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THE SYNTHESIS OF p-SUBSTITUTED D,L-PHENYLGLYCINES BY THE AMIDOALKYLATION OF BENZYLCHLORIDE AND N-BENZYLBENZAMIDE

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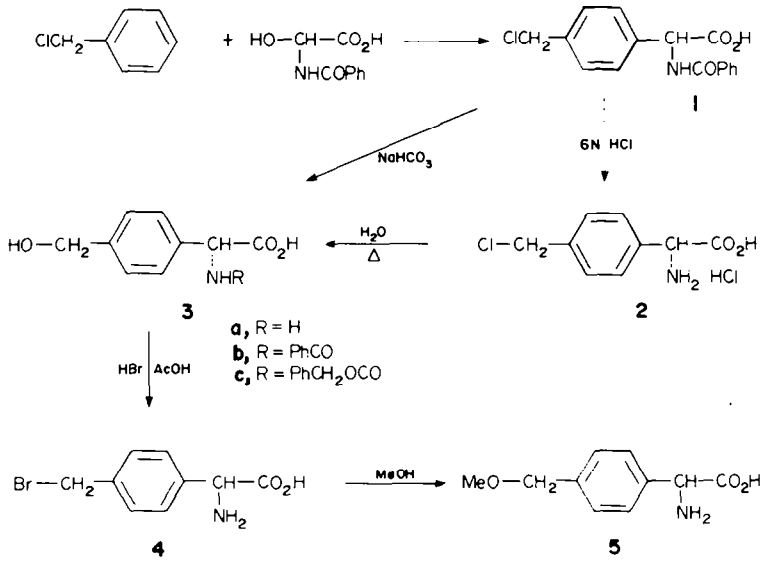
Abstract—The synthesis of *p*-hydroxymethyl (**3**), *p*-bromomethyl (**4**), *p*-methoxy-methyl (**5**), *p*-methylthiomethyl (**6**) and *p*-aminomethyl-d, l-phenylglycines by the amidoalkylation of benzylchloride and N-benzylbenzamide with α-hydroxyhippuric acid is described.

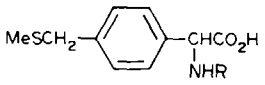
Aromatic α-amino acids of the phenylglycine type have found applications in the synthesis of semisynthetic penicillins and cephalosporins.[1] These amino acids are generally prepared from the corresponding aldehydes by the Strecker synthesis.[2] Recently we have described a new synthesis of aromatic α-amino acids based on the amidoalkylation of aromatic compounds with α-hydroxyhippuric acid and other glyoxylic acid-primary amide adducts.[3] Most of the reactions were carried out in concentrated sulfuric acid at room temperature.

Amidoalkylation of benzychloride with α-hydroxy-hippuric acid should afford a chloromethyl substituted phenylglycine derivative (**1**) which can be a useful intermediate in the synthesis of *p*-substituted phenylglycines having a *p*-halomethyl, *p*-hydroxymethyl, *p*-thiomethyl and *p*-aminomethyl groups.



It was indeed found that amidoalkylation of benzylchloride with hydroxyhippuric acid, in methanesulfonic acid as a solvent, at room temperature for 48 hr, afforded a mixture of the *ortho-para* isomers of the chloromethylated N-benzoylphenylglycine (57–69% crude). The *para* isomer (**1**) which predominated was separated by chromatography on a silica column, or more simply by trituration with chloroform carbon tetrachloride to give the desired N-benzoyl-*p*-chloromethylphenylglycine (**1**) in 35–54% yield. Hydrolysis in 6N HCl gave *p*-chloromethylphenylglycine (**2**) mixed with *p*-hydroxymethylphenylglycine (**3**). The nonhygroscopic mixture of hydrochlorides (**2** + **3**) was further hydrolysed in boiling water to the pure *p*-hydroxymethylphenylglycine (**3**). Treatment of the hydroxymethyl derivative (**3**) with hydrogen bromide in acetic acid at room temperature afforded *p*-bromomethylphenylglycine (**4**) in 81% yield. The bromomethyl group underwent solvolysis in boiling methanol to give *p*-methoxymethylphenyl-glycine **5**. Treatment of N-benzoyl-p-chloromethylphenylglycine with sodium methylmercaptide in methanol solution afforded N-benzoyl-*p*-methylthiomethyl-phenylglycine (**6b**) which was further hydrolyzed in 10% HCl to the free amino acid **6a**.

