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Hydrogenolysis of 5,6-dihydro-6-(*p*-methoxyphenyl)-6-methyl-5-oxo-2*H*-pyran-2-yl ethyl carbonate yielded dihydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3(4*H*)-one, **3**. Subsequently cyanohydrin **4**, derived from **3**, on reduction afforded 3-(aminomethyl)tetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol, **5**. The synthesis of *N*-dimethyl, *N*-isopropyl, *N*-imidazolyl as well as *N*-oxazoliny derivatives of **5** is presented. The synthesis of 6-(*p*-methoxyphenyl)-6-methyl-7-oxa-1,3-diazaspiro[4,5]decane-2,4-dione **10**, a spiro hydantoin prepared from ketone **3** is also reported.

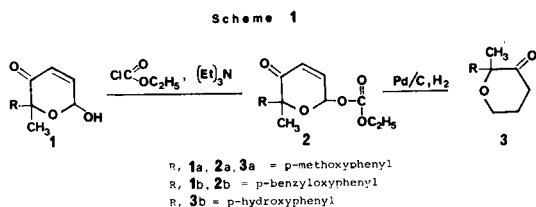
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## Introduction.

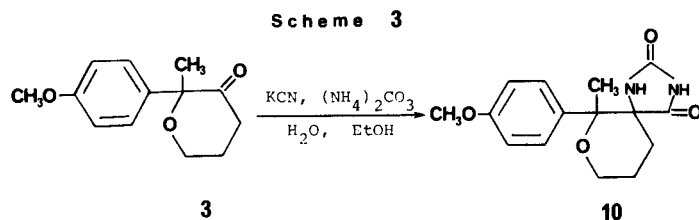
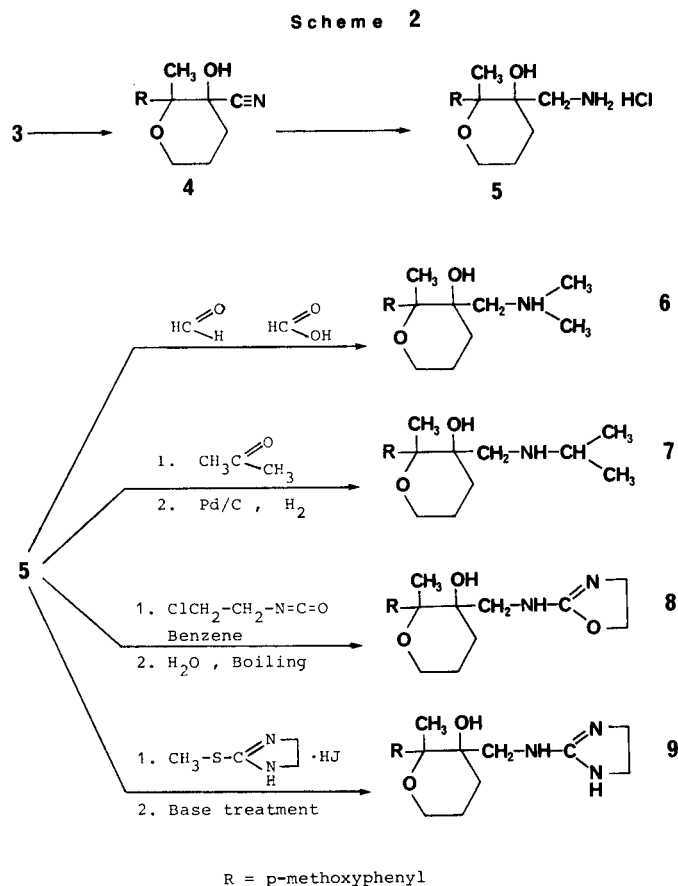
6-Hydroxy-2*H*-pyran-3(6*H*)-ones **1**, have been synthesized by various procedures [2]. Derivatives of 6-hydroxy-2*H*-pyran-3(6*H*)-ones have been reported as antimicrobials, coccidiostats [3,4] and as intermediates in the synthesis of sugars [5] disaccharides [5,6], maltol, isomaltol [2d], aminosugars [7], intermediates for the synthesis of anticancer-Pt complexes [8], pheromones [9] and antibiotics [10]. Their conformations [11], molecular structure and clarification of ambiguities in their isomerism [4] as well as the stereoselectivity in their synthesis have been reported [12].

