498. *The Use of Thiophen as a Chain-extender. Part III.* Synthetic Amino-acids.*

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The preparation of 9-aminodecanoic, 4-aminododecanoic, 5-aminotridecanoic, 4-amino-10-methylundecanoic, 10-amino-16-methylheptadecanoic, and 4-amino-10-methyldodecanoic acid by desulphurisation of suitably substituted thiophens with Raney nickel is described. The preparation of some derivatives of these acids and some allied intermediates is also described. A route to 2-2′-thienylpyrrolidine has given a moderate yield.

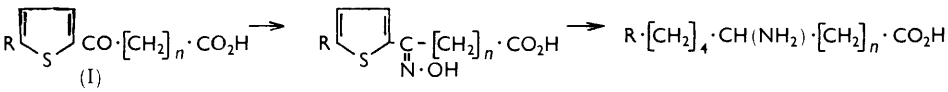
Although numerous methods of general application for the syntheses of α-amino-acids are known,[1] there are few general methods for the preparation of acids in which the amino-group is further along the chain. The desulphurisation of hydroxyimino-derivatives of thiophen keto-acids provides such a general method.

The preparation of amino-acids from thiophen derivatives has been the subject of

* Part II, *J.*, 1962, 350.

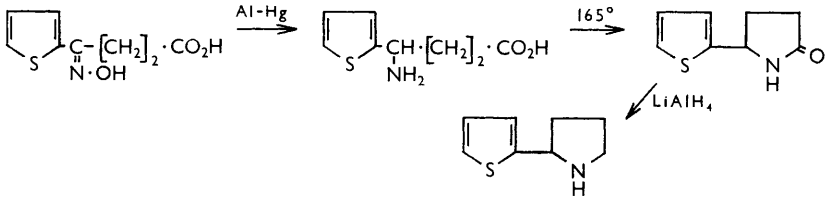
[1] Gilman, "Organic Chemistry," Wiley, New York, 1943, Vol. II. Chapter 14.

a number of communications. Gol'dfarb *et al.*[2,3] synthesised acids of general type $Me\cdot[CH_2]_3\cdot CH(NH_2)\cdot[CH_2]_n\cdot CO_2H$ where $n = 2$, 3, 4, and 7. Buu-Hoï and Sy [4] reported the synthesis of 5-aminopentanoic acid. Three possible methods for the preparation of α-amino-acids were investigated by Gol'dfarb, Fabrichnyi, and Shalavina.[5] Their first



(I)

method yielded 5-aminopentanoic acid in small yield by reduction and simultaneous ring opening of 2-nitro-5-thiophen-3-carboxylic acid. The second procedure involved the preparation of thienyl-amino-acids, and the third method consisted of simultaneous reduction of an oxime and ring opening. For the last route they gave 2-aminohexanoic acid as the only example, and in subsequent work, the thienyl-amino-acid was first prepared by reduction of the oxime with amalgamated aluminium. We have found that γ-amino-acids are obtainable in good yield by direct treatment of the thienyl-hydroxyimino-acids with Raney nickel, whereas reduction of the same compounds with amalgamated aluminium



results in poor yields of the thienyl-amino-acids. Gol'dfarb, Fabrichnyi, and Shalavina [6] have described the preparation of β-amino-acids by a somewhat different route, and also the preparation of 9-aminodecanoic acid.[7] More recently, the same workers have used 5-acyl-(2'-thenoyl)alkanoic acids as starting materials.[8]

Our first experiment was performed on γ-(5-acetyl-2-thienyl)butyric acid, which was converted into its oxime by hydroxylamine in alkaline solution. Desulphurisation yielded 9-aminodecanoic acid (45%). The technique was then applied to a group of thenoyl acids of general formula (I). Compounds where $n = 2$ readily formed oximes and were desulphurised to the corresponding amino-acids, which were characterised as their toluene-*p*-sulphonates. These amino-acids, when heated to their melting points, lost water, and cyclised to the lactam (2-substituted pyrrolidone).

