5-Methyl-5-nitrosohexan-2-one, reexamined

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Dedicated to Professor M. Tišler on the occasion of his 75th birthday
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Abstract
The conversion of 5-methyl-5-nitrohexan-2-one **1** into 5-methyl-5-nitrosohexan-2-one 5, isolated as the dimer **5a**, was reexamined. For all compounds prepared full experimental details including physical and NMR data with signal assignments are provided.

Keywords: Aliphatic nitro, hydroxylamino, nitroso compounds, aluminum amalgam reduction, mercuric oxide oxidation

Introduction

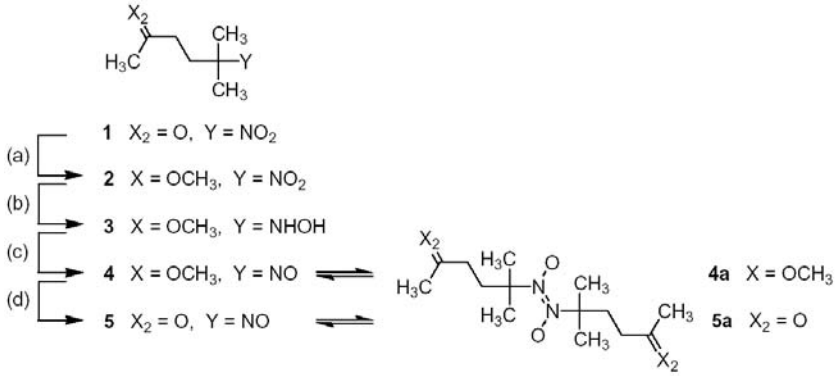
The condensation of aromatic nitroso compounds with primary aromatic amines is a general method for the preparation of unsymmetrical diazenes (azo compounds).[1] By contrast, this reaction is much less common in the aliphatic series; nitrosoalkanes appear to react more readily if they are substituted with electron-withdrawing groups as in nitrosoperfluoroalkanes.[2] However, since 4-methyl-4-nitrosopentan-2-one undergoes condensation with aniline furnishing the corresponding diazene[3] this reaction was considered to be applicable also to the homologous 5-methyl-5-nitrosohexan-2-one **5** (Scheme 1), and the formation of the desired diazene **6** (Scheme 2) was anticipated.

The preparation of the nitroso compound **5** by conversion of 5-methyl-5-nitrohexan-2-one **1** in the course of a multi-step synthesis has been reported[4] in the context of a study of the mass spectral fragmentation mechanism of the nitroso ketone dimer **5a**; the rather cursory synthetic procedures are lacking some physical data, and part of the spectroscopic data (^{1}H NMR) have not been unambiguously assigned. This prompts us to describe the detailed preparation of the title compound and its precursors; furthermore, all physical and NMR spectroscopic data including signal assignments based on two-dimensional NMR techniques are provided.

Results and Discussion

Nitro ketone **1** is readily accessible by base-induced addition of 2-nitropropane to but-3-en-2-one.[5] The strategy to convert the nitro group of **1** into the nitroso functionality of the desired

product **5** (Scheme 1) involves reduction to the hydroxylamine derivative and subsequent oxidation to the nitroso group. In order to prevent the interaction of the hydroxylamine functionality with the carbonyl group the latter has to be masked as ketal. Ketalization[6] with trimethyl orthoformate in the presence of water-free *p*-toluenesulfonic acid transformed the nitro ketone **1** into the nitro dimethyl ketal **2**. The literature lacks any data indicating the physical state of **2**.[4] Compound **2** is colorless oil that turned into a low melting solid (mp 8–10 °C) upon storage in the refrigerator. Nitro ketal **2** was reduced with aluminum amalgam[7] in ethanol/water yielding the hydroxylamine derivative **3,** a low-melting solid (the literature[4] does not provide any data referring to its physical state); in the solid state **3** is stable but solutions rapidly turn green due to air oxidation. The hydroxylamine **3** was oxidized with mercuric oxide,[8] the turquoise-blue color of the reaction solution is indicative of the nitroso functionality of **4**; the isolated product was the crystalline colorless dimer, the diazene 1,2-dioxide **4a**. Hydrolysis of the dimethyl ketal **4**/**4a** afforded the nitroso ketone **5**, the isolated product was the crystalline colorless dimer **5a**. The four-step conversion of the nitro ketone **2** into the nitroso ketone dimer **5a** was achieved with 49% overall yield.

