Tetrahedron Vol 32, pp 1571 to 1573 Pergamon Press 1976 Printed in Great Britain

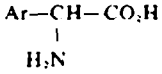
A NEW SYNTHESIS OF N-ACYL AROMATIC α-AMINO ACIDS—AMIDOALKYLATION OF AROMATIC AND HETEROCYCLIC COMPOUNDS WITH GLYOXYLIC ACID DERIVATIVES[1]

D. BEN-ISHAI,* I. SATATY and Z. BERNSTEIN
Department of Chemistry, Israel-Institute of Technology, Haifa, Israel

(*Received in the UK 15 January 1976; Accepted for publication 5 February 1976*)

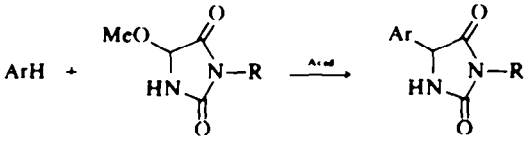
Abstract—The synthesis of N-acyl derivatives of aromatic α-amino acids **5** by the amidoalkylations of aromatic and heterocyclic compounds with glyoxylic acid amide adducts is described.

Aromatic amino acids of the phenylglycine type (**1**) have found applications in the synthesis of semisynthetic pencillins and cephalosporins.[2] Phenylglycine, *p*-hydroxphenylglycine and 3,5-dichloro-4-hydroxyphenylglycine are also present in the cyclic depsipeptides Enduracidim A and B.[3] These amino acids are generally prepared from the corresponding aldehydes by the Strecker synthesis.



1

In the course of a study on the chemistry of cyclic acylimines and 2-alkoxylactams it was found that 5-methoxyhydantoins (**2**) will amidoalkylate aromatic compounds in the presence of an acid catalyst to give 5-substituted hydantoins (**3**) which are known as synthetic precursors, or derivatives, of α-amino acids:[4]

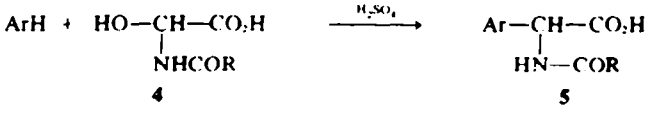


2 **3**

The cyclic structure of the hydantoin is not essential for the amidoalkylation of aromatic compounds. We have synthesized a number of open chain glyoxylic acid amide adducts of type **4** and found that they all will amidoalkylate aromatic and heterocyclic compounds (Table 1) to give, under acidic conditions, acyl derivatives of amino acids of type **5**.

The glyoxylic acid-amide adducts (**4**) were prepared, in high yields, from the commercially available glyoxylic acid hydrate and primary amides or primary carbamates.[5] The amidoalkylations of the less reactive aromatic compounds such as chlorobenzene, benzene, toluene and acetanilide were carried out in conc. sulfuric acid at room temperature for 48 hr to give the corresponding N-acyl derivatives of phenylglycine, *p*-chlorophenylglycine, *p*-methylphenylglycine and *p*-acetamidophenylglycine in 70–90% yield. In the case of the monosubstituted aromatic compounds the crude product was, according to the NMR spectrum, a mixture of *ortho* and *para* isomers. The *para* isomers which predominated were obtained pure on crystallization. The more reactive aromatic compounds naphthalene, anthracene, anisole, phenol and thiophene were amidoalkylated in a 10% (v/v) sulfuric-acetic acid mixture at room temperature for 48 hr. In the diluted sulfuric acid mixture the adduct of benzyl carbamate-glyoxylic acid is stable and can be used in the amidoalkylations of the more reactive aromatics. *p*-Cresol and *p*-hydroxybenzoic acid afforded in addition to the normal product the neutral coumaranones **6** in 65 and 42% yield.