The oxime of γ-(5-butyl-2-thenoyl)butyric acid (I; R = Bu, $n = 3$) was difficult to crystallise, and on desulphurisation produced a mixture of 5-aminotridecanoic acid together with its lactam. The oxime of the isobutyl analogue was an oil, which crystallised slowly during several months. No amino-acid could be isolated on desulphurisation. The oxime of 9-(5-isobutyl-2-thenoyl)nonanoic acid (I; R = Bu^i, $n = 8$) also took months to crystallise, and on desulphurisation produced a negligible yield of 10-amino-16-methyl-heptadecanoic acid. The results of these experiments are summarised in the Table.

The oximes of the butyl, isobutyl, and 2-methylbutyl acids ($n = 2$) were reduced to the corresponding thiophen amino-acids with aluminium amalgam in yields which were only 12%, 15%, and 11%, respectively. It is evident that direct simultaneous reduction and desulphurisation provides the better method in these cases.

[2] Gol'dfarb and Fabrichnyi, *Doklady Akad. Nauk S.S.S.R.*, 1955, **100**, 461.
[3] Gol'dfarb, Fabrichnyi, and Shalavina, *Doklady Akad. Nauk S.S.S.R.*, 1956, **109**, 305.
[4] Buu-Hoï and Sy, *Compt. rend.*, 1956, **242**, 2011.
[5] Gol'dfarb, Fabrichnyi, and Shalavina, *J. Gen. Chem.* (*U.S.S.R.*), 1956, **26**, 2893.
[6] Gol'dfarb, Fabrichnyi, and Shalavina, *J. Gen. Chem.* (*U.S.S.R.*), 1958, **28**, 213.
[7] Gol'dfarb, Fabrichnyi, and Shalavina, *J. Gen. Chem.* (*U.S.S.R.*), 1958, **28**, 2556.
[8] Gol'dfarb, Fabrichnyi, and Shalavina, *Zhur. obshchei Khim.*, 1959, **29**, 891.

R	Acid (I) *n*	Oxime Yield (%)	Oxime M. p.	Amino-acid Yield (%)	Amino-acid M. p.	Toluene-*p*-sulphonate monohydrate. M. p.	Cyclic lactam. M. p.
Bu	2	77	108—109°	66	165° (dec.)	110—114° 85—86 *	60—62°
	3	70	106—108	37	122—123 *	—	52
Bu^{i}	2	86	127—128	70	171 (dec.)	134	Oil
	3	†	83—85	—	—	—	—
	8	†	70—72	2	160—161 *	—	—
CHMeEt·CH_2 ...	2	77	103—104	66	165 (dec.)	121—122	32

* Anhydrous form. † Only a small portion was obtained crystalline.

The preparation of 2-2′-thienylpyrrolidine from β-2-thenoylpropionic acid oxime was carried out as shown above, the overall yield being 40%.

Experimental

The intermediates were prepared by standard methods as described in Part II.

9-*Aminodecanoic Acid.*—Acetylation of ethyl γ-thienylbutyrate (40 g.) with acetyl chloride (14 c.c.) gave, after redistillation, *ethyl γ-(5-acetyl-2-thienyl)butyrate* (31·8 g.), b. p. 168—170°/1·5 mm., n_D^{20} 1·5280 (Found: C, 60·1; H, 6·6. $C_{12}H_{16}O_3S$ requires C, 60·0; H, 6·7%). This product (25·6 g.) was added to hydroxylamine hydrochloride (7·6 g.) in 5% aqueous sodium hydroxide (60 c.c.). Ethanol (100 c.c.) was added, and the mixture heated under reflux for 15 min. Water (20 c.c.) was added, and the product kept at 0°. Next day the crude product was filtered off and recrystallised from cyclohexane (600 c.c.), giving the *hydroxyimino-ester* (15·1 g.), m. p. 57—59° (Found: C, 56·7; H, 6·2; N, 5·3. $C_{12}H_{17}NO_3S$ requires C, 56·5; H, 6·7; N, 5·5%). A further amount (3·4 g.) was obtained by repeating the reaction with recovered unchanged ketone.