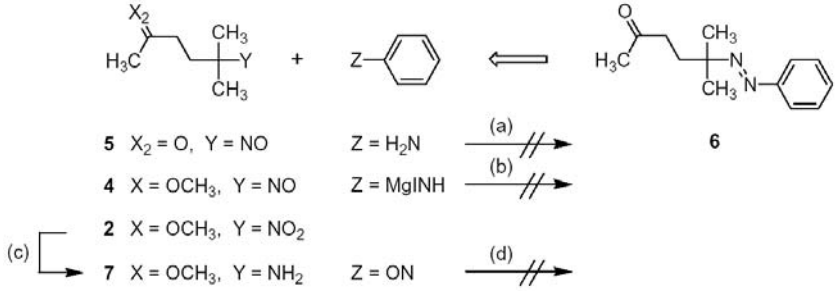


Scheme 1. (a) HC(OCH3)3, MeOH, TsOH, 60 °C, 24 h; 85%. (b) Al/Hg, H2O, EtOH; 94%. (c) HgO, CHCl3, reflux, 18 h; 75%. (d) TsOH·H2O, MeCN, H2O, 20 °C, 5 min; 81%.

When thin-layer chromatography (TLC) of the blue solution of the colorless dimers **4a** or **5a** was carried out immediately after the solution was prepared, only one spot was displayed (with upward tailing); this spot is attributed to the dimer **4a** or **5a**, respectively. Apparently, the concentration of the blue monomer (**4** or **5**) was too low for detection. However, when a concentrated solution of **4a** or **5a** was applied or a solution that was allowed to stand for a while (thereby establishing the equilibrium between dimer and monomer) the developing TLC-plate displayed a blue moving spot. This spot is attributed to the monomer **4** or **5**; it turned colorless after the solvent was evaporated (owing to dimer formation) and appeared at higher R_f-value in addition to the corresponding dimer spot at lower R_f-value.

The equilibration of dimers and monomers in solution (**4a** and **4**, **5a** and **5**) can be followed by ^{1}H NMR: In acetone-d_6 solution at 30 °C recording temperature the equilibrium was reached after 2 h, and the integration of significant signals of the two sets of ^{1}H NMR spectra revealed the equilibrium ratios between monomers and dimers: **4**/**4a** 90:10, **5**/**5a** 85:15.[10] Recording the NMR spectra immediately after dissolving the dimer **4a** or **5a** and observing the sets of shrinking and

growing signals allowed the assignment of the signals to dimer and monomer species,. Due to the low concentration of the dimers at equilibrium some of the ^{13}C NMR signals of **4a** and **5a** were observable only immediately after dissolution of these compounds. Application of two-dimensional NMR techniques (HMQC and HMBC) enabled the unambiguous assignment of ^{1}H and ^{13}C NMR signals of compounds **1**–**5**, **4a**, and **5a**.



Scheme 2. (a) AcOH or F3CCO2H/AcOH, CH2Cl2, 20 °C, 12 h. (b) Et2O, –10 °C; NH4Cl/H2O. (c) Raney-Ni, H2NNH2·H2O, EtOH. (d) AcOH, CH2Cl2, 20 °C, 12 h.

The purpose of the preparation of **5a** was to condense monomer **5** with aniline in anticipation of the formation of 5-methyl-5-(2-phenyl-1-diazenyl)hexan-2-one **6** (Scheme 2). Despite of examples of analogous condensation reaction[13] the acid catalyzed reaction (acetic acid, trifluoroacetic acid/acetic acid) of **5a**/**5** and aniline (at ambient temperature, 12 h) failed and led only to decomposition products. Also the reaction of **4a**/**4** with the Mg salt of aniline (prepared from aniline with isopropylmagnesium iodide) was unsuccessful.

