oxide was shaken in a Parr apparatus at 45 psi of hydrogen. After shaking for 6 hours, tlc (1:8:1 methanol/chloroform/ammonia, Rf 0.76) showed that the reaction was completed. Then the catalyst was removed by filtration and the solvent was azeotroped with the addtion of benzene under reduced pressure. The resulting residue was dissolved in chloroform and extracted with a saturated solution of sodium carbonate, washed with brine, dried over magnesium sulfate and evaporated to dryness. The amine was crystallized from acetone/ether giving 2.4 g (86%) of the title product, mp 118-119° dec; ir: ν max 3320 m (broad) [NH_2], 1745 s [O-C=O], 1265 s, 1095 m, 1020 s [C-O], 3040 w, 1615 m, 1510 s, 815 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.82 [m, 3H, H-Ar], 6.45 [m, 1H, H-C(6)], 5.92 [s, 2H, CH_2O], 5.16 [m, 1H, H-C(2)], 3.06 [m, 1H, H-C(3)], 2.30 [m, 4H, H-C(4,5)], 2.12 [s, 3H, CH_3], 1.96 [br, disappeared on addition of deuterium oxide, NH_2].

Anal. Calcd. for $C_{14}H_{17}NO_5$ (279.29): C, 60.20; H, 6.14; N, 5.02. Found: C, 59.88; H, 6.41; N, 4.83.

[6-Acetoxy-2-(3,4-dimethoxyphenyl)tetrahydro-2*H*-pyran-3-yl]-amine **15b**.

A solution of compound **9b** (3.09 g, 10 mmoles) in 80 ml glacial acetic acid was hydrogenated over 0.18 g of platinum oxide in a procedure similar to that for compound **15a**, giving 2.63 g (89%) of the amine; mp 126-128° dec; tlc 1:8:1 methanol/chloroform/-ammonia, Rf 0.69; ir: ν max 3300 s (broad) [NH_2], 1750 s [O-C=O], 1240 s, 1140 m, 1010 s [C-O], 3010 w, 1600 m, 1520 s, 805 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.98 [m, 3H, H-Ar], 6.35 [m, 1H, H-C(6)], 5.31 [m, 1H, H-C(2)], 3.95 [s, 6H, CH_3O], 3.16 [m, 1H, H-C(3)], 2.43 [m, 4H, H-C(4,5)], 2.10 [s, 3H, CH_3], 1.91 [br, disappeared on addition of deuterium oxide, NH_2].

Anal. Calcd. for $C_{15}H_{21}NO_5$ (295.33): C, 61.00; H, 7.17; N, 4.74. Found: C, 60.63; H, 7.35; N, 4.58.

[6-Acetoxy-3-*N*-benzylamino-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]carbonitrile **16a**.

A solution of **8a** (1.9 g, 6.8 mmoles) and potassium cyanide (0.45 g, 6.9 mmoles) in 25 ml of absolute methanol 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 (7:3 ether/hexane Rf 0.61) showed that the reaction was completed. The solvent was removed by evaporation under reduced pressure and the residue was partitioned in methylene chloride and water. The organic layer was separated, dried over magnesium sulfate and evaporated to dryness yielding 2.5 (92%) of the aminonitrile **16a**, mp 113-115°; ir: ν max 2210 w (sharp) [C≡N], 3320 m (sharp) [NH], 1745 s [O-C=O], 1265 s, 1095 m, 1030 s [C-O], 3030 w, 1610 m, 1500 s, 810 m, 750 s, 710 s [aromatic]; ^{1}H nmr (deuteriochloroform): δ 7.19 [s, 5H, H-Ar], 6.89 [m, 3H, H-Ar], 6.22 [m, 1H, H-C(6)], 5.95 [s, 2H, CH_2O], 4.71 [s, 1H, H-C(2)], 3.78 [m, 2H, CH_2N], 2.20 [m, 4H, H-C(4,5)], 2.12 [s, 1H, CH_3], 1.77 [br, disappeared on addition of deuterium oxide, NH].

