[Chem. Pharm. Bull. 31(12)4368–4375(1983)]

Nitration of 2-Cyclohexenone Derivatives and Some Reactions of the Products[1)]

KATSUHIDE MATOBA,* TAKASHI MORITA, and TAKAO YAMAZAKI

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930–01, Japan

(Received April 30, 1983)

5,5-Dimethyl-2-cyclohexenone (Ia) and isophorone (Ib) were nitrated with isoamyl nitrate using potassium metal in liquid ammonia to give 5,5-dimethyl-2-nitro-1,3-cyclohexadienol (III) and 3,5,5-trimethyl-2-nitro-2-cyclohexenone (IVb), respectively. Compound III was treated with diazomethane to give an oxime (VI) and an intermediate to VI (V). Compound VI was derived to 2-methoxy-4,4-dimethyl-2,5-cyclohexadienone (IX) *via* the nitrone (VIII) and then the hydroxydienone (IIb).

On the other hand, the reduction of IVb with sodium borohydride (SBH) was examined. The products were two epimeric nitro alcohols (Xa and XIa), a nitroketone (XII), and a nitro ester (XIII). Compound XIa was converted to Xa by using SBH or aqueous sodium hydroxide. Although the compound with axial acetate (XIc) was deacetoxylated under SBH reduction conditions, that with equatorial acetate (Xc) was inert to this reduction.

Keywords——α-nitro-α,β-unsaturated ketone; diazomethane; nitrone; 2-methoxy-2,5-cyclohexadienone; sodium borohydride; β-nitro alcohol; epimerization; deacetoxylation

The chemistry of aliphatic nitro compounds and their utility for organic syntheses have been extensively studied.[2)] The chemistry of nitro olefins is especially interesting from the viewpoint of reaction behavior,[3)] and an interesting and useful Diels–Alder reaction of β-nitro-α,β-unsaturated ketones was reported.[4)] On the other hand, no work on α-nitro-α,β-unsaturated ketones has yet appeared in the literature. Therefore, we investigated the nitration of 5,5-dimethyl-2-cyclohexenone (Ia), which was prepared from 3-ethoxy-5,5-dimethyl-2-cyclohexenone by reduction with lithium aluminum hydride.[5)] Compound Ia was metalated with potassium in liquid ammonia and then treated with isoamyl nitrate (method A) to give a crystalline compound after evaporation of the ammonia. The crude product was purified by recrystallization from methanol. In the nuclear magnetic resonance (NMR) spectrum, it exhibited two singlet signals at δ 1.00 (6H) and 2.42 ppm (2H) and two doublet signals at δ 5.76 and 6.75 ppm (each 1H). The infrared (IR) spectrum showed a strong absorption band at 1630 cm^{-1} due to potassium nitroenolate. The composition of this potassium salt was confirmed by the elemental analysis. However, the same salt could not be obtained by treatment of Ia with potassium *tert*-butoxide in *tert*-butanol followed by isoamyl nitrate (method B). Attempts to hydrolyze the salt with cold sulfuric acid in aqueous methanol to 5,5-dimethyl-3-cyclohexene-1,2-dione (IIa) or its enol isomer, 2-hydroxy-4,4-dimethyl-2,5-cyclohexadienone (IIb) (Nef reaction[6)]) were unsuccessful and gave only the corresponding neutralized product, as an oily substance, which exhibited an absorption band at 1585 cm^{-1} in the IR spectrum and a singlet signal at δ 2.60 ppm (2H) and two doublet signals coupled with each other at δ 5.58 and 6.55 ppm (each 1H) in the NMR spectrum. From these physical data, the structure of the neutralized product was suggested to be 5,5-dimethyl-2-nitro-1,3-cyclohexadienol (III) instead of the expected 5,5-dimethyl-2-nitro-2-cyclohexenone (IVa). By method A, the corresponding potassium salt was obtained from 3,5,5,-trimethyl-2-cyclohexenone (isophorone, Ib), but the salt could not be purified by recrystallization, so it was

neutralized with dilute sulfuric acid. The structure of the nitrated product, a crystalline compound, was established to be 3,5,5-trimethyl-2-nitro-2-cyclohexenone (IVb) by the following physical data. Compound IVb exhibited absorption bands at 1685 cm^{-1} due to the carbonyl group and at 1530 and 1380 cm^{-1} due to the nitro group in the IR spectrum, and it exhibited in the NMR spectrum four singlet signals at δ 1.08, 1.97, 2.36, and 2.45 ppm due to the geminal methyl, vinylic methyl, and two methylene protons, respectively. By method B, Ib gave IVb in 72.8% yield. Both of the nitrated products, III and IVb, were unstable and decomposed explosively when heated on a water bath even under a vacuum. Fortunately, the purification of III and IVb could be performed by recrystallization of the corresponding potassium salt and IVb itself, respectively. The potassium salt of IVb, which was obtained from IVb and potassium hydride in ether, exhibited a strong band at 1610 cm^{-1} due to potassium nitroenolate in the IR spectrum.

