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First Synthesis of Upper Rim Mono and Dinitrone Calix[4]arene Derivatives

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Abstract- A new class of calix[4]arene derivatives bearing one or two nitrone groups on the upper rim has been synthesized using the oxidation of chiral imines with hydrogen peroxide. The imine intermediates were obtained *via* amination of the diformyl derivative. The ^1H NMR spectra and X-ray data indicated a 1,3-disubstituted cone conformation for the imine derivatives and the existence of a single (*E,E*) isomer. The structural identity of the nitrone derivatives was confirmed from NMR, IR and ES-MS data. Both mono and dinitrone calix[4]arenes were in *E* configuration.

Keywords : calixarene ; nitrone function ; crystal structure

INTRODUCTION

Calix[n]arenes are a family of macrocyclic molecules consisting of *n-para* substituted phenol units connected through methylene bridges in their *ortho* position.¹ These molecules and their derivatives have been extensively studied for the past ten years for their interesting and versatile properties *e.g.* complexation, formation of supramolecular assemblies, design of biomimetics.

Nitrones have been known for many years², but interest in their chemistry has grown mostly due to their increasing use as synthons in cycloaddition reactions³, natural products synthesis⁴ and radical spin traps⁵. They can also be used as bacteria inhibitors⁶⁻⁷, or synthetic intermediates for biomimetic preparations⁸.

Nitrone derivatives are very efficient in trapping free radicals, especially for oxygen centered radicals in biological media.⁹ For such applications it would be interesting to incorporate the nitrone function into the calixarene core to achieve the elaboration of a three dimensional and conformationally rigid platform.

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It is known that the oxidation of imine derivatives with metachloroperbenzoic acid (MCPBA) or hydrogen peroxide led to the formation of the corresponding oxaziridines. The rearrangement of oxaziridine derivatives into nitrones, which involves the cleavage of the C-O bond, appears in the presence of strong Lewis acid as catalyst^{10,11} or high temperatures^{10,12}. Studies have shown that various factors can favour the transformation of an imine derivative into the corresponding nitrone. The conformation of the imine derivative plays an important role. Nucleophilic attack of the peroxide at the imino carbon atom (orthogonal to the imino plane) followed by intramolecular nucleophilic displacement leads to the formation of the oxaziridine derivative.^{13,14} By contrast, nitrone derivatives result from a concerted nucleophilic attack of the imino nitrogen atom on the peroxide (in the imino plane).^{14,15} Steric effects of substituted groups which hinder the approach of the peroxide to the imino carbon in a plane perpendicular to the C=N bond favour the nitrone formation. The nitrone formation is also observed with benzaldimine derivatives bearing electro donating groups at the para position.¹⁵ Finally, aprotic solvents and basic conditions favour the nitrone formation.¹⁶

In this paper, we describe for the first time the synthesis of calix[4]arenes bearing nitrone moieties at the upper rim.

RESULTS AND DISCUSSION

With the aim of synthesizing nitrone substituted calix[4]arene derivatives, we have developed a strategy in three steps involving a di-formylation reaction of the di-propoxycalixarene **1** (scheme 1) and its conversion into chiral imines. The starting calixarene derivative **1** was chosen in order to block two distal hydroxyl groups. The compound **2** was synthesized in two steps.¹⁷ After recrystallisation (CHCl₃ / MeOH), the diformylcalix[4]arene **2** was obtained in quantitative yield. Single crystal X-ray of **2** has been obtained. The crystallographic data have been recently reported by our group¹⁸ and shown that this compound adopts a "pinched" cone conformation.

The chiral imine derivatives **3ab** were prepared from the corresponding chiral amines^{19,20} ((R)-1-cyclohexylethylamine and (S)-1-phenylethylamine) and are obtained with good yields (81 and 72 % respectively). Their constitution was established by ¹H NMR, ¹³C NMR, ES-MS and X-ray data. The ¹H

NMR spectra of **3ab** contain the signal of the imine function (8.56 ppm) instead of the aldehyde singlet (9.81 ppm) identified for **2**. Such observations have been made on the ^{13}C NMR spectra with the imino signal (160 ppm) instead of the aldehyde signal (190 ppm). The single signal of the imine function in NMR suggests the presence of a single isomer which is the (*E,E*) isomer as confirmed by the X-ray data. Beside the AB systems for the methylene bridges, two singlets at 7.47 and 7.53 ppm are identified for the protons of the aromatic rings bearing the imine function which give rise to a 1,3-disubstituted cone conformation.

