  Bull. Chem. Soc. Jpn., 59, 815—818 (1986)

(*Z*)- and (*E*)-4,4-Dimethyl-5-oxo-2-pentenoic Acids and Their Derivatives

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(Received October 21, 1985)

(*Z*)-4,4-Dimethyl-5-oxo-2-pentenoic acid (**1**) exists almost exclusively in the hydroxy lactone form, the tautomeric equilibrium constant (K=[Ring]/[Chain]) being 2.8×10^3 in water as estimated by the pK_a method. Several examples are described of preference for ring forms of derivatives of **1**, which are capable of exhibiting ring-chain tautomerism. (*E*)-4,4-Dimethyl-5-oxo-2-pentenoic acid (**7**) reacts with thionyl chloride to afford a trimeric chloro lactone, which on treatment with water or aniline gives the corresponding hydroxy or anilino lactone. Compound **1** or **7** reacts with a variety of phenylhydrazines to yield dihydropyrazole derivatives, except for 2,4-dinitrophenylhydrazine which on reaction with **1** gives a 2,4-dinitrophenylhydrazino lactone.

Recently (*Z*)-4,4-dimethyl-5-oxo-2-pentenoic acid (**1**) has been concluded to exist predominantly in the hydroxy lactone form (**1r**) on the basis of its IR and ^{1}H NMR spectra.[1,2] It seems of interest to examine this compound in more detail since six-membered hydroxy lactones have rarely been reported[1-3] and little is known about their ring-chain tautomerism or derivatives; five-membered ones have been extensively studied.[4] We report in this paper an investigation of the tautomerism and derivatives of **1**. We also report on the cyclic trimers of (*E*)-4,4-dimethyl-5-oxo-2-pentenoic acid (**7**) and its chloride and anilide.

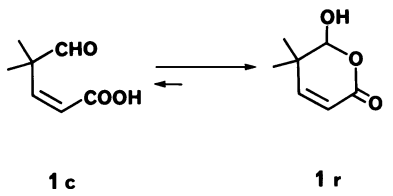


Fig. 1.

Although **1r** is the virtually sole detectable form, a rapid interconversion between **1r** and **1c** on the NMR time scale at ordinary temperature could be verified;[5] when less than one equivalent of *t*-butylamine as a base was added to **1** in water, the averaged resonances of **1r** and the *t*-butylammonium salt of **1c** appeared instead of the superposition of the individual ones.

The equilibrium constant, K, in water at 25 °C was estimated by the pK_a method. The observed pK_a value of **1** (7.63) can be related to p$K_{a,0}$ by Eq. 2[6]

$$K = [\mathbf{1r}]/[\mathbf{1c}], \quad (1)$$

$$pK_{a,0} = pK_a - \log(K+1), \quad (2)$$

where p$K_{a,0}$ denotes the hypothetical pK_a of **1c**. The p$K_{a,0}$ was estimated to be 4.18 from the pK_a of **7** (4.45) and the Hammett relations of the K_a values in (*Z*)- and (*E*)-3-substituted acrylic acids.[7] By applying Eq. 2 K was calculated to be 2.8×10^3. This strong preference of **1** for cyclization exhibits a marked contrast to the case of 5-oxoalkanoic acids which show no sign of cyclization.[4]

