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Syntheses of Some Branched-chain Nitrocycloalkanols[1]

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Base-catalyzed cyclizations of glutaraldehyde with nitroethane, β-nitropropionic acid, β-nitro-α-methoxypropionic acid, and methyl vinyl ketone were investigated. The structures of these resulting nitrocycloalkanols were determined by NMR analysis and chemical reactions.

The base-catalyzed cyclization of γ- and δ-dialdehydes with nitromethane to give nitrocycloalkanols has been developed into a useful method for the preparation of 3-amino-3-deoxyhexosides or analogous aminocycloalkanols.[3] Recently, it was also reported that cyclization of nitroethane with δ-dialdehydes obtained from hexopyranosides successfully gave some 3-deoxy-3-C-methyl-3-nitrohexopyranosides.[4]

In connection with other synthetic study, we were required to develop a method for the synthesis of 1-substituted 1-nitrocyclohexane derivatives. Accordingly, we investigated some analogous cyclization of glutaraldehyde with nitroethane, β-nitropropionic acid, and β-nitro-α-methoxypropionic acid, which forms the subject of this paper.

Following Lichtenthaler's method for preparing *trans*-2-nitrocyclohexane-1,3-diol[5] (I), glutaraldehyde was treated with nitroethane in the presence of sodium hydroxide at pH 9 to give a nitro-diol (IIa), $C_7H_{13}O_4N$, mp 134—136°, in 43% yield. Acetylation of IIa yielded a diacetate (IIb) of mp 86—87°. Hydrogenation of IIa over platinum in ethanol gave an amino-diol (IIIa), mp 219—220°, while in acetic acid it afforded a hydroacetate of IIIa, mp 191—195° (decomp.). IIa formed an amide-diacetate (IIIb) of mp 174—176°, which was treated with a base to give amide-diol (IIIc) of mp 153—155°. The NMR analysis of these acetates (IIb and IIIb) showed that each absorption corresponding to methyl protons of two O-acetyl groups was completely superimposed at 2.00 (for IIb) or at 2.08 (for IIIb) ppm, suggesting that these two O-acetyl groups had the same orientation, a *cis*-configuration. Treatment of the amino-diol (IIIa) with nitrous acid gave a crystalline unsaturated diol (IV) of mp 143—144° and an oily hydroxyaldehyde (V) of bp 120° (10 mmHg) (bath temp.). The infrared absorption of IV at 1654 and 902 cm^{-1} showed the presence of an exocyclic methylene group. V reduced the Tollen's reagent and Fehling solution, and its infrared spectrum exhibited absorptions at 2740 and 1727 cm^{-1} in addition to the hydroxyl absorption, indicating the presence of an aldehyde function. In addition, singlet signals in the NMR spectrum of V corresponding to methyl protons and an aldehyde proton also suggested that these functions were located on a quaternary carbon like V. The fact that the deamination of IIIa did not give any cyclohexanone derivative but yielded IV and V illustrated that the orientation of the amino group of IIIa was opposite to those of the two hydroxyl groups and presumably the deamination reaction proceeded by the pathway shown in Chart 1. On the

1) Presented at the Annual Meeting of the Pharmaceutical Society of Japan, October 1966, Sendai.
2) Location: *Hiromachi, Sinagawa-ku, Tokyo.*
3) H.H. Baer and H.O.L. Fischer, *J. Am. Chem. Soc.*, **81**, 5184 (1959); F.W. Lichtenthaler; *cf. Angew. Chem.*, **76**, 85 (1964) for a recent review.
4) S.W. Grunner, W.G. Overland, and N.R. Williams, *Chem. Ind.* (London), 1523 (1964); H.H. Baer and G.V. Rao, *Ann. Chem.*, **686**, 210 (1965).
5) F.W. Lichtenthaler, *Chem. Ber.*, **96**, 845 (1963).

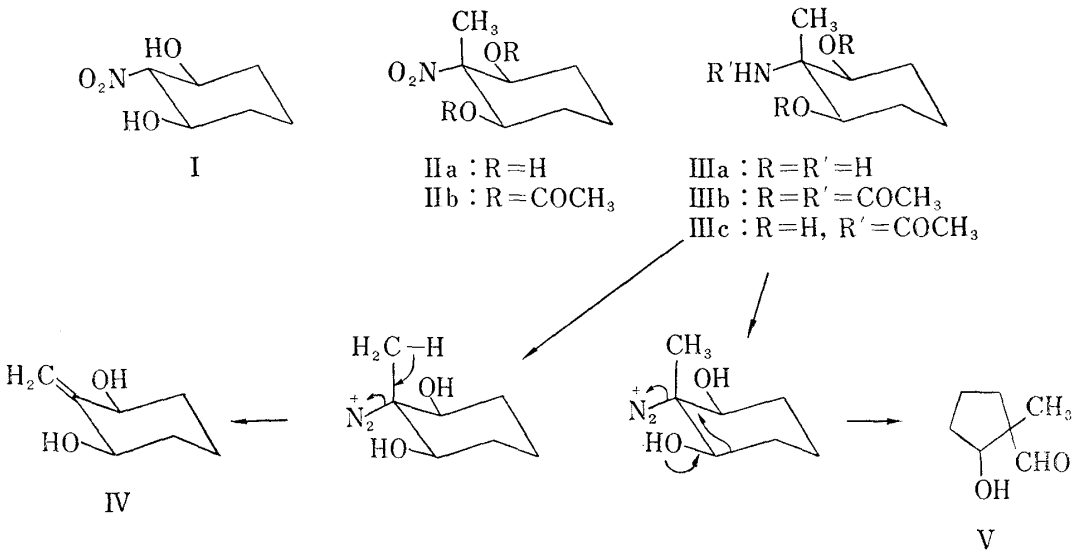


Chart 1

basis of these data, the nitro-diol (IIa) obtained by cyclization of glutaraldehyde with nitroethane was designated as 2β-methyl-2α-nitrocyclohexane-1β,3β-diol.

