Tetrahedron, 1962, Vol. 18, pp. 21 to 36. Pergamon Press Ltd. Printed in Northern Ireland

THIOPHENE AND ITS HOMOLOGUES AS STARTING COMPOUNDS FOR THE PREPARATION OF ALIPHATIC AMINO ACIDS

YA. L. GOL'DFARB, B. P. FABRICHNYĬ and I. F. SHALAVINA*

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Abstract—A method for the preparation of aliphatic amino acids from thiophene and its homologues has been developed.

The synthetic route to a variety of aliphatic amino acids involves the synthesis of the corresponding thiophene derivatives and subsequent Raney nickel reductive desulphurization. Long chain amino acids, both straight and branched, with a variable number of carbon atoms between the amino and the carboxylic groups have been prepared.

THIOPHENE is a highly reactive compound, which readily undergoes electrophilic substitution and forms metallic compounds thus providing ample opportunity for the preparation of various derivatives, which still exhibit some properties of the thiophene ring. On the other hand, a number of substituted thiophenes are apt to give sulfones, yielding nonaromatic compounds.[1] These properties, and the fact that thiophene and its homologues polymerize with ease,[2] provide new routes for synthesis and investigation, wider than those existing in the case of benzene.

Both the synthesis from thiophene and the study of other sulphur compounds were greatly facilitated by the work of Bougoult *et al.*, who were the first to show as early as 1939, Raney nickel to be an excellent desulphurizing agent and to propose it for the commercial purification of benzene from thiophene.[3] In a few years this property of nickel was applied to the structural investigation of some natural products, such as penicillin and biotin,[4] and ten years later the first application of Raney nickel to the synthesis of other compounds from thiophenes was reported.[5] More recently desulphurization of thiophene derivatives as a new method for the preparation of other compounds, predominantly aliphatic, began to attract attention of workers.†

At present the organic compounds prepared by this new method include aliphatic

* Communications should be addressed care of:–Prof. A. N. Nesmeyanov, Akademiya Nauk SSSR, Bolshaya Kaluzhskaya 14, Moscow.

† Some information on the synthesis of aliphatic compounds from thiophenes on Raney nickel desulphurization is to be found in the surveys by Venkataraman,[6] Broaty and Pallaud.[7] It should be mentioned, however, that the surveys are not quite complete, many useful methods, including those developed in our laboratory not being described.

[1] Ya. L. Gol'dfarb and M. S. Kondakova, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1131 (1952); *Chem. Abstr.* **48**, 1330 (1954); Ya. L. Gol'dfarb and M. L. Kirmalova, *Dokl. Akad. Nauk SSSR* **91**, 539 (1953); *Chem. Abstr.* **48**, 10723 (1954); J. L. Melles, *Rec. Trav. Chim.* **71**, 869 (1952).

[2] H. D. Hartough, *Thiophene and Its Derivatives* p. 165. Interscience, New York (1952).

[3] J. Bougault, E. Cattelain and P. Chabrier, *Bull. Soc. Chim. Fr.* **6**, 34 (1939); **7**, 780 (1940).

[4] Du Vigneaud, *J. Biol. Chem.* 146, 475 (1942); S. Harris, R. Mozingo, D. Wolf, A. Wilson and K. Folkers, *J. Amer. Chem. Soc.* **67**, 2102 (1945).

[5] F. F. Blicke and D. G. Sheets, *J. Amer. Chem. Soc.* **71**, 4010 (1949); D. Papa, E. Schwenk and H. Ginsberg, *J. Org. Chem.* **14**, 723 (1949).

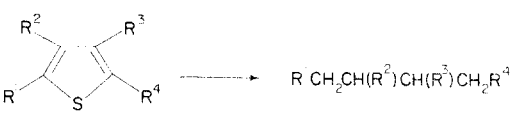
[6] K. Venkataraman, *J. Ind. Chem. Soc.* **35**, 1 (1958).

[7] M. Broaty and M. R. Pallaud, *Parf., Cos., Sav.* Vol. 2–12, 546 (1959).

hydrocarbons and alkyl benzenes,[1,8] long chain alcohols and glycols,[9] ethers,[10] ketones and acetals,[11] mono-, di- and hydroxy-carboxylic acids,[12] tertiary amines and aminoalcohols,[13] diamines,[14] macrocyclic ketones and diketones,[15] as well as many aliphatic amino acids.[16–22]

The great importance of the latter and the opportunities provided by the new method in synthetic work prompted the present survey of results obtained during 1955–1960. Experimental details are given in the references below.

The mechanism of Raney nickel–thiophene ring interaction involves the fission of the sulphur-carbon bond to yield NiS, and the hydrogenation of double bonds by hydrogen adsorbed on Raney nickel during its preparation. The process may be regarded as a reductive desulphurization which results in the formation from the thiophene ring of a substituted or unsubstituted tetramethylene group, $CH_2CH_2CH_2CH_2$, linking two hydrogen atoms in the case of thiophene itself or the respective substituents in the case of thiophene derivatives. The length and the branching of the hydrocarbon chain thus formed evidently depends on the length of the side-chain and on its position in the thiophene nucleus.



where R^1, R^2, R^3 and R^4 are hydrogen, hydrocarbon radicals, functional groups, etc.

[8] Ya. L. Gol'dfarb and I. S. Korsakova, *Dokl. Akad. Nauk SSSR* **96,** 283 (1954); *Chem. Abstr.* **49,** 5430 (1955); Ya. L. Gol'dfarb and Ya. L. Danyushevskiĭ, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1361 (1956); *Chem. Abstr.* **51,** 8065 (1957).

