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

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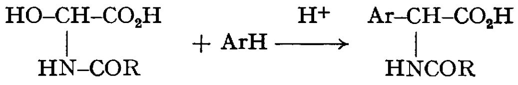
Summary The synthesis of *N*-acyl derivatives of aromatic α-amino acids (**2**) by the amidoalkylation of aromatic compounds with glyoxylic acid–amide adducts (**1**) and (**3**) is described.

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.



$$\begin{array}{c}\mathrm{HO{-}CH{-}CO_2H}\\ |\\ \mathrm{HN{-}COR}\end{array} + \mathrm{ArH} \xrightarrow{\mathrm{H^+}} \begin{array}{c}\mathrm{Ar{-}CH{-}CO_2H}\\ |\\ \mathrm{HNCOR}\end{array}$$

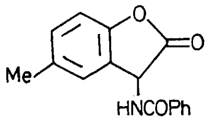
(**1**) (**2**)

a; R = Ph
b; R = $PhCH_2O$
c; R = MeO
d; R = $PhCH_2$

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 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*-benzyloxycarbonylglycine (**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*-benzoylphenylglycine[4] and *N*-benzoyl-2-thienylglycine[5] 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 *N*-carbethoxy-*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).

TABLE

Aromatic compound ArH	Adduct	Product m.p./°C	Yield %
Benzene	(**1a**)	169—171[4]	91
	(**1d**)	123—124	79
Chlorobenzene	(**1a**)	180—181	71
	(**3**)	124—125	68
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



(**4**)

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