The X-ray structure of **3a** (Fig. 1) confirms a cone conformation in the solid state in accordance with the solution data. From X-ray analysis it is shown that the unit contains one macrocycle, one dichloromethane and two methanol molecules. The calixarene compound and the dichloromethane of solvation have crystallographically imposed twofold symmetry. The dichloromethane lies within the calixarene cup and there are clear C-H... π interactions between the methylene C-H and an aromatic ring. The two cyclohexyl groups orient the edges of the rings inside the cavity of the calixarene. We found two kinds of hydrogen bonds : intramolecular hydrogen bond [OH (phenol)...O (ether)] and intermolecular hydrogen bonds [OH (methanol)...N (imine)]. The X-ray structure unequivocally establishes that the absolute configuration of the two asymmetric carbon atoms is *R* (the stereochemistry of the starting amine has been conserved). It is also unambiguous that the stereochemistry of the imine bond is *E* confirming the presence of a single (*E,E*) isomer as expected.

As observed for **3a**, the structure of **3b** (Fig. 2) shows a cone conformation. The calixarene compound and the dichloromethane of solvation have crystallographically imposed twofold symmetry. The two phenol moieties are orientated inside the cavity of the calixarene core whereas the methyl groups of the propyl chain are directed outside the cavity. Intramolecular hydrogen bonds between the protons of phenolic oxygen atoms and the adjacent ether bridges are observed, contributing to the cone conformation. As for compound **3a**, the X-ray structure of **3b** unequivocally establishes the configuration of this derivative. The absolute configuration of the two asymmetric carbon atoms is *S* (the stereochemistry of the starting amine has been conserved). It also confirms the presence of a single (*E,E*) isomer.

The oxidation reaction described by Kraeïm et al.²¹ yielded the nitron derivatives. The reaction of the imines derivatives **3ab** with hydrogen peroxide, bicarbonate and benzonitrile in a CH₂Cl₂/MeOH mixture has led to the formation of the expected dinitron derivatives **4ab** and also to the mononitron-monoformyl derivatives **5ab** and to benzamide (scheme 1). These compounds have been separated by chromatographic column. The structure of the four calixarene derivatives was determined by ¹H, ¹³C NMR, IR and Mass spectrometry (Tables 1 and 2). For compound **4a**, the HMQC cross peaks indicate that the proton at 7.21 ppm was correlated to the carbon at 133.92 ppm and the COSY cross peaks show that the proton of the CH=N(O) group is correlated to the doublet (8.08 ppm) attributed to the aromatic protons of the calixarene core. Thus 2D NMR analyses have confirmed the structure of the dinitron derivatives. A comparison of the ¹H NMR spectra of compounds **4** and **5** (Table 1) reveals that the majority of the signals are doubled for **5** indicating a dissymmetry in the molecule. Moreover, the characteristic singlets of the nitron and of the aldehyde have been observed for compounds **5**. This phenomenon of starting aldehyde returned from the imine oxidation as already been described.²² The ¹H NMR spectra of all four calixarene-nitron substituted **4** and **5** exhibit a single singlet for the CH=N(O) proton which demonstrates that the hydrogen peroxide oxidation didn't racemize the starting configuration. Both mono and di-nitron are still in *E* configuration. The ¹³C NMR chemical shifts of the methylene bridges indicated a cone conformation for the calixarene core in solution.

CONCLUSION

This work confirms that steric and mesomeric effects have a marked influence upon the oxydation reaction of imine function as described in the literature.¹⁵ The conformation of the calixarene imine derivatives may favoured the nitron formation. ¹H NMR spectra and X-ray data have indicated a 1,3-disubstituted cone conformation of the imine derivatives **3** and the existence of a single (*E,E*) isomer. To our knowledge, a unique exemple of calixarene bearing nitroxide radicals on the lower rim has been reported.²³ No calixarene functionalized with nitron at the upper rim has been described. Thus, we presented the first synthesis of mono and di-nitron substituted calix[4]arene derivatives. These compounds represent new rigid supports for further applications such as radicals trapping.

