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The Synthesis and The Configuration of 3-Aminotetrahydrothiophene-3-carboxylic Acids

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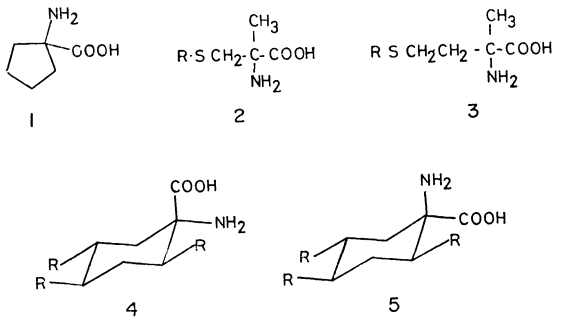
Several monomethylsubstituted 3-aminotetrahydrothiophene-3-carboxylic acids have been synthesized from the corresponding 3-ketotetrahydrothiophenes by the Strecker and the Bucherer-Bergs syntheses. In each case, the former synthesis leads to one stereoisomer, and the latter, to the opposite stereoisomer. The configurations of 3-amino-2-methyltetrahydrothiophene-3-carboxylic acids have been determined by a study of the NMR spectra; the others have been estimated on the basis of these results. The configurations do not contradict those first assigned to the alkyl substituted 1-amino-1-cyclohexanecarboxylic acids.

The anticancer activity of 1-amino-1-cyclopentanecarboxylic acid (**1**) was first described by Connors *et al.*,[1] and since then several alicyclic α-amino acids have been synthesized from their biological point of view.[2] This paper will deal with the syntheses of 3-aminotetrahydrothiophene-3-carboxylic acids as heterocyclic analogs of **1**. Our interest in these compounds also arises from the fact that some derivatives of DL-α-methylcysteine (**2**) and DL-α-methylethionine (**3**) promote tumor growth.[3]

Munday[4] and Brimelow *et al.*[5] reported that alkylsubstituted cyclohexanones yield, stereospecifically, different isomers of the corresponding α-amino acids, depending on the method of preparation (*i. e.*, the Strecker and the Bucherer-Bergs syntheses). Although their configurations were first assigned by Munday[4] to be **4** for the Strecker products and **5** for the Bucherer products, Cremlyn *et al.*[6] recently reported the opposite assignment. Thus, the configurational assignment remains equivocal because of the absence of conclusive proof.



We attempted both the Strecker and the Bucherer-Bergs syntheses for monomethylsubstituted 3-ketotetrahydrothiophenes. The elucidation of the stereoisomerisms of the two methods in this series is another

1) T. A. Connors and L. A. Elson, *Biochem. Pharmacol.*, **1**, 239 (1958).

2) T. A. Connors, L. A. Elson, A. Haddow, and W. C. J. Ross, *ibid.*, **5**, 108 (1960); A. B. Mauger and W. C. J. Ross, *ibid.*, **11**, 847 (1962); S. Aaronson and B. Bensky, *ibid.*, **11**, 983 (1962); P. Tailleur and L. Berlinguet, *Can. J. Chem.*, **40**, 2214 (1962).

3) G. E. W. Wolstenholme and C. M. O'Connor (Editors). "Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity," (1958), p. 99.

4) L. Munday, *J. Chem. Soc.*, **1961**, 4372.

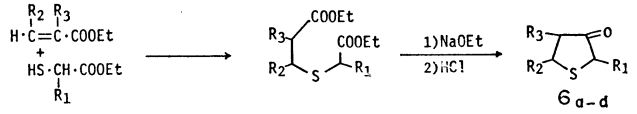
5) H. C. Brimelow, H. C. Carrington, C. H. Vasey, and W. S. Waring, *ibid.*, **1962**, 2789.

6) R. J. W. Cremlyn and M. Chisholm, *J. Chem. Soc., C*, **1967**, 2269; R. J. W. Cremlyn, R. M. Ellam, and T. K. Mitra, *Indian J. Chem.*, **8**, 219 (1970); *J. Chem. Soc., C*, **1971**, 1647.

purpose of the present paper.

