ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 8, pp. 1169–1173. © Pleiades Publishing, Inc. 2006.
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Reaction of Alkyl 5,5-Dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylates with Zinc Enolates Prepared from Zinc and 1-Arul-2-bromo-2-phenylethanones, 2 Bromoindanone, and 2-Bromo-6-methyltetralone

V.V. Shchepin[a], A.E. Korzun[a], M.I. Vakhrin[a], P.S. Silaichev[a], M.A. Ezhikova[b], and M.I. Kodess[b]

[a] *Perm State University, Perm, 614990 Russia*
[b] *Postovskii Institute of Organic Synthesis, Ural Division, Russian Academy of Sciences, Yekaterinburg, Russia*

Received March 28, 2005

Abstract—Alkyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylates react with zinc enolates prepared from 1-aryl-2-bromo-2-phenylethanones, 2-bromoindanone, 2-bromo-6-methyltetralone and zinc with formation of ethyl 4-(2-aryl-2-oxo-1-phenyl-ethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates, alkyl 5,5-dimethyl-2-oxo-4-(1-oxoindan-2-yl)tetrahydrofuran-3-carboxylates, and ethyl 5,5-dimethyl-4-(6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxotetrahydrofuran-3-carboxylate respectively, mainly as single diastereomers.

DOI: 10.1134/S1070428006080112

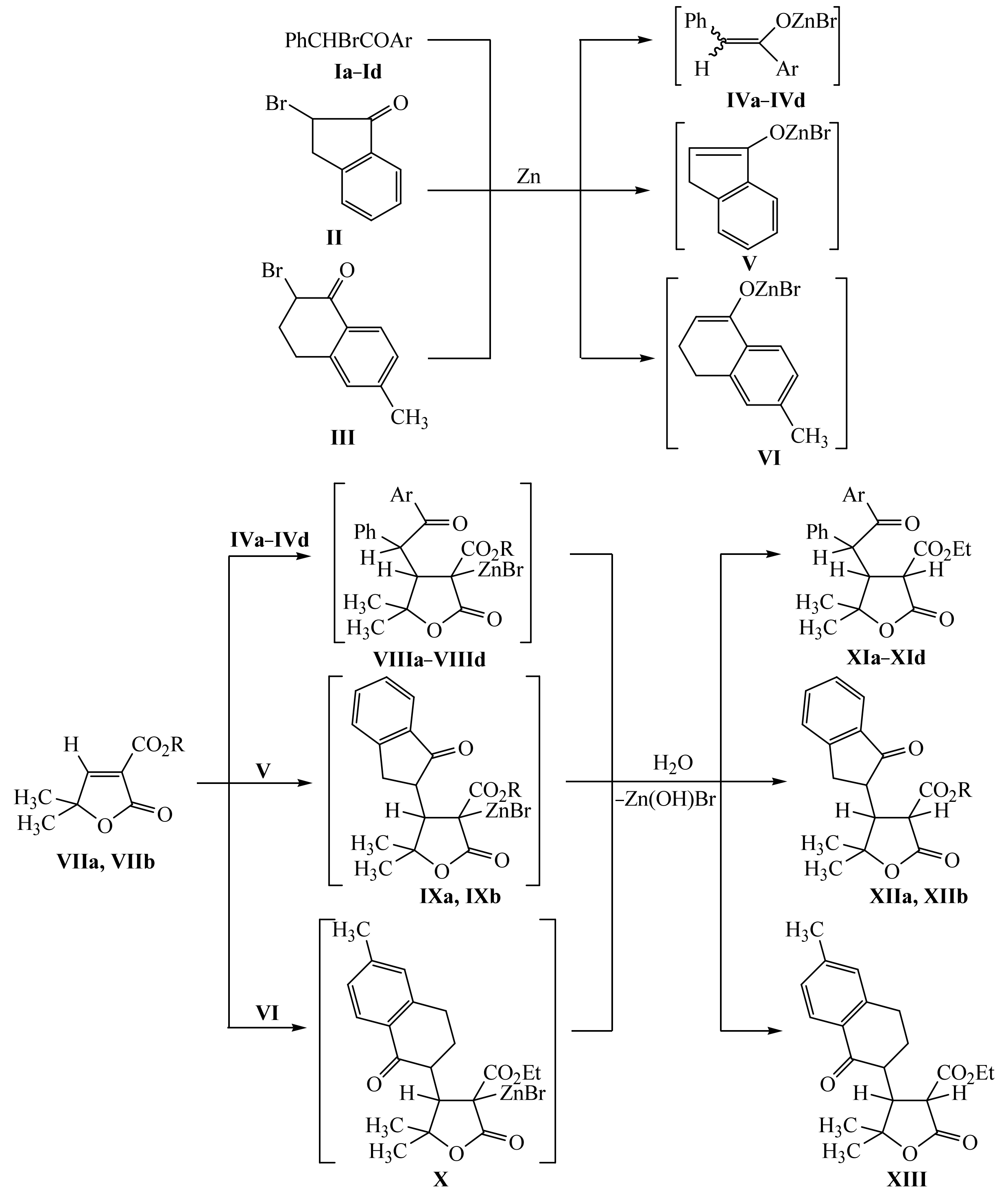
In extension of our research aimed at new functionalization methods for heterocycles possessing a double bond activated with elecron-withdrawing groups [1] we studied the reaction of alkyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylates with zinc enolates obtained from α-bromoketones **Ia–Id**, **II**, and **III**. The experiments demonstrated that in all instances the reaction of nucleophilic zinc enolates **IVa–IVd**, **V**, and **VI** with electrophilic substrates **VIIa** and **VIIb** proceeded regiospecifically along the scheme on the next page.