Furan and 5-methylfuran, which are very sensitive to acidic conditions, were found to react with methyl α-methoxy-N-benzyloxycarbonylglycine **7** in dry ether at room temperature and in the presence of boron trifluoride etherate to give the products **8** in 67 and 84% yield. The crystalline furylglycine derivative **8a** was hydrolyzed

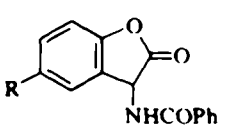


4

a: R = Ph
b: R = PhCH₂
c: R = MeO
d: R = PhCH₂O

5

a:	Ar = Ph,	R = Ph
b:	Ar = Ph,	R = PhCH₂
c:	Ar = p-MeC₆H₄,	R = Ph
d:	Ar = p-ClC₆H₄,	R = Ph
e:	Ar = p-AcNHC₆H₄,	R = Ph
f:	Ar = p-MeOC₆H₄,	R = Ph
g:	Ar = p-HOC₆H₄,	R = Ph
h:	Ar = C₁₀H₇,	R = MeO
i:	Ar = C₁₄H₉,	R = MeO
j:	Ar = p-HOC₆H₄,	R = PhCH₂O
k:	Ar = C₄H₃S,	R = Ph



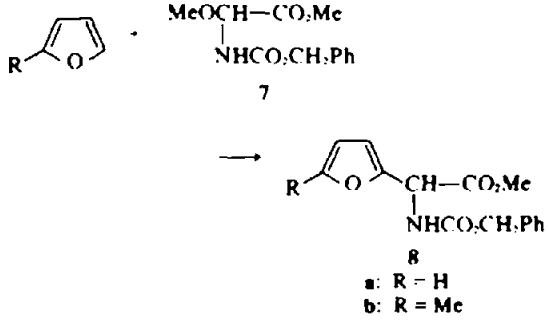
6

a: R = Me
b: R = CO₂H

Table 1. N-Acyl aromatic-α-amino acids

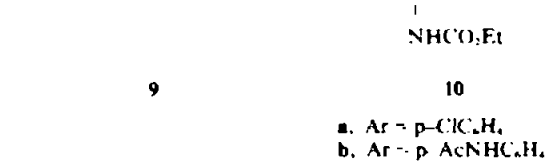
Compound	Yield %	M.p. °C	Molecular Formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
5a	91	172-173[2]							
5b	79	124	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	71.16	5.41	5.20
5c	86	166	$C_{16}H_{15}NO_5$	71.36	5.61	5.20	71.06	5.69	5.14
5d	79	181	$C_{15}H_{12}NO_3Cl$	62.19	4.18	4.60	61.79	4.40	4.83
5e	70	267	$C_{17}H_{16}N_2O_4$	65.37	5.16	8.97	65.08	5.25	8.79
5f	72	166	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	67.14	5.43	4.96
5g	57	200	$C_{15}H_{13}NO_4$	66.41	4.83	5.16	66.30	5.20	5.33
5h	41	187	$C_{14}H_{13}NO_4$	64.86	5.05	5.42	64.93	5.08	5.35
5i	68	206	$C_{18}H_{15}NO_4$	69.89	4.89	4.53	69.58	4.77	4.46
5j	51	186	$C_{16}H_{15}NO_5$	63.78	5.02	4.65	63.70	5.05	4.64
5k	92	145[3]							
11a	89	124	$C_{11}H_{12}NO_4Cl$	51.27	4.70	4.44	51.47	4.58	5.22
11b	84	178	$C_{13}H_{16}N_2O_5$	55.71	5.75	9.99	55.56	5.80	9.87

1. The compounds prepared showed characteristic IR absorptions at 3340-3300 and 1520-1540 cm^{-1} (NH) and CO absorption at 1725-1705 and 1690-1630 cm^{-1} (CO₂H and a characteristic doublet in the NMR of the α-hydrogen at δ 5.30-5.60 ppm (J = 8 cps) in DMSO-d_6.
2. Ref.[8] gives m.p. 174°.
3. Ref.[9] gives m.p. 143.5-144.5.



to the Cbz acid which was further hydrogenated to α-tetrahydrofurylglycine.

It was also found that glyoxylic acid bis ethyl carbamate (**10**) will also amidoalkylate benzene, chlorobenzene and acetanilide to give the corresponding N-carbethoxyphenylglycines. Under the same experimental conditions, conc. sulfuric acid, glyoxylic acid bisbenzamide did not react with benzene or chlorobenzene.



9 **10**

a, Ar = p-ClC₆H₄
b, Ar = p-AcNHC₆H₄

EXPERIMENTAL

M.ps are uncorrected, IR spectra were recorded on a Perkin-Elmer 237 spectrometer and NMR spectra were obtained on a Varian T-60 spectrometer.