[9] Ya. L. Gol'dfarb and M. L. Kirmalova, *Zh. Obshchei Khim.* **25,** 1373 (1955), *Chem. Abstr.* **50,** 6422 (1956); Ya. L. Gol'dfarb and Ya. L. Danyushevskiĭ, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1361 (1956); *Chem. Abstr.* **51,** 8065 (1957); Ya. L. Gol'dfarb and P. A. Konstantinov, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 992 (1956); *Chem. Abstr.* **51,** 5041 (1957).

[10] Ya. L. Gol'dfarb and P. A. Konstantinov, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 217 (1957); *Chem. Abstr.* **51,** 10474 (1957).

[11] Ya. L. Gol'dfarb and P. A. Konstantinov, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 121 (1959); *Chem. Abstr.* **53,** 16103 (1959).

[12] Ya. L. Gol'dfarb and M. L. Kirmalova, *Zh. Obshchei Khim.* **25,** 1373 (1955), *Chem. Abstr.* **50,** 6422 (1956); *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 570 (1955); *Chem. Abstr.* **50,** 6422 (1956); *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 479 (1957); *Chem. Abstr.* **51,** 15490 (1957).

[13] Ya. L. Gol'dfarb and M. B. Ibragimova, *Dokl. Akad. Nauk SSSR*, **106,** 469 (1956), *Chem. Abstr.* **50,** 13862 (1956); *Dokl. Akad. Nauk SSSR* **113,** 594 (1957); *Chem. Abstr.* **51,** 14720 (1957).

[14] T. I. Santalova, P. A. Konstantinov and Ya. L. Gol'dfarb, *Dokl. Akad. Nauk SSSR* **131,** 1102 (1960); *Chem. Abstr.* **54,** 21103 (1960).

[15] Ya. L. Gol'dfarb, S. Z. Taĭts and L. I. Belen'kiĭ, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1262 (1957); *Chem. Abstr.* **52,** 6310 (1958); *Zh. Obshchei Chim.* **29,** 3564 (1959), *Chim. Abstr.* **54,** 19639 (1960); S. Z. Taĭts and Ya. L. Gol'dfarb, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1698 (1960).

[16] Ya. L. Gol'dfarb, B. P. Fabrichnyĭ and I. F. Shalavina, *Dokl. Akad. Nauk SSSR* **100,** 461 (1955); *Chem Abstr.* **49,** 8244; *Zh. Obshchei Khim.* **26,** 2595 (1956); *Chem. Abstr.* **51,** 4043 (1957).

[17] Ya. L. Gol'dfarb, B. P. Fabrichnyĭ and I. F. Shalavina, *Zh. Obshchei Khim.* **28,** 213 (1958), *Chem. Abstr.* **52,** 12838.

[18] Ya. L. Gol'dfarb, B. P. Fabrichnyĭ and I. F. Shalavina, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1276 (1956); *Chem. Abstr.* **51,** 5702 (1957).

[19] Ya. L. Gol'dfarb, B. P. Fabrichnyi and I. F. Shalavina, *Zh. Obshchei Khim.* **26,** 2595 (1956); *Chem. Abstr.* **51,** 4943 (1957); *Dokl. Akad. Nauk SSSR* **109,** 305 (1956); *Chem. Abstr.* **51,** 1839 (1957); *Zh. Obshchei Khim.* **29,** 891 (1959), *Chem. Abstr.* **54,** 1483 (1960).

[20] Ya. L. Gol'dfarb, B. P. Fabrichnyĭ and I. F. Shalavina, *Zh. Obshchei Khim.* **28,** 2520 (1958); *Chem. Abstr.* **53,** 3052 (1959).

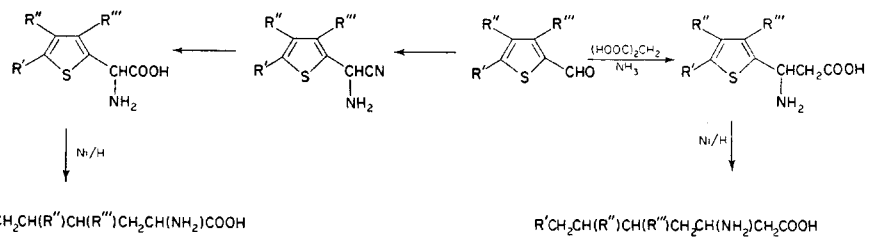
[21] Ya. L. Gol'dfarb, M. M. Polonskaya, B. P. Fabrichnyĭ and I. F. Shalavina, *Dokl. Akad. Nauk SSSR* **126,** 86 (1959), 21872 (1959).

[22] Ya. L. Gol'dfarb, B. P. Fabrichnyĭ and I. F. Shalavina, *Zh. Obshchei Khim.* **29,** 3636 (1959); *Chem. Abstr.* **54,** 19638 (1960).

Thus the synthesis of compounds with long chains, both straight and branched from thiophene, dithienylmethanes as well as from other thiophene systems is evident. For the preparation of aliphatic amino acids from thiophene derivatives various synthetic routes are presented.

