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An Unusual Dimerization in the Nitrosation Reaction of a Caryophyllene-type α,β-Unsaturated Oxime

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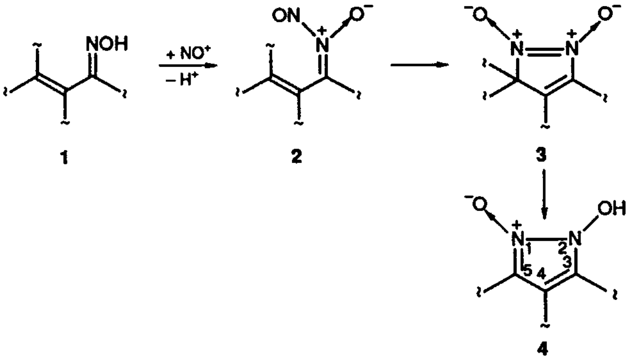
The treatment of two isomeric α,β-unsaturated oximes derived from the sesquiterpene hydrocarbon caryophyllene with nitrous acid, generated *in situ* from sodium nitrite and acetic acid, results in the formation of an unusual dimeric product whose structure was determined by X-ray crystallographic analysis.

α,β-Unsaturated acyclic oximes **1** react with nitrous acid, generated *in situ* from sodium nitrite and acetic acid, to give 1,2-diazoles **3** in good yields.[1] Oximes having at least one hydrogen at the β-carbon atom lead to pyrazole derivatives **4** (Scheme 1). Cyclization of the intermediate *N*-nitroso compound **2** is possible owing to the ability of the diene system to adopt an *s-cis* conformation. We have investigated the behaviour in this reaction of the model compound **6** in which the mobility of the diene system (its rotation around the central bond) is considerably limited.



Scheme 1

The unsaturated oximes **6a** (*Z*-isomer)† and **6b** (*E*-isomer)‡ are readily formed as a result of nitrosochlorination–dehydrochlorination[2] of a natural sesquiterpene hydrocarbon caryophyllene **5** ([α]$^{19}_{D}$ −8.9), isolated from the clove oil *Eugenia caryophyllata*. Oximes **6a** and **6b** are both nitrosated with sodium nitrite in the presence of acetic acid[1] to give the same product in the same yield. Thus, $NaNO_2$ powder (1.40 g,

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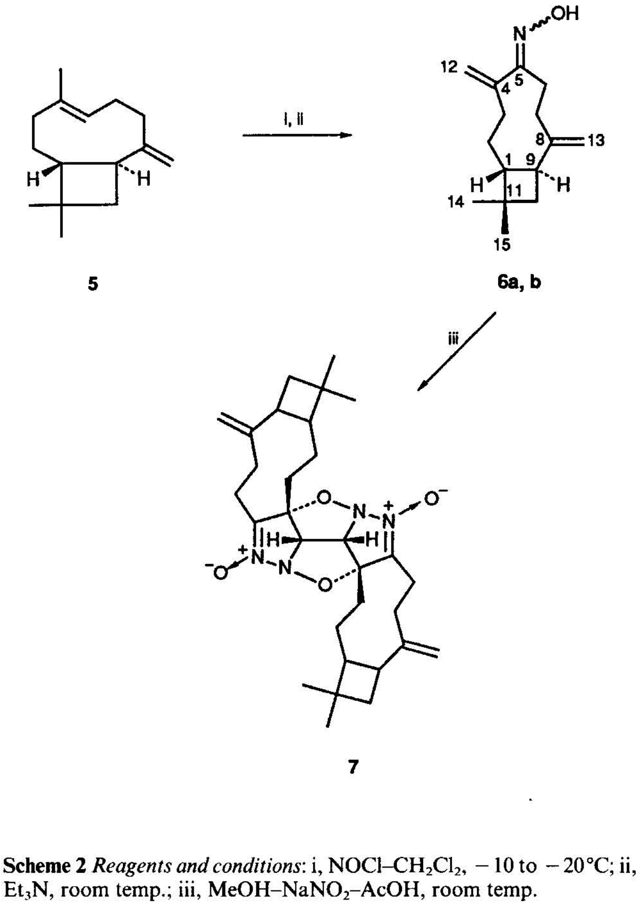
† Compound **6a**: m.p. 151–154 °C (decomp.) (MeCN); [α]$^{25}_{580}$ +151 (*c* 2.48, $CHCl_3$); ^1H NMR ($CDCl_3$, 200.13 MHz) δ 0.93 (s, 3H, 14-H_3), 0.95 (s, 3H, 15-H_3), 4.75 (s, 1H, 13-Ha), 4.77 (s, 1H, 13-Hb), 5.00 (d, 1H, 12-Ha, *J* 1.3 Hz), 5.20 (d, 1H, 12-Hb, *J* 1.3 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 51.04 (d, C-1), 29.54 (t, C-2), 32.29 (t, C-3), 145.31 (s, C-4), 159.88 (s, C-5), 36.28 (t, C-6), 34.23 (t, C-7), 152.08 (s, C-8), 44.06 (d, C-9), 37.90 (t, C-10), 33.59 (s, C-11), 116.43 (t, C-12), 110.00 (t, C-13), 22.05 (q, C-14), 29.92 (q, C-15).