Results and Discussion

Synthesis. The starting materials, 2-, 4-, and 5-methyl-3-ketotetrahydrothiophenes (**6b–d**, Table 1), were prepared in good yields by means of a modification of the method used by Woodward *et al.*[7] for the synthesis of 3-ketotetrahydrothiophene (**6a**) (Scheme 1).



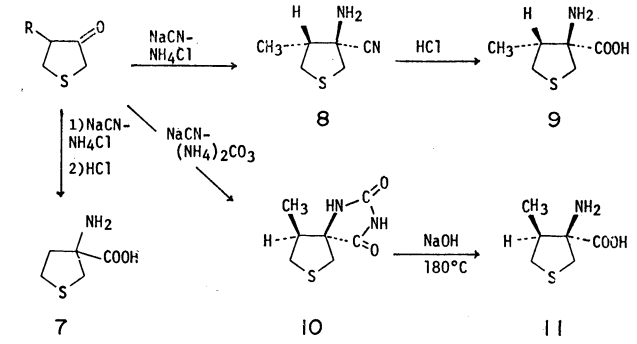
Scheme 1.

Table 1. 3-Ketotetrahydrothiophenes

No	Compound R_1	R_2	R_3	Bp °C/mmHg	Yield[a] %	IR[b] $\nu_{C=O}$
6a	H	H	H	73—75/16[c]	72[c]	1738
6b	CH_3	H	H	77—84/18	85	1737
6c	H	CH_3	H	77—82/17	77.5	1737
6d	H	H	CH_3	69—70/15	75	1740

a) Based on the mole of ethyl thioglycolate or ethyl thiolactate. b) All spectra were measured in liquid film state. c) Ref. 7: bp 74.5 °C/15 mmHg; 30% yield.

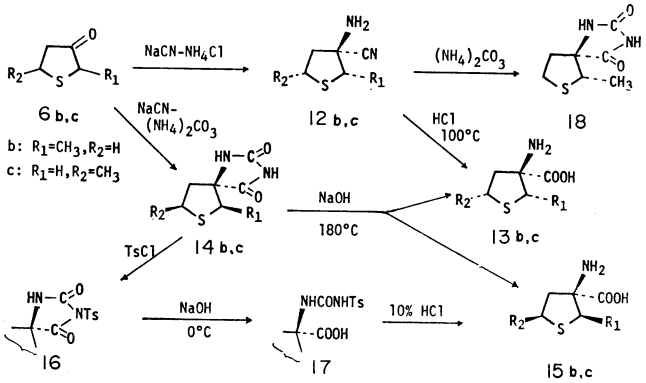
The Strecker reaction with 3-ketotetrahydrothiophene (**6a**) gave a 45% yield of 3-aminotetrahydrothiophene-3-carboxylic acid (**7**), in which case the hydrolysis of the intermediate amino nitrile was conducted by heating it with refluxing 20% hydrochloric acid for 12 hours. However, in the Strecker reaction with the 4-methyl ketone (**6d**) the hydrolysis of the amino nitrile (**8**) under similar conditions produced mainly the corresponding amide; prolonged heating for 2 days was required to give the amino acid (**9**). This resistance to hydrolysis seems to be attributable to the steric effect of the adjacent 4-methyl group. The Bucherer-Bergs reaction with the 4-methyl ketone (**6d**) afforded a 74% yield of the hydantoin (**10**) which was then hydrolyzed by heating with aqueous alkali in an autoclave at 180 °C for 30 hours to produce the amino acid (**11**).



Scheme 2.

The resulting amino acids (**9** and **11**) were indistinguishable from each other by their melting points or by their R_f values upon paper chromatography, but the NMR spectra (Table 2) of their hydrochlorides were obviously different, especially in the signals due to the 4-methyl protons; **9** showed at 1.05 ppm and **11** at 1.15 ppm. Thus, it is apparent that the Strecker product **9** (called the α-form) and the Bucherer product **11** (the β-form) are stereoisomers.

