

# C-Alkylation of nitroso chlorides with diethyl malonate: the X-ray structure of diethyl (±)-(1R\*,2S\*,5R\*)-2-{3(E)-hydroxyimino-2,6,6-trimethylbicyclo[3.1.1]-hept-2-yl}malonate

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The reactions of the nitroso chlorides of methylcyclohexene, limonene, 3-carene, and  $\alpha$ -pinene with an excess of diethyl malonate in the presence of anhydrous  $K_2CO_3$  at room temperature resulted in the C-alkylation and formation of  $\alpha$ -substituted oximes with a diethyl malonate moiety in 20–90% yields.

The reactions of nitroso chlorides (products of NOCl addition to olefins) with N-, O- and S-nucleophilic reagents are known to lead to  $\alpha$ -substituted oximes. The syntheses of  $\alpha$ -amino oximes are the most popular because of the use of terpenoid derivatives of this type<sup>1</sup> as new chiral chelating ligands.<sup>2</sup> There are many important organic enantioselective reactions leading by transition metal complexes with oxygen-containing ligands. We report now a new reaction of nitrosochlorides, i.e., C-alkylation with diethyl malonate leading to the new group of chiral ligands of the type of substituted malonates.

The transformation of nitroso chlorides to  $\alpha$ -substituted oximes is well known to proceed *via* elimination–addition with aliphatic nitroso olefins as unstable intermediates. Certain stable nitroso olefins can react with C-nucleophiles.<sup>3</sup> Because of an extreme instability of nitroso olefins derived from terpenes, the reaction of nitroso chlorides with diethyl malonate under typical reaction conditions usually resulted in dehydrochlorination instead of substitution and formation of unsaturated oximes. Nevertheless, we found that under specific reaction conditions the substitution products can be prepared in good yield and stereoselectivity (Scheme 1). Thus, freshly calcined powdered  $K_2CO_3$  (1.6 g, 0.01 mol) is added to freshly distilled diethyl malonate (20 g, 0.13 mol), and the mixture is stirred for 30 min followed by the addition of 0.01 mol of crystalline dimeric nitroso chloride<sup>†</sup> of methylcyclohexene **1**, limonene **2**, 3-carene **3** or  $\alpha$ -pinene **4**. The reaction mixture is stirred for 24 h at room temperature away from atmospheric moisture, diluted with MeOBu<sup>t</sup> (100 ml), washed with water (3×10 ml) and brine (10 ml) and dried over anhydrous  $Na_2SO_4$ . The removal of the solvent and the excess of diethyl malonate and the subsequent chromatography of the residue on a silica gel column (hexane–EtOAc) afford C-alkylation products **5**,<sup>‡</sup> **6**,<sup>§</sup> **7**<sup>¶</sup> or **8**<sup>††</sup> in 20–90% yield. A relatively low yield of crystalline pinane derivative **8** results from the moderate optical purity of the starting  $\alpha$ -pinene ( $[\alpha] +20$ , *ca.* 40% ee): the racemic form of compound **8** is a well-crystallised material in contrast to the optically active form.

The formation of reaction products can be easily explained by Scheme 2, which includes the formation of a nitroso olefin

as a dehydrochlorination product followed by the nucleophilic addition of the anion  $-CH(COOEt)_2$ . In this reaction sequence, the anion  $-CH(COOEt)_2$  should attack the carbon–carbon double bond in the nitroso olefin on the less hindered side. Thus, the configuration of reaction products corresponds to the configura-

