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Synthesis of 2t-Substituted-1r,3c-BIS(2′-Hydroxy-5-Substituted-Benzyl)-Imidazolidines by Reaction of 1,3-BIS(2′-Hydroxy-5′-Substituted-Benzyl)-Imidazolidines with Aromatic Aldehydes

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SYNTHETIC COMMUNICATIONS, 30(11), 2029–2040 (2000)

SYNTHESIS OF 2*t*-SUBSTITUTED-1*r*,3*c*-BIS(2'-HYDROXY-5'-SUBSTITUTED-BENZYL)-IMIDAZOLIDINES BY REACTION OF 1,3-BIS(2'-HYDROXY-5'-SUBSTITUTED-BENZYL)-IMIDAZOLIDINES WITH AROMATIC ALDEHYDES

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Abstract: A one-step synthesis of 2*t*-substituted-1*r*,3*c*-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines from 1,3-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines and aromatic aldehydes is reported. The relative stereochemistry of the five-membered ring was evident from ^{1}H NMR measurements combined with MMX calculations.

In a previous paper[1] we reported that the aminal carbon atom of 1,3-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines **(1)** is a reactive site towards formaldehyde that leads to the formation of 3,3'-ethylene-*bis*(3,4-dihydro-6-substituted-2H-1,3-benzoxazines) **(2)**. In continuation of our studies on the

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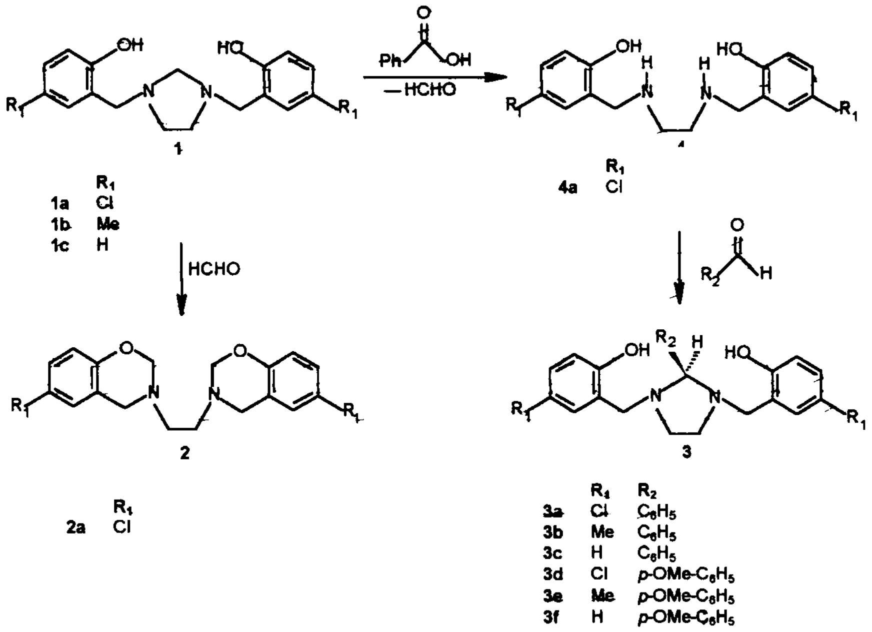
reactivity of these molecules, we describe our results using some aliphatic aldehydes like acetaldehyde, propionaldehyde and butyraldehyde, and some aromatic aldehydes like benzaldehyde, *p*-methoxybenzaldehyde, salicylaldehyde and *m*-nitrobenzaldehyde.

From the reaction of imidazolidines **1a-c** with aliphatic aldehydes, only complex reaction mixtures with resinous aspect were obtained. On the other hand, imidazolidines **1a-c** reacted with benzaldehyde and *p*-methoxybenzaldehyde affording 2*t*-substituted-1*r*,3*c*-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines[3] as the main reaction product. Furthermore, from the reaction of **1a** with benzaldehyde, along with the corresponding imidazolidine (**3a**), 3,3'-ethylene-



Scheme 1

bis(6-chloro-3,4-dihydro-2H-1,3-benzoxazines)[1] (**2a**), N,N'-*bis*(5'-chloro-2'-hydroxybenzyl)-ethylenediamine (**4a**) and benzoic acid were isolated. In the case of *m*-nitrobenzaldehyde and salicylaldehyde, no transformation was observed at conditions ranging from 72 hours at 60°C to 5 days under reflux.