Although the 2-methyl ketone (**6b**) similarly yielded the α-isomer (**13b**) *via* the Strecker reaction, the Bucherer reaction with **6b** followed by the alkaline cleavage of the resulting hydantoin (**14b**) gave a mixture (1 : 1 ratio, on the basis of the signals of the 2-methyl protons in its NMR spectrum) of the isomeric amino acids (**13b** and **15b**). Comparable results were also obtained in the case of the 5-methyl ketone (**6c**); the Strecker reaction gave the α-isomer (**13c**) while the Bucherer reaction produced a 1 : 1 mixture of **13c** and **15c**. This implies that the alkali-induced epimerization of the 2-methyl or the 5-methyl group, occupying the carbon atom adjacent to the sulfur atom, took place *via* carbanion formation during the hydrolysis of the hydantoin. The NMR spectra of the hydantoins (**14b** and **14c**) displayed sharp doublets due to the methyl protons at 1.08 and 1.28 ppm respectively, indicating that they are single isomers. Indeed, when Strecker's amino nitrile (**12b**) was treated with ammonium carbonate, the resulting hydantoin (**18**) was proved by a comparison of the NMR spectra to be isomeric with Bucherer's (**14b**). Therefore, the milder hydrolysis developed by Yamada *et al.*[8] was used for the Bucherer hydantoins (**14b** and **14c**); they were treated with *p*-toluenesulfonyl chloride to form the monotosylates (**16**). The treatment of **16** with cold aqueous alkali followed by the heating of the resulting hydantoic acids (**17**) with 10% hydrochloric acid afforded the desired amino acids (β-isomers), **15b** and **15c** respectively. These amino acids displayed NMR spectra different from those of the corresponding Strecker amino acids (Table 2).



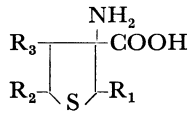
Scheme 3.

In all cases, the stereospecificities of both methods were determined to be >90% on the basis of the signals of the methyl protons in the NMR spectra of the crude products.

7) R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, **68**, 2229 (1946).

8) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 444 (1968).

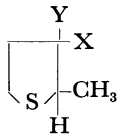
TABLE 2. 3-AMINOTETRAHYDROTHIOPHENE-3-CARBOXYLIC ACIDS



Compound			Strecker product					Bucherer product				
R_1	R_2	R_3	No	Mp[a] °C	R_f[b]	NMR[c] δ	Yield[d] %	No	Mp[a] °C	R_f[b]	NMR[c] δ	Yield[e] %
H	H	H	**7**	286.5—287.5(d)	0.35		45					
CH_3	H	H	**13b**	319—320(sub)	0.47	1.35	41.5	**15b**	256—257(d)	0.49	1.30	33.5
H	CH_3	H	**13c**	261—262(d)	0.54	1.45	36	**15c**	259—260(d)	0.54	1.40	15
H	H	CH_3	**9**	281—282(sub)	0.46	1.05	42	**11**	281—282(sub)	0.44	1.15	62

a) All melting points (capillary) are uncorrected. The symbols in parentheses show: d, decompose; sub, sublime. b) R_f values on paper chromatography; the solvent, *n*-butanol: acetic acid: water (4:1:1). c) Chemical shifts of the methyl protons of the hydrochlorides of these amino acids (in D_2O, at 60 MHz). d) Based on the corresponding 3-ketotetrahydrothiophenes. e) Based on the corresponding hydantoins.

TABLE 3. CHEMICAL SHIFTS OF 2-PROTONS AND 2-METHYL PROTONS IN THE DERIVATIVES OF 2-METHYL AMINO ACIDS (**13b** AND **15b**) (60 MHz)



Compound		Concn mg/ml	Solvent	Strecker product		Bucherer product	
X	Y			2-CH_3	2-H	2-CH_3	2-H
NH_3^+Cl	COOH	10	D_2O	1.35	3.68	1.30	4.05
NH_2	$COOCH_3$	7	$CDCl_3$	1.18	3.23	1.19	3.79
NH_2	CH_2OH	7	$CDCl_3$	1.24	3.15	1.23	3.29

The values are in ppm (δ) relative to internal tetramethylsilane.

