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The Synthetic Reactions of Aliphatic Nitro Compounds. VII.[1] The Synthesis of *α*-Amino Acids from the Nitroacetic Ester[2]

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As a short communication,[3] we previously reported the synthesis of DL-aspartic acid and DL-glutamic acid *via* the *C*-alkylation of nitroacetate[4] with halo esters. In this investigation, several neutral and basic amino acids were prepared by the same procedure.

$$\left.\begin{array}{l}\text{Method (i), } R^1X + NaO_2N{=}CHCO_2Me \\ \text{Method (ii), } R^1X + O_2NCH_2CO_2Me + CHO_3Na\end{array}\right]$$

$$\xrightarrow{-NaX} R^1\cdot CHR^2CO_2R^3 \quad \begin{array}{l}\mathbf{1}: R^2{=}NO_2;\ R^3{=}CH_3 \\ \mathbf{2}: R^2{=}NH_2;\ R^3{=}CH_3 \\ \mathbf{3}: R^2{=}NH_2;\ R^3{=}H\end{array}$$

Chart 1.

This procedure is carried out by the reaction of the halides either with the sodium salt of nitroacetate (Method i) or with nitroacetate and sodium methylate (Method ii) in dipolar aprotic solvents, as is shown in Chart 1. When methyl bromoacetate, methyl *β*-bromopropionate, methyl iodide, isopropyl iodide, benzyl bromide, *N*-(*β*-iodoethyl)-phthalimide, *N*-(*γ*-iodopropyl)-phthalimide, and *N*-(*δ*-iodobutyl)-phthalimide were used as the halogeno compounds in the above reaction, dimethyl nitrosuccinate[3] (**1a**), dimethyl α-nitroglutarate[3] (**1b**), methyl α-nitropropionate[2] (**1c**), methyl α-nitroisovalerate[2,11] (**1d**), methyl α-nitro-*β*-phenylpropionate[2] (**1e**), methyl α-nitro-*γ*-phthalimidobutyrate (**1f**), methyl α-nitro-*δ*-phthalimidovalerate (**1g**), and methyl α-nitro-*ε*-phthalimidocaproate (**1h**) respectively resulted as the corresponding *C*-alkylated products. They could be obtained as crystalline diethylammonium or ammonium salts.

Furthermore, by the catalytic hydrogenation of the nitroesters (**1**) and the subsequent hydrolysis of the corresponding amino esters (**2**), DL-aspartic acid (**3a**), DL-glutamic acid (**3b**), DL-alanine (**3c**), DL-valine (**3d**), DL-phenylalanine (**3e**), DL-*α*,*γ*-diaminobutyric acid (**3f**), DL-ornithine (**3g**), and DL-lysine (**3h**) were obtained. These results are summarized in Tables 1 and 2.

TABLE 2. α-NITROESTERS (**1**)

Compound	Bp, °C/mmHg (mp°C)	n_D^{20}
1a	70—72/0.05	1.4452
DS of **1a**	(103—104)	
1b	82—85/0.05[a]	1.4468
DS of **1b**	(62—65.5)	
1c	53—54/4[b]	1.4250[b]
DS of **1c**[12]	(110—114)	
1e	94—95/0.03~0.04[c]	1.5133
DS of **1e**	(116.5—119.5)	
1f	oily product	—
AS of **1f**	(135.5—140, dec.)	
1g	oily product	—
AS of **1g**	(163.5—165, dec.)	
1h	oily product	—
DS of **1h**	(119—123, dec.)	

DS: diethylammonium salt of **1**.
AS: ammonium salt of **1**.
a) Reported bp 116—118°C/2 mmHg.[10]
b) Reported bp 79°C/5 mmHg, n_D^{20} 1.4216[11]
c) Reported bp 110°C/0.01 mmHg, n_D^{20} 1.5100.[11]

TABLE 1. THE YIELDS OF RESPECTIVE REACTION STEPS

	Reaction condition	$R^1\cdot CH(NO_2)\cdot CO_2CH_3$ (**1**) (%)		$R^1\cdot CH(NH_2)CO_2CH_3$ (**2**) (%)	$R^1\cdot CH(NH_2)CO_2H$ (HCl salt) (**3**) (%)
		Method i	Method ii		
a	Room temp, overnight	23	66	90	94
b	60±5°C, 2 hr.	88.5	57	92.4	90
c	Room temp, overnight	74.5	—	88	96
d	Room temp, overnight	20	—	80	84
e	Room temp, overnight	50	52	80	96
f	70±5°C, 6 hr.	10.6	—	38 (as HCl salt)	quantitative[b]
g	70±5°C, 6 hr.	29	—	85	76[b]
h	Room temp, 20 hr.	12.3[a]	—	98	99[b]

Method (i) employed Na salt of nitroacetate.
Method (ii) employed nitroacetate and sodium methylate.
a) Ag salt of nitroacetate was employed.
b) $R^1{=}H_2N\text{-}(CH_2)_n\text{-}$ (**3f**: n=2, **3g**: n=3, **3h**: n=4)

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[1] Part VI: S. Zen and M. Koyama, This Bulletin, **44**, 2882 (1971).

[2] Presented at 24th Annual Meeting of Chemical Society of Japan, Osaka, April, 1971, Preprint Vol. III, p. 1530 (1971).

[3] S. Zen and E. Kaji, This Bulletin, **43**, 2277 (1970).

[4] S. Zen, M. Koyama, and S. Koto, *Kogyo Kagaku Zasshi*, **74**, 70 (1971).

Only when bromoacetate and sodium salt of nitroacetate were used was trimethyl β-nitrotricarballylate obtained as a by-product (in a 16.4% yield) in addition to the expected product, **1a**.

