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The Reaction of β-Nitroalcohols and Reactive Aldehydes*1

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Condensation of acyclic or cyclic β-nitroalcohols with aldehydes was examined. In the case of non-protected 1-deoxy-1-*C*-nitro-D-glycitols and benzaldehyde, products caused by aldehyde-exchange reaction were obtained. However, the reaction of 2-methoxy-1-nitropentane or non-protected 2-nitrocyclohexanol and reactive aldehydes (formaldehyde, acetaldehyde and *n*-butyl glyoxylate) in the presence of sodium hydrogencarbonate gave the corresponding condensation products.

It is well known that nitromethane undergoes condensation with equimolar amount of aldehydes or dialdehydes in the presence of an alkaline catalyst to give acyclic β-nitroalcohols or cyclic β,β′-dihydroxynitro derivatives.[1,2] However, the possibility of further condensation of the products with a second aldehyde has not been clarified. Successful condensation of nitroethanol with aldehydes[3,4] or dialdehyde[5] seems to be attributed to the high reactivity of formaldehyde, because nitroethanol is an equimolar condensation product of nitromethane and formaldehyde, and three moles of the latter can be condensed with the former as an exception.[6]

Another important factor in such a condensation is the relative stability of *aci*-nitro salts of a starting material, the expected product, nitromethane, and the condensation product between nitromethane and a second aldehyde, because nitromethane condensation is a kind of reversible reaction. Moreover, the condensation product between a cyclic β-nitroalcohol and a second aldehyde is a tertiary nitro derivative which cannot form an *aci*-nitro salt. Thus the use of a strong alkali as a catalyst is undesirable.

In this paper, the reactions of acyclic or cyclic β-nitroalcohols with aldehydes are described.

Results and Discussion

At first 1-deoxy-1-*C*-nitroglycitol was used as an acyclic β-nitroalcohol without protection of the hydroxyl group. The reaction of 2,3-*O*-isopropylidene-D-glycerinaldehyde[7] and nitromethane in the presence of triethylamine at room temperature gave a mixture of 1-deoxy-3,4-*O*-isopropylidene-1-*C*-nitro-D-*threo*- and -*erythro*-tetritol (**1**) in 60% yield as a distilled sirup. Only when the reaction period was shorter than 12 hr, the isomer which was deduced from the rotational value to have *threo* configuration[8,9] was obtained as crystals. Moreover, 1-deoxy-3,4;5,6-di-*O*-isopropylidene-1-*C*-nitro-D-glucitol (**2**) and -D-mannitol (**3**) were newly synthesized by acetonation of the corresponding glycitols.[10] 1-Acetamido-1-deoxy-D-glucitol (**4**) and D-mannitol (**5**) were also derived from the same compounds by hydrogenation and *N*-acetylation. The position of isopropylidene groups in **2** and **3** was proved by the fact that both compounds and their mixture obtained by the condensation of 2,3 ; 4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[11] with nitromethane were converted into the same α,β-unsaturated-nitro compound by acetylation and elimination.[12]

Treatment of **1** with benzaldehyde in the presence of sodium methoxide gave an intractable sirup,

*1 Part of this work was presented at the Autumn Meeting of the Chemical Society of Japan in October, 1969, in Nagoya.

1) Fr. W. Lichtenthaler, "Newer Method of Preparative Organic Chemistry," Vol. 4, Academic Press Inc., New York (1968), p. 115.

2) J. C. Sowden, "Advances in Carbohydrate Chemistry," Vol. 6, Academic Press Inc., New York (1951), p. 291.

3) J. Controulis, M. C. Rebstock and H. M. Crooks, *J. Amer. Chem. Soc.*, **71**, 2463 (1949).

4) J. C. Sowden, *ibid.*, **72**, 3325 (1950).

5) Fr. W. Lichtenthaler and H. Leinert, *Chem. Ber.*, **101**, 1815 (1968).

6) I. Gorsky and S. P. Makarov, *Chem. Ber.*, **67**, 996 (1934).

7) H. H. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).

