N-Acyl (Substituted) Phenylglycine Derivatives

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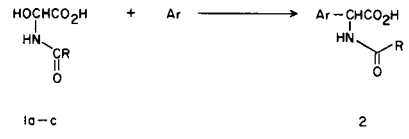
Amidoalkylation of three benzoheterocycles, benzimidazole-2-one, 1,3-dihydrobenzo[*c*]-thiophene 2,2-dioxide and 1,3-dihydro-2,1,3-benzothiadiazole using *N*-acylhippuric acids was successful. The corresponding phenylglycine analogs were prepared by removal of the *N*-acyl protecting group.

J. Heterocyclic Chem., **17**, 383 (1980).

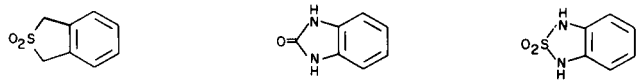
Ben-Ishai and coworkers have published a procedure for the synthesis of N-acylphenylglycine derivatives by an amidoalkylation reaction (1) (Scheme I). We would like to report examples in which Ar represents the benzoheterocyclic groups **3-5** and the effect of the heterocyclic substituent on the reactivity of the benzene ring toward the amidoalkylation reaction.

Scheme I



1a–c 2

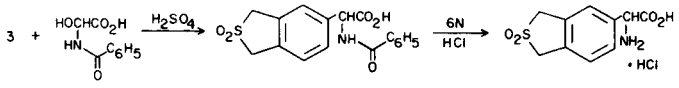
a, R = Ø; b, R = $OCH_2Ø$; c, R = O-t-Bu



3 4 5

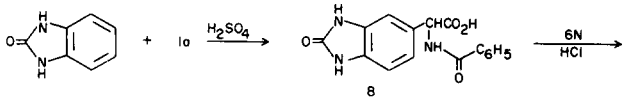
The three benzoheterocycles are arranged in order of increasing electron density (reactivity) of the benzene portion of the molecules. Compounds **3** and **5** were prepared by known procedures (2,3). Compound **3** proved to be quite unreactive, and required 72 hours reaction in concentrated sulfuric acid for a reasonable yield, using the stable hippuric acid **1a**. The benzamide **6** was hydrolyzed by 6*N* hydrochloric acid to give the amino acid hydrochloride (**7**) (Scheme II).

Scheme II



1a 6 7

Similarly, **4** reacted with **1a** in 18 hours to give the amino acid amide (**8**) which on hydrolysis gave the amino acid **9**.



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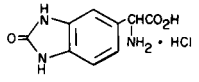

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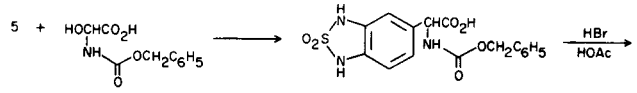
Compound **5** was more reactive toward amidoalkylation, reaction proceeding in acetic acid which contained 10% sulfuric acid catalyst. The CBZ protected hippuric acid was utilized, as it was felt that conditions necessary to remove the benzamide protecting group would destroy the benzothiadiazole ring system. The CBZ protected amino acid (**10**) was obtained as a foam we could not induce to crystallize and failed to pass elemental analysis. Removal of the CBZ group with 1*N* hydrobromic acid in acetic acid gave the amino acid hydrobromide salt **11**.



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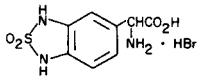

11

The reactivity of **5** to amidoalkylation prompted us to prepare the *t*-butoxycarbonyl hippuric acid **1c**. Attempts to react **1c** with **5** resulted in evolution of gas from the reaction mixture, which we assume to be isobutylene resulting from decomposition of **1c**.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were determined in pressed potassium bromide disks. All compounds gave spectra (ir, nmr) in agreement with the proposed structure.

N-t-Butoxycarbonyl-2-hydroxyglycine (**1c**).

