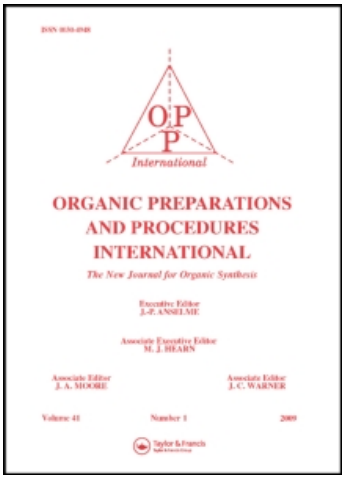

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IMPROVED SYNTHESIS OF NITRO DERIVATIVES OF N-PHENYLGLYCINE

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benzene was added dropwise to a suspension of N-chlorosuccinimide (13.35 g, 0.1 mol)[8] in 300 mL benzene containing isobutyraldehyde (7.21 g, 0.1 mol) stirred at 40°. After 12 hrs, the reaction mixture was filtered and the filtrate was concentrated to about 50 mL, then refiltered. In this manner, a nearly quantitative yield of succinimide was obtained. Concentration of the filtrate afforded a golden liquid which was distilled in vacuo to give 9.27 g (48%) of a colorless liquid, bp. 115-130°/2 mm, lit.[2] bp. 90-115°/7 mm, lit.[3,4] bp. 144-147°/14 mm; n_D^{20} 1.5460, lit.[3,4] n_D^{21} 1.5450; mp. of 2,4-dinitrophenylhydrazone 120-121° (EtOH), lit.[4] mp. 122°; ^{1}H NMR (60 MHz; CCl_4): δ 1.34 (s, 6H, CH_3), 3.49 (s, 2H, $CH_2C_6H_5$), 7.23 (s, 5H, C_6H_5), 9.24 (s, 1H, CHO).

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IMPROVED SYNTHESIS OF NITRO DERIVATIVES OF N-PHENYLGLYCINE

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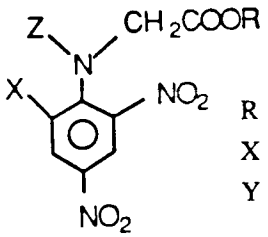
Nitro derivatives of N-phenylglycine which are structurally similar to stable explosives TNT (2,4,6-trinitrotoluene) and tetryl (N-methyl-N,2,4,6-tetranitroaniline) are used in different explosive formulations. Methods of synthesis and properties of three nitro derivatives of

N-phenylglycine and their methyl and ethyl esters, some of which are new compounds, are presented here. We reported the thermal decomposition characteristics of these compounds earlier.[1]



	1a	1b	1c	2a	2b	2c	3a	3b	3c
R	H	Me	Et	H	Me	Et	H	Me	Et
X	H	H	H	H	H	H	NO_2	NO_2	NO_2
Y	H	H	H	NO_2	NO_2	NO_2	H	H	H

The two acids 1a and 3a have been previously prepared.[2,3] The reported methods,[2-4] however, are not amenable to large scale synthesis. An attempt has therefore been made to improve the reaction conditions and determine the best isolation procedures to obtain these acids on a larger scale.

The yield of 1a could be improved from 70 to nearly 100% by removal of 80% of the alcohol contained in the reaction mixture by distillation under reduced pressure and precipitation of the product with acid instead of evaporating the mixture to dryness as suggested by Abderhalden et al.[2] Aniline and N-substituted anilines with nitro groups in the 2- and 4-positions are known to be susceptible to hydrolysis in basic media.[6] The removal of alcohol under low pressure possibly minimizes hydrolysis and accounts for the better yields obtained by this method. Selective N-nitration of 1a with nitric acid in the presence of acetic anhydride gave 2a. Compound 3a was obtained by an intramolecular rearrangement of 2a in the presence of concentrated sulfuric acid. The methyl and ethyl esters of the three acids were prepared by standard methods.[7] Acids 1a and 2a were prepared in batch sizes of up to 1 kg while 3a was prepared in batch size of 250 g by the procedures herein described. The yields of the nine compounds and their physical and IR spectral data are presented in Table 1.