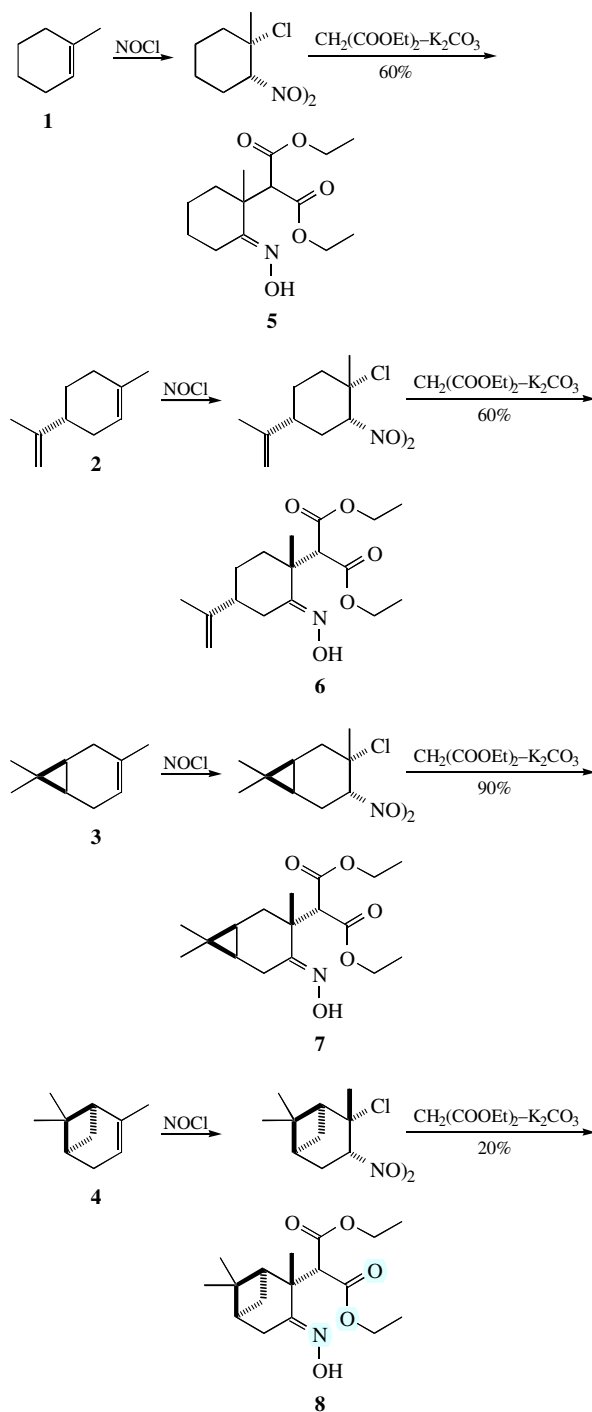
<sup>§</sup> (1R,4R)-2-[2(E)-Hydroxyimino-4-isopropenyl-1-methylcyclohexyl]-malonic acid diethyl ester **6**: yield 60%, colourless oil with  $[\alpha]_{578}^{20} -26$  (*c* 0.60, EtOH). <sup>1</sup>H NMR (500 MHz,  $CCl_4$ – $CDCl_3$  2:1 v/v)  $\delta$ : 1.21 (t, 3H, *J* 7.0 Hz), 1.27 (t, 3H, *J* 7.0 Hz), 1.37 (s, 3H), 1.44 (dddd, 1H, *J* 12, 3, 3, 2 Hz), 1.58 (ddd, 1H, *J* 14, 14, 4 Hz), 1.74 (dddd, 1H, *J* 14, 12, 12, 3 Hz), 1.77 (s, 3H), 1.84 (ddd, 1H, *J* 14, 3, 3 Hz), 2.08 (dddd, 1H, *J* 12, 12, 3, 3 Hz), 2.27 (dd, 1H, *J* 13, 13 Hz), 3.38 (dd, 1H, *J* 13, 3, 2 Hz), 3.87 (s, 1H), 4.11 (q, 1H, *J* 7.0 Hz), 4.05 (q, 1H, *J* 7.0 Hz), 4.17 (q, 2H, *J* 7.0 Hz), 4.74 (br. s, 1H), 4.75 (br. s, 1H), 9.15 (s, 1H, N=OH). <sup>13</sup>C NMR (125 MHz,  $CCl_4$ – $CDCl_3$  2:1 v/v)  $\delta$ : 13.96 (q), 14.06 (q), 20.20 (q), 20.89 (q), 25.33 (t), 26.19 (t), 36.92 (t), 42.58 (s), 44.10 (d), 54.11 (d), 60.74 (t), 60.89 (t), 109.77 (t), 147.56 (s), 160.80 (s), 166.7 (s), 167.02 (s). IR (KBr,  $\nu_{max}/cm^{-1}$ ): 3477 (O–H), 1755, 1731 ( $2CO_2^-$ ), 1645 (C=N), 943 (N–O). MS, *m/z* (%): 325.18955 (21, *M*<sup>+</sup>, calc. for  $C_{17}H_{27}NO_5$  325.18891), 308 (24), 280 (33), 166 (34), 165 (48), 161 (56), 149 (15), 148 (64), 135 (42), 123 (14), 107 (60), 105 (33), 41 (67), 29 (100). Found (%): C, 62.9; H, 8.4; N, 4.5. Calc. for  $C_{17}H_{27}NO_5$  (%): C, 62.75; H, 8.36; N, 4.30.

