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Optical Rotatory Dispersion Studies

XLVI *. Stereochemical Assignments through Anomalous Rotatory Dispersion Curves of α-Amino Acid Derivatives. 3-Phenyl-2-Thiohydantoins and N-Thionocarbethoxy Amino Acids

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Some derivatives of α-amino acids, whose optical rotatory dispersion curves can be used for establishing their absolute configurations, have been investigated. In particular, derivatives have been studied which are also employed in the sequential degradation of peptides, and the present paper is mainly concerned with the optical rotatory dispersion of 3-phenyl-2-thiohydantoins and N-thionocarbethoxy amino acids.

The use of optical rotatory dispersion measurements [1,2] for stereochemical assignments and conformational problems is now well established. The applicability of anomalous rotatory dispersion curves is, however, usually limited to optically active chromophores (*e.g.* carbonyl groups [3], disulfides [4], *etc.*), which absorb in a suitable spectral range with relatively low extinction. A number of important functional groups, however, do not satisfy these requirements. In order to circumvent this difficulty, we have been investigating the preparation of "chromophoric" derivatives which would exhibit Cotton effect curves in contrast to the plain curves [5] of the "non-chromophoric"

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parent. Obviously, such an approach would enormously increase the scope of rotatory dispersion applications in the field of organic chemistry and several recent publications have demonstrated the feasibility of such studies. Dithiocarbamates (I)[6], xanthates (II)[6], thioureas (III)[7] and osmates [8] have proved to be useful in yielding Cotton effect curves for the otherwise transparent amino, hydroxy, carboxylic acid or olefinic groups. While N-dithiocarbalkoxy (dithiocarbamate) derivatives of α-amino acids (I) have proved to be very suitable [6] for establishing the absolute configuration of the α-asymmetric center — a positive Cotton effect corresponding to the L-configuration, and a negative one corresponding to the D-configuration — we have nevertheless felt that it would be profitable to examine other derivatives of α-amino acids for the same purpose. In particular, it seemed appropriate to study derivatives which are also employed in the sequential degradation of peptides, and the present paper is concerned with two such derivatives.

3-PHENYL-2-THIOHYDANTOINS

One of the generally accepted chemical methods [9] for the stepwise degradation of a peptide sequence is due to Edman [10] and proceeds through the 5-substituted 3-phenyl-2-thiohydantoins (IV) [11]. These derivatives show strong ultraviolet absorption maxima near 267 mμ [12], whose intensity (log $\varepsilon > 4.2$) precludes rotation measurements through this absorption band. However, as shown in Fig. 1, for two typical cases (3-phenyl-2-thiohydantoins derived from alanine and tyrosine), there is also present a low intensity shoulder around 310 mμ and it is this absorption feature which prompted us to prepare the phenylthiohydantoins of several optically active α-amino acids for rotatory dispersion measurements. Edman [11] has called attention to the fact that in those instances where he examined optically active amino acids, the specific

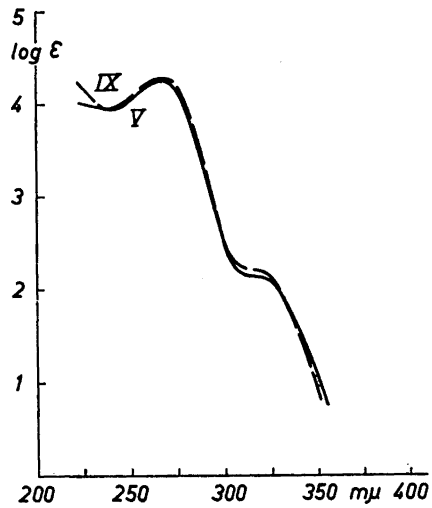


Fig. 1. Ultraviolet absorption in methanol of 5-methyl-3-phenyl-2-thiohydantoin (V) and 5-*p*-hydroxybenzyl-3-phenyl-2-thiohydantoin (IX).

rotation of the phenylthiohydantoins at the sodium D-line was either 0° or very low, indicating complete or partial racemization. If the electronic transition responsible for the 310 mμ absorption is "optically active", one could expect rather high rotations near the extrema of its Cotton effect and even partially racemized phenylthiohydantoins should yield measurable Cotton effects. As we have already pointed out elsewhere [13–15], for purposes of absolute configurational assignments the sign only (rather than the amplitude as well) of the Cotton effect is required and even partially racemized substances lend themselves to this approach [15].