## Results and Discussion.

In order to remove the 6-hydroxy-group from 6-hydroxy-2-disubstituted-2*H*-pyran-3(6*H*)-ones **1** we have converted them to their 6-*O*-carbonic acid ester **2** which upon hydrogenolysis yielded dihydro-2-disubstituted-2*H*-pyran-3(4*H*)-ones **3** as depicted in Scheme 1.



Hydrogen cyanide addition to **3** yielded tetrahydro-3-hydroxy-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-carbonitrile **4** which was reduced to amine **5**, which was derivatized as shown in Scheme 2 to yield **6**, **7**, **8** and **9**. On the other hand treatment of **3** with potassium cyanide and ammonium carbonate in ethanol-water (Bücherer reaction) gave 6-(*p*-methoxyphenyl)-6-methyl-7-oxa-1,3-diazaspiro[4,5]decane-2,4-one **10**, as it is depicted in Scheme 3.



## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The nmr spectra were determined using a Varian A-60A spectrometer and the chemical shifts ( $\delta$ ) are reported in parts per million downfield from TMS = 0. Analyses were done with a Perkin-Elmer Model 240 C, H, N analyser.

6-Hydroxy-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-one **1a**.

To a solution of furan (50 ml) in anhydrous ether (500 ml) cooled to 0° ± 2° butyllithium (170 ml, 2.2 *N* in hexane) was added under nitrogen. The reaction mixture was stirred for 1 hour at room temperature. Then it was cooled to 0° and *p*-methoxyacetophenone (50 g, melted) was added at such a rate that the temperature was maintained between 5° - 10°. The mixture was stirred for 3 hours, then water was added slowly. The organic layer was washed, dried and evaporated under reduced pressure to yield  $\alpha$ -*p*-methoxyphenyl- $\alpha$ -methylfurfuryl alcohol as a yellowish oil; ir (Nujol): 3580, 3460, 2830, 1240, 1168, 1662, 1600, 1575, 1502, 1000, 828 cm<sup>-1</sup>. The crude  $\alpha$ -*p*-methoxyphenyl- $\alpha$ -methylfurfuryl alcohol was dissolved in methylene chloride (950 ml) and the solution was cooled to 5°. *m*-Chloroperbenzoic acid (75 g) was then added portionwise under stirring. The reaction mixture was left under stirring for two and one half hours. At that time tlc, (ether-hexane, 6:4) showed that the reaction was complete. The mixture was cooled and filtered to remove the *m*-chlorobenzoic acid. The filtrate was washed with solutions of potassium iodide, sodium thiosulfate, sodium bicarbonate and dried with magnesium sulfate. Upon evaporation of the solvent in vacuum to a small volume, addition of ether and cooling, the title product was obtained. Crystallization from ether yielded pure material (mp 128-130°, 50 g). Mother liquors were pooled, evaporated and chromatographed on a silica gel column, yielding a second crop of 14 g to give a total yield 80%; ir (nujol):  $\nu$  max cm<sup>-1</sup> 3390 (OH), 1688 (conj ketone), 1262, 1175 (-OCH<sub>3</sub>), 1089 (C-O-C); <sup>1</sup>H nmr (perdeuterioacetone): 60 MHz  $\delta$  1.50 (3 H, s, angular -CH<sub>3</sub>), 3.73 (3 H, s, -OCH<sub>3</sub>), 5.33 (1 H, m, H-6), 6.10 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>4,6</sub> = 1.5 Hz, H-4), 6.03 (1 H, broad s, OH), 6.84 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>5,6</sub> = 1.5 Hz, H-5), 6.9 (2 H, d, J = 9 Hz Ar), 7.24 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>O<sub>4</sub>: C, 66.65; H, 6.02. Found: C, 66.54; H, 6.10.

2-(*p*-Benzyloxyphenyl)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one **1b**.