Anal. Calcd. for $C_{22}H_{22}N_2O_5$ (394.42): C, 66.99; H, 5.62; N, 7.10. Found: C, 66.78; H, 5.69; N, 7.35.

[6-Acetoxy-3-*N*-benzylamino-2-(3,4-dimethoxyphenyl)tetrahydro-2*H*-pyran-3-yl]carbonitrile **16b**.

A solution of **8b** (2.35 g, 8 mmoles) in 30 ml of 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 **16a**, yielding 2.9 g (89%) of the title product, mp 138-140° dec; tlc 1:1 ethyl acetate/hexane, Rf 0.28; ir: ν max 2210 m (sharp) [C≡N], 3300 m (sharp) [NH], 1750 s [O-C=O], 1250 s, 1140 m, 1030 s [C-O], 3040 w, 1600 m, 1515 s, 815 m, 750 m, 690 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 7.22 [s, 5H, H-Ar], 7.01 [m, 3H, H-Ar], 6.41 [m, 1H, H-C(6)], 4.89 [s, 1H, H-C(2)], 3.88 [s, 6H, CH_3], 3.74 [m, 2H, CH_2N], 2.30 [m, 4H, H-C(4,5)], 2.14 [s, 3H, CH_3], 1.84 [br, disappeared on addition of deuterium oxide, NH].

Anal. Calcd. for $C_{23}H_{26}N_2O_5$ (410.46): C, 67.30; H, 6.39; N, 6.83. Found: C, 67.16; H, 6.49; N, 7.01.

[6-Acetoxy-3-amino-2-(2,3-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride **17a**.

A solution of compound **16a** (1.26 g, 3.2 mmoles) in 80 ml of absolute ethanol and 3 ml of ethanolic hydrogen chloride (2*N*) containing 0.1 g of platinum oxide was shaken in a Parr apparatus at 50 psi of hydrogen. The reaction was run for 8 hours and tlc (2:8:1 methanol/chloroform/ammonia, Rf 0.62) showed that the reaction was ended. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure affording the title product as dihydrochloride salt, which was purified by washing with anhydrous ether and acetone yielding 1.16 g (95%) of analytically pure material mp 148° (turned ivory), 162-164° dec; ir: ν max 2970-2820 s (broad) [NH_3^+], 1580 m [δ as NH_3^+], 1520 m [δ s NH_3^+], 1745 s [O-C=O], 1610 m, 1500 m, 820 m [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.67 and 8.49 [br, disappeared on addition of deuterium oxide, NH_3^+], 6.73 [m, 3H, H-Ar], 6.23 [m, 1H, H-C(6)], 6.01 [s, 2H, CH_2O], 5.08 [s, 1H, H-C(2)], 3.62 [m, 2H, CH_2N], 2.20 [m, 4H, H-C(4,5)], 2.11 [s, 3H, CH_3].

Anal. Calcd. for $C_{15}H_{22}Cl_2N_2O_5$ (381.26): C, 47.25; H, 5.82; N, 7.35. Found: C, 47.01; H, 5.99; N, 7.31.

[6-Acetoxy-3-amino-2-(2,3-dimethoxyphenyl)tetrahydro-2*H*-pyran-3-yl]methylamine Dihydrochloride **17b**.

In a procedure similar to that for **17a**, a solution of compound **16b** (1.4 g, 3.4 mmoles) in 80 ml of absolute ethanol and 3 ml of ethanolic hydrogen chloride (2*N*) containing 0.1 g of platinum oxide was hydrogenated to afford 1.3 g (96%) of diamine dihydrochloride, mp 158° (turned ivory) 173-174° dec; tlc 2:8:1 methanol/chloroform/ammonia, Rf 0.59; ir: ν max 2980-2850 s (broad) [NH_3^+], 1585 m [δ as NH_3^+], 1515 m [δ s NH_3^+], 1750 s [O-C=O], 1610 m, 1505 s, 810 m [aromatic]; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 8.22 [br, disappeared on addition of deuterium oxide, NH_3^+], 6.83 [m, 3H, H-Ar], 6.29 [m, 1H, H-C(6)], 5.15 [s, 1H, H-C(2)], 3.91 [s, 6H, CH_3O], 3.65 [m, 2H, CH_2N], 2.23 [m, 4H, C(4,5)], 2.15 [s, 3H, CH_3].

