Some Derivatives of L-Cysteine Aldehyde. An Improved Preparation of S-Benzyl-N-phthaloyl-L-cysteine. Amino Acids XXXI*

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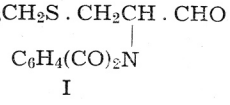
A method for the preparation of S-benzyl-N-phthaloyl-L-cysteine with $[\alpha]_D$ —167° is described.

According to the previously described procedure for the preparation of racemic S-benzyl-N-phthaloyl-cysteine aldehyde[3], the optically active compound was obtained showing $[\alpha]_D$ —103°. The following new compounds were prepared: S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene acetal, S-benzyl-L-cysteine aldehyde ethylene acetal, picrate of S-benzyl-L-cysteine aldehyde ethylene acetal, and 5-benzylthio-4-phthalimidopent-2-enoic acid, the vinylogue of S-benzyl-N-phthaloyl-cysteine.

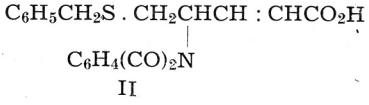
N-Phthaloyl derivatives of optically active amino acids are always obtained as optically pure compounds[1, 5]. Detailed investigation of the optical purity of S-benzyl-N-phthaloyl-L-cysteine and desulphurisation with Raney nickel to N-phthaloyl-L-alanine derivatives[2] showed that considerable racemisation occurred during the preparation of S-benzyl-N-phthaloyl-L-cysteine under the reaction conditions suitable for the preparation of optically active derivatives of other α-amino acids.

A few years ago we prepared in this manner partly racemic S-benzyl-N-phthaloylcysteine aldehyde (I)[3]. Now we have attempted the preparation of the vinylogue of cysteine from optically active S-benzyl-N-phthaloylcysteine aldehyde in the same way as we obtained the vinylogues of glycine[4] and L-alanine[5].

As the result of very extensive variations of experimental conditions for the preparation of S-benzyl-N-phthaloyl-L-cysteine, in the present paper we are giving the description of the preparation of this compound with $[\alpha]_D$ — 167°.



I



II

Besides S-benzyl-N-phthaloyl-L-cysteine aldehyde (I) we have also prepared S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene acetal, S-benzyl-L-cysteine aldehyde ethylene acetal, and 5-benzylthio-4-phthalimidopent-2-enoic acid (II) as the vinylogue of S-benzyl-N-phthaloylcysteine.

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Contrary to the vinylogues of glycine and L-alanine, which were obtained as optically active compounds, the vinylogue of cysteine was obtained in racemic form.

EXPERIMENTAL

All melting points are uncorrected:

Improved preparation of S-benzyl-N-phthaloyl-L-cysteine

A well powdered mixture of S-benzyl-L-cysteine (7.03 g., 0.033 mole $[\alpha]_D$ +28°) and phthalic anhydride (5.20 g., 0.035 mole) was heated on an oil bath (bath temp. 130—135°, melt temp. 110—115°) for half an hour under thorough stirring which was carried out for this preparation with a thermometer, but in larger preparations a Hershberg stirrer was used. The reaction mixture was dissolved in warm benzene (40 ml.). The insoluble residue was filtered off and petroleum ether (15 ml.) was added to the filtrate. After the mixture was left in an ice-box for two hours, a white oily precipitate separated which was removed by filtration. Yield of crude *S-benzyl-N-phthaloyl-L-cysteine* 4—6 g. (40—60%), $[\alpha]_D$ —105° to —125°. The mother liquor was diluted with petroleum ether (50 ml.) and after 3—5 minutes S-benzyl-N-phthaloyl-L-cysteine separated and was immediately collected; yield 2—4 g. (20—40%), $[\alpha]_D^{25}$ —135° to —145°. The mother liquor was left in an ice-box overnight, and white prisms of the optically very pure compound separated, 0.7—1 g (7—10%), $[\alpha]$ —165°. Recrystallization from dichloromethane-petroleum ether gave the analytical sample, m. p. 108°, $[\alpha]_D^{25}$ —167° ±0.1° (c, 0.56 in methanol).

