A REINVESTIGATION OF THE SYNTHESIS OF 1,2-DIHYDRO[1,2]DIAZEPIN-3-ONES FROM PYRONES

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Abstract - The reactions of 5-acetyl-6-hydroxy-4-(4-methoxyphenyl)-2H-pyran-2-one (5) and 4-(4-methoxyphenyl)-2H-pyran-2,6-dione (4) with hydrazine and phenylhydrazine respectively, gave the respective 1-amino-2-pyridones 8 and 11 rather than diazepinones 6 and 10, as previously reported. In addition, 4-(4-methoxyphenyl)-2-methyl-6-oxo-2H-pyran-3-carboxylic acid (14) gave p-methoxyacetophenone azine (16) upon treatment with hydrazine, rather than pyrazolodiazepinone 15.

A recent report by Pednekar, Samant and Deodhar[1] describes the preparation of 1,2-diazepin-3-ones from 5H-pyran-2,6-diones and hydrazines. We have reinvestigated this work and found it to be in error. The products are, instead, 1-amino-2-pyridones.

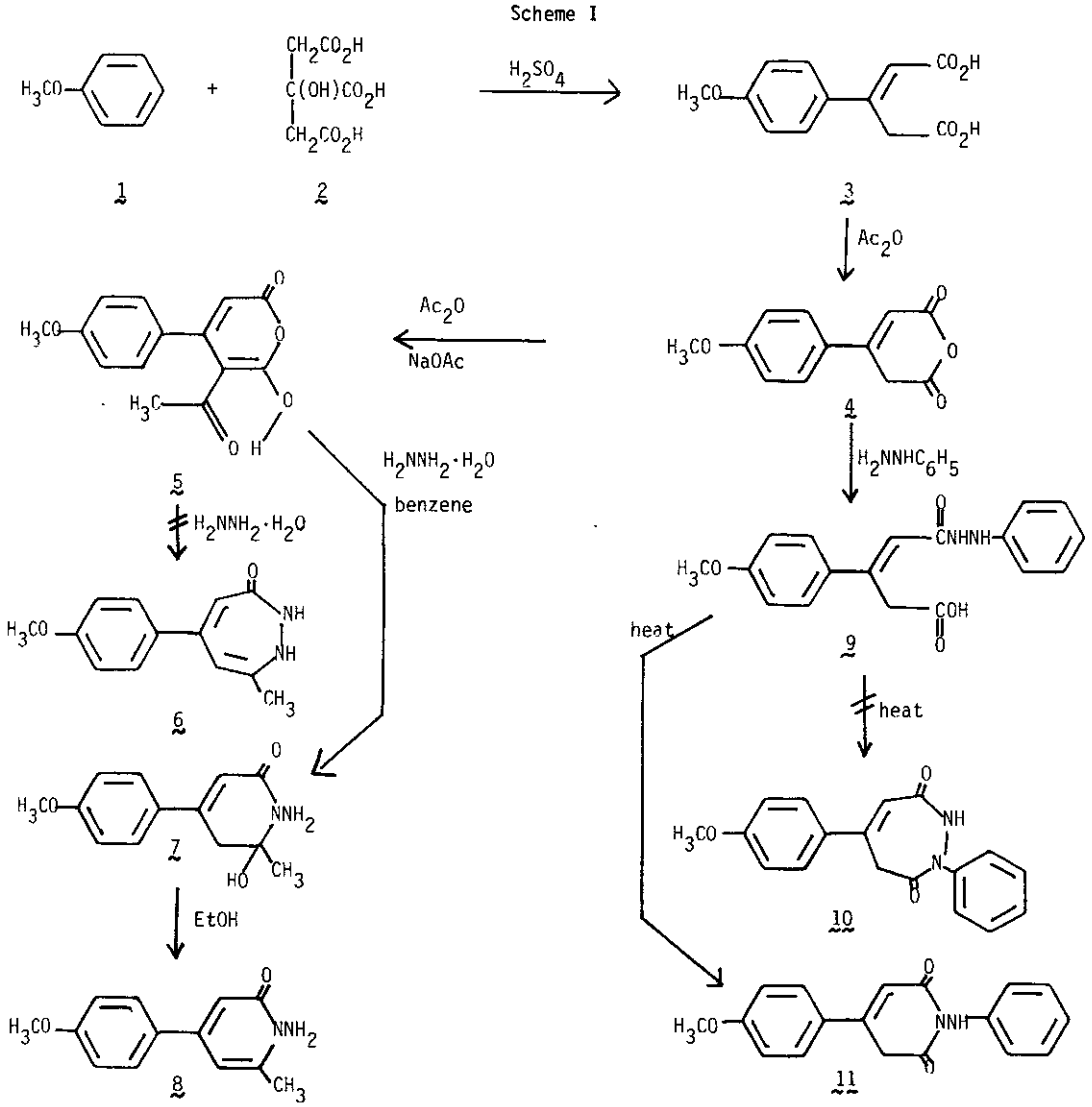
Treatment of anisole (1) and citric acid (2) with sulfuric acid gave 3-(4-methoxyphenyl)-2-pentenedioic acid (3), apparently by in situ decarboxylation and oxidation of 2 to acetone dicarboxylic acid followed by condensation with 3, as earlier described by Limaye and Bhave[2] (Scheme I). Cyclization of 3 with acetic anhydride afforded anhydride 4, which was converted to 5-acetyl-6-hydroxy-4-(4-methoxyphenyl)-2H-pyran-2-one (5) with sodium acetate and acetic anhydride.[1] The ^{1}H nmr spectrum of 5 was consistent with the enolized structure shown.