To a solution of furan (50 ml) in THF (400 ml) cooled to 50° *n*-butyllithium (50 ml, 22% in hexane) was slowly added under nitrogen. The reaction mixture was stirred at room temperature for one hour, then cooled to 5° and a solution of *p*-(benzyloxy)acetophenone (27 g in 100 ml of THF) was slowly added. The reaction mixture was stirred for about 3 hours at room temperature. At that time tlc (ether-hexane, 4:6, two passes, 6 cm) showed that the reaction was complete. Water was added slowly with stirring and the product,  $\alpha$ -(*p*-benzyloxyphenyl)- $\alpha$ -methylfurfuryl alcohol, was extracted with ether (4 x 400). Ether extracts were pooled, washed with water, dried over magnesium sulfate and evaporated under reduced pressure yielding an oily residue. To a solution of the oily residue of  $\alpha$ -(*p*-benzyloxyphenyl)- $\alpha$ -methylfurfuryl alcohol in methylene chloride (600 ml) cooled at 5°, *m*-chloroperbenzoic acid (25 g) was added portionwise with stirring. After three hours, tlc (ether-hexane 1:1) showed that the reaction was complete. The reaction mixture was cooled and *m*-chlorobenzoic acid removed by filtration. The filtrate was washed with solutions of potassium iodide, sodium thiosulfate, sodium bicarbonate, and dried over magnesium sulfate. The solvent was evaporated under reduced pressure yielding the title product (crude) which was crystallized from ether-hexane to give 26.1 g (70%) of melting at 82°; ir (potassium bromide):  $\nu$  max cm<sup>-1</sup> 3450 (OH), 1683 (conjugated carbonyl), 1612 (Ar), 1512 (Ar), 1260 (C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>O) 1108, 1095, 1050 (-C-O-), 820, 730 (Ar); <sup>1</sup>H nmr (deuteriochloroform): 60 MHz  $\delta$  1.6 (3 H, s, angular -CH<sub>3</sub>), 3.6 (1 H, b, s, -OH), 5.0 (2 H, s, -CH<sub>2</sub>-), 6.10 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>4,6</sub> = 2 Hz, H-4), 6.72 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>5,6</sub> = 2 H-5), 6.6 - 6.74 (9 H, m Ar).

*Anal.* Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>4</sub>: C, 73.33; H, 5.85. Found: C, 73.46; H, 5.97.

5,6-Dihydro-6-(*p*-methoxyphenyl)-6-methyl-5-oxo-2*H*-pyran-2-yl Ethyl Carbonate **2a**.

To a solution of 35.1 g (0.15 mole) of **1a** and 20.2 g (0.2 mole) of triethylamine in methylene chloride (400 ml) cooled to 0° ± 2°, ethyl chloroformate (38 g, 0.35 mole) was added with stirring at such a rate that the temperature of the reaction mixture was maintained between 5-10°. The reaction mixture was stirred for half an hour and then for 20 minutes at room temperature. Then it was cooled again and triethylamine (10.1 g, 0.1 mole) was added with stirring. Stirring was continued at room temperature and the reaction followed by tlc. When the reaction was complete (about three hours), the reaction mixture was washed, dried and filtered through silica gel pretreated with ether. The filtrate was evaporated under reduced pressure yielding 45 g of **2a** tlc one spot (hexane-ether, 1:1, yield quantitative by tlc). Crystallization from ether-hexane yielded analytically pure **2a** melting at 78.5-79° (36 g, 80%). Mother liquors of crystallization yielded an additional 3.1 g (total yield 87%); ir (Nujol):  $\nu$  max cm<sup>-1</sup> 1755 (carbonate carbonyl) 1680 (conjugated carbonyl), 1250, 1170 (O-CH<sub>3</sub>); <sup>1</sup>H nmr (perdeuterioacetone): 60 MHz  $\delta$  1.25 (3 H, t, J = 7 Hz, -CH<sub>3</sub> ethyl), 1.57 (3 H, s, ang CH<sub>3</sub>), 3.76 (3 H, s, -OCH<sub>3</sub>), 4.24 (2 H, q, J = 7 Hz, -CH<sub>2</sub>OCO-), 6.21 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>4,6</sub> = 1.5 Hz, H-4), 6.30 (1 H, m, H-6), 6.98 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>5,6</sub> = 1.5 Hz, H-5), 6.90 (2 H, d, J = 9 Hz Ar), 7.34 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>O<sub>6</sub>: C, 62.74; H, 5.92. Found: C, 62.51; H, 5.99.