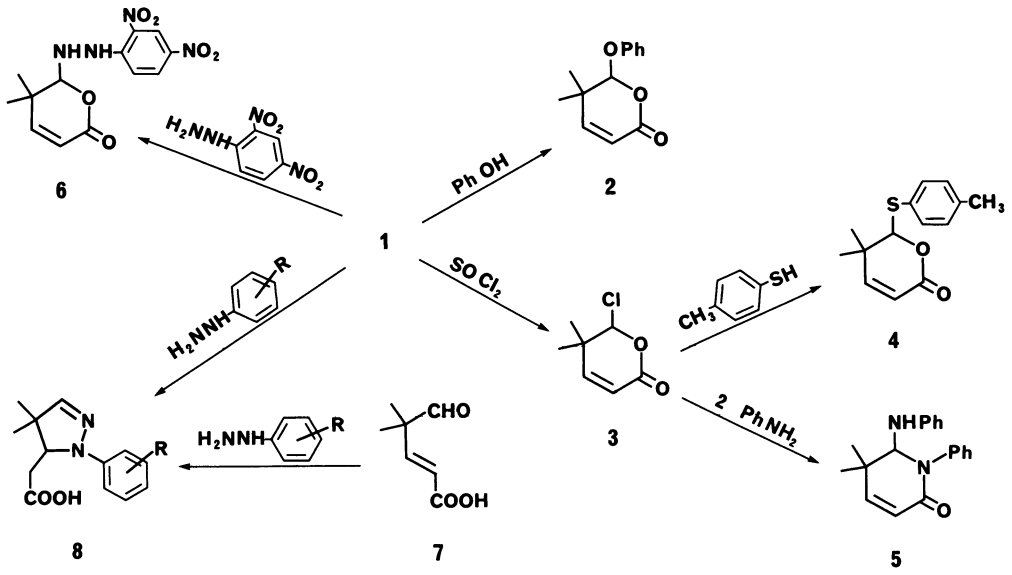


Fig. 2.

As described in our preceding paper,[2] methyl (*Z*)-4,4-dimethyl-5-oxo-2-pentenoate in methanol containing H_2SO_4 or sodium methoxide as a catalyst isomerizes almost completely to 6-methoxy-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one. Further examples of preference for ring forms of the derivatives of **1**, which are capable of exhibiting ring-chain tautomerism, are described below. Compound **1** reacted with phenol in the presence of H_2SO_4–H_3BO_3 as a catalyst[8] to give the phenoxy lactone **2**. Treatment of **1** with thionyl chloride yielded the chloro lactone **3**. Compound **3** on reaction with *p*-toluenethiol or two equivalents of aniline afforded the *p*-tolylthio lactone **4** or the anilino lactam **5**.

Compound **1** or the (*E*)-isomer **7**, prepared by hydrolysis of methyl (*E*)-5-(*t*-butylimino)-4,4-dimethyl-2-pentenoate,[2] reacted with a variety of phenylhydrazines to afford the dihydropyrazoles **8** (Tables 1 and 2). Structural assignment was based primarily on their ^1H NMR spectra. The methylene protons in **8** are rendered non-equivalent by the adjacent chiral center and form part AB of pattern ABX. 2,4-Dinitrophenylhydrazine, on the other hand, on reaction with **1** gave the hydrazino lactone **6**. Presumably, the nucleophilicity of the -NH- nitrogen of the initially formed hydrazone is insufficient for addition to moiety -CH=CH-CO_2H.

It is interesting to note that, when **7** was allowed to react with thionyl chloride, the trimeric chloro lactone **9** was obtained in 48% yield. The trimeric

Table 1. Yields, Melting Points, and Analytical Data of **8**

R	Formyl acid	Method	Yield %	Mp θ_m/°C	Found/%			Calcd/%		
					C	H	N	C	H	N
H	1	A	82	124.0—124.8	67.19	6.84	11.99	67.22	6.94	12.06
H	7	A	80							
p-NO_2	1	A	83	195.8—196.5	56.56	5.52	15.14	56.31	5.42	15.15
p-NO_2	7	A	90							
p-Cl	1	B	87	131.0—131.7	58.78	5.58	10.34	58.54	5.67	10.50
p-Cl	7	B	82							
p-Br	7	B	84	139.8—140.4	50.14	4.75	8.96	50.18	4.86	9.00
p-Me	7	B	80	153.3—154.2	68.57	7.30	11.37	68.27	7.37	11.37
p-MeO	7	B	70	121.0—121.6	64.30	7.01	10.66	64.11	6.92	10.68
m-NO_2	1	B	86	140.3—140.8	56.21	5.25	15.23	56.31	5.45	15.15
m-NO_2	7	B	84							
m-Cl	7	B[a]	88	124.7—126.2	58.38	5.60	10.44	58.54	5.67	10.50
m-Me	7	B	78	125.5—126.2	68.09	7.41	11.19	68.27	7.37	11.37

a) *m*-Chlorophenylhydrazine sulfate was used.