Starting materials. α-Hydroxyhippuric acid, α-hydroxy-N-benzyloxycarbonyl glycine and methyl α-methoxy-N-benzyloxycarbonylglycinate were prepared from glyoxylic acid and benzamide or benzyl carbamate respectively.[7] Glyoxylic acid bis ethyl carbamate (**9**) was prepared from glyoxylic acid and ethyl carbamate.[8]

α-Hydroxy-N-phenylacetylglycine (**4b**)

A mixture of phenylacetamide (6.75 g 0.05 mole) and glyoxylic acid monohydrate (5.5 g 0.07 mole) in acetone (75 ml) was refluxed overnight (17 hr). The solvent was evaporated and the residue was triturated with dry ether. The solid was filtered off and washed with dry ether; yield 8.1 g (77%); m.p. 90–91°; IR (KBr) 3450–3000; 1700 and 1635 cm^{-1}; NMR (DMSO-d_6): δ 8.91–8.73 (d, J = 8 Hz 1H) 7.31 (*s*, 5H) 5.53–5.36 (*t*, 1H); 3.50 (*s*, 2H). (Found: C, 57.65; H, 5.44; N, 6.66. $C_{10}H_{11}NO_4$ requires: C, 57.41; H, 5.30; N, 6.70%).

α-Hydroxy-N-methoxycarbonylglycine (**4c**)

A mixture of methyl carbamate (7.5 g, 0.01 mole) and glyoxylic acid monohydrate (9.2 g, 0.1 mole) in dry ether (100 ml) was stirred at room temp overnight. The crystalline product was filtered off and washed with dry ether to give 13.0 g (86%) adduct; m.p. 65°; IR (KBr) 3504–3300 (broad), 1700 and 1550 cm^{-1}; NMR(DMSO-d_6): δ 7.83 (d, 1H, J = 9 Hz), 5.2 (d, 1H, J = 9 Hz), 3.6 (s, 3H). (Found: C, 31.87; H, 4.75; N, 9.21. $C_4H_7NO_5$ requires: C, 32.22; H, 4.73; N, 9.40%).

Amidoalkylation of aromatics[7]

Procedure A. To a cooled (0°) suspension of the adduct **4a–d** (0.02 mole) in conc. H_2SO_4 (20 ml, Merck 96%) there was added with stirring the aromatic component (0.03–0.08 mole). Stirring was continued for 48 hr and the mixture was poured into ice and extracted with EtOAc. The EtOAc soln was washed with water dried over $MgSO_4$, filtered and evaporated. The residue obtained after the removal of the solvent was triturated with CCl_4, filtered and crystallized from EtOAc–light petroleum.

Procedure B. To a cooled (0°) suspension of the adduct **4a–d** (0.02 mole) in a mixture of H_2SO_4 (2 ml)–AcOH (18 ml) there was added with stirring the aromatic component (0.03–0.04 mole). Stirring was continued for 48 hr and the mixture was treated as described above. In the case of the less volatile aromatics the products were purified by alkali extraction and reacidification.

Amidoalkylation of p-cresol to give **6a**

p-Cresol (6.4 g, 0.06 mole) was amidoalkylated with α-hydroxyhippuric acid (5.85 g 0.03 mole) in H_2SO_4–AcOH mixture (30 ml) as described above in procedure B. Dry ether (50 ml) was added and the solid which separated was filtered, triturated with ether and filtered again. It was crystallized from EtOAc–light petroleum m.p. 228–229°; yield 5.26 (65.5%); IR (KBr): 3290, 1840, 1670 and 1550 cm^{-1}; NMR (CDCl$_3$ + TFA): δ 6.93–7.96 (m, 9H); 5.63–5.85 (*d*, 1H, J = 7 Hz); 2.32 (s, 3H) (Found: C, 71.48; H, 4.93; N, 5.12. $C_{16}H_{13}NO_3$ requires: C, 71.90; H, 4.90; N, 5.24%). The filtrate was poured into ice + water and extracted with EtOAc (3 × 75 ml). The organic layer was washed with $NaHCO_3$ aq acidified and extracted again with EtOAc to give N - benzoyl - 2 - hydroxy - 5 - methylphenylglycine which was recrystallized from EtOAc–light petroleum (40–60°); m.p. 175–176°, yield 1.73 g (20.0%). IR (KBr): 3420, 3160 (broad) 1715, 1625 and 1510 cm^{-1}; NMR (CDCl$_3$ + TFA): δ 8.15–6.75 (m, 9H) 6.20–6.00 (d, 1H, J = 7 Hz) 2.30 (s, 3H). (Found: C, 66.97; H, 5.38; N, 4.98. $C_{16}H_{15}NO_4$ requires: C, 67.36; 5.30; N, 4.91%).