"Soft" nucleophiles, zinc enolates, attack exclusively the C^4 atom of the heterocycle forming intermediates **VIIIa–VIIId**, **IXa**, **IXb**, and **X** which on hydrolysis are converted into the final products, ethyl 4-(2-aryl-2-oxo-1-phenylethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates **XIa–XId**, alkyl 5,5-dimethyl-2-oxo-4-(1-oxoindan-2-yl)tetrahydrofuran-3-carboxylates **XIIa** and **XIIb**, and ethyl 5,5-dimethyl-4-(6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxotetrahydrofuran-3-carboxylate (**XIII**).

The structure of compounds **XIa–XId**, **XIIa**, **XIIb**, and **XIII** was proved by elemental analysis, IR and ^1H NMR spectroscopy. The IR spectra of compounds **XIa–XId**, **XIIa**, **XIIb**, and **XIII** contain absorption bands of carbonyls of keto, lactone, and ester groups in the region 1680–1690, 1740–1750, 1775–1790 cm^{-1}, respectively. In the ^1H NMR spectra ($CDCl_3$) of compounds **XIa–XId** appear characteristic signals of protons in the regions 0.87–0.90 and 1.33–1.35, 3.37–3.43, 3.59–3.67, 4.60–4.67 ppm belonging to the protons of the two methyl groups CMe_2, to the proton C^3H, the proton C^4H, and the methine proton $C\underline{H}C_6H_5$ respectively.

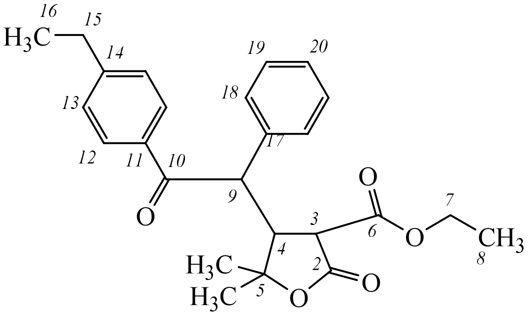
The comparison of characteristic signals in the ^1H NMR spectra (δ, ppm) of, for instance, ethyl 4-[2-(4-methylphenyl)-2-oxo-1-phenylethyl]-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (**XIa**) [0.89 s, 1.34 s (6H, Me_2C), 3.37 d (1H, C^3H, *J* 11 Hz), 3.60 d.d (1H, C^4H, *J* 11, 10.2 Hz), 4.63 d (1H, $C\underline{H}C_6H_5$, *J* 10.2 Hz)] with those of the reference compound, methyl 4-(1-methyl-2-oxo-2-phenylethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate [1.43 s, 1.56 s (6H, Me_2C), 2.96 d.d (1H, C^4H, *J* 11, 8.5 Hz), 3.89 m (1H, $C\underline{H}CH_3$), 3.95 d (1H, C^3H, *J* 11 Hz)] [1] reveals great difference in the chemical shifts of the signals in the spectra of these compounds. Actually, the replacement of the methyl in the reference by the phenyl in compound **XIa** resulted, firstly, in a significant deshielding of the protons in the $C\underline{H}C_6H_5$ group and C^4H amounting to 0.74 and 0.64 ppm respectively, and secondly, to a strong shielding of the protons belonging to one of the methyl groups CMe_2, and

