Russian Journal of General Chemistry, Vol. 73, No. 5, 2003, pp. 760–764. Translated from Zhurnal Obshchei Khimii, Vol. 73, No. 5, 2003, pp. 804–808.

Reaction of Zinc and Sodium Enolates of 3-Alkyl-6-aryl-5,5-dimethyl-2,3,5,6-tetrahydropyrane-2,4-diones with Acyl Chlorides or Benzyl Bromides

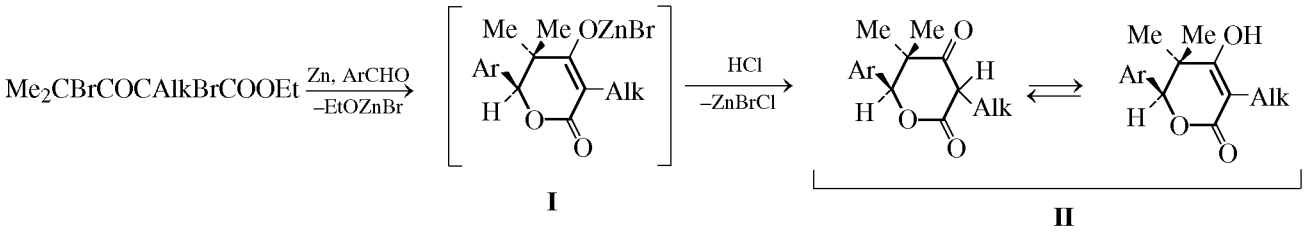
V. V. Shchepin, Yu. Kh. Sazhneva, N. Yu. Russkikh, and M. I. Vakhrin

Perm State University, Perm, Russia

Received April 18, 2001

Abstract—Zinc enolates of 3-alkyl-6-aryl-5,5-dimethyl-2,3,5,6-tetrahydropyrane-2,4-diones react with acyl chlorides to form O-acylation products, 4-acyloxy-3-alkyl-6-aryl-5,5-dimethyl-5,6-dihydropyrane-2-ones. Sodium enolates of these pyranediones react in DMSO with substituted benzyl bromides to give mainly C-alkylation products, 3-alkyl-6-aryl-3-(4-R-benzyl)-5,5-dimethyl-2,3,5,6-tetrahydropyrane-2,4-diones, as single geometric isomers. In some cases, O-alkylation products, 4-alkoxy-3-alkyl-6-aryl-5,5-dimethyl-5,6-dihydropyrane-2-ones, are formed as by-products (~10–15%).

Earlier we found that ethyl 2,4-dibromo-2,4-dimethyl-3-oxopentanoate reacts with zinc and aromatic aldehydes to form mainly 6-aryl-3,5,5-trimethyl-2,3,5,6-tetrahydropyrane-2,4-diones [1]. In that communication we also suggested that the reaction results in formation of zinc enolates of 6-aryl-5,5-dimethyl-3-R-2,3,5,6-tetrahydropyrane-2,4-diones **I** which hydrolize to give the final products, pyranediones **II**.



I **II**

To substantiate this suggestion, as well as to extend synthetic possibilities of the mentioned reaction, we studied the reaction of zinc enolates **I** with acyl chlorides and substituted benzyl bromides (Scheme 1).

On addition of acyl chlorides to the postreaction mixture we isolated 4-acyloxy-3-alkyl-6-aryl-5,5-dimethyl-5,6-dihydropyrane-2,4-diones **IIIa**–**IIIj** (Table 1) formed by O-acylation of zinc enolates **I**.