5,6-Dihydro-6-(*p*-benzyloxyphenyl)-6-methyl-5-oxo-2*H*-pyran-2-yl, Ethyl Carbonate **2b**.

To a solution of 126.5 g (0.41 mole) of **1b** and 41.4 g (0.41 mole) of triethylamine in methylene chloride (1500 ml) cooled to 0° ± 2°, ethyl chloroformate 70.75 ml (76 g, 0.70 mole) was added with stirring at such a rate that the temperature of the reaction mixture was maintained at 5-10°. The reaction mixture was stirred for 20-30 minutes at room temperature, then cooled again and 2.5 ml triethylamine was added with stirring. Stirring was continued at room temperature and the reaction, followed by tlc (ether-hexane, 1:1) was complete in approximately three hours. The reaction mixture was washed, dried, filtered and the filtrate concentrated and chromatographed over a short silica gel column. Chromatographic fractions were combined and evaporated yielding a residue which was crystallized from ether-hexane (or isopropyl alcohol) and gave 110 g (70%) of a product melting at 111°. Recrystallization from hexane gave 84 g (54%) of analytically pure **2b** (mp 114-115°); ir (chloroform):  $\nu$  max cm<sup>-1</sup> 1745 (O-COO-) and 1680 (conjugated carbonyl); <sup>1</sup>H nmr (deuteriochloroform): 60 MHz  $\delta$  1.35 (3 H, t, J = 7 Hz, -CH<sub>3</sub> of ethyl), 1.67 (3 H, s, ang CH<sub>3</sub>), 1.25 (2 H, q, J = 7 Hz -CH<sub>2</sub>- of ethyl), 5.00 (2 H, s, -CH<sub>2</sub>O-), 6.16 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>4,6</sub> = 2 Hz, H-4), 6.27 (1 H hidden dd, coincides with H-4, J<sub>4,6</sub> = J<sub>5,6</sub> = 2 Hz, H-6), 6.73 (1 H, dd, J<sub>4,5</sub> = 10 Hz, J<sub>4,6</sub> = 2 Hz, H-5), 6.9 (2 H, d, J = 9 Hz Ar), 7.3 (7 H, m, Ar).

*Anal.* Calcd. for C<sub>22</sub>H<sub>22</sub>O<sub>6</sub>: C, 69.10; H, 5.80. Found: C, 69.32; H, 5.93.

5,6-Dihydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3(4*H*)-one **3a**.

A solution of 10.2 g (0.033 mole) of **2a** in 400 ml of ethyl acetate, containing 3.5 g of 10% Pd/C was hydrogenolysed by treatment with hydrogen under atmospheric pressure at room temperature. A side arm was connected to the hydrogenolysis apparatus leading to a flask containing 4 *N* sodium hydroxide in order to trap the carbon dioxide evolved during hydrogenolysis. Hydrogenolysis was complete within 3 1/2 hours. The catalyst was filtered off and the filtrate was evaporated under reduced pressure yielding 7.4 g (100%) of **3a** pure by tlc (ether-hexane, 1:1) one spot and 97-98% pure by vpc, which was used without further purification for the next step synthesis; ir (chloroform):  $\nu$  max cm<sup>-1</sup> 1710 (ketone), 1600, 1575 and 1502 (Ar), 2835, 1240 and 1170 (OCH<sub>3</sub>); <sup>1</sup>H nmr (deuteriochloroform): 60 MHz  $\delta$  1.45 (3 H, s, ang -CH<sub>3</sub>), 2.10 (2 H, m, -CH<sub>2</sub>-C), 2.45 (2 H, m, adjacent to -CO-), 3.80 (2 H, s, -OCH<sub>3</sub>), 3.80 (2 H, m, CH<sub>2</sub>-O-), 6.86 (2 H, d, J = 9 Hz Ar), 7.24 (2 H, d, J = 9 Hz Ar).