Amidoalkylation of N-benzylbenzamide with α-



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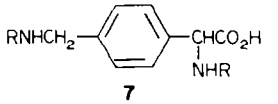
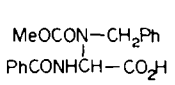
a, R = H
b, R = PhCO

hydroxyhippuric acid in concentrated sulfuric acid (96% Merck) afforded N,N'-dibenzoyl-*p*-aminomethylphenylglycine (**7a**) in 92% yield. The dibenzoyl derivative (**7a**) was hydrolysed in 6N HCl for 48 hr to give *p*-aminomethylphenylglycine which was characterized as the dihydrochloride (**7b**). This dibenzoyl derivative was identical with the dibenzoyl derivative prepared by the amination and benzoylation of **1**.



7

a, R = PhCO
b, R = H(2HCl)



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Reacting methyl N-benzylcarbamate with α-hydroxyhippuric acid in methanesulfonic acid gave only the N-alklyated product **8** and no C-alkylated product of type **7**. The N-alkylation is probably a reversible reaction and N-alkylation products can be isolated only if milder reaction conditions (methanesulfonic acid) are used. Acid hydrolysis of **8** gave benzylamine and benzoic acid and no amino acid derivatives.

If methyl α-methoxyhippurate was used, instead of α-hydroxyhippuric acid, in the amidoalkylation of benzylchloride in methanesulfonic acid, one obtained methyl N-benzoyl-*p*-chlorophenylglycinate (**9**) (methyl ester of **1**). The methyl ester was obtained in 51% yield as a crystalline material, after chromatography on a silica column.

The free amino acids described above were obtained as high melting crystalline materials. They gave positive ninhydrin tests and showed single spots on paper chromatography. The structure assignment to the *ortho-para* isomers is mainly based on the NMR spectra.

EXPERIMENTAL

General M.ps are uncorrected. The IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer; NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts are reported in ppm downfield from TMS. In the case of D_2O as a solvent TMS was used as external standard.

*N-Benzoyl-*p*-chloromethyl-*D,L*-phenyglycine* (**1**)

α-Hydroxyhippuric acid (1.95 g. 0.01 mol) and benzyl chloride (5.28 g. 0.04 mol) were suspended in cold anhyd methansulfonic acid (10 ml) and stirred at room temp. for 48 hr. The mixture was poured into ice water and extracted with EtOAC. The organic layer was washed several times with water, dried over $MgSO_4$, concentrated and chromatographed on a silica column (Merck, 160 g). Unreacted benzyl chloride was eluted first with CH_2Cl_2. The next fractions eluted with $CHCl_3$ (527 mg) showed in the NMR spectrum ($CDCl_3$ or DMSO-d_6) two CH doublets; one at 5.75 ppm was attributed to methine hydrogens of **1**, the other at 6.08, may be attributed to the more acidic methine hydrogens of the *o*-chloromethyl isomer. Using chloroform and $CHCl_3$ EtOAC 1:1 mixture almost pure **1** was eluted (1.735 g, 57%). Trituration with $CHCl_3$–CCL_4 mixture 1:2 (15 ml) gave a crystalline product (1.411 g, 46.5%). When the reactions were repeated on bigger scales, starting with α-hydroxyhippuric acid (11.7 g, 0.06 mol) and benzylchloride (30.6 g. 0.24 mol) in methansulfonic acid (60 ml), chromatography was omitted. After removing the unreacted benzylchloride *in vacuo* the residue was triturated with $CHCl_3$–CCl_4 mixture 1:2 (100 ml) yielding 5.4–7.3 g. (30–40%) of crystalline product; m.p. 167° (from $CHCl_3$ or from EtOAc-hexane). IR(KBr): 3370, 1740, 1630 cm^{-1}. NMR (DMSO-d_6) δ: 9.04 (d, 1, NH, J = 7 c/s); 7.35–8.15 (m, 9, aromatic); 5.72 (d, 1, CH, J=7 c/s); 4.80 (s, 2, CH_2). When D_2O was added to the sample the absorption at 7.22 collapsed to a singlet and the doublet at 9.04 disappeared. (Found: C, 63.73; H, 4.80; N, 4.50; Cl, 12.40. $C_{16}H_{14}NO_3Cl$ requires; C, 63.27; H, 4.64; N, 4.61; Cl, 11.67%).