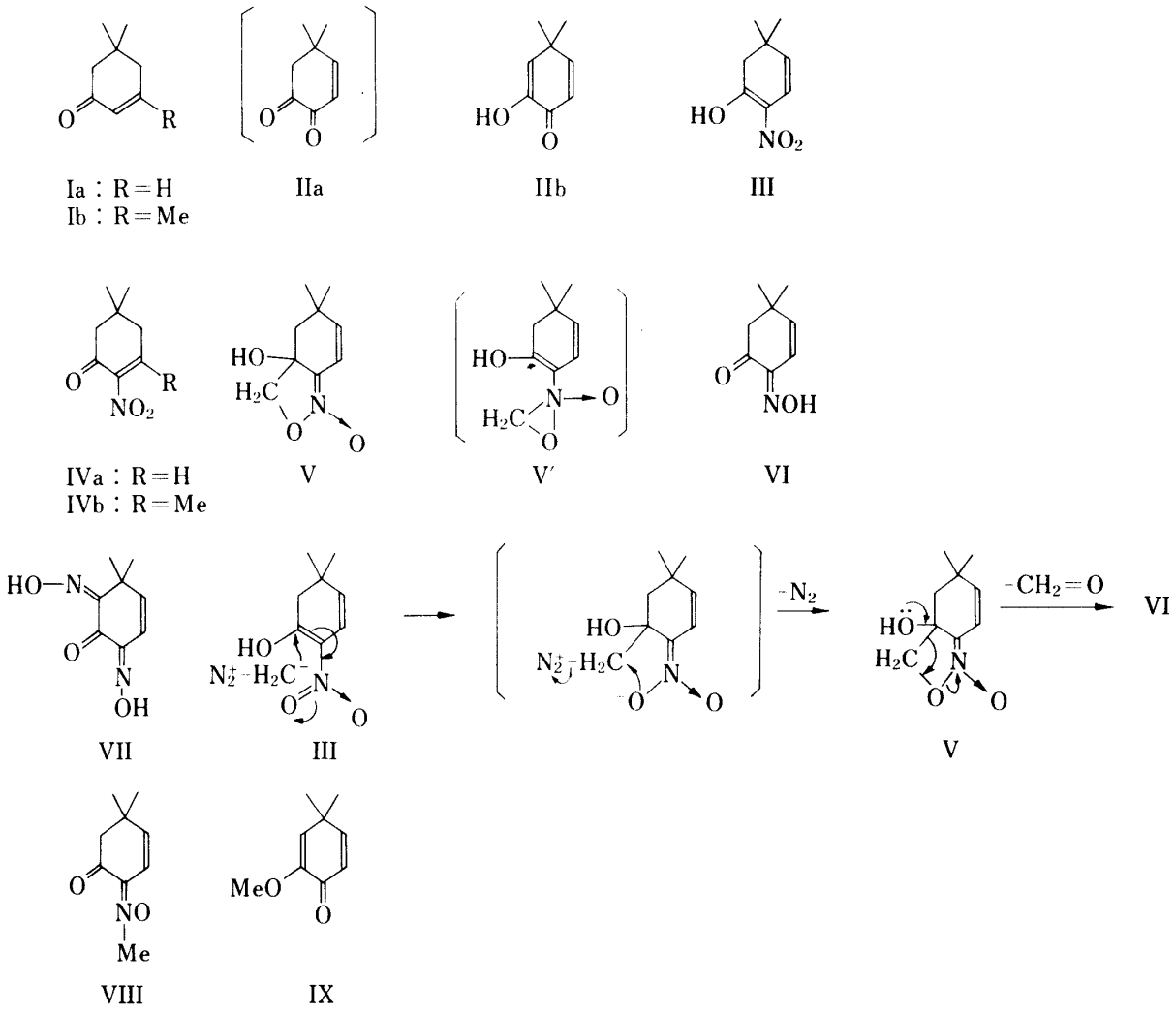

Chart 1

As the nitrated product, III, obtained from Ia has an enol function, it was treated with an excess of diazomethane to give mainly two products. From the following physical data and mechanistic consideration, they were suggested to be 3a-hydroxy-5,5-dimethyl-1-oxy-3,3a,4,5-tetrahydro-2,1-benzisoxazole (V) and 2-hydroxyimino-5,5-dimethyl-3-cyclohexenone (VI). Compound V exhibited in the IR spectrum a broad absorption band in the range of 3600—3200 cm^{-1} and a weak band at 1690 cm^{-1} due to the hydroxy and imine functions, respec-

tively. In the NMR spectrum, it exhibited three singlet signals at δ 1.10, 2.41 and 3.81 ppm and two doublet signals at δ 6.01 and 6.50 ppm due to two geminal methyl, two methylene and two vinylic protons, respectively. An alternative structure, epoxymethyleneimine (V′), might be adopted instead of V, judging from the literature,[7] but this structure was ruled out by the mass spectrum (MS), that is, the base peak, *m/e* 110, could be explained by the structure V, but not by the structure V′. On the other hand, VI exhibited absorption bands at 3220 and 1710 cm^{-1} due to hydroxy and carbonyl groups, respectively. It exhibited in the NMR spectrum two singlet signals at δ 1.12 and 2.60 ppm and two doublet signals at δ 6.37 and 6.95 ppm due to two geminal methyl, methylene and two vinylic protons, respectively. The isolated yields of V and VI were 2.9 and 36.8%, respectively. Compound V was unstable and changed gradually to VI on standing at room temperature. Therefore V is considered to be an intermediate in the formation of VI, which could also be obtained from the reaction of Ia with potassium metal and *n*-butyl nitrite in a yield of 38.6%. In this case, a small amount of 2,6-dihydroxyimino-5,5-dimethyl-3-cyclohexenone (VII) was isolated as a by-product. The proposed mechanism for the formation of VI *via* V from III is shown in Chart 1. Efforts to hydrolyze the oxime, VI, with titanium trichloride[8] were unsuccessful. Thus VI was further treated with an excess of diazomethane[9] to give a nitrone, 5,5-dimethyl-2-methylnitrono-3-cyclohexenone (VIII), quantitatively. Compound VIII exhibited in the NMR spectrum a signal due to nitronomethyl protons at δ 4.06 ppm. Compound VIII was hydrolyzed to IIb, the hydrolysate corresponding to VI, by treatment with 5% hydrochloric acid at room temperature. In the NMR spectrum of IIb, long-range coupling was observed between the C_3- and C_5-vinylic protons. The methylation of IIb could be performed as expected by treatment with dimethyl sulfate in basic medium to give 2-methoxy-4,4-dimethyl-2,5-cyclohexadienone (IX). However, with an excess of diazomethane, the starting material was recovered together with a small amount of the product IX, which was identified by comparison of its IR, NMR, and gas chromatography (GC) data with those of an authentic sample.[10] This product could be a useful model compound in biogenetic research. The method reported here affords a facile synthetic route to IX from Ia.