Table 2. Spectral Data of **8**

R	IR(KBr)/cm^{-1}	^1H NMR($CDCl_3$)[a]/δ(J/Hz)					
	C=O	$(CH_3)_2C$	CH_2	CH	CH=N	CO_2H	Others
H	1717	1.21 s and 1.23 s	2.50 dd and 2.75 dd (17, 9.5) (17, 4)	4.19 dd (9.5, 4)	6.51 s	11.40 br s	
p-NO_2	1698	1.23 s and 1.26 s	2.50 dd and 2.55 dd (17, 8) (17, 5)	4.34 dd (8, 5)	6.95 s	12.70 br s	
p-Cl	1704	1.25 s	2.53 dd and 2.66 dd (17, 9) (17, 4)	4.26 dd (9, 4)	6.56 s	11.35 br s	
p-Br	1704	1.24 s	2.53 dd and 2.66 dd (17, 9) (17, 4)	4.15 dd (9, 4)	6.54 s	10.80 br s	
p-Me	1698	1.20 s and 1.24 s	2.52 dd and 2.70 dd (17, 9.5) (17, 4)	4.13 dd (9.5, 4)	6.51 s	11.05 br s	2.25 s, $ArCH_3$
p-MeO	1712	1.17 s and 1.26 s	2.52 dd and 2.65 dd (17, 9) (17, 4.5)	3.97 dd (9, 4.5)	6.52 s	11.00 br s	3.74 s, OCH_3
m-NO_2	1698	1.29 s	2.56 dd and 2.69 dd (17, 8.5) (17, 5)	4.30 dd (8.5, 5)	6.61 s	10.30 br s	
m-Cl	1698	1.24 s	2.53 dd and 2.68 dd (17, 9) (17, 4)	4.20 dd (9, 4)	6.53 s	11.20 br s	
m-Me	1695	1.25 s	2.55 dd and 2.74 dd (17, 9) (17, 4)	4.20 dd (9, 4)	6.55 s	11.40 br s	2.32 s, $ArCH_3$

a) Aromatic protons are omitted. In the case of **8** (R=*p*-NO_2), $(CD_3)_2SO$ was used as a solvent.

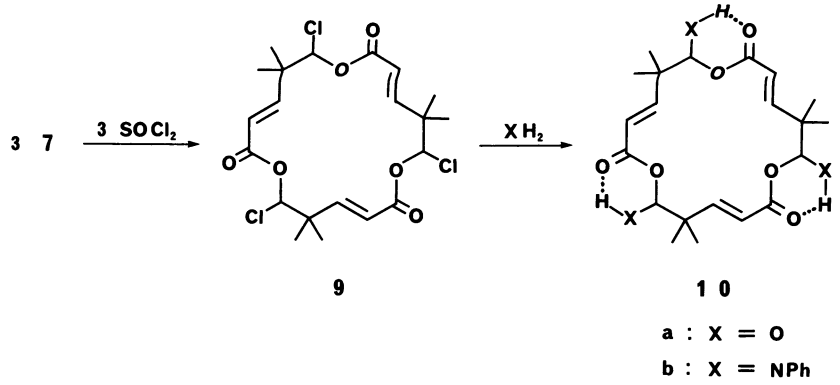


Fig. 3.

structure was confirmed by a relevant mass spectrum showing peaks at *m/z* 447 and 445 due to $(M-Cl)^+$ and further by vapor phase osmometry. With water or aniline **9** yielded the corresponding hydroxy (**10a**) [MS (CI) *m/z* 427 $(M+H)^+$] or anilino lactone (**10b**) [MS *m/z* 651 (M^+)]. In each of these crown-type compounds, the three methine protons occur as a single absorption in the ^1H NMR spectrum (δ 4.49—4.61). This suggests that these protons may have the cis configuration.

Experimental

All melting points and boiling points are uncorrected. IR spectra were recorded on a Hitachi 285 spectrometer. ^1H NMR data were obtained with a Hitachi R-24B spectrometer by using TMS or DSS as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000 spectrometer at 70 eV of ionization energy by use of a direct-inlet system. Microanalyses were performed at the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, the University of Tokyo.

Observation of Progress of the Neutralization of 1 by ^1H NMR Spectroscopy. To a solution of **1** (30.0 mg, 0.211 mmol) in D_2O (0.50 ml) was added *t*-butylamine (15.6 mg, 0.213 mmol) in six portions. A typical signal of **1r** at δ 5.43 due to the methine proton shifted, on addition of the base, toward 9.34 due to an aldehyde proton proportionally to the amount of the base added.

pK_a Measurements. pK_a values were determined at 25±0.1 °C in N_2 by titration of acids in water (0.05 M, 1 M=1 mol dm^{-3}) with aq NaOH (0.05 M) under control by a pH meter with glass and calomel electrodes. The instrument was calibrated by using 0.05 M potassium hydrogen phthalate (pH 4.01 at 25 °C) and 0.01 M sodium tetraborate (pH 9.18 at 25 °C).