During the progress of this study, Lichtenthaler and his group[6] announced in a short communication that the same cyclization of glutaraldehyde with nitroethane gave a nitro-diol of mp 113—114°, whose structure was assigned as IIa by NMR analysis of its derivatives.[7]

Condensation of glutaraldehyde with β-nitro-α-hydroxypropionic acid[8] did not give the desired product, but gave *trans*-2-nitrocyclohexane-1,3-diol (I) in 10% yield, which was identified with the authentic sample synthesized by a known method.[5] This result showed that β-nitro-α-hydroxypropionic acid was affected initially by a retro-aldol degradation to liberate nitromethane which underwent condensation with glutaraldehyde to yield I. Consequently, we attempted the cyclization with methyl α-methoxy-β-nitropropionate which was obtained by the treatment of β-nitroacrylic acid[8] with methanol in the presence of an acid.

Treatment of glutaraldehyde with methyl α-methoxy-β-nitropropionate at pH 9 afforded a complex mixture, from which could be isolated an unsaturated lactone (VIa) of mp 120—121° in 13% yield, and a nitro-lactone (VII) of mp 122—124° in 7% yield. Acetylation of VIa with acetic anhydride yielded an acetate (VIb) of mp 105—106°. The ultraviolet spectrum of VIa showed a broad maximum at 229 mμ and the infrared spectrum also showed absorptions at 1755 and 1675 cm^{-1} in addition to the hydroxyl absorption at 3480 cm^{-1}. The NMR spectrum of VIa exhibited no absorption corresponding to a proton on the double bond. These spectral data of VIa indicated the presence of α-methoxybutenolide system in the molecule. NMR analysis of VIa and VIb showed the presence of notable quartet signals (J=5.5 and 11 cps) centered at 4.93 ppm in the spectrum of VIa and analogous signals at 4.71 ppm in the spectrum of VIb and these signals correspond to one proton on the carbon bearing the O-function of the butenolide, illustrating that the proton had an *axial* configuration against the cyclohexane ring. On the other hand, triplet signals (J=2.5 cps) centered at

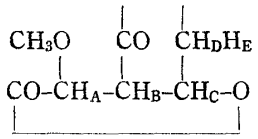
6) F.W. Lichtenthaler, H. Leinert, and H.K. Yahya, *Z. Naturforsch.*, **21b**, 1004 (1966).

7) Melting points of IIa and its derivatives described in this paper[6] did not agree with ours. On the other hand, Zen, *et al.* recently described in a short communication (S. Zen, Y. Takeda, A. Yasuda, and S. Umezawa, *Bull. Chem. Soc. Japan*, **40**, 431 (1967)) that the same cyclization of glutaraldehyde with nitroethane afforded the same nitro-diol of mp 135—136° and its structure was also assigned as IIa by NMR analysis of its derivatives. Physical constants of the nitrodiol and its derivatives described quite agree with ours.

8) H. Shechter, F. Conrad, A.L. Darlton, and R.B. Kaplan, *J. Am. Chem. Soc.*, **74**, 3053 (1952).

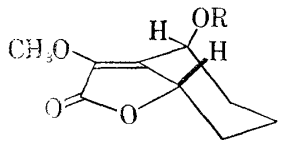
5.20 ppm and 6.02 ppm in the spectrum of VIa and VIb, respectively, also correspond to one proton of the carbon bearing the hydroxyl and acetoxy groups, and suggested that the proton had an *equatorial* configuration in both compounds. Consequently, steric formulas of VIa and VIb presumably reflected their NMR spectra.

The infrared spectrum of the nitro-lactone (VII) exhibited absorptions at 3550, 1783, and 1555 cm^{-1} corresponding to a hydroxyl, a γ-lactone, and a nitro groups, respectively. The presence of a methoxyl group was also shown by its NMR signal at 3.90 ppm. Presumably, its steric formula would be shown as VII from its NMR analysis which indicated that the *equatorial*-proton of the carbon bearing the O-function of the lactone ring corresponded to the triplet signals (J=3 cps) centered at 4.73 ppm, and the *axial*-proton of the carbon bearing the hydroxyl group corresponded to the multiplet (probably quartet) signals centered at 4.15 ppm. This observation was supported by the following series of chemical reaction. Hydrogenation of VII over platinum, followed by treatment with nitrous acid, yielded a keto-lactone (VIII) of mp 82—84°, which was accompanied by the same unsaturated lactone (VIa). The infrared spectrum of VIII exhibited no absorption corresponding to a hydroxyl group, but an absorption at 1730 cm^{-1} corresponding to a saturated ketone group in addition to that of the lactone group at 1791 cm^{-1}. Its NMR signals were presumably assignable as shown below, suggesting that its steric formula would be shown as VIII, having a *trans*-lactone, whose angular hydrogens were oriented axially. The formation of VIII by the degradation of VII proceeded through a possible intermediate (IX), followed by the hydride shift

