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SYNTHESIS OF DERIVATIVES OF OF Δ^2-IMIDAZOLIN-5-ONE AND IMIDAZOLIDINE CONTAINING RESIDUES OF STERICALLY-HINDERED PHENOLS

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1-Substituted 4-benzylidene-2-{β-[3,5-di(tert-butyl)-4-hydroxyphenyl]vinyl}-4-benzylidene-Δ^2-imidazolin-5-ones have been synthesized by the interaction of azomethines and N-acylhydrazones (derivatives of 3,5-di(tert-butyl)-4-hydroxybenzaldehyde) with 4-benzylidene-2-methyloxazol-5-one. The acylation of 1,2-bis[3,5-di(tert-butyl)-4-hydroxy-benzylideneamino]ethane with acid chlorides in acetonitrile in the presence of triethylamine leads to 1,3-diacyl-2-[3,5-di(tert-butyl)-4-hydroxyphenyl]imidazolidine.

Keywords: azomethines, N-acylhydrazones, imidazolidines, imidazolines, oxazolones, sterically-hindered phenols, condensation.

Among the derivatives of Δ^2-imidazoline containing residues of sterically-hindered phenols, inhibitors of cyclooxygenase and of 5-lipoxygenase [1], α-adrenoblockers [2, 3], low toxicity anti-inflammatory preparations [1, 4], and also substances with marked hypolipidemic [5], hypertensive [6], and antihypertensive action [2, 3, 7] are found. In addition, compounds of this type are of interest as highly effective antimicrobial additives for reactive fuel [8], inhibitors of hydrosulfide corrosion [9], and thermal polymerization of vinylaromatic monomers [10].

In the present work, continuing investigations on the synthesis of imidazolines with a shielded phenolic residue [11, 12], we report the preparation of Δ^2-imidazolin-5-ones and imidazolidines containing 3,5-di(*tert*-butyl)-4-hydroxyphenyl groups, using as synthons azomethines and N-acylhydrazones, *viz*. derivatives of 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde.

On interaction with benzylideneimines 4-arylidene-2-methyloxazol-5-ones are converted into 5-arylidene-2-styryl-Δ^2-imidazolin-5-ones [13-15]. The reaction probably comprises an initial Michael addition of the activated methyl group of the oxazol-5-one to the CH=N bond of the azomethine with subsequent recyclization of the resulting adducts into derivatives of Δ^2-imidazolin-5-one.

In the present work we decided to use this method for the synthesis of Δ^2-imidazolin-5-ones containing a shielded phenolic residue. For this purpose we investigated the interaction of 4-benzylidene-2-methyloxazol-5-one with N-alkyl(aryl, heteryl)-3,5-di(*tert*-butyl)-4-hydroxybenzylideneamines **1a-e**, and also with N-acylhydrazones of 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde **1f,g**.

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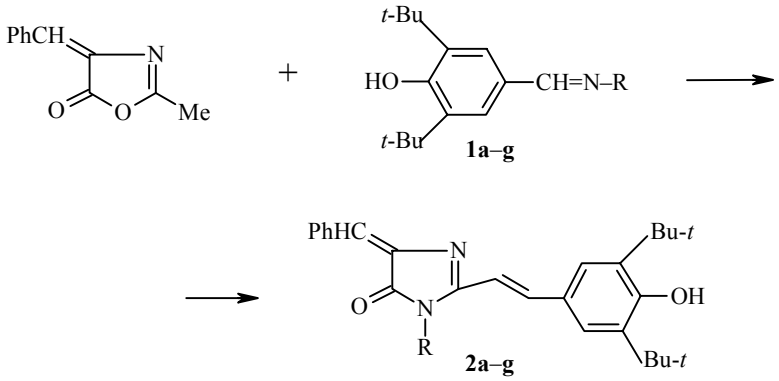
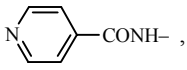
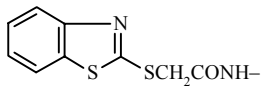