EXPERIMENTAL SECTION

General methods. Solvents were purified and dried by standard methods prior to use. All reactions were carried out under nitrogen. Column chromatography was performed with silica gel 60 (0.040-0.063 nm). Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained at 300.13 and 75 MHz (CDCl_3 , TMS as internal standard, chemical shifts in ppm, J in Hertz). Mass spectra were obtained by electrospray technique (positive mode). As verified by other authors²⁴ elemental analyses of calixarenes are very often incorrect because of the inclusion of solvent molecules and thus cannot be considered as an appropriate criterion of purity. Nevertheless, the identities of the reported compounds have been confirmed by their structural data.

11,23-Diformyl-26,28-di-propoxy-25,27-di-hydroxycalix[4]arene (2). A solution of di-propyloxycalix[4]arene **1** (2.1 g, 4.17 mmol) in 70 mL of CHCl_3 was cooled to 15°C . Then, SnCl_4 (5.01 mL, 42.72 mmol) and 1,1-dichlorodimethylether (0.963 mL, 10.62 mmol) were quickly added. The mixture was stirred at room temperature for 30 mn. The organic layer was washed with water, dried with Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was then recrystallized from $\text{CHCl}_3/\text{MeOH}$ to give 1.95 g of **2** as a white powder. Yield: 92 %. NMR data are in accordance with those described in the literature.¹⁷

5,17-Bis-[N-(S)-cyclohexylethylimino]-25,27-dipropyloxycalix[4]arene (3a). In a 100 mL three-necked flask equipped with stirrer and condenser, 0.156 g (0.27 mmol) of aldehyde **2** was dissolved in 40 mL of CH_2Cl_2 under nitrogen. (S)-cyclohexylamine (0.1 mL, 0.69 mmol) was added. The mixture containing molecular sieves ($4\text{\AA}$) was stirred at 40°C for 48h. The suspension was filtered off on celite and the solvent was removed *in vacuo*. The crude solid was recrystallized from $\text{CHCl}_3/\text{MeOH}$ to give 0.189 g of a white powder. Yield: 81 %. Mp = $220\text{--}222^\circ\text{C}$. $[\alpha]_D^{20} = +63.3$ ($c = 0.3$, CHCl_3). ^1H NMR: 0.88-1.85 (m + d, 34H, H-cy + CH_3CH , CH_3CH_2), 2.04-2.10 (m, 4H, CH_2CH_3), 2.90-2.96 (m, 2H, CHCH_3), 3.47 (AB, 4H, $J_{\text{AB}} = 12.81$, ArCH_2Ar), 4.00 (bt, 4H, CH_2O), 4.30 (AB, 4H, $J_{\text{AB}} = 13.02$, ArCH_2Ar), 6.77 (t, 2H, $J = 7.53$, $H\text{-Ar}$), 6.96-7.00 (bt, 4H, $H\text{-Ar}$), 7.48 (sb, 4H, $H\text{-Ar}$), 8.08 (s, 2H, OH), 8.57 (s, 2H, CH=N). RMN^{13}C : 11.28 (CH_3CH_2), 20.46 (CH_3CH), 23.89 (CH_2CH_3), 26.63, 26.84, 27.03, 30.30, 30.72 ($\text{CH}_2\text{-}$

cy), 31.64 (ArCH₂Ar), 44.14 (CH-cy), 72.67 (CHN), 78.87 (CH₂O), 125.74, 128.04, 128.92, 129.54, 133.38, 152.26, 156.19, 159.05 (CH=N). IR: 1637 (CH=N), 3221 (OH). ES-MS(+) for C₅₂H₆₆N₂O (783.1) m/z = 805.4 [M+Na]⁺, 783.6 [M+H]⁺, 392.3 [M+2H]²⁺.

