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Simple Synthesis of (±)-(*E*)-3-(4-Hydroxyphenyl)-*N*-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide, a Novel Phenolic Amide Derivative from the Bulbs of *Lilium regale* WILSON

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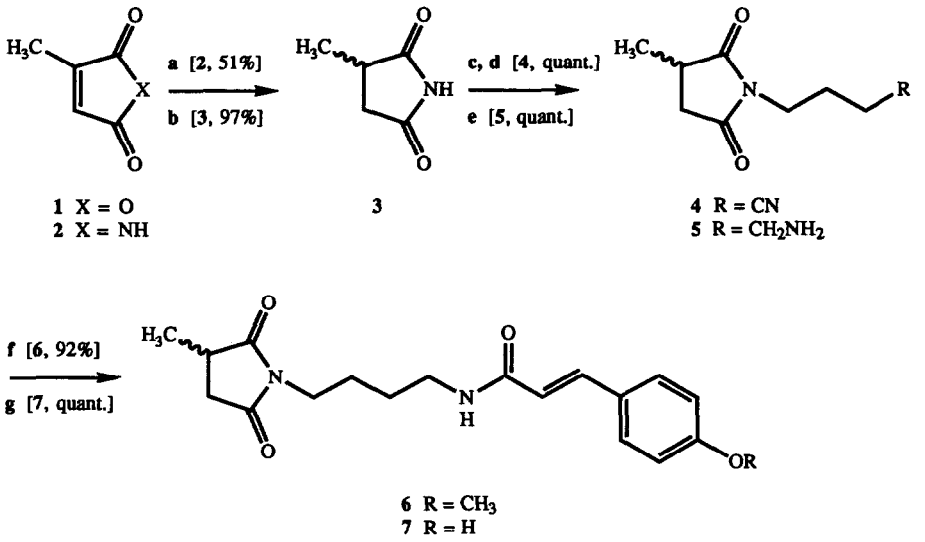
Abstract: A synthesis of (±)-(*E*)-3-(4-hydroxyphenyl)-*N*-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide (**7**) is described. This phenolic amide was prepared in six steps with an overall yield of 46%.

A reinvestigation of the methanolic extract of *Lilium regale* WILSON, undertaken by *Mimaki* and *Sashida*, led to isolation and characterization of the novel phenolic amide **7**.[1] Known from various plants, conjugates of hydroxycinnamic acid with aliphatic amines such as putrescine, spermidine and spermine are especially accumulated in their reproductive organs.[2] Some of the amides are suggested to protect the plants from viral, bacterial or fungal infection and may be produced as phytoalexins.[3] *L. regale* is known for its strong resistance to viral diseases.[4]

As we have a continuing interest in compounds of natural origin, especially the polyamine alkaloids,[5] we were prompted to investigate the synthesis and spectroscopic behavior of the putrescine alkaloid (±)-(*E*)-3-(4-hydroxyphenyl)-*N*-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide (**7**). In this paper, we describe a facile preparation of this phenolic amide, the structure of which was established by spectroscopic analysis and by comparison with published data of the natural product.

The synthesis of (±)-(*E*)-3-(4-hydroxyphenyl)-*N*-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide (**7**), as shown, begins by preparing citraconimide (**2**) using citraconic anhydride (**1**) and heating it under reflux in the presence of NH_4OAc/AcOH. This method to prepare the imide **2** was reported by *Earl et al.*,[6] but by a slight modification a higher yield was achieved (*vide infra*). The reaction proceeds through the 2-methylmaleamic acid intermediate to give **2** and substantial quantities of resinous byproducts presumably of the general formula -$[NRC(O)CH{=}CHC(O)]_x$-.[7]



a) NH_4OAc, AcOH b) H_2, Pd/C, EtOH c) Na/MeOH d) $Br(CH_2)_3CN$, DMF e) H_2, PtO_2, EtOH/HCl f) 4-methoxycinnamic acid, 1-methyl-2-chloromethylpyridinium iodide, Et_3N, CH_2Cl_2 g) BBr_3, CH_2Cl_2

Scheme

In the next step, **2** was hydrogenated in the presence of 10% Pd/C in EtOH. The few percent of imide **3** which had openned could easily be removed by chromatography. Reduction at this stage was very important because of polymerization found to occur when alkylation was directly attempted with **2**.

