STUDIES IN THE FIELD OF 2,1,3-THIA- AND -SELENADIAZOLES

LII. β-Phenylalanine Derivatives*

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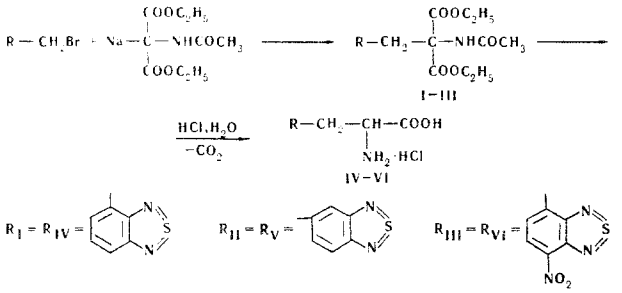
The reaction of 5-bromomethyl-, 4-bromomethyl-, and 4-bromomethyl-7-nitrobenzo-2, 1, 3-thiadiazoles with sodioacetylaminomalonic ester has given the corresponding malonates, which have been converted into the corresponding α-amino acids.

In the present paper we give the results of a study of the synthesis of derivatives of benzo-2,1,3-thiadiazole analogous to β-phenylalanine. These substances (IV–VI) were obtained by the reaction of the corresponding bromoethylbenzo-2,1,3-thiadiazoles with sodioacetylaminomalonic ester in a benzene-ethanolic medium with the subsequent acid hydrolysis and decarboxylation of the malonates (I–III) formed in the following way:



The malonates I–III all form readily at room temperature. The hydrolysis and decarboxylation of the malonate III presented considerably more difficulty than those of the malonates I and II. The action of an equivalent amount of triethylamine on ethanolic solutions of the hydrochlorides of IV and V gave the free acids VII and VIII respectively. With salicylaldehyde, the amino acid VII formed the azomethine derivative IX**.

EXPERIMENTAL

The 4-bromomethyl- and 5-bromomethyl-2, 1, 3-diazoles and 4-bromomethyl-7-nitrobenzo-2, 1, 3-thiadiazole were obtained as described previously [3].

4-(β, β-Diethoxycarbonyl-β-acetylaminoethyl)benzo-2, 1, 3-thiadiazole (I). With stirring, 2.17 g (0.01 mole) of acetylaminomalonic ester was added to a solution of 0.23 g (0.01 mole) of metallic sodium in 20 ml of absolute ethanol, the mixture was stirred at room temperature for 1 hr, and a solution of 2.29 g (0.01 mole) of 4-bromomethylbenzo-2, 1, 3-thiadiazole in 30 ml of dry benzene was added slowly. Stirring was continued for 8 hr at room temperature and then the precipitate was filtered off and washed with benzene, and the solvent was distilled off. Yield 3.1 g (92%). Thin white needles, mp 118–119° C (from aqueous ethanol). Found, %: N 11.35, 11.09; S 8.78, 8.93. Calculated for $C_{16}H_{19}N_3O_5S$, %: N 11.50; S 8.75 .

4-(β-Carboxy-β-aminoethyl)benzo-2, 1, 3-thiadiazole hydrochloride (IV). A mixture of 1.6 g of I and 25 ml of 20% hydrochloric acid was boiled for 6 hr. The clear solution was evaporated in vacuum with the addition of water in portions until a viscous paste had formed. Yield 1.6 g (83%). Yellowish powder with mp 216.0° C (decomp., from a mixture of ethanol and ether). Found, %: N 16.31, 16.18; Cl 13.42, 13.9. Calculated for $C_9H_9N_3O_2S \cdot HCl$, %: Cl 13.70; N 16.20. R_f 0.56.

4-(β-Carboxy-β-aminoethyl)benzo-2, 1, 3-thiadiazole (VII). This was obtained by adding 0.27 ml (0.002 mole) of triethylamine in 10 ml of ethanol to 0.5 g (0.0019 mole) of IV in 25 ml of absolute ethanol. The precipitate of the free amino acid that deposited was filtered off and washed with ethanol to give 0.40 g of white plates with mp 283–284° C (decomp) readily soluble in hot water and sparingly soluble in organic solvents and ethanol. Found, %: N 18.56, 18.48. Calculated for $C_9H_8N_4O_4S$, %: N 18.80.

4-(β-Carboxy-β-aminosalicylideneethyl)benzo-2, 1, 3-thiadiazole (IX). A solution of 0.54 ml (0.005 mole) of salicylaldehyde in 10 ml of ethanol was slowly added to a hot solution of 0.56 g (0.0025 mole) of VII in 60 ml of 50% ethanol. The yellow solution was heated at 80° C for 3 hr. After the solvent had been distilled off, 0.5 g (60%) of a yellowish substance with mp 312–314° C, sparingly soluble in organic solvents, was obtained. Found, %: N 17.42, 17.11. Calculated for $C_{16}H_{13}N_3O_3S$, %: N 17.00.

5-(β, β-Diethoxycarbonyl-β-acetylaminoethyl)benzo-2, 1, 3-thiadiazole (II). In a similar manner to the preparation of compound I, 5.32 g of 5-bromomethylbenzo-2, 1, 3-thiadiazole gave 5.8 g (69%) of a substance with mp 132–133° C (from ethanol). Found, %: N 11.00, 11.25; S 8.44, 8.27. Calculated for $C_{16}H_{19}N_3O_5S$, %: N 11.50; S 8.70.

5-(β-Carboxy-β-aminoethyl)benzo-2, 1, 3-thiadiazole hydrochloride (V). This was obtained from II in a similar manner to IV. White powder with mp 250° C (decomp., from a mixture of ethanol and ether). Yield 89%. Found, %: S 12.90, 12.69; Cl 14.16, 14.15 . Calculated for $C_9H_{10}N_3O_2S \cdot HCl$, %: S 12.40; Cl 13.70. R_f 0.36.

5-(β-Carboxy-β-aminoethyl)benzo-2, 1, 3-thiadiazole (VIII). This was obtained from V in a similar manner to VII. White powder with mp 278° C (from water). Found, %: N 18.71, 18.68. Calculated for $C_9H_8N_4O_4S$, %: N 18.80.

4-(β, β-Diethoxycarbonyl-β-acetylaminoethyl)-7-nitrobenzo-2, 1, 3-thiadiazole (III). This was obtained from 4-bromomethyl-7-nitrobenzo-2, 1, 3-thiadiazole in a similar manner to I. White plates with mp 205° C (from ethanol). Yield 91%. Found, %: N 13.95, 13.94; S 8.22, 8.34 . Calculated for $C_{16}H_{18}N_4O_7S$, %: N 13.60; S 7.80.

4-(β-Carboxy-β-aminoethyl)-7-nitrobenzo-2, 1, 3-thiadiazole hydrochloride (VI). This was obtained from III in a similar manner to IV. Boiling was carried out for 20 hr. Yellowish powder with mp 217° C (decomp, from ethanol and ether). Found, %: N 18.32, 18.54; Cl 12.03, 12.21. Calculated for $C_9H_8N_4O_4S \cdot HCl$, %: N 18.40; Cl 11.70. R_f 0.2.

The acids IV–VI were chromatographed on slow-filtering paper of the Leningrad paper mill previously purified with 0.1 N hydrochloric acid in the n-butanol–2-propanol–0.1 N HCl (2:1:1) system. The time of separation was 10–15 hr. The spots were developed with a 0.1% solution of ninhydrin.

*For communication LI, see [1].

**When the reaction was carried out with benzaldehyde it was impossible to isolate and characterize an azomethine derivative [2].

REFERENCES

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