Configurational Assignment. As has been described above, the amino nitriles (**8** and **12b**) strongly resisted toward hydrolysis. This suggests that the nitrile groups in the Strecker amino nitriles are located *cis* to the methyl groups. Strong support for this assignment is obtained from the studies of the NMR spectra of the 2-methyl amino acids.

For comparison, the 2-methyl amino acids (**13b** and **15b**) were converted to amino esters by treatment with thionyl chloride in methanol, and subsequently to amino alcohols by lithium aluminum hydride reduction. The chemical shifts of the 2-protons and the 2-methyl protons (they appear in the AX_3 pattern) of these compounds are given in Table 3.

In the cases of both the amino acids and the amino esters, the signals due to the 2-protons of the Bucherer products appear at a field lower by 0.37 and 0.56 ppm respectively than those for the Strecker products. It is known that, in a rigid ring system (*e.g.*, a three-membered ring and a rigid bicyclic system such as bicyclo[2,2,2]octane), a carboxyl substituent causes resonances due to the *cis*-vicinal protons to appear downfield of those due to the *trans*-vicinal protons.[9] Also, in the case of a five-membered ring, such an effect has recently been observed.[10] Consequently, our results indicate that the 2-protons are located *cis* to the carboxyl groups in the Bucherer products and *trans* in the Strecker products. In agreement with this assignment, a comparison of the signals of the 2-protons of the amino esters with those for the amino alcohols shows little difference in the case of the Strecker products, but the signal of the amino alcohol shifts 0.5 ppm to a higher field in the case of the Bucherer products.

As a result, the carboxyl group is introduced from the more hindered side of the starting ketone (**6b**) in the Strecker reaction and oppositely from the less hindered side in the Bucherer reaction. Therefore, in the cases of the 4-methyl and the 5-methyl amino acids also it seems to be reasonable to say that the carboxyl groups in the Strecker products are *cis* to the methyl groups, while they are *trans* in the Bucherer products.

These stereochemical results of both reactions are consistent with Munday's conclusion as to the alkyl amino-cyclohexane-carboxylic acids.

9) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2 Ed., Pergamon, London (1969), pp. 227—237.

10) K. Horikawa and S. Masuyama, This Bulletin, **43**, 551 (1970); T. Matsumoto, T. Okabe, and K. Fukui, *Chem. Lett.*, **1972**, 29.

Experimental

All the melting points are uncorrected. The IR spectra were measured on a JASCO Model IR-S Spectrometer. The NMR spectra were obtained on a 60 MHz Hitachi R-20 Spectrometer, using tetramethylsilane as the internal standard.

3-Ketotetrahydrothiophenes. A modification of the method of Woodward *et al.*[7] for the preparation of 3-ketotetrahydrothiophene (**6a**) was used for the compounds listed in Table 1; this method, in our hands, gave good yields of these compounds. The preparation of *2-methyl-3-ketotetrahydrothiophene (**6b**)* will be described as an example. To a stirred solution of ethyl thiolactate (53.6 g, 0.4 mol) containing piperidine (0.5 ml), methyl acrylate (38 g, 0.44 mol) was slowly added, while the mixture was maintained at 40—50 °C by occasional cooling. During the reaction, more piperidine (0.5 ml) was added. After the addition of methyl acrylate was complete, the mixture was warmed at 50 °C for 10 min, and then washed with ice water and dried over $MgSO_4$. A mixture of sodium ethoxide [prepared from sodium (11 g) and anhydrous ethanol (30 ml)] in dry benzene (400 ml) was heated at 75—80 °C and a solution of the above Michael-addition product in dry benzene (200 ml) was slowly added over a 1.5-h period. The temperature was then raised to 80—90 °C and the azeotropic mixture (150 ml) of benzene–ethanol was distilled. After cooling, 10% hydrochloric acid (200 ml) was added. The benzene layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The remaining residue of the Dieckmann product was refluxed with methanol (800 ml) and 20% hydrochloric acid (200 ml) for 4 h. The mixture was cooled in an ice bath, neutralized with a 20% sodium hydroxide solution, and then extracted with methylene chloride (3×100 ml). Drying over $MgSO_4$, the evaporation of the solvent, and the distillation of the residue gave a colorless liquid (39.4 g, 85%); bp 77—84 °C/18 mmHg.