The structure of compounds **3a-f** and **4a** were assigned on the basis of their spectroscopic data and the relative stereochemistry for **3a-f** was deduced from ^1H NMR measurements and MMX calculations[2] as detailed below.

EXPERIMENTAL

IR spectra were recorded from KBr pellets on a Perkin-Elmer 1750 FT-IR. ^1H and ^{13}C NMR were measured on a Brucker AC-500 spectrometer operating at 500 and 125 MHz, respectively or on a Varian XL-300GS spectrometer operating at 300 MHz for ^1H and 75.4 MHz for ^{13}C. In all cases $CDCl_3$ was used with TMS as the internal standard. Mass spectra were obtained by direct insertion using a Shimadzu 9020 DF mass spectrometer in the low resolution electron impact mode using an ionization potential of 20 eV. Melting points (uncorrected) were determined on an Electrothermal 9100 melting point apparatus. All new compounds gave satisfactory elemental analysis.

MMX calculations.

Molecular models were generated using MMX force field calculations which is a derived version of the MM2 program developed by N.L. Allinger (QCPE 395), University of Georgia, as implemented in the PC MODEL program.[2]

Synthesis of 2*t*-phenyl-1*r*,3*c*-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines (3a-c).

2*t*-phenyl-1*r*,3*c*-*bis*(2'-hydroxy-5'-chloro-benzyl)-imidazolidine (3a)

1,3-bis(2'-hydroxy-5'-chloro-benzyl)-imidazolidine (**1a**) (1.13 g, 3.2 mmol) was dissolved in 1,4-dioxane (4.0 mL) and benzaldehyde (0.65 mL, 6.4 mmol) was added. The reaction mixture was heated at 60° and stirred during 72 h. After this time, the solvent was evaporated at reduced pressure (20 mm Hg). The obtained resinous solid was purified by column chromatography on silica gel (100 g, Benzene: AcOEt 8:2) to afford **3a** in 40% yield. Colorless solid, mp 173-175°C. Anal. Calc. for $C_{23}H_{22}N_2O_2Cl_2$: C, 64.34; H, 5.17; N, 6.52; Cl, 16.52. Found: C, 64.36; H, 5.15; N, 6.53; Cl, 16.56.

2*t*-phenyl-1*r*,3*c*-*bis*(2'-hydroxy-5'-methyl-benzyl)-imidazolidine (3b)

1,3-bis(2'-hydroxy-5'-methyl-benzyl)-imidazolidine (**1b**) (1.0 g, 3.2 mmol) was dissolved in 1,4-dioxane (5.0 mL) and benzaldehyde (0.65 mL, 6.4 mmol) was added. The reaction mixture was heated at 60°C and stirred during 72 h. After this time, the solvent was evaporated at reduced pressure (20 mm Hg). The obtained resinous solid was purified by column chromatography on silica gel (80 g, Benzene: AcOEt 8:2) to afford **3b** in 29% yield. Colorless solid, mp 151-152°C. Anal. Calc. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.31; H, 7.25; N, 7.23.

2*t*-phenyl-1*r*,3*c*-*bis*(2'-hydroxy-benzyl)-imidazolidine (3c)

1,3-bis(2'-hydroxy-benzyl)-imidazolidine (**1c**) (0.9 g, 3.2 mmol) was dissolved in

1,4-dioxane (5.0 mL) and benzaldehyde (0.65 mL, 6.4 mmol) was added. The reaction mixture was heated at 60°C and stirred during 72 h. After this time, the solvent was evaporated at reduced pressure (20 mm Hg). The obtained resinous solid was purified by column chromatography on silica gel (80 g, Benzene: AcOEt 8:2) to afford **3c** in 35% yield. Colorless solid, mp 175-177°C. Anal. Calc. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.63; H, 6.72; N, 7.78.