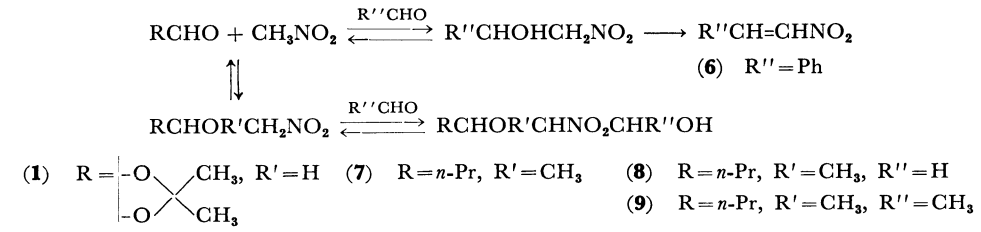
8) Y. Ohgo, J. Yoshimura, M. Kono and T. Sato, This Bulletin, **42**, 2957 (1969).

9) W. A. Bonner, *J. Amer. Chem. Soc.*, **73**, 3126 (1951).

10) J. C. Sowden and H. O. L. Fischer, *ibid.*, **69**, 1048 (1947).

11) L. F. Wiggins, *J. Chem. Soc.*, **1946**, 388.

12) E. Schmitt and G. Rutz, *Chem. Ber.*, **61**, 2142 (1928).

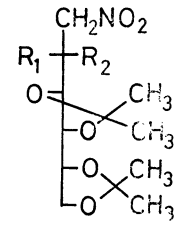


Scheme 1

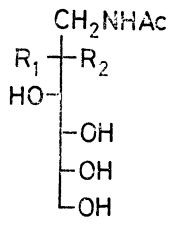
from which only β-nitrostyrene (**6**) was isolated as crystals. A similar condensation of **3** with benzaldehyde also gave a sirup. In order to identify the products, the sirup was hydrogenated, hydrolyzed, *N*-acetylated and then examined by paper chromatography. The chromatogram showed three main spots, two of which were identified by comparison with authentic samples to be **5** and β-acetamido-α-phenylethanol.[13] An attempted separation of the third compound by a magnesol-celite column was unsuccessful. However, the presence of D-arabinitol was ascertained. This indicates that an aldehyde-exchange reaction occurred as shown in Scheme 1.

In order to prevent such a reverse nitromethane condensation, it was deduced that the protection of the hydroxyl group of an acyclic β-nitroalcohol is necessary, and as mild an alkaline condition as possible should be used. For instance, Magerlein[14] reported recently the successful condensation of methyl 6-deoxy-6-nitro-1-thio-α-D-galactopyranoside with acetaldehyde in a total synthesis of lincomycin, in which the hydroxyl group is protected by the pyranoside ring formation. As a simple model compound to prove the above deduction, 2-methoxy-1-nitropentane (**7**) was prepared by the reaction of 1-nitro-1-pentene[12] and sodium methoxide in absolute methanol at 0—7°C. As expected, condensation of **7** with formaldehyde or acetaldehyde in the presence of sodium hydrogencarbonate at room temperature for a week gave the corresponding product (**8** and **9**) in 26 and 38% yield, respectively. When sodium hydroxide was used as a catalyst in the case of formaldehyde, a small amount of olefinic byproducts were detected in the NMR spectrum of distilled **8**, in which two doublets (τ 3.52 and 4.24, J=1.3 Hz) and one triplet (τ 2.86, J=3.7 Hz) indicated the presence of the corresponding 1-olefin and 2-olefin, respectively. Because the absorption of a conjugated nitro group (ν_{max} 1520 cm^{-1}) was observed in the IR spectrum of undistilled **8**, it is concluded that a strong alkaline condition induced the elimination of water or methanol. The condensation product between **7** and *n*-butyl glyoxylate could not be purely isolated. However, it was isolated as methyl

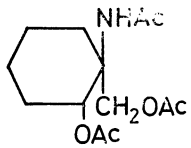
(**10**) $CH_3(CH_2)_2CH(OCH_3)CH(NH_2\cdot HCl)$-$CHOHCOOCH_3$



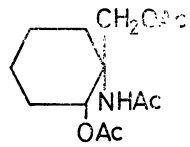
(**2**) R_1=H, R_2=OH
(**3**) R_1=OH, R_2=H



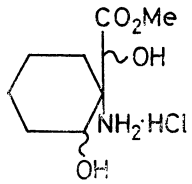
(**4**) R_1=H, R_2=OH
(**5**) R_1=OH, R_2=H



(**11a**)



(**11b**)



(**12**)

3-amino-2-hydroxy-4-methoxyheptanoate hydrochloride (**10**) by hydrogenation, esterification, and column-chromatography in 6% yield.

