# The Synthetic Reactions of Aliphatic Nitro Compounds. XI. The Synthesis of β-Amino-α-hydroxycarboxylic Acids and γ-Aminocarboxylic Acids[1]

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(Received May 31, 1976)

The *O*-alkylation of some nitroparaffins, 2-nitropropane, 2-nitrobutane, 1-nitropropane, and phenylnitromethane, with methyl bromoacetate in dipolar aprotic solvent led to α-hydroxy-β-nitrocarboxylates, which were converted into β-amino-α-hydroxycarboxylic acids. Several γ-aminocarboxylic acids were synthesized from the corresponding γ-nitrocarboxylates which were obtained *via* *C*-alkylation of the nitroparaffins with methyl β-bromopropionate.

The ambident reactivity of aliphatic nitro compounds has been known to undergo unique reactions with several electrophiles.[2-4] We have found that alkylation of α-carbon atom in nitroparaffins is useful for the formation of a C–C bond, considering that carbon alkylation is applicable to a rather limited case where some nitroparaffins are alkylated with α-halonitroparaffins or some benzyl halides.[5-7]

It has been already reported by Hass *et al.*[8] that oxygen alkylation is available for the synthesis of aldehydes. However, practical investigation of the ambident nitronate anion is limited to the field of a reaction involving radical anion intermediates.[9,10]

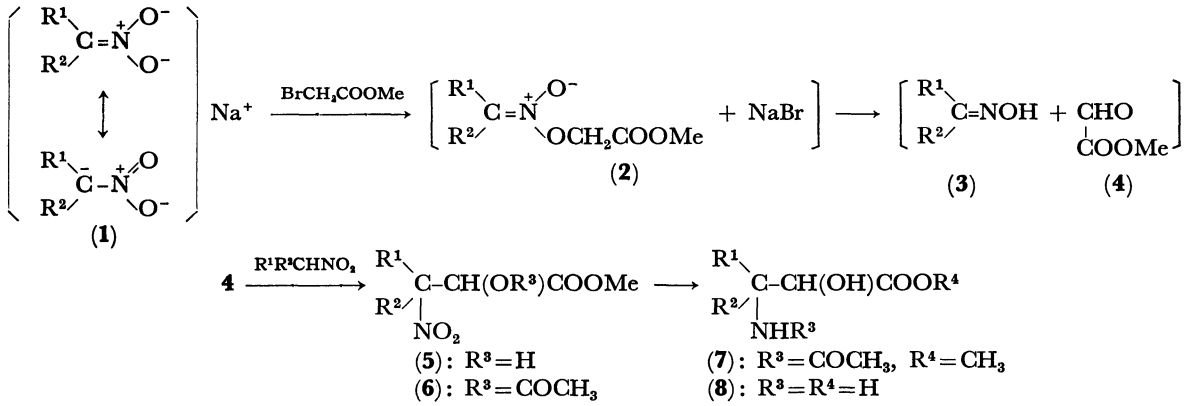
Recently we have found that the use of dipolar aprotic solvents such as *N,N*-dimethylacetamide in this reaction promotes carbon alkylation of nitroacetate anion, and that the orientation of alkylation depends on the kind of the electrophiles used. We have reported that several α-amino acids[11,12] and 4-substituted isoxazoline *N*-oxides[13] can be synthesized *via* alkylation of nitroacetate. Recent developments on amino acids of β- or γ-series which are themselves biologically active or the important components of several antibiotics[14-16] prompted us to explore new and general syntheses of these series of amino acids *via* alkylation of nitroparaffins.

For our purposes, attempted alkylation of several nitroparaffins, 2-nitropropane (**1a**), 2-nitrobutane (**1b**), 1-nitropropane (**1c**), and phenylnitromethane (**1d**), with bromoacetic ester and β-bromopropionic ester was carried out. The reaction of two equivalents of the aci-nitro compounds with methyl bromoacetate in a dipolar aprotic solvent produced α-hydroxy-β-nitroesters (**5**) which would be produced by the condensation of excess nitroparaffin with methyl glyoxylate (**4**) formed by the initial *O*-alkylation followed by degradation, as illustrated in Chart 1. This scheme was supported by the isolation of α-benzaldoxime (**3d**, $R^1=C_6H_5$, $R^2=H$) from the reaction mixture of **5d**, which was identified with an authentic sample. The structure of **5** was confirmed from the IR and NMR spectra and elemental analyses (Tables 1 and 2).

