Nitroethylene: A Novel Synthon for *N*-(2-Nitroethyl)-amino Compounds

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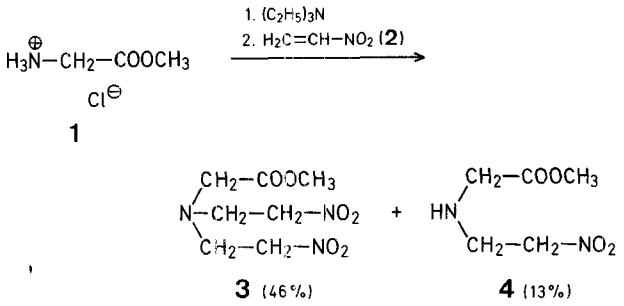
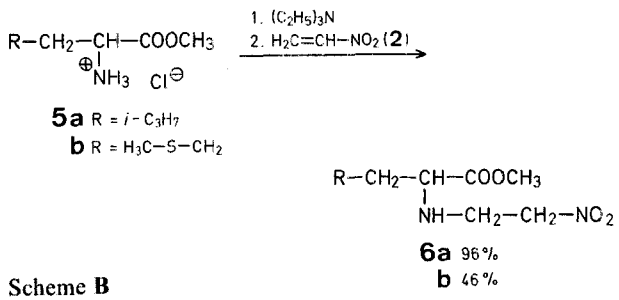
During studies on nitroethylene **(2)** as a useful synthon[1], it was observed that nitrogen bases reacted with **2** to give intractable products, whereas α-amino acid esters underwent clean addition giving rise to novel 2-nitroethyl Michael adducts. Thus, the reaction of glycine methyl ester **(1)** with **2** gave a 46% of yield of *N*-methoxycarbonylmethyl-*N*,*N*-bis[2-nitroethyl]amine **(3)** and 13% of *N*-methoxycarbonylmethyl-*N*-(2-nitroethyl)-amine **(4)** (Scheme A).



Scheme **A**

Reaction of **2** with the methyl esters of DL-leucine **(5a)** and L-methionine **(5b)** gave the mono-2-nitroethyl Michael adducts **6a** and **6b**, respectively (Scheme **B**).



Scheme **B**

A particularly noteworthy reaction of nitroethylene **(2)** is that leading to *N*-(2-nitroethyl)-proline methyl ester **(8)**,

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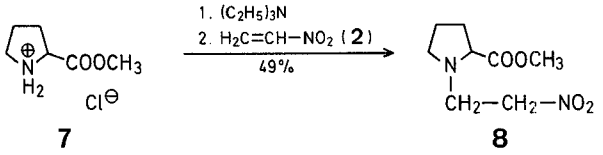
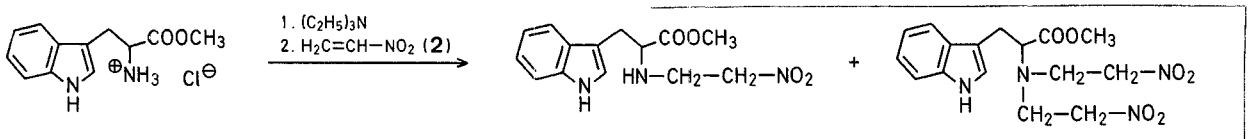
which has potential for further elaboration to a variety of naturally occurring bicyclic compounds.



7 8

An analogous result was the formation of *N*-(2-nitroethyl)-tryptophan methyl ester (**10**) as well as *N,N*-bis[2-nitroethyl]tryptophan methyl ester (**11**) by the reaction of nitroethylene (**2**) and tryptophan methyl ester (**9**) (Scheme C).



9 10 (42%) 11 (13%)

Scheme C

The ^{1}H-N.M.R. spectra of **10** and **11** clearly show that the indole-NH group is not involved. However, the formation of the bis-adduct in contrast to the exclusive formation of the mono-adduct in the case of leucine, where similar experimental conditions were followed, could be rationalized on the basis of an intramolecular nitroethylene transfer involving the indole-NH group.

All reactions are monitored by T.L.C. on silica gel plates using butanol/acetic acid/water (75:25:10) as solvent and iodine as developer.