It has been found that the *C*-alkylation reaction of nitroacetate with the halides takes place only in dipolar aprotic solvents, as is shown in Table 3. As for the influence of the variation in halogen atoms, the reaction is found to be promoted in the order of I>Br>Cl.

All new compounds reported above (in Table 2) gave satisfactory results in C, H, and N analyses.

TABLE 3. SOLVENT EFFECT ON THE YIELDS OF DIMETHYL α-NITROSUCCINATE (**1a**)

Solvent	Yield (%) of **1a**
Ethanol, methyl acetate, or dioxane	0
N-Methylacetamide	30
Dimethylformamide	57
Dimethylacetamide	66
Dimethyl Sulfoxide	55
Hexamethylphosphoramide	51

Experimental

Dimethyl α-Nitrosuccinate[5] *(1a) (A Typical Example of the General Procedure).* Method (i): Sodium salt of methyl nitroacetate (2.0 g, 14.2 mmol) was added to a solution of methyl bromoacetate (2.17 g, 14.2 mmol) in 50 ml of dimethylacetamide. This suspension was stirred overnight at room temperature. The reaction mixture was then added to 150 ml of water and extracted with benzene. The extract was concentrated, and the resultant syrup was subjected to fractional distillation under reduced pressure to give **1a** (0.63 g) in a 23% yield; IR (liquid film): 1745 (ester CO), 1565 and 1380 (C–NO$_2$) cm^{-1}, UV: $\lambda_{\max}^{\mathrm{MeOH}}$ 275 mμ (ε 290). When the product was allowed to stand, a crystalline trimethyl β-nitrotricarballylate separated. Colorless prismatic crystals (0.30 g) were collected; 16.4% yield; mp 88.5—89.5°C (from ether–isopropyl ether); IR (KBr): 1730 (ester CO), 1560 and 1370 (C–NO$_2$) cm^{-1}; UV: $\lambda_{\max}^{\mathrm{MeOH}}$ 283 mμ (ε 36). Found: C, 40.60; H, 4.68; N, 5.20%. Calcd for $C_9H_{13}NO_8$: C, 41.06; H, 4.94; N, 5.32%. An equimolar mixture of diethylamine and **1a** gave a diethylammonium salt of **1a** as a solid. Recrystallization from ethanol–ether gave needles; mp 103—104°C. Found: C, 44.90; H, 7.50; N, 10.11%.
Calcd for $C_{10}H_{20}N_2O_6$: C, 45.45; H, 7.58; N, 10.61%.

Method (ii): Sodium methylate (1.03N, 22.8 ml) in methanol was added to a solution of 3.1 g (26.1 mmol) of methyl nitroacetate and 4.0 g (26.1 mmol) of methyl bromoacetate in dimethylacetamide (100 ml). The mixture was stirred overnight at room temperature. The reaction mixture was then treated in a manner similar to that described in Method (i) to give a yellow syrup. After distillation, 3.3 g of **1a** were obtained. Yield, 66%.

Amino Esters (A Typical Procedure for the Catalytic Reduction of α-Nitroesters, 1a—h). A solution of **1a** (1.0 g, 5.24 mmol) in methanol (50 ml) was hydrogenated for 1 hr with 2 ml of the Raney Nickel T-1[6] catalyst at room temperature under 40—50 *psi* of hydrogen in a Parr low-pressure hydrogenator.[7] The filtrate from the nickel was evaporated *in vacuo* to dryness to give the product (**2a**, 0.17 g) in a 90% yield. The amino esters, **2a**—**h**, were prepared by the same procedure, **1a**—**e** were thus proved to be identical with the authentic samples prepared by the esterification of the corresponding standard DL-amino acids.

α-Amino Acids (A Typical Procedure for the Hydrolysis of the Amino Esters). A mixture of 200 mg of **2a** and 6 ml of 6N hydrochloric acid was heated in a sealed tube at 110°C for about 16 hr (or under reflux for about 16 hr). The solution was then evaporated to dryness, and the residual syrup was washed with ether and acetone to obtain a colorless powder of the HCl salt of DL-aspartic acid (**3a**) in a 94% yield. This product was found to be identical with the authentic sample in its melting point, the result of elementary analysis, the IR, the R_f value, and in the corresponding *N*-2,4-dinitrophenyl derivative[8]. **3b**—**h** were prepared in the same way as **3a** from the corresponding aminoesters (**2b**—**h**).[9] The results are shown in Table 1.

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5) Diethyl α-nitrosuccinate has been prepared from diethyl α-bromosuccinate and nitrite by R. Gelin and S. Gelin (*C.R. Acad. Sci., Paris*, **256**, 3705 (1963)).

6) X. A. Dominguez, I. C. Lopez, and P. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

7) Parr Instruments (U.S.A.).

8) R. R. Porter and F. Sanger, *Biochem. J.*, **42**, 287 (1948); F. C. Green and C. M. Kay, *Anal. Chem.*, **24**, 726 (1952); H. M. Rice and F. J. Sowden, *Can. J. Chem.*, **30**, 575 (1952).

9) **3f**—**h** were obtained after the removal of the *o*-phthalic acid precipitated from an acid-hydrolysis mixture.

10) From the addition of magnesium complex of nitroacetic acid to methyl acrylate, yield of **1b** was 5.4% (V. M. Belikov and Yu. N. Belokon, *Izv. Akad, Nauk. SSSR. Ser. Khim.*, **1964** (6), 1134; *Chem. Abstr.*, **61**, 7094 (1964); N. J. Leonard and G. L. Shoemaker, *J. Amer. Chem. Soc.*, **71**, 1762 (1949).

11) H. L. Finkbeiner and G. W. Wagner, *J. Org. Chem.*, **28**, 215 (1963).

12) W. Steinkopf reported only the ammonium salt of **1c** in *Ann.*, **434**, 30 (1923).