This oxime (7·8 g.) was heated for 1 hr. with 2N-sodium hydroxide (50 c.c.), and the sodium salt of the product (8·2 g.), m. p. 230° (decomp.), was isolated by dilution with water and saturation with carbon dioxide. The salt was dissolved in water, and an equivalent of acetic acid (1·75 c.c.) was added. After being kept at 0° overnight, the product was filtered off and recrystallised from aqueous ethanol, giving the *oxime-acid* (5·0 g.), m. p. 116—118° (Found: C, 53·3; H, 5·7; N, 6·0. $C_{10}H_{13}NO_3S$ requires C, 52·9; H, 5·8; N, 6·2%). This oxime (2 g.) and sodium carbonate (1·0 g.) in water (30 c.c.) containing ammonia solution (*d* 0·88; 15 c.c.) were stirred with Raney nickel (15 g.) (prepared by Brown's [9] method) at 90° for 4 hr. Whilst still hot, the nickel was filtered off and washed with hot water, and the combined filtrate and washings were neutralised with acetic acid and concentrated (20 c.c.) under reduced pressure. On cooling, 9-*aminodecanoic acid* (0·7 g.) crystallised; it formed plates, m. p. 203°, from water (Found: C, 64·4; H, 11·1; N, 7·4. $C_{10}H_{21}NO_2$ requires C, 64·1; H, 11·3; N, 7·5%). The acid (0·5 g.) in N-sodium hydroxide (14 c.c.) was shaken with toluene-*p*-sulphonyl chloride (0·5 g.) in ether (14 c.c.) for 4 hr. The aqueous layer was acidified to Congo Red with hydrochloric acid, to give the *toluene*-p-*sulphonyl derivative* (0·16 g.), colourless prisms, m. p. 84° (from benzene) (Found: C, 60·2; H, 7·9; N, 4·2. $C_{17}H_{27}NO_4S$ requires C, 59·8; H, 8·0; N, 4·1%).

4-*Aminodecanoic Acid.*—β-(5-Butyl-2-thenoyl)propionic acid (5 g.) on treatment with hydroxylamine, gave the *oxime* (4·06 g.), needles, m. p. 108—109° (from aqueous ethanol) (Found: C, 56·2; H, 6·4; N, 5·2. $C_{12}H_{17}NO_3S$ requires C, 56·5; H, 6·7; N, 5·5%). Desulphurisation of this product (2 g.) in the usual way yielded colourless plates (0·84 g.) on cooling, and a further crop (0·20 g.) on neutralisation of the filtrate. Thus obtained, 4-*aminododecanoic acid monohydrate* had m. p. 165° (decomp.), which was not raised on recrystallisation from water (Found: C, 61·9; H, 11·9; N, 6·0. $C_{12}H_{27}NO_3$ requires C, 61·8; H, 11·7; N, 6·0%). The *toluene*-p-*sulphonyl derivative* crystallised as the monohydrate, m. p. 110—114° (Found: C, 59·4; H, 8·6; N, 3·5. $C_{19}H_{33}NO_5S$ requires C, 58·9; H, 8·6; N, 3·6%), and from benzene as the anhydrous *form*, m. p. 85—86° (Found: C, 62·0; H, 8·9; N, 3·6. $C_{19}H_{31}NO_4S$ requires C, 61·8; H, 8·5; N, 3·8%). The *lactam* had m. p. 60—62° when crystallised from light petroleum (b. p. 40—60°) (Found: C, 72·9; H, 11·5; N, 7·0. $C_{12}H_{23}NO$ requires C, 73·0; H, 11·8; N, 7·1%).

