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SYNTHESIS OF MONO- AND DISUBSTITUTED Δ^2-IMIDAZOLINES CONTAINING FRAGMENTS OF STERICALLY HINDERED PHENOL

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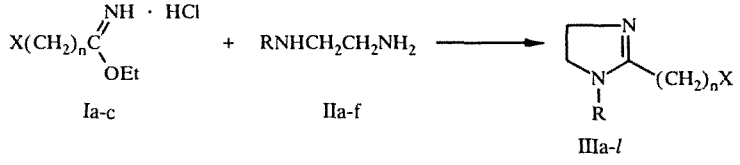
Condensation of hydrochlorides of iminoesters of acids of the sterically hindered phenol series with ethylenediamine and N-monosubstituted ethylenediamines was used to synthesize 2-substituted and 1,2-disubstituted Δ^2-imidazolines containing fragments of 2,6-di(tert-butyl)phenol.

Continuing our study of the synthesis of five- and six-membered nitrogen-containing heterocycles containing fragments of screened phenol [1-4], this paper reports the synthesis of Δ^2-imidazolines containing 3,5-di(tert-butyl)-4-hydroxyphenol substituents. Compounds of this type may be of interest as potential biologically active substances, antioxidants for polymer materials, antimicrobial additives to hydrocarbon fuels [5], etc.

It is well known that 2-substituted and 1,2-disubstituted Δ^2-imidazolines can be obtained by condensation of ethylenediamine or N-monosubstituted ethylenediamines with derivatives of carboxylic acids — esters, nitrile, thioamides, iminoesters, amidines, etc. [6-10]. In the present study, Δ^2-imidazolines of this type were obtained by using condensation of reactive hydrochlorides of iminoesters of carboxylic acids (Ia-c) with ethylenediamine (IIa) and N-monosubstituted ethylenediamines (IIb-f). This method makes it possible to synthesize 2-substituted (IIIa-c) and 1,2-disubstituted Δ^2-imidazolines (IIId-*l*) under mild conditions and in high yields (see Table 1).



Ia-c IIa-f IIIa-*l*

Ia, IIIa, d, g X = 4-HO-3,5-(t-Bu)$_2$C$_6$H$_2$, n = 1; Ib, IIIb, e, h-*l* X = 4-HO-3,5-(t-Bu)$_2$C$_6$H$_2$S, n = 1; Ic, IIIc, f X = 4-HO-3,5-(t-Bu)$_2$C$_6$H$_2$S, n = 2; IIa, IIIa-c R = H; IIb, IIId-f R = PhCH$_2$; IIc, IIIg, h R = NCCH$_2$CH$_2$; IId, IIIi, R = furfuryl; IIe, IIIk R = tetrahydrofurfuryl; IIf, III*l* R = thienyl-2-methyl.

1-(2-Cyanoethyl)-2-substituted Δ^2-imidazoles IIIg, h were also synthesized in 67-69% yield by cyanoethylating Δ^2-imidazolines IIIa, b in the presence of AV-17 anion exchange resin [11]. The properties of the synthesized compounds are listed in Table 1.

The IR spectra of Δ^2-imidazolines IIIa-*l* contain a strong absorption band in the region 1625-1605 cm^{-1}, characteristic of the stretching vibrations of C−N in dihydroazoles [8, 10, 12, 13]. Its position does not change on salt formation; this distinguishes Δ^2-imidazolines from other compounds containing the C=N group, the conversion of which into salts is accompanied by a shift of the analogous band to the high-frequency region [7]. The stretching and deformation vibrations of the methylene groups of the imidazoline ring are respectively represented by absorption bands of variable strength in the regions 2995-2880, 2910-2880, 1455-1445 cm^{-1} (scissor vibrations of CH_2), 1250-1240 cm^{-1} and 1015-1005 cm^{-1} [10, 13, 14]. In the spectra of 2-substituted Δ^2-imidazolines IIIa-c, the stretching vibrations of the N−H group of the imidazoline ring are manifested in the form of a broad absorption band in the region 3375-3345 cm^{-1} [13].

*Deceased.

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TABLE 1. Properties of the Synthesized Compounds