In Fig. 2 are reproduced the optical rotatory dispersion curves of the 3-phenyl-2-thiohydantoins derived from L-alanine (V), L-valine (VI) and L-proline (VII). All three show positive Cotton effects, suggesting that the earlier generalization [6] concerning the N-dithiocarbalkoxy α-amino acids (I), namely, that a positive Cotton effect is attributable to the L-configuration of the α-asymmetric center, applies here too. The location of the Cotton effect, with the first extremum appearing near 340 mμ, shows quite clearly that the 310 mμ ultraviolet band (Fig. 1) is responsible for the anomalous character of the dispersion curve. The amplitudes of the Cotton effects are quite small and this may possibly be due to partial racemization, as has been suggested by Edman [11].

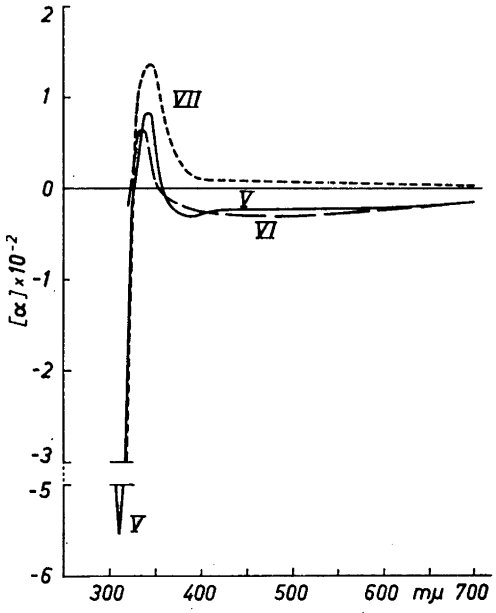


Fig. 2. Optical rotatory dispersion curves of 5-methyl-3-phenyl-2-thiohydantoin (V), 5-*iso*propyl-3-phenyl-2-thiohydantoin (VI) and 1,5-*cyclo*trimethylene-3-phenyl-2-thiohydantoin (VII).

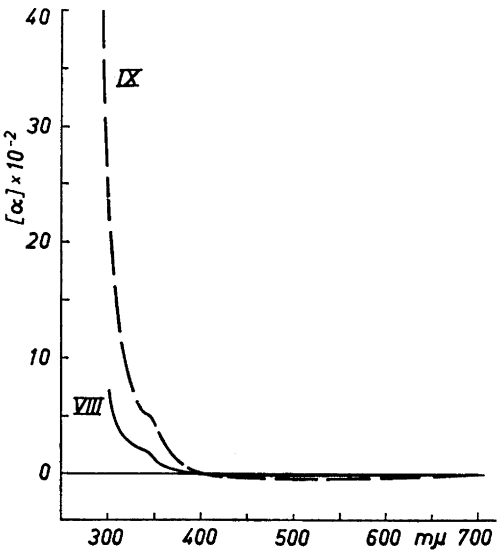
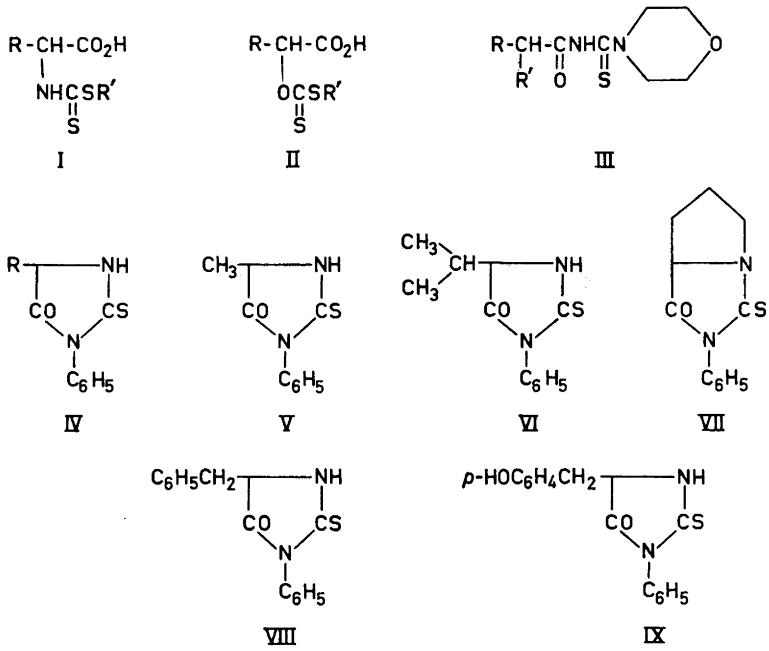


Fig. 3. Optical rotatory dispersion curves of 5-benzyl-3-phenyl-2-thiohydantoin (VIII) and 5-*p*-hydroxybenzyl-3-phenyl-2-thiohydantoin (IX).