Treatment of a benzene solution of 5 with hydrazine hydrate did **not** yield diazepinone 6 as reported by Pednekar, Samant and Deodhar.[1] The product of this reaction was, instead, 1-amino-5,6-dihydro-6-hydroxy-4-(4-methoxyphenyl)-6-methyl-2(1H)-pyridinone (7). When aminal 7 was heated with ethanol and the resulting solution cooled, the dehydrated aminopyridone 8, isomeric with diazepinone 6, crystallized. The ^{1}H nmr spectra of both 7 and 8 indicated that the same nitrogen atom of hydrazine was involved in the acylation condensation sequence, in that amino signals (singlets) were observed at appropriate field positions. Moreover, the presence of the amino group in 8 was confirmed by isolation and characterization of the benzylidene derivatives 12a and b, resulting from condensation with benzaldehyde and p-nitrobenzaldehyde, respectively

(Scheme II). We have previously ascertained the structures of aminoquinazolinones which were purported to be benzotriazepinones, by preparing benzylidene derivatives.[3,4]

Treatment of anhydride 4 with phenylhydrazine gave hydrazide 9, as reported by Pednekar, Samant and Doedhar[1] (Scheme I). However, thermolysis did **not** produce diazepinedione 10 as reported, but pyridinedione 11, instead. Structure 11 was unambiguously determined by conversion, by catalytic