Alternatively, the condensation of the aliphatic and aromatic reactants with reversed functionalities was considered, i.e. the reaction of 5,5-dimethoxy-2-methylhexan-2-amine **7** with nitrosobenzene (Scheme 2). To this goal, nitro ketal **2** was reduced with Raney-Ni and hydrazine hydrate, and the in situ formed amine **7** was treated with nitrosobenzene in acetic acid. This reaction also led only to decomposition products and did not provide the desired diazene **6**.

Experimental Section

General procedures. Spectroscopic data were recorded with the following instruments: Mattson Galaxy Series GL-3020 (IR); Bruker AM 300 (NMR: ^{1}H at 300 MHz, ^{13}C at 75 MHz). The assignment of ^{1}H and ^{13}C NMR signals is based on two-dimensional NMR techniques, heteronuclear multiple-quantum correlation (HMQC) and heteronuclear multiple-bond correlation (HMBC; weak correlations are placed in parentheses). Melting points (mp) were determined with a Kofler hot stage microscope (Reichert). Thin layer chromatography (TLC) was carried out on silica gel (Macherey-Nagel Polygram Sil G/UV254). PE refers to the petroleum ether fraction with boiling range 40–60 °C.

5-Methyl-5-nitrohexan-2-one (1). Prepared as described in the literature.[5] Colorless oil, bp 69–

71 °C (0.02 mbar), lit.[11] bp 88–91 °C (0.2 mm); n^{20} = 1.4460, lit.[11] n^{20} = 1.4450; *Rf* = 0.32 (ether/PE 1:1). IR (film): ν [cm^{-1}] 2993, 2941, 2876, 1718 (C=O), 1537 (ν_{as}NO2), 1474, 1398, 1373, 1348 (νsNO2), 1165, 856. ^{1}H NMR (CDCl3): δ 2.36 (t, *J* = 8.2 Hz, 2H, 3-CH2), 2.07 (t, *J* = 8.2 Hz, 2H, 4-CH2), 2.05 (s, 3H, 1-CH3), 1.47 (s, 6H, 2 CH3). ^{13}C NMR (CDCl3): δ 206.1 (C=O), 87.2 (5-C), 37.9 (3-CH2), 33.7 (4-CH2), 29.6 (1-CH3), 25.5 (2 CH3); HMQC ^{1}H/^{13}C: 2.36/37.9; 2.07/33.7; 2.05/29.6; 1.47/25.5. HMBC ^{1}H/^{13}C: 2.36/206.1, 87.2, (33.7);[12] 2.07/206.1, 87.2, (37.9), 25.5; 2.05/206.1, 37.9; 1.47/87.2, 33.7.

2,2-Dimethoxy-5-methyl-5-nitrohexane[4] (2). A stirred mixture of nitro ketone **1** (1.59 g, 10 mmol), trimethyl orthoformate (1.273 g, 12 mmol) and water-free *p*-toluenesulfonic acid[13] (10 mg, 0.06 mmol) in absolute methanol (20 mL) was heated to 60 °C for 24 h. Methyl formate as it was formed was continuously distilled off; after 20 h the distillation ceased. The reaction mixture was brought to ambient temperature, and a few drops of a methanolic solution of sodium methoxide [prepared by dissolving Na (0.5 g) in absolute methanol (10 mL)] were added. After addition of ether (20 mL) and water (20 mL) the organic layer was extracted with satd. NaCl solution (3 x 20 mL), the aqueous layer was extracted with ether (20 mL). The ether extracts were combined and dried (K2CO3), and the solvent was evaporated. The residual yellowish oil was distilled in high-vacuum yielding a colorless oil **2** (1.74 g, 8.49 mmol, 85%); bp 55 °C (0.03 mbar); n^{20} = 1.4433. Upon storage in theDrefrigerator the oil turned into a colorless solid **2**, mp 8–10 °C. IR (film): ~ν[cm^{-1}] 2991, 2947, 2831 (νH−CO), 1537 (νasNO2), 1456, 1398, 1379, 1348 (νsNO2), 1295, 1275, 1246, 1193, 1175, 1115 (νC−O), 1092, 1053 (νC−O), 854. ^{1}H NMR (acetone-*d*6): δ 3.09 (s, 6H, 2 CH3O), 1.93 (m, 2H, 4-CH2), 1.58 (s, 6H, 2 CH3), 1.52 (m, 2H, 3-CH2), 1.20 (s, 3H, 1-CH3).^{13}C NMR (acetone-*d*6): δ 101.1 (2-C), 88.4 (5-C), 47.5 (CH3O), 35.6 (4-CH2), 31.2 (3-CH2), 25.4 (2 CH3), 20.7 (1-CH3). HMQC ^{1}H/^{13}C: 3.09/47.5; 1.93/35.6; 1.58/25.4; 1.52/31.2; 1.20/20.7. HMBC ^{1}H/^{13}C: 3.09/101.1; 1.93/(101.1), (88.4), (31.2), (25.4); 1.58/88.4, 35.6; 1.52/(101.1), (88.4), (35.6), (20.7); 1.20/101.1, (47.5), 31.2.