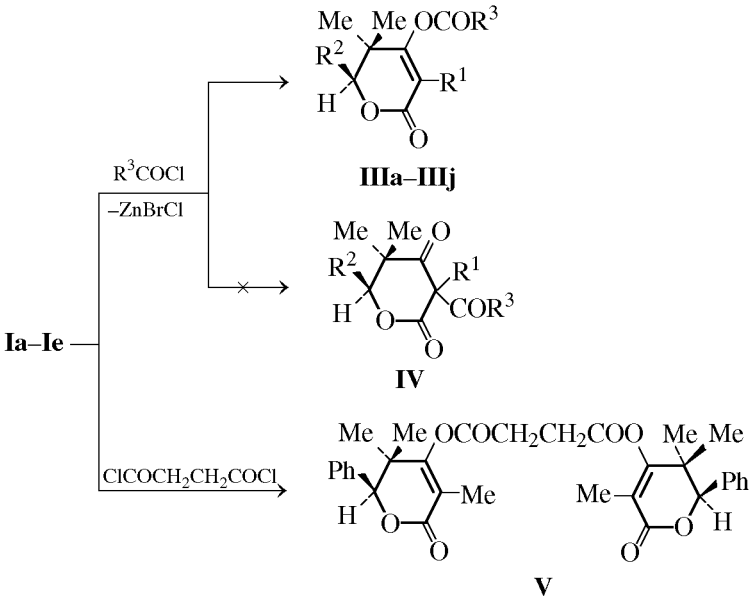
Alternative compounds **IV**, the products of C-acylation of zinc enolates **I**, were not found. Similar regiospecific O-acylation was earlier observed in the reaction of acyl chlorides with intermediately formed zinc enolates of 2-alkyl-3-oxoalkanoates [2, 3].

The reaction of zinc enolate of 3,5,5-trimethyl-6-phenyl-2,3,5,6-tetrahydropyrane-2,4-dione (**Ia**) with succinyl chloride proceeds similarly to give bis(3,5,5-trimethyl-6-phenyl-2-oxo-5,6-dihydropyran-4-yl) succinate (**V**).

The yields of compounds **IIIa**–**IIIj** are 37–80%. Their composition and structure were proved by elemental analysis and ^{1}H NMR and IR spectroscopy. The IR spectra contain characteristic absorption bands at 1730–1770 cm^{-1} and an absorption band of the double bond at 1670–1680 cm^{-1}. The ^{1}H NMR spectra show typical singlet signals at 0.77–1.05, 1.57–1.70, and 5.10–5.53 ppm, belonging to methyl (Me_2C, MeC) and methine (CHO) protons, respectively.

1070-3632/03/7305-0760 $25.00

Scheme 1.



I, R^1 = Me; R^2 = Ph (**a**), 4-BrC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**). **I**, R^1 = Et; R^2 = Ph (**e**). **III**, R^1 = Me, R^2 = Ph; R^3 = Me (**a**), *t*-Bu (**b**), Ph (**c**), 4-BrC_6H_4 (**d**). **III**, R^1 = Me, R^2 = 4-BrC_6H_4; R^3 = Me (**e**), Ph (**f**); **III**, R^1 = Me, R^2 = 4-ClC_6H_4; R^3 = Ph (**g**), 4-BrC_6H_4 (**h**). **III**, R^1 = Me, R^2 = 3,4-$(MeO)_2C_6H_3$, R^3 = Ph (**i**). **III**, R^1 = Et, R^2 = R^3 = Ph (**j**).

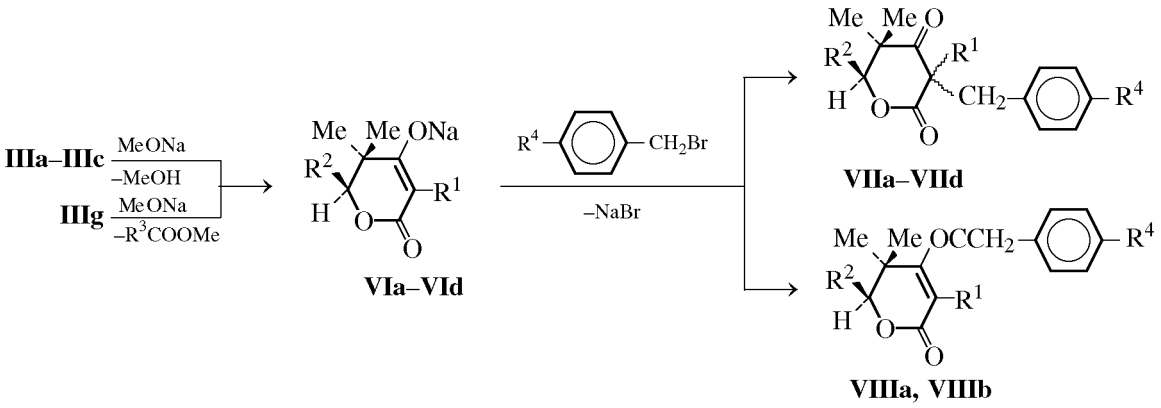
Attempted reaction zinc enolate **I** with substituted benzyl bromides failed. For this reason, we converted intermediate **I** it into a more nucleophilically active sodium enolate **VI** (Scheme 2).