5,5-Dimethyl-6-phenoxy-5,6-dihydro-2*H*-pyran-2-one (2). A mixture of **1** (1.50 g, 10.6 mmol), phenol (15.0 g, 159 mmol), H_2SO_4 (20 mg, 0.20 mmol), H_3BO_3 (5 mg, 0.08 mmol), and toluene (25 ml) was refluxed under a water separator for 1 h. Water (60 ml) was added, and the aq layer was separated and extracted with ether (2×30 ml). The combined organic layers were dried (Na_2SO_4), concentrated, and distilled, giving 1.89 g of a fraction, bp 130.0—132.0 °C/0.35 mmHg (1 mmHg=133.322 Pa), which on standing crystallized (mp 65.0—74.0 °C). Recrystallization from ethyl acetate afforded 1.42 g (62%) of **2**: Mp 74.0—76.8 °C; mp 76.5—77.5 °C after further recrystallization; IR (KBr) 1727 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.22 (s, 6H, $C(CH_3)_2$), 5.49 (d, *J*=1 Hz, 1H, CH), 5.86 (d, *J*=9.5 Hz, 1H, CH=CHCO), 6.58 (dd, *J*=9.5, 1 Hz, 1H, CH=CHCO), and 6.9—7.4 (m, 5H, ArH). Found: C, 71.69; H, 6.47%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%.

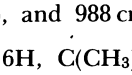
6-Chloro-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one (3). Thionyl chloride (7.00 g, 58.8 mmol) was added with stirring to **1** (7.11 g, 50.0 mmol) during 10 min. The mixture was allowed to stand at room temperature for 20 min and then heated at 65 °C for 20 min. Removal of the excess of thionyl chloride in vacuo and distillation gave 5.18 g (65%) of **3**: Bp 77.0—78.5 °C/0.55 mmHg; IR (neat) 1747 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.27 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 5.88 (d, *J*=9.5 Hz, 1H, CH=CHCO), 5.96 (d, *J*=1.5 Hz, 1H, CH), and 6.66 (dd, *J*=9.5, 1.5 Hz, 1H, CH=CHCO). Found: C, 52.17; H, 5.85%. Calcd for $C_7H_9ClO_2$: C, 52.35; H, 5.65%.

5,5-Dimethyl-6-(*p*-tolylthio)-5,6-dihydro-2*H*-pyran-2-one (4). A solution of **3** (1.50 g, 9.34 mmol) and *p*-toluenethiol (1.67 g, 13.4 mmol) in pyridine (8.0 ml) was refluxed for 5 h. Water (40 ml) was added and the mixture was extracted with ether (3×30 ml). The ethereal extract was dried (Na_2SO_4), concentrated, and distilled to give 1.93 g (83%) of **4**: Bp 141.0—143.0 °C/0.25 mmHg; mp 71.5—75.0 °C; mp 75.0—75.6 °C after recrystallization from cyclohexane; IR (KBr) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.22 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 2.26 (s, 3H, $ArCH_3$), 5.20 (s, 1H, CH), 5.74 (d, *J*=9.5 Hz, 1H, CH=CHCO), 6.51 (d, *J*=9.5 Hz, 1H, CH=CHCO), and 6.9—7.4 (m, 4H, ArH). Found: C, 67.74; H, 6.53%. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49%.

6-Anilino-5,5-dimethyl-1-phenyl-5,6-dihydro-2(1*H*)-pyridinone (5). A mixture of **3** (0.287 g, 1.79 mmol) and aniline (1.01 g, 10.8 mmol) was heated at 100 °C for 2 h. Water (5 ml) was added, and the mixture was extracted with ether (3×5 ml). The ethereal extract was dried (Na_2SO_4) and concentrated. After removal of the excess of aniline in vacuo, the residual solid was recrystallized from benzene–hexane, giving 0.326 g (62%) of **5**: Mp 135.5—139.0 °C; mp 141.0—141.7 °C after further recrystallization; IR (KBr) 3305 (NH), 1655 (C=O), and 1610 cm^{-1} (sh, C=C); ^1H NMR ($CDCl_3$) δ=1.20 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 4.42 (br d, *J*=11 Hz, 1H, NH), 4.92 (br dd, *J*=11, 1.5 Hz, 1H, CH), 6.00 (d, *J*=10 Hz, 1H, CH=CHCO), 6.32 (dd, *J*=10, 1.5 Hz, 1H, CH=CHCO), and 6.2—7.4 (m, 10H, ArH). Addition of

D_2O resulted in loss of the signal at 4.42 and collapse of the signal at 4.92 to a doublet (J=1.5 Hz). Found: C, 78.35; H, 6.91; N, 9.29%. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58%.

