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## Abstract

## Full Text

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# Preparation of Higher Aliphatic $\alpha$-Amino Acids from 2-Phenyl-4-(thenylidene)-5-oxazolones

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Earlier ($^{1,2}$) we proposed a method for preparing aliphatic $\alpha$-amino acids. It is based on reductive desulfurization (hydrogenolysis) with Raney nickel of $\alpha$-amino acids containing a thiophene nucleus, which, in turn, are synthesized by the classical Strecker method. This procedure makes it possible to obtain a variety of $\alpha$-amino acids, but its drawbacks are the low yields inherent in the Strecker method at the stage of formation of the $\alpha$-aminonitrile and the often not entirely satisfactory results at the hydrogenolysis stage. Later we showed ($^{3}$) that the yield in hydrogenolysis can be considerably increased by using acylamino acids instead of amino acids.

In recent years, the method for preparing $\alpha$-amino acids via oxazolones has found wide application. On hydrolysis they give unsaturated $\alpha$-acylamino acids, which are then reduced and saponified to $\alpha$-amino acids. This route gives acceptable results only when aromatic aldehydes are used (the yield of oxazolones from saturated aldehydes is substantially lower). However, this synthesis is multistage and is also associated with the inconvenience that higher aliphatic aldehydes are required for the preparation of higher amino acids.

These difficulties are largely eliminated when working according to a scheme based on the principle of reductive desulfurization that we used earlier:

$$(\mathrm{I})\quad \overset{R' \qquad R''}{[\text{Thiophene Structure}]}\quad \text{thiophene}-\mathrm{CHO} + \mathrm{HOOCCH_2NHCOC_6H_5} \xrightarrow[\mathrm{CH_3COONa}]{(\mathrm{CH_3CO})_2\mathrm{O}} (\mathrm{III}) \xrightarrow[\mathrm{NaOH}]{\mathrm{Ni/H}}$$

$$[(\mathrm{IV})\quad \text{thiophene}-\mathrm{CH{=}C(COOH)NHCOC_6H_5} \longrightarrow (\mathrm{V})\quad \text{thiophene}-\mathrm{CH_2CH(COOH)NHCOC_6H_5}] \longrightarrow$$

$$(\mathrm{VI})\quad \mathrm{RCH_2CH(R')CH(R'')CH_2CH_2CH(COOH)NHCOC_6H_5} \xrightarrow{\mathrm{HCl,\ H_2O}} (\mathrm{VII})\quad \mathrm{RCH_2CH(R')CH(R'')CH_2C}$$

(R, R$'$ and R$''$ = H, alkyl, or another substituent stable under the reaction conditions.)

Since here the oxazolone is formed by interaction with an aromatic aldehyde, the yields at this stage are high. On the other hand, the very fact that the thiophene system, capable of ring opening, participates in the reaction contains the possibility of chain elongation. As a result of such a process, the length of the substituent R is increased at once by four $CH_2$ groups. This eliminates the need to use higher aldehydes. The method we propose makes it possible to obtain $\alpha$-amino acids of normal and branched structure. The latter possibility is realized in cases where the substituent in the $\alpha$-position has branching or when it is attached to a $\beta$-carbon ato-

of the ring and, finally, when the aldehyde function is in the $\beta$-position.

Aldehydes of the thiophene series (I) are obtained in about 80% yield by direct formylation of thiophenes. With hippuric acid they form oxazolones in good yields, which can be further increased in comparison with those described (4) if the hippuric acid is taken in excess. Hydrolysis of oxazolones (III) to unsaturated benzoylamino acids (IV), their reduction to saturated benzoylamino acids (V), and hydrogenolysis of the latter are carried out in one operation by heating a methanolic solution of the oxazolone with skeletal nickel in the presence of alkali. The yield of aliphatic $\alpha$-benzoylamino acid under these conditions is about 90%, based on the oxazolone used. Saponification of benzoylamino acids (VI) to $\alpha$-amino acid hydrohalides is carried out by heating with a mixture of $CH_3COOH$ and HBr (see (5)) or HCl. Free $\alpha$-amino acids (VII) are obtained by dissolving the hydrohalides in dilute alkali and acidifying the solution with $CH_3COOH$. In obtaining $\alpha$-benzoylamino acids by hydrogenolysis of oxazolones in the presence of alkali, the need to wash skeletal Ni free of traces of alkali, which is a very lengthy operation, is eliminated. If, instead of 2-phenyl-4-(5 -ethylthenylidene-2 )-oxazolone (III, $R = C_2H_5$, $R'$ and $R'' = H$), the $\alpha$-benzoylamino-$\beta$-(5-ethylthenyl-2)-acrylic acid formed on its saponification is used (IV, $R = C_2H_5$, $R'$ and $R'' = H$) and the hydrogenolysis is carried out in dilute ammonia, then $\alpha$-benzoylaminopelargonic acid (VI, $R = C_2H_5$, $R'$ and $R'' = H$) is obtained in only 43% yield. Thus, the one-stage process has advantages over the two-stage process also with respect to yield.