Scheme A

The synthesis of thienyl amino acids having both functional groups in the side chain, from the respective aldehydes with subsequent Raney nickel treatment:

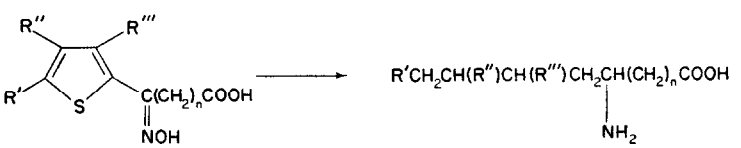


where R′, R″ and R‴ are H, or hydrocarbon radicals.

In this way α- and β-amino acids with both straight and branched chains may be synthesized. The branched chain acids are obtained when R″ and R‴ are hydrocarbon radicals, or when the aldehyde group is in β-position of the thiophene ring.

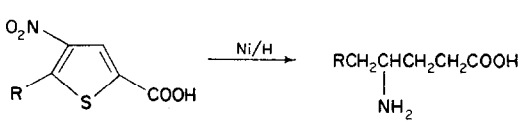
Scheme B

Synthesis of oximino acids with a variable number of carbon atoms between functional groups from respective ketocarboxylic acids with subsequent Raney nickel desulphurization:



Scheme C

Introduction of two functional groups, such as the carboxylic and the nitro group into the ring, the nitro group being reduced during the fission of the thiophene ring by Raney nickel:



By this method starting from compounds containing only one thiophene ring the β-, γ- or δ-amino acids may be obtained.

The results of experiments are listed in Tables 1–7. In Table 1 α-amino acids prepared according to Scheme A are described, including branched-chain α-amino-β-ethyl-caproic acid; its synthesis being as follows:

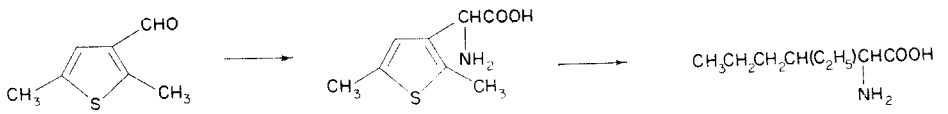
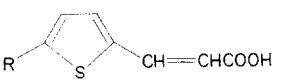
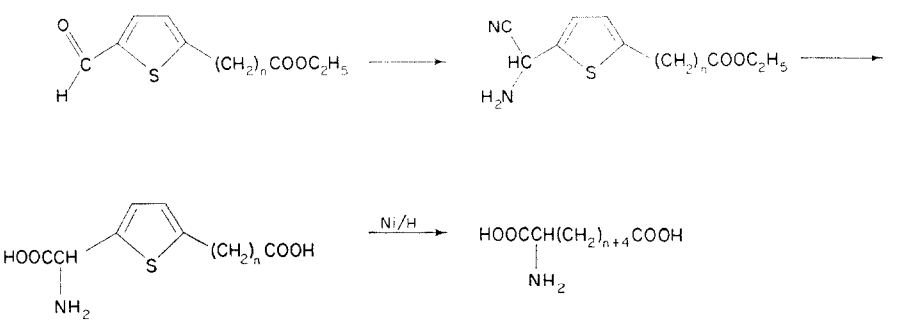


Table 2 summarizes β-amino acids prepared as shown in Scheme A, by reductive desulphurization of β-(2-thienyl)-β-aminopropionic acids, synthesized in their turn by the Rodionov method. The yields usually did not exceed 40 per cent, which is partly due to the formation of thienylacrylic acids as side products:



The latter have been isolated in every case when thiophene aldehydes were condensed with malonic acid. It follows from Table 2, that in Raney nickel desulphurization of β-(2-thienyl)-β-aminopropionic acids the yields of amino acids are not always satisfactory. The reason for the different effect of Raney nickel on acids of similar structure is still obscure. In this connection the following observation seems to be important: if at this stage of reaction the unsubstituted amino acids are replaced by their acetyl derivatives, the yields of the final products increase considerably. This favourable effect of the acylation of amino acids on the subsequent reductive desulphurization was confirmed in experiments with other types of amino acids.

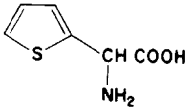
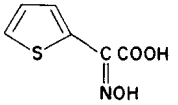
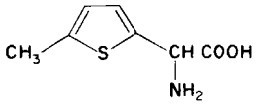
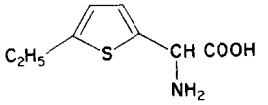
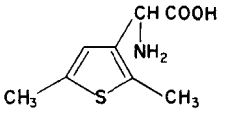
Presented below is the synthesis of two aminodicarboxylic acids which do not differ essentially from that already described for the α-amino acids:



Acids of the same type have been obtained by Raney nickel desulphurization of the respective oximinodicarboxylic acids (Scheme B), the last stage of the reaction proceeding with a good yield (see Table 3).