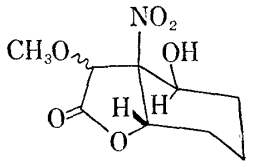


H_A : 4.30 (doublet, J_{AB}=10.5 cps)
H_B : 3.08 (quartet, J_{AB}=10.5, J_{BC}=12 cps)
H_C : 3.93 (multiplet, J_{BC}=12, J_{CD}=10.5, J_{CE}=4 cps)

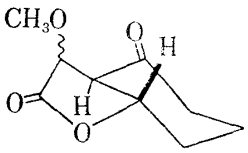
from the carbon bearing the hydroxyl group. VIII was an unstable material and converted to a brown gum on storage which was not investigated further due to the lack of the sample.



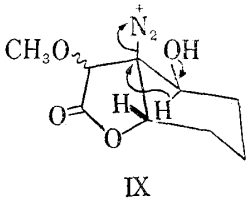
VIa : R=H
VIb : R=$COCH_3$



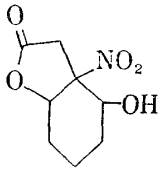
VII



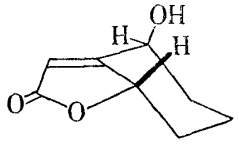
VIII



IX



X and XI



XII

Chart 2

Cyclization of glutaraldehyde with nitropropionic acid[9] in the presence of sodium hydroxide also yielded a complex mixture, from which was obtained a nitro-lactone (X) of mp 112—114° in a low yield. When this cyclization was carried out in the presence of Triton

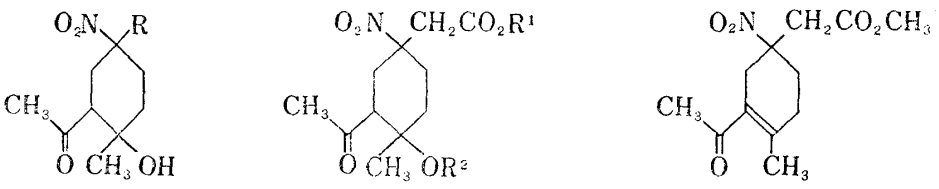
9) H.B. Hass, H. Feuer, and S.M. Pier, *J. Am. Chem. Soc.*, **73**, 1858 (1951).

B, the product was an isomeric nitro-lactone (XI) of mp 123—125° accompanied with a trace of X in a fair yield. Acetylation of XI afforded an acetate of mp 98°. In this reaction with nitropropionic acid, any unsaturated lactone corresponding to VIa could not be isolated; however, with methyl nitropropionate, the cyclization of glutaraldehyde in the presence of sodium carbonate afforded an unsaturated lactone (XII) of mp 101—103° in 5% yield, although the significance of this result is not still obvious. Acetylation of XII also yielded an acetate as a colorless liquid.

The ultraviolet spectrum of XII showed a maximum at 212 mμ, and the infrared spectrum at 1729 and 1647 cm^{-1}, indicating the presence of a butenolide group. The NMR analysis also suggested the steric configuration of XII; the multiplet signals centered at 5.07 ppm, which corresponded to one proton of the carbon bearing the O-function of the lactone ring, is due to coupling with protons of the neighbouring methylene with $J=10$ and 6.5 cps, in addition to a coupling with α-proton of the lactone ring ($J=1.5$ cps). This was indicative of the *axial* configuration of this angular hydrogen. The hydrogen on the carbon bearing the hydroxyl group was shown by triplet signals centered at 4.88 ppm ($J=2$ cps), which also indicated that the hydrogen was in an *equatorial* configuration. The structures of both nitro-lactones (X and XI) were shown by infrared absorptions at 1770 and 1780 cm^{-1} corresponding to the γ-lactone group and at 1550 cm^{-1} to the nitro group respectively; however, their NMR spectra did not afford any satisfactory data concerning their steric configurations.

It would be concluded that this cyclization of glutaraldehyde with nitro alkane derivatives would not develop into a preparative method, because the reaction products are not simple to be easily isolated and their yield is not generally satisfactory. In addition, formation of the unsaturated lactones (VI and XII) or presumable removal of an angular nitro group from some nitro-lactones remains a puzzle. We attempted the conversion of the nitro-lactone (VII or XI) with bases to the corresponding unsaturated lactones (VI or XII) but it was not successful, and yielded a complex mixture from which any unsaturated lactone could not be detected.

In 1961, Feuer and Harmetz[10] reported that a Michael-type condensation of a nitroalkane with two equivalents of methyl vinyl ketone, followed by cyclization, afforded a nitrocyclohexanol (XIII). Treatment of β-nitropropionic acid with two equivalents of methyl vinyl ketone in the presence of Triton B in methanol afforded a branched nitrocyclohexanol (XIVa) of mp 156° in 28% yield, and its isomer (XIVb) of mp 165° in 20% yield. XIVa and XIVb formed the corresponding methyl esters of mp 94° (XVa) and of mp 99° (XVb) by treatment with diazomethane, and by further acetylation with acetic anhydride and *p*-toluenesulfonic acid, the corresponding methyl ester monoacetates, mp 87° (XVIa) and mp 126° (XVIb), respectively. Both the methyl esters (XVa or XVb), on treatment with *p*-toluenesulfonic acid, were converted into the same unsaturated ketone (XVII) of bp 150—170° (0.04 mmHg) (bath temp.). Dehydration of XVb in this reaction was found to be easier than that of XVa.