2-(Hydroxyamino)-5,5-dimethoxy-2-methylhexane[4] (3). Aluminum foil[6] (3 g, 110 mmol, 0.02–0.03 mm thick) was cut to ribbons (25 x 2.5 cm), and each strip (approx. 190 mg) was rolled to a cylinder (1 cm diameter). Each aluminum coil was dipped (15 sec) into a solution of HgCl2 (0.81 g, 3 mmol) in water (40 mL); each amalgamated coil was rinsed with ether followed by ethanol before it was inserted into a 3-necked round-bottom flask (250 mL) equipped with a dropping funnel, a heavy-duty reflux condenser and filled with ether (150 mL) and water (10 mL). To the vigorously magnetically stirred heterogeneous mixture was added drop-wise (at such a rate to keep the ether refluxing) a solution of the nitro ketal **2** (11.9 g, 58 mmol) in ether (10 mL). The initial reaction (for 5−7 min) was very fierce, and additional cooling with an ice-bath was necessary to keep the reaction under control. After complete addition of **2**, stirring was continued for another 30 min (or until gas evolution had ceased). The gelatinous precipitate was left to settle (up to 1 h), and the supernatant colorless solution was decanted and filtered through a funnel with a cotton plug. The residual grey sludge was washed with ether (2 x 50 mL), and the extracts were combined with the filtrate. The ether solution was washed, in turn, with NaOH solution (2 M, 2 x 25 mL) and satd. NaCl solution. After drying (MgSO4) the solvent was removed under vacuum at a maximum temperature of 40 °C, and the color of the solution turned

slightly green. The residual crude product was distilled in high-vacuum affording a colorless oil **3**, bp 92 °C (0.04 mbar); when ~vstored in the refrigerator the strongly fishy smelling oil turned into a colorless crystalline [cmsolid **3** (800 mg, 4.18 mmol, 94%), mp 20–22 °C; *Rf* = 0.69 (ether/PE 1:1). IR (film):] 3430 (sh), 3340 (sh), 3254, 2961, 2829 (νH−CO), 1458, 1433, 1379, 1363, 1290, 1278, 1242, 1194, 1173, 1117 (νC−O), 1078, 1055 (νC−O), 849. ^{1}H NMR (acetone-*d*6): δ 7.5–4.5 (2 very broad s, 2H, OH, NH), 3.09 (s, 6H, 2 CH3O), 1.63–1.52 (m, 2H, 4-CH2), 1.46–1.36 (m, 2H, 3-CH2), 1.18 (s, 3H, 6-CH3), 1.02 (s, 6H, 2 CH3). ^{13}C NMR (acetone-*d*6): δ 101.9 (5C), 56.6 (2-C), 47.4 (br s, CH3O), 32.9 (3-CH2), 30.9 (4-CH2), 24.1 (2 CH3), 20.7 (6-CH3). HMQC ^{1}H/^{13}C: 3.09/47.4; 1.63–1.52/30.9; 1.46–1.36/32.9; 1.18/20.7. HMBC ^{1}H/^{13}C: 3.09/101.9; 1.63–1.52/101.9, 56.6, 32.9, 20.7; 1.46–1.36/101.9, 56.6, 30.9, 24.1; 1.18/101.9, (47.4), 30.9; 1.02/56.6, 32.9, 24.1.