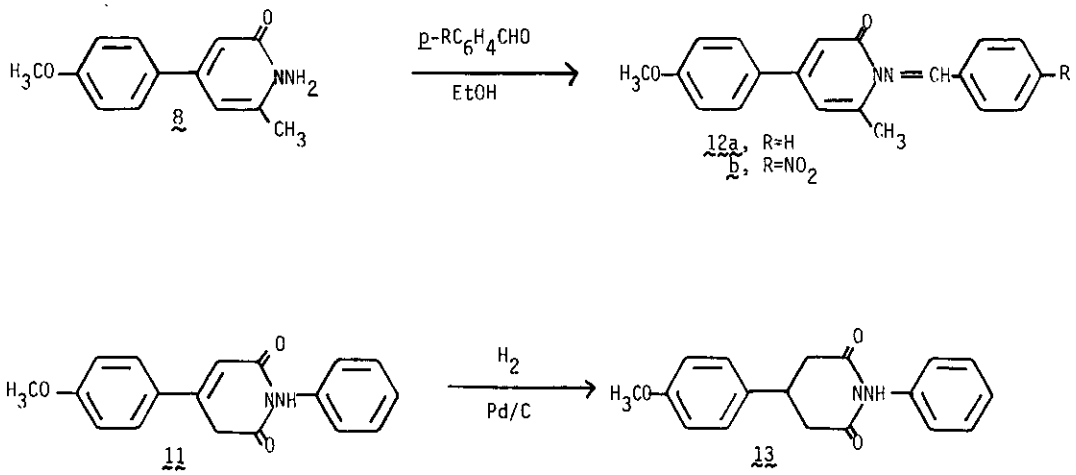
Scheme I



reduction, to piperidinedione 13. The ^{13}C nmr spectrum of 13 clearly showed it was a symmetrical structure. Had diazepinedione 10 been the product resulting from 4 and phenylhydrazine, reduction would have given an unsymmetrical dihydro derivative.

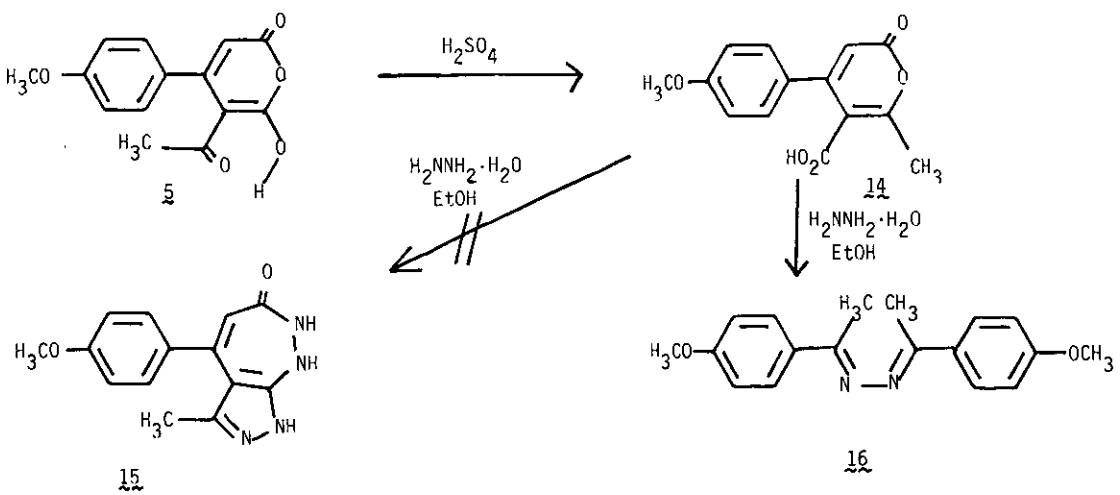
We also prepared 4-(4-methoxyphenyl)-2-methyl-6-oxo-2H-pyran-3-carboxylic acid (14), by treating 5 with sulfuric acid as shown in Scheme III. Pednekar, Samant and Doedhar[1] reported that 14, when treated with hydrazine, gave pyrazolodiazepinone 15, mp 200-201°C. However, when we repeated this reaction and isolated the product in precisely the same way, we obtained a

Scheme II



product whose ir spectrum matched that reported for 15 and whose melting point (196-197°C) was essentially the same, which we assigned as p-methoxyacetophenone azine (16). The elemental analysis, mass spectrum and ^{1}H nmr spectrum were in agreement with this structure. An ^{1}H nmr

Scheme III



spectrum was not reported for compound 15. We have recently isolated an azo compound analogous to 16 (p-aminoacetophenone azine) from the reaction of 2-chloro-4-(4-nitrophenyl)thiazole with hydrazine hydrate.[5] In both of these cases hydrazine is retrograding the heterocycle to a 2-carbon fragment, allowing a reaction to occur which would result from the condensation of hydrazine with two equivalents of the corresponding acetophenones.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Model 1310 spectrophotometers, nmr spectra with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, Ohio.

