

Synthesis of β -Alethine and Analogues

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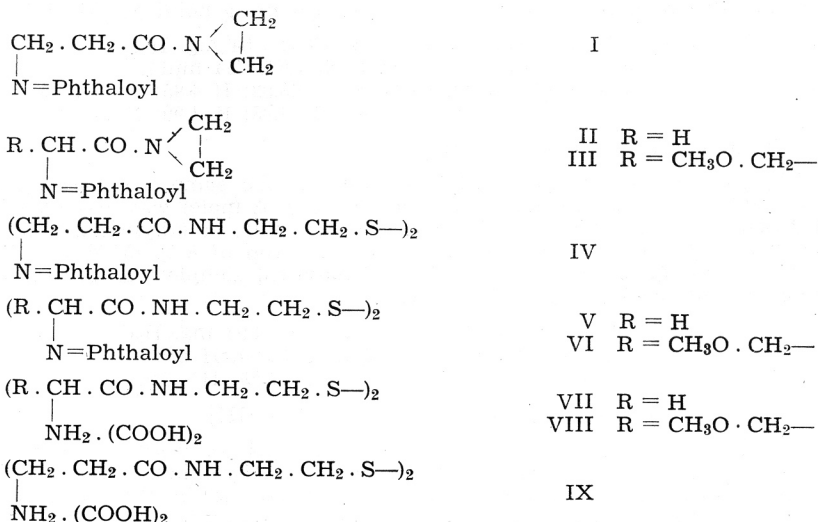
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In the past few years many papers have appeared relating to the problem of the synthesis of β -alethine^{1*} an intermediate in the synthesis of panthetine.

A more recent publication² on the synthesis of β -alethine and analogues has prompted us to publish our own results on the synthesis of β -alethine and analogues derived from glycine and O-methyl-DL-serine.

The following methods were used for the preparation of these compounds: N-Phthaloyl derivatives of the corresponding amino acid chlorides were condensed with ethylenimine in the usual manner^{3, 4} and the ethylenimides I, II and III were thus obtained.



The ethylenimides I, II and III were then treated with hydrogen sulfide in ethanol according to the procedure described by Mills and Bogert⁵. After the hydrogen sulfide was removed the residue was oxidized with air and the corresponding N-phthaloyl derivatives of β -alanyl-, glycy- and O-methyl-N-phthaloyl-DL-seryl-cystamine were obtained (IV, V and VI). The compound IV was prepared by Karrer *et al.*⁶ by condensation of N-phthaloyl- β -alanyl chloride with cystamine in chloroform.

* The name β -alethine is proposed by King *et al.* (see ref. 1.) for N(β -alanyl)-2-aminoethyl disulfide in conformance with nomenclature of panthetine.

Hydrazinolysis of the phthaloyl group of the compounds IV, V and VI afforded the amines which were isolated in the form of their oxalates (VII, VIII and IX).

Cystamines VII, VIII and IX can be easily converted to panthetine and analogues according to the methods previously published.^{2, 6} Since the method described in this paper can be extended to some other amino acids, we consider that by this route a series of biologically interesting compounds can be prepared.

EXPERIMENTAL*

β -Phthalimidopropionyl-ethylenimide (I)

A mixture of 1.22 g. (0.0284 mole) of ethylenimine and 2.88 g. (0.0284 mole) of triethylamine in 50 ml. of dry benzene was placed in a three-necked flask equipped with a mechanical stirrer, dropping funnel and a condenser. The flask was immersed into an ice-bath and with rapid stirring a solution of 6.5 g. (0.0274 mole) of β -phthalimidopropionyl chloride in 130 ml. of dry benzene was added dropwise in the course of half an hour. The temperature of the benzene solution was kept at 5–10°. The reaction mixture was then stirred for one hour at room temperature. Triethylamine hydrochloride was removed by suction and washed with three 10-ml. portions of benzene. Evaporation of benzene at a reduced pressure afforded a crop of 6 g. of white crystalline product. The crude ethylenimide was recrystallized from 20 ml. of ethanol to give 5.5 g. (82.0%) of white crystals; m. p. 98–100°. An analytical sample was recrystallized three times from ethanol to a melting point of 104–105°.

Anal. 16.90 mg. subst.: 39.62 mg. CO₂, 7.54 mg. H₂O
 5.30 mg. subst.: 0.549 ml. N₂ (30°, 754 mm.)
 C₁₃H₁₂O₃N₂ (244.24) calc'd.: C 63.92; H 4.95; N 11.47%
 found: C 63.98; H 4.99; N 11.57%

Phthalimidoacetyl-ethylenimide (II)

Ethylenimide II was prepared essentially in the same way as described for ethylenimide I. Phthalimidoacetyl chloride (6.7 g., 0.03 mole) was dissolved in 50 ml. of dry benzene and condensed with 1.33 g. (0.031 mole) of ethylenimine in the presence of 3.14 g. (0.031 mole) of triethylamine. A crop of 6 g. (86.5%) of the crude product was obtained; m. p. 110–112°. An analytical sample was crystallized from ethanol in long needles and melted at 116°.