Synthesis of 2*t*-(4"-methoxyphenyl)-1*r*,3*c*-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines (3d-f)

2*t*-(4"-methoxyphenyl)-1*r*,3*c*-*bis*(2'-hydroxy-5'-chloro-benzyl)-imidazolidine (3d). To a solution of 1,3-bis(2'-hydroxy-5'-chloro-benzyl)-imidazolidine (**1a**) (0.5 g, 1.41 mmol) in 1,4-dioxane (4.0 mL), *p*-methoxy benzaldehyde (0.34 mL, 2.83 mmol) was added and the reaction mixture heated under reflux for 50 h. After this time, the solvent was evaporated at reduced pressure (20 mm Hg). The obtained resinous solid was purified by column chromatography on silica gel (80 g, Benzene: AcOEt 8:2) to afford **3d** in 25% yield. Colorless solid, mp 187-189°C. Anal. Calc. for $C_{24}H_{24}N_2O_3Cl_2$: C, 62.75; H, 5.27; N, 6.10; Cl, 15.43. Found: C, 62.76; H, 5.25; N, 6.11; Cl, 15.42

2*t*-(4"-methoxyphenyl)-1*r*,3*c*-*bis*(2'-hydroxy-5'-methyl-benzyl)-imidazolidine (3e). To a solution of 1,3-bis(2'-hydroxy-5'-methyl-benzyl)-imidazolidine (**1b**) (0.44 g, 1.41 mmol) in 1,4-dioxane (4.0 mL), *p*-methoxy benzaldehyde (0.34 mL, 2.83 mmol) was added and the reaction mixture heated under reflux for 50 h. After this time, the solvent was evaporated at reduced pressure (20 mm Hg). The obtained resinous solid was purified by column chromatography on silica gel (80 g, Benzene: AcOEt 8:2) to afford **3e** in 18 % yield. Colorless solid, mp 132-134°C. Anal. Calc. for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.63; H, 7.25; N, 6.70

2*t*-(4"-methoxyphenyl)-1*r*,3*c*-*bis*(2'-hydroxy-benzyl)-imidazolidine (3f).

To a solution of 1,3-bis(2'-hydroxy-benzyl)-imidazolidine (**1c**) (0.40 g, 1.41 mmol) in 1,4-dioxane (4.0 mL), *p*-methoxy benzaldehyde (0.34 mL, 2.83 mmol) was added and the reaction mixture heated under reflux for 50 h. After this time, the solvent was evaporated at reduced pressure (20 mm Hg). The obtained resinous solid was purified by column chromatography on silica gel (80 g, Benzene: AcOEt 8:2) to afford **3f** in 28 % yield. Colorless solid, mp 160-162°C. Anal. Calc. for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.18. Found: C, 73.84; H, 6.70; N, 7.19.

N,N'-bis(5'-chloro-2'-hydroxybenzyl)-ethylenediamine (4a).

Colorless solid, mp 138°C; ^1H NMR δ 2.85 (4H, *s*, N-CH_2-CH_2-N) 3.90 (4H, *s*, CH_2-Ar), 6.75 (2H, *d*, $J_{3',4'}$ = 8.2 Hz, H-3'), 6.95 (2H, *d*, $J_{4',6'}$ = 2.1 Hz, H-6'), 7.12 (2H, *dd*, $J_{3',4'}$ = 8.2 Hz, $J_{4',6'}$ = 2.1 Hz, H-4'); ^{13}C NMR δ 47.8 (N-CH_2-CH_2-N), 52.2 (CH_2-Ar), 117.8, C-3'), 125.4 (C-1'), 126.0 (C-5'), 129.6 (C-4'), 130.2 (C-6'), 156.2 (C-2').

RESULTS AND DISCUSSION

From the reaction of imidazolidines **1a-c** with acetaldehyde, propionaldehyde

Table 1. Mass Spectra of **3a-f**. *m/z* (rel. int.).