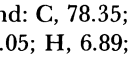
6-(2,4-Dinitrophenylhydrazino)-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one (6). To a hot solution of 2,4-dinitrophenylhydrazine (0.204 g, 1.03 mmol) in 0.1 M HCl (60 ml) was added **1** (0.141 g, 0.992 mmol) in water (2.0 ml). The mixture was heated under reflux for 8 h. The crude solid was collected, washed with water, dried, and recrystallized from ethyl acetate to afford 0.163 g (51%) of **6**: Mp 173.5—176.0 °C; mp 176.0—176.5 °C after an additional recrystallization from benzene; IR (KBr) 3370, 3348 (NH), 1670 (C=O), and 1614 cm^{-1} (C=C); ^1H NMR [$(CD_3)_2SO$] δ=1.19 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 4.81 (dd, J=5, 1 Hz, 1H, CH), 5.82 (d, J=9.5 Hz, 1H, CH=C<u>H</u>CO), 6.58 (dd, J=9.5, 1 Hz, 1H, C<u>H</u>=CHCO), 6.79 (br d, J=5 Hz, 1H, N<u>H</u>NHAr), 7.26—8.82 (m, 3H, ArH), and 9.97 (br s, 1H, NHN<u>H</u>Ar). Addition of D_2O resulted in loss of the signals at 6.79 and 9.97 and collapse of the signal at 4.81 to a doublet (J=1 Hz). Found: C, 48.25; H, 4.19; N, 17.24%. Calcd for $C_{13}H_{14}N_4O_6$: C, 48.45; H, 4.38; N, 17.38%.

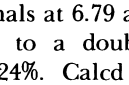
(*E*)-4,4-Dimethyl-5-oxo-2-pentenoic Acid (7). A mixture of methyl (*E*)-5-(*t*-butylimino)-4,4-dimethyl-2-pentenoate[2] (21.2 g, 0.100 mol) and 4 M HCl (150 ml) was refluxed for 5 h. The reaction mixture was extracted with ether (3×50 ml). The ethereal extract was washed with water, dried (Na_2SO_4), concentrated, and distilled to give 10.6 g (75%) of **7**: Bp 115.0—117.0 °C/0.20 mmHg; mp 55.5—56.1 °C; IR (KBr) 3000 (OH), 2815, 2700 (CHO), 1720, 1682 (C=O), 1635 (C=C), and 988 cm^{-1}  ; ^1H NMR (CCl_4) δ=1.28 (s, 6H, $C(CH_3)_2$), 5.81 (d, J=16 Hz, 1H, CH=C<u>H</u>COOH), 7.00 (d, J=16 Hz, 1H, C<u>H</u>=CHCOOH), 9.37 (s, 1H, CHO), and 11.98 (br s, 1H, COOH). Found: C, 58.85; H, 7.16%. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09%.

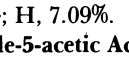
1-Aryl-4,4-dimethyl-4,5-dihydro-1*H*-pyrazole-5-acetic Acids (8). Typical examples are as follows:

A: A solution of *p*-nitrophenylhydrazine (0.161 g, 1.05 mmol) in acetic acid–water (1:1, w/w) (3.0 ml) was refluxed with **1** (0.144 g, 1.01 mmol) for 3 h. Water (5.0 ml) was added and the mixture was cooled. The crystalline product was collected, washed with water, and dried, giving 0.234 g (83%) of **8** (R=*p*-NO_2), mp 195.3—196.3 °C. An analytical sample was prepared by recrystallization from ethanol–cyclohexane.

B: A solution of *p*-chlorophenylhydrazine hydrochloride (0.186 g, 1.04 mmol) and anhydrous sodium acetate (0.085 g, 1.04 mmol) in acetic acid–water (1:1, w/w) (3.0 ml) was refluxed with **7** (0.142 g, 1.00 mmol) for 3 h. Working up as described above gave 0.219 g (82%) of **8** (R=*p*-Cl), mp 128.0—130.0 °C. An analytical sample was prepared by recrystallization from ethanol–cyclohexane.