5,6-Dihydro-2-(*p*-hydroxyphenyl)-2-methyl-2*H*-pyran-3(4*H*)-one **3b**.

A solution of 19.1 g (0.05 mole) of **2b** in ethyl acetate-ethanol (9:1) was hydrogenated using 2.5 g of 10% Pd/C as a catalyst. The hydrogen pressure was kept at 50 psi and after 3 hours the hydrogenation was interrupted in order to flash away the carbon dioxide produced in the reaction. The apparatus was refilled with fresh hydrogen and hydrogenation

was continued for an additional hour. At that time tlc (ether-hexane, 1:1) showed that the reaction was complete. The catalyst was removed by filtration and the filtrate was evaporated yielding a residue which was crystallized from ether-hexane and gave 9.1 (89%) of **3b**, mp 94-95°; ir (chloroform):  $\nu$  max  $\text{cm}^{-1}$  3580 (OH), 3370 (OH-assoc), 1705 (carbonyl), 1075 (ether), 830 (Ar);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.5 (3 H, s, angular  $-\text{CH}_3$ ), 1.85-2.35 (2 H, m,  $-\text{CH}_2-$ ), 2.35-2.70 (2 H, m, adjacent to carbonyl), 3.75-3.95 (2 H, m,  $\text{CH}_2\text{-O}$ ), 6.8 (1 H, s, phenolic H), 6.9 (2 H, d, J = 9 Hz Ar), 7.2 (2H, d, J = 7 Hz, Ar).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_3$ : C, 69.88; H, 6.84. Found: C, 70.04; H, 6.94.

Tetrahydro-3-hydroxy-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-carbonitrile **4**.

To a cold solution of ammonium chloride (5.3 g) and potassium cyanide (6.6 g) in water-ethanol (120:20) 8.8 g of **3a** was added dropwise with stirring. The dropping funnel was washed with some ethanol (10 ml) and added to the reaction mixture. A white precipitate appeared in a short time. Stirring was continued for an additional 10 hours and the mixture filtered yielding 9 g (90%) of **4** melting at 135-136° (hexane-ether);  $\nu$  max  $\text{cm}^{-1}$  ir (chloroform): 3550, 3400 (OH/NH), 2830, 1238, 1170 ( $\text{OCH}_3$ ), 2225 ( $\text{C}\equiv\text{N}$ ), 1600, 1572, 1500 (Ar), 1090 ( $\text{C-O-C}$ );  $^1\text{H}$  nmr (deuteriochloroform): 60 MHz  $\delta$  1.57 (3 H, s, ang  $-\text{CH}_3$ ), 2.10 (4 H, m,  $-\text{CH}_2-\text{CH}_2-$ ), 3.12 (1 H, s, OH), 3.80 (3 H, s,  $-\text{OCH}_3$ ), 3.90 (2H, bm,  $-\text{OCH}_2-$  overlap with  $-\text{OCH}_3$ ), 6.92 (2 H, d, J = 9 Hz Ar), 7.60 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{O}_3\text{N}$ : C, 67.99; H, 6.93; N, 5.66. Found: C, 67.89; H, 6.77; N, 5.92.

3-(Aminomethyl)tetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol **5** Hydrochloride.

Compound **4** (24.5 g, 0.1 mole), was hydrogenated over platinum oxide (2 g) in acetic acid (about 200 ml) to which concentrated hydrochloric acid (10-12 ml) has been added. The reaction was run under 50 psi for 3 hours, then as an additional amount (1 g) of fresh catalyst was added and the hydrogenation continued for an additional 3 hours; at that point tlc (methylene chloride-methanol, 1:1) showed that the reaction was complete. The catalyst was removed by filtration and the solvent evaporated to dryness under reduced pressure yielding crude **5** (free amine) which was converted to its hydrochloride salt. The crude hydrochloride salt was washed with ether, boiling ether, and crystallized from methanol-ether yielding 22 g (77%) of analytically pure **5** as its hydrochloride salt melting at 244-246°; ir (Nujol):  $\nu$  max  $\text{cm}^{-1}$  3380 (OH/NH), 1240, 1175 ( $\text{O-CH}_3$ ), 1090 ( $-\text{CH}_2\text{-O-CH}_2-$ );  $^1\text{H}$  nmr (deuterium oxide): 60 MHz  $\delta$  1.73 (3 H, s, ang  $-\text{CH}_3$ ), 1.97 (4H, m,  $-\text{CH}_2\text{CH}_2-$ ), 2.40 (1 H, d, J = 13.5 Hz,  $-\text{CH}_2\text{-N}$ ), 3.38 (1 H, d, J = 13.5 Hz,  $-\text{CH}_2\text{-N}$ ), 3.87 (3 H, s,  $\text{O-CH}_3$ ), 4.00 (2 H, unresolved m appearing as t, J = 5 Hz,  $\text{O-CH}_2$ ), 7.05 (2 H, d, J = 9 Hz Ar), 7.60 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{21}\text{NO}_3\cdot\text{HCl}$ : C, 58.34; H, 7.69; N, 4.86; Cl, 12.32. Found: C, 58.25; H, 7.82; N, 4.81; Cl, 12.42.