Scheme.



of proton C^{3}H that suffer a considerable upfield shift by ~0.5–0.6 ppm. The latter fact suggests that these protons are located on the same side of the ring with the phenyl-containing substituent at the C^4 atom. Inasmuch as the coupling constants in both compounds have close values the configuration of the substances should be similar.

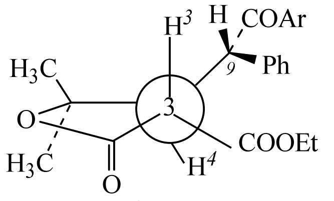
To gain more information on the structure of compounds **XIa** and **XIb** we carried out of thorough



XIb

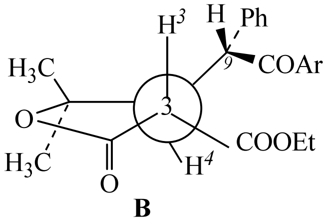
investigation of compound **XIb** by means of ^{1}H and ^{13}C NMR spectroscopy (see EXPERIMENTAL).

Presumably compound **XIb** may form as racemic mixture containing equal amounts of enantiomeric pairs:



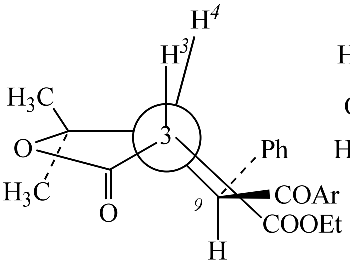
A

$C^3(R)$, $C^4(S)$, $C^9(S)$



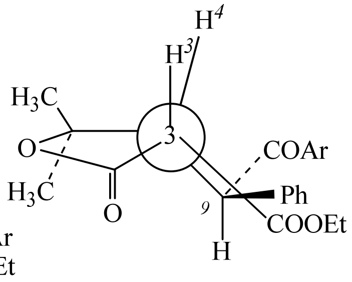
B

$C^3(R)$, $C^4(S)$, $C^9(S)$



C

$C^3(R)$, $C^4(S)$, $C^9(S)$



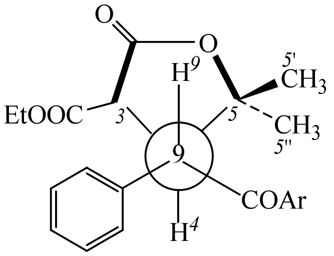
D

$C^3(R)$, $C^4(S)$, $C^9(S)$

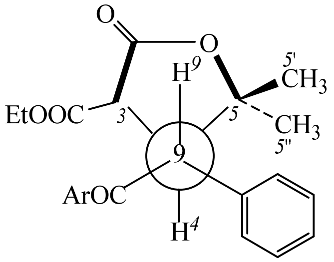
Ar = 4-EtC_6H_4.

(**A–A'**), $C^3(R)$, $C^4(S)$, $C^9(S)$–$C^3(S)$, $C^4(R)$, $C^9(R)$; (**B–B'**), $C^3(R)$, $C^4(S)$, $C^9(R)$–$C^3(S)$, $C^4(R)$, $C^9(S)$; (**C–C'**), $C^3(R)$, $C^4(R)$, $C^9(S)$–$C^3(S)$, $C^4(S)$, $C^9(R)$; and (**D–D'**), $C^3(R)$, $C^4(R)$, $C^9(R)$–$C^3(S)$, $C^4(S)$, $C^9(S)$. The Newman projections of diastereomers **A**–**D** are given above.