When an aromatic ring is present in the *a*-amino acid, the situation is altered. The phenylthiohydantoins of L-phenylalanine (VIII) and L-tyrosine (IX) exhibit rotatory dispersion curves (Fig. 3) which are characterized by a very steep rise in rotation below 350 mμ, this being particularly pronounced with the tyrosine derivative (IX). The Cotton effect associated with the 310 mμ absorption band can now only be seen as a slight irregularity in the dispersion curves, the dominant factor presumably being the second ultraviolet absorption maximum through which rotation measurements cannot be conducted with the currently available instruments. It would appear, however, that the positive sign of these dispersion curves can be utilized for stereochemical purposes in an analogous manner to the plain curves of simpler carboxylic acids [14].



N-THIONOCARBETHOXY *a*-AMINO ACIDS

Kenner and Khorana [16] have pointed out that N-thionocarbethoxy derivatives of peptides, readily prepared by the action of dialkylxanthates, constitute useful intermediates for peptide degradation. In spite of its promise, this approach does not appear to have been widely used in peptide chemistry and the British workers limited their model experiments to optically inactive substrates. In order to examine the suitability of N-thionocarbethoxy derivatives (X) of *a*-amino acids for rotatory dispersion work, it was first necessary to determine whether the C=S grouping in this moiety possessed a suitable ultraviolet absorption band. Careful ultraviolet measurements showed that

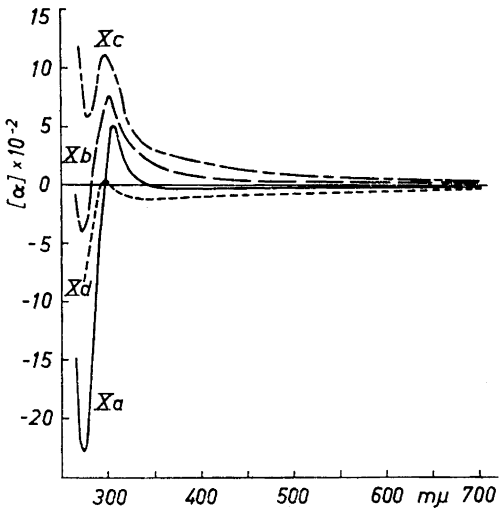


Fig. 4. Optical rotatory dispersion curves of N-thionocarbethoxy L-alanine (Xa), N-thionocarbethoxy L-methionine (Xb), N-thionocarbethoxy L-phenylalanine (Xc) and N-thionocarbethoxy S-benzyl-L-cysteine (Xd).

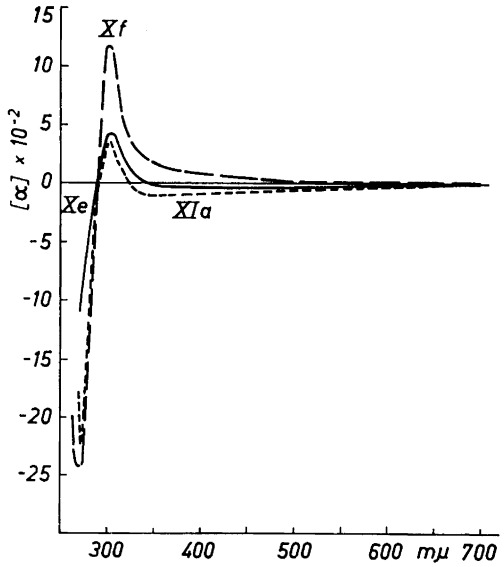


Fig. 5. Optical rotatory dispersion curves of N-thionocarbethoxy L-valine (Xe), N-thionocarbethoxy L-leucine (Xf) and N-thionocarbethoxy L-proline (XIa).

while the principal ultraviolet absorption band of such derivatives occurs at 247 mμ (log $\varepsilon \sim 4.2$) *, there is present in the spectrum a very slight shoulder between 280—285 mμ. If "optically active", the low extinction (log $\varepsilon \sim 2.2$) of this absorption band would lend itself to experimentally measurable Cotton effects and this prompted us to synthesize a number of optically active N-thionocarbethoxy α-amino acids (X).

