4-ALKYLCARBONYLMETHYLIDENEISOQUINOLINES. A SYNTHETIC AND MECHANISTIC STUDY

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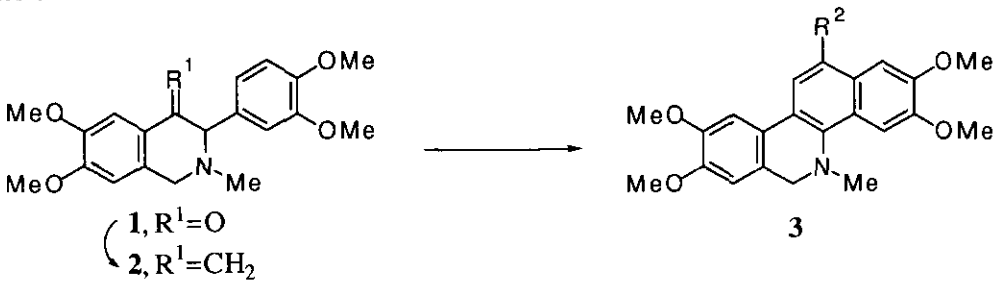
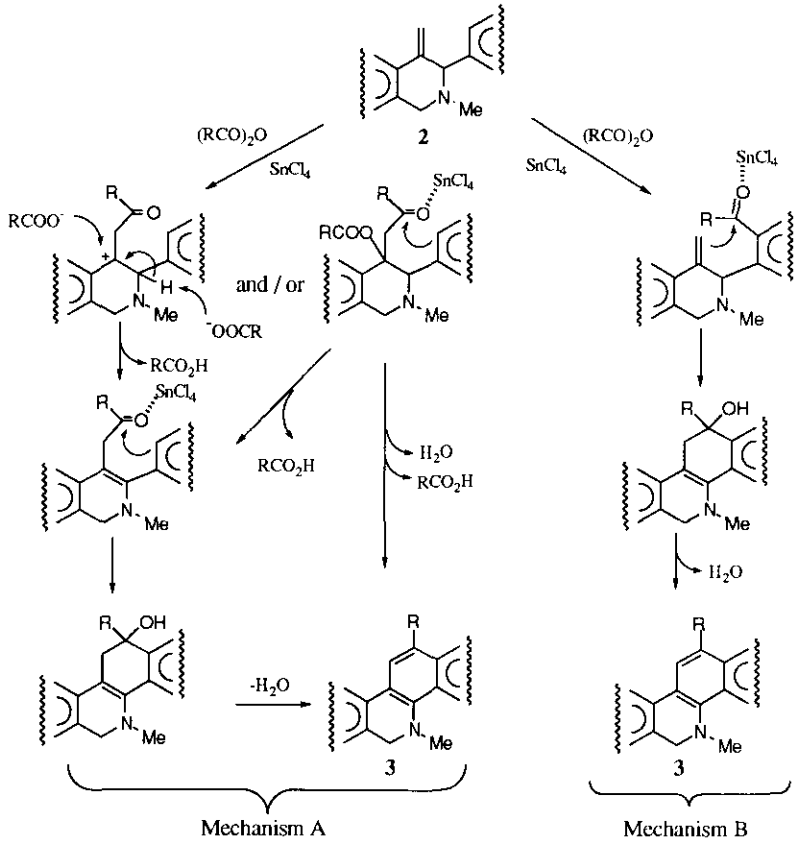
Abstract-An efficient preparation of 4-alkylcarbonylmethylideneisoquinoline derivatives *via* a modification of Jones oxidation and alkene acylation conditions is reported. In addition, evidence on the mechanism involved in the formation of 12-alkylbenzo[*c*]phenanthridines from 3-aryl-4-methylideneisoquinolines is presented.

