A Novel Synthesis for DL-Aspartic Acid and DL-Glutamic Acid[*1]

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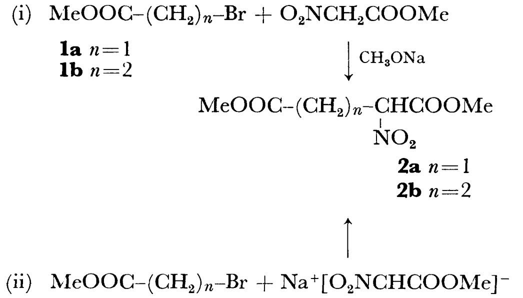
Our current interest in the synthesis of various amino acids[1)] from α-nitroesters has led us to attempt to find an every method of synthesizing DL-aspartic acid and DL-glutamic acid.[*2]

The synthesis of α-nitrodicarboxylates by the *carbon-alkylation reaction* of methyl nitroacetate with the halo-ester of carboxylic acid consists of the following steps:



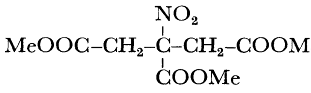
In the first method (i) sodium methylate is added to methyl nitroacetate and **1a** (or **1b**) to yield **2a** (or **2b**); the second method (ii) yields the same *C*-alkylated derivatives (**2a** and **2b**) by the reaction of sodium salt of methyl nitroacetate with **1a** (or **1b**).

Dimethyl nitrosuccinate[2)] (**2a**): following Step i, an equimolecular reaction takes place between methyl nitroacetate and methyl bromoacetate (**1a**) in a dipolar aprotic solvent (such as dimethylacetamide or dimethylformamide) in the presence of sodium methylate (such as the 1N methanol solution) when it is stirred overnight at room temperature. The reaction product was extracted with benzene (from the water layer which resulted from adding water and benzene to the reaction mixture). The benzene was first distilled out; when the **2a** was further distilled under reduced pressure, its yield was 66%; bp. 70—72°C/0.05 mmHg, n_D^{20} 1.4452, IR (liquid film): 1745 (ester CO), 1565 and 1380 (C–NO_2) cm^{-1}, $\lambda_{\max}^{\mathrm{MeOH}}$ 275 mμ (ε 290). Diethylammonium salt of **2a** recrystallized from ethanol - ether, melted at 103—104°C. Following Step ii, **2a** was synthesized in a 23% yield, and also the trimethyl ester of β-nitrotricarballic acid (**3a**) was obtained as colorless prismatic crystals in a 29% yield by recrystallization from an ether-isopropylether mixture; mp 88.5—89.5°C, IR (KBr): 1730 (ester CO), 1560 and 1370 (C–NO_2) cm^{-1}, $\lambda_{\max}^{\mathrm{MeOH}}$ 283 mμ (ε 36).

The catalytic hydrogenation[*3] of **2a** with Raney Nickel T-1[3)] under 40 p.s.i.g. gave the corresponding ester of aspartic acid in a 90% yield. By the hydrolysis of the product with 6N hydrochloric acid, DL-aspartic acid was obtained in a 94% yield as HCl salt.

Dimethyl α-nitroglutarate[4)] (**2b**): in a similar way, **2b** was given in an 88.5% yield by the reaction of the sodium salt of methyl nitroacetate with **1b**.

DL-Glutamic acid was then synthesized in a total yield of 83.2% from **2b** by hydrogenation and subsequent hydrolysis following the above-mentioned procedure.



$$MeOOC{-}CH_2{-}\overset{NO_2}{\underset{COOMe}{C}}{-}CH_2{-}COOMe$$

(**3a**)

Investigations into the uses of this *C*-alkylation reaction using other halogeno-compounds with the nitro ester and into the mechanism of this reaction are now in progress.

[*1] Part IV in the series, "The Synthetic Reactions of Aliphatic Nitro Compounds,"

1) S. Zen, Y. Takeda, A. Yasuda and S. Umezawa, This Bulletin, **40**, 431 (1967); S. Zen, A. Yasuda, H. Hashimoto and Y. Takeda, *Nippon Kagaku Zasshi*, **90**, 110 (1969).

[*2] Presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970; Preprint, Vol. III (1970), p. 1671.

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

[*3] Hydrogenation apparatus, Paar Instruments.

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

4) V. M. Belikov and Yu. N. Belokon, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, **1964**(6), 1134; *Chem. Abstr.*, **61**, 7094 (1964).