Next the reduction of IVb by using sodium borohydride (SBH) is described. Many reports on the reduction of α-nitroketones have appeared,[11] but none on α-nitro-α,β-unsaturated ketones. Compound IVb was treated with an equivalent amount of SBH in ethanol at room temperature for a long time to give mainly the all-*trans* nitroalcohol, 3,5,5-trimethyl-2-nitrocyclohexanol (Xa), which exhibited a multiplet signal between δ 3.4 and 4.6 ppm due to the C_2- and C_1-protons in the NMR spectrum. Compound Xa was derived to the corresponding *p*-nitrobenzoate (PNB), Xb, which exhibited in the NMR spectrum a triplet signal (J=10 Hz) at δ 4.40 ppm and a triplet-of-doublets signal (J=10 and 4.5 Hz) at δ 5.71 ppm due to the C_2- and C_1-protons, respectively. From these coupling constants, the conformation of Xa was determined. An isomer of Xa, the *cis*-nitroalcohol (XIa), was mainly obtained by reduction under ice-cooling. In the NMR spectra, XIa exhibited a double-doublet signal (J=10.5 and 2 Hz) at δ 4.10 ppm and a multiplet signal ($J_{H/2}$=6 Hz) at δ 4.42 ppm due to the C_2- and C_1-proton, respectively, and its PNB derivative (XIb) exhibited similar signals at δ 4.25 and 5.72 ppm due to the C_2- and C_1-proton, respectively. When XIb was prepared from XIa by treatment with *p*-nitrobenzoyl chloride in pyridine at room temperature, the starting material, XIa, was recovered in about 50% yield, but in the case of Xb such recovery was not observed. This behavior of XIa confirmed that XIa has an axial hydroxy group. In a similar fashion, XIa was scarcely acetylated by treatment with acetic anhydride in pyridine at room temperature, although Xa was smoothly acetylated to the all-*trans* nitroacetate, 1-acetoxy-3,5,5-trimethyl-2-nitrocyclohexane (Xc) under similar conditions. The XIa–acetate (XIc) could be obtained with difficulty by warming XIa with acetic anhydride in pyridine for 3 h on a water bath.