*Methyl N-benzoyl-*p*-chloromethyl-*D,L*-phenylglycinate* (**9**)

Methyl α-methoxyhippurate (13.36 g. 0.06 mol) and benzylchloride (30 g. 0.24 mol) were dissolved in cold anhyd methansulfonic acid (60 ml) and stirred at room temp. for 48 hr. A similar workup was applied as in the case of acid **1**. The crude ester was chromatographed on a silica column using as eluent benzene–$CHCl_3$. 9.79 g, (51.2%) were obtained and recrystallized from EtOAc–hexane, m.p. 112–113°. IR($CHCl_3$): 3420, 1735, 1660 cm^{-1}. NMR (DMSO-d_6) δ: 9.40 (d, 1, NH, J = 7 c/s); 7.45–8.20 (m, 9, aromatic); 5.80 (d, 1, CH, J=7 c/s); 4.82 (s, 2, CH_2); 3.70 (s, 3, OCH_3) (Found: C, 64.33; H, 4.96; N, 4,46; Cl, 11.04. $C_{17}H_{16}NO_3Cl$ requires; C, 64.04; H, 5.04; N, 4.39; Cl, 11.12%).

*p-Hydroxymethyl-*D,L*-phenylglycine hydrochloride* (**3a**)

Compound **1**, (5 g) was hydrolysed during 18 hr in boiling 6N HCl (150 ml). The mixture was cooled, filtered from benzoic acid, extracted once with benzene and concentrated to dryness under reduced pressure. The residue contained, according to NMR spectrum, **2** (60%) and **3a** (40%). The *p*-chloromethyl group gave in DMSO-d_6 sol a singlet at 4.75 ppm whereas *p*-hydroxymethyl group appeared at 4.54 ppm. Upon paper chromotography, using n-BuOH: water: AcOH mixture (10:1:3) as eluent (5% EtOH soln of ninhydrin as developing reagent), **2** had $R_f = 0.50^4$, **3a** had R_f 0.17.

When the crude mixture of hydrochlorides was further hydrolysed in boiling water (100 ml) for 12 hr, concentrated to dryness and triturated with acetone pure **3a** was isolated (2.98 g, 82%), m.p. 171–173 (dec) (from EtOH-ether). IR(KBr) 1730, 1620, 1500, 1000 cm^{-1}. NMR (DMSO-d_6 and two drops of D_2O) δ: 7.40 (s, 4, aromatic); 5.00 (s, 1, CH); 4.54 (s, 2, CH_2); $R_f = 0.1$ (n BuOH: H_2O: AcOH). (Found: C, 49.57; H, 5.60; N, 6.29; Cl, 16.08. $C_9H_{12}NO_3Cl$ requires C, 49.67; H, 5.55; N, 6.43; Cl, 16.25%). The zwitterion was prepared in MeOH soln by precipitation with triethylamine. It has m.p. 214–216° (dec).