XIII : R=Alkyl

XIVa,b : $R^1=H$, $R^2=H$
XVa,b : $R^1=CH_3$, $R^2=H$
XVIa,b : $R^1=CH_3$, $R^2=COCH_3$

XVII

Chart 3

10) H. Feuer and B. Harmetz, *J. Org. Chem.*, **26**, 1061 (1961).

This fact suggested that XVa and XVb were isomeric in relation between the hydroxyl group of the β-position of the carbonyl group and the hydrogen of its α-position, and the hydroxyl group of XVb was in a more favorable configuration to dehydration. Structural studies of these nitrocyclohexanols are now in progress.

Experimental

Melting points are not corrected. Ultraviolet spectra were determined on a Beckman Model DK-2, infrared spectra on a Perkin-Elmer Model 21, and proton magnetic resonance spectra (NMR) on a Varian A-60 spectrometer. The removal of solvents *in vacuo* was accomplished by a rotating flash evaporator at 20—30 mm and usually at 35—50°. Plates for thin-layer chromatography were prepared with Silica Gel G (E. Merck AG) and visualization of spots was usually effected by spraying conc. H_2SO_4, followed by heating.

2-Methyl-2-nitrocyclohexane-1,3-diol (IIa)——A mixture of 50 ml of 25% aqueous glutraldehyde, 60 ml of H_2O, 100 ml of MeOH, and 25 g of $EtNO_2$ was adjusted to pH 9 by adding dropwise 10% NaOH solution (about 25 ml) under cooling. The solution was allowed to stand at room temperature overnight with stirring. Then the ice-cooled solution was acidified with 10% H_2SO_4 and extracted continuously with ether. After drying over anhyd. Na_2SO_4, the extract was evaporated *in vacuo* to give a brown oil, from which a crystalline mass was obtained on digesting with $CHCl_3$. The crude product of IIa was recrystallized from benzene–EtOH to yield 9.4 g (43% yield) of IIa as needles of mp 134—136°. IR (Nujol) cm^{-1}: ν_{O-H} 3350, $\nu_{N=O}$ 1550. NMR (C_5D_5N) δ, ppm: 6.8—7.3 (HO–, broad, 1H), 4.4—4.8 (–$\underset{|}{C}$H–O–, broad, 2H), 1.95 (CH_3–, singlet 3H). *Anal.* Calcd. for $C_7H_{13}O_4N$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.86; H, 7.56; N, 7.90.

The diacetate of IIa (IIb) was prepared as follows: A mixture of 430 mg of IIa, 30 ml of Ac_2O, and 4 drops of conc. H_2SO_4 was warmed at 50° for 30 min on a steam bath. The cooled solution was poured into H_2O for decomposition of excess of Ac_2O and then extracted 5 times with benzene. After being dried over anhyd. Na_2SO_4, the extract was evaporated *in vacuo*. Recrystallization of the resulting crystallline residue from ether–hexane afforded 494 mg of IIb, mp 86—87°. IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1750, $\nu_{N=O}$ 1550. NMR ($CDCl_3$) δ, ppm: 5.3—5.6 (–$\underset{|}{C}$H–O–, broad, 2H), 2.0 (CH_3COO–, singlet, 6H), 1.70 (CH_3–, singlet, 3H). *Anal.* Calcd. for $C_7H_{11}O_4N$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.82; H, 6.59; N, 5.33.

2-Methyl-2-aminocyclohexane-1,3-diol (IIIa)——The nitro-diol (IIa) (2.50 g) was hydrogenated over 2 g of Pt at room temperature in 50 ml of AcOH. One mole of H_2 was taken up during 3 days. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give 3.10 g of a crystalline residue which was recrystallized from AcOEt–EtOH to give 1.51 g of a hydroacetate of IIIa as a powder of mp 187—195° (decomp.). Analytical sample was prepared by further recrystallization from AcOEt–EtOH to fine needles of mp 191—195° (decomp.). IR (Nujol) cm^{-1}: ν_{OH} 3340. NMR (D_2O) δ, ppm: 3.4—3.9 (–$\underset{|}{C}$H–O–, multiplet, 2H), 1.90 (CH_3COO–, singlet, 3H), 1.22 (CH_3–, singlet, 3H). *Anal.* Calcd. for $C_7H_{15}O_2N \cdot CH_3COOH$: C, 52.66; H, 9.33; N, 6.82. Found: C, 52.44; H, 9.31; N, 6.84.

In the other run, hydrogenation of IIa was carried out in EtOH and the treatment of the reaction mixture as described above afforded IIIa, mp 219—220° (from EtOH). *Anal.* Calcd. for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.02; H, 10.95; N, 9.65.

A mixture of 100 mg of IIIa, 2 ml of pyridine, and 0.5 ml of Ac_2O was allowed to stand at room temperature for 5 hr. Crystals obtained by removal of the solvent *in vacuo* were recrystallized from benzene to give an amide-diacetate (IIIb) as needles mp 174—176°. IR (Nujol) cm^{-1}: ν_{N-H} 3300, 3080, $\nu_{C=O}$ 1654, 1565 (N-acetyl), 1746 (O-acetyl). NMR ($CDCl_3$) δ, ppm: 1.36 (CH_3–, singlet, 3H), 1.88 ($CH_3\underset{|}{C}ON$–, singlet, 3H), 2.08 (CH_3COO–, singlet, 6H), 5.4—5.9 (–NH– and –$\underset{|}{C}$H–O–, complex absorption, 3H), 1.2—2.2 (complex absorption, 6H). *Anal.* Calcd. for $C_{13}H_{21}O_5N$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.79; H, 7.72; N, 5.35.