Very recently,[1] a novel approach to the synthesis of the benzo[*c*]phenanthridine skeleton from easily accesible 3-aryl-4-isoquinolinone precursors of type (**1**) has been published (see Scheme 1), where a Peterson olefination[2] followed by an alkene acylation-cyclodehydration tandem reaction featured the reported synthesis. Precedents for the mentioned alkene acylation transformation can be found in the literature[3] but, to the best of our knowledge, there is only one more example where the combination of an alkene acylation and a cyclodehydration processes has been employed in a one-pot procedure for a related synthesis.[4]



Scheme 1

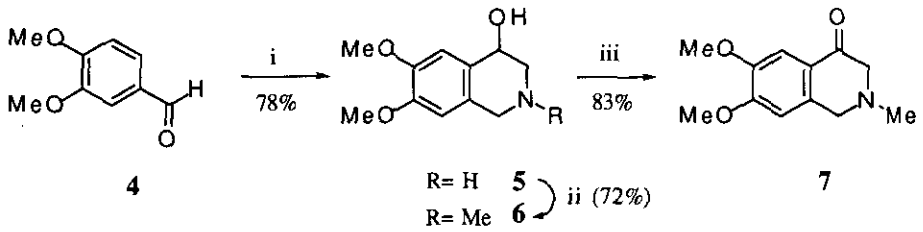
On the other hand, needless to say the enormous benefits that the detailed knowledge of the operating mechanism would report (for this and any other reaction) and, for that reason, additional experiments have been designed and carried out in our laboratory to understand the above mentioned transformation of isoquinoline (**2**) into benzo[*c*]phenanthridines (**3**). Two plausible mechanisms (A and B in Scheme 2) could be envisaged for this transformation, and in order to distinguish between both possible pathways, isoquinoline precursors (**8**) and (**11**) have been prepared and made to react under alkene acylation conditions. Thus, the application of both methylenation and subsequent acylation conditions to C-3 unsubstituted isoquinolines of type (**7**) could provide not only new C-4 functionalised isoquinoline derivatives, but also additional proofs of the mechanism involved in the somewhat unexpected tetracycle formation of benzo[*c*]phenanthridines (**3**). The most outstanding results are presented in this paper.



Scheme 2

In order to attain the above mentioned objectives, isoquinolinone (**7**) was readily prepared in three steps from veratraldehyde (**4**) following the Bobbitt modification of the Pomeranz-Fritsch reaction[5] and

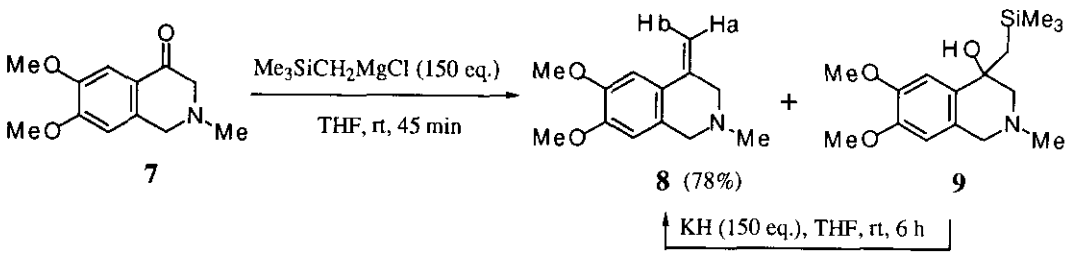
subsequent *N*-methylation[6] to preserve the amino group from undesired oxidative processes. Although oxidation of simple 4-hydroxytetrahydroisoquinolines to the corresponding 4-(3*H*)-isoquinolinone has been already reported by Gensler *et al.*,[7] the oxidation of tetrahydroisoquinolinol (**6**) under the latter conditions afforded the corresponding 4-oxo derivative (**7**) with a poor yield (25%). Consequently, our modification of the Jones oxidation reaction[8] (for more details see Experimental Section) was then applied thus affording the target heterocycle (**7**) in good yield (see Scheme 3).



i: 1. $(EtO)_2CHCH_2NH_2$, C_6H_6, reflux; 2. H_2 / Pd-C; 3. 6M HCl
ii: HCHO, $NaBH_3CN$, MeCN
iii: Jones reagent, acetone, -17°C, 10 min