The rotatory dispersion results are summarized in Figs. 4—6 and demonstrate clearly that the inflection in the ultraviolet absorption spectrum near 280 mμ is responsible for the observed Cotton effects. The rotatory dispersion curves of N-thionocarbethoxy L-alanine (Xa), L-methionine (Xb), L-phenylalanine (Xc) and S-benzyl-L-cysteine (Xd) shown in Fig. 4, as well as those of N-thionocarbethoxy L-valine (Xe), L-leucine (Xf) and L-proline (XIa) collected in Fig. 5, are unexceptional. All of them exhibit positive Cotton effect curves in accordance with expectation [6] for members of the L-series. The only exception from this generalization is found in Fig. 6 in which are shown the rotatory dispersion curves of N-thionocarbethoxy allohydroxy-L-proline (XIb) and hydroxy-L-proline (XIc). The former again shows a positive Cotton effect, as did the corresponding derivative XIa of L-proline (Fig. 5),

* This strong absorption maximum may prove useful in some analytical applications involving N-thionocarbethoxy intermediates.

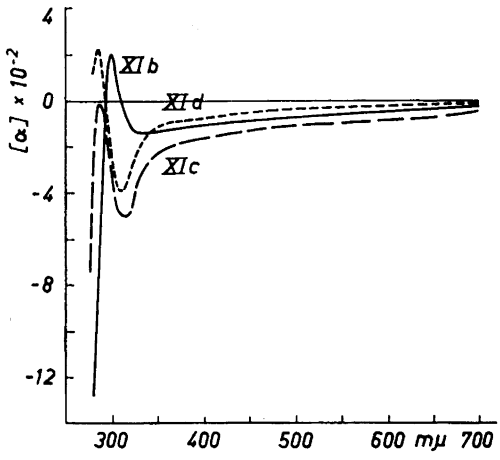


Fig. 6. Optical rotatory dispersion curves of N-thionocarbethoxy allohydroxy-L-proline (XIb), N-thionocarbethoxy hydroxy-L-proline (XIc) and N-thionocarbethoxy acetoxy-L-proline (XId).

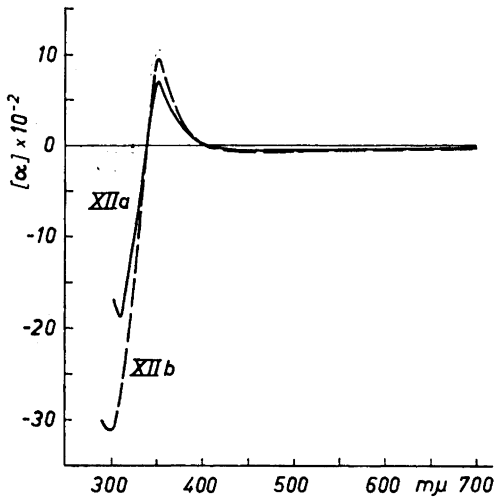


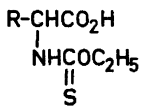
Fig. 7. Optical rotatory dispersion curves of N-dithiocarbethoxy hydroxy-L-proline (XIIa) and N-dithiocarbethoxy allohydroxy-L-proline (XIIb).

but the hydroxy-L-proline analog (XIc) exhibits a negative Cotton effect. This anomaly cannot be ascribed to the free hydroxy function, since N-thionocarbethoxy acetoxy-L-proline (XId) behaved similarly (see Fig. 6). No uncertainty can be attached to the structure of the derivative obtained from hydroxy-L-proline, since the analytical and spectroscopic properties are in agreement with formulation XIc. Furthermore, the identical product was obtained by direct treatment of hydroxy-L-proline with O-ethyl methyl-xanthate, as well as from acetoxy-L-proline *via* the derivative XId followed by saponification.

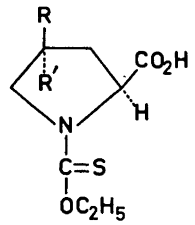
In order to examine further the anomalous behaviour of N-thionocarbethoxy hydroxy-L-proline (XIc), we have now synthesized the corresponding dithiocarbamate, N-dithiocarbethoxy hydroxy-L-proline (XIIa), as well as N-dithiocarbethoxy allohydroxy-L-proline (XIIb), as these two amino acid derivatives were not included in our earlier study. As shown in Fig. 7, both XIIa and XIIb exhibit positive Cotton effect curves, in accordance with the earlier enunciated [6] generalization that N-dithiocarbalkoxy *a*-amino acids of the L-series possess positive Cotton effects.