3-(4-Methoxyphenyl)-2-pentenedioic Acid (3). A mixture of 50.0 g (0.238 mol) of citric acid (2) and 80 ml of conc H_2SO_4 was stirred for 30 min and then warmed to 70°C and stirred for 15 min. Gas evolution (CO_2) was apparent. The solution was cooled to 10°C and 20 ml of anisole (1) was added. After 2 h of stirring, the solution was poured into 300 ml of cold water and the crystalline solid was collected, washed with water and dried to give 6.20 g (11%) of 3, mp 172-174°C (dec) (water) [lit.[2] mp 176°C (dec)]; ir (Nujol) 3600-2200 (OH), 1710 (C=O), 1685 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6) δ 15.2 (broad s, 2H, OH), 7.50 (d, J=8.5 Hz, 2H, H ortho to vinyl), 6.90 (d, J=8.5 Hz, 2H, H ortho to OCH_3), 6.20 (s, 1H, vinyl), 4.15 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3); ms (70 eV, chemical ionization, methane) 237 (M^++1), 265 (M^++29), 277 (M^++41).

4-(4-Methoxyphenyl)-2H-pyran-2,6(3H)-dione (4). A solution of 18.7 g (79.2 mmol) of 3 in 40 ml of acetic anhydride was heated at reflux for 10 min. Upon cooling, a white, crystalline solid formed which was collected, washed with ether-hexane and dried to give 12.9 g (75%) of 4, mp 160°C (lit.[2] mp 160°C); ir (Nujol) 1790 (C=O), 1735 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$ and DMSO-d_6) δ 7.60 (d, J=9 Hz, 2H, H ortho to vinyl), 6.95 (d, J=9 Hz, 2H, H ortho to OCH_3), 6.50 (t, J=1.5 Hz, 1H, vinyl), 3.97 (d, J=1.5 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3).

5-Acetyl-6-hydroxy-4-(4-methoxyphenyl)-2H-pyran-2-one (5).[6] A mixture of 5.00 g (22.9 mmol) of 4, 5.00 g of anhydrous sodium acetate and 7.5 ml of acetic anhydride was heated in an oil bath at 80°C for 20 min. The red solution was poured into cold water (100 ml) and acidified with conc HCl (7.5 ml). The resulting solid was collected and washed with water to give 5.75 g (97%) of 5,

mp 127-128°C (benzene-hexane) (lit.[7] mp 132°C); ir (Nujol) 1755 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.21 (d, J=8.8 Hz, 2H, H ortho to vinyl), 6.98 (d, J=8.8 Hz, 2H, H ortho to OCH_3), 5.80 (s, 1H, vinyl), 3.87 (s, 3H, OCH_3), 1.77 (s, 3H, $COCH_3$), 1.60 (broad s, 1H, OH); ms (70 eV, electron impact) m/e 260 (molecular ion).

1-Amino-5,6-dihydro-6-hydroxy-4-(4-methoxyphenyl)-6-methyl-2(1H)-pyridinone (7). Hydrazine hydrate (2 ml) was slowly added to a solution of 520 mg (2.00 mmol) of 5 in 40 ml of benzene. After 2 h of stirring at room temperature, the benzene supernatant was decanted and the gummy solid was washed with additional benzene. Trituration of the residue with ethanol gave a white solid which was collected to afford 380 mg (76%) of 7, mp 140-141°C; ir (KBr) 3400-2700 (broad stretching, with spikes at 3300 and 3200), 1645 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6) δ 7.60 (d, J=8.8 Hz, 2H, H ortho to vinyl), 6.98 (J=8.8 Hz, 2H, H ortho to OCH_3), 6.24 (s, 1H, vinyl), 5.6 (very broad signal, 2H, NH_2, D_2O-exchangeable), 4.6 (very broad signal, 1H, OH, D_2O-exchangeable), 3.79 (s, 3H, OCH_3), 2.96 (m, 2H, CH_2), 1.57 (s, 3H, CCH_3); ^{13}C nmr (DMSO-d_6) δ 165.0 (C-2), 160.7 (C-4'), 146.0 (C-4), 129.5 (C-1'), 127.7 (C-2'), 115.4 (C-3), 114.4 (C-3'), 85.7 (C-6), 55.6 (OCH_3), 40.8 (C-5), 27.1 (CH_3); ms (70 eV, chemical ionization, methane) 249 (M^++1), 277 (M^++29), 289 (M^++41).