As seen from the above scheme, sodium enolate **VI** is formed both from pyranediones **II** and from their acyl derivatives **III**. This result is yet another evidence that the acylation of zinc enolate **I** with acyl chlorides involves attack of zinc enolate **I** on the O-nucleophilic center.

Table 1. Yields, constants, ^{1}H NMR spectra (in DMSO-d_6), and elemental analyses of 4-acyloxy-3-alkyl-6-aryl-5,5-dimethyl-5,6-dihydropyrane-2-ones **IIIa**–**IIIj**

Comp. no.	Yield, %	bp, °C (*p*, mm) or mp, °C	^{1}H NMR spectrum, δ, ppm				
			CMe_2	H	R^1	R^2	R^3
IIIa[a]	37	188–190 (6)	0.77 s	5.10 s	1.57 s (Me)	7.18 s (Ph)	2.12 s (Me)
IIIb	40	113–116	0.92 s, 0.97 s	5.40 s	1.63 s (Me)	7.40 s (Ph)	1.33 s (*t*-Bu)
IIIc	79	176–177	1.02 s, 1.05 s	5.50 s	1.70 s (Me)	7.43 s (Ph)	7.62 t, 7.77 t, 8.12 d (Ph)
IIId	73	155–156	1.03 s, 1.05 s	5.50 s	1.70 s (Me)	7.43 s (Ph)	7.83 d, 8.05 d (4-BrC_6H_4)
IIIe	65	128–129	0.87 s, 0.97 s	5.40 s	1.67 s (Me)	7.35 d, 7.60 d (4-BrC_6H_4)	2.30 s (Me)
IIIf	80	159–160	1.00 s, 1.05 s	5.48 s	1.70 s (Me)	7.40 d, 7.58 d (4-BrC_6H_4)	7.60 t, 7.75 t, 8.10 d (Ph)
IIIg	84	187–188	1.00 s, 1.05s	5.53 s	1.70 s (Me)	7.47 s (4-ClC_6H_4)	7.63 t, 7.77 t, 8.12 d (Ph)
IIIh	67	160–161	1.00 s, 1.03 s	5.53 s	1.70 s (Me)	7.46 s (Ph)	7.81 d, 8.03 d (4-BrC_6H_4)
IIIi	59	149–150	1.05 s	5.40 s	1.70 s (Me)	6.96 s, 7.00 s [3,4-$(MeO)_2C_6H_3$]	7.63 t, 7.76 t, 8.12 d (Ph)
IIIj	78	163–164	1.03 s	5.47 s	1.02 t, 2.12 d.q, 2.22 d.q (Et)	7.43 s (Ph)	7.63 t, 7.77 t, 8.11 d (Ph)

Scheme 2.



II, R^1 = Me, R^2 = Ph (**a, b**), 4-BrC_6H_4 (**c**). **VI**, R^1 = Me, R^2 = Ph (**a, b**), 4-BrC_6H_4 (**c**), 4-ClC_6H_4 (**d**). **VII**, R^1 = Me, R^2 = Ph, R^4 = Br (**d**), NO_2 (**b**); R^2 = 4-BrC_6H_4, R^4 = Br (**c**); R^2 = 4-ClC_6H_4, R^4 = Br (**d**). **VIII**, R^1 = Me, R^2 = Ph, R^4 = Br (**a**); R^2 = 4-BrC_6H_4, R^4 = Br (**b**).

Table 1. (Contd.)

Comp. no.	Found, %		Formula	Calculated, %	
	C	H		C	H
IIIa[a]	69.91	6.42	$C_{16}H_{18}O_4$	70.07	6.57
IIIb	72.00	7.50	$C_{19}H_{24}O_4$	72.15	7.59
IIIc	74.85	5.88	$C_{21}H_{20}O_4$	75.00	5.95
IIId	60.52	4.47	$C_{21}H_{19}BrO_4$	60.72	4.58
IIIe	65.22	4.75	$C_{16}H_{17}BrO_4$	65.39	4.82
IIIf	60.60	4.52	$C_{21}H_{19}BrO_4$	60.72	4.58
IIIg	57.85	5.06	$C_{21}H_{19}ClO_4$	68.02	5.13
IIIh	55.91	3.93	$C_{21}H_{18}BrClO_4$	56.06	4.00
IIIi	69.56	6.00	$C_{23}H_{24}O_6$	69.67	6.06
IIIj	75.20	6.19	$C_{22}H_{22}O_4$	75.43	6.29

[a] In CCl_4.