Preparation of coumaranone **6b**. This compound was prepared by procedure A from *p*-hydroxybenzoic acid (2.7 g 0.02 mole) and α-hydroxyhippuric acid (1.95 g 0.01 mole) in 10 ml H_2SO_4. Addition of dry ether (50 ml) precipitated **6b** which was filtered off triturated with ether and crystallized from EtOAc–light petroleum (40–60°); m.p. 298–299°; yield 1.25 g (42.3%). IR (KBr): 3360–3240, 1750, 1710, 1600, 1640 and 1540 cm^{-1}; NMR (CDCl$_3$ + TFA): δ, 8.43–7.25 (m, 9H) 5.65–5.83 (m, 1H). (Found: C, 60.21; H, 3.89; N, 4.31. $C_{16}H_{11}NO_5$ requires: C, 64.64; H, 3.73; N, 4.71%).

Methyl-N-benzyloxycarbonyl-α-furylglycinate

To a soln of methyl α - methoxy - N - benzyloxycarbonyl - glycine[7] (7.59 g 0.03 mole) in 120 ml dry ether was added consequently 6 ml BF_3 - etherate (dist.) and 9 ml furan (dist.). The mixture was stirred at ambient temp for 72 hr, and then poured into a mixture of EtOAc (100 ml) and ice-saturated $NaHCO_3$ (50 ml). The aqueous phase was further extracted with EtOAc (2 × 50 ml), the organic extract was washed with water, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The crude product solidified upon standing. It was chromatographed on a florisil column (220 g, 60–100 mesh) and eluted with benzene-methylene chloride (1:1). Trituration with light petroleum ether afforded the crystalline product (67%) which melted at 78–79° after crystallization from EtOAc-light petroleum; IR ($CHCl_3$): 3410, 1730 and 1710 cm^{-1}; NMR ($CDCl_3$): δ, 7.36 (s, 3H), 6.34 (d, 2H, J = 0.5 Hz), 5.51 (d, 1H, J = 8 Hz), 5.13 (s, 2H) and 3.37 (s, 3H). (Found: C, 62.14; H, 5.17; N, 4.89. $C_{14}H_{15}NO_5$ requires. C, 62.28; H, 5.23; N, 4.84%).

N-Benzyloxycarbonyl-α-furylglycine

To a soln of methyl α - furyl - N - benzyloxycarbonylglycinate (2.89 g 0.01 mole) in 40 ml EtOH (95%) was added at once KOH (0.75 g 0.011 mole) pellets. The hydrolysis was allowed to proceed at ambient temp during 48 hr, (the pH of the soln should be kept basic). The EtOH was removed *in vacuo* and the residue dissolved in water (50 ml) and washed three times with ether (3 × 50 ml). The aqueous phase was added dropwise into an ice cooled acidic soln of phosphoric acid (10%). The acidic soln was extracted with EtOAc (3 × 75 ml) and the combined extracts washed once with water, dried over $MgSO_4$, then evaporated to dryness in *vacuo*. The residue afforded after trituration with ether 84.5% crude acid; m.p. 122°.[8]

For analysis the acid was recrystallized from methylene chloride: m.p. 124.5–125.0° (it can be recrystallized also from MeOH m.p. 123–124°). IR ($CHCl_3$): 3410, 1750 and 1710 cm^{-1}; NMR ($CDCl_3$): δ 10.4 (s, 1H), 7.40 (s, 5H), 6.41 (d, 2H, J = 0.5 Hz) 5.80 (s, 1H, broad), 5.56 (*d*, 1H, J = 8 Hz), 5.16 (s, 2H). In D_2O the doublet at 5.56 turned into a singlet and the singlet at 5.8 disappeared. (Found: C, 60.98; H, 4.73, N, 5.20. $C_{14}H_{13}NO_5$ requires: C, 61.09; H, 4.76; N, 5.09%).