Hydrogenolysis of oxazolones in methanol, but in the absence of alkali, led to the formation in good yield of methyl esters of $\alpha$-benzoylamino acids $RCH_2CH(R')CH(R'')CH_2CH_2CH(NHCOC_6H_5)COOCH_3$ (VIII).

## Experimental Part

**2-Phenyl-4-(5 -ethylthenylidene-2 )-oxazolone** (III, $R = C_2H_5$, $R'$ and $R'' = H$). To 18.6 g (1.2 mol) of II and 8.8 g of fused anhydrous $CH_3COONa$ was added 12.0 g (1 mol) of 5-ethyl-2-thiophenaldehyde (I, $R = C_2H_5$, $R'$ and $R'' = H$). The mixture was heated for 2 h at 100°. To the solidified mass 25 ml of alcohol was added; the crystals were filtered off and washed with alcohol and ether. The precipitate was boiled with 750 ml of water. 17.7 g of oxazolone was obtained, yield 73%, m.p. 110.2–110.8° (from a mixture of benzene with hexane). Literature data (4): yield 60%, m.p. 107.5-109°. When equimolecular amounts of aldehyde and II were used, we obtained an oxazolone yield of 62%.

**2-Phenyl-4-(thenylidene-2 )-oxazolone** (III, $R, R'$ and $R'' = H$) was obtained from 2-thiophenaldehyde using an excess of II; yield 72%, m.p. 174-175°. Literature data (4): yield 68%, m.p. 174.5-175.5°.

**2-Phenyl-4-(5 -isobutylthenylidene-2 )-oxazolone** [III, $R = (CH_3)_2CHCH_2$, $R'$ and $R'' = H$], not previously described, was obtained by condensation of 5-isobutyl-2-thiophenaldehyde with a 20% excess of II. Yield 68%, m.p. 135.5-136° (from dilute alcohol).

$C_{18}H_{17}O_2NS$. Found, %: C 69.27, 69.19; H 5.32, 5.33; S 10.37, 10.47
Calculated, %: C 69.42; H 5.50; S 10.30

**$\alpha$-Benzoylamino-$\beta$-(5-ethylthenyl-2)-acrylic acid** (IV, $R = C_2H_5$, $R'$ and $R'' = H$). 34 g of 2-phenyl-4-(5 -ethylthenylidene-2 )-oxazolone was boiled to dissolution with stirring with a solution of 5.5 g NaOH in 3.5 l of water; the solution was filtered and acidified with HCl. The precipitate was filtered off and washed with water. 24.6 g of product was obtained, yield 63%, m.p. 198-200°. After recrystallization from dilute alcohol, m.p. 204-205°.

$C_{16}H_{15}O_3NS$. Found, %: C 63.88, 63.80; H 5.20, 4.99; N 4.78, 4.76; S 10.59, 10.62
Calculated, %: C 63.77; H 5.02; N 4.65; S 10.64

**$\alpha$-Benzoylamino-$\beta$-(5-isobutylthienyl-2)-acrylic acid** (IV, $R = (CH_3)_2CHCH_2$, $R'$ and $R'' = H$) was obtained analogously, but part of the oxazolone did not saponify and was filtered off. Yield 79%, mp 167-169°. After recrystallization from dilute alcohol, mp 173-173.5°.

$C_{18}H_{19}O_3NS$. Found, %: C 65.35, 65.43; H 5.77, 5.72; S 9.96, 9.78.
Calculated, %: C 65.63; H 5.81; S 9.73.

**$\alpha$-Benzoylaminopelargonic acid** (VI, $R = C_2H_5$, $R'$ and $R'' = H$). To a suspension of 12.0 g of 2-phenyl-4-(5 -ethylthienylidene-2 )oxazolone in 500 ml of hot methanol, 3.0 g of NaOH was added. To the almost colorless solution at 55-60°, about 75 g of skeletal Ni was added. Stirring at 60-65° was continued for 5 h. The solution gave a negative test for sulfur ([3]). The Ni was filtered off and washed with warm methanol. The filtrates were evaporated in vacuo. The residue was dissolved in 50 ml of 5% NaOH, the solution was filtered and acidified with dilute HCl. An oil separated, which soon crystallized. The crystals were filtered off and washed with water. Obtained 10.6 g (yield 90.5%) of a substance with mp 114-121°. After recrystallization from toluene, mp 126-127°. Literature data ([6]): mp 128°.

$C_{16}H_{23}O_3N$. Found, %: C 69.19, 69.42; H 8.18, 8.23; N 5.20, 5.07.
Calculated, %: C 69.28; H 8.36; N 5.05.