5,17-Bis-[N-(L)-phenylethylimino]-25,27-dipropoxyxycalix[4]arene (3b). Same procedure with 0.156 g of aldehyde **2** (0.27 mmol) and 0.1 mL of chiral amine (0.81 mmol). Yield: 72 %. $[\alpha]_D^{20}$ = -5.7 (c = 0.3, CHCl₃). ¹H NMR: 1.32 (t, 6H, J = 7.35, CH₃CH₂), 1.62 (d, 6H, J = 6.57, CHCH₃(NH)), 2.05-2.12 (m, 4H, CH₂CH₃), 3.47 (AB, 4H, J_{AB} = 12.99, ArCH₂Ar), 4.01 (t, 4H, J = 6.42, CH₂O), 4.31 (AB, 4H, J_{AB} = 12.99, ArCH₂Ar), 4.52 (q, 2H, J = 6.57, CHCH₃), 6.76 (t, 2H, J = 7.53, H-Ar), 6.95 (d, 4H, J = 7.35, H-Ar), 7.36 (t, 6H, J = 7.14, H-Ph), 7.45 (d, 4H, J = 7.17, H-Ph), 7.53 (s, 4H, H-Ar), 8.25 (s, 2H, OH), 8.58 (s, 2H, CH=N); ¹³C NMR: 11.28 (CH₃CH₂), 23.90 (CH₂CH₃), 24.86 (CH₃CH(N)), 31.64 (ArCH₂Ar), 69.77 (CHN), 78.87 (CH₂O), 125.72, 126.11, 127.12, 127.93, 128.50, 128.91, 129.17, 129.92, 132.67, 133.29, 145.76, 152.15, 156.48, 160.02 (CH=N). IR: 1637 (CH=N). ES-MS(+) for C₅₂H₅₄N₂O₄ (771.01) m/z = 771.5 [M+H]⁺, 386.2 [M+2H]²⁺.

General procedure for the preparation of the nitrone derivatives

In a 100 mL flask, a mixture of dichloromethane (10 mL), methanol (30 mL), sodium bicarbonate (100 mg, 1.2 mmol), benzonitrile (1 mmol, 0.1 mL), imine (0.13 mmol), hydrogen peroxide (11 mmol) was stirred at room temperature for 72h. The mixture was then treated with 25 mL of water, extracted with chloroform (3 × 20 mL). The organic layer was separated, dried with Na₂SO₄ and the solvent was removed *in vacuo*. The crude product was then eluted from a column of silica gel to give the mono or disubstituted nitrone derivative.

5,17-Bis-[N-(S)-cyclohexylethyl nitronyl]-25,27-dipropoxyxycalix[4]arene (4a). The crude product was then eluted from a column of silica gel with AcOEt/hexane (1/1) to give 0.034 mmol of a white solid (R_f = 0.11). Yield: 26 %. Mp = 277-280 °C. $[\alpha]_D^{20}$ = +22.8 (c = 0.39, CHCl₃). ¹H NMR: 1.28-2.10 (m, 38H, CH₃CH + H-cy + CH₃CH₂ + CH₂CH₃), 3.44-3.48 (dd, J_{AB} = 13.17, 4H, ArCH₂Ar), 3.55 (m, 2H, CHCH₃), 4.00 (t, 4H, J = 6.21, CH₂O), 4.30 (AB, 4H, J_{AB} = 13.17, ArCH₂Ar), 6.77 (t, 2H, J = 7.71, H-Ar), 7.01 (d, 4H, J = 7.71, H-Ar), 7.21 (s, 2H, N=CH), 8.08 (bs, 4H, H-Ar), 8.83 (s, 2H, OH); ¹³C NMR: 11.29

(CH_3CH_2), 17.31 (CH_3CH), 23.88 (CH_2CH_3), 26.05, 26.44, 26.64, 29.82, 30.52 (CH_2 -cy); 31.77 ($ArCH_2Ar$), 40.77 (CH -Cy), 77.39 ($CHN(O)$), 78.79 (CH_2O), 122.29, 125.83, 128.47, 130.04, 133.30, 133.90 ($CH=N(O)$), 152.13, 156.03 (C, Ar). ES-MS(+) for $C_{52}H_{66}N_2O_6$ (815.1) m/z = 837.4 $[M+Na]^+$, 815.5 $[M+H]^+$, 853.5 $[M+K]^+$, 408.4 $[M+2H]^{2+}$.