N-Methoxycarbonylmethyl-*N,N*-bis[2-nitroethyl]amine (3) and *N*-Methoxycarbonyl-*N*-(2-nitroethyl)-amine (4):
Triethylamine (0.64 g, 6.4 mmol) is added to an ice-cooled and stirred suspension of glycine methyl ester hydrochloride[2] (**1**; 0.8 g, 6.4 mmol) in dry ether (20 ml). A solution of nitroethylene (**2**; 0.47 g, 6.4 mmol) in dry benzene (5 ml) is then added, the reaction mixture is stirred at ~10 °C for 30 h, treated with another portion of nitroethylene (0.5 g, 6.8 mmol) in benzene (5 ml), and then after 52 h with a final aliquot of triethylamine (0.320 g, 3.1 mmol) and nitroethylene (0.3 g, 4.1 mmol). The reaction mixture is stirred for 24 h, the supernatant liquid is decanted, the residue washed with ether (3 × 10 ml), the combined extracts evaporated in vacuo, and the resulting viscous residue (1.289 g) chromatographed on silica gel. Elution with ethyl acetate/petroleum ether (1:1) gives **3**; yield: 0.66 g (46%), which is further purified by bulb-to-bulb distillation; b.p. 110–130 °C/0.05 torr. Crystallization from benzene/petroleum ether gives yellowish needles; m.p. 69–70 °C.

$C_7H_{13}N_3O_6$	calc.	C 35.74	H 5.57
(235.2)	found	35.80	5.8

I.R. (KBr): ν = 1725 (ester), 1535, 1370 cm^{-1} (nitro).

^{1}H-N.M.R. ($CDCl_3$): δ = 4.54 (t, CH_2—NO_2); 3.72 (s, $COOCH_3$); 3.55 (s, N—CH_2—$COOCH_3$); 3.38 ppm (t, N—CH_2—CH_2).

Further elution with ethyl acetate/petroleum ether (6:4) gives the mono adduct **4** as a yellow liquid; yield: 0.128 g (13%).

$C_5H_{10}N_2O_4$	calc.	C 37.03	H 6.22
(162.2)	found	37.2	5.67

I.R. (neat): ν = 1730 (ester), 1545, 1365 (nitro) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 4.46 (t, CH_2—NO_2); 3.73 (s, $COOCH_3$); 3.52 (s, N—CH_2—$COOCH_3$); 3.41 ppm (t, N—CH_2—CH_2).

N-(2-Nitroethyl)-DL-leucine Methyl Ester (6a):
Triethylamine (0.5 g, 5 mmol) is added to a well-stirred and ice-cooled suspension of DL-leucine methyl ester hydrochloride[3] (**5a**; 1.0 g, 5.5 mmol) in dry ether (20 ml) followed after an interval of 5 min by a solution of nitroethylene (**2**; 0.4 g, 5.5 mmol) in dry benzene (4 ml). The reaction mixture is stirred at ~10 °C for 24 h and then treated with another portion of nitroethylene (0.4 g) in dry benzene (4 ml). After 3 days, the supernatant liquid is decanted, the residue extracted with ether (3 × 10 ml), and the extracts evaporated in vacuo to give almost pure (T.L.C.) **6a**; yield: 1.153 g (96%); b.p. 120 °C/0.1 torr.

$C_9H_{18}N_2O_4$	calc.	C 49.53	H 8.31
(218.3)	found	49.52	7.96

I.R. (neat): ν = 1730 (ester), 1550, 1365 cm^{-1} (nitro).

^{1}H-N.M.R. ($CDCl_3$): δ = 4.46 (t, CH_2—NO_2); 3.75 (s, $COOCH_3$); 3.6–3.0 (m, CH—NH—CH_2); 2.2 (br, NH); 0.9 ppm [—$CH(CH_3)_2$].