It seems that this reaction is well suited for secondary rather than primary nitroparaffins except for phenylnitromethane. In the alkylation of nitromethane or nitroethane with methyl bromoacetate, similar products that were expected were not obtained under analogous conditions, since the products from primary nitro compounds would still have an active hydrogen which would undergo subsequent alkylation or side reaction.

The compound **5b** or **5c** was confirmed by NMR to be a diastereomeric mixture consisting of *erythro* and *threo* isomers in a ratio of *ca.* 1 : 1, as shown in Table 2. This result agreed well with a previous report on the ethyl ester of **5c**.[17]

Catalytic hydrogenation of **5** in methanol usually gave a mixture of products which could not be purified further. Subsequently *O*-acetyl derivatives (**6**) of **5** were prepared and subjected to hydrogenation over a Raney nickel catalyst to yield the corresponding β-amino-esters (**7**). From the spectroscopic data of **7**, *O*→*N* migration of acetyl group seems to be occurred to give




**a**: $R^1=R^2=CH_3$; **b**: $R^1=C_2H_5$, $R^2=CH_3$; **c**: $R^1=C_2H_5$, $R^2=H$; **d**: $R^1=C_6H_5$, $R^2=H$

Chart 1.

TABLE 1. METHYL α-HYDROXY- AND α-ACETOXY-β-NITROCARBOXYLATES (**5** and **6**)

| Compound No. | $R^1$ | $R^2$ | Bp °C/Torr (Mp °C) | Yield (%) | Formula | Found (%) | | | Calcd (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | C | H | N |
| **5a** | $CH_3$ | $CH_3$ | 75.7—77.5/0.3 | 48 | $C_6H_{11}NO_5$ | 40.56 | 6.23 | 7.57 | 40.68 | 6.26 | 7.91 |
| **5b** | $C_2H_5$ | $CH_3$ | 74—75/0.3 | 52 | $C_7H_{13}NO_5$ | 43.72 | 6.72 | 6.93 | 43.42 | 6.63 | 7.33 |
| **5c** | $C_2H_5$ | H | 85—87/0.3 | 11 | $C_6H_{11}NO_5$ | 40.41 | 6.33 | 7.64 | 40.68 | 6.26 | 7.91 |
| **5d** | $C_6H_5$ | H | (109—110) | 68 | $C_{10}H_{11}NO_5$ | 53.18 | 4.89 | 6.26 | 53.33 | 4.92 | 6.22 |
| **6a** | $CH_3$ | $CH_3$ | (67—68) | 63 | $C_8H_{13}NO_6$ | 43.84 | 5.98 | 6.39 | 44.04 | 6.09 | 6.34 |
| **6b** | $C_2H_5$ | $CH_3$ | 74—75/0.04 | 54 | $C_9H_{15}NO_6$ | 46.08 | 6.44 | 5.85 | 46.35 | 6.48 | 6.01 |
| **6c** | $C_2H_5$ | H | 85—90/0.02 | 85 | $C_8H_{13}NO_6$ | 43.58 | 5.97 | 6.14 | 43.84 | 5.98 | 6.39 |
| **6d** | $C_6H_5$ | H | (64—65) | 85 | $C_{12}H_{13}NO_6$ | 53.85 | 5.01 | 5.02 | 53.93 | 4.90 | 5.24 |