Compound	Empirical formula	mp, °C	R_f (solvent system)	mp., °C*2 of picrates	ESR specrum, δ, ppm,‡ SSCC (J), Hz				Yield, %
					protons of imidazoline ring (4H)	*t*-Bu (18H) s	OH (1H) s	other protons	
IIIa	$C_{18}H_{28}N_2O$	167...168	0,65 (a)	144...145	4,32 s	1,66	4,80	3,63 (2H, s, CH_2), 7,24 (2H, s, H_{arom}), 8,15 (2H, b.s, NH)	83
IIIb	$C_{18}H_{28}N_2OS$	133...135	0,54 (a)	153...154	4,22 s	1,74	4,94	3,92 (2H, s, CH_2), 7,12 (2H, s, H_{arom}), 8,10 (2H, b.s, NH)	72
IIIc	$C_{19}H_{30}N_2OS$	148...149	0,48 (a)	158...159,5	4,30 s	1,50	5,16	4,08...4,16 (4H, m, CH_2CH_2), 7,30 (2H, s, H_{arom}), 8,24 (2H, d.d, NH)	77
IIId	$C_{25}H_{34}N_2O$	Oil	0,56 (b)	147...149	4,08...4,15 m	1,70	5,08	3,40 (2H, d, 1-CH_2, J = 0,8), 3,80 (2H, s, CH_2), 6,78...7,10	70
IIIe	$C_{25}H_{34}N_2OS$	125...127	0,79 (a)	135...137	4,18...4,28 m	1,66	4,88	3,32 (2H, d, 1-CH_2, J = 0,7), 3,95 (2H, s, CH_2), 6,88...7,08 (5H, m, Ph), 7,22 (2H, s, H_{arom})	78
IIIf	$C_{26}H_{36}N_2OS$	118...119,5	0,62 (b)	159...160	4,10...4,22 m	1,58	5,12	3,44 (2H, d, 1-CH_2, J = 0,9), 3,80...4,02 (4H, m, CH_2CH_2), 6,90...7,10 (5H, m, Ph), 7,30 (2H, s, H_{arom})	74
IIIg	$C_{21}H_{31}N_3O$	75...76	0,82 (a)	162...164	4,15...4,26 m	1,60	4,94	2,84 (2H, t, CH_2CN), 3,42 (2H, t, CH_2N), 3,82 (2H, s, CH_2), 7,25 (2H, s, H_{arom})	85
IIIh	$C_{21}H_{31}N_3OS$	83...84	0,58 (b)	145...146	4,08...4,18 m	1,70	5,15	2,70 (2H, t, CH_2CN), 3,54 (2H, t, CH_2N), 3,98 (2H, s, CH_2), 7,18 (2H, s, H_{arom})	82
IIIi	$C_{23}H_{32}N_2O_2S$	Oil	0,48 (b)	130...131	4,22...4,33	1,55	5,02	3,38 (2H, d, 1-CH_2, J = 0,8), 3,90 (2H, s, CH_2), 6,24 (1H, d.d., 3-H of furan J_{35} = 0,9), 6,46 (1H, d.d, 4-Hof furan, J_{34} = 3,3), 7,12 (1H, d.d, 5-H of furan J_{45} = 1,9), 7,30 (2H, s, H_{arom})	76
IIIk	$C_{23}H_{36}N_2O_2S$	Oil (n_D^{20} 1,5482)	0,50 (b)	172...173	4,20...4,35 m	1,66	4,96	1,82...1,96 (4-H, m, 3-and4-CH_2 TGF), 3,10 (2H, d, 1-CH_2, J = 1,3), 3,80 (2H, s, CH_2), 3,97...4,08 (3H, m, CH_2OCH), 7,14 (2H, s, H_{arom})	70
IIIl	$C_{23}H_{32}N_2OS_2$	Oil (n_D^{20} 1,5524)	0,72 (a)	150...152 (dec.)	4,08...4,17 m	1,58	5,10	3,40 (2H, d, 1-CH_2, J = 1,5), 3,96 (2H, s, CH_2), 6,62...7,08 (3H, m, thiophene 7,24 (2H, s, H_{arom})	79

*Compounds recrystallized: IIIa, b) from 20:1 benzene–chloroform mixture; IIIc, e, h) from 5:1 benzene–hexane mixture; IIIf, g) from benzene–cyclohexane mixture.

*2Picrates recrystallized: IIIa, c, d, i) from 2-propanol; IIIb, e, f, h) from aqueous ethanol; IIIg, k, *l*) from aqueous acetone.

*3Spectra of compounds IIIa-c recorded in CH_3COOH; spectra of compounds IIId-f, i-*l*) in CD_3OD; spectra of compounds IIIg h) in $CDCl_3$.

In addition to the absorption bands indicated above, there are also those due to the fragment of sterically hindered phenol: a narrow band at 3655-3640 cm^{-1}, characteristic of screened hydoxyl [1-4, 15]; two bands of medium strength in the range 1260-1210 pertaining to vibration of Ar−OH bonds is screened phenols [16], and two groups of bands in the region 885-870 and 830-820 cm^{-1} (nonplanar deformation vibrations of the tetrasubstituted ring).

In the ESR spectra (see Table 1) of 2-substituted Δ^2-imidazolines IIIa-c taken in CF_3COOH the signals of imidazoline ring protons, with an intensity of four proton units, are manifested as singlets in the range 4.22-4.32 ppm. Spectra of salts of Δ^2-imidazolines IIIa-c formed in CF_3COOH solution do not show any splitting of the signals of methylene protons of the imidazoline ring into a doublet owing to the spin−spin interaction with the hydrogen atom of the NH group, and there are only singlets corresponding to four magnetically equivalent protons. This effect can be explained by the fact that the imidazolinium cation is planar, and the dihedral angle between the N−H bonds and the adjacent C−H bond is close to 90°, resulting in the absence of spin−spin interaction [8, 14]. All the signals of the NH groups of imidazoline rings in the spectra of compounds IIIa-c are represented in the form of broadened singlets with an intensity of two proton units in the range 8.10-8.24 ppm [8].

