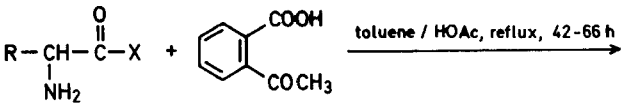
3-Methylenephthalidylamino Acids

Charles A. PANETTA*, Adrian L. MILLER

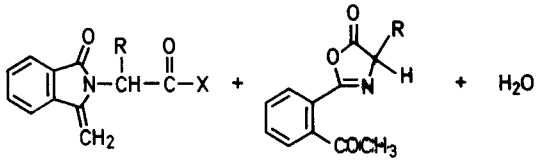
Department of Chemistry, The University of Mississippi, University, Mississippi 38677, U.S.A.

Several amino acids have been found to condense readily with *o*-acetylbenzoic acid to afford 3-methylenephthalidylamino acids (MPID-amino acids, **2**) and 4-substituted 2-aryl-5-oxo-4,5-dihydro-1,3-oxazoles, **3** (Tables 1 and 2). The former are novel derivatives of the amino acids. The general procedure involved heating equimolar amounts of **1** and *o*-acetylbenzoic acid in toluene and acetic acid for several hours while the water produced by the reaction was continuously removed. A similar condensation of *o*-acetylbenzoic acid with aniline has been reported in the literature[1].

However, the facile reaction of this reagent with amino acids and the cleavage of the resultant product, **2**, with hydrazine are novel developments.

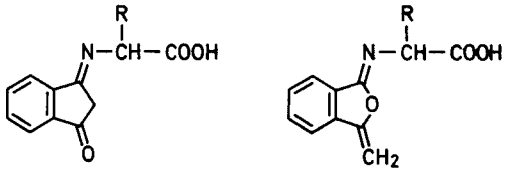


1a-f



2a-f **3a-f**

The structure of **2** was established mainly from spectral and reactivity data. The carbonyl stretching region of the infrared spectra of the 3-methylenephthalidylamino acids always showed two strong bands at 1730–1750 and 1705–1725 cm^{-1}. These were assigned to condensed γ-lactam and carboxylic carbonyl groups, respectively. Imine-containing structures (**4** and **5**) were disregarded because of the well-established lability of imines to aqueous acid.



4 **5**

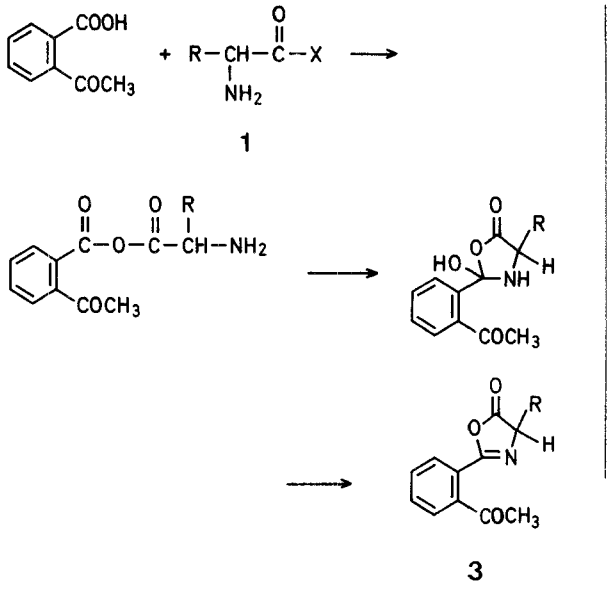
MPID-Amino acids are stable to these conditions. For example, MPID-gly (**2a**) was recovered in over 75% yield after a 10 h reflux period in aqueous acetic acid (82:18, v/v). MPID-Amino acids gave negative tests with 2,4-dinitrophenylhydrazine in aqueous alcohol and sulfuric acid.

Finally, the reaction of MPID-amino acids with hydrazine (see below) established a structural similarity with the well-known phthaloylamino acids.

A non-acidic oxazolone by-product, **3**, was isolated from some of the preparations of MPID-amino acids. For example, the preparation of MPID-valine afforded a 62% yield of the derivatized amino acid, **2c**, and an 18% yield of 2-(2-acetylphenyl)-4-isopropyl-5-oxazolone (**3**, R = isopropyl). The structure was established using mass spectra, I.R. spectra, and elemental analysis data. Yields of **3** are listed in Table 2. This by-product probably resulted through the usual azlactonization mechanism or by the one illustrated below.