TABLE 2. IR AND NMR DATA OF METHYL α-HYDROXY- AND α-ACETOXY-β-NITROCARBOXYLATES (**5** and **6**)

| Compound No. | ν (liquid film) $cm^{-1}$ | | | δ (100 MHz) in $CDCl_3$ | | | | Composition[a] *erythro : threo* |
|---|---|---|---|---|---|---|---|---|
| | C-$NO_2$ | C=O | OH | α-H | β-H or -$CH_3$ | OH or $COCH_3$ | $CO_2CH_3$ | |
| **5a** | 1545, 1350 | 1750 | 3450 | 4.65 (d) | 1.63 (s)<br>1.67 (s) | 3.47 (d) | 3.87 (s) | — |
| **5b** | 1550, 1360 | 1740 | 3460 | 4.59 (d)<br>4.65 (s) | 1.46 (s)<br>1.54 (s) | 3.27 (d) | 3.78 (s)<br>3.82 (s) | 1 : 1 |
| **5c** | 1550, 1370 | 1750 | 3500—3400 | 4.40 (d—d)[b]<br>*ca.* 4.6 (?)[c] | 4.5—4.8 (m) | 3.18 (d) | 3.84 (s) | 1 : 1 |
| **5d**[f] | 1550, 1350 | 1750 | 3450 | 4.90 (broad) | 5.80 (d) | *ca.* 3.6 (broad) | 3.73 (s) | ? |
| **6a**[f] | 1550, 1350 | 1750 | — | 5.57 (s) | 1.68 (s) | 2.13 (s) | 3.78 (s) | — |
| **6b** | 1555, 1380 | 1755 | — | 5.56 (s)<br>5.60 (s) | 1.60 (s)<br>1.64 (s) | 2.10 (s)<br>2.17 (s) | 3.76 (s)<br>3.79 (s) | 1 : 1 |
| **6c** | 1560, 1380 | 1750 | — | 5.40 (d)[d]<br>5.61 (d)[e] | 4.65—4.95 (m) | 2.16 (s) | 3.79 (s) | 1 : 1 |
| **6d**[f] | 1550, 1350 | 1750 | — | 5.83 (s) | 5.83 (s) | 2.13 (s) | 3.50 (s) | ? |

a) The composition was determined by the signal intensity of α-H or β-$CH_3$. b) $J_{\alpha,\beta}$ =4.0 Hz. c) $J_{\alpha,\beta}$ was not observed because of the overlapping to β-H. d) e) $J_{\alpha,\beta}$ were 6.8 and 4.2 Hz respectively. f) IR spectrum was measured in KBr disk.

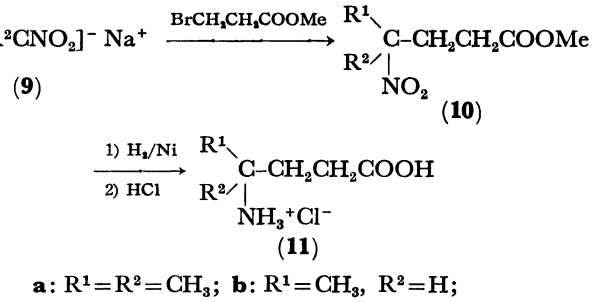
TABLE 3. METHYL γ-NITROCARBOXYLATES (**10**)

| Compound No. | $R^1$ | $R^2$ | Bp (°C/Torr) | $n_D^{20}$ | Yield (%) |
|---|---|---|---|---|---|
| **10a** | $CH_3$ | $CH_3$ | 57/0.1 | 1.4408[a] | 85 |
| **10b** | $CH_3$ | H | 51/0.1 | 1.4361[b] | 24 |
| **10c** | $C_2H_5$ | H | 52/0.2 | 1.4368[c] | 34 |
| **10d** | $C_6H_5$ | H | 113/0.04 | 1.5150[d] | 37 |

a) Reported[18] bp. 79 °C/1 Torr, $n_D^{20}$ 1.4408. b) Reported[19] bp. 91 °C/4 Torr, $n_D^{25}$ 1.436. c) Reported[20] bp. 97 °C/2 Torr, $n_D^{20}$ 1.4371. d) Reported[21] bp. 128—134 °C/1 Torr, $n_D^{18}$ 1.5164.

methyl β-acetamido-α-hydroxycarboxylates (**7**). The IR spectra of **7** showed a strong absorption at 1640—1650 $cm^{-1}$, typical of an amide, and a broad NH peak appeared at δ 5.8—6.1 region in its NMR spectra. **7** was readily hydrolyzed by treatment with 6 M hydrochloric acid under refluxing for 16 h, giving β-amino-α-hydroxycarboxylic acid hydrochloride as a viscous oil. Deionization through an ion-exchange resin (IR-45, OH form or Dowex 50 W, Na form) column followed by recrystallization gave free amino acids (**8**) as colorless crystals.