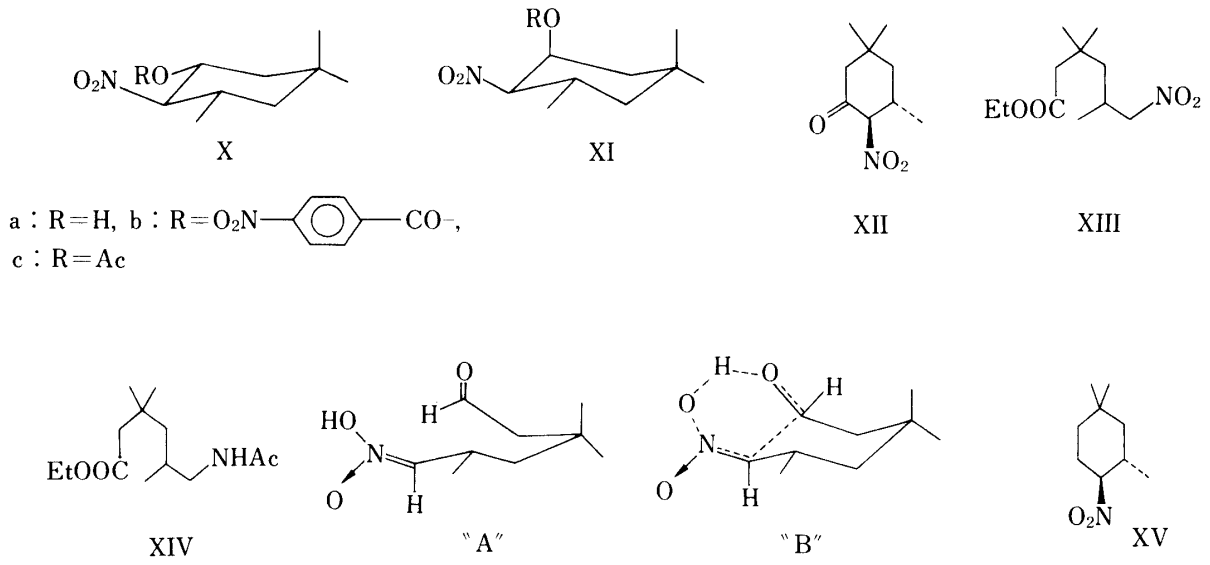

Chart 2

On the reduction of IVb, small amounts of two compounds were obtained together with the two major nitroalcohols, Xa and XIa, mentioned above. One was a crystalline compound, mp 89—90 °C, and exhibited a carbonyl band at 1730 cm^{-1} in the IR spectrum and a doublet signal ($J=12$ Hz) at δ 4.90 ppm due to the C_2-proton in the NMR spectrum. From the physical data, it was suggested to be *trans*-3,5,5-trimethyl-2-nitrocyclohexanone (XII), and this was confirmed by the elemental analysis. Recently Zajac *et al.*[11b] reported that the melting point of XII was 92.5—93.5 °C. The other product was an oily one. The existence of carbonyl and nitro groups in the molecule was suggested by the IR spectrum, and the 200 MHz NMR spectrum showed that it contains two tertiary methyl, secondary methyl, ethoxy, nitromethylene, and isolated methylene groups. In the MS, the parent peak corresponded to $C_{11}H_{21}NO_4$. From these physical data and mechanistic considerations, this oily product was suggested to be ethyl 3,3,5-trimethyl-6-nitrohexanoate (XIII), which may be formed by the attack of ethoxy anion on the carbonyl carbon of XII. Compound XIII was reduced catalytically in the presence of Raney nickel in acetic acid to the corresponding amino ester, which was derived to an amide ester, ethyl 6-acetylamino-3,3,5-trimethylhexanoate (XIV). The results of these reductions with SBH in ethanol are summarized in Table I.

α-Acetoxy nitro compounds are, in general, converted to the corresponding deacetoxylated compounds by SBH reduction. This method has been applied to the syntheses of various nitro compounds.[13] Thus, we investigated the behavior of the nitroacetates (Xc and XIc) toward SBH in ethanol. Prior to this experiment, studies on the nitroalcohols (Xa and XIa) were carried out. Although the *trans*-nitroalcohol, Xa, was stable to the reduction conditions, the *cis*-nitroalcohol, XIa, was changed to Xa in 86% yield, and the conversion could also be achieved by treatment of XIa with ethanolic sodium hydroxide in 90.2% yield. This transformation of XIa to Xa may proceed through an aci-nitro aldehyde intermediate ("A"). However, the corresponding reduced product from "A," for example, 6-nitro-3,3,5-trimethylhexanol, could not be detected among the products from IVb. All attempts to trap the intermediate using benzaldehyde or benzylamine were unsuccessful. Judging from these results, XIa may be epimerized to Xa through the six-membered intermediate ("B") rather than "A."

Next the deacetoxylation reactions of Xc and XIc were examined. Although XIc was deacetoxylated under SBH reduction conditions to give 2,4,4-trimethyl-1-nitrocyclohexane (XV) in good yield, Xc was inert to this reaction. Such inertness of a β-acetoxynitro

TABLE I. Results of Reduction with SBH in EtOH

Run No.	Starting material	Method of[a] addition	mol eq of SBH	Reaction conditions	Product distribution[b]				
					XII	Xa	XIa	XIII	IVb
1	IVb	R	0.5	1.5 h In ice-bath	16.4		13.2		36.4
2	IVb	R	1.5	1.5 h In ice-bath	3.0	17.5	40.9		
3	IVb	R	2.0	3.3 h In ice-bath		24.3	71.4		
4	IVb	R	1.0	48 h At r.t.		76.1			
5	IVb	N	1.0	1.5 h At r.t.	10.8	32.5		21.0	
6	XII	R	1.0	1.5 h In ice-bath			55.6	10.6	
7	XII	R	1.9	1.5 h At r.t.		90.0			

a) N, normal addition (IVb was added to an ethanolic solution of SBH); R, reverse addition (SBH was added to an ethanolic solution of IVb or XII).
b) Isolated yields (%).

compound towards deacetoxylation has not previously been reported in the literature. This phenomenon may be explained in terms of a *trans* anti-coplanar relationship between the acetoxy group and the proton at the carbon bearing the nitro group in XIc.

Experimental

All melting points are uncorrected. IR spectra were determined by using a JASCO IRA-1 diffraction grating spectrophotometer; absorption data are given in cm^{-1}. NMR spectra were recorded on JEOL PMX-60 and Varian XL-200 spectrometers with tetramethylsilane (TMS) as an internal standard unless otherwise mentioned. The chemical shifts and coupling constants (J) are given in δ and Hz, respectively. MS were measured with a JEOL JMS D-200 (70 eV, direct inlet system) spectrometer. Ultraviolet (UV) spectra were obtained in MeOH with a Hitachi 200-10 spectrophotometer, and absorption maxima are given in nm. GC was done on a Shimadzu GC-6AM machine equipped with a stainless steel column (3 mm × 2 m) of 5% SE-30. The carrier gas was N_2 (40 ml/min). All solvents were removed by evaporation under reduced pressure.

5,5-Dimethyl-2-nitro-1,3-cyclohexadienol (III)[14]——5,5-Dimethyl-2-cyclohexenone (Ia, 8.1 g, 65.3 mmol) was added dropwise over 10 min to a solution of KNH_2 [prepared from K (2.5 g, 64.1 mmol) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ in liquid ammonia (*ca.* 200 ml)]. The mixture was stirred for 2 h, then isoamyl nitrate (14.8 g, 111.3 mmol) was added dropwise over 1 h at −78 °C. The mixture was then stirred overnight and the ammonia was allowed to evaporate off to give a yellow substance, which was washed with anhyd. Et_2O on a filter and recrystallized from MeOH. Potassium salt of III: mp 288—289 °C (dec.). The yield was 7.1 g (52.3%). IR (Nujol): ν 1630. NMR (D_2O, internal standard: DSS): 1.00 (6H, s, geminal CH_3), 2.42 (2H, s, $>CH_2$), 5.76 and 6.75 (each 1H, d, J=11, C_3– and C_4–H). *Anal.* Calcd for $C_8H_{10}KNO_3$: C, 46.36; H, 4.86; N, 6.76. Found: C, 46.17; H, 4.84; N, 7.18.