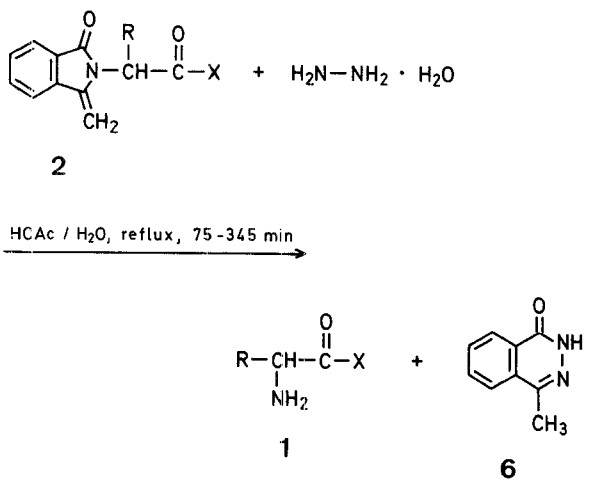
MPID-Glycylglycine (**2f**) was prepared by two separate routes. The first employed the usual condensation of glycylglycine with *o*-acetylbenzoic acid (75% yield) and the second involved the reaction of the mixed anhydride of MPID-glycine and isobutyl chloroformate with glycine and triethylamine in toluene (29% yield).

MPID-Amino acids, **2**, may be readily cleaved with hydrazine to afford the free amino acids and 1-methyl-4-phthalazone (**6**)[2]. A mixture of the MPID-amino acid, acetic acid, water, and 85% hydrazine hydrate (5 to 10-fold excess) was heated to the reflux temperature for a period specified in Table 3. 1-Methyl-4-phthalazone (**6**) precipitated and the aqueous



filtrate was concentrated to afford the freed amino acids, **1**. Yields are listed in Table 3.

All of the asymmetric amino acids used in this study were of the L-configuration and a preliminary study on the possibility of racemization during these reactions was made. In a typical experiment, MPID-L-ala (**2b**) was prepared in the normal manner and then, the alanine was recovered from this derivative by reaction with hydrazine. The optical purity of the recovered alanine was only 20%. When the 10-fold excess of hydrazine hydrate was reduced to an equimolar amount, the optical purity of the product increased slightly



to 28%. The other asymmetric amino acids were similarly racemized except for valine, which was recovered in 100% optical purity when the toluene solvent, used during the preparation of **2c**, was replaced with benzene. This change, however, did not reduce the amount of racemization of the other amino acids.

General Procedure for the Preparation of MPID-Amino Acids (2):

A mixture of *o*-acetylbenzoic acid (4.1 g, 25 mmol), toluene (40 ml), acetic acid (4.6 ml), and an amino acid (25 mmol) was heated under reflux temperature while the aqueous condensate was passed through a Dean-Stark water trap. The reaction time varied for the different amino acids (see Table 1). The toluene and acetic acid were removed by distillation under reduced pressure and the oily residue was dissolved in ether (100 ml). This organic

Table 1. Preparation of MPID-Amino Acids, **2**

Product **2**	R	X	Reaction time	Yield (%)	m.p.[a]	Molecular formula[b]
a	H	OH	42 h	64	202.8–203.2°	$C_{11}H_9NO_3$ (203.2)
b	CH_3	OH	57 h	53	179.0–180.5°	$C_{12}H_{11}NO_3$ (217.2)
c	*i*-C_3H_7	OH	53 h	62	216.5–217.5°	$C_{26}H_{38}N_2O_3$ (426.6)
d	*i*-C_4H_9	OH	66 h	56	200.0–202.0°	$C_{15}H_{17}NO_3$ (259.3)
e	$C_6H_5CH_2$	OH	48 h	82	191.0–192.0°	$(C_{30}H_{38}N_2O_3)_2 \cdot H_2O$ (483.6)[c]
f	H	$NHCH_2COOH$	46 h	75	212.2–213.2°	$C_{13}H_{12}N_2O_4$ (260.3)

[a] Corrected; optical purity was not known; all chiral amino acids used were of the L-configuration.

[b] All products gave satisfactory microanalysis (C ±0.26%, H ±0.22%, N ±0.35%); analyses carried out by Bristol Laboratories, Syracuse, N. Y., or Chemalytics, Inc., Tempe, Arizona.

[c] Dicyclohexylamine salt.