3-Dimethylaminomethyltetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol **6** Hydrochloride.

A mixture of 35% formaldehyde (2.16 g) and 88% formic acid (1.3 g) was added with cooling and stirring to 3-(aminomethyl)tetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol **5** (2.51 g, 0.01 mole). The reaction mixture was heated gradually with stirring and refluxed for four hours, then cooled and treated with a concentrated solution of sodium hydroxide and extracted with benzene (3 X 70 ml). The combined extracts were dried and evaporated under reduced pressure, yielding an amine which was converted to its hydrochloride salt in the usual manner (ethereal hydrogen chloride-methanol). Upon recrystallization from methanol-ether, 1.3 g (39.1%) of **6** was obtained, melting at 211°. On a second run utilizing 3.7 g of the starting amine, 1.95 g of formaldehyde and 2.24 g formic acid the above synthesis afforded 2.6 g (55%) of **6** hydrogen chloride; ir (Nujol):  $\nu$  max  $\text{cm}^{-1}$  3240 (OH/NH), 2640 ( $\text{NH}^+$ ), 1236, 1170 ( $\text{O-CH}_3$ ), 1095 ( $-\text{CH}_2\text{-O-CH}_2-$ );  $^1\text{H}$  nmr (deuteriochloroform): (as free base) 60 MHz  $\delta$  1.6 (3 H, s, ang  $\text{CH}_3$ ); 1.5-2.0 (4 H, m,  $-\text{CH}_2-\text{CH}_2-$ ), 1.9

(6 H, s,  $-\text{N}(\text{CH}_3)_2$ ), 2.24, 2.27 (2 H, two s,  $\text{CH}_2\text{-N}$ ), 3.76 (3 H, s,  $-\text{O-CH}_3$ ), 3.80 (2 H, m,  $-\text{CH}_2\text{-O}$ ), 4.20 (1 H, bs, OH), 6.76 (2 H, d, J = 9 Hz Ar), 7.45 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{25}\text{NO}_3\cdot\text{HCl}$ : C, 60.84; H, 8.29; N, 4.42. Found: C, 60.91; H, 8.35; N, 4.30.

Tetrahydro-3-(isopropylamino)methyl-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol **7** Hydrochloride.