*N-Benzoyl-*p*-hydroxymethyl-*D,L*-phenylglycine* (**3b**)

Compound **1** (1 g) was dissolved in water (25 ml) containing K_2CO_3 (200 mg) and left overnight at room temp. The soln acidified and extracted with EtOAC. After evaporation, the residue, was crystallized from EtOAC–Hexane (470 mg, 50%) m.p. 179°. IR(KBr): 1730, 1640 cm^{-1}. NMR (DMSO-d_6) δ: 8.96 (d, 1, NH, J = 7 c/s); 7.2–8.2 (m, 9, aromatic); 5.68 (d, 1, CH, J = 7 c/s); 4.75 (s, 2, CH_2). (Found: C, 67.23; H, 5.33; N, 4.86. $C_{16}H_{15}NO_4$ requires: C, 67.36; H, 5.30; N, 4.91%).

*N-Benzyloxycarbonyl-*p*-hydroxymethyl-*D,L*-phenylglycine* (**3c**)

Compound **3a** (1.1 g.) was treated with carbobenzoxychloride under Schotten–Baumann reaction conditions using 10% $NaHCO_3$ as base. The product **3c** (1.066 g, 66%) had m.p. 117–118° (from EtOAc-hexane). IR(KBr); 3380, 3280, 1730, 1680 cm^{-1}. ($CHCl_3$): 1770 sh, 1730 cm^{-1}. NMR (DMSO-d_6) δ: 8.09 (d, 1, NH, J=7 c/s); 7.38 (s, 9, aromatic); 5.28 (d, 1, CH, J=7 c/s); 5.08 (s, 2, CH_2), 4.50 (s, 2, CH_2OH). (Found: C, 64.67; H, 5.34; N, 4.53. $C_{17}H_{17}NO_5$ requires. C, 64.75; H, 5.43; N, 4.53%).

*p-Bromomethyl-*D,L*-phenylglycine hydrobromide* (**4**)

Zwitterion **3a** (4g) was dissolved in HBr–AcOH mixture (32%, 100 ml). Upon standing (72 hr) **4** precipitated. Precipitation was completed by the addition of abs ether (100 ml). The solvent was decanted and the ppt was washed several times with ether and dried in high vacuum (5.25 g, 81%) m.p. 204–206° (dec). IR(KBr): 1740, 1680 sh cm^{-1}. NMR (DMSO-d_6 and D_2O) δ: 7.48 (s, 4,

aromatic); 5.12 (s, 1, CH); 4.68 (s, 2, CH_2). R_f = 0.46[4] (n BuOH: H_2O: AcOH; 10:1:3). (Found: C, 33.41; H, 3.82; H, 4.32; Br, 48.82: $C_9H_{11}NO_2Br_2$ requires: C, 33.26; H, 3.41; N, 4.30; Br, 49, 17%).

p-*Methoxymethyl*-D,L-*phenylglycine* (**5**)

Compound **4** (2.08 g.) was boiled in abs MeOH (70 ml) for 48 hr. The MeOH was distilled and was replaced by 5% HCl (100 ml) and the mixture was left for 24 hr at room temp. to hydrolyse small amounts of ester. After lyophilization the residue was dissolved in MeOH and treated with triethylamine to precipitate zwitterion **5** (997 mg. 80.5%) m.p. 234° (dec). IR(KBr) 1660 sh, 1620 sh. 1585 cm $^{-1}$. NMR (D_2O and one drop of TFA) δ: 7.44 (s, 4, aromatic); 5.08 (s, 1, CH); 4.36 (s, 2, CH_2); R_f = 0.35 (n BuOH: H_2O: AcOH; 10:1:3). (Found: C, 61.18; H, 6.55; N, 7.15. $C_{10}H_{13}NO_3$ requires: C, 61.52; H, 6.71; N, 7.18%).