*3-Aminotetrahydrothiophene-3-carboxylic Acid (**7**).* A solution of 3-ketotetrahydrothiophene (6.4 g, 0.063 mol) in methanol (30 ml) was added to a solution of ammonium chloride (8.9 g) and sodium cyanide (7.5 g) in concentrated ammonium hydroxide (51 ml). The mixture was cooled in an ice-salt bath, saturated with ammonia gas, and then shaken at room temperature for 2 days in a tightly sealed bottle. The mixture was diluted with water (100 ml) and extracted with ether (3×50 ml). The extract was washed with water, dried over K_2CO_3, and evaporated *in vacuo*. The remaining residue of the amino nitrile was refluxed with 20% hydrochloric acid (40 ml) for 12 h. After the subsequent evaporation of the solvent *in vacuo*, the residue was dissolved in water (30 ml) and the solution was decolorized with charcoal and again evaporated to dryness *in vacuo*. The resultant solids were extracted with ethanol. After filtration, pyridine was added to the cold filtrate and the mixture was allowed to stand overnight in the refrigerator. The white precipitate was collected by filtration, yielding the amino acid (**7**) (4.6 g, 45%), which was subsequently purified by recrystallization from water. Mp 286.5—287.5 °C (decomp.).

Found: C, 36.34; H, 6.95; N, 8.40%. Calcd for $C_5H_9NO_2S \cdot H_2O$: C, 36.35; H, 6.71; N, 8.47%.

*3-Amino-5-methyltetrahydrothiophene-3-carboxylic Acid (α-Isomer, **13c**).* By the procedure described for **7**, this was prepared from **6c** (5.8 g, 0.05 mol), yielding 2.9 g (36%). Mp 261—262 °C (decomp.).

Found: C, 45.02; H, 7.37; N, 8.95%. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.87; N, 8.68%.

*3-Amino-4-methyltetrahydrothiophene-3-carboxylic Acid (α-Isomer, **9**).* This was prepared from **6d** (11.6 g, 0.1 mol) by a procedure virtually identical with that described for **7**, but the hydrolysis of the resulting amino nitrile (**8**) to the amino acid (**9**) required heating with 20% hydrochloric acid for 2 days, thus yielding 6.8 g (42%). Mp 281—282 °C (decomp.).

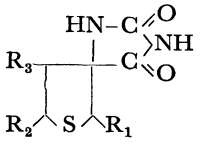
Found: C, 43.26; H, 7.21; N, 8.07%. Calcd for $C_6H_{11}NO_2S \cdot 1/3H_2O$: C, 43.09; H, 7.03; N, 8.37%.

*3-Amino-2-methyltetrahydrothiophene-3-carboxylic Acid (α-Isomer, **13b**).* By the procedure described for **9**, this was prepared from **6b** (11.6 g, 0.1 mol), yielding 6.7 g (41.5%). Mp 319—320 °C (sublime).

Found: C, 44.68; H, 7.21; N, 8.26%. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.87; N, 8.68%.