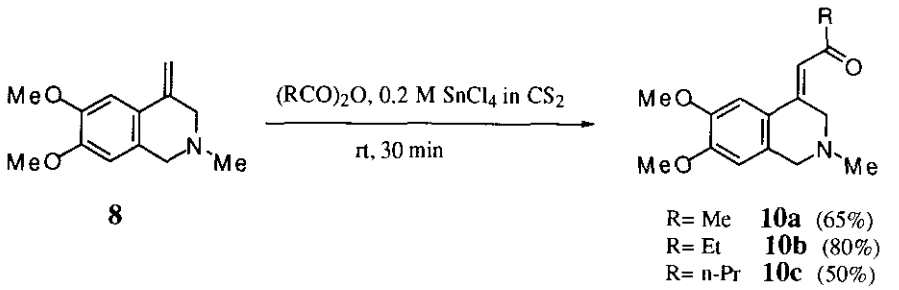
Scheme 3

The next step, the access to the corresponding 4-methylideneisoquinoline (**8**) by a Peterson methylenation reaction, was only achieved by using 150 equivalents of trimethylsilylmethylmagnesium chloride and potassium hydride (see Scheme 4) as reported for 3-aryl-4-isoquinolinones (**1**),[1] though lower temperatures were required in this case (25°C *vs* 90°C). It has to be pointed out that the synthetic intermediate (**9**) was identified by ^{1}H-NMR, but not isolated, so it could be transformed into isoquinoline (**8**) in a one-pot procedure. Taking into account the observed unstability of the carbonyl derivative (**7**) and its 3-arylated analog (**1**), it could be stated that a great excess of the reagents promote a significant increase in the reaction rates for both substrates (**7**) and (**1**), therefore avoiding undesired decomposition and aromatization processes.[9] Besides, the steric hindrance at C-4 position caused by the bulky aryl substituent at C-3 would explain the higher temperatures (90°C) required for the addition of the organosilicon reagentto 3-arylated substrates such as **1**, and, in fact, the non-hindered isoquinolinone precursor (**7**) undertook the latter methylenation reaction faster even at room temperature.



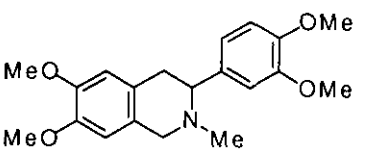
Scheme 4

Following with our research objectives, new 4-alkylcarbonylmethylidenetetrahydroisoquinolines (**10**) were obtained with good yields from methylidene derivative (**8**) using anhydrous CS_2 as solvent. Besides, unlike 3-arylated derivatives (Scheme 1), room temperature and shorter reaction times were enough for olefin (**8**) to react, thus providing evidence of the steric hindrance caused by the aryl group at C-3. With regard to the stereochemistry of the α,β-unsaturated ketones (**10**), a Z configuration was assigned on the basis of routine NOE experiments.[10]



Scheme 5

Finally, in order to have complementary models to rationalize the behavior observed for 3-arylisoquinoline derivative (**2**),[1] the acylation conditions cited above ($(RCO)_2O$, 0.2 M $SnCl_4$ in CS_2 or CH_2Cl_2) were applied to the known 3-arylisoquinoline (**11**),[11] which presented no substitution at C-4. In this experiment, acylation of the 3-aryl ring by a Friedel-Crafts type reaction was not observed, and only unreacted material was recovered, even when more severe reaction conditions were applied.



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Therefore, taking into account both the easy alkene acylation of 4-methylidene derivative (**8**) and the lack of reactivity of 3-arylisoquinoline (**11**) under similar reaction conditions, we may conclude that a tandem process alkene acylation-carbocyclization, *Mechanism A*, is the most adequate one to explain the

regioselective formation of 12-alkyl-5,6-dihydrobenzo[*c*]phenanthridines (**3**) from 3-aryl-4-methylidene-isoquinolines (**2**).

To sum up, a series of highly valuable 4-methylidene- and 4-alkylcarbonylmethylideneisoquinolines have been efficiently prepared from 4-isoquinolones by an optimized procedure involving Peterson olefination followed by alkene acylation. Besides, our results have provided definitive proofs to unambiguously establish the mechanism involved in the formation of 12-alkylbenzo[*c*]phenanthridines from 3-aryl-4-methylideneisoquinolines.