As seen from the ^{1}H NMR spectrum, the large coupling constant $J_{HC^3C^4H}$ 11.2 Hz evidences a large dihedral angle Θ^1 of the H–C^3–C^4–H bond and a *trans*-location of H^3 and H^4 protons in the diastereomers **A** and **B** [2, 3].



A



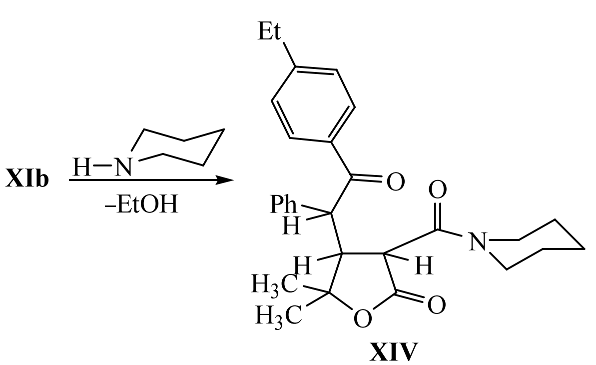
B

trans-Position of the protons H^3 and H^4 in the diastereomers **A** and **B** is confirmed by the 2D NOESY spectrum. In the spectrum a cross-peak is observed between the proton H^4 and protons of the methyl group $C^{5''}$, whereas the protons of the methyl group $C^{5'}$ form cross-peaks with protons H^3 and H^9. Our results are consistent with the published data [4]. It is known that in 3,4,5-trimethyltetrahydrofuran-2-ones the coupling constant $J_{3,4}$ for the *trans*,*trans*-isomer is 11.5 Hz, and for the *cis*,*cis*-isomer, 7 Hz.

The large value $J_{HC^4C^9H}$ ~10.8 Hz in its turn testifies to the prevalence of the transoid position of the hydrogen atoms H–C^4–C^9–C–H in the diastereomers **A** and **B**.

In the 2D NOESY spectrum a cross-peak is observed between the protons of the $C^{5'}$ group and protons with a signal at δ 7.50 ppm which belongs to the *ortho*-protons of the phenyl group. The protons of the $C^{5''}$ methyl group also give a weak cross-peak with the above mentioned phenyl protons. These finding apparently testify to the presence of a diastereomer of the **B** type.

In order to test the reactivity of compounds **XIa–XId** obtained and to prepare therefrom new nitrogen-containing compounds we investigated the reaction of compound **XIb** with piperidine. The reaction was carried out by boiling the reagents in *O* xylene for 6 h. It turned out that the amine attack was directed at the ester group carbon of the electrophilic substrate **XIb** resulting in the formation of 5,5-dimethyl-4-[2-oxo-1-phenyl-2-(4-ethylphenyl)-ethyl]-3-(piperidine-1-carbonyl)dihydrofuran-2-one (**XIV**).



XIV

The composition and structure of compound **XIV** was proved by elemental analysis, IR and ^{1}H NMR spectroscopy. The IR spectra of compound contain the absorption bands of amide, keto, and lactone carbonyl groups in the region 1640, 1690, 1770 cm^{-1} respectively. In the ^{1}H NMR spectrum were observed the characteristic signals and coupling constants of the following protons ($CDCl_3$), δ, ppm: 3.71 d (1H, C^3H, J 8.7 Hz), 4.41 d.d (1H, C^4H, J 11.4, 8.7 Hz), 4.65 d (1H, $C\underline{H}C_6H_5$, J 11.4 Hz). In the spectrum ($CDCl_3$) of ethyl ester **XIb** corresponding to this amide these parameters were as follows: 3.40 d (1H, C^3H, J 11 Hz), 3.60 d.d (1H, C^4H, J 11, 10 Hz), 4.67 d (1H, $C\underline{H}C_6H_5$, J 10 Hz). The comparison of the spectral characteristics shows that the substitution of the ester group in compound **XIb** by an amide one in compound **XIV** resulted in a deshielding of proton C^3H by ~0.3 ppm and of proton C^4H by ~0.8 ppm, whereas the chemical shift of the proton in the $C\underline{H}C_6H_5$ group virtually remained unchanged. The introduction of a bulky group instead of the ethoxycarbonyl one is likely to affect to a certain extent the dihedral angles HC^3C^4H and HC^4C^9H as seen from the changes in the values of the corresponding constants, but the configuration of the chiral centers apparently remains the same as in diastereomer of compound **XIb**.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from mulls of individual compounds in mineral oil. ^{1}H NMR spectra of compounds **XIa–XIc**, **XIIb**, and **XIII** in $CDCl_3$ solution were registered on a spectrometer Tesla BS-567A (100 MHz), internal reference HMDS, spectra of compounds **XId**, **XIIa**, and **XIV**, in $CDCl_3$ solution on a spectrometer Mercury-Plus 300 (300 MHz), spectra of compound **XIb**, in DMSO-d_6 on a spectrometer Bruker DRX-400 (400 MHz), internal reference TMS. ^{13}C NMR spectrum of compound **XIb** was recorded on a spectrometer Bruker DRX-400 (100 MHz).