Sodium enolate **VI** was reacted with *para*-substituted benzyl bromides both in methanol (method *a*) and DMSO (method *b*). It was found that both reactions give mainly C-alkylation products, 3-alkyl-6-aryl-3-(4-R^4-benzyl)-5,5-dimethyl-2,3,5,6-tetrahydropyrane-2,4-diones **VIIa**–**VIId** in yields of 9–12% (in MeOH) and 50–68% (in DMSO) (Table 2).

Compounds **VIIb** and **VIId** contained no admixtures of O-alkylation products. Their ^{1}H NMR spectra displayed typical singlet signals at 0.67–0.93, 1.53, and 3.38–3.73 ppm, belonging to methyl (Me_2C, Me) and methine protons, respectively, and a doublet at 2.98–3.47 ppm from methylene protons.

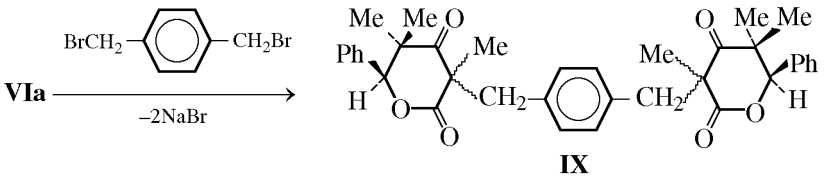
Compounds **VIIa** and **VIIc** were found to contain ~10–15% admixtures of O-alkylation products, 3-alkyl-6-aryl-4-(4-R^4-benzyloxy)-5,5-dimethyl-5,6-dihydropyran-2-ones (**VIIIa, VIIIb**). Thus, in the ^{1}H NMR spectrum of compound VIIa we observed, along with signals of the major product, signals belonging to the O-alkylation product, δ, ppm: 0.90 s, 1.03 s (CMe_2), 2.00 s (Me), 5.03 s (CHO), and 4.87 and 5.23 d.d (CH_2). By recrystallization of 3-(4-bromobenzyl)-3,5,5-trimethyl-6-phenyl-2,3,5,6-tetrahydropyrane-2,4-dione (**VIIa**) containing ~15% of 4-(4-bromobenzoyloxy)-3,5,5-trimethyl-6-phenyl-5,6-dihydropyran-2-one (**VIIIa**) from acetone we were able to separate these two compounds. First compound **VIIIa** was isolated, 174–175°C, and then, after evaporation of most acetone, pure compound **VIIa**, mp 119–120°C. The IR spectrum of compound **VIIIa** displayed typical absorption bands of the double bond (1640 cm^{-1}) and the carbonyl group (1720 cm^{-1}).

It should be noted that C-alkylation products **VIIa**–**VIId** are formed as single geometric isomers. Their IR spectra show characteristic carbonyl absorption bands at 1715–1760 cm^{-1}.

The reaction of sodium enolate **VIa** and α,α'-dibromo-*p*-xylene in methanol gave α,α'-di(3,5,5-trimethyl-6-phenyl-2,4-dioxo-2,3,5,6-tetrahydropyran-3-yl)-*p*-xylene (**IX**) as a single geometric isomer, mp 275–276°C (Scheme 3).

Similar reaction of sodium enolate **VIa** with α,α'-dibromo-*p*-xylene in DMSO resulted in isolation of two products with different melting points (195–196 and 275–276°C). The different chemical shifts, specifically of the CHO proton (δ, ppm: 3.57 s and 3.87 s, respectively) in the ^{1}H NMR spectra of these two

Scheme 3.