A solution of 162 mg of IIIb in 10 ml of NH_3-saturated MeOH was allowed to stand at room temperature for 2 hr. Evaporation of MeOH *in vacuo* afforded an amide-diol (IIIc), mp 153—155° (needles from $CHCl_3$–benzene). IR (Nujol) cm^{-1}: ν_{O-H} and $_{N-H}$ 3340, 3220, 3080, $\nu_{C=O}$ 1643, 1556. *Anal.* Calcd. for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.29; H, 9.11; N, 7.63.

Deamination of 2-Methyl-2-aminocyclohexane-1,3-diol (IIIa)——To the ice-cooled solution of 630 mg of IIIa in 3 ml of AcOH and 6 ml of H_2O was added dropwise a solution of 4.5 g of $NaNO_2$ in 9 ml of H_2O under stirring. The resulting solution was allowed to stand under stirring for 30 min, then neutralized with 10% NaOH solution, and extracted 4 times with AcOEt. After drying over anhyd. Na_2SO_4, the extract was evaporated and gave 255 mg of an oily residue which partly crystallized on standing. The crude crystals (31 mg) were collected, washed with $CHCl_3$, and recrystallized from benzene–EtOH to yield 2-methylenecyclohexane-1,3-diol (IV) as needles of mp 141—143.5°. IR (Nujol) cm^{-1}: $\nu_{C=C}$ 1654, ν_{C-H} 1800, 902. NMR (D_2O) δ, ppm: 4.99 (triplet, $J=1.8$ cps, 2H), 3.85—4.26 (multiplet, 2H), 0.95—2.3 (complex absorption, 6H). *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.50; H, 9.33.

The oily residue left after the crude IV was filtered off was chromatographed on 5 g of silica gel. Evaporation of the $CHCl_3$ eluate afforded 100 mg of an oil (V) which exhibited one spot on thin-layer chromatography. The analytical sample, bp 120° (10 mmHg) (bath temp.), was prepared by distillation. IR (liquid) cm^{-1}: ν_{O-H} 3400, $\nu_{C-H(-CHO)}$ 2740, $\nu_{C=O}$ 1727. NMR ($CDCl_3$) δ, ppm: 9.59 (-CHO, singlet, 1H), 4.36 (-$\underset{|}{C}$H-O-, triplet, J=6.5 cps, 1H), 2.89 (-OH, singlet, 1H), 1.11 (CH_3-, singlet, 3H). *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.03; H, 9.46.

Evaporation of the $CHCl_3$-EtOH (1—2%) eluate of the chromatography afforded 39 mg of an additional crop of IV.

Methyl α-Methoxy-β-nitropropionate and Methyl β-Nitropropionate——A solution of 19.5 g of β-nitroacrylic acid[8] in abs. MeOH (200 ml) containing 50 mg of *p*-TsOH was refluxed for 15 hr. The resulting mixture was concentrated and fractionally distilled, giving 19.0 g (70% yield) of methyl α-methoxy-β-nitropropionate, bp 105° (6 mmHg). IR (liquid) cm^{-1}: $\nu_{C=O}$ 1757, 1745 (shoulder), $\nu_{N=O}$ 1565. NMR ($CDCl_3$) δ, ppm: 3.54 (CH_3O-), 3.84 (CH_3COO-), 4.35—4.85 (complex absorption, 3H). *Anal.* Calcd. for $C_5H_9O_5N$: C, 36.81; H, 5.56; N, 8.59. Found: C, 36.91; H, 5.54; N, 8.87.

To a solution of 20 g of β-nitropropionic acid[8] in ether was added dropwise a solution of CH_2N_2 in ether. The resulting mixture was evaporated and distilled, giving 19.9 g (89% yield) of methyl β-nitropropionate, bp 99° (8 mmHg). IR (liquid) cm^{-1}: $\nu_{C=O}$ 1743, $\nu_{N=O}$ 1562. *Anal.* Calcd. for $C_4H_7O_4N$: C, 36.09; H, 5.30; N, 10.52. Found: C, 36.04; H, 5.42; N, 10.12.