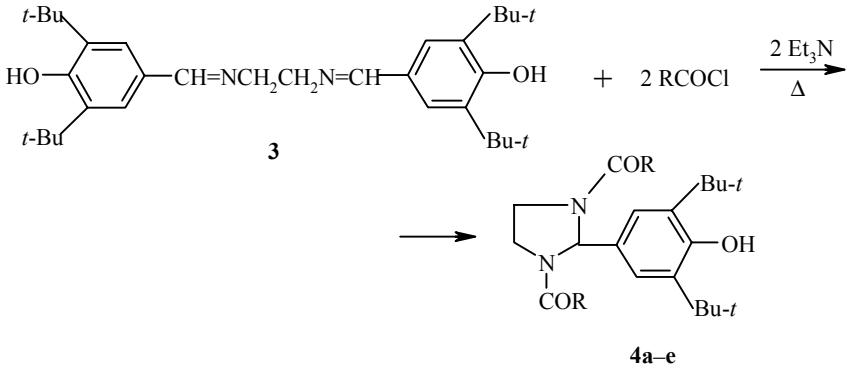
1, **2** **a** R = C_8H_{17}, **b** R = Ph, **c** R = Bn, **d** R = 4-HOC_6H_4, **e** R = 2-thiazolyl,

f R =  , **g** R = 

It was established that brief boiling of equimolar amounts of the reactants in acetic acid formed 1-R-4-benzylidene-2-{β-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]vinyl}-Δ^2-imidazolin-5-ones **2a-g** in 67-80% yield. On carrying out the reaction in alcohol or dioxane (boiling, 5-6 h) only starting materials were isolated from the reaction mixture.

It is known [16] that bisazomethines obtained from ethylenediamine and aldehydes interact with acid chlorides in polar solvents (such as acetonitrile) to give as the sole reaction product the difficultly available 2-substituted 1,3-diacylimidazolidines. It seemed of interest in this connection to carry out the analogous condensation using 1,2-bis[3,5-di(*tert*-butyl)-4-hydroxybenzylideneamino]ethane (**3**) as the initial bisazomethine.

By acylating bisazomethine **3** with aromatic and heteroaromatic acid chlorides in acetonitrile (boiling, 2-3 h) in the presence of triethylamine (molar ratios 1:2:2) the 1,3-diacyl-2-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]imidazolidines **4a-e** were formed in good yield (see Table 1).



a R = Ph, **b** R = 4-ClC_6H_4, **c** R = 4-$O_2NC_6H_4$, **d** R = 2-furyl, **e** R = 2-thienyl

It should be noted that on carrying out the reaction of bisazomethine **3** with benzoyl chloride and triethylamine in a low polarity solvent such as benzene (ε = 2.28) or dichloromethane (ε = 8.9), the yield of the target 1,3-diaroylimidazolidine **4a** did not exceed 28-33% even after boiling for 10-12 h. Significant resinification of the reaction mixtures was observed in these cases.

TABLE 1. Characteristics of the Synthesized Derivatives of Δ^2-Imidazolin-5-one **2a-g** and Imidazolidine **4a-e**

Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C*	*Rf**[2]	^{1}H NMR spectrum, δ, ppm. (*J*, Hz)*[3]	Yield, %
		C	H	N				
1	2	3	4	5	6	7	8	9
2a	$C_{34}H_{46}N_2O_2$	79.26 / 79.37	9.05 / 8.95	5.63 / 5.45	87-88	0.81	1.15 (3H, t, Me); 1.50 (18H, br. s, *t*-Bu); 1.62-1.88 (12H, m, CH_2); 2.56 (2H, t, CH_2N); 5.05 (1H, s, OH); 6.60 (1H, d, CH=CH, *J* = 16.3); 6.86-7.01 (5H, m, Ph); 7.14 (2H, s, H_{Ar}); 7.30 (1H, d, CH=CH, *J* = 16.3); 7.94 (1H, s, PhCH=)	70
2b	$C_{32}H_{34}N_2O_2$	80.18 / 80.33	7.04 / 7.11	6.03 / 5.85	146.0-147.5	0.66	1.55 (18H, br. s, *t*-Bu); 5.12 (1H, s, OH); 6.64 (1H, d, CH=CH, *J* = 16.7); 6.80-6.94 (10H, m, 2Ph); 7.18 (2H, s, H_{Ar}); 7.34 (1H, d, CH=CH, *J* = 16.7); 8.14 (1H, s, PhCH=)	63
2c	$C_{33}H_{36}N_2O_2$	80.63 / 80.49	7.24 / 7.32	5.87 / 5.69	134-135	0.72	1.62 (18H, s, *t*-Bu); 2.37 (2H, s, $PhCH_2$); 4.96 (1H, s, OH); 6.72 (1H, d, CH=CH, *J* = 16.0); 6.92-7.06 (10H, m, 2Ph); 7.18 (2H, s, H_{Ar}); 7.34 (1H, d, CH=CH, *J* = 16.0); 8.05 (1H, s, PhCH=)	75
2d	$C_{32}H_{34}N_2O_3$	77.54 / 77.73	6.75 / 6.88	5.54 / 5.67	167-168.5	0.57	1.56 (18H, s, *t*-Bu); 4.98 (1H, s, OH); 5.49 (1H, s, OH); 6.65 (1H, d, CH=CH, *J* = 17.2); 7.00-7.24 (6H, m, H_{Ar}); 7.38 (1H, d, CH=CH, *J* = 17.2); 8.24 (1H, s, PhCH=)	67
2e	$C_{29}H_{31}N_3O_2S$	71.86 / 71.75	6.26 / 6.39	8.47 / 8.65	180-182	0.63	1.57 (18H, s, 2 *t*-Bu); 5.10 (1H, s, OH); 6.66 (1H, d, CH=CH, *J* = 16.0); 6.78 (1H, d, 5-H_{Het}, J_{45} = 3.5); 6.92-7.02 (5H, m, Ph); 7.18 (2H, s, H_{Ar}); 7.23 (1H, d, 4-H_{Het}, J_{45} = 3.5); (1H, d, CH=CH, *J* = 16.0); 8.12 (1H, s, PhCH=)	80
2f	$C_{32}H_{34}N_4O_3$	73.40 / 73.56	6.64 / 6.51	10.86 / 10.73	154.0-155.5	0.40	1.64 (18H, s, *t*-Bu); 5.03 (1H, s, OH); 6.70 (1H, d, CH=CH, *J* = 16.6); 6.94-6.98 (5H, m, Ph); 7.10 (2H, s, H_{Ar}); 7.30 (1H, d, CH=CH, *J* = 16.6); 7.72-7.88 (4H, m, H_{Het}); 8.20 (1H, s, PhCH=); 10.48 (1H, br. s, NH)	61