<sup>¶</sup> (1S,3R,6R)-2-[4(E)-2-Hydroxyimino-3,7,7-trimethylbicyclo[4.1.0]-hept-3-yl]malonic acid diethyl ester **7**: yield 90%, white crystals with mp 90 °C (from hexane) and  $[\alpha]_{578}^{20} +14$  (*c* 1.16, EtOH). <sup>1</sup>H NMR (500 MHz,  $CDCl_3$ – $[^2H_5]$ pyridine, 3:1 v/v)  $\delta$ : 0.72 (ddd, 1H, *J* 9.5, 8.8, 6.1 Hz), 0.82 (s, 3H), 0.89 (ddd, 1H, *J* 9.1, 8.8, 1.4 Hz), 1.01 (s, 3H), 1.14 (t, 3H, *J* 7.2 Hz), 1.24 (t, 3H, *J* 7.1 Hz), 1.16 (dd, 1H, *J* 15.4, 6.1 Hz), 1.36 (s, 3H), 2.43 (dd, 1H, *J* 15.4, 9.5 Hz), 2.44 (dd, 1H, *J* 19.1, 9.1 Hz), 3.00 (dd, 1H, *J* 18.9, 1.4 Hz), 4.02 (dddd, 2H, *J* 10.7, 7.3, 7.3, 7.3 Hz), 4.07 (s, 1H), 4.17 (q, 2H, *J* 7.3 Hz), 8.6 (s, 1H, N=OH). <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ – $[^2H_5]$ pyridine, 3:1 v/v)  $\delta$ : 12.99 (q), 13.16 (q), 13.92 (q), 14.10 (t), 16.65 (q), 16.69 (s), 17.95 (d), 18.37 (d), 27.09 (q), 31.11 (t), 39.81 (s), 53.43 (d), 59.55 (t), 158.18 (s), 166.22 (s), 166.58 (s). IR (KBr,  $\nu_{max}/cm^{-1}$ ): 3467 (O–H), 1756, 1731 ( $2CO_2^-$ ), (C=N), 922 (N–O). MS, *m/z* (%): 325.18924 (17, *M*<sup>+</sup>, calc. for  $C_{17}H_{27}NO_5$  325.18891), 308.3 (14), 280 (24), 166 (40), 165 (100), 161 (19), 150 (36), 149 (14), 148 (45), 123 (32), 105 (18), 41 (23), 29 (28). Found (%): C, 62.2; H, 8.5; N, 4.3. Calc. for  $C_{17}H_{27}NO_5$  (%): C, 62.75; H, 8.36; N, 4.30.