The Cotton effects associated with the dispersion curves of N-dithiocarbalkoxy (I) or N-thionocarbalkoxy (X) derivatives of *a*-amino acids are due to interaction of the electrons involved in the appropriate transition of the C=S chromophore (which give rise to the low-intensity ultraviolet absorption band) with the partially unshielded nuclei of other substituents in the asymmetric environment. It seems likely that a given "rotometer" of the substituent attached to the nitrogen predominates in the amino acid derivatives

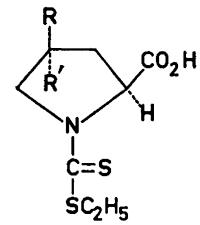
under discussion, so that the disposition in space of the other substituents with respect to the C=S chromophore is always similar. This explains why the same sign of the Cotton effect is observed for members of identical absolute configuration and why this generalization applies to the dithiocarbalkoxy (I) as well as to the thionocarbalkoxy (X) derivatives. In view of this apparently systematic behaviour, the exception of N-thionocarbethoxy hydroxy-L-proline (XIc), (Fig. 6), when contrasted with the "normal" behaviour of the corresponding N-dithiocarbethoxy derivative XIIa (Fig. 7), suggests that the C=S chromophore of the former has in some way been forced into an unusual spatial position.



Xa R = CH_3
b R = $CH_3SCH_2CH_2$
c R = $C_6H_5CH_2$
d R = $C_6H_5CH_2SCH_2$
e R = $(CH_3)_2CH$
f R = $(CH_3)_2CHCH_2$



XIa R = R′ = H
b R = OH; R′ = H
c R = H; R′ = OH
d R = H; R′ = OAc



XIIa R = H; R′ = OH
b R = OH; R′ = H

The amplitudes of the Cotton effects of the N-dithiocarbalkoxy (I) and N-thionocarbalkoxy (X) derivatives were found to be relatively large, and it seemed likely that only little racemization, if any, had occurred during the preparation of these derivatives. In order to determine the extent of racemization, we performed lithium aluminum hydride reductions of the crude N-dithiocarbethoxy L-alanine and N-thionocarbethoxy L-alanine. Reduction of carbamates usually yield N-methylamines [17] and accordingly we obtained N-methylalaninol. The specific rotations were found to be +35.8° for the reduction product of N-dithiocarbethoxy L-alanine and +36.6° for that of N-thionocarbethoxy L-alanine. Authentic N-methyl-L-alaninol, obtained from a purified sample of N-dithiocarbethoxy L-alanine which was undoubtedly optically pure [18], had a specific rotation of 38.0°. Apparently, at least for the alanine derivatives, there is little racemization in the preparation of the dithiocarbethoxy and thionocarbethoxy derivatives, in contrast to the situation obtaining with Edman's phenylthiohydantoins.

CONCLUSION

Of the three α-amino acid derivatives (I, IV, X) which lend themselves to stereochemical assignments by consideration of their anomalous optical rotatory dispersion, the dithiocarbamates (I)[6] appear to be the most useful

ones, particularly since their relevant absorption band (*ca.* 330 mμ) occurs in a more convenient region. Furthermore, no exceptions have been noted to the generalization that L-amino acid derivatives show positive Cotton effect curves, this being true even of N-dithiocarbethoxy hydroxy-L-proline (XIIa). In terms of ease of preparation, N-thionocarbethoxy derivatives (X) are equally satisfactory and since their rotatory dispersion curves have proved to be quite instructive (Figs. 4—6), the actual choice of derivative may well depend on other factors (ease of crystallization or preparation incidental to peptide degradation). The reduced amplitude of the Cotton effect of the phenylthiohydantoins (IV) makes them less desirable for the purposes described in this paper.

EXPERIMENTAL

All rotatory dispersion measurements were determined in methanol solution (22—25°) by Mrs. R. Records and Mrs. T. Nakano, by means of an automatically recording Rudolph spectropolarimeter. The data are reported below in the manner outlined in Ref.[5]

3-Phenyl-2-thiohydantoins (IV)

These were prepared by the method of Edman [11] by dissolving the amino acid in 50 % aqueous pyridine, adjusting the pH to 9 with 1 N sodium hydroxide and stirring with phenyl*iso*thiocyanate at 40° until alkali consumption stopped (the pH being maintained at 9 by addition of alkali). After extraction with benzene (discarded), the aqueous solution containing the phenylthiocarbamate derivative was adjusted to pH 2.5 by means of hydrochloric acid and left at room temperature for two days. The thiohydantoin was then filtered and recrystallized, the melting points agreeing in every instance with those reported by Edman [11].

