SYNTHESIS AND PROPERTIES OF FURAN DERIVATIVES.

3.* SYNTHESIS OF 1,2-DISUBSTITUTED Δ^2-IMIDAZOLINES CONTAINING FURFURYL AND TETRAHYDROFURFURYL GROUPS

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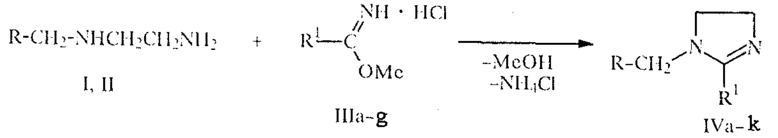
The condensation of N-furfuryl- and N-tetrahydrofurfurylethylenediamines with hydrochloride salts of iminoesters of carboxylic acids gives 1,2-disubstituted Δ^2-imidazolines containing furfuryl or tetrahydrofurfuryl groups at N^1.

In a continuation of our work on the synthesis of furyl-containing heterocycles [2-4], we report the preparation of 1,2-disubstituted Δ^2-imidazolines containing a furfuryl or tetrahydrofurfuryl group at N^1.

There is only limited information in the literature on the preparation and properties of Δ^2-imidazolines containing furan fragments [5-8] and there are no data on their tetrahydrofuran analogs. On the other hand, such compounds hold interest as intermediates in organic synthesis [8-10] and as potential biologically active substances.

1,2-Disubstituted Δ^2-imidazolines may be obtained by the condensation of N-monosubstituted ethylenediamines with carboxylic acid derivatives such as esters, nitriles, thioamides, iminoesters, and amidines [6, 10, 11]. However, such reactions involving heteryl-substituted ethylenediamines have not been described in the literature.

In order to obtain these compounds, we used the condensation of N-furfuryl- (I) and N-tetrahydrofurfurylethylenediamines (II) with the reactive hydrochloride salts of iminoesters of carboxylic acids IIIa-IIIg. This method permits us to synthesize 1,2-disubstituted Δ^2-imidazolines IVa-IVk under mild conditions in high yields (Table 1).



I, IVa-f) R = 2-furyl; II, IVg-k) 2-tetrahydrofuryl; IIIa, IVa, g) R^1 = Me; IIIb, IVb, h) R^1 = Ph, IIIc, IVc, i) $R^1 = PhCH_2$; IIId, IVd) $R^1 = Me_2C(NO_2)CH_2CH_2$; IIIe, IVe, j) R^1 = 4-nitro-2-furyl; IIIf, IVf) R^1 = 3-indolylmethyl; IIIg, IVk) R^1 = 3-indolyl.

The IR spectra of Δ^2-imidazolines IVa-IVk have strong bands at 1625-1605 cm^{-1} characteristic for C=N stretching vibrations in dihydroazoles [12, 13]. The stretching and deformation vibrations of the methylene groups of the imidazoline ring give rise to bands of variable intensity at 2990-2980, 2915-2875, and 1450-1440 cm^{-1} (CH_2 scissor vibrations) 1255-1240, and

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*For communication 2, see [1].

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TABLE 1. Characteristics of Compounds Synthesized