*Bucherer Hydantoins, **10**, **14b** and **14c** (β-Isomers).* The usual method was used for the preparation of all the Bucherer hydantoins listed in Table 4. The preparation of *4-methyltetrahydrothiophene-3-*spiro*-5'-hydantoin* (**10**) will be described as an example. A mixture of **6d** (9.2 g, 0.0793 mol), ammonium carbonate (24 g), and 60% aqueous ethanol (130 ml) was warmed at 50 °C; a solution of sodium cyanide (4.1 g) in water (20 ml) was added with stirring. The reaction mixture was stirred at 50—60 °C for 3 h, and then at 85 °C for 1 h. After concentration to 70 ml *in vacuo*, the solution was acidified to pH 6 by the addition of 20% hydrochloric acid and then allowed to stand overnight at 5 °C. The precipitate was collected by filtration and re-

Table 4. Properties of hydantoins



No	Compound			Mp, °C	Yield, %	NMR[a] (Assignment)
	R_1	R_2	R_3			
10	H	H	CH_3	173.5—175	74	0.96, d (4-CH_3)
14c	H	CH_3	H	240—243	72	1.28, d (5-CH_3)
14b	CH_3	H	H	172.5—176	61	1.08, d (2-CH_3) 3.60, q (2-H)
18[b]	CH_3	H	H	180—181.5	35	1.16, d (2-CH_3) 3.40, q (2-H)

a) Measured in DMSO-d_6. Symbols show: d, doublet; q, quartet. b) Prepared from **6b** *via* the amino nitrile (**12b**).

crystallized from aqueous ethanol, yielding 10.9 g (74%).

Found: C, 45.21; H, 5.02; N, 15.15; S, 17.25%. Calcd for $C_7H_{10}N_2O_2S$: C, 45.12; H, 5.40; N, 15.03; S, 17.20%.

*2-Methyltetrahydrothiophene-3-spiro-5'-hydantoin(α-Isomer, **18**).* The amino nitrile (**12b**) [prepared from **6b** (3.22 g, 0.0278 mol) *via* the Strecker route] was added to a stirred mixture of ammonium carbonate (8.5 g) and 60% aqueous ethanol (45 ml); the mixture was then stirred at 55—60 °C for 3 h, and subsequently at 85 °C for 1 h. The evaporation of the ethanol, the acidification (to pH 6) of the residue, and the filtration of the precipitate gave the crude hydantoin. Pure **18** was obtained by dissolving it in a 1M sodium hydroxide solution (30 ml); the solution was washed with ethyl acetate and adjusted to pH 6 with 20% hydrochloric acid. The precipitate was collected by filtration, washed with 40% aqueous ethanol, and dried *in vacuo*. Yield 1.82 g (35%).

Found: C, 45.00; H, 5.43; N, 15.12%. Calcd for $C_7H_{10}N_2O_2S$: C, 45.12; H, 5.40; N, 15.03%.

*3-Amino-4-methyltetrahydrothiophene-3-carboxylic Acid (β-Isomer, **11**).* A solution of **10** (10.5 g, 0.0565 mol) in a 1 M sodium hydroxide solution (60 ml) was heated in an autoclave at 180 °C for 30 h, and then decolorized with charcoal and evaporated to dryness *in vacuo*. The residue was suspended in ethanol (50 ml), and lactic acid (6 g) was added. The mixture was stirred at room temperature for 1 h, and then allowed to stand overnight in the refrigerator. The precipitate was collected by centrifuge. The product was purified by dissolving it in 5% ammonium hydroxide (50 ml), and the solution was decolorized with charcoal and concentrated to 10 ml *in vacuo*. The white crystals were collected by filtration, yielding 5.6 g (62%). Mp 281—282 °C (sublime).

Found: C, 44.46; H, 7.03; N, 8.99%. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.87; N, 8.68%.