The structures of the compounds were confirmed by the spectral data. In addition to the characteristic IR absorptions listed, all compounds exhibited strong absorptions corresponding to the asymmetric and symmetric stretchings of the nitro groups. UV absorptions, caused by ortho and para nitroanilino transitions observed on 1a, 3a and their esters, are absent in 2a-2c due to the strong electron withdrawing nature of the nitro group on the amino nitrogen. The magnitude of chemical shifts observed at δ 1.33-4.30 for methyl and ethyl groups and at δ 3.83-5.50 for methylene hydrogens and the pattern of ^1H NMR spectra are in agreement with the assigned structures. The aromatic hydrogens were observed in the δ 8-9 region with the characteristic ortho and/or meta coupling.

TABLE 1. Yields, mps. and Spectral Data of Compounds 1-3

Compd.	Yield (%)	lit. yield	mp. (°C)	lit. mp.	IR (KBr, cm^{-1})
1a	100	70[2]	205	205[2]	3362(N-H); 1420(CH_2 def.); 1715(C=O)
1b	85	78[5]	126	124[5]	3352(N-H); 1425(CH_2 def.); 1760(C=O); 1245(C-O)
1c	87	85[2]	142-144	144[2]	3345(N-H); 1412(CH_2 def.); 1740(C=O); 1245(C-O)
2a	75	-	161(dec.)	-	1425(CH_2 def.); 1737(C=O)
2b	82	-	126-127	-	1422(CH_2 def.); 1745(C=O); 1240(C-O)
2c	86	-	99-100	-	1422(CH_2 def.); 1755(C=O); 1240(C-O)
3a	80	-	162-163	161[4]	3240(N-H); 1410(CH_2 def.); 1708(C=O)
3b	80	-	128-129	-	3260(N-H); 1420(CH_2 def.); 1735(C=O); 1245(C-O)
3c	83	-	91	-	3260(N-H); 1422(CH_2 def.); 1730(C=O); 1240(C-O)

EXPERIMENTAL SECTION

Laboratory reagent grade chemicals were used in all synthesis. The mps. were determined on a Toshniwal melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a Perkin Elmer 457 IR spectrophotometer and the UV spectra (acetonitrile) on a Shimadzu-500 UV-VIS spectrophotometer. ^1H NMR spectra ($CDCl_3$) were obtained on a Varian FT-80A NMR spectrometer with tetramethylsilane as internal standard.

N-(2,4-Dinitrophenyl)glycine (1a).- To a solution of 1-chloro-2,4-dinitrobenzene (160 g, 0.8 mole) in 800 mL of ethanol was added a solution of 144 g (1.6 mole) potassium bicarbonate and 60 g (0.8 mole) glycine in 400 mL water. The mixture was refluxed until a clear solution resulted (2 hrs). Ethanol (600 mL) was removed by distillation under reduced pressure (~20 mm of Hg) at 50°. The residue was cooled, diluted with water to twice its volume and acidified with conc. hydrochloric acid to precipitate 190 g (100%) of 1a. Recrystallisation from 1:1 acetic acid-water resulted in 182 g (96%) of golden yellow crystals, mp. 205°, lit.[2] mp. 205°.

UV(CH_3CN) λ_{max} (log ε_{max}): 344(4.00); 416(3.48); 264(4.01); 240(3.91) nm.

N-(2,4-Dinitrophenyl)-N-nitroglycine (2a).- This procedure was an adaptation of the method of Bordwell and Garbisch[8] but used perhaps for the first time for the nitration of aromatic amines. Nitric acid (160 mL, density 1.48 g/mL) was added dropwise to 1360 mL acetic anhydride placed in a 3 L beaker; the temperature of the mixture was maintained at 20-25°. The mixture

was cooled to -6° and 4.7 mL conc. sulfuric acid was added. Dry 1a (135 g, 0.56 mole) was added in small quantities; the temperature of the reactants was kept in the range of -7 to -5°. The reaction mixture was stirred for an additional 1.5 hr at the same temperature. It was then poured into 3.5 L water and the solution kept at 45-50° for 0.5 hr whereupon 2a separated out as fine light yellow crystals. The mixture was cooled, the crystals were collected and washed twice with ice-cold water. The product thus obtained (120 g, 75%, mp. 159°) was purified by precipitation of its solution in acetone into water with stirring followed by recrystallision from water, mp. 161° (dec.); recovery 90%.