Ethyl 4-(2-aryl-2-oxo-1-phenyl-ethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates XIa–XId. To 2 g of fine zinc turnings in 7 ml of ethers and 7 ml of ethyl acetate was added 0.011 mol of ethyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**VIIb**) and 0.014 mol of 1-aryl-2-bromo-2-phenylethanone **Ia**–**Id**. The mixture was heated till the process started, and then the reaction proceeded with self-heating. On completion of the reaction the mixture was boiled for 15 min. On cooling the reaction mixture was hydrolyzed with 10% aqueous HCl, extracted with ether, the organic layer was separated, washed with 10% sodium hydrogen carbonate till neutral, dried with sodium sulfate, the solvent was distilled off, and the final products were purified by double recrystallization from methanol.

Ethyl 4-(2-oxo-2-*p*-tolyl-1-phenyl-ethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (XIa). Yield 79%, mp 176–177°C. IR spectrum, ν, cm^{-1}: 1685 ($C=O_{keto}$), 1745 ($C=O_{ester}$), 1790 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 0.89 s, 1.34 s (6H, Me_2C), 1.15 t (3H, $OCH_2\underline{Me}$, J 7 Hz), 2.27 s (3H, $\underline{Me}C_6H_4$), 3.37 d (1H, C^3H, J 11 Hz), 3.60 d.d (1H, C^4H, J 11, 10 Hz), 4.11 q (2H, $OC\underline{H}_2Me$, J 7 Hz), 4.63 d (1H, $C\underline{H}C_6H_5$, J 10 Hz), 6.95–7.75 m (9H, C_6H_5, 4-$MeC_6\underline{H}_4$). Found, %: C 73.11; H 6.61. $C_{24}H_{26}O_5$. Calculated, %: C 73.08; H 6.64.