EXPERIMENTAL

Melting points were measured in a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer in $CHCl_3$ and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 (250 MHz for ^1H and 62.83 MHz for ^{13}C. Chemical shifts (δ) were measured in ppm relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26 for ^1H or 77.00 for ^{13}C) as internal standards. Multiplicities are indicated by s (singlet), t (triplet) and m (multiplet). Coupling constant, *J*, is reported in Hertz. ^1H-{^1H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet in $CDCl_3$ solvent.[12] ^{13}C-DEPT experiments were used to assist with the assignation of the signals. GCMS was developed on a Hewlett-Packard 5890 spectrometer. Data are reported in the form m/z (intensity relative to base=100). Combustion analyses were performed on a Perkin-Elmer 2400 CHN apparatus. Solvents were either purified according to methods described by Perrin *et al.*[13] or used as received from the manufacturers, depending on their purity. TLC was performed on plates coated to a thickness of 0.2 mm with Merck kieselgel 60 F_{254} using UV light (254 nm) and Dragendorff's reagent[14] as developing agents. Air-pressure chromatography was carried out on kieselgel 60 (70-230 mesh ASTM). Evaporation of solvents under reduced pressure was performed in a Heidolph VV 60 rotatory evaporator.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-4-ol (**5**) was prepared starting from veratraldehyde (**4**) as reported by Wykypiel and Seebach[15] by means of a modification of the Pomeranz-Fritsch reaction.[5]

6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (6). Formaldehyde (0.83 mL of a 37% solution in water, 11.1 mmol) was added to a stirred suspension of secondary amine (**5**) (200 mg, 0.95 mmol) in dry acetonitrile (50 mL) under nitrogen. After stirring for 1 h, $NaBH_3CN$ (300 mg, 4.8 mmol) was added. The mixture was allowed to stir at rt until complete consumption of the starting material was observed (16 h, monitored by TLC, 20% MeOH/CH_2Cl_2 as developing solvent), and then water (10 mL) was added. After evaporating *in vacuo*, the residue was dissolved in water and extracted with CH_2Cl_2 (6 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a brown oil. Crystallization from ethyl acetate afforded *N*-methyl derivative (**6**) (152 mg, 72%) as a white powder, mp. 124-126°C (EtOAc) (lit.,[16] 127-128°C (50% hexane/benzene))

6,7-Dimethoxy-2-methyl-4(3*H*)-isoquinolinone (7). Jones reagent[17] (10 drops, ~10 mmol) was added to a stirred solution of tetrahydroisoquinolin-4-ol (**6**) (100 mg, 0.45 mmol) in acetone (75 mL) at -18 °C. After stirring for 10 min at the same temperature, methanol (18 mL) was added, and the resulting green suspension was allowed to stir for 5 min. The reaction mixture was filtered, and the filtrate was evaporated *in vacuo* to give a green oil which was dissolved in water (20 mL) and HCl (2 mL of a 1 mol·l^{-1} solution in water). After washing with ether (3 x 10 mL), the aqueous layer was basified to pH 10 with NH_4OH solution (30% in water) and extracted with ether (5 x 15 mL). The basic organic extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford an oil which was crystallized from ethyl acetate yielding isoquinolinone (**7**) (82 mg, 83%) as a yellow powder, mp 117-120°C (EtOAc) (lit.,[18] 252-253°C (HCl salt from MeOH)), R_f (10% MeOH/CH_2Cl_2) 0.6. IR: ν_{max} 1670 (C=O st). ^{1}H-NMR ($CDCl_3$): δ 2.48 (3H, s, NMe), 3.26 (2H, s, H-3), 3.67 (2H, s, H-1), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 6.64 (1H, s, H-8), 7.47 (1H, s, H-5). ^{13}C-NMR ($CDCl_3$): δ 45.2 (NMe), 55.9 (OMe), 56.0 (C-1), 57.0 (OMe), 63.8 (C-3), 107.8, 107.9 (C_{arom}-H), 123.4, 137.1 (C_{arom}-C), 148.4, 153.9 (C_{arom}-O), 193.5 (CO). MS: (m/z, %) 221 (M^+, 77), 220 (37), 192 (44), 178 (67), 151 (100), 135 (17), 77 (25). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.14; H, 6.90; N, 6.28.

