[CONTRIBUTION FROM THE CHEMICAL INSTITUTE, FACULTY OF SCIENCE, UNIVERSITY OF ZAGREB]

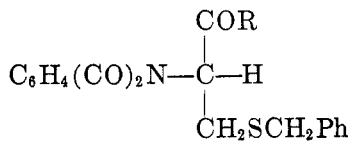
SYNTHESIS OF L-β-AMINO-γ-BENZYLTHIOBUTYRIC ACID. [L-β-AMINO-S-(BENZYL)HOMOCYSTEINE.] AMINO ACIDS. VI.[1]

K. BALENOVIĆ AND D. FLEŠ

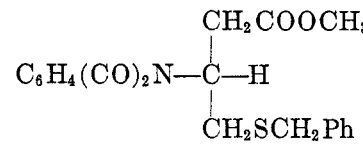
Received October 2, 1951

Very little has been published about the synthesis of optically active β-amino acids, and our knowledge of their physiological activity is also very limited.

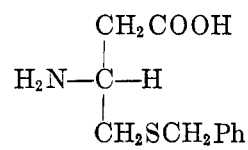
We have considered that it would be interesting to investigate the physiological properties of β-amino acids, homologs of the naturally occurring amino acids, and we have prepared S-(benzyl)-L-β-aminohomocysteine (V) as starting material for the synthesis of optically active β-amino acids containing sulfur.



I R = OH
II R = Cl
III R = CHN_2



IV



V

It has been shown that N-phthaloyl derivatives of the α-amino acids can be converted into the corresponding homologous β-amino acids by the Arndt-Eistert reaction (1). Following this method we have recently prepared β-aminohomotyrosine, β-amino-3,5-diiodohomotyrosine (2), and β-aminohomoleucine (3).

As starting material for the present synthesis, we have prepared the undescribed S-(benzyl)-N-phthaloyl-L-cysteine (I), which was converted into the chloride (II) and the diazoketone (III). From this compound we prepared the methyl ester of the β-amino acid (IV) by the Arndt-Eistert reaction (4). By homologization of S-(benzyl)-L-cysteine, L-β-amino-γ-benzylthiobutyric acid (V) was obtained, which showed, after two recrystallizations, the constant $[\alpha]_D$ +6.3° (*c*, 2.067 in 2 *N* HCl) and $[\alpha]_D$ +19.00° (*c*, 1.364 in 2 *N* NaOH).

We do not offer any definite conclusions about the configuration of β-amino-S-(benzyl)homocysteine (V), but we propose that it is of the L-series of amino acids, the Arndt-Eistert reaction being anionotropic, and not leading to the Walden rearrangement.

[1] Paper V, Balenović, Bregant, Cerar, and Tkalčić, *J. Org. Chem.*, **16**, 1308 (1951).

EXPERIMENTAL

Melting points are uncorrected unless otherwise stated.

S-(Benzyl)-N-phthaloyl-L-cysteine. (I). A well powdered mixture of 7.03 g. (1/30 mole) of S-(benzyl)-L-cysteine prepared according to du Vigneaud, Audrieth, and Loring (5), and 5.14 g. (1/30 mole) of phthalic anhydride was heated during 30 minutes in an oil-bath. The temperature inside the flask did not rise above 135–140°. The reaction mixture was then cooled and dissolved in 100 ml. of benzene, the undissolved residue removed by filtration, and the solution evaporated to a volume of about 30 ml. White crystals (5.8 g.) were obtained, m.p. 123–124°. After standing for a while, more crystals separated from the oily residue; the total yield was 6.8 g. (60%). A sample was purified for analysis by recrystallization, first from 50% methanol, and then from benzene-petroleum ether (1:10); m.p. 128–129.5° (with previous softening and darkening). The substance readily dissolved in methanol, benzene, and ether, but was insoluble in petroleum ether and water. From a mixture of methanol and water it separated in fine needles; $[\alpha]_D^{21.5}$ − 82.3° ±0.8° (*c*, 2.418 in methanol).

Anal. Calc'd for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43.
Found: C, 63.69; H, 4.72.

N-Phthaloyl-S-(benzyl)-L-cysteinyl chloride. (II). S-(Benzyl)-N-phthaloyl-L-cysteine (5.8 g.) and 5 ml. of thionyl chloride were refluxed for 1 hour. The excess thionyl chloride was removed by evaporation under reduced pressure, during which operation the crystals of chloride separated. The crystallization was accelerated by adding a little anhydrous ether. Yield, 6 g. of chloride. The crude material (0.9 g.) was dissolved in 150 ml. of petroleum ether; a small quantity of chloride separated, along with red resinous impurities. The petroleum ether solution was freed from these impurities and evaporated under reduced pressure. The crystalline chloride remained in clusters of fine needles, m.p. 93–94°, yield 80%. Recrystallized for analysis from anhydrous ether; $[\alpha]^{21.5}$ −16.2° ±1.6° (*c*, 2.548 in benzene).

Anal. Calc'd for $C_{18}H_{14}ClNO_3S$: C, 60.08; H, 3.92.
Found: C, 60.34; H, 4.25.