Compound	Chemical formula	n_D^{20}	R_f*	mp, °C picrates*2	PMR spectrum, δ, ppm*3	Yield, %
IVa	$C_9H_{12}N_2O$	1,5158*4	0,36 (a)	134...135	2,35 (3H, s CH_3), 3,38 (2H,d, 1-CH_2, J = 0,8 Hz), 4,08...4,20 (4H, m, CH_2CH_2), 6,24... 6,54 (1H,d.d, 4-H, J_{34} = 3,2 Hz), 7,25 (1H,d.d, 5-H, J_{45} = 1,9Hz)	68
IVb	$C_{14}H_{14}N_2O$	1,5530*4	0,50 (a)	124...125	3,32 (2H, d, 1-CH_2, J = 0,9 Hz), 4,18...4,28 (4H, m, CH_2CH_2), 6,16 (1H, d.d,3-H, J_{35} = = 0,8 Hz), 6,48 (1H, d.d, 4-H, J = 3,5 Hz), 6,78...7,15 (5H,m, H_{arom}) 7,28 (1H,d.d, 5-H, J_{45} = 1,7 Hz)	70
IVc	$C_{15}H_{16}N_2O$	1,5234	0,44 (a)	121...121,5	3,48 (2H,d , 1-CH_2, J = 0,7 Hz), 3,83 (2H,s , 2-CH_2), 4,16...4,28 (4H,m , CH_2CH_2), 6,18 (1H, d.d, 3-H, J = 0,7 Hz), 6,62 (1H,d.d, 4-H, J_{34} = 3,4 Hz), 6,80...7,08 (5H,m , H_{arom}),7,24 (1H, d.d, 5-H, J_{45} = 1,8 Hz)	85
IVd	$C_{13}H_{19}N_3O_3$	1,4927	0,40 (a)	—	1,86 (6H,br.s , CH_3), 3,40 (2H,d, 1-CH_2, J = 0,8 Hz), 3,85...4,22 (8H,m , CH_2), 6,24 (1H, d.d, 3-H, J_{35} = 0,9 Hz), 6,46 (1H,d.d, 4-H, J_{34} = 3,3Hz), 7,24 (1H,d.d, 5-H, J_{45} = 1,7Hz)	86
IVe	$C_{12}H_{11}N_3O_4$	1,4834	0,74 (b)	139...140,5	3,34 (2H,d, 1-CH_2, J = 0,7 Hz), 4,21...4,32 (4H,m,, CH_2CH_2), 6,25 (1H, d.d,3-H, J_{35} = = 0,9 Hz), 6,52 (1H,d.d, 4-H, J_{34} = 3,7 Hz), 6,78 (1H,d , 3-H, J_{34} = 4,0Hz),7,26 (1H, d.d, 5-H, J_{45} = 1,9 Hz), 7,54 (1H, d, 4-H, J_{34} = 4,0 Hz)	71
IVf	$C_{17}H_{17}N_3O$	—	0,42 (c)	179...180,5 (c dec.)	3,46 (2H, d, 1-CH_2, J = 0,7 Hz), 4,12...4,26 (4H,m, CH_2CH_2), 4,36 (2H,s, CH_2), 6,28 (1H, d.d, 3-H, J_{35} = 0,8 Hz), 6,46 (1H, d.d, 4-H, J_{34} = 3,8 Hz), 6,85...7,10 (4H, m, H_{arom}), 7,27 (1H, d.d,5-H, J_{45} = 1,7 Hz), 7,58 (1H, d,2-H indole, J = 1,2 Hz), 8,08 (1H, br.s NH)	82
IVg	$C_9H_{16}N_2O$	1,5582*4	0,18 (b)	195...198	1,70...2,12 (4H, m, 3-and 4-CH_2 THF), 2,30 (3H, s, CH_3), 3,15 (2H, d, 1-CH_2, J = 2,6 Hz), 3,76...4,08 (3H, m, CH_2OCH), 4,20...4,34 (4H, m, CH_2CH_2)	63
IVh	$C_{14}H_{18}N_2O$	1,5562*4	0,26 (c)	133...134	1,74...2,25 (4H, m, 3-and 4-CH_2 THF), 3,26 (2H,d, 1-CH_2, J = 1,8Hz), 3,70...4,12 (3H, m, CH_2OCH), 4,18...4,30 (4H, m, CH_2CH_2), 6,74...7,08 (5H,m, H_{arom})	72
IVi	$C_{15}H_{20}N_2O$	1,5355	0,39 (c)	168...169	1,82...2,18 (4H, m, 3-and 4-CH_2 THF), 3,24 (2H, d, 1-CH_2, J = 2,0 Hz), 3,78 (2H, s, 2-CH_2), 3,89...4,08 (3H, m, CH_2OCH), 4,18...4,32 (4H, m, CH_2CH_2), 6,89...7,10 (5H, m, H_{arom})	87
IVj	$C_{12}H_{15}N_3O_4$	1,5014	0,64 (c)	170...172	1,74...2,16 (4H,m, 3-and 4-CH_2 THF), 3,10 (2H, d, 1-CH_2, J = 2,3 Hz), 3,72...4,00 (3H, m, CH_2OCH), 4,18...4,27 (4H, m, CH_2CH_2), 6,52 (1H, d, 3-H furan, J_{34} = 3, 9Hz), 7,32 (1H, d, 4-H furan)	80
IVk	$C_{16}H_{19}N_3O$	—	0,51 (c)	145...146 (c dec.)	1,84...2,25 (4H,m, 3-and 4-CH_2 THF), 3,18 (2H,d, 1-CH_2, J = 1,9Hz), 3,84...4,10 (3H,m, CH_2OCH), 4,18...4,35 (4H, m, CH_2CH_2), 6,74...6,92 (4H, m, H_{arom}), 7,35 (1H, d, 2-H indole, J = 1,4 Hz), 8,02 (1H, br.s, NH)	69

