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A New Synthesis of N-Acyl Aromatic α-Amino Acids; Amidoalkylation of Aromatic Compounds with Glyoxylic Acid Derivatives

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Summary The synthesis of N-acyl derivatives of aromatic α -amino acids (2) by the amidoalkylation of aromatic compounds with glyoxylic acid-amide adducts (1) and (3) is described.

AROMATIC amino acids of the phenylglycine type have been used in the syntheses of semi-synthetic penicillins and cephalosporins.¹ p-Hydroxyphenylglycine and 3,5-dichloro-4-hydroxyphenylglycine are also present in cyclic depsipeptides enduracidin A and B.² These amino acids are generally prepared from the corresponding aldehydes by the Strecker synthesis.³

We now report a new, direct synthesis of acyl derivatives of aromatic amino acids (2) using aromatic compounds and glyoxylic acid-amide adducts (1) as starting materials.

$$\begin{array}{cccc} \mathrm{HO-CH-CO_{2}H} & \mathrm{H^{+}} & \mathrm{Ar-CH-CO_{2}H} \\ | & + \mathrm{ArH} \longrightarrow & | \\ \mathrm{HN-COR} & & \mathrm{HNCOR} \\ & & & (1) & & (2) \\ \mathrm{R} = \mathrm{Ph} & & \mathbf{c}; \ \mathrm{R} = \mathrm{MeO} \\ \mathrm{R} = \mathrm{PhCH_{2}O} & & \mathbf{d}; \ \mathrm{R} = \mathrm{PhCH_{2}} \end{array}$$

The reaction of α -hydroxyhippuric acid (1a) with benzene, chlorobenzene or acetanilide in concentrated sulphuric acid at room temperature gave N-benzoylphenylglycine (2, Ar = R = Ph), or its p-chloro or p-acetamido derivative in 70—90% yield. (Table.) The amidoalkylations of anisole phenol, thiophen, naphthalene, and anthracene with (1) were carried out at room temperature in a 10% (v/v) sulphuric-acetic acid mixture. Using monosubstituted

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aromatic compounds the crude product was, according to the n.m.r. spectrum, a mixture of ortho- and para-isomers. The para-isomer which predominated was obtained pure on crystallization. The reaction of α -hydroxy-N-benzyloxy-

TABLE

Aromatic cor	npour	nd	Product		
ArH	r • • • •		Adduct	m.p./°C	Yield %
Benzene			(1a)	169 - 1714	91
011 1			(1d)	123 - 124	79
Chlorobenzen	le	••	(1a) (3)	180 - 181 124 - 125	71
Acetanilide			(1a)	266 - 267	70
			(3)	177 - 178	70
Anisole			(1a)	165 - 166	72
Phenol			(1a)	189 - 190	57
			(1b)	184 - 185	42
Thiophen		••	(1a)	145^{5}	92
Naphthalene			(1c)	186 - 187	41
Anthracene			(1c)	206	68

carbonylglycine (1b) with phenol and trituration of the crude product with ether afforded pure N-benzyloxycarbonyl-p-hydroxyphenylglycine in 42% yield. The structure of the products was assigned based on their i.r. and n.m.r. spectra and on satisfactory elemental analyses. N-benzoylphenylglycine⁴ and N-benzoyl-2-thienylglycine⁵ have been described previously. Glyoxylic acid bisethylcarbamate $(3)^6$ was also found to react in concentrated sulphuric acid with chlorobenzene or acetanilide to give the corresponding N-carbethoxy-p-chlorophenylglycine or Ncarbethoxy-p-acetamidophenylglycine (Table). Reaction of



p-cresol with (1a) in sulphuric-acetic acid mixture gave the lactone (4) (m.p. 228° , 45% yield) as the main reaction product while p-chlorophenol gave N-benzoyl-2-hydroxy-5-chlorophenylglycine (m.p. 162° , 57% yield).

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