N-*Benzoyl*-p-*methylthiomethyl*-D,L-*phenylglycine* (**6b**)

Compound **1**, (6.06 g. 0.02 mol) was treated with 1N methanolic soln of MeSNa (50 ml) for 24 hr. The MeOH was evaporated, and the residue dissolved in water and extracted with ether. The water layer was acidified with 10% HCl and extracted with EtOAc. The organic layer was concentrated, yielding after recrystallization from EtOAc-hexane **5** (5.27 g, 86%) m.p. 144°–145°. IR ($CHCl_3$): 3400, 1720, 1650 cm^{-1}; (KBr) 3290, 1700, 1640 cm^{-1}. NMR (DMSO-d_6) δ; 9.04 (d, 1, NH, J=7 c/s); 7.3–8.2 (m, 9 aromatic); 5.68 (d, 1, CH, J=7 c/s); 3.75 (s, 2 CH_2); 2.05 (s, 3, CH_3). (Found: C, 64.83; H, 5.44; N, 4.49; S, 10.05. $C_{17}H_{17}NO_3S$ requires. C, 64.75; H, 5.43; N, 4.44; S, 10.15%).

p-*Methylthiomethyl*-D,L-*phenylglycine* (**6a**)

A suspension of **6** (1.8 g, 5.7 mmol) in 10% HCl (60 ml) was refluxed for 48 hr under N_2. After cooling, the benzoic acid was filtered off and the aqueous soln was extracted once with benzene and then lyophilized. The residue was triturated with ether yielding a white non-hygroscopic compound (1.14 g, 81%); m.p. 216° (dec from MeOH-ether). IR (KBr): 1720 cm^{-1}; NMR (D_2O with one drop TFA) δ: 7.4 (s, 4, aromatic); 5.1 (s, 1, CH); 3.5 (s, 2, CH_2); 1.9 (s, 3 CH_3); R_f = 0.49[4] with tailing (n BuOH: H_2O: AcOH). (Found: C, 48.28; H, 5.68; N, 5.78; S, 12.34; Cl, 14.13. $C_{10}H_{14}NO_2SCl$ requires: C, 48.48; H, 5.69; N, 5.65; S, 12.94; Cl, 14.31%). Zwitterion had m.p. 231° (dec).

N,N'-*Dibenzoyl*-p-*aminomethyl*-D,L-*phenylglycine* (**7a**)

α-Hydroxyhippuric acid (5.85 g. 0.03 mol) and N-Benzylbenzamide (9.49 g. 0.045 mol) were suspended in cold H_2SO_4 (Merck, 96%, 30 ml) and stirred at room temp. for 48 hr. The mixture was poured into ice water and extracted with EtOAc. The organic layer was washed 3 times with water and extracted with 10% $NaHCO_3$. From the neutral EtOAc layer the unreacted N-benzylbenzamide was recovered. The $NaHCO_3$ soln was acidified with conc HCl, extracted with EtOAc and concentrated. The residue was triturated with ether yielding (10.71 g, 92%) of N,N'-dibenzoyl-*p*-aminomethyl-D,L-phenylglycine. m.p. 216° (from EtOAc-MeOH). IR (KBr): 3280, 1710, 1640, 1530 cm^{-1}, NMR (DMSO-d_6) δ: 9.03 (d, 2, NH); 7.3–8.2 (m, 14, aromatic); 5.70 (d, 1, CH, J=7 c/s); 4.55 (d, 2, CH_2, J=5 c/s). When D_2O and TFA were added to the sample the doublets at 5.70 and 4.55 ppm collapsed to singlets. (Found: C, 70.95; H, 4.98; N, 7.27. $C_{23}H_{20}N_2O_4$ requires: C, 71.12; H, 5.19; N, 7.21%). The same acid was obtained in 55% yield when 1 was treated with methanolic soln of ammonia and acylated with benzoyl chloride under Schotten–Baumann reaction conditions.