3a	428(M^+,11), 351(33), 287(35), 246(25), 169(40), 141(100), 118(30)
3b	388(M^+,63), 267(100), 239(20), 226(61), 150(25), 121(22)
3c	360(M^+,40), 283(42), 252(13), 180(10), 125(10), 107(100), 91(18)
3d	458(M^+,7), 351(17), 316(38), 276(70),148(91), 141(76), 121(100), 91(19)
3e	418(M^+,7), 311(8), 297(26), 256(24), 177(9), 148(38), 121(100), 91(44)
3f	390(M^+,10), 283(40), 242(12), 121(85), 107(100), 91(35)

and butyraldehyde complex untractable reaction mixtures were obtained, whereas with benzaldehyde and *p*-methoxybenzaldehyde exchange at the aminal position was achieved, to afford the corresponding 2*t*-substituted-1*r*,3*c*-*bis*(2'-hydroxy-5'-substituted-benzyl)-imidazolidines **3a-f**. The best results with *p*-methoxybenzaldehyde were obtained when the reaction mixture was heated in dioxane under reflux. On the other hand, imidazolidines **1a-c** with *m*-nitrobenzaldehyde and salicylaldehyde, after several reaction condition assays, gave no transformation since starting materials were recovered almost quantitatively.

The mass spectra revealed that all compounds have the expected molecular weight and the fragmentation patterns confirm the structures.(Table 1)

The ^1H NMR spectra of **3a-f** (Table 2) show at 2.6 and 3.4 ppm an AA'BB' system[3] corresponding to the CH_2-CH_2 fragment, and AB system signals at 3.3 and 4.0 ppm, corresponding to the benzylic protons. These chemical shifts are in agreement with those described[4] for similar compounds. The aminal methine group of **3a-f** resonates at 3.8 ppm.

Table 2. ^{1}H NMR Chemical Shift Data of **3a-f**.

	3a	**3b**	**3c**	**3d**	**3e**	**3f**
N-CH_2-N	3.80	3.78	3.80	3.75	3.70	3.75
CH_2-CH_2	2.68	2.65	2.67	2.65	2.60	2.63
	3.34	3.32	3.39	3.32	3.28	3.36
Ph-CH_2	3.30	3.27	3.32	3.27	3.22	3.30
	3.96	3.98	4.01	3.98	3.97	4.03
H3'	6.70	6.67	6.94	6.71	6.65	6.97
H4'	7.08	6.92	7.13	7.08	6.90	7.95
H6'	6.92	6.73	6.78	6.92	6.72	6.78
H2", H6"	7.46	7.51	7.52	7.41	7.41	7.44
H3", H5"	7.46	7.44	7.45	6.97	6.95	6.95
H4"	7.46	7.39	7.41	---	---	---
OMe	---	---	---	3.80	3.77	3.78

The ^{13}C assignments for **3a-f** were done by means of heteronuclear correlation experiments (^{13}C-^{1}H) and are summarized in Table 3.

From the reaction of **1a** with benzaldehyde, along with the corresponding imidazolidine **3a**, 3,3'-ethylene-*bis*(6-chloro-3,4-dihydro-2H-1,3-benzoxazine) (**2a**),[1] N,N'-*bis*(5'-chloro-2'-hydroxy-benzyl)-ethylenediamine (**4a**) and benzoic acid were isolated. The ^{1}H and ^{13}C NMR spectra of **4a** were essentially similar to those of **1a**, although they did not show the signals due to the aminal group *ca.* 3.50 and 74.5 ppm respectively, and both, ^{1}H and ^{13}C NMR signals of **4a** are slightly shifted to higher fields.

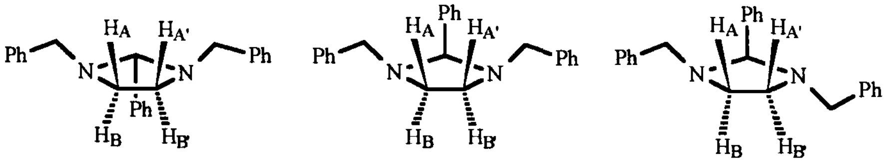
Table 3. ^{13}C NMR Chemical Shift Data of **3a-f**.