5-Methyl-3-phenyl-2-thiohydantoin (V), R.D. (Fig. 2), *c*, 0.105: $[a]_{700}$ −8°, $[a]_{589}$ −19°, $[a]_{342.5}$ +84°, $[a]_{310}$ −553°, $[a]_{290}$ −36°.

5-Isopropyl-3-phenyl-2-thiohydantoin (VI), R.D. (Fig. 2), *c*, 0.100: $[a]_{700}$ −8°, $[a]_{589}$ −18°, $[a]_{335}$ +64°, $[a]_{322.5}$ −20°.

1,5-Cyclotrimethylene-3-phenyl-2-thiohydantoin (VII), R.D. (Fig. 2), *c*, 0.102: $[a]_{700}$ +4°, $[a]_{589}$ +6°, $[a]_{342.5}$ +137°, $[a]_{310}$ −311°.

5-Benzyl-3-phenyl-2-thiohydantoin (VIII), R.D. (Fig. 3), *c*, 0.105: $[a]_{700}$ −15°, $[a]_{589}$ −25°, $[a]_{340}$ +200° (inflect.), $[a]_{295}$ +866°.

5-p-Hydroxybenzyl-3-phenyl-2-thiohydantoin (IX), R.D. (Fig. 3), *c*, 0.102: $[a]_{700}$ −31°, $[a]_{589}$ −39°, $[a]_{340}$ +520° (inflect.), $[a]_{292.5}$ +4040°.

N-Thionocarbethoxy *a*-amino acids (X)

These were prepared according to the procedure of Kenner and Khorana [16], except that the L-amino acid was used in each instance. All of the derivatives showed the typical ultraviolet absorption maximum at 247 mμ (log. ε ~4.2) with a slight shoulder in the 280—285 mμ region.

N-Thionocarbethoxy-L-alanine (Xa), m.p. 80° (from chloroform/light petroleum). (Found: C 40.84; H 6.27; N 8.04; S 18.27. $C_6H_{11}NO_3S$ requires C 40.68; H 6.26; N 7.91; S 18.06.)

R.D. (Fig. 4), *c*, 0.195 (0.039 below 290 mμ): $[a]_{700}$ −10°, $[a]_{589}$ −22°, $[a]_{305}$ +512°, $[a]_{275}$ −2 305°, $[a]_{264}$ −1 460°.

N-Thionocarbethoxy L-methionine (Xb), viscous oil, R.D. (Fig. 4), *c*, 0.115 (0.057 below 290 mμ): $[a]_{700}$ 0°, $[a]_{589}$ +2°, $[a]_{302.5}$ +758°, $[a]_{272.5}$ −402°, $[a]_{267.5}$ −105.

N-Thionocarbethoxy L-phenylalanine (Xc), m.p. 87° (from ether/light petroleum). (Found: C 57.14; H 5.98; N 5.65; S 12.31. $C_{12}H_{15}NO_3S$ requires C 56.91; H 5.97; N 5.53; S 12.64.)

R.D. (Fig. 4), *c*, 0.410 (0.082 below 350 mμ): $[a]_{700}$ +30°, $[a]_{589}$ +55°, $[a]_{298}$ +1 116°, $[a]_{277.5}$ +578°, $[a]_{270}$ +1 200°.

N-Thionocarbethoxy S-benzyl-L-cysteine (Xd), viscous oil, R.D. (Fig. 4), *c*, 0.098: $[a]_{700}$ −41°, $[a]_{589}$ −55°, $[a]_{300}$ +21°, $[a]_{275}$ −775°.

N-Thionocarbethoxy L-valine (Xe), m.p. 65° (from benzene/light petroleum). (Found: C 46.97; H 7.38; N 6.81; S 15.33. $C_8H_{15}NO_3S$ requires C 46.82; H 7.37; N 6.83; S 15.59.)

R.D. (Fig. 5), *c*, 0.510 (0.102 below 300 mμ): $[a]_{700}$ −16°, $[a]_{589}$ −23°, $[a]_{302.5}$ +441°, $[a]_{275}$ −1 080°.