1-Amino-4-(4-methoxyphenyl)-6-methyl-2(1H)-pyridinone (8). A mixture of 380 mg (1.53 mmol) of 7 and 125 ml of ethanol was heated at reflux. After 1 h, the resulting solution was concentrated to 20 ml and cooled, and the resulting white needles were collected and dried to give 170 mg (48%) of 8, mp 173-174°C; ir (KBr) 3285 and 3195 (NH_2), 1645 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6) δ 7.67 (dd, J=2.4 Hz, 9.3 Hz, 2H, H ortho to vinyl), 7.02 (dd, J=2.4 Hz, 9.3 Hz, 2H, H ortho to OCH_3), 6.58 (d, J=2.2 Hz, 1H, vinyl), 6.52 (d, J=2.2 Hz, 1H, vinyl), 6.08 (s, 2H, NH_2, D_2O-exchangeable), 3.80 (s, 3H, OCH_3), 2.43 (s, 3H, CCH_3); ^{13}C nmr (DMSO-d_6) δ 160.5 (C-2 or C-4'), 160.2 (C-4' or C-2), 147.8 (C-4), 146.1 (C-6), 129.6 (C-1'), 128.2 (C-2'), 114.7 (C-3'), 109.1 (C-3), 103.7 (C-5), 55.6 (OCH_3), 19.3 (CH_3); ms (70 eV, chemical ionization, methane) 231 (M^++1), 259 (M^++29), 271 (M^++41); Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.83; H, 6.12; N, 12.11.

3-(4-Methoxyphenyl)-2-pentendioic Acid 1-(2-Phenylhydrazide) (9). A mixture of 4.36 g (20.0 mmol) of 4, 2.50 g (23.0 mmol) of phenylhydrazine and 450 ml of benzene was heated at reflux for 2 h. The mixture was cooled and the solid was collected, washed with ether and dried to give 6.27 g (96%) of 9, mp 173-174°C (ethanol) (lit.[1] mp 170-171°C); ir (Nujol) 3400-2400 (NH and OH, with spike at 3260), 1695 (acid C=O), 1650 (hydrazide C=O); nmr (DMSO-d_6) δ 12.33 (s, 1H, CO_2H), 9.68 (s, 1H, CONH), 7.70 (s, 1H, CONHNH), 7.54 (d, J=8.8 Hz, 2H, H ortho to vinyl), 7.03 (t, J=8

Hz, 2H, H meta to NH), 6.98 (d, J=8.8 Hz, 2H, H ortho to OCH_3), 6.64 (t, J=8 Hz, 1H, H para to NH), 6.55 (d, J=8 Hz, 2H, H ortho to NH), 4.18 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3); ms (70 eV, electron impact) m/e 326 (molecular ion).

4-(4-Methoxyphenyl)-1-(phenylamino)-2,6(1H,3H)-pyridinedione (11). A 2.00-g (6.13 mmol) quantity of 9 was heated neat in an oil bath at 185-190°C for 30 min. The resulting solid was recrystallized (2-methoxyethanol) to give 1.39 g (74%) of 11, mp 196-197°C; ir (Nujol) 3300 (NH), 1710 and 1665 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 7.54 (d, J=9 Hz, 2H, H ortho to vinyl), 7.30-7.20 (m, 3H, H meta and para to NH), 6.99 (d, J=9 Hz, 2H, H ortho to OCH_3), 6.84 (d, J= 7.8 Hz, 2H, H ortho to NH), 6.65 (s, 1H, NH), 6.59 (s, 1H, vinyl), 4.02 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3); ms (70 eV, chemical ionization, methane) 309 (M^++1), 337 (M^++29), 349 (M^++41); Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 69.98; H, 5.25; N, 8.92. Found: C, 69.79; H, 5.24; N, 8.93.