‡ Compound **6b**: m.p. 90–92.5 °C (MeCN); [α]$^{25}_{580}$ −133 (*c* 2.05, $CHCl_3$); ^1H NMR [$CDCl_3$–CCl_4 (1:2 v/v), 200.13 MHz] δ 0.96 (s, 3H, 14-H_3), δ 0.97 (s, 3H, 15-H_3), 4.83 (s, 1H, 13-Ha), 4.88 (s, 1H, 13-Hb), 5.09 (s, 1H, 12-Ha), 5.18 (s, 1H, 12-Hb); ^{13}C NMR [$CDCl_3$–CCl_4 (1:2 v/v), 50.32 MHz] δ 51.71 (d, C-1), 29.94 (t, C-2), 33.08 (t, C-3), 145.71 (s, C-4), 160.25 (s, C-5), 28.00 (t, C-6), 33.44 (t, C-7), 153.24 (s, C-8), 45.53 (d, C-9), 40.43 (t, C-10), 33.30 (s, C-11), 117.35 (t, C-12), 112.06 (t, C-13), 22.18 (q, C-14), 30.11 (q, C-15).

20.3 mmol) was added to a solution of oxime **6a** (1.12 g, 4.6 mmol) in 25 ml of MeOH, then 2.10 g (34.9 mmol) of AcOH was added at room temperature with vigorous stirring. The mixture was allowed to stand for 5 h. Then it was poured into water (60 ml), extracted with Et_2O (4 × 20 ml), the ethereal solution was washed with water (3 × 15 ml) and 0.5 mol dm^{-3} Na_2CO_3 (2 × 15 ml), dried and concentrated at reduced pressure to produce 1.23 g of the crude produce. After addition of Et_2O to the product, white needles of compound **7** were precipitated (60% yield) (Scheme 2).

Spectroscopic analysis of compound **7**§ shows that it is a 'dimer' rather than a usual derivative of type **4**. Its structure was solved by X-ray analysis. Compound **7** may be regarded formally as the product of oxidative dimerization of a type **4** intermediate, especially as the reaction mixture contains an excess of oxidising nitrous acid. It is known, however, that pyrazoles **4** react with an excess of nitrous acid to yield products of NO_2 group addition at the C-4 atom of the pyrazole fragment.[1]



Scheme 2 *Reagents and conditions*: i, $NOCl–CH_2Cl_2$, − 10 to − 20 °C; ii, Et_3N, room temp.; iii, $MeOH–NaNO_2–AcOH$, room temp.