On cyclic β-nitroalcohols, Lichtenthaler and Leinert[5] reported that the condensation of glutardialdehyde and nitroethanol afforded 2-hydroxymethyl-*r*-2-nitrocyclohexan-*t*-1,*t*-3-diol. However, it decomposes to *r*-2-nitrocyclohexan-*t*-1,*t*-3-diol with liberation of formaldehyde in higher pH regions, and the reverse reaction did not take place. Instead of nitroethanol, ethyl nitroacetate was reported as an reactive nitro compound in a similar cyclisation.[15] Recently, Sakai described that the condensation of glutardialdehyde and α-methoxy-β-nitropropionic acid in the presence of sodium hydroxide gave a lactone of the aimed compound (7%) and the corresponding unsaturated

13) A. Pictet and A. Gams, *Chem. Ber.*, **43**, 2389 (1915).
14) B. J. Magerlein, *Tetrahedron Lett.*, **1970**, 33.
15) S. Zen, Y. Takeda, A. Yasuda and S. Umezawa, This Bulletin, **40**, 431 (1967).

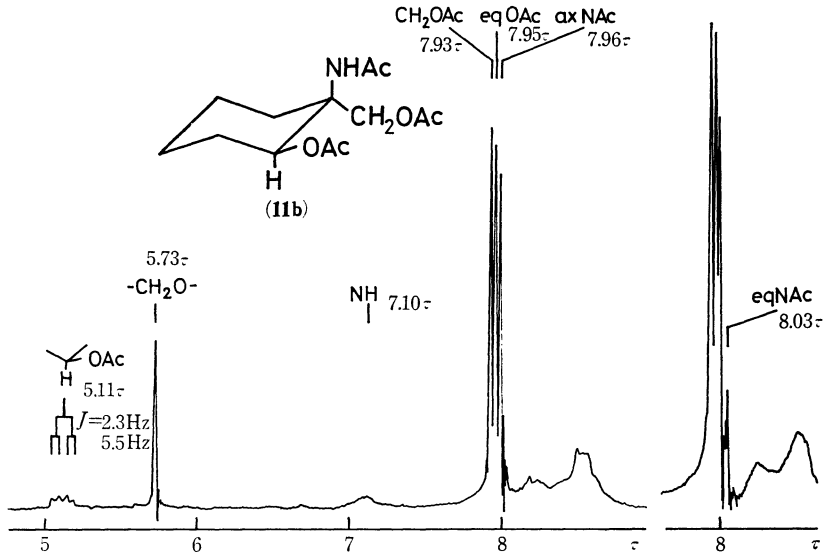


Fig. 1. NMR spectrum of **11b** and a mixture of **11a** and **11b** ($CDCl_3$, 100 MHz).

lactone (13%) in which the nitro group was eliminated.[16] In our experiments, 2-nitrocyclohexanol[17] and formaldehyde were treated under the same conditions as mentioned before, and the sirupy product was directly hydrogenated, acetylated and distilled to give the corresponding triacetate (**11**) in a total yield of 65%. The NMR spectrum of **11** indicated the presence of acetoxymethyl group (τ 7.93), equatorial-acetoxy group (τ 7.95), axial-acetamido group (τ 7.96) and equatorial-acetamido group (τ 8.03) as characteristic signals.[18] Because of the low intensity of the latter, it was deduced that **11** is a mixture of *r*-1-acetamido-*t*-2-acetoxy-1-acetoxymethylcyclohexane (**11a**) and its *c*-2-isomer (**11b**), and the latter is the main product. In fact, crystalline **11b** was obtained by standing for two months as shown in Fig. 1. Similarly, the condensation product of 2-nitrocyclohexanol with *n*-butyl glyoxylate was isolated as methyl α-(1-amino-2-hydroxycyclohexyl)glycolate hydrochloride (**12**) in a total yield of 12%, by hydrogenation, esterification and column-chromatography. However, the configuration of isomers in **12** could not be analyzed.

From these results, it is concluded that acyclic β-nitroalcohols in which the hydroxyl group is protected by ether-linkage and cyclic β-nitroalcohols without protection are successfully condensed with reactive aldehydes such as formaldehyde, acetaldehyde and glyoxylic acid in a weak alkaline condition.

16) K. Sakai, S. Oida and E. Ohki, *Chem. Pharm. Bull.* Tokyo, **16**, 1048 (1968).

17) H. Baldock, N. Levy and C. W. Fcaife, *J. Chem. Soc.*, **1949**, 2627.