Anal. 12.70 mg. subst.: 29.13 mg. CO₂, 4.94 mg. H₂O
 C₁₂H₁₀O₃N₂ (230.22) calc'd.: C 62.60; H 4.38%
 found: C 62.59; H 4.35%

α -Phthalimido- β -methoxypropionyl-ethylenimide (III)

α -Phthalimido- β -methoxypropionyl chloride⁷ (2.4 g., 0.009 mole) dissolved in 20 ml. of dry benzene and 0.392 g. (0.0091 mole) of ethylenimine were condensed in the presence of 0.92 g. (0.0091 mole) of triethylamine in the same manner as described for ethylenimide I. The crude product (1.9 g.) was crystallized from 12 ml. of ethanol to give 1.4 g. (57.0%) of prismatic crystals; m. p. 94–95°. A sample for analysis was crystallized twice from ethanol to a melting point of 100–101°.

Anal. 18.92 mg. subst.: 42.51 mg. CO₂, 8.58 mg. H₂O
 6.40 mg. subst.: 0.588 ml. N₂ (26°, 757 mm.)
 C₁₄H₁₄O₄N₂ (274.27) calc'd.: C 61.31; H 5.15; N 10.21%
 found: C 61.31; H 5.07; N 10.45%

Bis[N-(β -phthalimidopropionyl)-2-aminoethyl]-disulfide (IV)

One hundred and fifty milliliters of abs. ethanol were placed in a three necked flask equipped with a mechanical stirrer, dropping funnel and a gas-inlet and outlet

* Melting points are uncorrected.

tube. The flask was immersed into an ice-bath and dry hydrogen sulfide was passed through the solution, while a solution of 2.5 g. of the compound I dissolved in 150 ml. of abs. ethanol was added dropwise during 3—4 hours with continued bubbling of dry hydrogen sulfide. After standing overnight in the refrigerator, the solution was evaporated *in vacuo*, the white residue suspended in 100 ml. of abs. ethanol and oxidized with air. The ethanol was evaporated and the residue crystallized from 50% acetic acid. After standing for 48 hours in a refrigerator, 1.5 g. of a crystalline product was obtained; m. p. 185—190°. A sample for analysis was crystallized from 50% acetic acid; m. p. 211° (reported⁶ m. p. 210—212°).

Anal. 13.74 mg. subst.: 28.22 mg. CO₂, 5.61 mg. H₂O
 4.45 mg. subst.: 0.412 ml. N₂ (29°, 754 mm.)
 15.27 mg. subst.: 5.42 ml. 0.02 N NaOH
 C₂₆H₂₆O₆N₄S₂ (554.63) calc'd.: C 56.30; H 4.73; N 10.10; S 11.56%
 found: C 56.04; H 4.56; N 10.38; S 11.35%

Bis[N-(phthalimidoacetyl)-2-aminoethyl]-disulfide (V)

A solution of 2.1 g. of the compound II dissolved in 50 ml. of abs. ethanol was added dropwise into 80 ml. of abs. ethanol while a stream of dry hydrogen sulfide was passed through it. After standing overnight in a refrigerator the solvent was evaporated and the residue oxidized with air. Crystallization from ethanol afforded 1.5 g. (62.4%) of white needles; m. p. 168—170°. The analytical sample was crystallized from ethanol to a melting point of 174—175°.

Anal. 20.81 mg. subst.: 41.43 mg. CO₂, 7.84 mg. H₂O
 3.70 mg. subst.: 0.351 ml. N₂ (25°, 756 mm.)
 20.53 mg. subst.: 7.82 ml. 0.02 N NaOH
 C₂₄H₂₂O₆N₄S₂ (526.58) calc'd.: C 54.74; H 4.22; N 10.62; S 12.18%
 found: C 54.32; H 4.21; N 10.80; S 12.18%

Bis[N-(α -phthalimido- β -methoxypropionyl)-2-aminoethyl]-disulfide (VI)

A solution of 4 g. of the compound III dissolved in 100 ml. of abs. ethanol was added dropwise into 150 ml. of abs. ethanol while a stream of dry hydrogen sulfide was passed through it. After standing overnight in a refrigerator, the solvent was evaporated and the residue oxidized with air. Crystallization from ethanol afforded 2.6 g. (58%) of white needles; m. p. 135—137°. A sample for analysis was crystallized from ethanol to a melting point of 137—133°.