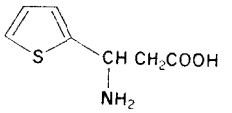
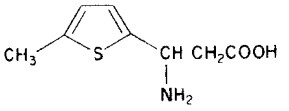
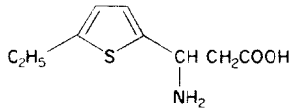
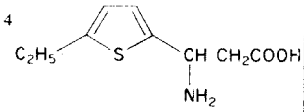
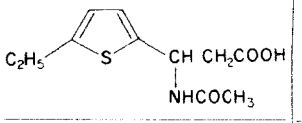
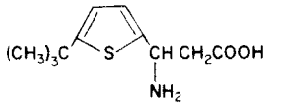
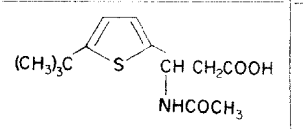
Possible applications of the reductive desulphurization method to oximino acids described above are presented in more detail in Table 4, where amino acids prepared by this method are arranged in order of an increasing number of methylene groups between the amino and the carboxylic groups. This number can be large if thiophene is acylated by a long chain acid chloride (4 and 7). The same results may be achieved,

TABLE 1

	Starting compound of the thiophene series	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1		α-aminocaproic acid $CH_3(CH_2)_3CH(NH_2)COOH$	275–277[a]	59	benzoyl deriv., 132[b]	16
2		α-aminocaproic acid $CH_3(CH_2)_3CH(NH_2)COOH$	273–274[a]	50	benzoyl deriv., 132[b]	16
3		α-aminoenanthic acid $CH_3(CH_2)_4CH(NH_2)COOH$	279–280[c]	53	benzoyl deriv., 133–134[d]	16
4		α-aminocaprylic acid $CH_3(CH_2)_5CH(NH_2)COOH$	270–271[e]	41	benzoyl deriv., 125–126[f]	16
5		α-amino-β-ethylcaproic acid $CH_3CH_2CH_2CH(C_2H_5)CH(NH_2)COOH$	244–246	51	*p*-toluenesulphonyl deriv., 105·5–107	16

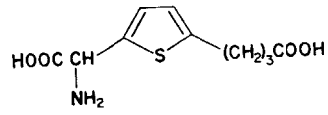
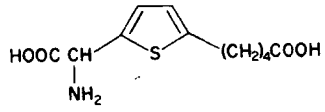
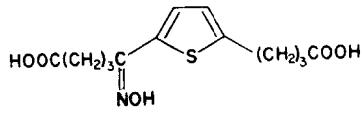
[a] The melting point reported by different authors varies from 273° to 327° see e.g. H. Kudielka, *Monatsh.* **29**, 353 (1908); M. S. Dunn, T. W. Brophy, *J. Biol. Chem.* **99**, 221 (1932); A. Darapsky, *J. Pr. Chem.* **146**, 219 (1936).
[b] m.p. 134°. E. Fischer, *Ber. Dtsch. Chem. Ges.* **33**, 2382 (1900).
[c] m.p. 281°. N. F. Albertson, *J. Amer. Chem. Soc.* **68**, 450 (1946).
[d] m.p. 135°. H. Kudielka, *Monatsh.* **29**, 353 (1908).
[e] m.p. 270°. N. F. Albertson, *J. Amer. Chem. Soc.* **68**, 450 (1946).
[f] m.p. 128°. N. F. Albertson, *J. Amer. Chem. Soc.* **68**, 450 (1946).

TABLE 2

Starting compound of the thiophene series	Intermediate	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1 		β-aminoenanthic acid $CH_3(CH_2)_3CHCH_2COOH$ | NH_2	201–202	79	HCl salt 115–116; acetyl deriv 74·5–76; *p*-toluene sulphonyl deriv. 94–95; 4-butyldihydrouracil 168	17
2 		β-aminocaprylic acid $CH_3(CH_2)_4CHCH_2COOH$ | NH_2	202–204[a]	low	4-amyldihydrouracil 181–182[b]	17
3 		β-aminopelargonic acid $CH_3(CH_2)_5CHCH_2COOH$ | NH_2	205[c]	low	4-hexyldihydrouracil, 185–186	17
4 		β-acetamidopelargonic acid $CH_3(CH_2)_5CHCH_2COOH$ | $NHCOCH_3$	99–105	77·5		17
5 		β-acetamido-θ, θ-dimethyl-pelargonic acid $CH_3C(CH_3)_2(CH_2)_4CHCH_2COOH$ ↓ H_2O | $NHCOCH_3$	111–112	55		17
6		β-amino-θ, θ-dimethyl-pelargonic acid $CH_3C(CH_3)_2(CH_2)_4CHCH_2COOH$ | NH_2	197–198		HCl salt 195–196	17

[a] m.p. 204–206°. K. Lang, F. Adikes, *Z. physiol. Chem.* **269**, 236 (1941).
[b] m.p. 182–184°. K. Lang, F. Adikes, *Z. physiol. Chem.* **269**, 236 (1941).
[c] m.p. 205–206°. V. M. Rodionov and V. K. Zorrykina, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 216 (1943).

TABLE 3

Starting compound of the thiophene series	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1 	α-aminosebacic acid $HOOCCH(CH_2)_7COOH$ | NH_2	233–234[a]	83	*p*-toluenesulphonyl deriv. 94–95; HCl salt, 156–158	18
2 	α-amino-1,9-nonanedicarboxylic acid $HOOC\,CH(CH_2)_8COOH$ | NH_2	226–228	78	HCl salt, 149–151	18
3 	δ-aminobrassylic acid $HOOC(CH_2)_3CH(CH_2)_7COOH$ | NH_2	139·5–140	63	*p*-toluenesulphonyl deriv. 114–115, HCl salt, 143–145	18

[a] m.p. 228° W. Treibs, H. Reinheckel, *Chem. Ber.* **89**, 51 (1956).