18) Fr. W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, **1967**, 577.

Experimental

The solutions were evaporated under diminished pressure at a bath temperature not exceeding 45°C. All melting points are uncorrected. Optical rotations were measured in a 0.5-dm tube with a Carl Zeiss Photoelectric Precision Polarimeter. The NMR spectra were taken in deuteriochloroform with a JNM-4H-100 MHz Spectrometer, using tetramethylsilane as an internal standard.

1-Deoxy-3,4-*O*-isopropylidene-1-*C*-nitro-D-*threo*-and-*erythro*-tetritol (1). A solution of 2,3-*O*-isopropylidene-D-glycerinaldehyde[7] (14 g, 110 mmol), nitromethane (20 m*l*, 370 mmol) and triethylamine (10 m*l*, 73 mmol) in ethanol (40 m*l*) was allowed to stand for two days at room temperature, and then concentrated to give a sirup (21 g) which was distilled at 103—104°C/0.05 mmHg. Yield, 60% (12 g); $[\alpha]_D^{23}$ +9.5° (*c* 0.16, ethanol); IR (cm^{-1}) : 3430 (OH), 1540 and 1370 (NO_2).

Found: C, 43.22; H, 7.20; N, 7.25%. Calcd for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.33%.

When the reaction period was shorter than 12 hr, a part of the distilled product crystallized gradually. After recrystallisation from ether-petroleum ether it showed mp 58–59°C, $[\alpha]_D^{23}$ +17.6° (*c* 1.0, ethanol), and the analytical values consisted with the theoretical. The configuration of this isomer was deduced to be *threo* from the rotational value.[8,9]

1-Deoxy-3,4 ; 5,6-di-*O*-isopropylidene-1-*C*-nitro-D-glucitol (2). A solution of 1-deoxy-1-*C*-nitro-D-glucitol[10] (4 g, 19 mmol) and concentrated sulfuric acid (1.44 g) in acetone (90 m*l*) was allowed to stand overnight at room temperature, poured into aqueous sodium hydrogencarbonate (3 g), and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to give a sirup which was distilled at bp 131—133°C/0.03—0.04 mmHg. Yield, 3.2 g (60%), $[\alpha]_D^{23}$ +2.7°

(*c* 2.58, ethanol).

Found: C, 49.62; H, 7.31; N, 4.87%. Calcd for $C_{12}H_{21}NO_7$: C, 49.47; H, 7.27; N, 4.81%.

1-Deoxy-3,4 ; 5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol (3). Treatment of 1-deoxy-1-*C*-nitro-D-mannitol[10] in just the same manner as above gave the corresponding product in 65% yield. Bp 126—128°C/0.02—0.03 mmHg, $[\alpha]_D^{23}$ +15.3° (*c* 1.13, ethanol).

Found: C, 49.73; H, 7.64; N, 5.02%. Calcd for $C_{12}H_{21}NO_7$: C, 49.47; H, 7.27; N, 4.81%.

Treatment of 2,3 ; 4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose with nitromethane in the same manner as in the case of **1** gave a mixture of **2** and **3** in 65% yield (Found: C, 49.25; H, 7.24; N, 4.63%). Bp 130—132°C/0.03—0.04 mmHg, $[\alpha]_D^{23}$ +11.8° (*c* 1.10, ethanol). Conversion of this sirup, **2** and **3** to the corresponding same nitroolefine by the usual method[12] gave a sirup which could not be distilled. However, the consumption of bromine in chloroform by these sirups indicated that **2** and **3** have a free hydroxyl group at C-2 position.

1-Acetamido-1-deoxy-D-glucitol (4). A solution of 1-deoxy-1-*C*-nitro-D-glucitol[10] (3 g, 14.2 mmol) in absolute ethanol (60 m*l*) was shaken with hydrogen in the presence of 10% of palladium-charcoal (2 g) until the hydrogen uptake ceased, and then filtered. Acetic anhydride (3 g, 30 mmol) was added to the filtrate, which was concentrated after the reaction mixture had been allowed to stand for several hr at room temperature. The residue was crystallized from ethanol to give the product in 82% (2.8 g) yield. Mp 124—125°C, $[\alpha]_D^{23}$ −19.4° (*c* 1.03, methanol).

Found: C, 43.05; H, 7.80; N, 6.31%. Calcd for $C_8H_{17}NO_6$: C, 43.04; H, 7.68; N, 6.28%.