N-(2-Nitroethyl)-L-methionine Methyl Ester (6b):
Triethylamine (0.393 g, 3.8 mmol) is added to a well stirred and ice-cooled suspension of L-methionine methyl ester hydrochloride[2] (**5b**; 0.55 g, 0.0028 mol) in dry ether (20 ml) and then after 5 min treated with a solution of nitroethylene (**2**; 0.39 g, 5.3 mmol) in dry benzene (4 ml). The reaction mixture is stirred for 48 h, the supernatant liquid decanted, the residue extracted with ether (2 × 10 ml), and the combined extracts evaporated. The residue (0.672 g) is chromatographed on silica gel, elution with ethyl acetate/benzene (1:9) gives **6b**; yield: 0.302 g (46%); b.p. 110–130 °C/0.1 torr.

$C_8H_{16}N_2O_4S$	calc.	C 40.68	H 6.78
(236.2)	found	41.17	6.50

I.R. (neat): ν = 3400 (NH), 1724 (ester), 1545, 1365 cm^{-1} (nitro).

^{1}H-N.M.R. ($CDCl_3$): δ = 4.48 (t, CH_2—NO_2), 3.75 (s, CO—OCH_3), 3.6–3.0 (m, CH—NH—CH_2), 2.55 (t, CH_2—S), 2.09 ppm (s, CH_3—S).

N-(2-Nitroethyl)-L-proline Methyl Ester (8):
Triethylamine (0.3 g, 2.9 mmol) is added to an ice-cooled and stirred suspension of L-proline methyl ester hydrochloride[4] (**7**; 0.45 g, 2.7 mmol) in dry ether (20 ml) followed after 5 min by a solution of nitroethylene (**2**; 0.25 g, 3.4 mmol) in dry benzene (3 ml). The reaction mixture is stirred at ~10 °C for 48 h, decanted, and evaporated to give **8**; yield: 0.268 g (49%); b.p. 100–110 °C/0.1 torr.

$C_8H_{14}N_2O_4$	calc.	C 47.52	H 6.98
(202.2)	found	47.50	6.39

I.R. (neat): ν = 1730 (ester), 1545, 1368 cm^{-1} (nitro).

^{1}H-N.M.R. ($CDCl_3$): δ = 4.52 (t, CH_2—NO_2); 3.72 ppm (s, $COOCH_3$).

***N,N*-Bis[2-nitroethyl]-L-tryptophan Methyl Ester (11) and *N*-(2-Nitroethyl)-tryptophan Methyl Ester (10):**
Triethylamine (0.40 g, 4.0 mmol) is added to an ice-cooled and stirred suspension of L-tryptophan methyl ester hydrochloride[2] (**9**; 1.018 g, 4.0 mmol) in dry ether (30 ml) followed by a solution of nitroethylene (**2**; 0.302 g, 4.0 mmol) in dry benzene (3 ml). The reaction mixture is stirred for 35 h, treated with another portion of nitroethylene (0.15 g, 0.002 mol) in benzene (2 ml), stirred for 12 h, decanted, and the residue is extracted with ether (3 × 10 ml). The combined extracts are evaporated and the reddish residue (1.417 g) is chromatographed on silica gel; elution with ethyl acetate/benzene (15:85) gives **10** as a yellow viscous liquid; yield: 0.497 g (42%).

$C_{14}H_{17}N_3O_4$	calc.	C 57.72	H 5.83
(291.3)	found	57.60	5.40

I.R. (neat): ν = 3400 (NH), 1723 (ester), 1540, 1365 cm^{-1} (nitro).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.19 (NH); 7.7–6.9 (m, H_{arom}); 4.36 (t, CH_2—NO_2); 3.68 (s, $COOCH_3$); 2.1 ppm (br, NH).

Further elution with ethyl acetate/benzene (1:4) gives **11** as a yellow liquid; yield: 0.191 g (13%).

$C_{16}H_{20}N_4O_6$	calc.	C 52.74	H 5.53
(364.4)	found	52.70	5.5

I.R. (neat): $\nu = 1723$ (ester), 1545, 1365 cm^{-1} (nitro).

^1H-N.M.R. ($CDCl_3$): $\delta = 8.14$ (NH); 7.7–6.8 (m, H_{arom}); 4.25 (t, $C\underline{H}_2—NO_2$); 3.9–2.9 [m, indolyl-$C\underline{H}_2$, $C\underline{H}—N(C\underline{H}_2)_2$]; 3.68 ppm (s, $COOC\underline{H}_3$).

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