6,7-Dimethoxy-2-methyl-4-methylidene-1,2,3,4-tetrahydroisoquinoline (8). Trimethylsilylmethylmagnesium chloride (13.5 ml of a 1 mol·L^{-1} solution in THF,[19] 13.5 mmol) was added dropwise to solid isoquinolinone (**7**) (20 mg, 0.09 mmol) under nitrogen at 0 °C. After stirring the resulting solution

for 45 min at rt, the mixture was cooled to 0°C and NH_4Cl (10 mL of a saturated solution in water) was added dropwise. The aqueous layer was extracted with ether (5 x 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate. Evaporation *in vacuo* afforded a yellow oil which was dissolved in 5% MeOH/CH_2Cl_2, filtered through silica gel (70-230 mesh ASTM), and evaporated *in vacuo*. Although β-silylcarbinol (**9**) was not isolated, it could be identified on the basis of the following ^{1}H-NMR specroscopic data of the resulting syrup: ^{1}H-NMR ($CDCl_3$): δ 0.01 (9H, s, $SiMe_3$), 6.50 (1H, s, H-8), 7.10 (1H, s, H-5). This yellow oil was dissolved in dry THF (3 mL) under nitrogen at rt, then added to a stirred suspension of KH (35% in paraffin oil, previously washed with hexane, 560 mg, ~14 mmol) in dry THF (10 mL). After stirring for 6 h, the mixture was cooled to 0°C and NH_4Cl (10 mL of a saturated solution in water) was added dropwise. The aqueous layer was extracted with ether (5 x 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate. Evaporation *in vacuo* afforded a yellow oil which was purified by air pressure column chromatography using 50% MeOH/EtOAc as eluent. The alkene (**8**) was obtained (15.5 mg, 78% overall yield) as a colourless oil, R_f (50% MeOH/CH_2Cl_2) 0.4. IR: ν_{max} 1600 (C=C st). ^{1}H-NMR ($CDCl_3$): δ 2.44 (3H, s, NMe), 3.30 (2H, s, H-3), 3.61 (2H, s, H-1), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 4.92 (1H, s, H_a), 5.43 (1H, s, H_b), 6.53 (1H, s, H-8), 7.13 (1H, s, H-5). ^{13}C-NMR ($CDCl_3$): δ 44.8 (NMe), 55.8, 55.9 (OMe), 58.1, 60.0 (C-1, C-3), 105.7 (=CH_2), 105.9, 108.9 (C_{arom}-H), 124.2, 127.5, 139.2 (C_{arom}-C, C-4), 147.9, 149.1 (C_{arom}-O). MS: (m/z, %) 219 (M^+, 100), 204 (12), 202 (18). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.19; H, 7.82; N, 6.39. Found: C, 71.12; H, 7.79; N, 6.40.

6,7-Dimethoxy-2-methyl-4-methylcarbonylmethylidene-1,2,3,4-tetrahydroisoquinoline (10a). Typical procedure. $SnCl_4$ (6 mL of a 0.2 mol·L^{-1} solution in CS_2, 1.2 mmol) was added dropwise to a stirred solution of alkene (**8**) (100 mg, 0.45 mmol) and acetic anhydride (4 mL, 42 mmol) in dry CS_2 (0.5 mL) under nitrogen at 0°C. After stirring for 1h at rt, ice (~0.2 g) was added, and the stirring was continued for 5 min. The organic solvent was evaporated *in vacuo* (T < 50 °C) and the resulting aqueous suspension was washed with hexane (2 x 10 mL), basified to pH 10 with a saturated solution of K_2CO_3 in water and extracted with hexane (3 x 10 mL). The combined basic hexane layers were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a brown oil which was purified by air pressure column chromatography using 50% MeOH/EtOAc (1:1) as eluent. The 4-methylcarbonylmethylildene-isoquinoline derivative (**10a**) was obtained (76.3 mg, 65%) as a reddish oil, R_f (50%MeOH/EtOAc) 0.7.