	3a	**3b**	**3c**	**3d**	**3e**	**3f**
N-C-N	89.6	89.9	89.1	88.6	89.5	88.6
CH_2CH_2	50.1	50.9	50.0	50.0	50.7	50.4
C1'	122.6	121.5	121.2	123.7	121.6	122.0
C2'	156.3	155.4	156.0	155.7	155.4	156.1
C3'	117.5	116.4	114.8	117.3	116.2	115.0
C4'	128.8	130.0	128.7	128.8	130.0	128.6
C5'	124.1	128.9	118.3	122.6	128.9	119.2
C6'	128.0	129.5	129.0	128.0	129.3	129.1
C1"	136.5	137.6	137.0	127.7	130.4	130.5
C2", C6"	128.5	129.2	128.2	129.7	129.5	128.1
C3", C5"	129.5	129.9	129.1	114.8	115.3	115.1
C4"	130.5	130.6	130.0	161.0	161.4	161.2
benzylic C	55.0	56.4	56.1	55.2	55.4	56.2
OMe	---	---	---	55.0	55.9	55.3

According to a previous report,[4] the isolation of N,N'-*bis*(5'-chloro-2'-hydroxybenzyl)-ethylenediamine (**4a**) allows to propose the reaction pathway depicted in Scheme 1. Benzoic acid, obtained in the reaction by oxidation of benzaldehyde, breaks the N1-C2 and N2-C2 bonds affording formaldehyde and amine **4a**, which allows the formation of **3a** by reaction with benzaldehyde. On the other hand, reaction of formaldehyde with **1a** affords *bis*-benzoxazine **2a**.[1]

There are three possible arrangements (**A**-**C**) for the relative stereochemistry of **3**, as shown in Scheme 2. Since, as mentioned above, the ^1H NMR spectra of these compounds show AA'BB' systems for the CH_2-CH_2 fragment, stereostructure **C** is discarded. The minimum energy conformation of stereostructures **A** and **B** were calculated using a simplified model, having unsubstituted phenyl groups, by means of MMX molecular modeling. These type of minimun energy calculations have been used succesfully for many conformational flexible systems.[2,5].This showed that the relative stereochemistry corresponds to **A** which is more stable than **B** by nearly 6 kcal/mol.

The values of dihedral angles obtained from the MMX calculations were used to calculate the coupling constants for the CH_2-CH_2 fragment using generalized Karplus-type equations.[6] These in turn were used as the initial input data for the spin-spin simulation of the AA'BB' system of **3a** and **3b** using the LAOCOON III PC program.[7] The individual signals are assigned since it has been described[8,9] that protons *cis* to the nitrogen lone pair are shifted to lower fields. The AA'BB' system data for **3a** and **3b** are shown in Table 4 and the coupling constant values are in good agreement with those described for similar compounds[10]., as also deduced from extensive use of spin-spin calculations by means of the LAOCOON III program.



A **B** **C**

Scheme 2

Table 4. ^{1}H NMR data of AA'BB' system of **3a** and **3b** (at 300 MHz).

	3a	**3b**
$\delta_A = \delta_{A'}$	804.4	795.6
$\delta_B = \delta_{B'}$	1003.4	999.1
$J_{AA'}$	9.4	9.4
$J_{AB} = J_{A'B'}$	-10.1	-10.1
$J_{AB'} = J_{A'B}$	5.7	5.7
$J_{BB'}$	7.7	7.8
RMS error	0.09	0.09

Error for δ and J are smaller than 0.03 Hz

Considering the coupling constants obtained from the spin-spin simulation, we attempted to verify the minimum energy conformation by means of MMX molecular modeling. However this approach failed due to the impossibility to find a minimum energy conformation in which all calculated coupling constants were in agreement with the observed values. Therefore, we obtained the energy values for a wide range of dihedral angles of the CH_2-CH_2 system, which revealed a large isoenergetic region. The total energy in this isoenergetic region is mainly composed by stretching, bending, torsion and van der Waals energies, which contribute with 2.5, 11.8, 57.2, and 27.5 %, respectively. It is therefore concluded that the CH_2-CH_2 fragment has conformational flexibility in the isoenergetic region over a torsion angles range of ±30°.

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