5,17-Bis-[N-(L)-phenylethynitronyl]-25,27-dipropoxycalix[4]arene (4b). The crude product was then eluted from a column of silica gel with AcOEt/hexane (1/1) to give 0.046 mmol of a white solid (R_f = 0.11). Yield: 35 %. M_p = 224-227°C. $[\alpha]_D^{20}$ = +16.9 (c = 0.51, $CHCl_3$). 1H NMR: 0.90 (t, 6H, J = 7.17, CH_3CH_2), 1.90 (d, 6H, J = 6.78, CH_3CH), 2.01-2.08 (m, 4H, CH_2CH_3), 3.42 (AB, 4H, J_{AB} = 13.17, $ArCH_2Ar$), 3.98 (t, 4H, J = 6.24, CH_2O), 4.24 (AB, 4H, J_{AB} = 13.17, $ArCH_2Ar$), 5.13 (q, 2H, J = 6.78, $CHCH_3$), 6.72 (t, 2H, J = 7.53, $H-Ar$), 6.95 (t, 4H, J = 7.53, $H-Ar$), 7.35(s, 2H, $CHN(O)$), 7.36-7.52 (m, 6H, $H-Ar$), 7.53 (d, 4H, J = 7.53, $H-Ar$), 8.01 (s, 2H, $H-Ar$), 8.11 (s, 2H, $H-Ar$), 8.76 (s, 2H, OH); ^{13}C NMR: 11.25 (CH_3CH_2), 19.46 (CH_3CH), 23.87 (CH_2CH_3), 31.69 ($ArCH_2Ar$), 74.65 (CHN), 78.75 (OCH_2), 122.33, 125.76, 127.71, 128.46, 129.13, 129.67, 130.08, 133.14 (C, Ar), 133.58 ($CH=N$), 139.25, 152.09, 156.18 (C, Ar). ES-MS(+) for $C_{52}H_{54}N_2O_6$ (802.01) m/z = 803.3 $[M+H]^+$, 825.2 $[M+Na]^+$.

5-Formyl-17-[N-(S)-cyclohexylethynitronyl]-25,27-dipropoxycalix[4]arene (5a). The crude product was then eluted from a column of silica gel with AcOEt/hexane (1/1) to give 0.051 mmol of a white solid (R_f = 0.36). Yield: 39 %. M_p = 247-249°C. 1H NMR: 1.27-2.10 (m, 24H, H -cy + CH_3CH_2 + CH_2CH_3 + CH_3CH), 3.46-3.56 (m, 5H, $CHCH_3$ + $ArCH_2Ar$), 3.98-4.04 (m, 4H, CH_2O), 4.28-4.35 (dd, 4H, J_{AB} = 13.20, 4H, $ArCH_2Ar$), 6.80 (t, 2H, J = 7.53, $H-Ar$), 6.94 (d, 2H, J = 7.71, $H-Ar$), 7.04 (d, 2H, J = 7.53, $H-Ar$), 7.22 (s, 1H, $CH=N(O)$), 7.64 (s, 2H, $H-Ar$), 8.05 (s, 1H, $H-Ar$), 8.14 (s, 1H, $H-Ar$), 8.83 (s, 1H, OH), 9.30 (s, 1H, OH), 9.80 (s, 1H, CHO); ^{13}C NMR: 11.31 (CH_3CH_2), 17.32 (CH_3CH), 23.89 (CH_2CH_3), 26.03, 26.62, 29.82, 30.10, 30.51 (CH_2 -cy), 40.78 (CH -cy), 77.42 ($CHN(O)$), 78.90 (CH_2O), 122.42, 125.98, 128.89, 129.16, 129.50, 130.02, 131.30, 132.69 (C, Ar), 133.42 ($CH=N$) 152.10, 155.94 (C, Ar), 191.37 (CHO). IR: 1672 (CHO). ES-MS(+) for $C_{44}H_{51}NO_6$ (689.89) m/z = 690.3 $[M+H]^+$.