TABLE 4

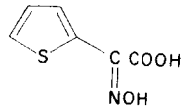
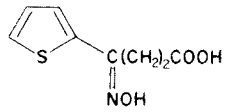
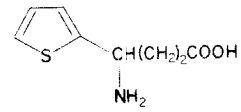
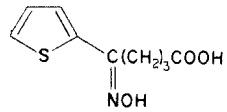
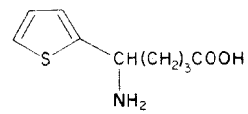
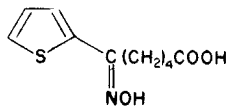
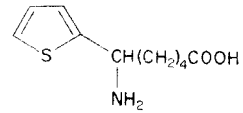
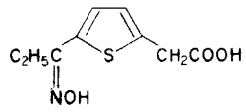
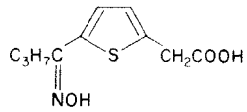
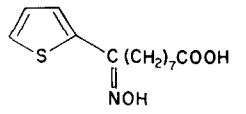
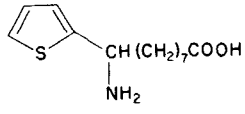
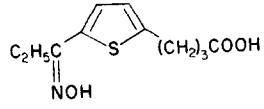
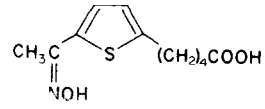
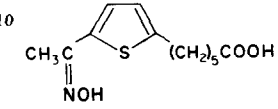
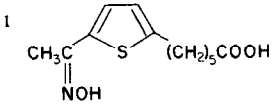
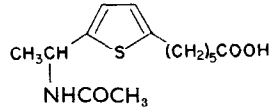
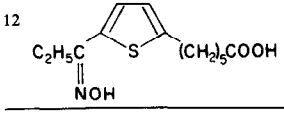
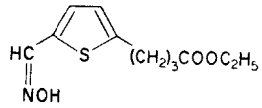
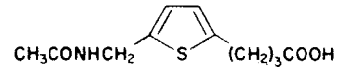
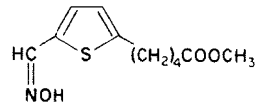
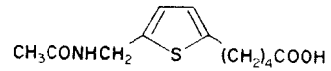
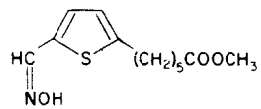
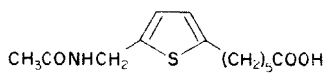
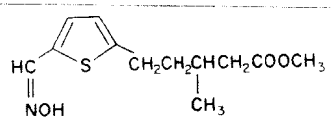
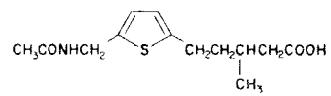
	Starting compound of the thiophene series	Intermediate	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1			α-aminocaproic acid $CH_3(CH_2)_3CH(NH_2)COOH$	273–274[a]	50	benzoyl deriv. 132[b]	16
2			ζ-aminocaprylic acid $CH_3(CH_2)_3CHCH_2CH_2COOH$ NH_2	147–149	73	*p*-toluenesulfonyl deriv. 99–100	19
3			δ-aminopelargonic acid $CH_3(CH_2)_3CH(CH_2)_3COOH$ NH_2	129–129·5	53	*p*-toluenesulphonyl deriv. 96·5–98	19
4			ε-aminocapric acid $CH_3(CH_2)_3CH(CH_2)_1COOH$ NH_2	190·5–192	40	*p*-toluenesulphonyl deriv. 98–98·5	19
5			ζ-aminopelargonic acid $CH_3CH_2CH(CH_2)_5COOH$ NH_2	167–168	50	benzoyl deriv 112–113·5	24
6			ζ-aminocapric acid $CH_3CH_2CH_2CH(CH_2)_5COOH$ NH_2	149–150	52	*p*-toluenesulphonyl deriv. 91·5–93	24

TABLE 4 (*continued*)

7			θ-aminotridecanoic acid $CH_3(CH_2)_3CH(CH_2)_7COOH$ NH_2	127–129	47	*p*-toluenesulphony deriv. 58–59	19
8			9-aminoundecanoic acid $CH_3CH_2CH(CH_2)_7COOH$ NH_2	166–168	50	HCl salt, 131–132	19
9			10-aminoundecanoic acid $CH_3CH(CH_2)_8COOH$ NH_2	185–186[c]	40	HCl salt, 152–153; acetyl deriv. 94–95; benzenesulphonyl deriv. 126–127[d]	19
10			11-aminolauric acid $CH_3CH(CH_2)_9COOH$ NH_2	199–200	49	HCl salt, 125·5–126·5	19
11			11-acetamidolauric acid $CH_3CH(CH_2)_9COOH$ $NHCOCH_3$	94–95	43·5		19
12			11-aminotridecanoic acid $CH_3CH_2CH(CH_2)_9COOH$ NH_2	162·5–164	24	HCl salt, 139–140	

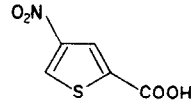
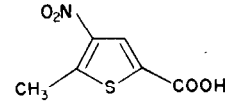
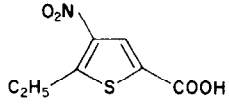
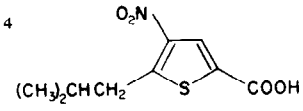
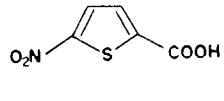
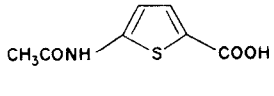
[a] The melting point reported by different authors varies from 273° to 327°. See e.g. H. Kudielka, *Monatsh.* **29**, 353 (1908); M. S. Dunn and T. W. Brophy, *J. Biol. Chem.* **99**, 221 (1932); A. Darapsky, *J. Prakt. Chem.* **146**, 219 (1936).
[b] m.p. 134° E. Fischer, *Ber. Dtsch. Chem. Ges.* **33**, 2382 (1900).
[c] m.p. 186–187°. R. Aelion and G. Champatier, *C.r.* **225**, 631 (1946); m.p. 186° B. Flachenträger and F. Halle, *Z. physiol. Chem.* **159**, 289 (1926).
[d] m.p. 126–127° B. Flachenträger and F. Halle, *Z. physiol. Chem.* **159**, 289 (1926).