Anal. 10.23 mg. subst.: 23.74 mg. CO_2, 4.20 mg. H_2O
8.39 mg. subst.: 0.306 ml. N_2 (22.8°, 749 mm.)
4.41 mg. subst. requires 1.32 ml. 0.02 *N* NaOH (S-determination)
$C_{18}H_{15}O_4NS$ (341.37) calc'd.: C 63.32; H 4.43; N 4.11; S 9.39%
found: C 63.35; H 4.59; N 4.15; S 9.57%

For most preparations S-benzyl-N-phthaloyl-L-cysteine showing $[\alpha]_D$ —145° to —150° was used, contrary to earlier preparations[6], where the preparation of S-benzyl-N-phthaloyl-L-cysteine with $[\alpha]_D$ —82° was described.

S-Benzyl-N-phthaloyl-L-cysteine aldehyde (I)

This compound was first described by Balenović, Bregant, Cerar, Fleš and Jambrešić[3] as crystals with the m. p. 119—120°, and $[\alpha]_D$—1.8°, obtained by reduction of S-benzyl-N-phthaloyl-L-cysteinyl chloride with $[\alpha]_D$—16.2° with Pd-$BaSO_4$ catalyst at 100—110°. We prepared S-benzyl-N-phthaloyl-L-cysteine aldehyde starting with S-benzyl-N-phthaloyl-L-cysteine showing $[\alpha]_D$—150°. From this compound the corresponding chloride with $[\alpha]_D^{16}$—136° ± 1° (c, 1.44 in benzene) was obtained in the manner described earlier[6]. Rosenmund-Zetzsche reduction of this chloride (2 g.) with 5% Pd-$BaSO_4$ catalyst (2.5 g.) at 120—125° (oil bath temperature) during ten hours gave 1.75 g. (97%) of S-benzyl-N-phthaloyl-L-cysteine aldehyde as a yellow oil showing $[\alpha]_D^{16}$ —102° ±1° (c, 2.2 in benzene). Fractional precipitation with petroleum ether gave the pure compound as a colourless oil with $[\alpha]_D^{17}$ —103° ±1° (c, 1.2 in benzene). The same aldehyde described previously[3] with the m. p. 119—120° and $[\alpha]_D$—1.8° was evidently the racemic compound contaminated with small quantities of the L-isomer.

Anal. 10.20 mg. subst.: 24.66 mg. CO_2, 4.22 mg. H_2O
6.29 mg. subst.: 0.227 ml. N_2 (19.6°, 753 mm.)
$C_{18}H_{15}NO_3S$ (325.37) calc'd.: C 66.44; H 4.65; N 4.31%
found: C 66.00; H 4.63; N 4.23%

S-Benzyl-N-phthaloyl-L-cysteine aldehyde ethylene acetal

A mixture of S-benzyl-N-phthaloyl-L-cysteine aldehyde (3.25 g., 0.01 mole, $[\alpha]_D$—102°), ethanediol (2.5 ml.) and p-toluenesulphonic acid (0.1 g.) in benzene (150 ml.) was refluxed during five hours in a flask provided with a total condensation take-off adapter. The reaction mixture was cooled, washed with water, dried (Na_2SO_4), and evaporated to dryness. The yellow oily residue solidified to a semi-crystalline mass after several days. Yield 3.5 g. (97%) of crude *S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene acetal.* A sample of this solid (0.6 g.) was dissolved in benzene and filtered through an alumina column (10 g. of Al_2O_3). The filtrate was evaporated to dryness and recrystallized from dichloromethane-petroleum ether. White prisms of the constant m. p. 95—97° were obtained, showing $[\alpha]_D^{12}$ —78° ± 0.5° (c, 2.8 in benzene).

Anal. 9.94 mg. subst.: 23.72 mg. CO_2, 4.53 mg. H_2O
$C_{20}H_{19}NO_4S$ (369.42) calc'd.: C 65.02; H 5.18%
found: C 65.14; H 5.10%

The sample not purified by chromatography showed a higher optical activity, but gave somewhat lower analytical values for carbon.