2,2-Dimethoxy-5-methyl-5-nitrosohexane[4] 4 and (*E*,*Z*)-1,2-bis(4,4-dimethoxy-1,1-di-methylpentyl)diazene 1,2-dioxide[4] (4a). To a solution of hydroxylamine **3** (0.80 g, 4.2 mmol) in chloroform (10 mL) was added HgO (1.30 g, 6 mmol). The reaction mixture was vigorously stirred and heated to reflux; after 30 min the solution turned blue, and a black sludge (Hg) separated. After 18 h the solvent was evaporated, the residue was mixed with a small volume of ether, and the sludge consisting of Hg and HgO was removed by filtration through a short silica gel column. The turquoise-blue filtrate was dried (MgSO4), the solvent was evaporated, and the residue turned crystalline upon adding some pentane, cooling in an ice-bath and scratching. The crystals were filtered off, and treatment of the filtrate in the same way afforded an additional crop. The collected product was recrystallized from pentane to yield colorless prisms **4a** (600 mg, 1.59 mmol, 75%); mp 57–58 °C (pentane), lit.[4] mp 57– 58 °C (pentane); *Rf* = 0.38 (dimer **4a**), 0.65 (monomer **4**) (ether/PE 1:1). **Dimer 4a**: IR (KBr): ~ν[cm^{-1}] 3008, 2999, 2988, 2955, 2833 (νH−CO), 1637, 1618, 1474, 1458, 1383, 1370, 1294, 1265 (νas ON=NO), 1244, 1221, 1188, 1175, 1117 (νC−O), 1092, 1072, 1057 (νC−O), 1038, 851. ^{1}H NMR (acetone-*d*6; 10% **4a**)[14] : δ 3.11 (s, 12H, 4 CH3O), 2.10 (m, 4H, 2-CH2), 1.54 (s, 12H, 4 CH3), 1.50 (m, 4H, 3-CH2), 1.20 (s, 6H, 5-CH3). ^{13}C NMR (acetone-*d*6):[15] δ = 101.40 (4-C), 79.0 (1-C), 47.5 (CH3O), 32.0 (2-CH2), 31.4 (3-CH2), 24.0 (1,1-(CH3)2), 20.8 (5-CH3). HMQC ^{1}H/^{13}C: 3.11/47.5; 2.10/32.0; 1.54/24.0; 1.50/31.4; 1.20/20.8. HMBC ^{1}H/^{13}C: 3.11/101.40; 2.10/101.40, (79.0), (31.4), 24.0; 1.54/79.0, 32.0; 1.50/(101.40), 79.0, (32.0), 20.8; 1.20/(101.40), 31.4.

Monomer 4. ^{1}H NMR (acetone-*d*6; 90% **4**)[14]: δ3.08 (s, 6H, 2 CH3O) 2.04 (m, 2H, 4-CH2), 1.36 (m, 2H, 3-CH2), 1.23 (s, 3H, 1-CH3), 1.13 (s, 6H, 2 CH3). ^{13}C NMR (acetone-*d*6): δ101.43 (2-C), 99.0 (5-C), 47.4 (2 CH3O), 31.8 (4-CH2), 30.6 (3-CH2), 24.0 (2 CH3), 20.6 (1CH3), 20.5 (2 CH3). HMQC ^{1}H/^{13}C: 3.08/47.4; 2.04/31.8; 1.36/30.6; 1.23/20.6; 1.13/20.5. HMBC ^{1}H/^{13}C: 3.08/101.43; 2.04/(101.43), 99.0, 30.6, 20.5; 1.36/101.43, (99.0), 31.8, (20.6); 1.23/101.43, 30.6; 1.13/99.0, 31.8.