Table 2. 4-Substituted 2-(2-Acetylphenyl)-5-oxo-4,5-dihydro-1,3-oxazoles (**3**) formed as By-products

Product	Yield (%)	m.p.	Molecular formula	I.R. ($CHCl_3$): ν_{max} (cm^{-1})	Mass spectra (*m/e*)
3a	1	oil	$C_{11}H_9NO_3$ (203.2)	1770, 1710, 1640	–
3b	3	oil	$C_{12}H_{11}NO_3$ (217.2)	1770, 1705, 1640	–
3c	18	104.5–106.5°	$C_{14}H_{15}NO_3$[a] (245.3)	1775, 1705, 1600, 1450, 1300	245 ($M^{\oplus}$)
3d	34	oil	$C_{15}H_{17}NO_3$ (259.3)	1768, 1700, 1630	–
3e	16	oil	$C_{18}H_{15}NO_3$ (293.3)	1780, 1705, 1635	–
3f	0	–	–	–	–

[a] Gave satisfactory microanalysis (< ±0.2%).

Table 3. Reaction of MPID-Amino Acids, **2**, with Hydrazine

Compound	Reaction Duration (min)	Yield of Amino Acid **1** (%)	Yield of Phthalazone **6** (%)[a]
2a	75	84	84
2b	90	88	89
2c	225	63	81
2d	240	68	73
2e	300	80	61
2f	345	53	71

[a] m.p. range <4°.

solution was extracted with 1 normal sodium hydrogen carbonate solution (4 × 15 ml). The resultant ether solution was washed, dried, and distilled in vacuo and the residual oil was triturated with a small amount of ether to afford an oil or crystals of the by-product oxazolone, **3**; yields of **3** are listed in Table 2.

The sodium hydrogen carbonate solution from above was stirred with ether (100 ml) while the pH was adjusted to 2.0 with 1 normal hydrochloric acid. The aqueous acid solution was extracted with more ether (2 × 100 ml) and the ether extracts were combined and dried with $MgSO_4$. The solvent was removed in vacuo and the residual MPID-amino acids, **2**, were recrystallized from aqueous ethanol (see Table 1 for data on these products).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.8$ (m, 4 H_{arom}), 5.4 (d, 1H, vinyl), 5.0 ppm (d, 1H, vinyl).

General Procedure for the Deprotection of MPID-Amino Acids (2):

The protected amino acid (2.3 mmol) was added to a mixture of acetic acid (1.0 ml, 15.8 mmol), water (4 ml), and 85% hydrazine hydrate (0.86 ml, 23 mmol). The solution was heated under reflux temperature for the period specified in Table 3. 1-Methyl-4-phthalazone (**6**), which precipitated during this time, was collected, washed with water and dried (yields are listed in Table 3): m.p. 223.0–225.5° (from ethanol); lit.[2] m.p. 222°.

$C_9H_8N_2O$	calc.	C 67.49	H 5.03	N 17.49
(160.2)	found	67.59	5.11	17.61

I.R. (Nujol): $\nu_{max} = 1639, 1587, 1538\ cm^{-1}$.

The aqueous filtrate obtained after the filtration of **6** was concentrated in vacuo. The oily residue was treated with cold acetone which caused the freed amino acids (**1a–e**) and glycylglycine (**1f**) to separate as crystalline solids which were identified by their I.R. spectra. Yields are listed in Table 3.

MPID-Glycylglycine (2f) from MPID-Glycine and Glycine:

A mixture of MPID-glycine (**2a**, 0.5 g, 2.3 mmol), triethylamine (2.3 mmol, 0.32 ml), and toluene (7 ml) was stirred and cooled to −5°. Isobutyl chloroformate (0.3 ml, 2.3 mmol) was added at a rate such that the temperature of the reaction mixture never went above −5°. This mixture was then stirred for 40 min at the same temperature. A solution of glycine (0.17 g, 2.3 mmol) and 1 normal sodium hydroxide solution (2.3 ml, 2.3 mmol) was added and the resultant mixture was allowed to warm to room temperature during a 4 h period. Water (50 ml) was added and this mixture was extracted with ether (3 × 20 ml). The aqueous layer was separated and acidified to pH 2 with 1 normal hydrochloric acid. MPID-Glycylglycine (**2f**) precipitated; yield: 182 mg (29%): m.p. 206.0–210° (from ethanol). This was identical with the product prepared from *o*-acetylbenzoic acid and glycylglycine.

This work was partially supported under Grant 33582 of the National Science Foundation.

Received: May 19, 1976

[1] P. M. Pojer, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **21**, 1375 (1968).

[2] S. Gabriel, A. Neumann, *Ber. Dtsch. Chem. Ges.* **26**, 705 (1893).