N-Thionocarbethoxy L-leucine (Xf), m.p. 79° (from benzene/light petroleum). (Found: C 49.62; H 7.73; N 6.44; S 14.90. $C_9H_{17}ON_3S$ requires C 49.34; H 7.82; N 6.39; S 14.62.)

R.D. (Fig. 5), *c*, 0.290 (0.058 below 290 mμ): $[a]_{700}$ 0°, $[a]_{589}$ 0°, $[a]_{302.5}$ + 1 175°, $[a]_{270}$ −2 440°, $[a]_{265}$ −1 995°.

N-Thionocarbethoxy L-proline (XIa), m.p. 69° (from ether/light petroleum). (Found: C 47.15; H 6.51; N 6.94; S 16.12. $C_8H_{13}NO_3S$ requires C 47.29; H 6.45; N 6.89; S 15.75.)

R.D. (Fig. 5), *c*, 0.113: $[a]_{700}$ −23°, $[a]_{589}$ −42°, $[a]_{302.5}$ + 375°, $[a]_{271}$ −2 220°, $[a]_{269}$ −1 785.

N-Thionocarbethoxy allohydroxy-L-proline (XIb), m.p. 107−8° (from chloroform/light petroleum). (Found: C 43.84; H 6.16; N 6.13; S 14.86. $C_8H_{13}NO_4S$ requires C 43.83; H 5.98; N 6.39; S 14.60.)

R.D. (Fig. 6), *c*, 0.121: $[a]_{700}$ −27°, $[a]_{589}$ −53°, $[a]_{325}$ −136°, $[a]_{300}$ +207°, $[a]_{280}$ −1 270°.

N-Thionocarbethoxy hydroxy-L-proline (XIc), m.p. 124° (from chloroform/light petroleum). (Found: C 43.98; H 5.88; N 6.42; S 14.62. $C_8H_{13}NO_4S$ requires C 43.83; H 5.98; N 6.39; S 14.60.)

R.D. (Fig. 6), *c*, 0.096: $[a]_{700}$ −37°, $[a]_{589}$ −79°, $[a]_{312.5}$ −507°, $[a]_{285}$ −10°, $[a]_{275}$ −729°.

N-Thionocarbethoxy acetoxy-L-proline (XId). O-Acetylhydroxy-L-proline [19] (1.8 g) was dissolved in water (15 ml) and 2-methoxyethanol (60 ml) containing O-ethyl methyl xanthate (5 ml) added. The solution was kept for 24 h at pH 8.5 (glass electrode) by the gradual addition of N sodium hydroxide (autotitrator). Isolation of the product in the usual manner afforded the N-thionocarbethoxy derivative (1.81 g) as a viscous oil.

R.D. (Fig. 6), *c*, 0.116; $[a]_{700}$ −14°, $[a]_{589}$ −21°, $[a]_{310}$ −382°, $[a]_{285}$ +217°.

A sample was hydrolysed at pH 12 (autotitrator) in 80 % 2-methoxy-ethanol for 24 h, and furnished N-thionocarbethoxy hydroxy-L-proline, m.p. and mixed m.p. 123−4°.

N-Dithiocarbethoxy α-amino acids (XII)

These were prepared in the same manner as previously described [6,17]. The derivatives showed the typical ultraviolet absorption maxima at 333, 278, and 251 mμ. ($\log \varepsilon \sim 1.8$, 4.0 and 4.0).

N-Dithiocarbethoxy hydroxy-L-proline (XIIa), m.p. 89−91° (from ether/light petroleum). (Found: N 5.90; S 26.90. $C_8H_{13}NO_3S_2$ requires N 5.95; S 27.25.

R.D. (Fig. 7), *c*, 0.18: $[a]_{700}$ −38°, $[a]_{589}$ −51°, $[a]_{352.5}$ +690°, $[a]_{310}$ −1 780°, $[a]_{300}$ −1 585.

N-Dithiocarbethoxy allohydroxy-L-proline (XIIb), m.p. 115−117° (from ether/light petroleum). (Found: N 5.87; S 27.52. $C_8H_{13}NO_3S_2$ requires N 5.95; S 27.25.)

R.D. (Fig. 7), *c*, 0.083 (0.017 below 350 mμ): $[a]_{700}$ −41°, $[a]_{589}$ −48°, $[a]_{352.5}$ +945°, $[a]_{300}$ −3 140°, $[a]_{295}$ −3 010°.