[9] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

5-Aminotridecanoic Acid.—γ-(5-Butyl-2-thenoyl)butyric acid (5·75 g.), on treatment with hydroxylamine as above, gave a gum which crystallised on agitation and was recrystallised from aqueous ethanol, to give the *oxime* (4·25 g.), prisms, m. p. 106—108° (Found: C, 58·2; H, 7·0; N, 4·9. $C_{13}H_{19}NO_3S$ requires C, 58·0; H, 7·1; N, 5·2%). Desulphurisation of this oxime (0·7 g.) gave a product which, after removal of the nickel, was kept at 3° for 3 days. The crystalline product which was filtered off was *6-octyl-2-piperidone*, m. p. 52° (Found: C, 73·4; H, 11·9; N, 6·3. $C_{13}H_{25}NO$ requires C, 73·9; H, 11·9; N, 6·6%). Neutralisation of the filtrate with acetic acid gave an oil, which solidified and from ethanol gave *5-aminotridecanoic acid* (0·22 g.), prisms, m. p. 122—123° (Found: C, 67·7; H, 11·5; N, 5·6. $C_{13}H_{27}NO_2$ requires C, 68·1; H, 11·9; N, 6·1%).

4-Amino-10-methylundecanoic Acid.—β-(5-Isobutyl-2-thenoyl)propionic acid (5 g.) was converted into its *oxime* (4·54 g.), needles, m. p. 127—128° (from aqueous ethanol) (Found: C, 56·5; H, 6·9; N, 5·2. $C_{12}H_{17}NO_3S$ requires C, 56·5; H, 6·7; N, 5·5%). Desulphurisation of this product (2·0 g.) yielded *4-amino-10-methylundecanoic acid monohydrate* (1·17 g.), plates, m. p. 171° (decomp.) (from water) (Found: C, 61·5; H, 11·5; N, 6·0. $C_{12}H_{27}NO_3$ requires C, 61·8; H, 11·7; N, 6·0%). The *toluene-p-sulphonyl derivative* crystallised from benzene as the monohydrate, m. p. 134° (Found: C, 59·3; H, 8·4; N, 4·0. $C_{19}H_{33}NO_5S$ requires C, 58·9; H, 8·6; N, 3·6%). The *lactam* is a liquid at room temperature (Found: C, 73·4; H, 12·0; N, 6·9. $C_{12}H_{23}NO$ requires C, 73·0; H, 11·8; N, 7·1%).

Attempted Desulphurisation of the Oxime of γ-(5-Isobutyl-2-thenoyl)butyric Acid.—Hydroxylamine hydrochloride (2·1 g.) in water (12 c.c.) was added to a solution of γ-(5-isobutyl-2-thenoyl)butyric acid (2·6 g.) in 2N-sodium hydroxide (30 c.c.), and the mixture heated under reflux for 10 hr. Dilution and acidification with hydrochloric acid gave a product (2·5 g.), m. p. 60—65°, which could not be recrystallised. A solution in dioxan was allowed to evaporate slowly; the oil which separated crystallised during 3 months. A portion was recrystallised from a large volume of light petroleum (b. p. 40—60°), to give the *oxime* as needles, m. p. 83—85° (Found: C, 58·2; H, 7·0; N, 5·1. $C_{13}H_{19}NO_3S$ requires C, 58·0; H, 7·1; N, 5·2%). No amino-acid could be isolated when this oxime was desulphurised.

10-Amino-16-methylheptadecanoic Acid.—9-(5-Isobutyl-2-thenoyl)nonanoic acid (3·45 g.) was converted by hydroxylamine into a yellow viscous oil (2·55 g.). Crystals, which appeared after several months, were recrystallised from a large volume of light petroleum (b. p. 40—60°) to yield the *oxime* as needles, m. p. 70—72° (Found: C, 64·1; H, 8·7; N, 3·9. $C_{18}H_{29}NO_3S$ requires C, 63·7; H, 8·6; N, 4·1%). On desulphurisation in the usual way this oxime (2·06 g.) yielded *10-amino-16-methylheptadecanoic acid* (0·04 g.), m. p. 160—161° (from aqueous ethanol) (Found: C, 72·5; H, 12·7; N, 4·8. $C_{18}H_{37}NO_2$ requires C, 72·2; H, 12·5; N, 4·7%).