IX

Table 2. Yields, constants, ^{1}H NMR spectra, and elemental analyses of 3-alkyl-6-aryl-3-(4-R^4-benzyl)-5,5-dimethyl-2,3,5,6-tetrahydropyrane-2,4-diones (**VIIa**–**VIId**)

Comp. no.	Yield, %	mp, °C (solvent)	^{1}H NMR spectrum, δ, ppm					Solvent
			CMe_2	CH	R^1	R^2	CH_2 (4-R$^4C_6H_4$)	
VIIa	50	119–120 (acetone)	0.68 s, 0.90 s	3.47 s	1.53 s (Me)	7.33 s (Ph)	2.98 d, 3.33 d (CH_2, *J* 12 Hz), 7.00 d, 7.43 d (4-BrC_6H_4)	$CDCl_3$
VIIb	68	170–173 (acetonitrile)	0.70 s, 0.93 s	3.73 s	1.53 s (Me)	6.80–7.48 · (Ph)	3.07 d, 3.47 d (CH_2, *J* 12 Hz), 7.30 d, 8.13 d (4-$NO_2C_6H_4$)	$CDCl_3$
VIIc[a]	12,[b] 62	141–142 (acetone)	0.85 s, 0.93 s	4.60 s	1.41 s (Me)	7.15 d, 7.55 d (4-BrC_6H_4)	2.93 d, 3.35 d (CH_2, *J* 12 Hz), 7.05 d, 7.49 d (4-BrC_6H_4)	DMSO-d_6
VIId	9,[b] 57	140–141 (methanol)	0.67 s, 0.87 s	3.38 s	1.53 s (Me)	6.97 d, 7.23 d (4-ClC_6H_4)	2.98 d, 3.32 d (CH_2, *J* 12 Hz), 6.85 d, 7.40 d (4-BrC_6H_4)	$CDCl_3$

Table 2. (Contd.)

Comp. no.	Found, %		Formula	Calculated, %	
	C	H		C	H
VIIa	62.79	5.21	$C_{21}H_{21}BrO_3$	62.84	5.24
VIIb	65.58	5.65	$C_{21}H_{21}NO_5$	68.66	5.72
VIIc[a]	52.35	4.12	$C_{21}H_{20}Br_2O_3$	52.50	4.17
VIId	57.80	4.53	$C_{21}H_{20}BrClO_3$	57.86	4.59

[a] Compound **VIIc** contains minor amounts of the O-acylation product (ca. 10%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 s, 1.00 s (6H, Me_2), 1.95 s (3H, Me), 5.02 d, 5.25 d (2H, CH_2), 5.23 s (1H, CH), 7.33 d, 7.49 d (4H, 4-BrC_6H_4), 7.39 d, 7.55 d (4H, 4-BrC_6H_4). [b] Yields of compound prepared by method *a*.

compounds suggest formation of two geometric isomers in a 1 : 9 ratio. No signals assignable to the O-alkylation products were found in the spectra of both isomers.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded for DMSO-d_6 solutions on Bruker DRX-500 (**IIIe, IIIf, VIIc, VIId**) and Bruker AM-300 (**IIIb**–**IIId, IIIg**–**IIIj, V**) instruments, and for CCl_4 and $CDCl_3$ on an RYa-2310 (60 MHz) spectrometer (**III, VIIa**–**VIIc, VIII, IX**).

4-Acyloxy-3-alkyl-6-aryl-5,5-dimethyl-5,6-dihydropyran-2-ones IIIa–**IIIj.** To 10 g of finely chipped zinc, catalytic amounts of mercuric chloride, 10 ml of ether, and 30 ml of ethyl acetate, a mixture of 0.05 mol of ethyl 2-alkyl-2,4-dibromo-4-methyl-3-oxopentanoate and 0.05 mol of corresponding aldehyde in 10 ml of a mixture of solvents was added dropwise with stirring. The reaction mixture was refluxed for 15 min, cooled, and then 0.1 mol of corresponding acyl chloride in 10 ml of a mixture of solvents and 0.1 mol of tributylamine was added dropwise with cooling. To bring the reaction to completion, the reaction mixture was heated for 15 min and then cooled and hydrolyzed with 10% HCl. The reaction products were extracted with ether. The extracts were dried with sodium sulfate, and the solvents were removed in vacuo. Compounds **IIIb**–**IIIj** were crystallized from petroleum ether (70–100°C)–CCl_4 (1 : 1), and compound **IIIa** was twice distilled in vacuo.