Alkylation was accomplished then by addition of 4-bromobutyronitrile to the dry sodium salt of **3** in absolute DMF.[8] After heating under reflux, the DMF was evaporated and the residue treated with CH_2Cl_2 to deliver after further purification **4** in a quantitative yield.

The transformation of the nitrile group in **4** to the corresponding primary amine by catalytic hydrogenation was seen as the best method for reduction.[9] In fact, (±)-*N*-(4-aminobutyl)-3-methylsuccinimide (**5**) was quantitatively won in form of its HCl salt by treatment of **4** with H_2 (*ca.* 3 atm) and PtO_2 in ethanolic HCl.

Following, the carboxamide **6** could be prepared in 92% yield when equimolar amounts of the primary amine **5** and 4-methoxycinnamic acid were treated with 1.2 molar amounts of *Mukaiyama's* reagent[10] (1-methyl-2-chloropyridinium iodide) in the presence of 2.4 molar amounts of Et_3N.

Finally, the demethylation of the carboxamide **6** proved not to be a trivial affair. For deprotection the use of NaCN/DMSO and iodotrimethylsilane were tried, but both methods failed. The demethylation was carried out with BBr_3 which delivered the product **7** in quantitative yield.

This preparation gave (±)-(*E*)-3-(4-hydroxyphenyl)-*N*-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide (**7**) in 46% overall yield. The first step, the preparation of the imide, remains problematic though because of its elusiveness to a simple high yield production.[6,7,11]

EXPERIMENTAL

General. All chemicals used were of high commercial quality. Solvents used for chromatography were distilled as usual prior to use. Melting points were determined on a *Mettler FP-5* instrument. UV, in nm (log *e*), and IR spectra were measured on a *Perkin-Elmer 555* and *Perkin-Elmer 781* spectrophotometers respectively. ^{1}H-NMR spectra were carried out on either on a *Bruker AC-300* or *AM-400* spectrometer; ^{13}C-NMR (at 50.4 MHz) on a *Varian XL-200*. Chemical shifts are reported in ppm (δ scale) with $CDCl_3$, unless otherwise stated, as internal standard. EI-MS (at 70 eV) or CI-MS (NH_3 as reactant gas) were measured either on a *Varian MAT 112S* or *Finnigan MAT TSQ 700* mass spectrometer. Intensities for EI are only given for values ≥ 10%, except for $M^{+\cdot}$, from m/z ≥ 40. For flash chromatography, *Merck* silica gel 60 (0.04-0.06 mm) was used. TLC were done on precoated Kieselgel 60 F_{254} aluminum plates (*Merck*); spots visualized under UV light (254 nm) and by staining reagents.

***Citraconimide* (2).** NH_4OAc (35 g, 454 mmol, predried for 2 h/3 x 10^{-2} Torr) and citraconic anhydride (**1**, 25 ml, 179 mmol) were added to AcOH (50 ml) and heated under reflux. After 2 h, the solution was cooled to room temperature and evaporated *in vacuo* at 70°. Ice water (200 ml) was added to the dark syrupy residue and this was followed by extraction with EtOAc (8 x 25 ml) and CH_2Cl_2 (2 x 25 ml). The combined organic extracts were evaporated to give a yellow solid which was then bulb-to-bulb distilled; the fraction distilling at 120-130° (air bath temperature)/3 x 10^{-2} Torr was collected as a colorless solid (10.93 g, 55%). Subsequent purification by flash chromatography (EtOAc/hexane 1:1) afforded **2** (10.06 g, 51%). M.p. (toluene): 104.5-106° (lit.,[6] 103.5-105.5°). IR (KBr): 3380*s*, 3250*m*, 3080*m*, 2985*m*, 2940*m*, 1690*s* + 1645*s* (imide-(CO)), 1590*m*, 1545*s*, 1535*s*, 1520*s*, 1465*m*, 1430*m*, 1370*s*, 1330*m*, 1305*m*, 1275*s*, 1250*m*, 1205*m*, 1165*s*, 1125*m*, 1075*w*, 1040*w*, 1020*w*, 1010*w*, 955*m*, 900*w*, 885*w*, 875*w*, 810*w*, 795*w*, 775*w*, 760*w*, 735*w*, 690*w*, 625*w*. ^{1}H-NMR (400 MHz, (d_6)-DMSO): 10.68 (br. *s*, NH, exchangeable); 6.50-6.45 (*m*, H-C(4)); 1.93 (*d*, *J* = 1.8, CH_3). ^{1}H-NMR (400 MHz): 7.27 (br. *s*, NH); 6.35-6.30 (*m*, H-C(4)); 2.08 (*d*, *J* = 1.8, CH_3). ^{13}C-NMR: 171.7, 170.6 (2 *s*, CO); 146.7 (*s*); 128.3 (*d*); 10.8 (*q*). CI-MS: 223 (100, $[2M + 1]^+$), 112 (89, $[M + 1]^+$). Anal. calc. for $C_5H_5NO_2$ (111.10): C 54.06, H 4.54, N 12.61; found: C 53.96, H 4.52, N 12.69.