L-1-Diazo-4-benzylthio-3-phthalimidobutanone-(2) (III). A solution of 5.1 g. of S-(benzyl)-N-phthaloyl-L-cysteinyl chloride in 150 ml. of ether was gradually added during 30 minutes to 250 ml. of a 0.4 *M* ethereal solution of diazomethane, at 0–5°. The mixture was left for 2 hours at 0°, when the crystallization of the diazo ketone began. The ether was evaporated to a volume of about 30 ml., and the pale yellow diazo-ketone collected and washed with two 10-ml. portions of ether. There was obtained 3.2 g. (62%) of diazoketone, m.p. 104–105°. Repeated recrystallization from a mixture of ethyl acetate and petroleum ether yielded long, pale yellow needles, m.p. 107–107.5°; $[\alpha]_D^{25}$ −28.1° ±0.09° (*c*, 2.169 in ethyl acetate).

Anal. Calc'd for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14.
Found: C, 62.50; H, 4.26.

Methyl ester of L-2-phthalimido-3-benzylthiobutyric acid (IV). A suspension of 3.0 g. of diazo ketone in 18 ml. of methanol was heated under reflux, and a freshly prepared suspension of silver oxide gradually added. The reaction was complete after 4 hours, and 500 mg. of Ag_2O were needed. The reaction mixture was treated with a little charcoal and filtered hot. The residue was thoroughly washed with three 5-ml. portions of methanol. After evaporating the methanol, 2.4 g. of brown oil remained. It was extracted with five 70-ml. portions of petroleum ether (50–60°). After evaporating the petroleum ether, 1.6 g. (52.5%) of yellowish crystalline product, m.p. 59°, were obtained. After being twice recrystallized from methanol, the substance had the constant m.p. 65–66°, and separated from methanol in needles. It can be distilled at 180–185°/0.05 mm. without decomposition; $[\alpha]_D^{25}$ +9.4° ±1° (*c*, 1.288 in methanol).

Anal. Calc'd for $C_{20}H_{19}NO_4S$: C, 65.03; H, 5.18.
Found: C, 64.93, 64.95; H, 5.26, 5.47.

Hydrochloride of L-2-amino-3-benzylthiobutyric acid. L-β-Amino-S-(benzyl)homocysteine

hydrochloride. The crude crystalline ester (738 mg., 0.002 mole) was shaken during 1 hour with 20 ml. of methanol and 3 ml. of 2 *N* NaOH (0.003 mole) at room temperature. The solution was then acidified to Congo Red, and the methanol removed under reduced pressure. After the addition of 100 ml. of water a brown oil separated. The mixture was transferred to a separatory-funnel with 50 ml. of ether. The water layer was shaken out with three 20-ml. portions of ether. All the ether extracts were collected and dried on Na_2SO_4, filtered, and the ether removed under reduced pressure.

The oily residue (about 700 mg.) was boiled for 1 hour with 15 ml. of 20% hydrochloric acid, 35 ml. of water was added, and the mixture shaken out with four 20-ml. portions of ether. After removing the ether, 303 mg. of phthalic acid was obtained, with dark oily impurities. From the water layer 300 mg. (57.5%) of L-β-amino-S-(benzyl)homocysteine hydrochloride were obtained after evaporating the water. The crude product was dissolved in 25 ml. of water, treated with charcoal and concentrated to about 2 ml. On the addition of 4 ml. of concentrated hydrochloric acid, the pure *hydrochloride* separated in platelets, m.p. 188° (with previous softening at 185°).

Anal. Calc'd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.16.
Found: C, 50.17; H, 6.01.

L-*2-Amino-3-benzylthiobutyric acid.* L-*β-Amino-S-(benzyl)homocysteine* (V). The hydrochloride (150 mg.) was dissolved in 5 ml. of water and neutralized by adding a few drops of concentrated ammonia, so that the solution remained slightly acid (*p*H 6). Small platelets of the free acid soon began to separate. After being twice recrystallized from water, the m.p. reached 195–196° (corr., with decomposition, previously darkening at 190°) and remained constant; $[\alpha]_D^{23}$ +19.0° ±1° (*c*, 1.364 in 2 *N* NaOH); $[\alpha]_D^{26}$ +6.3° ±1° (*c*, 2.068 in 2 *N* HCl).

Anal. Calc'd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71.
Found: C, 58.82; H, 6.93.

Acknowledgment. We are indebted to Dr. L. Filipović of our microanalytical laboratory for having carried out the microanalyses.

SUMMARY

A synthesis is described of the optically active L-β-amino-S-(benzyl)homocysteine (V), a starting material for the preparation of optically active, sulfur-containing β-amino acids.

ZAGREB, YUGOSLAVIA

REFERENCES

(1) BALENOVIĆ, *Experientia*, **3**, 369 (1947).
(2) BALENOVIĆ, THALLER, AND FILIPOVIĆ, *Helv. Chim. Acta*, **34**, 744 (1951).
(3) BALENOVIĆ AND BROVET-KEGLEVIĆ, *Arhiv. kem.*, **22**, (1951), in press.
(4) *Cf. e.g.* BACHMANN AND STRUVE, *Org. Reactions*, **2**, pp. 38–62 (1944).
(5) DU VIGNEAUD, AUDRIETH, AND LORING, *J. Am. Chem. Soc.*, **52**, 4500 (1930).