5-Methyl-5-nitrosohexan-2-one[4] 5 and **(*E*,*Z*)-1,2-bis(1,1-dimethyl-4-oxopentyl)diazene 1,2-dioxide**[4] (**5a).** A mixture of nitroso dimethyl ketal dimer **4a** (529 mg, 2.75 mmol) in moist acetonitrile (10 mL, 3% H2O) and *p*-toluenesulfonic acid monohydrate (10 mg) was stirred at ambient temperature for 5 min. The mixture was washed with satd. aqueous NaHCO3 solution

followed by satd. aqueous NaCl solution; the organic layer was dried (MgSO4) and concentrated in vacuum at ambient temperature. The residual blue oil upon cooling in the refrigerator and scratching in the presence of little pentane turned into a colorless crystalline solid **5a** (320 mg, 1.12 mmol, 81%); mp 54-55 °C (pentane), lit.[4] mp 53–55 °C (pentane); *Rf* = 0.14 (dimer **5a**), 0.51 (monomer **5**) (ether/PE 1:1).**Dimer 5a**: IR (KBr): ~ν[cm^{-1}] 3009, 2997, 2979, 2941, 1713 (C=O), 1637, 1473, 1448, 1414, 1389, 1369, 1358, 1300, 1267 (νas ON=NO), 1238, 1211, 1177, 1157, 1130. ^{1}H NMR (acetone-*d*6, 15% 5a)[14]: δ 2.43 (m, 4H, 3-CH2), 2.26 (m, 4H, 4-CH2), 2.08 (s, 6H, 5-CH3), 1.51 (s, 12H, 4 CH3). ^{13}C NMR (acetone-*d*6):[15] δ 206.33 (C=O), 78.9 (1-C), 38.4 (3-CH2), 31.2 (2-CH2), 29.22 (5-CH3), 23.6 (1,1-(CH3)2). HMQC ^{1}H/^{13}C: 2.43/38.4; 2.26/31.2; 2.08/29.22; 1.51/23.6. HMBC ^{1}H/^{13}C: 2.43/206.33, 78.9, (31.2), (29.22); 2.26/ 206.33, 78.9, (38.4), 29.22, 23.6; 2.08/206.33, 38.4; 1.51/ 78.9, 31.2.

Monomer 5. ^{1}H NMR (acetone-*d*6, 85%)[14]: δ 2.35 (m, 2H, 3-CH2), 2.20 (m, 2H, 4-CH2), 2.07 (s, 3H, 1-CH3), 1.09 (s, 6H, 2 CH3). ^{13}C NMR (acetone-*d*6): δ 206.40 (C=O), 98.6 (5-C), 37.4 (3-CH2), 30.7 (4-CH2), 29.17 (1-CH3), 20.4 (2 CH3). HMQC ^{1}H/^{13}C: 2.35/37.4; 2.20/30.7; 2.07/29.17; 1.09/20.4. HMBC ^{1}H/^{13}C: 2.35/206.40, 98.6, 30.7, (29.17); 2.20/206.40, 98.6, 37.4, 20.4; 2.07/206.40, 37.4; 1.09/98.6, 30.7.

References and Notes

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8. Originally,[4] sodium hypobromite has been employed for the oxidation of **3**; yellow or red mercuric oxide proved to be a more convenient oxidation reagent providing a higher yield of **4a**.
9. Reported overall yield: 4 26%.
10. In $CDCl_3$ solution different monomer/dimer ratios have been reported.[4] **4**/**4a** 70:30, **5**/**5a** 35:65; it is not clear if these figures refer to equilibrium conditions.
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12. No HMBC ^{1}H/^{13}C correlation cross-peak was observed at 2.36/29.
13. *p*-Toluenesulfonic acid monohydrate was dehydrated at 100 °C for 1 h.
14. Equilibrium ratio.
15. Some ^{13}C signals were detectable only with a freshly prepared solution of the dimer **4a** or **5a** before the equilibrium shifted to the predominant monomer **4** or **5**, respectively.