***(±)-3-Methylsuccinimide* (3).** The imide **2** (2.5 g, 22.5 mmol) was dissolved in EtOH (25 ml) containing a suspension of 10% Pd/C (125 mg) and stirred overnight under a blanket of H_2 (1 atm). The solution was filtered through cotton wool and evaporated to dryness yielding **3** as an oil, which on standing slowly crystallized. The purified **3** (2.43 g, 97%) was obtained as a colorless solid by flash chromatography (EtOAc/hexane 1:1). M.p. (toluene): 63.5-64.5° (lit.,[12] 62°). IR (KBr): 3500 (br.), 3060*m*, 2980*m*, 2940*w*, 2880*w*, 2760*w*, 1765*s* + 1710*s* (imide-(CO)), 1560*w*, 1540*w*, 1455*w*, 1415*w*, 1380*m*, 1350*m*, 1315*m*, 1290*m*, 1250*w*, 1205*s*, 1180*s*, 1120*w*, 1085*w*, 1035*m*, 930*w*, 890*w*, 795*m*, 725*w*, 640*w*. ^{1}H-NMR (400 MHz): 8.70 (br.

s, NH); 3.00-2.85 (*m*, 2 H-C(4)); 2.45-2.30 (*m*, H-C(3)); 1.35 (*d*, *J* = 7.1, CH_3). ^{13}C-NMR: 181.1, 176.8 (2 *s*, CO); 37.6 (*t*); 36.1 (*d*); 16.5 (*q*). EI-MS: 113 (39, $M^{+\bullet}$), 70 (32), 44 (11), 43 (12), 42 (100), 41 (34). Anal. calc. for $C_5H_7NO_2$ (113.12): C 53.09, H 6.24, N 12.38; found: C 53.15, H 6.26, N 12.26.

***(±)-N-(3-Cyanopropyl)-3-methylsuccinimide* (4).** Sodium (230 mg, 10 mmol) was firstly placed in MeOH (25 ml) followed by addition of imide **3** (1.13 g, 10 mmol). After complete dissolution, the solvent was evaporated to give a colorless crystalline mass. DMF (25 ml) and 4-bromobutyronitrile (1.98 ml, 20 mmol) were then added and the mixture was heated under reflux while stirring for 1 h. The DMF was removed *in vacuo* and the residue treated with CH_2Cl_2 (25 ml) from which the precipitate was filtered off. The filtrate was then washed (H_2O), dried ($MgSO_4$), and evaporated and the residual oil purified by flash chromatography (EtOAc/hexane 1:1) delivering **4** (1.80 g, quant.) as a colorless oil. IR (Film): 3600*w*, 3460*w*, 2980*w*, 2940*m*, 2880*w*, 2250*w* (CN), 1775*m* + 1705*s* (imide-(CO)), 1440*m*, 1405*s*, 1375*m*, 1360*m*, 1290*w*, 1265*w*, 1250*m*, 1220*w*, 1200*w*, 1195*w*, 1165*s*, 1120*w*, 1090*w*, 1070*w*, 1020*m*, 920*w*, 890*w*, 840*w*, 780*w*, 750*w*, 690*w*. ^{1}H-NMR (300 MHz): 3.63 (*t*, *J* = 7.0, NCH_2); 3.00-2.85 (*m*, 2 H); 2.40-2.30 (m, 1H); 2.36 (*t*, *J* = 7.0, CH_2CN); 1.97 (*tt*, *J* = 7.0, 7.0, CH_2CH_2CN); 1.35 (*d*, *J* = 7.2, CH_3). ^{13}C-NMR: 180.5, 176.5 (2 *s*, CO); 118.9 (*s*, CN); 37.6, 36.3 (2 *t*); 34.6 (*d*); 23.5 (*t*); 16.4 (*q*); 15.1 (*t*). EI-MS: 180 (42, $M^{+\bullet}$), 127 (56), 114 (74), 111 (48), 73 (60), 68 (47), 54 (43), 42 (81), 41 (100). Anal. calc. for $C_9H_{12}N_2O_2$ (180.21): C 60.00, H 6.71, N 15.54; found: C 60.14, H 6.90, N 15.28.