Bis(3,5,5-trimethyl-6-phenyl-2-oxo-5,6-dihydropyran-4-yl) succinate (V) was prepared similarly to compounds **IIIa**–**IIIj** using 0.05 mol of succinyl chloride. Yield 30%, mp 198–199°C (from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 s, 1.00 s (6H, Me_2), 1.65 s (3H, Me), 3.03 s (2H, CH_2), 5.40 s

(1H, CH), 7.40 s (5H, C_6H_5). Found, %: C 70.19; H 6.15. $C_{32}H_{34}O_8$. Calculated, %: C 70.33; H 6.23.

3-Alkyl-6-aryl-3-(4-R-benzyl)-5,5-dimethyl-2,3,5,6-tetrahydropyrane-2,4-diones VIIa–VIId. *a*. To sodium methylate prepared from 0.03 mol of sodium and 10 ml of MeOH, 0.02 mol of 3-alkyl-6-aryl-5,5-dimethyl-2,3,5,6-tetrahydropyran-2-one or 0.02 mol of 3-alkyl-6-aryl-4-cyloxy-5,5-dimethyl-5,6-dihydropyrane-2-one was added, followed by 0.02 mol of substituted *p*-bromobenzaldehyde, and the mixture was stirred at 30–40°C for 30 min. After the reaction had been complete, the alcohol was distilled off, the mixture was hydrolyzed, extracted with ether, the solvents were removed, and the residue was recrystallized from metanol.

b. To sodium methylate prepared from 0.03 mol of sodium and 10 ml of methanol and dissolved in 15 ml of DMSO, 0.02 mol of 3-alkyl-6-aryl-5,5-dimethyl-2,3,5,6-tetrahydropyran-2-one was added. The alcohol formed was distilled off a water-jet-pump vacuum. Then 0.02 mol of substituted benzyl bromide was added, the mixture was stirred at 30–40°C for 30 min and then poured into water. The precipitate formed was filtered off and recrystallized from methanol, acetonitrile, or acetone.

4-(4-Bromobenzoyloxy)-3,5,5-trimethyl-5,6-dihydropyran-2-one (VIIIa) was synthesized similarly to compounds **VIIa–VIIId** by method *b*, using 0.02 mol each of 3,5,5-trimethyl-6-phenyl-2,3,5,6-tetrahydropyrane-2,4-dione and 4-bromobenzyl bromide. Yield 11%, mp 174–175°C (from acetone). ^{1}H NMR spectrum ($CDCl_3$ + CCl_4), δ, ppm: 0.90 s, 1.03 s (6H, Me_2), 2.00 s (3H, Me), 4.87 d, 5.23 d (2H, CH_2, *J* 12 Hz), 5.03 s (1H, CH), 7.23 d, 7.53 d (4H, 4-BrC_6H_4), 7.30 s (5H, C_6H_5). Found, %: C 62.70; H 5.16. $C_{21}H_{21}BrO_3$. Calculated, %: C 62.84; H 5.24.

α,α'-Bis(3,5,5-trimethyl-6-phenyl-2,4-dioxo-2,3,5,6-tetrahydropyran-3-yl)-*p*-xylene. *a*. The synthesis was performed by procedure *a* for compounds **VIIa–VIId**, using 0.04 mol of 3,5,5-trimethyl-6-phenyl-2,3,5,6-tetrahydropyrane-2,4-dione and 0.02 mol of α,α'-dibromo-*p*-xylene. Yield 10%, mp 275–276°C (from acetonitrile). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.72 s, 0.93 s (6H, Me_2), 1.47 s (3H, Me), 2.93 d, 3.30 d (2H, CH_2), 3.87 s (1H, CH), 7.00 s (5H, C_6H_5), 6.87–7.10 m (4H, C_6H_4). Found, %: C 76.24; H 6.62. $C_{36}H_{38}O_6$. Calculated, %: C 76.33; H 6.71.

b. The synthesis was performed by procedure *b* described for compounds **VIIa–VIId**. Yield 6%, mp 195–196°C (from acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.70 s, 0.88 s (6H, Me_2), 1.50 s (3H, Me), 2.92 d, 3.33 d (2H, CH_2), 3.57 s (1H, CH), 7.00 s (5H, C_6H_5), 6.73–7.33 m (4H, C_6H_4). Found, %: C 76.19; H 6.65. $C_{36}H_{38}O_6$. Calculated, %: C 76.33; H 6.71. Isomer with mp 275–276°C (from acetone). Yield 54%. ^{1}H NMR spectrum corresponds to that given for the product prepared by method *a*.

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