The composition of the isomers of **8b** and **8c** was observed to be almost one isomer on the basis of NMR signals for β-$CH_3$ proton (δ 1.27) for **8b** and α-proton (δ 4.08) for **8c**, whereas crude products (**8b** and **8c**) consist of a mixture of two diastereomers in which β-$CH_3$ proton was observed at δ 1.27 and 1.23 for **8b** and α-proton at δ 4.08 and 4.16 for **8c**. β-Phenylisoserine (**8d**) was separated into two isomers under ion-




(**9**) (**10**) (**11**)

**a**: $R^1=R^2=CH_3$; **b**: $R^1=CH_3$, $R^2=H$;
**c**: $R^1=C_2H_5$, $R^2=H$; **d**: $R^1=C_6H_5$, $R^2=H$

Chart 2.

exchange chromatography, and its results are shown in Table 4. On the other hand, the alkylation reaction of **9a—9d** with methyl β-bromopropionate in *N,N*-dimethylacetamide proceeds preferentially *via* carbon alkylation to yield methyl γ-nitrocarboxylates (**10a—d**) as shown in Chart 2. **10a—d** showed physical constants identical with reported values as well as in IR and NMR spectra and elemental analyses. The catalytic reduction products of **10a—d** were obtained as chromatographically homogeneous syrups. These products were subsequently hydrolyzed with 6 M hydrochloric acid to the corresponding γ-amino acids (**11a—c**) as their hydrochloride and purified by recrystallization. The results are summarized in Table 4.

Table 4. β-Amino-α-hydroxycarboxylic acids (**8**) and γ-aminocarboxylic acid hydrochlorides (**11**)

| Compound No. | $R^1$ | $R^2$ | Mp (°C) | $R_f$ [a] | Yield [b] (%) |
|---|---|---|---|---|---|
| **8a** | $CH_3$ | $CH_3$ | 278—279 (dec.) [c] | 0.56 | 42 |
| **8b** | $C_2H_5$ | $CH_3$ | 217—218 (dec.) [d] | 0.72 | 54 |
| **8c** | $C_2H_5$ | H | 267—268 (dec.) [e] | 0.37 | 31 |
| **8d** | $C_6H_5$ | H | 240 (dec.) [f] | 0.79 | 24 |
| **8d** | $C_6H_5$ | H | 265 (dec.) [g] | 0.70 | 28 |
| **11a** | $CH_3$ | $CH_3$ | 178—179 [h] | 0.49 | 51 |
| **11b** | $CH_3$ | H | 139—140 [i] | 0.49 | 77 |
| **11c** | $C_2H_5$ | H | 118—119 [h] | 0.53 | 75 |

a) Paper chromatography on Toyo Roshi filter paper No. 525; solvent, 1-butanol: acetic acid: water (4: 1: 1). b) Based on the corresponding α-hydroxy-β-nitroesters or γ-nitroesters. c) Reported[22] mp. 276.5—277 °C (dec.). d) Found: C, 48.96; H, 8.94; N, 9.45%. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52%. e) Found: C, 44.88; H, 8.26; N, 10.28%. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52%. f) Reported[23] mp. 230—232 °C. g) Reported[23] mp. 275—280 °C. h) The free amino acid has been reported in the literature[15]. i) Reported[19] mp. 135 °C.

## Experimental

All boiling and melting points are uncorrected. The IR spectra were measured on a JASCO Model IRA-1 spectrometer. The NMR spectra were recorded with a 100 MHz JEOL PS-100 spectrometer. Tetramethylsilane was used as an internal standard for deuteriochloroform and tetradeuteriomethanol solution and sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used in deuterium oxide solution. The peak positions are given in δ value.