(3*E*,9*E*,15*E*)-6,12,18-Trichloro-5,5,11,11,17,17-hexamethyl-1,7,13-trioxacyclooctadeca-3,9,15-triene-2,8,14-trione (9). Thionyl chloride (8.85 g, 74.4 mmol) was added dropwise to **7** (10.0 g, 70.3 mmol) during 10 min. The mixture was allowed to stand overnight at room temperature. The resulting solid was recrystallized from chloroform to give 3.59 g of **9**, mp 153.5—156.7 °C. Further recrystallization from the mother liquor afforded an additional 1.87 g, mp 150.5—155.0 °C; overall yield 48%. The pure sample after additional recrystallizations had mp 156.8—157.5 °C: IR (KBr) 1754 (C=O),1628 (C=C), and 987 cm^{-1}  ; ^1H NMR ($CDCl_3$) δ=1.15 (s, 18H, $6CH_3$), 4.61 (s, 3H, 3CH), 6.01 (d, J=15.5 Hz, 3H, 3CH=C<u>H</u>CO), and 7.18 (d, J=15.5 Hz, 3H, 3C<u>H</u>=CHCO); MS *m/z* (rel intensity) 447 (6), 446 (2), 445 (9), and 125 (100). Found: C, 52.48; H, 5.46; Cl, 22.04%; M, 480 (measured with a Corona 117 vapor pressure osmometer). Calcd for $C_{21}H_{27}Cl_3O_6$: C, 52.35; H, 5.65; Cl, 22.08%; M, 481.8.

Compound 10a. A solution of 0.483 g (1.00 mmol) of **9** in 50 ml of tetrahydrofuran containing 1.0 ml of water was kept at room temperature for 15 h. The solution was concentrated in vacuo to ca. 2 ml. Water (10 ml) was added and the mixture was extracted with chloroform (3×20 ml). The chloroform extract was dried (Na_2SO_4) and evaporated in vacuo. The residual solid was dried at 110 °C in vacuo for 3 h and recrystallized from chloroform to afford 0.378 g (88%) of **10a**: Mp 200.3—201.8 °C; IR (KBr) 3000 (OH), 1692 (C=O), 1649 (C=C), and 983 cm^{-1}  ; ^1H NMR ($CDCl_3$) δ=1.10 (s, 18H, $6CH_3$), 4.51 (s, 3H,3CH), 5.82 (d, J=16 Hz, 3H, 3CH=C<u>H</u>CO), 7.02 (d, J=16 Hz, 3H, 3C<u>H</u>=CHCO), and 11.8 (br s, 3H, 3OH); MS (CI) *m/z* 427 $(M+H)^+$. Found: C, 59.14; H, 6.99%. Calcd for $C_{21}H_{30}O_9$: C, 59.14; H, 7.09%.

Compound 10b. To a stirred solution of **9** (0.482 g, 1.00 mmol) in chloroform (20 ml) was added a solution of aniline (0.281 g, 3.02 mmol) and triethylamine (0.304 g, 3.00 mmol) in chloroform (5 ml) during 15 min. Stirring was continued for an additional 3 h. The mixture was washed with water (3×25 ml) and dried (Na_2SO_4). The solvent was removed in vacuo and the residual solid was recrystallized from chloroform, giving 0.546 g (84%) of **10b**: Mp 138.5—140.5 °C; mp 141.0—142.0 °C after further recrystallization; IR (KBr) 3270 (NH), 1663 (C=O), and 977 cm^{-1}  ; ^1H NMR ($CDCl_3$) δ=1.01 (br s, 18H, $6CH_3$), 4.49 (s, 3H, 3CH), 6.01 (d, J=15 Hz, 3H, 3CH=C<u>H</u>CO), 6.92 (d, J=15 Hz, 3H, 3C<u>H</u>=CHCO), 6.9—7.7 (m, 15H, ArH), and 8.45 (br s, 3H, 3NH); MS *m/z* 651 (M^+). Found: C, 71.59; H, 6.84; N, 6.39%. Calcd for $C_{39}H_{45}N_3O_6$: C, 71.87; H, 6.96; N, 6.45%.

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