A mixture of *t*-butyl carbamate (2.3 g., 0.02 mole) and 20 ml. of a 1*N* solution (sieve dried) of gloxylic acid hydrate in ether was stirred at room

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temperature for 3 days. The solution was diluted with 40 ml. of pentane, chilled to −20° and the precipitate was collected by filtration to give 2.5 g. of solid, m.p. 95° dec.; nmr (DMSO-d_6): δ 1.3 (S, 9H); δ 5.08 (d, J = 4, 1H); δ 7.28 (d, J = 4, 1H); δ 7.5-9.3 (b, 2H); deuterium oxide exchange δ 1.3 (S, 1H); δ 4.58 (S, 3H); δ 5.1 (S, 1H).

Anal. Calcd. for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33. Found: C, 44.19; H, 7.03; N, 7.19.

α-(Benzyloxycarbonyl)amino-1,3-dihydro-2,1,3-benzothiadiazole-5-acetic Acid 2,3-Dioxide (**10**).

A mixture of acetic acid (47 ml.), concentrated sulfuric acid (4.7 ml.), **5** (4 g., 23.5 mmoles) and **1b** (5.3 g., 23.5 mmoles) was stirred at room temperature for 5 hours, and poured into water (500 ml.). The aqueous mixture was extracted with ethyl acetate (2 × 300 ml.). The organic extracts were washed with water and extracted with aqueous sodium bicarbonate. The basic extracts were acidified and the acidified mixture was extracted with ethyl acetate. The extracts were dried and evaporated to give 7.5 g. of a foam which we were unable to crystallize. The material was used as is to prepare the amino acid; nmr (DMSO-d_6): δ 5.02 (S, 2H), δ 5.42 (d, J = 4, 1H), δ 5.7-6.6 (b, 2H); δ 6.8-7.0 (m, 2H); δ 7.3 (S, 5H), δ 7.6-7.8 (m, 1H); δ 10.2-10.7 (b, 1H).

α-Amino-1,3-dihydro-2,1,3-benzothiadiazole-5-acetic Acid 2,2-Dioxide (**11**).

Compound **10** (25.4 g., 67.3 mmoles) was dissolved in acetic acid (100 ml.) and 70 ml. of a 2*N* solution of hydrobromic acid in acetic acid was added. The mixture was stirred at 25° for 2 hours and the acetic acid was removed on a rotary evaporator. The residue was solidified with ether, filtered and vacuum dried. This material was dissolved in water and the *p*H of the solution was adjusted to 3 with amberlite IR-45 resin. The resin was filtered off and the filtrate was chilled, filtered to give 8 g. of solid, m.p. >270°; ir: 3250, 3000, 1620, 1500, 1400, 1320, 1300, 1280, 1130, 940, 860, 820, and 750 cm^{-1}; nmr (DMSO-d_6): δ 4.9 (S, 1H); δ 6.5 (S, 7H); δ 6.7-6.9 (m, 2H).

Anal. Calcd. for $C_8H_9N_3O_4S$: C, 39.50; H, 3.73; N, 17.27; S, 13.18. Found: C, 39.12; H, 3.78; N, 17.33; S, 12.99.

α-(Benzoylamino)-1,3-dihydrobenzo[c]thiophene-5-acetic Acid 2,2-Dioxide (**6**).

Compound **3** (8.4 g., 50 mmoles) and the hippuric acid (1A) (9.95 g., 50 mmoles) were dissolved in concentrated sulfuric acid (100 ml.) and the mixture was stirred at 25° for 72 hours, poured into ice water (600 ml.), and the aqueous mixture was extracted with ethyl acetate (2 × 300 ml.). The combined organic extracts were extracted with aqueous sodium bicarbonate. The basic extracts were layered with ethyl acetate, acidified with 1*N* hydrochloric acid and layers were separated. The ethyl acetate extracts were washed with brine and evaporated. The residue was recrystallized from ethyl acetate to give 7.8 g. of white solid, m.p. 234-235°; ir: 3350, 3250, 1720, 1640, 1610, 1580, 1540, 1500, 1400, 1310, 1220, 1140, 1110, 720, 700 cm^{-1}; nmr: δ 4.40 (S, 4H); δ 5.77 (d, J = 7.5, 1H); δ 6.6-7.1 (b, 1H); δ 7.3-7.55 (m, 6H); δ 7.82-8.0 (m, 2H); δ 10.0 (d, J = 7.5, 1H).