3-(Aminomethyl)tetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol (2.51 g, 0.01 mole), methylene chloride (20-50 ml), anhydrous acetone (20 ml) and some activated molecular sieve 1.5 g were placed in a round bottom flask equipped with a Dean-Stark trap. Some methylene chloride was removed by the Dean-Stark trap and the reaction mixture was allowed to reflux gently for 6 hours and then allowed to stand overnight. In a second run, methylene chloride was replaced by anhydrous methanol and the Dean-Stark trap was not used. The formation of the Schiff base was checked as follows. A few drops of the reaction mixture were placed on an ir, sodium disc and the organic solvent was removed by a stream of nitrogen. Absorption at 1685  $\text{cm}^{-1}$  indicated the formation of the Schiff base. The organic solvents (methylene chloride-acetone) were removed by distillation under reduced pressure and anhydrous methanol added. To the methanolic solution of the Schiff base cooled at 0-5°, sodium borohydride (2-2.5 g) was added portionwise in such a rate that the temperature was kept between 0-8°. The reaction mixture was allowed to reach room temperature and stirring continued for 6 hours. Methanol was partially removed and aqueous hydrochloric acid added. The acidic solution was basified with aqueous ammonia (or sodium hydroxide solution), sodium chloride solution was added and the title compound amine was extracted with chloroform (3 X 100 ml). The combined chloroform extracts were dried and evaporated under reduced pressure. The title product amine was converted to its hydrochloride salt in the usual manner to give 2.1 g (62%) pure product, melting at 238° after being recrystallized from methanol/ether. When the Schiff base was reduced catalytically (10% Pd/C, 10% on weight base and solvent methanol) the yield was increased to 85%; ir (chloroform):  $\nu$  max  $\text{cm}^{-1}$  3330, 3200 (OH/NH), 2700 (NH), 1600, 1500 (Ar);  $^1\text{H}$  nmr (deuteriochloroform): 60 MHz (free base)  $\delta$  0.67 and 0.75 (6 H, two doublets J = 6 Hz,  $-\text{NH-CH}(\text{CH}_3)_2$ ), 1.4-1.9 (4 H, m,  $-\text{CH}_2-\text{CH}_2-$ ), 2.3 (1 H, m, OH), 2.07 (1 H, d, J = 12.5 Hz  $-\text{CH}_2\text{-NH}$ ), 3.0 (1 H, d, J = 12.5 Hz  $-\text{CH}_2\text{-NH}$ ), 3.77 (2 H, s,  $-\text{O-CH}_3$ ), 3.85 (2 H, m,  $-\text{CH}_2\text{-O}$ ), 6.8 (2 H, d, J = 9 Hz Ar), 7.50 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{27}\text{O}_3\text{N}\cdot\text{HCl}$ : C, 61.89; H, 8.55; N, 4.24. Found: C, 62.08; H, 8.59; N, 4.08.

Tetrahydro-3-(2-oxazolin-2-yl)aminomethyl-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol **8**.

To a solution of 3-(aminomethyl)tetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol (1.88 g) in ether (or ether-THF or THF), 2-chloroethyl isocyanate (1.5 g in 10 ml of benzene) was added dropwise with stirring. Stirring was continued for twenty five minutes. At that point tlc (dichloromethane-methanol, 85:15) showed that the reaction was complete. The reaction mixture was evaporated to dryness under reduced pressure yielding a gummy residue of  $\beta$ -chloroethylurea derivative which was dissolved in 15-20 ml of ethanol and added dropwise to 250 ml of boiling water, during fifteen minutes. The mixture was boiled for an additional ten minutes, yielding a clear solution. The water solution of **8**, hydrochloride salt was treated with concentrated ammonium hydroxide solution (or sodium hydroxide solution) and extracted with ether *several times*. (The product is not very soluble in ether). Upon evaporation of ether, 1.68 g (70%) of **8** was obtained as crystalline product melting at 160-161°. On a second run when methylene chloride was used for the extraction the yield was increased to 75%; ir (chloroform):  $\nu$  max  $\text{cm}^{-1}$  3450, 3200 ( $-\text{OH/NH}$ ), 1667 ( $-\text{C}=\text{N}$ ), 1602, 1512, 1502 (Ar);  $^1\text{H}$  nmr (deuteriochloroform): (free base) 60 MHz  $\delta$  1.64 (1 H, s, ang  $-\text{CH}_3$ ), 1.82 (4 H, m,  $-\text{CH}_2\text{CH}_2$ ), 3.2 (2 H, m,  $-\text{CH}_2\text{NH-C(O)=N}$ ), 3.6 (4 H, m, oxazole H), 3.8 (2 H, m,  $-\text{CH}_2\text{-O}$ ), 3.8 (3 H, s,  $\text{O-CH}_3$ ), 4.8 (2 H, s, NH + OH), 6.8 (2 H, d, J = 8.5 Hz Ar), 7.32 (2 H, d, J = 8.5 Hz Ar).

*Anal.* Calcd. for  $C_{17}H_{24}O_4N_4$ : C, 63.73; H, 7.55; N, 8.74. Found: C, 63.97; H, 7.58; N, 8.60.