TABLE 5

	Starting compound of the thiophene series	Intermediate	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1			9-acetamidopelargonic acid $CH_3CONH(CH_2)_8COOH$ ↓ H_2O	71–72	83·5		20
2			9-aminopelargonic acid $H_2N(CH_2)_8COOH$	185–186[a]		HCl salt, 132–133[b]	20
3			10-acetamidocapric acid $CH_3CONH(CH_2)_9COOH$ ↓ H_2O	120–121	72		20
4			10-aminocapric acid $H_2N(CH_2)_9COOH$	185–187[c]		HCl salt, 157–159	20
5			11-acetamidoundecanoic acid $CH_3CONH(CH_2)_{10}COOH$ ↓ H_2O	83–84	65		20
6			11-aminoundecanoic acid $H_2N(CH_2)_{10}COOH$	184–186[d]		HCl salt, 144–145	20
7			10-acetamido-3-methylcapric acid $CH_3CONH(CH_2)_7CHCH_2COOH$ ↓ H_2O CH_3	74–75	62		20
8			10-amino-3-methylcapric acid $H_2N(CH_2)_7CHCH_2COOH$ CH_3	178–179		HCl salt, 83–84	20

[a] m.p. 177°, 186–187° Fr. pat. 988699, *Chem. Abstr.* **50**, 10764 (1956); W. Treibs and S. Hauptmann, *Chem. Ber.* **89**, 117 (1956).
[b] m.p. 115°, 128–129°, 130–133° E. Votocek and V. Prelog, *Coll. Czech. Chem. Comm.* **1**, 55 (1929); W. Treibs and S. Hauptmann, *Chem. Ber.* **89**, 117 (1956). D. D. Coffman, N. L. Cox, E. L. Martin, W. E. Mochel and F. J. van Natta, *J. Polymer Sci.* **3**, 85 (1948).
[c] m.p. 185–186°. D. D. Coffman, N. L. Cox, E. L. Martin, W. E. Mochel and F. J. van Natta, *J. Polymer Sci.* **3**, 85 (1948).
[d] m.p. 186–187°. D. D. Coffman, N. L. Cox, E. L. Martin, W. E. Mochel and F. J. van Natta, *J. Polymer Sci.* **3**, 85. (1948).

TABLE 6

	Starting compound of the thiophene series	Intermediate	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1			γ-aminovaleric acid $CH_3CHCH_2CH_2COOH$ (NH$_2$)	206–207[a]	72	benzoyl deriv. 131–133[b]	22
2			γ-aminocaproic acid $CH_3CH_2CHCH_2CH_2COOH$ (NH$_2$)	181–182[c]	76	benzoyl deriv. 143·5–144·5[d]	22
3			γ-aminoenanthic acid $CH_3CH_2CH_2CHCH_2CH_2COOH$ (NH$_2$)	161–161·5	46	benzoyl deriv. 126–127	22
4			γ-amino-ζ-methylcaprylic acid $CH_3CH(CH_3)CH_2CH_2CHCH_2CH_2COOH$ (NH$_2$)	173 174	84	benzoyl deriv. 117–119; HCl salt, 155–156	22
5			δ-acetamidovaleric acid $CH_3CONH(CH_2)_4COOH$ ($\downarrow -H_2O$)	72–73	96		21
6			δ-aminovaleric acid $H_2N(CH_2)_4COOH$			HCl salt, 85–87[e] benzoyl deriv. 103–106[f]	21

[a] m.p. 193°, 214° J. Tafel, *Ber. Dtsch. Chem. Ges.* **19**, 2414 (1886); E. Fischer and R. Groh, *Liebigs. Ann.* **383**, 368 (1911).
[b] m.p. 132, 133° L. Senfter and J. Tafel, *Ber. Dtsch. Chem. Ges.* **27**, 2313 (1894); E. Fischer and R. Groh, *Liebigs. Ann.* **383**, 368 (1911).
[c] m.p. 180–181°, 187° A. Müller and E. Feld, *Manatsh.* **58**, 22 (1931); A. A. Strepikheev, S. M. Skuratov, S. M. Shtekher, R. S. Muromova, E. P. Brykina and O. N. Kachinskaya, *Dokl. Akad. Nauk SSSR* **102**, 543 (1955).
[d] m.p. 146·5–147° A. Müller and E. Feld, *Monatsh.* **58**, 22 (1931).
[e] m.p. 84–86° C. Rath, *Liebigs Ann.* **489**, 107 (1931).
[f] m.p. 106–107° O. Wallach, *Liebigs. Ann.* **312**, 180 (1900).