This potassium salt (1.6 g) was added portionwise to 50% H_2SO_4–$CHCl_3$ (1 : 1) at 0 °C. The mixture was stirred for 1 h, then the organic layer was separated, washed with brine and dried. The solvent was removed to give a viscous oil (1.4 g), which could not be distilled without explosive decomposition. However, it was found from the NMR analysis to be almost pure. III: IR (film): ν_{OH} 3500—3000, ν 1585. NMR (CCl_4): 1.13 (6H, s, geminal CH_3), 2.60 (2H, s, $>CH_2$), 5.58 and 6.55 (each 1H, d, J=9.5, C_3– and C_4–H), 14.7 (1H, br s, –OH). $FeCl_3$ test: positive (brown-black).

3,5,5-Trimethyl-2-nitro-2-cyclohexenone (IVb)——1) In a manner (method A) similar to that used in the preparation of III, the reation of K (1.5 g, 38 mmol), isophorone (Ib, 5.3 g, 38 mmol), and isoamyl nitrate (8.9 g, 70 mmol) gave the potassium salt of IVb, which was neutralized with dil. H_2SO_4 in $CHCl_3$. The crude IVb obtained after evaporation of the solvent was purified through an SiO_2 column. Elution with benzene gave IVb, which was recrystallized from aq. EtOH. mp 48—50 °C (yellow prisms). The yield was 3.0 g (44.1%). IR (Nujol): $\nu_{C=O}$ 1685, ν_{NO} 1530, 1380. UV, λ_{max} 235 (*cf*: Ib, λ_{max} 236). NMR (CCl_4): 1.08 (6H, s, geminal CH_3), 1.97 (3H, s, vinylic CH_3), 2.36

and 2.45 (each 2H, s, $2\times CH_2<$). $FeCl_3$ test: negative. *Anal.* Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.00, H, 7.20; N, 7.66.

2) (Method B) A solution of Ib (2 g, 14.5 mmol) in anhyd. Et_2O and then isoamyl nitrate (6.2 g, 46.6 mmol) were added successively over each 1 h to a solution of *tert*-BuOK [prepared from K metal (1.2 g, 30.8 mmol)] in *tert*-BuOH at room temperature. After being stirred overnight, the mixture was poured into ice-water, and extracted with Et_2O. The residue obtained from the Et_2O layer was purified by SiO_2 column chromatography. Elution with benzene provided pure IVb in a yield of 72.8%.

IVb–potassium salt was quantitatively obtained by treatment of IVb in Et_2O with a small excess of KH (20.6% in oil). mp 176—180 °C (recrystallized from MeOH). IR (Nujol): ν 1610. NMR (D_2O, internal standard: DSS): 1.03 (6H, s, geminal CH_3), 2.03 (3H, s, vinylic CH_3), 2.31 (2H, s, $>CH_2$), 5.60 (1H, s, vinylic H). *Anal.* Calcd for $C_9H_{12}KNO_3\cdot 0.7H_2O$: C, 45.96; H, 5.55; N, 6.37. Found: C, 46.21; H, 5.77; N, 5.99.

Reaction of III with CH_2N_2——An excess of CH_2N_2 etherate was added to a methanolic solution of III (0.9 g) under ice-cooling. The reaction took place spontaneously with gas evolution, and then the mixture was allowed to stand overnight. The residue obtained after evaporation of the solvent was separated by SiO_2 column chromatography. 3a-Hydroxy-5,5-dimethyl-1-oxy-3,3a,4,5-tetrahydro-2,1-benzisoxazole (V) and 2-hydroxyimino-5,5-dimethyl-3-cyclohexenone (VI) were eluted with benzene and $CHCl_3$ in yields of 40 mg (2.9%) and 430 mg (36.8%), respectively. V: mp 71—73 °C (yellow needles from aq. MeOH). $FeCl_3$ test: positive (black). IR ($CHCl_3$): ν_{OH} 3600—3200 (w and br) $\nu_{C=N}$ 1690 (w) ν_{NO} 1520 (s). NMR (CCl_4): 1.10 (6H, s, geminal CH_3), 2.41 and 3.81 (each 2H, s, $>CH_2$), 6.01 and 6.50 (each 1H, d, $J=10.5$, vinylic H). MS *m/e* (%): 183 (M^+, 65), 153 (VI, 28), 110 ($(CH_3)_2C^+-CH=CH-C\equiv N\rightarrow O$, base peak). *Anal.* Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.14; H, 7.26; N, 7.82. VI: mp 132—134 °C (white plates from hexane–benzene). $FeCl_3$ test: positive (black). IR (Nujol): ν_{OH} 3140, $\nu_{C=O}$ 1715, ($CHCl_3$): ν_{OH} 3220, $\nu_{C=O}$ 1710. NMR ($CDCl_3$): 1.12 (6H, s, geminal CH_3), 2.60 (2H, s, $>CH_2$), 6.37 and 6.95 (each 1H, d, $J=10.5$, C_3– and C_4–H). MS *m/e* (%): 153 (M^+, base peak), 136 (M^+-OH, 33), 94 ($(CH_3)_2C^+-CH=CH-C\equiv N$, 94). *Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.73; H, 7.24; N, 8.90.