5-Formyl-17-[N-(L)-phenylethynitronyl]-25,27-dipropoxycalix[4]arene (5b). The crude product was then eluted from a column of silica gel with AcOEt/hexane (1/1) to give 0.041 mmol of a white solid (R_f = 0.60). Yield: 31 %. M_p = 212-215°C. 1H NMR: 128-136 (t, 6H, J = 7.35, CH_3CH_2), 1.90 (d, 3H, J = 6.78, CH_3CH), 2.01-2.1 (m, 4H, CH_2CH_3), 3.47 (AB, 4H, J_{AB} = 13.35, $ArCH_2Ar$), 3.99-4.03 (m, 4H, CH_2O), 4.26-4.34 (dd, 4H, J = 12.81, $ArCH_2Ar$); 5.13 (q, 1H, J = 6.78, $CHCH_3$), 6.72-6.77 (m, 2H, $H-Ar$), 6.93-7.12 (m, 4H, $H-Ar$), 7.36 (s, 1H, $CH=N(O)$), 7.38-7.51 (m + s, 3H, $H-Ar$), 7.53 (d, 2H, J = 6.96, $H-Ar$), 7.64 (s, 2H, $H-Ar$), 8.04 (s, 1H, $H-Ar$), 8.11 (s, 1H, $H-Ar$), 8.81 (s, 1H, OH), 9.26 (s, 1H, OH), 9.81 (s, 1H, CHO); ^{13}C NMR: 11.29 (CH_3CH_2), 19.43 (CH_3CH), 31.69 ($ArCH_2Ar$), 74.67 ($CHN(O)$), 78.88 (OCH_2), 122.46, 125.93, 127.68, 128.33, 128.87, 129.13, 129.94, 130.17, 131.33, 132.63 (C, Ar), 133.38 ($CH=N(O)$), 139.22, 150.26, 152.09, 156.08, 160.15 (C, Ar), 191.38 (CHO). IR: 1673 (CHO). ES-MS(+) for $C_{44}H_{45}NO_6$ (683.84) m/z = 684.2 $[M+H]^+$, 706.2 $[M+Na]^+$.

X-ray analysis of 3ab

Single crystals of **3a** and **3b** were obtained from a saturated dichloromethane / methanol solution. Data were collected at 293 K for **3a** and 173 K for **3b** on a Nonius Kappa CCD with Mo- $K\alpha$ radiation. Final unit cell parameters were obtained by means of a least-squares refinement. The structure has been solved by direct methods using SHELXS97. ²⁵ Usual non-H atoms were refined isotropically except for some disordered solvents. Hydrogen were calculated at theoretical positions and refined riding. The crystallographic data were reported on Table 1.

CCDC reference numbers 239937 for **3a** and 239938 for **3b**.

Crystal data for derivative 3a : $C_{55}H_{76}Cl_2N_2O_6$, M = 930.51, T = 293(2) K, a = 16.224(2), b = 16.224(3), c = 20.088(4) Å, α = 90°, β = 90°, γ = 90°, V = 5287.3(15) Å³, space group P4(1)2(1)2, Z = 4, μ = 0.188 mm⁻¹, D_c = 1.171 g.cm⁻³, wR_2 = 0.1639, R $[I > 2\sigma(I)]$ = 0.0667.

Crystal data for derivative 3b : $C_{55}H_{56}Cl_2N_2O_4$, M = 878.36, T = 173(2) K, a = 15.297(2), b = 15.297(2), c = 19.770(4) Å, α = 90°, β = 90°, γ = 90°, V = 4626.1(13) Å³, space group P4(1)2(1)2, Z = 4, μ = 0.188 mm⁻¹, D_c = 1.229 g.cm⁻³, wR_2 = 0.1982, R $[I > 2\sigma(I)]$ = 0.0739.

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Table 1. Selected ^1H NMR chemical shifts (ppm) of **4ab** and **5ab** in CDCl_3 .

	4a	4b	5a	5b
$\text{CH}=\text{N}(\text{O})$	7.21	7.35	7.22	7.36
OH	8.83	8.76	8.83 and 9.30	8.81 and 9.26
CH_2	3.48 (d) and	3.42 (d) and	3.46-3.56 (dd)	3.47 (dd)
(bridges)	4.30 (d)	4.24 (d)	4.28-4.35 (dd)	4.26-4.34 (dd)
	AB system	AB system	2 AB systems	2 AB systems
CHO	/	/	9.80	9.81

Table 2. Selected ¹³C NMR chemical shifts (ppm) of **4ab** and **5ab** in CDCl₃.

	4a	4b	5a	5b
CH=N(O)	133.92	133.58	133.42	133.38
CH ₂	31.69	31.77	30.51	31.69
(bridges)				
CHO	/	/	191.37	191.38

Fig. 1. X-ray crystal structure of **3a** included dichloromethane and methanol. The hydrogen bonds are indicated by dash lines.

Fig. 2. X-ray crystal structure of **3b**. The hydrogen bonds are indicated by dash lines.