Ethyl 4-[2-oxo-1-phenyl-2-(4-ethylphenyl)ethyl]-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (XIb). Yield 82%, mp 147–148°C. IR spectrum, ν, cm^{-1}: 1680 ($C=O_{keto}$), 1750 ($C=O_{ester}$), 1790 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H, $H^{5''}$), 1.09 t (3H, H^8, J 7.1 Hz), 1.15 t (3H, H^{16}, J 7.6 Hz), 1.43 s (3H, $H^{5'}$), 2.63 q (2H, H^{15}, J 7.6 Hz), 3.55 d.d (1H, H^4, $J_{4,3}$ 11.2, $J_{4,9}$ 10.8 Hz), 4.05 d.q (1H, H^{7b}, J 10.7, 7.1 Hz), 4.06 d (1H, H^3, $J_{3,4}$ 11.2 Hz), 4.11 d.q (1H, H^{7a}, J 10.7, 7.1 Hz), 5.01 d (1H, H^9, $J_{9,4}$ 10.8 Hz), 7.25 t.t (1H, H^{20}, J 7.3, 1.2 Hz), 7.33 m (4H, H^{19}, H^{13}), 7.50 d.d (2H, H^{18}, J 8.3 Hz), 8.00 d (2H, H^{12}, J 8.4 Hz). ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 0.88 s, 1.34 s (6H, Me_2C), 1.12 t (6H, $OCH_2\underline{Me}$, 4-$\underline{Me}CH_2C_6H_5$, J 7 Hz), 2.56 q (2H, 4-$MeCH_2C_6H_5$, J 7 Hz), 3.40 d (1H, C^3H, J 11 Hz), 3.60 d.d (1H, C^4H, J 11, 10 Hz), 4.10 q (2H, $OC\underline{H}_2Me$, J 7 Hz), 4.67 d (1H, $C\underline{H}C_6H_5$, J 10 Hz), 7.00–7.40 m, 7.73 d (9H, C_6H_5, 4-$EtC_6\underline{H}_4$, J 8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.60 (C^8), 15.08 (C^{16}), 22.82 ($C^{5'}$), 27.98 ($C^{5''}$), 28.09 (C^{15}), 52.01, 52.05 (C^4, C^9), 52.29 (C^3), 60.96 (C^7), 85.98 (C^5), 127.85 (C^{20}), 128.09, 128.91 (C^{19}, C^{13}), 129.06 (C^{12}), 129.30 (C^{18}), 133.03, 136.08 (C^{17}, C^{11}), 150.19 (C^{14}), 168.52 (C^6), 170.92 (C^2), 196.73 (C^{10}). Found, %: C 73.50; H 6.94. $C_{25}H_{28}O_5$. Calculated, %: C 73.51; H 6. 91.

Ethyl 4-[2-oxo-1-phenyl-2-(4-chlorophenyl)-ethyl]-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (XIc). Yield 85%, mp 182–183°C. IR spectrum, ν, cm^{-1}: 1690 ($C=O_{keto}$), 1740 ($C=O_{ester}$), 1790 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 0.89 s, 1.35 s (6H, Me_2C), 1.16 t (3H, $OCH_2\underline{Me}$, J 7 Hz), 3.37 d (1H, C^3H, J 11 Hz), 3.59 d.d (1H, C^4H, J 11, 10 Hz), 4.12 q (2H, $OC\underline{H}_2Me$, J 7 Hz), 4.60 d (1H, $C\underline{H}C_6H_5$, J 10 Hz), 7.12–7.35 m, 7.73 d (9H, C_6H_5, 4-ClC_6H_4, J 8 Hz).

Found, %: C 66.62; H 5.56; Cl 8.58. $C_{23}H_{23}ClO_5$. Calculated, %: C 66.59; H 5.59; Cl 8.55.

Ethyl 4-[2-(4-bromophenyl)-2-oxo-1-phenylethyl]-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (XId). Yield 76%, mp 178–179°C. IR spectrum, ν, cm^{-1}: 1690 ($C=O_{keto}$), 1740 ($C=O_{ester}$), 1790 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 0.87 s, 1.35 s (6H, Me_2C), 1.16 t (3H, $OCH_2\underline{Me}$, *J* 7 Hz), 3.43 d (1H, C^3H, *J* 11 Hz), 3.68 d.d (1H, C^4H, *J* 11, 10.8 Hz), 4.16 m (2H, $OC\underline{H}_2Me$), 4.64 d (1H, $C\underline{H}C_6H_5$, *J* 10.8 Hz), 7.15–7.40 m (5H, C_6H_5) 7.48 d, 7.74 d (4H, 4-$BrC_6\underline{H}_4$, *J* 8 Hz). Found, %: C 66.17; H 5.02; Br 17.43. $C_{23}H_{23}BrO_5$. Calculated, %: C 66.14; H 5.05; Br 17.40.

Methyl 5,5-dimethyl-2-oxo-4-(1-oxoindan-2-yl)-tetrahydrofuran-3-carboxylate (XIIa) was obtained analogously to compounds **XIa**–**XId** but using methyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**VIIa**) and 2-bromoindanone (**II**). Yield 79%, mp 135–137°C. IR spectrum, ν, cm^{-1}: 1690 ($C=O_{keto}$), 1745 ($C=O_{ester}$), 1785 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 1.40 s, 1.61 s (6H, Me_2C), 2.80–3.00 m, 3.23–3.35 m, (4H, C^4H, $CHCH_2$), 3.56 d (1H, C^3H, *J* 11.5 Hz), 3.56 s (3H, OMe), 7.20–7.70 m (4H, C_6H_4). Found, %: C 67.57; H 5.98. $C_{17}H_{18}O_5$. Calculated, %: C 67.54, H 6.00.