4-Amino-10-methyldodecanoic Acid.—β-(5-2′-Methylbutyl-2-thenoyl)propionic acid (0·5 g.) on treatment with hydroxylamine gave the *oxime* (4·05 g.), m. p. 103—104°, needles from aqueous ethanol (Found: C, 57·9; H, 7·0; N, 5·3. $C_{13}H_{19}NO_3S$ requires C, 58·0; H, 7·1; N, 5·2%). Desulphurisation of this product (2·0 g.), and working up in the usual way, yielded *4-amino-10-methyldodecanoic acid monohydrate* (1·12 g.), m. p. 165° (decomp.), plates from water (Found: C, 62·9; H, 11·9; N, 5·7. $C_{13}H_{29}NO_3$ requires C, 63·1; H, 11·8; N, 5·7%). The *toluene-p-sulphonyl derivative* crystallised from benzene as the monohydrate, m. p. 121—122° (Found: C, 59·6; H, 8·6; N, 3·5. $C_{20}H_{35}NO_5S$ requires C, 59·8; H, 8·8; N, 3·5%). When the amino-acid was heated to its m. p., water was evolved. Crystallisation of the product from light petroleum (b. p. 40—60°) gave the *lactam*, m. p. 32° (Found: C, 73·5; H, 11·8; N, 6·8. $C_{13}H_{25}NO$ requires C, 73·9; H, 11·9; N, 6·6%).

2-2′-Thienylpyrrolidine.—Hydroxylamine hydrochloride (5·6 g.) in water (32 c.c.) and β-2-thenoylpropionic acid (6 g.) in 2N-sodium hydroxide (70 c.c.) were heated for 1 hr. Acidification, and crystallisation from aqueous ethanol, gave colourless needles of the oxime (5·44 g.), m. p. 137—138° (lit.,[3] 135°). This oxime (4·8 g.) was treated with aluminium amalgam (10 g.) in water (100 c.c.). Cooling was necessary at first, and after 3 hr. the whole was filtered, and the filtrate evaporated to dryness under reduced pressure. The colourless residue, which coloured on exposure to air, crystallised from aqueous ethanol, giving γ-amino-γ-2-thienylbutyric acid, needles, m. p. 166—167° (lit.,[3] 170—171°). This acid (3 g.) was heated in an open flask at 165° until evolution of water ceased. The solidified product crystallised from light petroleum (b. p. 80—100°), giving *5-2′-thienyl-2-pyrrolidone* (2·3 g.), needles, m. p. 112—113° (Found: C, 57·6; H, 5·4; N, 8·2. C_8H_9NOS requires C, 57·5; H, 5·4; N, 8·4%).

The product (1·9 g.) suspended in dry ether (150 c.c.) was slowly added, with stirring, to a

suspension of lithium aluminium hydride (0·9 g.) in dry ether (50 c.c.). Then the mixture was heated with stirring under reflux for 3 hr. Ether, saturated with water (100 c.c.), was run in slowly with cooling in ice. Water was then added, the ethereal solution was decanted from the alumina, and the dried (Na_2SO_4) ethereal solution was evaporated. Distillation of the residual oil yielded 2-2′-thienylpyrrolidine (1·3 g.), b. p. 75—77°/1·0 mm., n_D^{25} 1·5630 (Kirchner and Jones [10] give b. p. 88—89°/3 mm., n_D^{25} 1·5625). The picrate, crystallised from ethanol, had m. p. 187° (lit.,[10] 187·6°).

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Manresa Road, London, S.W.3. [*Received, February* 13*th*, 1962.]

[10] Kirchner and Jones, *J. Amer. Chem. Soc.*, 1940, **62**, 218.