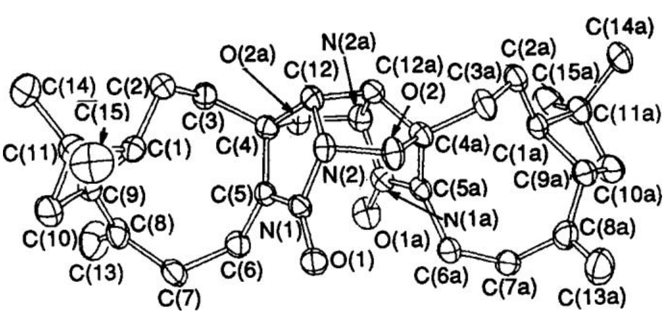


Fig. 1 Molecular structure of **7** from X-ray diffraction data

Fig. 1 shows the structure of molecule **7**.¶ The molecule has an approximate C_2 symmetry axis crossing it in the middle of the C(12)—C(12a) bond and transforming one half of the molecule into another with mean deviation 0.078 Å and maximum deviation 0.147 Å (in solution the molecule seems to possess a C_2 symmetry axis, since the ^{13}C NMR spectrum shows only 15 carbon signals). The variation of bond lengths within 3σ is consistent with this symmetry type except for the C(10)—C(11) and C(10a)—C(11a) bond lengths which vary within 4σ. The nine-membered rings have a twist-boat–chair conformation.[3] The isoxazoline rings have an envelope form where the O(2) and O(2a) atoms deviate from the ring planes by 0.367 Å and 0.398 Å, respectively. The same conformation is observed for the diazo rings, the deviating atoms being N(2) and N(2a) rather than C(12) and C(12a) (the deviations are 0.247 Å and 0.283 Å, respectively). Thus, the double bonds in these rings are twisted, the torsion angles C(4)—C(5)—N(1)—N(2) and C(4a)—C(5a)—N(1a)—N(2a) being 7.7(6)° and 10.8(6)°. It is worthwhile to note the shorter bond lengths [N(1)—O(1) 1.256(6) Å and N(1a)—O(1a) 1.254(7) Å] of the nitrone group as compared with literature data: 1.304(15) Å,[4] 1.293(3) Å,[5] and 1.27 Å.[6] The observed lengths [N(2)—O(2) 1.416(5) Å and N(2a)—O(2a) 1.418(5) Å] proved to be close to the literature value (1.425 Å[4]) for isoxazole. The bonds N(1)—N(2) 1.486(6) Å and N(1A)—N(2A) 1.485(8) Å are longer than the expected value [1.420(15) Å] for the fragment $N_{pyramidal}(3)$—$N_{planar}(3)$.[4]

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§ Compound **7**: m.p. 215–217 °C (MeCN); $[\alpha]^{26}_{580}$ +97.8 (*c* 2.29, $CHCl_3$); UV λ_{max}/nm (EtOH) 272 sh (logϵ 3.48), 235 (4.46), 206 (4.45); IR ν_{max}/cm^{-1} (KBr): 3066 (=C—H), 1635 (C=C), 1598 (=N→O), 961 (N—O), 914 (=CH_2); MS *m/z* (70 eV) 522 (M^+, 4%), 261 (M^+/2, 100%); ^1H NMR ($CDCl_3$, 200.13 MHz) δ 0.88 (s, 3H, 14-H_3), 0.90 (s, 3H, 15-H_3), 2.47 (ddd, 1H, 9-H, $J_{9,1}$ 9.55, $J_{9,10\alpha}$ 9.5, $J_{9,10\beta}$ 9.5 Hz), 3.00 (m, 1H), 4.76 (s, 1H, 13-Ha), 4.82 (s, 1H, 13-Hb), 4.93 (s, 1H, 12-H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 44.46 (d, C-1), 25.52 (t, C-2*), 29.16 (t, C-3*), 95.80 (s, C-4), 127.69 (s, C-5), 27.53 (t, C-6*), 26.34 (t, C-7*), 151.64 (s, C-8), 42.58 (d, C-9), 38.54 (t, C-10), 34.51 (s, C-11), 76.53 (d, C-12), 113.21 (t, C-13), 21.17 (q, C-14), 29.52 (q, C-15) (* denotes assignments which may be reversed).

¶ *Crystal data* for **7**: $C_{30}H_{42}N_4O_4$, $M = 522.68$, trigonal, space group $P3_2$, $a = b = 13.154(2)$ Å, $c = 15.547(3)$ Å, $\gamma = 120°$. Crystal dimensions 0.19 × 0.24 × 1.5 mm^3, $V = 2329.7(7)$ Å^3, $Z = 3$, $D_c = 1.12$ g cm^{-3}, $\mu = 0.57$ cm^{-1}, $F(000) = 846$, Syntex-P2_1 diffractometer with graphite-monochromated Cu-Kα-radiation, $\lambda = 1.54178$ Å, θ–2θ scan, $2\theta < 100°$, $I > 2\sigma(I)$, 1534 unique absorption-corrected intensities. The structure was solved using SHELX86, refinement was carried out using SHELX76 by full-matrix least-squares procedures (all non-H atoms anisotropic, H atoms isotropic). The final residuals R and R_w are 0.044 and 0.045. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, *J. Chem. Soc., Chem. Commun.*, Issue No. 1, 1992.