TABLE 7

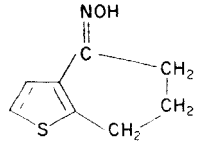
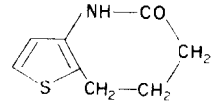
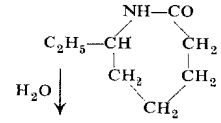
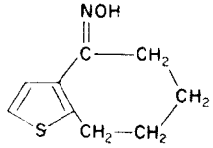
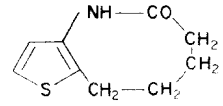
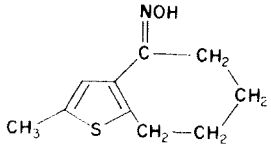
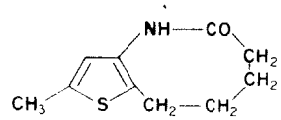
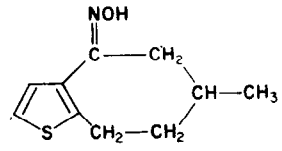
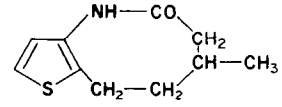
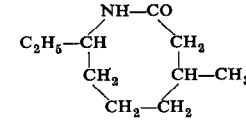
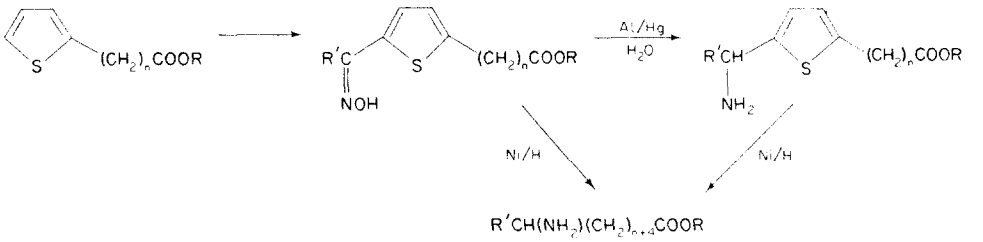
	Starting compound of the thiophene series	Intermediate	Aliphatic amino acid	m.p. °C	Yield, per cent	Derivative, m.p. °C	References
1			ε-ethyl-ε-caprolactam 	90·5–91[a]	82		24
2			ε-aminocaprilic acid $CH_3CH_2CH(CH_2)_4COOH$ NH_2	187–188[b]	74	*p*-toluenesulphonyl deriv. 103–104·5	24
3			ζ-ethyl-ζ-enantholactam*	49–50·5	87		24
4			ζ-propyl-ζ-enantholactam+	23	78		24

TABLE 7 (*continued*)

5			3-methyl-7-ethylenantholactam 	81·5–82·5	73		24
6			ζ-amino-β-methylpelargonic acid $CH_3CH_2CH(CH_2)_3CHCH_2COOH$ (NH$_2$, CH$_3$)	164–165	83	*p*-toluenesulfonyl deriv. 71–72·5	24

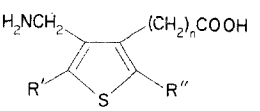
* The lactam was hydrolysed to give ζ-aminopelargonic acid, identical with that listed in Table 4, No. 5.
† The lactam was hydrolysed to give ζ-aminocapric acid identical with that listed in Table 4, No. 6.
[a] m.p. 93·1–93·3° F. Somlo, G. Lemetre, U. Giolitti, A. Mirabini and S. Pierucci, *Chim. & Ind. (Milan)* **39**, 905 (1957).
[b] m.p. 191–192° H. Shechter and J. C. Kirk, *J. Amer. Chem. Soc.* 73 3087 (1951)

in the case of compounds with a short chain in the 2-position of the thiophene ring by introducing the carbonyl group into 5-position. In this manner the length of the chain between the amino and the carboxylic group can be increased by four units (see Table 4, 5, 6, 8). This modification of Scheme B is represented below. The

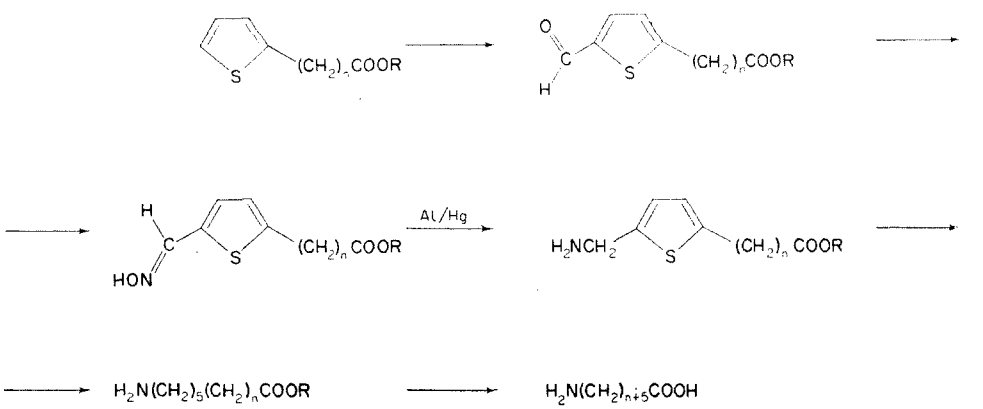


oximino acid is usually converted to the aliphatic acid by heating with Raney nickel, the double bonds being hydrogenated and the oximino group being reduced to the amino group simultaneously in the course of desulphurization. In order to obtain better yields of the final product, the following course has proved to be more effective. The reduction of the oximino acid to the amino acid, which still contains the thiophene ring, by amalgamated aluminium in dilute alcohol, with the subsequent fission of the ring in the amino acid or in its acetyl derivative.