This same benzoylamino acid was obtained by hydrogenolysis of $\alpha$-benzoylamino-$\beta$-(5-ethylthienyl-2)-acrylic acid in the presence of dilute ammonia solution. Yield 43%, mp 110–118°. After recrystallization from dilute alcohol and toluene, mp 125.5–126°.

$\alpha$-**Benzoylaminoenant[h]ic acid** (VI, R, R′ and R″ = H) was obtained by hydrogenolysis of 2-phenyl-4-(thienylidene-2 )-oxazolone. Yield 88.5%, mp 132-132.5° (from dilute alcohol). Literature data ($^6$): mp 135°. A mixed sample of the substance obtained with an authentic specimen prepared earlier ($^2$) melted at 132–133°.

**2-Benzoylamino-9-methyldecanoic acid** (VI, R = $(CH_3)_2CHCH_2$, R′ and R″ = H), not described previously, was obtained by hydrogenolysis of 2-phenyl-4-(5 -isobutylthienylidene-2 )-oxazolone. Yield 87%, mp 138–140°. After recrystallization from dilute alcohol, mp 142–143°.

$C_{18}H_{27}O_3N$. Found, %: C 70.48, 70.36; H 8.60, 8.72; N 4.56, 4.56.
Calculated, %: C 70.79; H 8.91; N 4.59.

**Methyl ester of** $\alpha$-**benzoylaminopelargonic acid** (VIII, R = $C_2H_5$, R′ and R″ = H). To a solution of 12.0 g of 2-phenyl-4-(5 -ethylthienylidene-2 )-oxazolone in 600 ml of methanol at 55°, about 75 g of skeletal Ni was added. Stirring at 60–65° was continued for 8 h (until a negative reaction for S). The nickel was filtered off and washed with warm methanol. The filtrates were evaporated in vacuo. Weight of the residue 7.1 g. Yield 58%, mp 49.5–50.5° (from dilute alcohol).

$C_{17}H_{25}O_3N$. Found, %: C 69.54, 69.72; H 8.42, 8.63; N 5.02, 4.75.
Calculated, %: C 70.07; H 8.64; N 4.81.

The substance showed no depression of the melting point in a mixed sample with a specimen obtained by the action of diazomethane on $\alpha$-benzoylaminopelargonic acid.

**Methyl ester of 2-benzoylamino-9-methyldecanoic acid** (VIII, R = $(CH_3)_2CHCH_2$, R′ and R″ = H) was obtained by hydrogenolysis of 2-phenyl-4-(5 -isobutylthienylidene-2 )-oxazolone under conditions analogous to those given for the preparation of $CH_3(CH_2)_6CH(NHCOC_6H_5)COOCH_3$.

Yield 87%, mp 49–51°. After recrystallization from dilute methanol, mp 54-54.5°.

Found, %: C 71.24, 71.15; H 9.19, 9.09; N 4.37, 4.25
$C_{19}H_{29}O_3N$. Calculated, %: C 71.44; H 9.15; N 4.38

The substance showed no depression of the melting point in a mixed sample with a specimen of the methyl ester obtained by the action of diazomethane on 2-benzoylamino-9-methyldecanoic acid.

$\alpha$-**Aminopelargonic acid** (VII, R = $C_2H_5$, R′ and R″ = H). To a boiling mixture of 5.0 g of $\alpha$-benzoylaminopelargonic acid (mp 114–120°) with 100 ml of dilute (1 : 1) HCl, $CH_3COOH$ was added until a solution formed. Boiling was continued for 20 h. The solution was treated with charcoal, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 100 ml of warm water, and $C_6H_5COOH$ was extracted with benzene. The aqueous layer was alkalized with 20% NaOH, filtered, and acidified with $CH_3COOH$ to litmus. The precipitate was filtered off and washed with water. Weight 2.3 g, yield 74%, mp 257-260° (with decomposition)*. After recrystallization from dilute $CH_3COOH$, mp 278-279°. Various authors ([7,8]) report melting points for this amino acid from 236-256° to 278°.

**2-Amino-9-methyldecanoic acid** (VII, R = $(CH_3)_2CHCH_2$, R′ and R″ = H), not previously described, was obtained by saponification of 2-benzoylamino-9-methyldecanoic acid with a mixture of HBr and $CH_3COOH$. Yield 79%, mp 237-239°. After recrystallization from dilute $CH_3COOH$, mp 250-251° (with decomposition).

Found, %: C 65.40, 65.37; H 11.21, 11.27; N 6.49, 6.43
$C_{11}H_{23}O_2N$. Calculated, %: C 65.63; H 11.51; N 6.96

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* The melting points of the amino acids were determined in a sealed capillary. The melting point strongly depends on the heating rate of the apparatus.

*Note: Figure translations are in progress. See original paper for figures.*

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