Condensation of Glutaraldehyde with Methyl α-Methoxy-β-nitropropionate——To a solution of 8 g (0.02 mole) of 25% aqueous glutaraldehyde and 5.3 g (0.034 mole) of methyl α-methoxy-β-nitropropionate in 24 ml of 80% aqueous MeOH, was added dropwise 1 ml of 20% NaOH solution, adjusting to pH 9. The solution was allowed to stand for 1.5 hr in an ice-bath with stirring and, after further addition of 1 ml of 10% NaOH solution, stood overnight at room temperature. The resulting mixture was concentrated *in vacuo* to about 20 ml at room temperature, then poured into water, and extracted three times with $CHCl_3$. The combined extracts were dried over anhyd. Na_2SO_4 and evaporated *in vacuo*, giving 4.2 g of an oily mixture whose thin-layer chromatogram exhibited 5—6 spots. This product was chromatographed on 50 g of silica gel. From the benzene eluate, 0.68 g of methyl α-methoxy-β-nitropropionate was recovered. From the benzene-$CHCl_3$ (3:1 v/v) fraction 0.43 g of a crystalline material was obtained whose recrystallization from benzene-hexane gave 0.31 g (7% yield) of the nitro-lactone (VII) as needles of mp 122—124°. IR (Nujol) cm^{-1}: ν_{O-H} 3550, $\nu_{C=O}$ 1783, $\nu_{N=O}$ 1555. NMR ($CDCl_3$) δ, ppm: 2.95 (-OH, doublet, J=3 cps, disappeared by addition of an acid, 1H), 3.90 (-OCH_3, singlet, 3H), 4.15 (-$\underset{|}{C}$H-OH, multiplet, 1H), 4.73 (-$\underset{|}{C}$H-OCO-, triplet, J=3 cps, 1H), 4.83 (-O-$\underset{|}{C}$H-COO-, singlet, 1H). *Anal.* Calcd. for $C_9H_{13}O_6N$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.54; H, 5.75; N, 6.03.

Evaporation of the benzene-$CHCl_3$ (1:1 v/v) eluate afforded an oily unseparable mixture (1.7 g) whose infrared spectrum showed absorptions corresponding to nitro, hydroxyl, and ester functions. Evaporation of the $CHCl_3$ and $CHCl_3$-MeOH (1—2%) fractions and recrystallization of the residue from benzene yielded 0.51 g (14% yield) of the unsaturated lactone (VIa) as leaflets of mp 120—121°. IR (Nujol) cm^{-1}: ν_{O-H} 3480, $\nu_{C=O}$ 1755, $\nu_{C=C}$ 1675. UV (EtOH) λ_{max} 229 mμ (ε 12000). NMR ($CDCl_3$) δ, ppm: 3.30 (-OH, broad singlet, disappeared by addition of an acid, 1H), 3.96 (CH_3O-, singlet, 3H), 4.93 (-$\underset{|}{C}$H-O-CO-, quartet J=5.5 cps and J=11 cps, 1H), 5.20 (-$\underset{|}{C}$H-OH, triplet, J=2.5 cps, 1H). *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.29; H, 6.60.

Its acetate (VIb) was obtained by treatment of VIa with Ac_2O containing a trace of *p*-TsOH, as leaflets of mp 105—106° (from benzene-hexane). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1779, $\nu_{C=C}$ 1685 (unsaturated γ-lactone); $\nu_{C=O}$ 1739 (acetyl). NMR ($CDCl_3$) δ, ppm: 2.03 (-OCH_3, singlet, 3H), 4.03 (-$OCOCH_3$, singlet, 3H), 4.71 (-$\underset{|}{C}$H-O-CO-, quartet, J=6 and 10.5 cps, 1H), 6.02 (-$\underset{|}{C}$H-OCO-CH_3, triplet, J=2.5 cps, 1H). *Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.22; H, 6.20.

Hydrogenation of the Nitro-lactone (VII), followed by Deamination——The nitro-lactone (VII) (0.5 g) was hydrogenated over Pt (0.5 g) in 15 ml of AcOH, absorbing 254 ml of H_2 during 40 min. After the catalyst was filtered off, the mixture was evaporated *in vacuo*, remaining 541 mg of a syrup. IR (liquid) cm^{-1}: 3550, 3400, 1788, 1580 (broad). This syrup (291 mg) was dissolved in a mixture of 1.5 ml of AcOH and 3 ml of H_2O, and to the resulting solution was dropped a solution of 2.2 g of $NaNO_2$ in 4.5 ml of H_2O under ice-cooling. After standing for 2 hr, the reaction mixture was diluted with H_2O (5 ml) and extracted three times with benzene. The extract was dried over anhyd. $MgSO_4$ and evaporated, leaving 194 mg of a yellow residue, which partly crystallized on standing. This syrup was chromatographed on 10 g of silica gel. Evaporation of the $CHCl_3$ eluate (70 ml) and recrystallization from benzene-hexane afforded 104 mg (48% yield) of the keto-lactone (VIII) as prisms of mp 82—84°. IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1791 (lactone), 1730 (ketone). *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.93; H, 6.51.

From the $CHCl_3$-MeOH (2%) fraction was obtained 10 mg of the unsaturated lactone (VIa), mp 117—119°, which was identical with the sample described before.

Condensation of Glutaraldehyde with Methyl β-Nitropropionate——To an ice-cooled mixture of 2 g (0.005 mole) of 25% aqueous glutaraldehyde, 1.33 g (0.010 mole) of methyl β-nitropropionate, 5 ml of MeOH, and 2 ml of H_2O was dropped a solution of 1.06 g (0.010 mole) of Na_2CO_3 in 3.5 ml of H_2O. After standing in an ice-bath for 1 hr, the mixture was allowed to stand with stirring overnight at room temperature. The resulting mixture was diluted with H_2O and extracted three times with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$ and evaporated *in vacuo*. The resulting colored residue (364 mg) was chromatographed on 6 g of silica gel and gave the following products:

	Eluant		Product
1	benzene–$CHCl_3$ (1:2 v/v)	20 ml	25 mg a yellow syrup
2	$CHCl_3$	20 ml	10 mg mp 184—188°
3	$CHCl_3$	20 ml	20 mg mp 162—166°
4	$CHCl_3$	60 ml	50 mg mp 99—102°
5	$CHCl_3$–MeOH (1—10%)		20 mg a syrup