In the ESR spectra of 1,2-disubstituted Δ^2-imidazolines IIId-*l* the proton signals of the imidazoline ring are manifested in the form of an asymmetric multiplet in the range 4.08-4.35 ppm (AA'BB' system). The proton signals of the methylene groups in the 1 position in the spectra of compounds IIId-f, i-*l* are observed in the form of doublets at 3.10-3.44 ppm with an SSCC of 0.7-1.5 Hz [10]. For all the synthesized Δ^2-imidazolines IIIa-*l*, the proton signals of the hydroxyl groups are represented in the spectra in the form of singlets in the range 4.80-5.16 ppm, this being characteristic of screened phenols [15, 17]. The proton signals of the tert-butyl groups are in the form of singlets in the range 1.50-1.74 ppm. To the two magnetically equivalent protons of the hydroxyaryl fragments correspond singlet signals at 7.14-7.30 ppm [3, 17].

EXPERIMENTAL

The spectra were recorded with a Bruker IFS-48 instrument (suspensions in Vaseline oil or KBr pellets). The ESR spectra were obtained with a Bruker WP-100 SY spectrometer (100 MHz), with TMS as the internal standard. The course of the reaction and purity of the compounds obtained were checked by TLC on Al_2O_3 (Brockmann activity grade III) in the solvent systems 15:1 benzene−methanol (a) and 20:1 CCl−methanol (b); the development was carried out with iodine vapor. The melting points were determined on a Boetius micro hot stage.

The data of ultimate analyses of the synthesized compounds for C, H, and N correspond to the calculated data.

Hydrochlorides of ethyl iminoesters of 3,5-di(tert-butyl)-4-hydroxyphenyl acetic acid (Ia), [3,5-di(tert-butyl)-4-hydroxyphenylthio]acetic acid (Ib), and β-[3,5-di(tert-butyl)-4-hydrophenylthio]propionic acid (Ic) had been synthesized earlier [3]. The initial N-benzyl- (IIb) [18], N-(2-cyanoethyl)- (IIc) [19], N-(furfuryl-2)- (IId) [20], N-tetrahydro(furfuryl-2)- (IIe) [10] and N-tetrahydro(furfuryl-2)- (IIe) [10] and N-(thienyl-2)ethylenediamine (IIf) [21] were obtained by use of the well-known methods indicated above.

General Method of Synthesis of 2-Substituted (IIIa-c) and 1,2-Disubstituted Δ^2-Imidazolines (IIId-*l*). To an agitated solution of 10 mmoles of ethylenediamine IIa-f in 15 ml of absolute methanol at 0°C is added in portions 10 mmoles of hydrochloride of iminoester Ia-c. The reaction mixture is agitated for 1 h at 20°C and 2 h at 60°C, cooled to 0°C, and a solution of sodium methoxide, prepared from 0.23 g (10 mmoles) of sodium in 8 ml of absolute methanol, is added dropwise. The mixture obtained is allowed to stand for 1 h at 0°C, the NaCl precipitate is filtered off, and the filtrate is evaporated at reduced pressure. The residue is extracted with hot acetone (2 × 15 ml), the extract is concentrated to a volume of 5-7 ml and chromatographed on a column with Al_2O_3 (80 × 4.5 cm), and the elution is carried out with a mixture of 15:1 benzene−methanol or 20:1 chloroform−acetone (when Δ^2-imidazolines IIIh-*l* are obtained). The isolated compounds are additionally purified by crystallization from suitable solvents (see Table 1) or rechromatographed on a column with Al_2O_3 (Δ^2-imidazolines IIId, i-*l*).

2-[3,5-Di(tert-butyl)-4-hydrophenylmethyl]-1-(2-cyanoethyl)-Δ^2-imidazoline (IIIg). To an agitated mixture of 2.88 g (10 mmoles) of Δ^2-imidazoline IIIa and 0.8 g of anion-exchanger resin AV-17 in 30 ml of ethanol is added dropwise 1.06 g (20 mmoles) of freshly distilled acrylonitrile. The reaction mixture is agitated for 1.5 h at 60°C and cooled to 20°C, the catalyst is filtered off, and the filtrate is evaporated at reduce pressure. The residue is chromatographed on a column with Al_2O_3 (90 × 4.5 cm), a 15:1 mixture of benzene−methanol is used for elution, and 2.28 g (67%) of Δ^2-imidazoline IIIg is obtained.

Similarly, compound IIIh is synthesized from Δ^2-imidazoline IIIb in 69% yield.

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