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*Solvents given in parentheses.

*2Picrates crystallized from methanol (IVa, IVc), aqueous ethanol (IVb, IVg-IVk), from aqueous acetone (IVf).

*3The spectra of IVa, IVd, IVg, and IVi were taken in $CDCl_3$, the spectra of IVb, IVc, IVe, IVh, and IVj were taken in CD_3OD, the spectra of IVf and IVk were taken in DMSO-d_6.

*3bp, °C (1 mm Hg): 103-104°C (IVa), 144-146 (IVb), 97-100 (IVg), and 159-160 (IVh).

1015-1000 cm^{-1} [13, 14]. The spectra of all the compounds have bands at 1295-1280 and 1030-1020 cm^{-1} assigned to C—N stretching vibrations [14]. In addition to these vibrations, the spectra of Δ^2-imidazolines IVa-IVf also have bands due to the 2-substituted furan fragment [12]: 3170-3160 (ν_{CH}), 1590-1560, 1520-1500, 1395-1370 (ν_{ring}) 1145-1035 (β_{CH}), 1005-990 (ring breathing vibrations), 960-945 (γ_{CH}), 890-880, and 780-755 cm^{-1} (β_{ring}). The spectra of Δ^2-imidazolines IVg-IVk have bands of variable intensity characteristic for the tetrahydrofuran group [12]: 2960-2875 (ν_{CH}), 1490-1470 (CH_2 scissor vibrations), 1175-1160 and 1070-1060 (ν_{ring}), 970-965 (β_{CH_2}),and 915-895 cm^{-1} (ring breathing vibrations).

The signals for the imidazoline ring protons in the PMR spectra of Δ^2-imidazolines IVa-IVk (see Table 1) appear as an asymmetrical multiplet at 4.08-4.35 ppm (AA'BB' system). The signals of the protons of the methylene groups at N^1 in the spectra of IVa-IVf are seen as doublets at 3.32-3.48 ppm (J = 0.7-0.9 Hz) [15], while these signals in the spectra of IVg-IVk are seen at 3.10-3.26 ppm (J = 1.8-2.6 Hz). The furan ring protons in the spectra of Δ^2-imidazolines IVa-IVf give three groups of signals as a doublet of doublets at 6.16-6.28 ppm (3-H, J_{35} = 0.7-0.9 Hz), 6.46-6.62 (4-H, J_{34} = 3.2-3.8 Hz), and 7.24-7.28 ppm (5-H, J_{45} = 1.7-1.9 Hz), which is characteristic for 2-substituted furans [12, 15]. The spectra of Δ^2-imidazolines IVg-IVk have upfield signals for the four protons of the 3- and 4-CH_2 groups of the tetrahydrofuran ring as multiplets at 1.70-2.25 ppm [16]. The signals of the protons of the CH_2OCH fragment appear in these spectra as asymmetrical multiplets at 3.70-4.12 ppm, which is characteristic for 2-substituted tetrahydrofurans.