Crystals obtained from the fraction 4 was recrystallized from benzene to 41 mg (5% yield) of the unsaturated lactone (XII) as plates of mp 101—103°. IR (Nujol) cm^{-1}: ν_{O-H} 3460, 3350, $\nu_{C=O}$ 1729, $\nu_{C=C}$ 1647. UV (EtOH) λ_{max} 212 mμ (ε 13500). NMR ($CDCl_3$) δ, ppm: 3.35 (–OH, singlet, disappeared on addition of an acid, 1H), 4.88 (–$\underset{|}{C}$H–OH, triplet, J=2 cps, 1H), 5.07 (–$\underset{|}{C}$H–OCO–, multiplet, J=10, 6.5 and 1.5 cps, 1H), 5.72 (–CH=$\underset{|}{C}$, doublet, J=1.5 cps, 1H). *Anal.* Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.29; H, 6.57.

Treatment of XII with Ac_2O containing a trace of TsOH afforded an acetate which could not be crystallized. IR (liquid) cm^{-1}: 1755 (broad), 1660. NMR (CCl_4) δ, ppm: 2.00 (singlet, 3H), 4.82 (multiplet, J=10.5, 6 and 1.5 cps, 1H), 5.72 (triplet, J=2 cps, 1H), 5.79 (doublet, J=1.5 cps, 1H).

The water layer remaining after the extraction was acidified with dil. HCl and extracted three times with AcOEt. The combined extracts were evaporated to give 494 mg of a complex mixture whose further separation was not successful. The use of NaOH or Dowex 1-X8 as a condensation catalyst in the cyclization reaction yielded an unseparable mixture.

Condensation of Glutaraldehyde with β-Nitropropionic Acid——i) To a mixture of 8 g of 25% aqueous glutaraldehyde, 40 ml of H_2O, and 2.86 g of β-nitropropionic acid was dropped 10% NaOH solution and the mixture was adjusted to pH 8. The resulting mixture was allowed to stand for 14 hr with stirring, acidified with 10% H_2SO_4, and extracted with AcOEt. The extract was dried over anhyd. $MgSO_4$ and evaporated, giving 3.25 g of a syrup which was chromatographed on silica gel. The fraction eluted with benzene, after evaporation, afforded 93 mg of the nitro-lactone (X) as prisms of mp 112—114° (from benzene). IR (Nujol) cm^{-1}: ν_{O-H} 3400, $\nu_{C=O}$ 1770, $\nu_{N=O}$ 1550. NMR ($CDCl_3$) δ, ppm: 3.3 (–CH_2–COO–, doublet, 2H), 4.25 (–$\underset{|}{C}$H–OH, multiplet, 1H), 5.20 (–$\underset{|}{C}$H–OCO–, triplet, J=5 cps, 1H). *Anal.* Calcd. for $C_8H_{11}O_5N$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.75; H, 5.60; N, 6.94.

ii) A solution of 4.8 g of nitropropionic acid in 50 ml of H_2O was adjusted to pH 6 with 10% NaOH solution. To the mixture was added 16 g of 25% aqueous glutaraldehyde, the resulting mixture was adjusted again to pH 9 with Triton B–MeOH solution (40%), and allowed to stand overnight. The mixture was acidified with 5% H_2SO_4 and extracted with AcOEt. The extract was dried over anhyd. Na_2SO_4 and evaporated *in vacuo*, giving 8.5 g of the crude crystals of XI which was purified by column chromatography; and thus 3.24 g of the isomeric nitrolactone (XI), mp 123—125° and 45 mg of X, mp 114° were obtained. IR (Nujol) cm^{-1}: ν_{O-H} 3420, $\nu_{C=O}$ 1780, $\nu_{N=O}$ 1550. NMR ($(CD_3)_2CO$) δ, ppm: 3.2 (–CH_2–COO–, double doublet, J=18 cps, 2H), 4.4—5.1 (multiplet, 3H). *Anal.* Calcd. for $C_8H_{11}O_5N$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.96; H, 5.58; N, 7.09.

By treatment with Ac_2O containing a small amount of TsOH, XI formed an acetate as needles of mp 98° (from *i*-Pro_2O–hexane). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1795 (lactone), 1750 (acetyl), $\nu_{N=O}$ 1550. NMR ($CDCl_3$) δ, ppm: 2.1 (CH_3COO– singlet, 3H), 3.2 (–CH_2–COO–, doublet, J=17 cps, 2H), 5.0 (–$\underset{|}{C}$H–OCO–, triplet, J=7 cps, 1H), 5.7 (–$\underset{|}{C}$H–$OCOCH_3$, quartet, J=11 and 6 cps, 1H). *Anal.* Calcd. for $C_{10}H_{13}O_6N$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.40; H, 5.57; N, 5.77.