Using in this case, as well as in others, 2-thienyl-alcanoic acids as starting compounds, some long chain ω-amino acids, both straight and branched, with an even or odd number of C-atoms (see Table 5) were prepared. The example chosen (Table 5, 8) illustrates the introduction of the substituent, which gives rise to branching upon the acylation of thiophene by β-methyl-γ-carbomethoxybutyrylchloride. As other possible starting compounds for the preparation of branched amino acids, β-substituted amino acids of the thiophene series may be used, for instance:



The following scheme represents the synthesis of ω-amino acids mentioned above

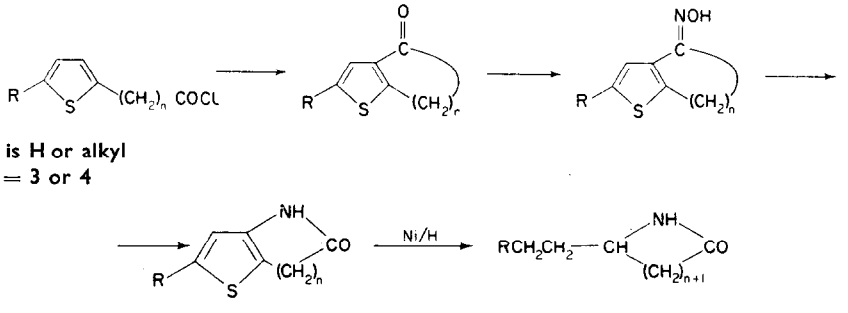


At first it was considered that Scheme C would be the simplest for the preparation

of amino acids from thiophene. However, the attempted desulphurization of 5-nitro-2-thiophenecarboxylic acid by Raney nickel provided only a small yield of δ-amino-valeric acid. An attempt to increase the yield was made by using acetic anhydride as medium, since it was observed that an acetylamino acid undergoes fission more smoothly than an amino acid. Under these conditions the intermediate thiophene-carboxylic acid was expected to form the more stable 5-acetylamino-2-thiophene-carboxylic acid. However, from the reaction mixture obtained by the Raney nickel treatment only the latter acid and not its desulphurization product was isolated.[21] Since the Raney nickel desulphurization of 5-acetylamino-2-thiophenecarboxylic acid in water usually yields the expected δ-acetylaminovaleric acid,[23] it was apparent that acetic anhydride de-activates Raney nickel.[21] This was confirmed in other cases and if necessary such a method may be used to terminate the reaction at any stage.

The fact, that 5-amino-2-thiophenecarboxylic acid was found unstable under the conditions of reductive desulphurization does not indicate the instability of the isomeric 4-amino acid, the reactivity of thiophene derivatives being known to change considerably when the functional group is shifted from the α- to the β-position. Actually the Raney nickel desulphurization of 4-nitro-2-thiophenecarboxylic acid in aqueous media furnished the expected γ-aminovaleric acid in good yield. Similar results have been obtained with other 4-nitro acids (see Table 6). Evidently amino acids with longer chains, both straight and branched, may be prepared by this simple method, using thiophene compounds with various radicals in the 2-position of the ring.

Under the conditions of Raney nickel desulphurization of thiophene derivatives the amide bond proved to be completely stable. Consequently, the method described above was applied to the preparation of C-substituted lactams,[24] particularly to that of eight-membered C-substituted ζ-enantholactams, which have not been reported in the literature. The study of compounds of this type can considerably contribute to the knowledge of polycondensation reactions. Presented below is the outline of the synthetic method chosen:



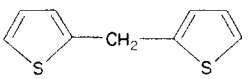
The intermolecular acylation being the first stage of reaction yielded about 80 per cent in every case investigated. No difficulties were encountered during the oximation and the Beckmann rearrangement, as well as during Raney nickel desulphurization, which proceeded with good yields (see Table 7). The structures of the final ε- and ζ-lactams were confirmed by hydrolysis, to yield ζ-amino-pelargonic

[23] N. P. Buu-Hoi and M. Sy, *C. R. Acad. Sci., Paris*, **242**, 2011 (1956).

[24] Ya. L. Gol'dfarb, B. P. Fabrichnyĭ and I. F. Shalavina, *Zh. Obshchei Khim.* **31**, 315 (1961).

and ε-aminocapric acid, which were also prepared by other methods (see Table 4), as well as ε-aminocaprylic acid, reported earlier in the literature.

Although some acids prepared by this method could be obtained more easily in other ways, examples were needed to demonstrate the identity of the acids prepared by the new method. On the other hand, it will be seen from the Tables that reductive desulphurization permits the synthesis of a vast variety of amino acids, which are difficult or practically impossible to prepare by any of the methods previously reported. The data does not cover the wide range of amino acids, varying both in type and in chain length. In this connection di-(2-thienyl)-methane may be mentioned and appears



to be a promising starting compound for the synthesis of new amino acids. It is readily available and already has been used for the preparation of carboxylic acids, alcohols, etc.

It is the simplicity of the operations and wide applicability that render the method extremely valuable. Indeed the treatment with Raney nickel is usually carried out in methyl or ethyl alcohol or in aqueous media at 60–70°, while nickel may be easily recovered from the worked-up Raney catalyst by quite simple operations with insignificant losses. As regards thiophene it is now being produced in the United States on a large scale, using sulphur and C_4-hydrocarbons from petroleum as raw materials. In due course thiophene and its homologues may be widely used for the synthesis of compounds of other series.