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2O_5$ (397.30): C, 48.37; H, 6.60; N, 7.05. Found: C, 48.03; H, 6.88; N, 7.12.

N-[2-Acetoxy-6-(3,4-dimethoxyphenyl)tetrahydro-2*H*-pyran-5-yl]-acetamide **18**.

A solution of compound **9b** (1 g, 3.2 mmoles) in acetic acid/-acetic anhydride (30:10 ml) was hydrogenated over 0.1 g of 10% Pd/C. The hydrogenation was run under 35 psi pressure for 2 hours. At that time tlc (1:8:2 methanol/ethyl acetate/hexane, Rf 0.37) showed that the reaction was completed. The catalyst was removed by filtration and the solvent was azeotroped with toluene. The remaining residue was crystallized from ethyl acetate/ether yielding 0.85 g (78%) of the title product, mp 186-187°; ir: ν max 3310 m [NH], 1540 m [δ NH], 1750 s [O-C=O], 1640 s [N-C=O], 1240 s, 1130 m, 1030 s [C-O], 3020 w, 1600 m, 1515 s, 820 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.85 [m, 3H, H-Ar], 6.22 [m, 1H, H-C(2)], 5.15 [d, J = 1.8, 1H, H-C(6)], 4.35 [br, disappeared on addition of deuterium oxide, CONH], 3.83 [s, 6H, CH_3O], 2.95 [m, 1H, H-C(5)], 2.15 [s, 3H, CH_3CO], 2.10 [m, H-C(3,4)], 1.95 [s, 3H, CH_3NH].

Anal. Calcd. for $C_{17}H_{23}NO_6$ (337.36): C, 60.52; H, 6.87; N, 4.15. Found: C, 60.40; H, 6.79; N, 4.19.

N-[6-(3,4-Dimethoxyphenyl)-2-hydroxytetrahyro-2*H*-pyran-5-yl]-acetamide **19**.

A solution of compound **18** (0.8 g, 2.4 mmoles) in 80 ml absolute methanol was reacted with sodium methoxide (0.026 g, 0.5 mmoles) as described for compound **10a** yielding 0.65 g (93%) of the title product, (mp 124-126°; tlc 1:8:2 methanol/ethyl acetate/hexane, Rf 0.24) ir: ν max 3320 m [NH], 3260 s [OH], 1635 s [NHC=O], 1260 s, 1135 m, 1020 s [C-O], 3060 w, 1610 m, 1515

s, 805 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 6.90 [m, 3H, H-Ar], 6.20 [m, 1H, H-C(2)], 5.31 [d, J = 2, 1H, H-C(6)], 4.90 [br, disappeared on addition of deuterium oxide, NH], 4.28 [br, disappeared on addition of deuterium oxide, OH], 3.90 [s, 6H, CH_3O], 3.25 [m, 1H, H-C(5)], 1.98 [m, 4H, H-C(3,4)], 1.87 [s, 3H, CH_3N].

Anal. Calcd. for $C_{15}H_{21}NO_5$ (295.33): C, 61.00; H, 7.17; N, 4.74. Found: C, 60.76; H, 7.33; N, 4.81.

5-Acetylamino-6-(3,4-dimethoxyphenyl)-δ-valerolactone **20**.