***(±)-N-(4-Aminobutyl)-3-methylsuccinimide* (5).** To a solution of concentrated aqueous HCl (6.2 ml, 64.4 mmol) in EtOH (100 ml) was added PtO_2 (325 mg). This catalyst was firstly activated by agitation for 1 h under a blanket of H_2 (3 atm). Addition of **4** (4.64 g, 25.7 mmol) followed, and the mixture was further shaken for 8 h under H_2. The mixture was filtered then through cotton wool and evaporated yielding **5**•HCl (5.70 g, quant.) as a colorless oil. IR ($CHCl_3$): 3450 (br.), 3035 (br., NH_3^+), 2970 (br.), 1770*m* + 1700*s* (imide-(CO)), 1610*m* + 1515*m* (NH_3^+), 1455*m*, 1440*m*, 1405*s*, 1365*m*, 1345*m*, 1290*m*, 1235*m*, 1145*m*, 1095*w*, 1050*w*, 1015*w*, 915*w*, 890*w*, 710*w*, 690*w*, 660*w*. ^{1}H-NMR (300 MHz, DMSO): 7.91 (br. *s*, NH_3^+); 3.40-3.30 (*m*, 2 H); 2.90-2.70 (*m*, 4 H); 2.35-2.25 (*m*, 1 H); 1.60-1.45 (*m*, 4 H); 1.19 (*d*, *J* = 6.8, CH_3). CI-MS: 369 (100, $[(2M + 1)]^+$), 185 (86, $[M + 1]^+$).

***(±)-(E)-3-(4-Methoxyphenyl)-N-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide* (6).** To a suspension of 1-methyl-2-chloropyridinium iodide (3.07 g, 12 mmol) in CH_2Cl_2 (100 ml) was added 4-methoxycinnamic acid (1.78 g, 10 mmol) and Et_3N (3.35 ml, 24 mmol) under a N_2 atmosphere. The addition of **5** (2.43 g, 11 mmol), dissolved in a solution of CH_2Cl_2 (10 ml) and Et_3N (1.5 ml, 11 mmol), was then added dropwise to the mixture while stirring. Afterwards, the mixture was heated under reflux and for 1 h. Upon cooling to room temperature, Et_2O (200 ml) was added and the resulting mixture was washed with a 5% aqueous HCl solution (3 x 100 ml) and with H_2O (1 x 100 ml). The organic layer was then evaporated and the residue, purified by flash chromatography (EtOAc), yielded the carboxamide **6** (3.16 g, 92%) as a colorless solid. M.p. (EtOAc): 122.5-123.5°. IR ($CHCl_3$): 3450*w* (NH), 3000*m*, 2940*w*, 2870*w*, 2840*w*, 1765*m* + 1700*s* (imide-(CO)), 1625*m* (amide-(CO)), 1605*m*, 1575*w*, 1515*s* (arom. ring), 1460*w*, 1440*m*, 1420*w*, 1400*m*, 1370*m*, 1340*w*, 1305*w*, 1285*m*, 1255*m*, 1195*w*, 1175*s*, 1130*w*, 1030*m*, 980*w*, 825*m* (arom. ring). ^{1}H-NMR (300 MHz): 7.55 (*AX*d, *J* = 15.6, 1 H); 7.42 (*d*, *J* = 8.7, 2 arom. H); 6.86 (*d*, *J* = 8.7, 2 arom. H); 6.27 (*AX*d, *J* = 15.6,