Anal. Calcd. for $C_{13}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06; S, 9.28. Found: C, 59.05; H, 4.71; N, 3.66; S, 9.04.

α-Amino-1,3-dihydrobenzo[c]thiophene-5-acetic Acid 2,2-Dioxide, Hydrochloride, Hemihydrate (**7**).

Compound **6** (17.25 g., 50 mmoles) was suspended in 500 ml. of 6*N* hydrochloric acid and the mixture was heated at reflux temperature for 5 hours. The mixture was chilled and filtered to remove benzoic acid. The filtrate was concentrated to 100 ml., chilled and filtered to give 10.7 g. of solid, m.p. 194-196°; ir: 3500, 3000, 2900, 2500, 1750, 1610, 1590, 1540, 1310, 1240, 1220, 1145, 1105 cm^{-1}; nmr (DMSO-d_6): δ 4.55 (S, 4H); δ 5.08 (S, 1H); δ 7.52 (S, 3H); δ 8.4-9.2 (b, 5H).

Anal. Calcd. for $C_{10}H_{12}NO_4S \cdot HCl \cdot \frac{1}{2} H_2O$: C, 41.88; H, 4.57; N, 4.88; S, 11.18; H_2O, 3.14. Found: C, 41.86; H, 4.52; N, 4.89; S, 11.16; H_2O, 3.4.

α-(Benzoylamino)-2,3-dihydro-2-oxo-1*H*-benzimidazole-5-acetic Acid (**8**).

Compound **1a** (19.5 g., 0.1 mole) and benzimidazolone (13.4 g., 0.1 mole) were dissolved in concentrated sulfuric acid (200 ml.) and the solution was stirred at room temperature for 18 hours, poured into ice water. The aqueous mixture was filtered and the precipitate was redissolved in aqueous sodium bicarbonate (filtered off some unreacted benzimidazolone). The product was precipitated from aqueous sodium bicarbonate solution by addition of 1*N* hydrochloric acid to give 15.2 g. of white solid m.p. 257-258°. Recrystallization from isopropyl alcohol gave the analytical sample, m.p. 262°; ir (potassium bromide): 1740, 1680, 1650, 1540, 1480, 800, 740 and 720 cm^{-1}; nmr (DMSO-d_6): δ 5.65 (d, J = 4, 1H), δ 7.0-8.27 (m, 8H); δ 9.12 (d, J = 4, 1H); δ 10.75 (S, 2H).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.39; H, 4.55; N, 13.26.

α-Amino-2,3-dihydro-2-oxo-1*H*-benzimidazole-5-acetic Acid (**9**).

The benzamide (**8**) (11.2 g., 36 mmoles) was suspended in 6*N* hydrochloric acid (900 ml.) and the mixture was heated at reflux temperature for 5 hours, chilled and filtered. The filtrate was evaporated and the residue was redissolved in aqueous methyl alcohol and *p*H of solution was adjusted to 4.5 with aqueous ammonium hydroxide. The mixture was chilled and filtered to give 6.3 g. of white solid, m.p. >270°; ir (potassium bromide): 3400, 3200, 1670, 1650, 1600, 1500, 1380, 1370, 1340, 1290, 1270, 1015, 900, 755, 730 and 710 cm^{-1}. The compound was too insoluble for an nmr to be obtained.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.76; H, 4,37; N, 19.86.

REFERENCES AND NOTES

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(2) J. A. Oliver and P. A. Orgley, *Chem. Ind.* (London), 1024 (1965).

(3) U.S. Patent 3,177,221 (McNeil Laboratories); *Chem. Abstr.*, **63**, 611 (1965).