α-Tetrahydrofuryglycine

A soln of N - benzyloxycarbonyl - α - furylglycine (1.36 g) in 40 ml MeOH containing 170 mg Pd/C 10% was subjected to hydrogenolysis at ambient temp and 32.0 psi pressure for 40 hr. Filtration and evaporation *in vacuo* gave the amino acid, m.p. 213.5–215.5° (dec) in 60% yield. For analysis the acid was recrystallized from MeOH; m.p. 226–227°. IR (KBr) 3400, 2650, 1645 and 1570 cm^{-1}; NMR (D_2O): δ 2.74 (*m*, 3H) 1.17–0.6 (*m*, 4H). (Found: C, 49.48; H, 7.52; N, 9.54. $C_6H_{11}NO_3$ requires C, 49.64; H, 7.64; N, 9.65%).

Methyl N - benzyloxycarbonyl - 5 - methyl - 2 - furylglycine

This compound was prepared from methyl α - methoxy - N - benzyloxycarbonylglycinate (5.06 g, 0.02 mole) and 2-methylfuran (7.2 ml, 0.08 mole) in dry ether (80 ml) and in the presence of BF_3 etherate (4 ml) as described above. The oily product which was obtained after chromatography crystallized on trituation with hexane; yield 84.5% m.p. 53–54°; IR ($CHCl_3$) 3435, 1745, 1720 and 1500 cm^{-1}; NMR ($CDCl_3$): δ 7.08 (s, 5H) 6.28 (d, 1H; J = 3 Hz); 5.98 (m, 1H), 5.7 (shoulder, 1H) 5.5 (d, 1H, J = 8 Hz), 5.19 (s, 2H) 3.8 (s, 3H) 2.29 (s, 3H). (Found: C, 63.18; H, 5.52; N, 4.58. $C_{16}H_{17}NO_5$ requires: C, 63.36; H, 5.65; N, 4.62%); MS: *m/e* 303.

The methyl ester was hydrolyzed to the corresponding Cbz acid as described above, m.p. 73–74°; IR ($CHCl_3$), 3580, 3430, 1730 and 1560 cm^{-1}; NMR ($CDCl_3$): δ 7.36 (s, 5H), 6.28 (d, 1H, J = 3 Hz), 5.91 (d, 2H, J = 3 Hz), 5.46 (d, 1H, J = 9 Hz), 5.12 (s, 2H), 2.23 (s, 3H). (Found: C, 62.45; H, 5.41; N, 4.75. $C_{15}H_{15}NO_5$ requires: C, 62.28; H, 5.23; N, 4.84%).

REFERENCES

[1]D. Ben-Ishai, I. Sataty and Z. Berler, *Chem. Commun.* 349 (1975)

[2]*Penicillins and Cephalosporins. Their Chemistry and Biology* (Edited by E. H. Flynn) Chap. 12. Academic Press, New York (1972).

[3]H. A. James, *Amino Acids, Peptides and Related Compounds*, p. 219. Organic Chemistry Series No. 6 Butterworths (1973).

[4]D. Ben-Ishai, G. Ben-Et and A. Warshawsky, *J. Heter. Chem.* 7, 1289 (1970).

[5]G. Zoller and D. Ben-Ishai, *Tetrahedron* 31, 863 (1975).

[6]A. Hantzsch, *Ber. Dtsch. Chem. Ges* 27, 1248 (1894).

[7]H. E. Zaugg and W. B. Martin, *Org. React* 14, 52 (1965). *Synthesis* 49 (1970).

[8]S. Searle and G. J. Cvejanovitch, *J. Am. Chem. Soc.* 72, 3200 (1950).

[9]S. Nishamura, S. Otsuka and E. Imoto, *Nippon Kagaku* 82, 1688 (1961); *Chem. Abstr.*, 58, 11464e (1963).

[10]F. P. Doyle, G. R. Foster, J. H. C. Naylor and H. Smith, *J. Chem. Soc.* 1440 (1962).