Tetrahydro-3-(1-imidazolin-2-ylamino)methyl-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol **9**-Maleate.

In a flask, equipped with a reflux condenser leading to an absorption tower containing sodium hydroxide, was placed 3-(aminomethyl)tetrahydro-2-(*p*-methoxyphenyl)-2-methyl-2*H*-pyran-3-ol (5 g or 0.02 mole), butanol (30 ml) and 2-methyl mercapto-4,5-dihydroimidazole hydroiodide (4.15 g). Upon refluxing for five hours the reaction was complete. Heating was stopped and the reaction mixture was left at room temperature overnight resulting in the crystallization of **9** as the hydroiodide. The reaction mixture was cooled and 2.4 g (27%) of **9**-HI melting at 190° were separated by centrifugation. The mother liquor was treated with concentrated ammonium hydroxide (or sodium hydroxide solution) and 2.01 g of **9** as the free base was extracted with chloroform, giving a total yield of 54%. The title product hydroiodide (6.6 g prepared as described above) was treated with concentrated, ammonium hydroxide (or sodium hydroxide solution) and extracted with chloroform. The chloroform solution was dried and evaporated under reduced pressure yielding 3.2 g (50%) of **9** which was converted to its maleate, melting at 180-181°; ir (Nujol):  $\nu$  max  $cm^{-1}$  3385, 3150 (-OH/NH), 2700 (NH<sup>+</sup>), 1670 (C=N-), 1595, 1580, 1500 (Ar), 1237, 1170 (OCH<sub>3</sub>); <sup>1</sup>H nmr (deuteriomethanol): 60 MHz  $\delta$  1.6 (3 H, s, ang CH<sub>3</sub>), 1.6-2.0 (4 H, m, -CH<sub>2</sub>CH<sub>2</sub>-), 2.72 (1 H, d, J = 13.5 Hz -CH<sub>2</sub>NH-C(=N)-N-), 3.25 (1 H, d, J = 13.5 Hz -CH<sub>2</sub>NH-C(=N)-N-), 3.45 (4 H, s, imidazole H), 3.78 (3 H, s, -O-CH<sub>3</sub>), 3.85 (3.75-3.95) (2 H, m, -CH<sub>2</sub>-O), 6.25 (2 H, s, -CH=CH-), 6.8 (2 H, d, J = 9 Hz Ar), 7.50 (2 H, d, J = 9 Hz Ar).

*Anal.* Calcd. for  $C_{21}H_{29}N_3O_7$ : C, 57.92; H, 6.71; N, 9.65. Found: C, 57.64; H, 6.73; N, 9.43.

6-(*p*-Methoxyphenyl)-6-methyl-7-oxa-1,3-diazaspiro[4,5]decane-2,4-dione **10**.

A mixture of **3** (10.2 g, 0.046 mole), potassium cyanide (18 g), ammonium carbonate (22.8 g), ethanol (200 ml) and water (200 ml) was stirred at 55-60° for 10 hours (overnight). The solution was then concentrated to almost half volume. The crystals which separated upon cooling were collected by filtration, and crystallized from ethanol 11.42 g (85%) as needles melting at 242-243°; ir:  $\nu$  max  $cm^{-1}$  3300, 1750, 1700, 1606, 1573, 1505, 1247, 1180, 1088; <sup>1</sup>H nmr (DMSO): 60 MHz  $\delta$  ~ 1.60 (4 H, m, -CH<sub>2</sub>-CH<sub>2</sub>-), 1.72 (3 H, s, angular -CH<sub>3</sub>), 3.82 (3 H, s, -O-CH<sub>3</sub>), 3.82-4.10 (2

H, m, CH<sub>2</sub>O), 6.81 (2 H, d, J = 9 Hz Ar), 7.30 (2 H, d, J = 9 Hz Ar), 8.23 (1 H, s, -NH- of hydandoin), 8.33 (1 H, s, NH- of hydandoin).

*Anal.* Calcd. for  $C_{15}H_{18}N_2O_4$ : C, 62.05; H, 6.25; N, 9.65. Found: C, 61.99; H, 6.28; N, 9.68.

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