1-Acetamido-1-deoxy-D-mannitol (5). 1-Deoxy-1-*C*-nitro-D-mannitol was treated in just the same manner as above to give **5** in 75% yield. Mp 149—150°C, $[\alpha]_D^{23}$ −15.5° (*c* 1.10, methanol).

Found: C, 42.98; H, 7.62; N, 6.30%. Calcd for $C_8H_{17}NO_6$: C, 43.04; H, 7.68; N, 6.28%.

Reaction of 1 or 3 with benzaldehyde. To an ice-cooled solution of **1** (10.3 g, 51.8 mmol), benzaldehyde (6 g, 56.5 mmol) in methanol (20 m*l*) was added a solution of metal sodium (1.19 g), in methanol (20 m*l*), and allowed to stand overnight at room temperature. The reaction mixture was neutralized with 2 N hydrochloric acid (26 m*l*) and concentrated. The resulting sirup was redissolved in ethanol, filtered, and evaporated. Distillation of a part of the sirup was unsuccessful. An attempt to fractionate the sirup from ethanol-petroleum ether gave 0.8 g of β-nitrostyrene as crystals (mp 56—57°C, lit,[19] 57—58°C), but other products could not be identified even by paper chromatography.

A solution of **3** (6 g, 20.6 mmol), benzaldehyde (3 g, 28 mmol) and triethylamine (0.8 m*l*) in methanol (10 m*l*) was allowed to stand at room temperature until the mutarotation ceased (about 12 hr), and concentrated to dryness. The sirup obtained was hydrogenated in absolute ethanol in the presence of palladium-charcoal, hydrolyzed with 2N-hydrochloric acid, and then *N*-acetylated. The sirupy product showed three main spots; R_f=0.21, 0.62 and 0.84, on paper chromatography, using ethyl acetate-pyridine-water (12 : 5 : 4 in volume) as a developer and potassium permanganate as a detecting reagent. Of the spots, the first and the third were identified by comparison with authentic samples to be **5** and β-acetamido-α-phenylethanol,[13] respectively. An attempted column-chromatographic separation of the other compound, using magnesol-celite (1 : 1 in weight) as a carrier and petroleum ether-benzene, ethanol-benzene, ethanol-methanol in turn as effluents, resulted in the compounds eluating in the order of larger R_f value, though the pure compound could not be isolated. Rechromatography of an enriched part of the desired compound showed a similar result, except that D-arabinitol (R_f= 0.40) was ascertained.

2-Methoxy-1-nitropentane (7). To a solution of metal sodium (4.8 g, 208 mmol) in absolute methanol (100 m*l*) was added 1-nitro-1-pentene[12] (23 g, 200 mmol) slowly at 0—7°C, because of exothermic reaction. After being stirred for one hr at 10°C, the reaction mixture was poured into 50% acetic acid under cooling, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, and evaporated. Distillation of the residual sirup gave the main fraction which boils at 83—85°C/13 mmHg, as colorless liquid in 75% yield. IR (cm^{-1}): 1548 and 1380 (NO_2), 1099 (C–O–C).

Found: C, 48.99; H, 9.12; N, 9.35%. Calcd for $C_6H_{13}NO_3$: C, 48.69; H, 8.90; N, 9.52%.

3-Methoxy-2-nitrohexan-1-ol (8). A solution of **7** (3.0 g, 20 mmol), formaldehyde (1.6 g of 37% aqueous solution, 20 mmol) and sodium hydrogencarbonate (1.6 g, 20 mmol) in 50% methanol was allowed to stand at room temperature for a week, neutralized with IR-120 ion-exchanger, and evaporated. Distillation of the residual sirup at 98—99°C/2 mmHg gave 1.4 g (38%) of colorless liquid. IR (cm^{-1}): 3410 (OH), 1541 and 1375 (NO_2), 1090 (C–O–C).

Found: C, 47.70; H, 8.54; N, 7.69%. Calcd for $C_7H_{15}NO_4$: C, 47.44; H, 8.53; N, 7.91%.

4-Methoxy-3-nitroheptan-2-ol (9). Acetaldehyde (3.3 g, of 80% aqueous solution, 60 mmol) and **7** (3.0 g, 20 mmol) was treated by the same procedure as mentioned above, and a fraction which boils at 118—121°C/11 mmHg was obtained in 26.2% yield. IR (cm^{-1}): 1545 and 1379 (NO_2).

Found: C, 50.41; H, 8.80; N, 7.33%. Calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.95; N, 7.33%.