EXPERIMENTAL

The IR spectra were taken neat and in methylene chloride on a UR-20 spectrometer. The PMR spectra were taken on a Bruker WP-80 SY spectrometer with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Brockmann grade-III-activity alumina in 10:1 heptane—2-propanol (a), 20:1 CCl_4—methanol (b), and 10:1 benzene—methanol (c). The plates were developed with iodine vapor.

N-Furfurylethenediamine (I) [17], and the hydrochloride salts of the iminoesters of acetic (IIIa) [18], benzoic (IIIb) [18], phenylacetic (IIIc) [19], 4-methyl-4-nitropentanoic (IIId) [20], 5-nitrofuran-2-carboxylic (IIIe) [6], 3-indolylacetic (IIIf) [21], and 3-indolecarboxylic acids (IIIg) [21] were obtained according to reported procedures.

The elemental analysis data for C, H, and N for IVa-IVh were in accord with the calculated values.

N-Tetrahydrofurfurylethylenediamine (II). A sample of 24.0 g (0.2 mole) 2-chloromethyltetrahydrofuran was added dropwise to a stirred solution of 50.0 g (1 mole) 100% ethylenediamine in 150 ml absolute ethanol at 45-50°C. The reaction mixture was heated at reflux with stirring for 24 h and cooled to 0°C. A solution of sodium ethylate prepared from 4.6 g (0.2 g-atom) sodium in 150 ml absolute ethanol was added dropwise with stirring. The mixture was maintained for 1 h at 0°C and the NaCl precipitate was filtered off. The filtrate was evaporated at reduced pressure and the residue was distilled in vacuum, collecting the fraction with bp 92-95°C (6 mm Hg) to give 12.9 g (45%) diamine II, n_D^{20} 1.4756; dipicrate, mp 165-166°C (from ethanol) (bp 106-107°C (10 mm Hg), n_D^{20} 1.4750 [17]).

1-Furfuryl-2-methyl-Δ^2-imidazoline (IVa). A sample of 5.5 g (50 mmoles) iminoester IIIa was added in portions to a stirred solution of 7.0 g (50 mmoles) diamine I in 20 ml absolute methanol at 0°C. The reaction mixture was stirred for 1 h at 0°C and for 2 h at 60°C and cooled to 0°C. A solution of sodium methylate prepared from 1.15 g (20 mmoles) sodium in 20 ml absolute methanol was added dropwise with stirring. The mixture was maintained for 1 h at 0°C and the NaCl precipitate was filtered off. The solvent was removed and the residual oil was distilled in vacuum in an inert gas stream.

Δ^2-Imidazolines IVb, IVg, and IVh were obtained analogously.

1-Furfuryl-2-benzyl-Δ^2-imidazoline (IVc) was obtained from 3.5 g (25 mmoles) diamine I and 4.2 g (25 mmoles) iminoester IIIc as described above for IVa. The residue after removal of the solvent was extracted with three hot 50-ml chloroform portions. The extract was evaporated at reduced pressure and the residual oil was subjected to chromatography on a 90×4.5-cm alumina column using 20:1 chloroform—ethanol as the eluent.

Δ^2-Imidazolines IVd-IVf and IVi-IVk were obtained analogously.

The Δ^2-imidazoline products IVa-IVk are colored oils with good solubility in alcohols, acetone, chloroform, methylene chloride, dioxane, and acetonitrile. These compounds are insoluble in water, hydrocarbons, and ether. All these compounds, except IVd, form picrates with a sharp melting point.

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