2,6-Dihydroxyimino-5,5-dimethyl-3-cyclohexenone (VII)——Ia (4.2 g, 33.9 mmol) was added dropwise over 10 min to a solution of KNH_2 (prepared from K (1.3 g, 33.3 mmol) in the presence of a catalytic amount of $Fe(NO_3)_3\cdot 9H_2O$ in liq. NH_3 (*ca.* 100 ml)). After the mixture had been stirred for 2 h, *n*-butyl nitrite (3.5 g, 34.0 mmol) was added dropwise over 1 h at −78 °C. The mixture was then stirred overnight and the NH_3 was allowed to evaporate off to give a black residue, which was washed with anhyd. Et_2O. The solid residue was dissolved in water and acidified with 5%HCl with ice-cooling. The solution was extracted with Et_2O and the Et_2O extract was separated by SiO_2 column chromatography. VI (2 g, 38.6%) and VII (0.15 g, 2.4%) were eluted with benzene and $CHCl_3$–MeOH (19 : 1), respectively. VII: mp 210 °C (recrystallized from aq. MeOH). NMR (DMSO-d_6): 1.33 (6H, s, geminal CH_3), 5.90 (1H, d, $J=10.5$, C_3–H), 6.60 (1H, d, $J=10.5$, C_4–H). *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.75; H, 5.50; N, 15.22.

5,5-Dimethyl-2-methylnitrono-3-cyclohexenone (VIII)——An excess of CH_2N_2 etherate was added to a methanolic solution of VI with ice-cooling. The mixture was allowed to stand overnight, then the solvent was removed to give a residue, which was purified by SiO_2 column chromatography. VIII was obtained in the $CHCl_3$ eluate. The yield was quantitative. mp 51—54 °C (recrystallized from aq. MeOH). NMR (CCl_4): 1.16 (6H, s, geminal CH_3), 2.50 (2H, s, $>CH_2$), 4.06 (3H, s, >N(O)Me), 6.00 (1H, d, $J=10$, C_3–H), 6.83 (1H, d, $J=10$, C_4–H). *Anal.* Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: 64.56; H, 8.00; N, 8.67.

2-Hydroxy-4,4-dimethyl-2,5-cyclohexadienone (IIb)——VIII (0.1 g) was treated with 10% HCl–aq. MeOH (1 : 1, 5 ml) and the mixture was stirred at room temperature for 1 h, then diluted with water and extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated to give IIb as an oily compound in quantitative yield. NMR ($CDCl_3$): 1.30 (6H, s, geminal CH_3), 5.97 (1H, d, $J=3.5$, C_3–H), 6.24 (1H, d, $J=10$, C_6–H), 6.87 (1H, dd, $J=10$, 3.5, C_5–H).

2-Methoxy-4,4-dimethyl-2,5-cyclohexadienone (IX)——A 10% aq. NaOH solution was added dropwise to the mixture of IIb and Me_2SO_4 (3 mol eq) at 80 °C until it was no longer consumed. The Et_2O extract was washed with brine, dried and evaporated. The residue was fractionated by SiO_2 column chromatography. IX was eluted with hexane–Et_2O (4 : 1) in quantitative yield. GC (140 °C): t_R 4.1 min. NMR (CCl_4): 1.27 (6H, s, geminal CH_3), 3.58 (3H, s, OMe), 5.69 (1H, d, $J=2$, C_3–H), 6.08 (1H, d, $J=9.5$, C_6–H), 6.73 (1H, dd, $J=9.5$, 2, C_5–H). IX was identified by IR, NMR, and GC comparisons with an authentic sample prepared from 4,4-dimethyl-2-cyclohexenone.[10]

All-*trans* 3,5,5-trimethyl-2-nitrocyclohexanol (Xa)——SBH (mol eq) was added portionwise to an ethanolic solution of IVb (0.9 g) at room temperature over 15 min. The mixture was stirred for 48 h, diluted with ice-water, and extracted with Et_2O. The organic layer was washed with brine, dried and then concentrated. GC (180 °C) t_R 1.4 min. NMR (CCl_4): 0.96 (3H, d, $J=7$, C_3–CH_3), 1.06 and 1.10 (each 3H, s, geminal CH_3), 3.4—4.6 (2H, m, C_1– and C_2–H), 3.5 (1H, br s, –OH). mp 63—65 °C (recrystallized from hexane). IR (Nujol): ν_{OH} 3610, ν_{NO} 1550, 1375. *Anal.* Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.83; H, 9.04; N, 7.48. The yield was 0.7 g (76.1%).

Xa–PNB (Xb): mp 138—140 °C (recrystallized from aq. EtOH). NMR ($CDCl_3$): 4.40 (1H, t, $J=10$, C_2–H), 5.71 (1H, td, $J=4.5$, 10, C_1–H), 8.18 and 8.31 (each 2H, d, $J=8$, aromatic H). *Anal.* Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13;

H, 5.99; N, 8.33. Found: C, 57.21; H, 6.04; N, 8.28. The yield was 78.4%.

Xa–acetate (Xc): GC (180 °C) t_R 1.6 min. IR (film): $\nu_{C=O}$ 1745, ν_{NO} 1550, 1370. NMR (CCl_4): 0.85 (3H, d, $J=7$, C_3–CH_3), 0.98 and 1.13 (each 3H, s, geminal CH_3), 4.06 (1H, t, $J=11$, C_2–H), 5.30 (1H, td, $J=11$, 4.5, C_1–H). MS *m/e* (%): 230 ($M^+ + 1$, 2.5), 183 ($M^+ - NO_2$, 2.9), 123 ($M^+ - NO_2 - AcOH$, base peak), 43 (Ac^+, 80). The acetylation yield was 82.2%.