1 H); 5.98 (br. *s*, NH); 3.81 (*s*, OCH_3); 3.51 (*t*, *J* = 7.0, 2 H); 3.44-3.35 (*m* , 2 H); 2.95-2.77 (*m*, 2 H); 2.33-2.26 (*m*, 1 H); 1.69-1.50 (*m*, 4 H); 1.32 (*d*, *J* = 7.1, CH_3). ^{13}C-NMR: 180.4, 176.3, 166.3 (3 *s*, CO); 160.5 (*s*, arom. C); 139.9 (*d*); 129.0 (*d*, 2 arom. C); 127.4 (*s*, arom. C); 118.5 (*d*); 113.5 (*d*, 2 arom. C); 55.1 (*q*, OCH_3); 38.9, 38.0, 36.1 (3 *t*); 34.4 (*d*); 26.6, 25.0 (2 *t*); 16.5 (*q*). EI-MS: 344 (3, $M^{+\bullet}$), 205 (24), 177 (26), 176 (14), 162 (14), 161 (100), 133 (27). CI-MS: 346 (23, $[M + 2]^+$), 345 (100, $[M + 1]^+$). Anal. calc. for $C_{19}H_{24}N_2O_4$ (344.41): C 66.26, H 7.02, N 8.13; found: C 66.14, H 7.20, N 8.32.

(±)-(E)-3-(4-Hydroxyphenyl)-N-[4-(3-methyl-2,5-dioxo-1-pyrrolidinyl)butyl]-2-propenamide (7). Under a N_2 atmosphere, a solution of **6** (100 mg, 0.29 mmol) in CH_2Cl_2 (2.5 ml) was cooled in a dry ice/2-propanol bath to which BBr_3 (0.09 ml, 0.96 mmol) was introduced using a syringe. The bath was then removed and the mixture was stirred for 30 min, poured into ice water, stirred for a further 30 min, saturated with salt and finally extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent removed, yielding **7** (96 mg, quant.) as a colorless solid. M.p. (MeOH): 192.5-193.0°. UV (EtOH): 308 (4.36), 292 (4.37), 225 (4.17), 203 (4.35). UV (ca. 1.3 x 10^{-3}M NaOH/EtOH soln.): 353, 312 sh, 235. IR (KBr): 3450*m*, 3350*s* (NH), 3125*s* (OH), 3020*m*, 2960*m*, 2875*m*, 2820*m*, 2780*w*, 2700*w*, 2630*w*, 1900*w*, 1770*m* + 1695*s* (five-membered cyclic imide), 1655*s* (sec. amide, A band, C=O), 1605*s*, 1585*s*, 1520*s* (arom. ring), 1555*s*, (sec. amide, B band, NH), 1455*s*, 1410*s*, 1375*s*, 1350*s*, 1315*s*, 1285*s*, 1250*s*, 1230*s*, 1205*m*, 1175*s*, 1140*m*, 1100*m*, 1085*m*, 1035*w*, 995*m*, 965*w*, 955*w*, 920*w*, 905*w*, 885*w*, 860*w*, 840*s*, 795*w*, 750*m*, 715*w*, 655*w*, 635*w*. ^{1}H-NMR (400 MHz, C_5D_6N): 11.98 (br. *s*, OH); 8.50 (br. *t*, *J* = 5.5, NH); 8.05 (*AXd*, *J* = 15.6, 1 H); 7.50 (*d*, *J* = 8.5, 2 H); 7.08 (*d*, *J* = 8.5, 2 H); 6.76 (*AXd*, *J* = 15.6, 1 H); 3.60-3.50 (*m*, 4 H); 2.83 (*dd*, *J* = 16.6, 9.0, 1 H); 2.85-2.75 (*m*, 1 H); 2.27 (*dd*, *J* = 13.1, 3.6, 1 H); 1.67 (*m*, 4 H); 1,18 (*d*, *J* = 7.1, CH_3). ^{13}C-NMR (C_5D_6N): 181.0, 176.8, 166.8 (3 *s*, CO); 160.6 (*s*, arom. C); 140.2 (*d*); 130.1 (*d*, 2 arom. C); 127.2 (*s*, arom. C); 119.6 (*d*); 116.9 (*d*, 2 arom. C); 39.5, 38.6, 36.7 (3 *t*); 35.1 (*d*); 27.7(*t*); 25.8 (*t*); 16.5 (*q*). EI-MS: 330 (6, $M^{+\bullet}$), 204 (10), 183 (23), 162 (12), 148 (13), 147 (100), 119 (19), 91 (19), 70 (19), 69 (17), 65 (11), 57 (33), 56 (15), 55 (21). CI-MS: 331 (83, $[M + 1]^+$). Anal. calc. for $C_{18}H_{22}N_2O_4$ (330.39); C 65.44, H 6.71, N 8.48; found: C 65.73, H 6.57, N 8.23.

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