To an ice cold solution of **19** (0.5 g, 1.7 mmoles) in 80 ml of acetone, Jones reagent [15] (0.6 ml) was added dropwise. After stirring for additional 20 minutes, tlc (1:8:2 methanol/ethyl acetate/hexane, Rf 0.52) showed that the reaction was completed. Then the solid inorganic byproducts were eliminated by decantation, the liquid layer was evaporated to dryness and the remaining residue was partitioned in ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated to dryness. The resulting oily residue was crystallized by addition of ether yielding 0.46 g (93%) of the title product, mp 154-155°; ir: ν max 3320 m [NH], 1740 s [O-C=O], 1670 s [NHC=O], 1260 s, 1120 m, 1010 m, [C-C], 3070 w, 1590 m, 1505 s, 810 m [aromatic]; ^{1}H nmr (deuteriochloroform): δ 7.03 [m, 3H, H-Ar], 6.31 [m, 1H, H-C(6)], 5.78 [br, disappeared on addition of deuterium oxide, NH], 3.95 [s, 6H, CH_3O], 2.86 [m, 1H, H-C(5)], 2.53 [m, 4H, H-C(3,4)], 2.04 [s, 3H, CH_3N].

Anal. Calcd. for $C_{15}H_{19}NO_5$ (293.31): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.21; H, 6.73; N, 4.60.

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REFERENCES AND NOTES

[1] Presented in part at XIth International Symposium on Medicinal Chemistry, Jerusalem, Israel, September 1990, Abstract 57; For previous publications in the series see: M. P. Georgiadis in Trends in Medicinal Chemistry 88, H. Van Der Goot, G. Domany, L. Pallos and H. Timmerman eds, Elsevier Science Publishers, Amsterdam, The Netherlands, 1989, p 197.

[2a] D. E. Nichols, D. H. Lloyd, A. J. Hoffman, M. B. Nichols and G. K. W. Yim, *J. Med. Chem.*, **25**, 530 (1982); [b] C, Naranjo, A. T. Shulgin, and T. Sargent, *Med. Pharmacol. Exp.*, **17**, 359 (1967).

[3] A. Weil, *Psychedelic Drugs*, **8**, 335 (1976).

[4] G. Greer in MDMA: A New Psychotropic Compound and its Effects in Humans, Copyright 1983 by G. Greeer, M. D., Santa Fe, NM.

[5] D. E. Nichols, A. J. Hoffman, R. A. Oberlander, P. Jacob and A. T. Shulgin, *J. Med. Chem.*, **29**, 2009 (1986).

[6] D. E. Nichols, W. K. Brewster, M. P. Johnson, R. A. Oberlander and R. M. Riggs, *J. Med. Chem.*, **33**, 703 (1990) and references within.

[7] R. Imhof, E. Kyburz and J. J. Daly, *J. Med. Chem.*, **27**, 165 (1984).

[8] 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.

[9a] A. B. Reitz, M. A. Avery, R. P. Rosenkranz, M. S. Verlander, K. L. Melmon, B. B. Hoffman, Y. Akita, N. Castagnoli and M. Goodman, *J. Med. Chem.*, **28**, 642 (1985); [b] D. E. Nichols, *J. Psychoact. Drugs*, **19**, 33 (1987).

[10] D. Beaumont, R. D. Waigh, M. Sunphanich and M. W. Nott, *J. Med. Chem.*, **26**, 507 (1983).

[11] S. M. Nanvati and R. B. Silverman, *J. Med. Chem.*, **32**, 2419 (1989).

[12] O. Achmatowicz, P. Bukowski, B. Schechner, Z. Swierzchowska and A. Zamojski, *Tetrahedron*, **27**, 1973 (1971).

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

[14] M. P. Georgiadis, S. A. Haroutounian and J. C. Bailar Jr., *J. Heterocyclic Chem.*, **25**, 995 (1988).

[15] Jones reagent was prepared by dissolving 2.67 g of chromic trioxide in 2.3 ml of concentrated sulfuric acid and diluted with water to a volume of 10 ml.