Diastereomer of Xa (XIa)——SBH (0.5 g, 13.2 mmol) was added portionwise to an ethanolic mixture of IVb (1.2 g, 6.6 mmol) with ice-cooling over 10 min. The reaction mixture was stirred for 3.3 h in an ice-bath. The crystalline compound obtained after usual work-up was fractionally recrystallized from hexane. XIa: 875 mg (71.4%), Xa: 298 mg (24.3%). XIa: mp 73—75 °C GC (180 °C): t_R 1.2 min. IR (Nujol): ν_{OH} 3570, ν_{NO} 1540, 1380. NMR ($CDCl_3$): 0.93 and 1.12 (each 3H, s, geminal CH_3), 0.98 (3H, d, $J=7$, C_3–CH_3), 2.62 (1H, br s, –OH), 2.5—2.8 (1H, m, C_3–H), 4.10 (1H, dd, $J=10.5$, 2, C_2–H), 4.42 (1H, m, $J_{H/2}=6$, C_1–H). *Anal.* Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.54; H, 9.24; N, 7.40.

XIa–PNB (XIb): mp 169—171 °C (recrystallized from aq. EtOH). NMR (CCl_4): 4.25 (1H, dd, $J=12$, 3, C_2–H), 5.72 (1H, m, $J_{H/2}=7$, C_1–H), 8.16 and 8.34 (each 2H, d, $J=7$, aromatic H). *Anal.* Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.18; H, 5.94; N, 8.40. The yield of XIb from XIa was 44% and XIa was recovered in 50% yield.

XIa–acetate (XIc): A mixture of XIa (47 mg), Ac_2O (1 ml), and pyridine (3 ml) was heated on a water bath for 2 h. Water was added to decompose excess Ac_2O. The solid obtained after concentration of the mixture was recrystallized from aq. EtOH. mp 92—94 °C. XIc: 30 mg (52.1%). GC (180 °C) t_R 1.8 min. NMR (CCl_4): 0.95 and 1.12 (each 3H, s, geminal CH_3), 1.02 (3H, d, $J=7.5$, C_3–CH_3), 2.15 (3H, s, –Ac), 4.13 (1H, dd, $J=11$, 3.5, C_2–H), 5.50 (1H, br s, $J_{H/2}=9$, C_1–H). MS *m/e* (%): 230 ($M^+ + 1$, 0.5), 183 ($M^+ - NO_2$, 5.6), 123 ($M^+ - NO_2 - AcOH$, base peak), 43 (Ac^+, 73). *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.45; H, 8.23; N, 6.25. The mother liquor was acidified with 5%HCl and extracted with CH_2Cl_2. The extract was dried, and XIa (13 mg, 27.7%) was obtained by evaporation of the CH_2Cl_2. XIa was identified by means of NMR.

***trans*-3,5,5-Trimethyl-2-nitrocyclohexanone (XII)**——SBH (91 mg, 2.4 mmol) was added to an ethanolic solution of IVb (865 mg, 4.7 mmol) with ice-cooling. The mixture was stirred for 1.5 h in an ice-bath. The residue obtained after usual work-up was fractionated by SiO_2 column chromatography. Elution with benzene gave XII (140 mg, 16.4%), IVb (181 mg, 36.4%), and XIa (114 mg, 13.2%) successively. XII: mp 89—90 °C (lit.[11b] mp 92.5—93.5 °C) (recrystallized from aq. EtOH). IR (Nujol): $\nu_{C=O}$ 1730, ν_{NO} 1555, 1390. NMR (CCl_4): 1.02 and 1.13 (each 3H, s, geminal CH_3), 1.10 (3H, d, $J=6$, C_3–CH_3), 2.30 (2H, br s, –CO–CH_2–), 2.4—3.1 (1H, m, C_3–H), 4.90 (1H, d, $J=12$, C_2–H). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.50; H, 8.06; N, 7.66.

Ethyl 3,3,5-Trimethyl-6-nitrohexanoate (XIII)——A solution of IVb (0.29 g, 1.6 mmol) in EtOH was added to an ethanolic solution of SBH (62 mg, 1.6 mmol) over 10 min at r.t. The mixture was stirred for 1.5 h at r.t. and worked up in the usual manner to give an oily compound, which was fractionated by SiO_2 column chromatography. Elution with benzene gave XIII (76.9 mg, 21.1%), XII (31.6 mg, 10.8%), and Xa (96.2 mg, 32.5%) successively. XIII: GC (180 °C) t_R 3.0 min, (150 °C) t_R 7.2 min. NMR ($CDCl_3$): 1.06 (6H, s, geminal CH_3), 1.08 (3H, d, $J=7$, C_5–CH_3), 1.26 (3H, t, $J=7$, –CH_2–CH_3), 1.32 (1H, dd, $J=15$, 6, C_4–H), 1.46 (1H, dd, $J=15$, 4, C_4–H), 2.24 (2H, s, C_2–H), 2.3—2.5 (1H, m, C_5–H), 4.14 (2H, q, $J=7$, –OCH_2–), 4.20 (1H, dd, $J=12$, 10, C_6–H), 4.41 (1H, dd, $J=12$, 7, C_6–H). MS *m/e* (%): 232 ($M^+ + 1$, 0.8), 186 (M – OEt, 33).