*3-Amino-2-methyltetrahydrothiophene-3-carboxylic Acid (β-Isomer, **15b**).* This was prepared by the use of the method of Yamada *et al.*[8] A solution of tosyl chloride (19 g, 0.1 mol) in acetone (50 ml) was slowly added over a period of 6 h to a stirred solution of **14b** (9 g, 0.484 mol) in acetone (150 ml), while the mixture was maintained at pH 9—10 by the dropwise addition of a 1 M potassium hydroxide solution (210 ml). The mixture was then stirred for additional 10 h. The acetone was evaporated *in vacuo* and the precipitate was collected by filtration. The filtrate was acidified with acetic acid and extracted with ethyl acetate. After the evaporation of the ethyl acetate, the residue was combined with the precipitate and the mixture was stirred with 1 M aqueous sodium hydroxide (100 ml) at 0—10 °C for 5 h. The insoluble material was filtered and the filtrate was acidified with 20% hydrochloric acid. The white precipitate of the hydantoic acid (**11**) was collected by filtration and heated with 10% hydrochloric acid (100 ml) at 90—98 °C for 3 h. The mixture was then allowed to stand overnight in the refrigerator. The precipitate was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in ethanol (50 ml), and after the addition of pyridine, the solution was left overnight at 5 °C. The white precipitate was collected by filtration and dried *in vacuo*. Yield 2.6 g (33.4%). Mp 256—257 °C (decomp.).

Found: C, 38.33; H, 7.06; N, 7.47%. Calcd for $C_6H_{11}NO_2S \cdot 3/2\ H_2O$: C, 38.28; H, 7.49; N, 7.44%.

*3-Amino-5-methyltetrahydrothiophene-3-carboxylic Acid (β-Isomer, **15c**).* By the procedure described for **15b**, this was prepared from **14c** (15% yield). Mp 259—260 °C (decomp.).

Found: C, 42.05; H, 7.53; N, 8.17%. Calcd for $C_6H_{11}NO_2S \cdot 1/2\ H_2O$: C, 42.33; H, 7.10; N, 8.22%.

Methyl 3-Amino-2-methyltetrahydrothiophene-3-carboxylate (β-Isomer). A slurry of **15b** (4.28 g, 0.0266 mol) in anhydrous methanol (15 ml) was treated at 0 °C with thionyl chloride (3.3 ml). The mixture was refluxed for 3 h, and then evaporated to dryness *in vacuo*. The residue was shaken for 30 min with dry chloroform (50 ml) saturated with ammonia gas. After filtration, the filtrate was evaporated *in vacuo*. The oily residue was purified through a neutral alumina column with benzene, yielding the amino ester (3.84 g, 82.5%). Tlc indicated the presence of a single component. IR (liquid film): 3300 (NH), 1730 (C=O) cm^{-1}. NMR ($CDCl_3$): see Table 3.

Methyl 3-Amino-2-methyltetrahydrothiophene-3-carboxylate (α-Isomer). By the procedure described above, this was prepared from **13b** (2.36 g, 0.0146 mol), yielding 1.75 g (68%). IR (liquid film): 3300 (NH). 1730 (C=O) cm^{-1}. NMR ($CDCl_3$): see Table 3.

3-Amino-3-hydroxymethyl-2-methyltetrahydrothiophene (β-Isomer). A solution of 3.75 g (0.0212 mol) of the amino ester (β-isomer) in anhydrous tetrahydrofuran (20 ml) was slowly added to an ice-cooled slurry of lithium aluminum hydride (1.2 g, 0.0315 mol) in anhydrous ether (150 ml). The mixture was stirred at room temperature for 2 days and then decomposed with water (3 ml). A 10% sodium hydroxide solution (32 ml) was then added and the aqueous layer was extracted with chloroform containing ethanol. The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The remaining residue of the amino alcohol was purified through a neutral alumina column with benzene to give a colorless liquid (3.01 g, 96%). Tlc indicated the presence of a single component. IR (liquid film): 3250 (OH, NH) cm^{-1}. NMR ($CDCl_3$): see Table 3.

3-Amino-3-hydroxymethyl-2-methyltetrahydrothiophene (α-Isomer). By the procedure described above, this was prepared from 1.75 g (0.01 mol) of the amino ester (α-isomer), yielding 1.02 g (70%). IR (liquid film): 3250 (OH, NH) cm^{-1}. NMR ($CDCl_3$): see Table 3.

The authors wish to thank Mr. Takuzo Fujino for his microanalysis and Mr. Yoshio Takai for his measurement of the NMR spectra.