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
2g	$C_{35}H_{36}N_4O_3S_2$	67.16 / 67.30	5.61 / 5.77	9.18 / 8.97	162-163	0.52	1.52 (18H, s, *t*-Bu); 3.72 (2H, s, CH_2CO); 4.94 (1H, s, OH); 6.72 (1H, d, CH=CH, *J* = 17.2); 6.88-6.92 (5H, m, Ph); 7.15 (2H, s, H_{Ar}); 7.33 (1H, d, CH=CH, *J* = 17.2); 7.82-7.94 (4H, m, H_{Het}); 8.20 (1H, s, PhCH=); 10.06 (1H, br. s, NH)	66
4a	$C_{31}H_{36}N_2O_3$	76.63 / 76.86	7.32 / 7.44	6.02 / 5.78	Oil	0.84	1.54 (18H, s, *t*-Bu); 3.90-4.26 (4H, m, $2CH_2$); 5.05 (1H, s, OH); 7.05 (1H, br. s, 2-H); 7.16 (2H, s, H_{Ar}); 7.22-7.29 (10H, m, 2Ph)	62
4b	$C_{31}H_{34}Cl_2N_2O_3$	67.41 / 67.27	6.06 / 6.14	4.92 / 5.06	122.0-123.5	0.60	1.64 (18H, s, *t*-Bu); 4.42-4.60 (4H, m, $2CH_2$); 4.98 (1H, s, OH); 6.90 (1H, br. s, 2-H); 7.12 (2H, s, H_{Ar}), 7.66-7.70 (4H, m, H_{Ar}); 8.00-8.05 (4H, m, H_{Ar})	56
4c	$C_{31}H_{34}N_4O_7$	64.70 / 64.81	6.05 / 5.92	10.04 / 9.76	138-140	0.52	1.50 (18H, s, *t*-Bu); 3.96-4.37 (4H, m, $2CH_2$); 5.18 (1H, s, OH); 7.04 (1H, br. s, 2-H); 7.20 (2H, s, H_{Ar}); 7.78-7.83 (4H, m, H_{Ar}); 8.18-8.23 (4H, m, H_{Ar})	60
4d	$C_{27}H_{32}N_2O_5$	70.01 / 69.83	6.82 / 6.90	5.87 / 6.03	Oil	0.70	1.58 (18H, s, *t*-Bu); 4.10-4.38 (4H, m, $2CH_2$); 4.96 (1H, s, OH); 6.58 (2H, dd, 3-H_{Het}, J_{35} = 0.9); 6.92 (2H, dd, 4-H_{Het}, J_{34} = 3.5); 7.10 (1H, br. s, 2-H) 7.18 (2H, s, H_{Ar}); 7.48 (2H, dd, 5-H_{Het}, J_{45} = 1.8)	65
4e	$C_{27}H_{32}N_2O_3S_2$	65.21 / 65.32	6.56 / 6.45	5.81 / 5.64	87-89	0.82	1.65 (18H, s, *t*-Bu); 4.08-4.50 (4H, m, $2CH_2$); 5.08 (1H, s, OH); 7.12 (1H, br. s, 2-H); 7.22 (2H, s, H_{Ar}); 7.65-7.94 (6H, m, H_{Het})	58

* Compounds **2a-c** from benzene; **2d,e,g, 4c** from 2-propanol; **2f** from dioxane–water 3:1; **4b** from ethanol–water 1:1; **4e** from benzene–hexane 1:1.

*[2] Solvent systems: benzene–acetone, 20:1 (compounds **2a-g**); chloroform–methanol, 30:1 (compounds **4a-e**).

*[3] The spectra of compounds **2a-g**, **4c** were recorded in DMSO-d_6, and of compounds **4a,b,d,e** in $CDCl_3$.

The composition and structures of the synthesized compounds **2a-g** and **4a-e** were confirmed by data of elemental analysis, and IR and ^{1}H NMR spectroscopy. In the IR spectra of Δ^2-imidazolin-5-ones **2a-g** two intense absorption bands were observed at 1680-1690 and 1605-1610 cm^{-1}, assigned respectively to the stretching vibrations of the carbonyl and C=N groups and are typical for oxo derivatives of 4,5-dihydroazoles [15, 17]. Two medium intensity absorption bands were also present in the spectra of these compounds at 3070-3125 and 1665-1670, and an intense band at 970-980 cm^{-1} characteristic of the vibrations of an α,β-disubstituted vinyl grouping with the *E*-configuration [18].

In the IR spectra of compounds **4a-e** there were a series of medium intensity absorption bands at 1160-1170, 1110-1115, and 1035-1050 cm^{-1} characteristic of the vibrations of the imidazolidine ring [17]. The intense absorption maxima at 1645-1650 cm^{-1} must be assigned to the stretching vibrations of the carbonyl group (amide I band) [18].

In addition to the vibrations indicated above there were also absorption bands in the spectra of all the synthesized compounds caused by the sterically-hindered phenol fragment. These were a narrow band at 3640-3655 cm^{-1} (shielded hydroxyl) [10-12, 19], two medium intensity bands at 1210-1250 cm^{-1} assigned to the Ar–OH bond in shielded phenols [20], and two groups of bands at 870-885 and 820-830 cm^{-1} (out-of-plane deformation vibrations of a tetrasubstituted benzene ring).