Methyl 3-Amino-2-hydroxy-4-methoxyheptanoate Hydrochloride (10). Treatment of **7** (3.0 g, 20 mmol), *n*-butyl glyoxylate (2.6 g, 20 mmol) and sodium hydrogen carbonate (2.5 g, 30 mmol) in 50% methanol (30 m*l*) by the same method as above gave crude 2-hydroxy-4-methoxy-3-nitroheptanoic acid in 70% yield. For the sake of identification, the sirup was hydrogenated in methanol in the presence of Raney nickel at 40°C under 90 kg/cm², and the filtrate was concentrated after removal of the catalyst. The remaining sirup in 2N sodium hydroxide (10 m*l*) was extracted with ether, acidified with hydrochloric acid, and concentrated. The residual sirup in methanol was filtered, and concentrated. The operation was repeated twice. The sirup was then chromatographed on a silicagel column (1.6 × 35 cm) using benzene-methanol (8 : 2 v/v) solution as an eluent. Fractions No. 3—4 in each 20 m*l* fractionation contained the

19) D. E. Worrall, "Organic Syntheses," Coll. Vol. I, p. 413 (1934).

methyl ester hydrochloride in the total yield of 6%. IR (cm^{-1}): 1740 (CO), 1625 (NH).

Found: C, 44.84; H, 6.98; N, 5.59%. Calcd for $C_9H_{19}NO_4Cl$: C, 44.73; H, 8.34; N, 5.80%.

Condensation of 2-Nitrocyclohexanol with Formaldehyde. A solution of 2-nitrocyclohexanol[17] (3.0 g, 20 mmol), formaldehyde (5.0 g of 37% aqueous solution, 60 mmol) and sodium hydrogencarbonate (4.0 g, 50 mmol) in 50% methanol (60 ml) was allowed to stand for a week at room temperature, neutralized with 2N hydrochloric acid, and concentrated. The resulting sirup in methanol was filtered, and the filtrate was evaporated. The operation was repeated twice. The sirup (3.9 g) obtained was hydrogenated in the presence of Raney nickel at 40°C under 110 kg/cm^2, and then the aminodialcohol obtained (3.2 g) was acetylated by the usual manner. The resulting triacetate was distilled at 149°C/0.1 mmHg. Yield, 3.5 g (65%). IR (cm^{-1}): 1740 and 1650 (CO), 1540 (NH), 1244 (C–O–C).

Found: C, 57.46; H, 7.95; N, 5.33%. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16%.

The main component of the triacetate; *r*-1-acetamido-*c*-2-acetoxy-1-acetoxymethylcyclohexane **(11b)**, crystallized on standing for two months showed mp 91—92°C, and the analytical values were consistent with the theoretical.

Condensation of 2-Nitrocyclohexanol with *n*-Butyl Glyoxylate. A solution of 2-nitrocyclohexanol (4.1 g, 28 mmol), *n*-butyl glyoxylate (5.2 g, 40 mmol) and sodium hydrogencarbonate (4.2 g, 50 mmol) in 50% methanol (50 m*l*) was allowed to stand for a week at room temperature, neutralized with 2N hydrochloric acid, and then extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated to give a sirup (5.3 g). The sirup was hydrogenated in methanol in the presence of Raney nickel at 40°C under 120 kg/cm^2 for 5 hr. The reaction mixture was filtered, and the filtrate was evaporated. The sirup obtained was dissolved in 20 m*l* of alkaline water (0.8 g of sodium hydroxide), and extracted with ether. The water layer was acidified with hydrochloric acid, and concentrated. Extraction of the residue with methanol gave the hydrochloride in 60% (3.0 g) overall yields. The paper chromatogram of the hydrochloride, using *n*-butanol - acetic acid - water (4 : 1 : 5 in volume) as a developer and ninhydrine as a detecting reagent, showed two violet spots; R_f=0.48 and 0.43. Fractionation on silicagel column (1.6×35 cm) using benzene-methanol (8 : 2 v/v) gave pure methyl α-(1-amino-2-hydroxycyclohexyl)glycolate hydrochlride (**12**) in 12% yield as a sirup. IR (cm^{-1}) : 1749 (CO), 1630 (NH).

Found: C, 45.10; H, 8.77; N, 5.97%. Calcd for $C_9H_{18}NO_4Cl$: C, 45.85; H, 7.69; N, 5.94%.

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