Anal. 14.84 mg. subst.: 29.77 mg. CO₂, 6.40 mg. H₂O
 5.38 mg. subst.: 0.441 ml. N₂ (26°, 754 mm.)
 24.08 mg. subst.: 7.94 ml. 0.02 N NaOH
 C₂₈H₃₀O₈N₄S₂ (614.68) calc'd.: C 54.71; H 4.92; N 9.12; S 10.43%
 found: C 54.74; H 4.82; N 9.28; S 10.52%

Bis[N-(amino-acetyl)-2-aminoethyl]-disulfide dioxalate (VII)

The phthalimido derivate V (2.63 g., 0.005 mole) was refluxed for one hour with 22 ml. (0.011 mole) of 0.5 N hydrazine hydrate in abs. ethanol. The solvent was removed *in vacuo* and the residue treated with 10 ml. of water. The solution was adjusted to pH 5 with glacial acetic acid, the phthalylhydrazide was filtered off and washed with 10 ml. of water. The water solution was evaporated *in vacuo* to give 1.3 g. of a very hygroscopic oil. The crude base (1.3 g.) was dissolved in 40 ml. of abs. ethanol and a solution of 1.1 g. (0.012 mole) of anhydrous oxalic acid in 40 ml. of abs. ethanol was added. After standing for one hour at room temperature, the crystalline precipitate was removed by filtration under suction, washed with ethanol and dried *in vacuo*. The product crystallized in the form of needles and melted at 175°. An analytical sample was purified by crystallization from a mixture of ethanol-water (5 : 1); m. p. 184—185°.

Anal. 15.31 mg. subst.: 18.07 mg. CO₂, 6.50 mg. H₂O
 4.37 mg. subst.: 0.480 ml. N₂ (29°, 755 mm.)
 15.60 mg. subst.: 7.2 ml. 0.02 N NaOH
 C₁₂H₂₂O₁₀N₄S₂ (446.46) calc'd.: C 32.28; H 4.97; N 12.55; S 14.36%
 found: C 32.21; H 4.75; N 12.33; S 14.74%

Bis[N-(α -amino- β -methoxypropionyl)-2-aminoethyl]-disulfide dioxalate (VIII)

The compound VI (1.14 g., 0.0018 mole) was treated with 8 ml. of 0.5 N hydrazine hydrate in the same manner as described for the preparation of the compound VII. The crude base (550 mg.) was dissolved in 5 ml. of abs. ethanol and impurities were precipitated by addition of 2 ml. of ether. The supernatant liquid was evaporated in vacuo to give 300 mg. of the crude base. This product was treated with 250 mg. of oxalic acid and the precipitated oily oxalate was purified as follows: the crude oxalate was dissolved in 7 ml. of hot ethanol and 2 ml. of ether were added. The solution was decanted, evaporated in vacuo and the white oily residue thoroughly dried in a high vacuum. All attempts to crystallize the oxalate were unsuccessful and the product was analysed without further purification.

Anal. 11.83 mg. subst.: 15.61 mg. CO₂, 6.35 mg. H₂O
 3.71 mg. subst.: 0.343 ml. N₂ (28°, 759 mm.)
 13.30 mg subst.: 5.1 ml. 0.02 N NaOH
 C₁₆H₃₀O₁₂N₄S₂ (534.56) calc'd.: C 35.95; H 5.66; N 10.48; S 12.00%
 found: C 36.01; H 6.00; N 10.47; S 12.25%

Bis[N-(β -amino-propionyl)-2-aminoethyl]-disulfide dioxalate (IX)

The oxalate IX was prepared in the same manner as described for VII. The crude oxalate melting at 90—93°, was purified for analysis from a mixture of ethanol-water (5 : 1); m. p. 91—93°.

Anal. 11.98 mg. subst.: 15.64 mg. CO₂, 5.83 mg. H₂O
 4.10 mg. subst.: 0.431 ml. N₂ (25°, 755 mm.)
 C₁₄H₂₆O₁₀N₄S₂ (474.51) calc'd.: C 35.44; H 5.52; N 11.81%
 found: C 35.62; H 5.44; N 11.96%

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IZVOD

Sinteza β -aletina i analoga

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Djelovanjem etilenimina na kloride N-ftaloil- β -alanina, glicina i O-metil-serina, priređeni su pripadni etilenimidi (I, II i III). Djelovanjem sumporovodika na etilenimide I, II i III, dobiveni su ovi spojevi: bis(N-ftaloil- β -alanil)-cistamin (IV), bis(N-ftaloil-glicil)-cistamin (V) i bis(N-ftaloil-O-metil-seril)-cistamin (VI). Cistaminski derivati IV, V i VI prevedeni su hidrazinolizom u slobodne baze, koje su izolirane u obliku oksalata (VII, VIII i IX). Priređeni oksalati mogu poslužiti kao međuprodukti za sintezu pantetina i analoga.

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