S-Benzyl-L-cysteine aldehyde ethylene acetal

To a solution of S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene acetal (7.38 g., 0.02 mole) in ethanol (150 ml.) was added an ethanolic 1 *M* solution of hydrazine hydrate (20 ml., 0.022 mole). The reaction mixture was refluxed for three hours, and then cooled. The phthalyl hydrazide was filtered off and thoroughly washed with dichloromethane. (Total quantity of phthalyl hydrazide 81%.) The crude *S-benzyl-L-cysteine aldehyde ethylene acetal* was purified by distillation over powdered sodium hydroxide, b. p. 105—110°/0.01 mm., $[\alpha]_D^{16}$ —54° ± 1° (c, 1.07 in n/10 hydrochloric acid).

Anal. 11.87 mg. subst.: 26.27 mg. CO_2, 7.60 mg. H_2O
$C_{12}H_{17}NO_2S$ (239.32) calc'd.: C 60.22; H 7.16%
found: C 60.40; H 7.17%

Picrate, yellow needles from ethyl acetate-petroleum ether, m. p. 183—184°.

Anal. 5.53 mg. subst.: 9.38 mg. CO_2, 2.15 mg. H_2O
$C_{18}H_{20}N_4O_9S$ (468.43) calc'd.: C 46,15; H 4.30%
found: C 46.29; H 4.35%

5-Benzylthio-4-phthalimidopent-2-enoic acid. (II)

To a solution of S-benzyl-N-phthaloyl-L-cysteine aldehyde (2.5 g., 0.008 mole, $[\alpha]_D$—101°) in freshly distilled pyridine (5 ml.) finely powdered malonic acid (1.6 g., 0.015 mole) was added at room temperature. The reaction mixture was left at room temperature overnight, and heated during eight hours at 45—50°. It was then acidified with 10% sulphuric acid, extracted with ether, and the ether extracts dried (Na_2SO_4). After evaporation of the ether, the yellow viscous oily *5-benzylthio-4-phthalimidopent-2-enoic acid* remained, yield 2.4 g. (92%). This oil was dissolved in acetone, filtered through alumina, and after evaporation of the filtrate the residual oil was repeatedly recrystallized from dichloromethane-petroleum ether to the constant m. p. 141—142°. The analytical sample showed no optical activity.

Anal. 9.85 mg. subst.: 23.59 mg. CO_2, 4.17 mg. H_2O
$C_{20}H_{17}NO_4S$ (367.40) calc'd.: C 65.38; H 4.66%
found: C 65.38; H 4.74%

Results of the investigation of biological activities of these compounds will be published elsewhere.

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REFERENCES

1. cf. e. g. J. C. Sheehan, D. W. Chapman and R. W. Roth, *J. Am. Chem. Soc.* **74** (1952) 3822.
2. K. Balenović and D. Fleš, *J. Chem. Soc.* **1952**, 468.
3. K. Balenović, N. Bregant, D. Cerar, D. Fleš, and I. Jambrešić, *J. Org. Chem.* **18** (1953) 297.
4. K. Balenović, I. Jambrešić and B. Urbas, *J. Org. Chem.* **19** (1954) 1589.
5. K. Balenović and D. Cerar, *J. Chem. Soc.* **1955**, 1631.
6. K. Balenović and D. Fleš, *J. Org. Chem.* **17** (1952) 347.

IZVOD

Neki derivati L-cisteinaldehida. Poboljšana priprava S-benzil-N-ftaloil-L-cisteina. Aminokiseline XXXI

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Opisuje se metoda za dobivanje S-benzil-N-ftaloil-L-cisteina $[\alpha]_D$—167°. Prema prije opisanoj metodi[3] za dobivanje racemičnog S-benzil-N-ftaloil-cistein-aldehida dobiven je optički aktivni spoj sa $[\alpha]_D$—103°. Priređeni su ovi novi spojevi: S-benzil-N-ftaloil-L-cisteinaldehid etilen acetal, S-benzil-L-cisteinaldehid etilen acetal, pikrat S-benzil-L-cisteinaldehid etilen acetala, i 5-benziltio-4-ftalimidopent-2-enska kiselina, vinilog S-benzil-N-ftaloilcisteina.

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