<sup>††</sup> (±)-(1R\*,2S\*,5R\*)-2-{3(E)-Hydroxyimino-2,6,6-trimethylbicyclo[3.1.1]-hept-2-yl}malonic acid diethyl ester **8**: yield 20%, white crystals with mp 88 °C (from hexane). <sup>1</sup>H NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 0.90 (s, 3H), 1.18 (t, 3H, *J* 7.0 Hz), 1.19 (t, 3H, *J* 7.0 Hz), 1.26 (s, 3H), 1.33 (d, 1H, *J* 11 Hz), 1.52 (s, 3H), 1.92 (m, 1H), 2.13 (dd, 1H, *J* 6.0, 6.0 Hz), 2.27 (m, 1H), 2.42 (dd, 1H, *J* 2.2, 18.5 Hz), 2.94 (ddd, 1H, *J* 18.5, 2.8, 2.8 Hz), 3.69 (s, 1H), 4.05 (m, 4H), 9.23 (s, 1H, N=OH). <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ )  $\delta$ : 13.97 (q), 14.04 (q), 21.63 (q), 22.85 (q), 27.93 (q), 29.15 (t), 30.22 (t), 37.86 (d), 39.97 (s), 46.32 (s), 50.10 (d), 57.76 (d), 60.47 (t), 60.75 (t), 160.19 (s), 166.51 (s), 166.58 (s). IR (KBr,  $\nu_{max}/cm^{-1}$ ): 3467 (O–H), 1756, 1731 ( $2CO_2^-$ , C=N), 922 (N–O). MS, *m/z* (%): 325.18923 (4, *M*<sup>+</sup>, calc. for  $C_{17}H_{27}NO_5$  325.18891), 308 (6), 280 (18), 166 (100), 165 (32), 161 (23), 149 (11), 148 (41), 121 (19), 110 (48), 106 (18), 105 (16), 79 (25), 69 (45), 67 (33), 43 (52), 29 (85). Found (%): C, 62.9; H, 8.3; N, 4.1. Calc. for  $C_{17}H_{27}NO_5$  (%): C, 62.75; H, 8.36; N, 4.30.

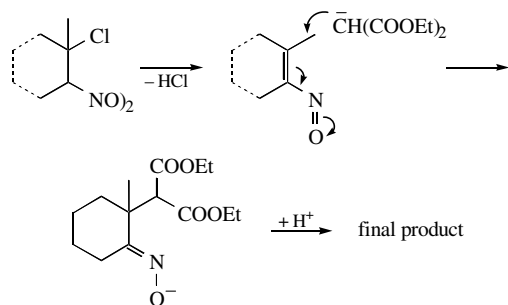
<sup>†</sup> Prepared by a common method on the treatment of the olefin with gaseous NOCl followed by crystallization of the crude product from  $CHCl_3$ –MeOH.

<sup>‡</sup> (±)-2-(2-Hydroxyimino-1-methylcyclohexyl)malonic acid diethyl ester **5**: colourless oil, yield 60%. <sup>1</sup>H NMR (500 MHz,  $CCl_4$ – $CDCl_3$ , 2:1 v/v)  $\delta$ : 1.20 (t, 3H, *J* 7.1 Hz), 1.21 (t, 3H, *J* 7.1 Hz), 1.31 (s, 3H), 1.44 (dddd, 1H, *J* 12, 3, 3, 3 Hz), 1.50–1.70 (m, 4H), 2.21 (m, 1H), 2.46 (ddd, 1H, *J* 16, 6, 6 Hz), 2.62 (ddd, 1H, *J* 16, 6, 6 Hz), 3.82 (s, 1H), 4.04–4.16 (4H), 8.76 (s, 1H, N=OH). <sup>13</sup>C NMR (125 MHz,  $CCl_4$ – $CDCl_3$ , 2:1 v/v)  $\delta$ : 14.051 (q), 14.055 (q), 20.78 (t), 21.21 (t), 22.50 (q), 24.78 (t), 35.78 (t), 42.29 (s), 56.55 (d), 60.59 (t), 60.81 (t), 167.46 (s), 167.74 (s), 161.94 (s). IR (neat,  $\nu_{max}/cm^{-1}$ ): 3465 (O–H), 1755, 1730 ( $2CO_2^-$ ), 1642 (C=N), 947 (N–O). MS, *m/z* (%): 285.15782 (15, *M*<sup>+</sup>, calc. for  $C_{14}H_{23}NO_5$  285.15761), 240 (25), 239 (21), 194 (35), 166 (21), 161 (45), 126 (55), 125 (77), 108 (25), 96 (16), 95 (100), 81 (21), 67 (29), 55 (20), 41 (28), 29 (47).