*Typical Procedure.* *Methyl α-Hydroxy-β-nitroisovalerate (5a)*: 1 M sodium methoxide (10 ml) was added to a stirred solution of 2-nitropropane (1.73 g, 20 mmol) and methyl bromoacetate (1.53 g, 10 mmol) in 30 ml of *N,N*-dimethylacetamide. After agitation at room temperature overnight, the reaction mixture was poured into 150 ml of ice-cold water covered with 50 ml of benzene. The aqueous phase was extracted four more times with 50 ml portions of benzene. After the benzene extract had been washed with four 50 ml portions of water, benzene layer was dried over anhydrous sodium sulfate. The benzene was removed under reduced pressure. Rectification of the residue yielded 0.85 g of **5a** in 48% yield. Bp, elemental analysis, and spectroscopic data were shown in Table 1 and 2. **5b—5d** were also obtained in a similar procedure. **5c** and **5d** were purified by column chromatography on silica gel (hexane/ethyl acetate as eluant) before distillation.

*Methyl α-Acetoxy-β-nitroisovalerate (6a).* Concds ulfuric acid (0.05 ml) was added to a stirred solution of **5a** (1 g, 5.65 mmol) in 10 ml of acetic anhydride under ice-cooling. When stirring was continued for an additional 1 h, all the starting material was consumed as shown by silica gel TLC (hexane–ethyl acetate, 2: 1). The reaction mixture was poured into 50 ml of water and extracted with diethyl ether (3×25 ml). The combined extracts were washed with water, dried over anhydrous sodium sulfate, and solvent was evaporated. Recrystallization or sublimation of the resultant solid-residue gave 0.78 g (63%) of colorless crystals. **6b—6d** were also obtained under analogous conditions. The results are summarized in Table 1 and 2.

*β-Amino-α-hydroxyisovaleric Acid (8a).* A methanolic slurry of Raney nickel T-1 catalyst (1.5 ml) was added to a solution of **6a** (0.73 g, 3.33 mmol) in 40 ml of methanol. The mixture was hydrogenated at room temperature under 3.5 kg/cm² of hydrogen atmosphere in a Parr low-pressure hydrogenator. The catalyst was filtered and the filtrate was evaporated to afford 0.73 g of deep yellow oil (**7a**). **7a** was subjected to next step without further purification except **7b** and **7c** which were passed through ion-exchange resin (Dowex 50 W, H form).

A 0.5 g (2.64 mmol) portion of **7a** was refluxed with 6 M hydrochloric acid (8 ml) for 16 h. After evaporation of the solvent the residual oil was dissolved in water and deionized through a column of basic resin (IR-45, OH form, water as an eluant). Concentration of the eluant gave 0.4 g of amorphous solid. The crude solid was recrystallized from aqueous ethanol to yield 0.15 g of colorless crystals in 42% yield. **8b—8d** were prepared in a similar way as **8a** from the corresponding α-acetoxy-β-nitro esters (**6b—6d**). The results are summarized in Table 4.

*Methyl γ-Nitroisocaproate (10a)* To a stirred solution of 2-nitropropane (1.0 g, 11.24 mmol) and methyl β-bromopropionate (1.88 g, 11.24 mmol) in 20 ml of anhydrous *N,N*-dimethylacetamide, was added 11.24 ml of 1 M sodium methoxide. The mixture was stirred at room temperature overnight. The resultant yellow liquid was worked up as in the procedure for **5a**. The crude yellow oil was purified by distillation to yield 1.67 g (85%) of colorless oil (**10a**). **10b—10d** were also obtained in analogous way. The results are summarized in Table 3.

*γ-Aminoisocaproic Acid (11a).* **10a** (1.5 g, 8.57 mmol) was hydrogenated in 80 ml of methanol in the presence of Raney nickel T-1 (2 ml of methanolic slurry) with a low pressure hydrogen (3.5 kg/cm²) for 1.5 h at room temperature. The catalyst was filtered off and the solvent was removed. The residue was subsequently hydrolyzed without further purification. Hydrolysis was carried out by refluxing with 6 M hydrochloric acid for 16 h. After evaporation the residual solid was washed with anhydrous ether and acetone. Recrystallization from methanol–ether afforded 0.73 g (51%) of analytically pure **11a**. **11b—11c** were also obtained in a similar way. The results are summarized in Table 4.

The authors are indebted to Miss Kazuko Shibuya, Messrs. Kazuo Yamaji and Toshihide Kamiya for their technical assistance.

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