Ethyl 5,5-dimethyl-2-oxo-4-(1-oxoindan-2-yl)-tetrahydrofuran-3-carboxylate (XIIb) was obtained analogously to compounds **XIa**–**XId** but using 2-bromoindanone (**II**). Yield 72%, mp 159–161°C. IR spectrum, ν, cm^{-1}: 1685 ($C=O_{keto}$), 1740 ($C=O_{ester}$), 1780 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 1.03 t (3H, $OCH_2C\underline{H}_3$, *J* 7 Hz), 1.38 s, 1.59 s (6H, Me_2C), 2.70–3.45 m (4H, C^4H, $CHCH_2$), 3.50 d (1H, C^3H, *J* 11.5 Hz), 4.00 m (2H, $OC\underline{H}_2CH_3$), 7.15–7.63 m (4H, C_6H_4). Found, %: C 68.37; H 6.39. $C_{18}H_{20}O_5$. Calculated, %: C 68.34; H 6.37.

Ethyl 5,5-dimethyl-4-(6-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxotetrahydrofuran-3-carboxylate (XIII) was obtained analogously to compounds **XIa**–**XId** but using 2-bromo-6-methyltetralone (**III**). Yield 68%, mp 104–106°C. IR spectrum, ν, cm^{-1}: 1685 ($C=O_{keto}$), 1740 ($C=O_{ester}$), 1775 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 1.16 t (3H, $OCH_2C\underline{H}_3$, *J* 7 Hz), 1.33 s, 1.55 s (6H, Me_2C), 1.80–2.30 m, 2.40–2.70 m, 2.80–3.05 m (6H, C^4H, CHC_2H_4), 2.27 s (3H, $\underline{Me}C_6H_3$), 3.70 d (1H, C^3H, *J* 11.5 Hz), 4.05 q (2H, $OC\underline{H}_2CH_3$, *J* 7 Hz), 6.85 s, 6.92 d, 7.63 d (3H, C_6H_3). Found, %: C 68.78; H 7.00. $C_{20}H_{24}O_5$. Calculated, %: C 69.75; H 7.02.

5,5-Dimethyl-4-[2-oxo-1-phenyl-2-(4-ethylphenyl)ethyl]-3-(piperidine-1-carbonyl)dihydrofuran-2-one (XIV). To 0.0016 mol of compound **XIb** dissolved in 6 ml of *o*-xylene was added 0.0017 mol of piperidine. The mixture was heated for 6 h. On distilling off the solvent the precipitate of the corresponding amide was twice recrystallized from methanol. Yield 34%, mp 192–194°C. IR spectrum, ν, cm^{-1}: 1640 ($C=O_{amide}$, 1695 ($C=O_{keto}$), 1770 ($C=O_{lactone}$). ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, 4-$\underline{Me}CH_2C_6H_5$, *J* 7.8 Hz), 1.00–1.50 m, 2.84–3.03 m, 3.11–3.28 m (10H, $C_5H_{10}N$), 1.25 s 1.59 s (6H, Me_2C), 2.59 q (2H, 4-$MeC\underline{H}_2C_6H_5$), 3.71 d (1H, C^3H, *J* 8.7 Hz), 4.41 d.d (1H, C^4H, *J* 11.4, 8.7 Hz), 4.65 d (1H, $C\underline{H}C_6H_5$, *J* 11.4 Hz), 7.10–7.30 m, 7.85 d (9H, C_6H_5, 4-$EtC_6\underline{H}_4$). Found, %: C 75.11; H 7.45; N 3.14. $C_{28}H_{33}NO_4$. Calculated, %: C 75.14; H 7.43; N 3.13.

The study was carried out under a financial support of the Russian Foundation for Basic Research (grants nos. 04-03-96036, 04-03-97505).

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