Ethyl 6-Acetylamino-3,3,5-trimethylhexanoate (XIV)——XIII was reduced with Raney Ni under an H_2 atmosphere at r.t. in an autoclave (50 atm) for 18 h. The filtrate was concentrated to give an oily residue, which was successively acetylated at r.t. The crude product after the usual work-up was fractionated by SiO_2 column chromatography. An oily compound obtained from the $CHCl_3$–MeOH (19 : 1) eluate was microdistilled. The yield of XIV from XIII was about 80%. bp < 160 °C (0.2 mmHg) GC (200 °C) t_R 3.2 min. NMR (CCl_4): 0.97 (6H, s, geminal CH_3), 1.24 (3H, t, $J=7$, –CH_2–CH_3), 1.91 (3H, s, –Ac), 3.00 (2H, br t, $J=5.5$, –NH–CH_2–), 4.07 (2H, q, $J=7$, –OCH_2–). MS *m/e* (%): 243 (M^+, 12), 198 (M – OEt, 20), 156 (*m/e* 198-ketene, base peak). *Anal.* Calcd for $C_{13}H_{25}NO_3 \cdot 0.6H_2O$: C, 61.43; H, 10.39; N, 5.51. Found: C, 61.53; H, 10.03; N, 5.34.

Transformation of XIa to Xa——a) Using SBH: SBH (10.5 mg, 0.28 mmol) was added to an ethanolic solution of XIa (33.7 mg, 0.18 mmol). After being stirred at r.t. for 1.5 h, the mixture was worked up in the usual manner to give Xa (29.0 mg, 86.0%). The purity of Xa was checked by GC and NMR.

b) Using aq. NaOH: A 10% aq. NaOH solution (3 drops) was added to an ethanolic solution of XIa (10.2 mg). After being neutralized with AcOH, the mixture was extracted with CH_2Cl_2. The organic layer was evaporated after dryness to give Xa (9.2 mg, 90.2%).

Attempts to Trap Intermediate "A"——SBH (3 mol eq) or 10% aq. NaOH solution (5 drops) was added to an ethanolic solution of XIa (*ca.* 50 mg) and benzaldehyde or benzylamine (each 1 mol eq) at r.t. The usual work-up after 1 h gave Xa in a crystalline state in moderate yield in all cases. NMR and GC were used for identification of Xa.

Deacetoxylation of Xc——Xc (87.1 mg, 0.38 mmol) was treated with SBH (60.4 mg, 1.6 mmol) in EtOH at r.t. for 1.5 h. After usual work-up, Xc (75.6 mg, 86.8%) was recovered (checked by GC and NMR).

Deacetoxylation of XIc——XIc (42 mg, 0.18 mmol) was treated with SBH (28.5 mg, 0.75 mmol) in the same manner as mentioned above to give 2,4,4-trimethyl-1-nitrohexane (XV). GC (180 °C) t_R 1.2 min (*cf.* XIc: 1.8 min). MS

m/e (%): 125 ($M-NO_2$, 25), 69 ($C_5H_9^+$, base peak). IR (film): ν_{NO} 1550, 1370. NMR (CCl_4): 0.91 and 1.00 (each 3H, s, geminal CH_3), 1.00 (3H, d, $J=8$, $>CH-\underline{CH_3}$), 4.02 (1H, td, $J=10$, 2.5, $>CH-NO_2$).

Acknowledgement The authors wish to express their gratitude to Prof. E. Yoshii of this faculty for his valuable advice and encouragement, and to Mr. M. Ogawa for the elemental analyses.

References and Notes

1) A part of this work was presented at the 56th Meeting of the Hokuriku Branch of the Pharmaceutical Society of Japan, Kanazawa, June 1982, and reported in a preliminary form; K. Matoba and T. Yamazaki, *Chem. Pharm. Bull.*, **30**, 3863 (1982).
2) N. Ono and A. Kaji, *Yuki Gosei Kagaku Kyokai Shi*, **38**, 115 (1980).
3) E. J. Corey and H. Estreicher, *J. Am. Chem. Soc.*, **100**, 6294 (1978).
4) E. J. Corey and H. Estreicher, *Tetrahedron Lett.*, **1981**, 603.
5) W. F. Gannon and H. O. House, "Organic Synthesis," Coll. Vol. V, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 294.
6) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).
7) H. J. Backer, *Rec. Trav. Chim.*, **69**, 610 (1950) [*Chem. Abstr.*, **44**, 7222*e* (1950)].
8) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, **1971**, 195.
9) B. Eistert, R. Mueller, H. Selzer, and E. A. Hackmann, *Chem. Ber.*, **97**, 2469 (1964).
10) K. Matoba, N. Karibe, and T. Yamazaki, *Chem. Pharm. Bull.*, **30**, 3906 (1982).
11) *a*) A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, **33**, 1733 (1968); *b*) P. Dampawan and W. W. Zajac, Jr., *Tetrahedron Lett.*, **23**, 135 (1982); *c*) *Idem*, *J. Org. Chem.*, **47**, 1176 (1982).
12) P. J. Moles and S. T. Reid, *Tetrahedron Lett.*, **1976**, 2283; R. G. Duranleau and R. F. Love, U. S. patent 3816410 (1974) [*Chem. Abstr.*, **81**, 49286 (1974)].
13) G. B. Backman and R. J. Maleski, *J. Org. Chem.*, **37**, 2810 (1972). M. Yoshikawa, Y. Ikeda, H. Kayakiri, and I. Kitagawa, *Heterocycles*, **17**, 209 (1982).
14) R. H. Fischer and H. M. Weitz, *Synthesis*, **1980**, 261.