4-(4-Methoxyphenyl)-6-methyl-1-[(phenylmethylene)amino]-2(1H)-pyridinone (12a) and p-Nitro Analog (12b). A solution of 230 mg (1.00 mmol) of 8 and 170 mg (1.60 mmol) of benzaldehyde in 25 ml of ethanol was heated at reflux for 27 h. The solution was cooled and the yellow, crystalline solid collected to give 270 mg (85%) of 12a, mp 178°C (ethanol); ir (Nujol) 1650 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 9.13 (s, 1H, CH=N), 7.89 (dd, J=1.7 Hz, 8.0 Hz, 2H, H ortho to C=N), 7.62-7.43 (m, 4H, H meta to C=N and ortho to vinyl), 6.98 (ddd, J=ca. 2 Hz, ca. 2 Hz, 8.8 Hz, 2H, H ortho to OCH_3), 6.74 (d, J=1.9 Hz, 1H, C-3 H), 6.35 (d, J=1.9 Hz, 1H, C-5 H), 3.86 (s, 3H, OCH_3), 2.44 (s, 3H, CCH_3); ms (70 eV, electron impact) m/e 318 (molecular ion); Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.40; H, 5.71; N, 8.75.

The p-nitro analog 12b was prepared from 8 and p-nitrobenzaldehyde in 52% yield: mp 192-193°C; Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.57. Found: C, 66.16; H, 4.68; N, 11.58.

4-(4-Methoxyphenyl)-1-(phenylamino)-2,6-piperidinedione (13). A solution of 500 mg (1.62 mmol) of 11 in 40 ml of acetic acid was hydrogenated in a Parr apparatus in the presence of 10% Pd/C at ca. 50 psi for 3 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was triturated with water and the solid collected to give 340 mg (68%) of 13, mp 155° (ethanol-water); ir (Nujol) 3330 (NH), 1740 (sh) and 1700 (C=O) cm^{-1}; ^{13}C nmr δ 170.2 (C-2 and C-6), 159.1 (C-OCH_3), 146.1 (C-NH), 131.9 (C para to OCH_3), 129.2 (2C meta to NH), 127.4 (2C meta to OCH_3), 122.4 (2C ortho to NH), 114.8 (C para to NH), 114.6 (2C ortho to OCH_3), 55.4 (OCH_3), 40.2 (C-3 and C-5), 33.6 (C-4); ms (70 eV, chemical inonization) 311 (M^++1), 339 (M^++29), 351

(M^++41); Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.51; H, 5.89; N, 8.85.

4-(4-Methoxyphenyl)-2-methyl-6-oxo-2H-pyran-3-carboxylic Acid (14). A 5.00-g (19.2 mmol) quantity of 5 was dissolved in 10 ml of cold 90% H_2SO_4. The solution was left at room temperature for 4 h and poured into ice water. The resulting solid was collected, washed with water and partitioned between ether and aqueous sodium carbonate. The aqueous layer was acidified and the resulting solid was collected and recrystallized (methanol-water) to give 3.66 g (73%) of 14, mp 182-184°C (lit.[7] mp 181°C); ir (Nujol) 3400-2300 (OH), 1735 (lactone C=O), 1690 (acid C=O) cm^{-1}; nmr (DMSO-d_6) δ 7.38 (d, J=8.8 Hz, 2H, H ortho to vinyl), 7.02 (d, J=8.8 Hz, 2H, H ortho to OCH_3), 6.18 (s, 1H, vinyl), 3.80 (s, 3H, OCH_3), 2.38 (s, 3H, CCH_3); ms (70 eV, electron impact) m/e 260 (molecular ion).

1-(4-Methoxyphenyl)ethanone [1-(4-Methoxyphenyl)ethylidene]hydrazone (16). A solution of 1.04 g (4.00 mmol) of 14 and 8 ml of hydrazine monohydrate in 80 ml of ethanol was heated at reflux for 2 h. The solution was concentrated by Kugelrohr distillation to leave 1.03 g of material, which was subjected to flash chromatography on silica gel. Elution with ethyl acetate removed 260 mg (22%) of 16, mp 196-197°C (ethanol); ir (KBr) 2940 (CH), 2845 (CH), 1600 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 7.88 (d, J=9.03 Hz, 4H, H ortho to C=N), 6.93 (d, J=9.03 Hz, 4H, H ortho to OCH_3), 3.86 (s, 6H, both OCH_3), 2.32 (s, 6H, both CCH_3); ms (70 eV, electron impact) m/e 296 (molecular ion); Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.86; H, 6.75; N, 9.28.

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