Methyl N,N'-dibenzoyl-*p*-aminomethyl-D,L-phenylglycinate was obtained quantitatively by esterification with diazomethane, m.p. 178°. IR ($CHCl_3$) 3420, 1740, 1660 cm^{-1}. NMR ($CDCl_3$) δ: 7.15–8.0 (m, 14, aromatic); 6.8 (v broad, NH); 5.72 (d, 1, CH, J=7 c/s); 4.60 (d, 2, CH_2, J=5 c/s); 3.80 (s, 3, CH_3). (Found: C, 71.77; H, 5.39; N, 6.96: $C_{24}H_{23}N_2O_4$ requires: C, 71.62; H, 5.51; N, 6.96%).

p-*Aminomethyl*-D,L-*phenylglycine dihydrochloride* (**7B**)

The acid **8a** (5 g.) was hydrolysed in boiling 6N HCl (180 ml) for 48 hr. Benzoic acid was filtered and the aqueous soln was extracted with benzene and lyophilized. The residue was triturated several times with ether until a nonhygroscopic solid was obtained (3.15 g, 95%), m.p. above 300° (dec from MeOH-ether). IR(KBr): 1740, 1710 cm^{-1}; NMR (D_2O) δ: 7.5 (s, 4, aromatic); 5.1 (s, 1, CH); 4.1 (s, 2, CH_2). (Found: C, 43.04; H, 5.65; N, 11.20; Cl, 27.71. $C_9H_{14}N_2Cl_2$ requires: C, 42.72; H, 5.57; N, 11.08; Cl, 28.02%). R_f = 0.69 (MeOH: H_2O: Py, 40:20:2) Lysine had R_f = 0.72 under the same conditions.

p-*Aminomethyl*-D,L-*phenylglycine monohydrochloride* (**7c**)

Dihydrochloride **8b** was treated with pyridine in MeOH soln. The ppt was filtered off and triturated with EtOH. It melted with dec above 300°. IR (KBr): 1595, 1500 1450, 1400 cm^{-1}, NMR(D_2O) δ: 7.44 (s, 4, aromatic); 4.75 (s, 1, CH); 4.05 (s, 2, CH_2). (Found: C, 49.87; H, 6.06; N, 12.76; Cl, 16.17. $C_9H_{13}N_2O_2Cl$ requires: C, 49.90; H, 6.04; N, 12.93; Cl, 16.25%).

N-*Methoxycarbonyl*-α-*benzylaminohippuric acid* (**8**)

α-Hydroxyhippuric acid (1.95 g, 0.01 mol) and methyl N-benzylcarbamate (3.2 g, 0.02 mol) were suspended in cold methansulfonic acid (10 ml) and stirred at room temp. for 24 hr. The mixture was poured into ice water, and extracted with ether. The ether layer was washed with 10% $NaHCO_3$ and concentrated to yield the unreacted methyl N-benzylcarbamate. $NaHCO_3$ soln was acidified with 10% HCl, extracted with EtOAc. After concentration, the residue was triturated with ether yielding a crystalline compound (1.4 g, 41%) m.p. 161°–162°. IR (KBr): 3400, 1725, 1690, 1655 cm^{-1}. NMR (DMSO-d_6) δ: 9.1 (d, 1, NH, J = 8 c/s) 7.1–7.9 (m, 10, aromatic), 6.45 (d, 1, CH, J = 8 c/s); 4.40 and 4.76 (q, 2, CH_2, J = 16 c/s). 4.68 (bs, 3, CH_3). (Found: C, 63.04; H, 5.62; N, 8.28. $C_{18}H_{18}N_2O_5$ requires: C, 63.15; H, 5.30; N, 8.18%).

REFERENCES

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

[2]*Synthetic Production and Utilization of Amino Acids* (Edited by T. Kaneko, Y. Izumi, I. Chiba and T. Itoh), Kodansha, Tokyo and Wiley New York (1974).

[3]D. Ben-Ishai, I. Satati and Z. Bernstein, *Tetrahedron* **32**, 1571 (1976).

[4]D,L-Phenylglycine had a R_f value of 0.37 under the same conditions (butanol: water: acetic acid 10:1:3).