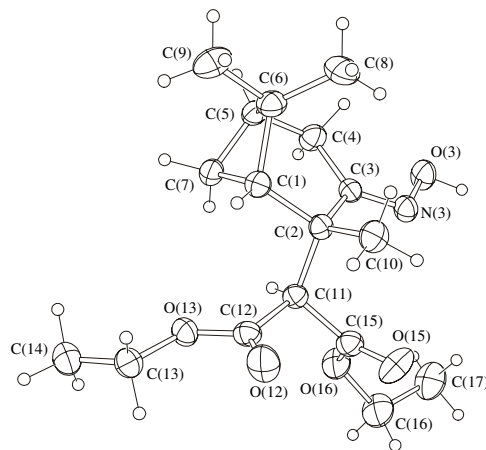


Scheme 1

tion of other  $\alpha$ -substituted oximes, which are formed in the reactions of the same nitroso chlorides with nucleophilic reagents, inducing elimination–addition reactions.



Scheme 2



**Figure 1** Molecular structure of compound 8 in a crystal. Selected bond lengths (Å): C(1)–C(2) 1.548(2), C(1)–C(6) 1.578(2), C(2)–C(3) 1.533(2), C(2)–C(11) 1.579(2), N(3)–C(3) 1.272(2), O(3)–N(3) 1.4155(18), C(5)–C(6) 1.544(2). The molecules of 8 are connected into centrosymmetric pairs by H-bonds O(3)H...N(3) [H...N distance of 1.96(3) Å, OH...N angles of 160(2)°].

Analysis of high-field 2D  $^1\text{H}$ – $^1\text{H}$  and  $^{13}\text{C}$ – $^1\text{H}$  correlation NMR spectra of new compounds 5–8 showed that all the compounds are C-alkylation products formed as a single stereoisomer. A comparison of the NMR data for the new compounds synthesised with published data for the corresponding  $\alpha$ -amino oximes<sup>4</sup> demonstrated that the alkylation products belong to the same configurational series as 3-carene, limonene and  $\alpha$ -pinene derived  $\alpha$ -amino oximes. The configuration of pinane-type derivative 8 was solved by X-ray crystallography (Figure 1).<sup>‡‡</sup>

Compounds 5–8 are colourless materials, which are stable in air, sparingly soluble in water and hydrocarbons and readily soluble in chloroform, alcohols and dimethyl sulfoxide.



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<sup>‡‡</sup> Crystallographic data for compound 8:  $\text{C}_{17}\text{H}_{27}\text{NO}_5$ ,  $M = 325.40$ , crystal class monoclinic, space group  $P2_1/c$ ,  $a = 7.3705(4)$ ,  $b = 25.5180(14)$ ,  $c = 9.3758(4)$  Å,  $\beta = 92.442(4)^\circ$ ,  $V = 1761.80(16)$  Å<sup>3</sup>,  $Z = 4$ ,  $d_{\text{calc}} = 1.227$  g cm<sup>−3</sup>,  $\mu = 0.09$  mm<sup>−1</sup>,  $\lambda = 0.71073$  Å, crystal size 0.5×0.7×1.0 mm. A Bruker P4 diffractometer with graphite-monochromated MoK $\alpha$  radiation was used to measure the unit cell dimensions and to collect data ( $\theta$ – $2\theta$  scans,  $\theta < 25^\circ$ ). Absorption corrections were applied by the integration method (transmission 0.94742–0.96118). The structure was solved by direct methods and refined by a full matrix least-squares anisotropic-isotropic (for atom H) procedure using the SHELXS-97 and SHELXL-97 programs. The hydrogen atom positions were located from a D-map. The final indexes are  $wR_2 = 0.1325$ ,  $\text{GOF} = 1.032$  for all 3056  $F^2$  and  $R_1 = 0.0450$  for 2666  $F_0 > 4\sigma$ . The ethyl acetate group O(16)C(16)C(17) is disordered over two positions with a 0.839:0.161(9) ratio.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 210848. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

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