In the ^{1}H NMR spectra of the synthesized compounds the signal of the hydroxyl proton was a singlet at 4.94-5.18 ppm, which is characteristic of shielded phenols [19, 21]. The signals of the protons of the *tert*-butyl groups were observed as singlets at 1.50-1.65 ppm. The singlet signals at 7.14-7.22 ppm were assigned to the magnetically equivalent protons of the hydroxyaryl fragment [21].

In the spectra of the Δ^2-imidazolin-5-ones the signals of the vinylic protons were displayed as two doublets at 6.60-6.72 and 7.28-7.38 ppm with coupling constant J_{AB} = 16.0-17.2 Hz, which is confirmation of the *E* configuration of the vinylic fragment [18, 22]. The signal of the benzylidene proton was observed as a singlet at low field at 7.94-8.24 ppm which is characteristic of compounds of this type.

In the spectra of compounds **4a-e** the signal of the proton at position 2 of the imidazolidine ring appeared as a broad singlet at low field at 6.90-7.12 ppm. The signals of the methylene group protons (4-CH_2 and 5-CH_2) were observed as expanded multiplets at 3.90-4.60 ppm (ABA'B' spin system [18, 22]). Broadening of the signals of the imidazolidine ring protons may be caused by the weak nonequivalence of the protons of the NCH_2CH_2N grouping due to the quadrupole relaxation of the nitrogen nuclei [16].

EXPERIMENTAL

The IR spectra were taken on a Bruker IFS-48 instrument in KBr disks or in a thin film. The ^{1}H NMR spectra were recorded on a Bruker WP-250 (250 MHz) spectrometer, internal standard was TMS. A check on the progress of reactions and the purity of the compounds obtained was effected by TLC on Al_2O_3 of Brockmann activity grade III, visualization was with iodine vapor.

The initial N-octyl- (**1a**) [23], N-phenyl- (**1b**) [24], N-benzyl- (**1c**) [24], N-(4-hydroxyphenyl)- (**1d**) [24], and N-(2-thiazolyl)-3,5-di(*tert*-butyl)-4-hydroxybenzylideneamine (**1e**) [23], the N-(4-pyridylcarbonyl)-hydrazone (**1f**) [25] and N-(2-benzothiazolylthioacetyl)hydrazone of 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde (**1g**) [26], and also 1,2-bis[3,5-di(*tert*-butyl)-4-hydroxybenzylideneamino]ethane (**3**) [24] were obtained by known methods.

1-R-4-Benzylidene-2-{β-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]vinyl}-Δ^2-imidazolin-5-ones (2a-g). A mixture of azomethine **1a-e** or N-acylhydrazone **1f,g** (10 mmol) and 4-benzylidene-2-methyl-5-oxazolone (1.87 g, 10 mmol) in acetic acid (35 ml) was boiled with stirring for 4 h, cooled to 20°C, and poured into ice water (150 ml). The solid which separated was filtered off, washed on the filter with 3% $NaHCO_3$ solution (2 × 20 ml), dried in vacuum over P_2O_5, and crystallized from a suitable solvent (see Table 1).

1,3-Diacyl-2-[3,5-di(*tert*-butyl)-4-hydroxyphenyl]imidazolidines (4a-e). A solution of the appropriate acid chloride (14 mmol) in anhydrous acetonitrile (10 ml) was added dropwise to a stirred mixture of bisazomethine **3** (3.44 g, 7 mmol) and triethylamine (1.4 g, 14 mmol) in anhydrous acetonitrile (50 ml) at 20°C. The reaction mixture was boiled with stirring for 3 h, then evaporated to dryness under reduced pressure. The residue was extracted with hot chloroform (3 × 20 ml), the extract was concentrated to 12-15 ml, and chromatographed on a column (60 × 4.5 cm) of Al_2O_3 eluting with benzene–methanol, 10:1. After removing the solvent, compounds **4a,d** were obtained as viscous noncrystallizing bright yellow oils, compounds **4b,c,e** were obtained as viscous oils, which crystallized on keeping for 3 days at -15°C with periodic rubbing. The solid substances obtained in this way were crystallized again from a suitable solvent.

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