Anal. Calcd. for $C_8H_6N_4O_8$: C, 33.56; H, 2.10; N, 19.58. Found: C, 33.91; H, 2.21; N, 19.72

UV (CH_3CN) λ_{max} ($\log \varepsilon_{max}$): 232(4.27) nm.

N-(2,4,6-Trinitrophenyl)glycine (3a).- To 200 mL conc. sulfuric acid, 2a (75 g) was added in small quantities. The solution was stirred for 3 hrs and then added dropwise to 1 L of water (kept at 40-45°) with stirring whereupon 3a separated out (60 g, 80%), mp. 155-157°. It was recrystallised from water (recovery 83%, mp. 163°, lit.[4] mp. 161°). TLC studies and comparison of IR spectra confirmed the identity of this compound with that obtained by the method of Hirayama.[3] Compound 3a could not be prepared by direct nitration of 1a using any of the conventional nitrating methods. Condensation of picryl chloride with glycine[3] always yielded large amounts of picric acid and poor yields of 3a.

UV(CH_3CN) λ_{max} ($\log \varepsilon_{max}$): 326(3.89); 430(3.54); 256(3.90) nm.

Esterification of Acids 1a, 2a and 3a. General Procedure for the Synthesis of 1b, 1c, 2b, 2c, 3b and 3c.- The methyl and ethyl esters of the acids were prepared by refluxing 0.5 mole of the acid for 4-5 hrs with about 16 moles of the alcohol in the presence of 5 mL sulfuric acid. The yields and the mp. of each of the esters are listed in the Table. The esters were recrystallised from ethanol.

Methyl ester of 2a (2b):

Anal. Calcd. for $C_9H_8N_4O_8$: C, 36.01; H, 2.67; N, 18.67
Found : C, 36.28; H, 2.85; N, 18.41

UV(CH_3CN) λ_{max} ($\log \varepsilon_{max}$): 232(4.22) nm.

Ethyl ester of 2a (2c):

Anal. Calcd. for $C_{10}H_{10}N_4O_8$: C, 38.22; H, 3.18; N, 17.83
Found: C, 37.83; H, 3.01; N, 17.67

UV(CH_3CN) λ_{max} ($\log \varepsilon_{max}$): 232(4.25) nm.

Methyl ester of 3a (3b):

Anal. Calcd. for $C_9H_8N_4O_8$: C, 36.01; H, 2.67; N, 18.67
Found : C, 36.31; H, 2.77; N, 18.47

UV(CH_3CN) λ_{max} ($\log \varepsilon_{max}$): 331(4.13); 406(3.66); 248(4.00) nm.

Ethyl ester of 3a (3c):

Anal. Calcd. for $C_{10}H_{10}N_4O_8$: C, 38.22; H, 3.18; N, 17.83

Found: C, 38.55; H, 3.41; N, C, 38.55; H, 3.41; N, 17.60

UV(CH_3CN) λ_{max} (log ε_{max}): 332(4.16); 406(3.87); 248(4.00) nm.

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AN EFFICIENT METHOD FOR THE SYNTHESIS OF N-(p-AMINOBENZOYL)AMINO ACIDS

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p-Aminobenzoyl-L(+)-glutamic acid (2a) is a key intermediate in the preparation of folic acid, a well-known hematopoietic vitamin. A number of methods have been reported for the preparation of N-(p-aminobenzoyl)amino acids from N-(p-nitrobenzoyl)amino acids.[1-5] In particular, these procedures have not been useful for the preparation of p-aminobenzoyl-L(+)-glutamic acid (2a) because of low yields,[1,2] tedious workup procedures and costly reagents such as Pt, Pd, Zn and Ni, etc. In connection with our studies on the synthesis of biologically active amino compounds, we now report a facile process for the manufacture of N-(p-aminobenzoyl)amino acids (2) by the reduction of corresponding N-(p-nitrobenzoyl)amino acids (1) using iron and sodium chloride in water.