N-Methyl-L-alaninol

N-Dithiocarbethoxy-L-alanine was prepared according to Fredga [18]. The product was recrystallized four times from carbon tetrachloride, m.p. 107, $[a]^{23}_D$ −27.3° (*c*, 1.9 in benzene). Fredga reported for the optically pure product, m.p. 106−107°, $[a]^{25}_D$ −27.2° (c, 1.9 in benzene).

A solution of the N-dithiocarbethoxy-L-alanine (2.0 g) in dry tetrahydrofuran (50 ml) was added dropwise to a solution of lithium aluminum hydride (2 g) in tetrahydrofuran (200 ml). After the addition was complete, the mixture was heated under reflux for about 20 h, cooled, and excess hydride decomposed with saturated aqueous sodium sulphate solution. The dried (Na_2SO_4) solution was filtered, evaporated and the residue distilled,

to yield 0.70 g of N-methyl-L-alaninol, b.p. 64–65°/11 mm, $[\alpha]^{23}_D$ +38.0° (*c*, 2.0 in ethanol). (Found: C 53.85; H 12.40; N 15.80. $C_4H_{11}NO$ requires C 53.89; H 12.44; N 15.71.

Reduction of crude N-dithiocarbethoxy-L-alanine

L-alanine (1.8 g) was converted to the N-dithiocarbethoxy derivative in the usual manner, and the crude product reduced without prior purification. The reduction and work-up procedures were as described above. $[\alpha]^{22}_D$ +35.8° (*c*, 2.1 in ethanol). (Found: C 53.72; H 12.45; N 15.75. $C_4H_{11}NO$ requires C 53.89; H 12.44; N 15.71.

Reduction of crude N-thionocarbethoxy-L-alanine

L-alanine (1.8 g) was converted to the N-thionocarbethoxy derivative in the usual manner, and the crude product reduced without prior purification. The reduction and work-up procedures were as described above. $[\alpha]^{18}_D$ +36.6° (*c*, 4.9 in ethanol). (Found: C 53.52; H 12.45; N 15.73. $C_4H_{11}NO$ requires C 53.89; H 12.44; N 15.71.

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REFERENCES

1. Djerassi, C. *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill Book Co., New York 1960.
2. Djerassi, C. *Bull. soc. chim. France* **1957** 741; Djerassi, C. Record Chem. Progr. *Kresge-Hooker Sci. Lib.* 20 (1959) 101; Klyne, W. in Raphael, R. A., Taylor, E. C. and Wynberg, H. Advances in Org. Chem. **1** (1960) 239. Leemann, H. G. *Chimia* **14** (1960) 1; Nakanishi, K. *Kagaku no Ryoiki* **13** (1959) 2.
3. For leading references see chapter 4–13 in Ref.[1]
4. Djerassi, C., Fredga, A. and Sjöberg, B. *Acta Chem. Scand.* **15** (1961) 417.
5. For nomenclature see chapter 2 in Ref. [1]
6. Sjöberg, B., Fredga, A. and Djerassi, C. *J. Am. Chem. Soc.* **81** (1959) 5002.
7. Djerassi, C. and Undheim, K. *J. Am. Chem. Soc.* **82** (1960) 5755.
8. Bunnenberg, E. and Djerassi, C. *J. Am. Chem. Soc.* **82** (1960) 5953.
9. Thompson, E. O. P. in Raphael, R. A., Taylor, E. C. and Wynberg, H. *Advances in Org. Chem.* **1** (1960) 149.
10. Edman, P. *Acta Chem. Scand.* **4** (1950) 283.
11. Edman, P. *Acta Chem. Scand.* **4** (1950) 277.
12. Dahlerup-Peterson, B., Linderstrøm-Lang, K. and Ottesen, M. *Acta Chem. Scand.* **6** (1952) 1135; Fraenkel-Conrat, H. and Harris, J. I. *J. Am. Chem. Soc.* **76** (1954) 6058.
13. See Ref.[1] pp. 135 and 206.
14. Sjöberg, B. *Acta Chem. Scand.* **14** (1960) 273.
15. Sjöberg, B. *Arkiv Kemi* **15** (1960) 473.
16. Kenner, G. W. and Khorana, H. G. *J. Chem. Soc.* **1952** 2076.
17. Gaylord, N. G. *Reduction with Complex Metal Hydrides*, Interscience Publ., New York 1956.
18. Fredga, A. *Svensk Kem. Tidskr.* **54** (1942) 26.
19. Sakami, W. and Toennies, G. *J. Biol. Chem.* **144** (1942) 203.

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