IR: ν_{max} 1655 (C=O st) and 1604 (C=C st). ^{1}H-NMR ($CDCl_3$): δ 2.30 (3H, s, $COCH_3$), 2.44 (3H, s, NMe), 3.50 (2H, s, H-1), 3.82 (2H, s, H-3), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 6.57 (1H, s, H-8), 6.61 (1H, s, =CHCO), 7.17 (1H, s, H-5). ^{13}C-NMR ($CDCl_3$): δ 32.1 ($CO\underline{C}H_3$), 45.2 (NMe), 55.8, 56.0 (OMe), 56.5, 57.3 (C-1, C-3), 106.2, 108.3, 116.1 (C_{arom}-H, =$\underline{C}$HCO), 123.4 (C-4), 142.7, 148.1 (C_{arom}-C), 149.1, 151.2 (C_{arom}-O), 201.1 (CO). MS: (m/z, %) 261 (M^+, 56), 260 (81), 244 (13), 218 (39), 205 (13), 202 (14).

When the same procedure was performed on alkene (**8**) (100 mg, 0.45 mmol) using propionic anhydride as reagent (5.4 mL, 42 mmol), **4-ethylcarbonylmethylidene-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (10b)** was obtained (99 mg, 80%) as a colourless oil, R_f (50%MeOH/EtOAc) 0.7. IR: ν_{max} 1652 (C=O st), 1602 (C=C st). ^{1}H-NMR ($CDCl_3$): δ 1.14 (3H, t, *J* 7.0, $CH_2C\underline{H}_3$), 2.49 (3H, s, NMe), 2.65 (3H, q, *J* 7.0, $C\underline{H}_2CH_3$), 3.51 (2H, s, H-1), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 3.96 (2H, s, H-3), 6.58 (1H, s, H-8), 6.61 (1H, s, =CHCO), 7.18 (1H, s, H-5). ^{13}C-NMR ($CDCl_3$): δ 8.2 ($\underline{C}H_2CH_3$), 37.7 ($CH_2\underline{C}H_3$), 45.2 (NMe), 55.8, 56.0 (OMe), 56.6, 57.3 (C-1, C-3), 106.2, 109.2, 115.6 (C_{arom}-H, =$\underline{C}$HCO), 123.7 (C-4), 142.7, 148.1 (C_{arom}-C), 149.1, 151.2 (C_{arom}-O), 201.1 (CO). MS: (m/z, %) 275 (M^+, 16), 274 (16), 247 (23), 221 (14), 204 (100). *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.78; H, 7.61; N, 5.14.

When the same procedure was performed on alkene (**8**) (100 mg, 0.45 mmol) using butyric anhydride as reagent (6.9 mL, 42 mmol), **6,7-dimethoxy-2-methyl-4-propylcarbonylmethylidene-1,2,3,4-tetrahydroisoquinoline (10c)** was obtained (65 mg, 50%) as a colourless oil, R_f (50%MeOH/EtOAc) 0.7. IR: ν_{max} 1650 (C=O st) and 1605 (C=C st). ^{1}H-NMR ($CDCl_3$): δ 0.96 (3H, t, *J* 7.4, $CH_2C\underline{H}_3$), 1.67 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.45 (3H, s, NMe), 2.56 (2H, t, *J* 7.4, $C\underline{H}_2CH_2CH_3$), 3.51 (2H, s, H-1), 3.89 (3H, s, OMe), 3.92 (3H, s, OMe), 3.95 (2H, s, H-3), 6.60 (1H, s, H-8), 6.61 (1H, s, =CHCO), 7.18 (1H, s, H-5). ^{13}C-NMR ($CDCl_3$): δ 13.8 ($\underline{C}H_2CH_3$), 14.2 ($CH_2\underline{C}H_3$), 17.8 ($CO\underline{C}H_2$), 45.3 (NMe), 56.1, 56.7 (OMe), 57.4, 60.4 (C-1, C-3), 106.3, 109.2, 115.9 (C_{arom}-H, =$\underline{C}$HCO), 123.2 (C-4), 132.8, (C_{arom}-C), 148.1, 149.2, 151.2 (C_{arom}-C, C_{arom}-O), 200.8 (CO). MS: (m/z, %) 289 (M^+, 34), 218 (100), 177 (13). *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.55; H, 8.02; N, 4.84. Found: C, 70.48; H, 8.09; N, 4.81.

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