Condensation of Methyl Vinyl Ketone with β-Nitropropionic Acid, 1-Methyl-2-acetyl-4-carboxymethyl-4-nitrocyclohexan-1-ol (XIVa and XIVb)——A solution of 11.9 g of β-nitropropionic acid in 40 ml of H_2O was neutralized with 5% NaOH solution and adjusted to pH 10 with 10% methanolic Triton B. To the cooled solution was added dropwise 14.0 g of methyl vinyl ketone and the resulting mixture was allowed to stand for 2 days. After being acidified with 10% HCl, the mixture was extracted 5 times with AcOEt. The extract was dried over anhyd. Na_2SO_4 and evaporated *in vacuo*, giving 28.9 g of a brown residue. Crystals obtained on digestion with ether were collected and recrystallized from benzene–AcOEt, yielding 4.20 g of XIVa, mp 156°. IR (Nujol) cm^{-1}: ν_{O-H} 3460 $\nu_{C=O}$ 1740, 1700, $\nu_{N=O}$ 1550. NMR (C_5D_5N) δ, ppm: 1.32 (CH_3– singlet, 3H), 2.20 (CH_3CO–, singlet, 3H), 3.30 (–$\underset{|}{C}$–CH_2–COO–, broad, 2H). *Anal.* Calcd. for $C_{11}H_{17}O_6N$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.71; H, 6.62; N, 5.27.

Treatment of XIVa with CH_2N_2 gave a methyl ester (XVa), mp 94° (from *i*-Pro_2O). IR (Nujol) cm^{-1}: ν_{O-H} 3510, $\nu_{C=O}$ 1745, 1700, $\nu_{N=O}$ 1542. NMR ($CDCl_3$) δ, ppm: 1.19 (CH_3–, singlet, 3H), 2.29 (CH_3CO–, singlet, 3H), 3.69 (CH_3OCO–, singlet 3H). *Anal.* Calcd. for $C_{12}H_{19}O_6N$: C, 52.74; H, 7.01; N, 5.13. Found: C, 53.10; H, 7.12; N, 5.06.

Further treatment of the methyl ester (XVa) with Ac_2O containing a small amount of TsOH gave an acetate (XVIa) of mp 87° (from *i*-Pro_2O). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1742, 1705, $\nu_{N=O}$ 1555. NMR ($CDCl_3$) δ, ppm: 1.61 (CH_3–, singlet, 3H), 2.05 (CH_3COO–, singlet, 3H), 2.24 (CH_3CO–, singlet, 3H), 3.71 (CH_3OCO–, singlet, 3H). *Anal.* Calcd. for $C_{14}H_{21}O_7N$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.34; H, 6.88; N, 4.55.

The filtrate left after the removal of the crude crystals of XIVa and the mother liquor from the recrystallization of XIVa were combined and chromatographed on silica gel, giving an additional crop of XIVa (3.0 g) and its isomer (XIVb) (5.22 g). The latter was recrystallized from benzene–AcOEt, forming prisms of mp 165°. IR (Nujol) cm^{-1}: ν_{O-H} 1745, 1700, $\nu_{N=O}$ 1545. NMR (C_5D_5N) δ, ppm: 1.36 (CH_3–, singlet, 3H), 2.42 (CH_3CO–, singlet, 3H), 3.32 (–$\underset{|}{C}$–CH_2–COO–, broad, 2H). *Anal.* Calcd. for $C_{11}H_{17}O_6N$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.07; H, 6.75; N, 5.38.

Treatment of XIVb with CH_2N_2 also gave a methyl ester (XVb), mp 99° (from benzene–*i*-Pro_2O). IR (Nujol) cm^{-1}: ν_{O-H} 3460, $\nu_{C=O}$ 1745, 1695, $\nu_{N=O}$ 1550. NMR ($CDCl_3$) δ, ppm: 1.19 (CH_3–, singlet, 3H), 2.30 (CH_3CO–, singlet, 3H), 3.70 (CH_3OCO–, singlet, 3H). *Anal.* Calcd. for $C_{12}H_{19}O_6N$: C, 52.74; H, 7.01; N, 5.13. Found: C, 53.01; H, 6.95; N, 5.11.

Further treatment of XVb with Ac_2O–TsOH afforded an acetate (XVIb), mp 126° (from *i*-Pro_2O). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1745, 1705, $\nu_{N=O}$ 1548. NMR ($CDCl_3$) δ, ppm: 1.48 (CH_3–, singlet, 3H), 2.02 (CH_3COO–, singlet, 3H), 2.30 (CH_3CO–, singlet, 3H), 3.72 (CH_2OCO–, singlet, 3H). *Anal.* Calcd. for $C_{14}H_{21}O_7N$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.38; H, 6.72; N, 4.73.

1-Methyl-2-acetyl-4-methoxycarbonylmethyl-4-nitrocyclohex-1-ene (XVII)——A solution of 153 mg of the methyl ester (XVa) in 10 ml of anhyd. benzene containing 10 mg of TsOH was refluxed for 10 hr, when the spot of XVa disappeared from the thin-layer chromatogram. After being washed with H_2O and dried on anhyd. Na_2SO_4, the reaction mixture was evaporated *in vacuo* and distilled, giving an unsaturated ketone (XVII) of bp 150—180° (0.04 mmHg) (bath temp.). IR (liquid) cm^{-1}: $\nu_{C=O}$ 1745, 1690, $\nu_{C=C}$ 1630, NMR ($CDCl_3$) δ, ppm: 1.90 (CH_3–$\underset{|}{C}$=, triplet, 3H), 2.29 (CH_3CO–, singlet, 3H), 3.71 (CH_3OCO–, singlet, 3H). *Anal.* Calcd. for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.29; H, 6.98; N, 5.48.

Treatment of XVb with TsOH in boiling benzene for 2 hr as described for XVa gave the same unsaturated ketone (XVII). These products were identified by infrared and NMR spectrometry.

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