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MANIPULATION OF THE CARBOXYL GROUPS OF α-AMINO-ACIDS AND PEPTIDES USING RADICAL CHEMISTRY BASED ON ESTERS OF N-HYDROXY-2-THIOPYRIDONE

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Abstract - Photolysis of α-amino-acid or peptide esters derived from N-hydroxy-2-thiopyridone in the presence of t-butylthiol affords the expected decarboxylation products in good yield. The reaction can be applied to the α-carboxyl or to the side chain carboxyl of glutamic and aspartic acids and thus permits the preparation of a number of useful synthons. Photolysis of side chain esters in the presence of a suitable halogen atom transfer reagent gives halides often in good yield and, especially in the case of aspartic acid derivatives, without racemisation.

Thiohydroxamic esters (mixed anhydrides) are an excellent source of disciplined radicals.[1,2] They also serve equally well for the generation of aminyl and aminium radicals, of which the latter are of considerable synthetic interest.[3]

Now that the first inventive phase of this work has been nearly completed, we can give more attention to the application to synthesis, especially of Natural Products. For example, we have recently described a simple synthesis of the 25-hydroxy-cholesterol side chain starting with an appropriate bile acid.[4]

This kind of radical chemistry is well suited to the manipulation of amino-acids and peptides. When the centre of asymmetry is not converted to a radical, its stereochemical integrity is preserved completely. In a recent article[5] we have given a number of examples. Other cases in point are our synthesis of L-vinylglycine[6] and the short routes to L-selenomethionine and L-selenocystine.[7]

However, our first investigation in peptide chemistry was a study of the decarboxylation of α-amino-acids, which was extended to manipulation of side chain carboxyl groups. A preliminary communication has already appeared.[8]

For the work with amino-acids and peptides a convenient procedure for α-decarboxylation was as follows. The amino-acid was N-protected with the t-butyloxycarbonyl (Boc) or the benzyloxycarbonyl (Z) groups. The protected acid 1 was then reacted at - 15°C in dry tetrahydrofuran under an inert atmosphere with isobutyl chloroformate in the presence of N-methylmorpholine[9] (Scheme 1).

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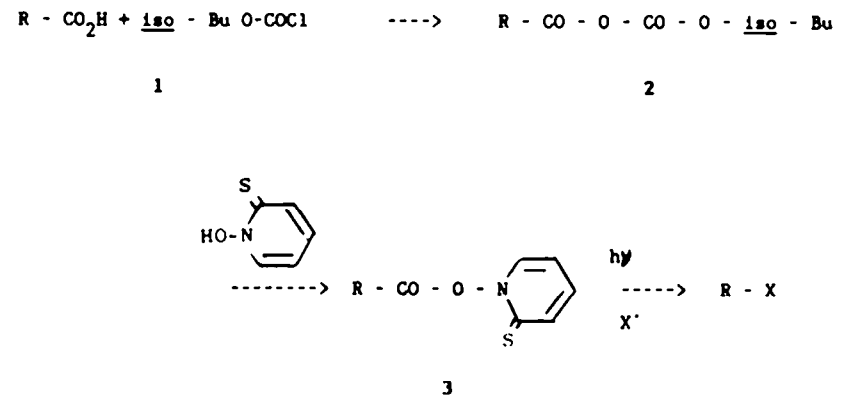


Scheme 1

After 5 minutes, the mixed anhydride 2 was treated at the same temperature with N-hydroxy-2-thiopyridone with addition of the appropriate amount of triethylamine. After one hour at - 15°C the formation of the ester was complete. The precipitated N-methylmorpholine hydrochloride was filtered off and the filtrate was irradiated with two 100 watt tungsten lamps at room temperature after addition of the appropriate radical yielding reagent.

Exactly the same procedure could be applied to side chain carboxyl groups derived from aspartic and glutamic acids. In this case, of course, the α-carboxyl had to be protected by one of the standard groups.

Irradiation in the presence of t-butyl thiol afforded in each case the expected[1] decarboxylated products mostly in good yield. Yields of isolated products are reported with the formulae.

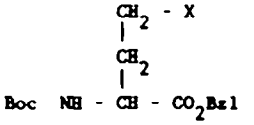
The side chain decarboxylations of 4 and 6 provide simple syntheses of optically active α-aminobutyric acid, which could be in either configuration. Similarly the decarboxylation of 8 provides alanine. This could be a preparation of D-alanine.

The α-decarboxylation of 10, 12 and 14 proceeds in good yield. Clearly provided one can get labelled t-butyl thiol the synthesis of 15 could be a source of labelled GABA. The case of threonine is interesting, since the change from 16 to 17 gives an optically active synthon, which could be easily modified on nitrogen.

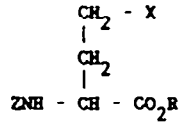
The α-decarboxylation of 18 and 20 affords good yields. It is of interest that the hydroxyl groups in 16 and 20 did not need protection, whilst the arginine side chain in 18 was well protected by just a nitro group.

With compounds 22 and 24 we returned again to side chain decarboxylation. Next we examined derivatives of tryptophan and of 5-hydroxytryptophan. Derivative 26 was α-decarboxylated in excellent yield without any interference from the indole nucleus. Derivative 28 gave a lower yield of decarboxylated product 29 and there may have been some complication from the nucleophilicity of the phenolic hydroxyl.

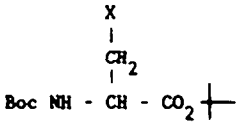
In the case of proline derivative 30 the yield of 31 was excellent. The more interesting example was the 4-hydroxyproline 32, which gave 33 in 69% yield, with only marginal interference from the unprotected hydroxyl group. The compound 33 is another optically active synthon. Its enantiomer was recently prepared from pyroglutamic acid[10] (m.p. 60-62°C, $[\alpha]_D$ + 22° in $CHCl_3$) and from malic acid[11] (m.p. 60-61°C, $[\alpha]_D$ + 13° in $CHCl_3$). Our specimen had m.p. 58°C with $[\alpha]_D$ - 30° in MeOH. N-Protected hydroxyproline can also be decarboxylated electrochemically[12].



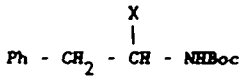
4 X = CO_2H
5 X = H (78% from 4)
40 X = Br (82%)
41 X = Cl (43%)
42 X = I (49%)
52 X = S(2)Py (48%)



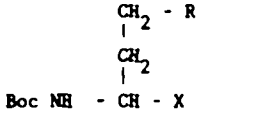
6 X = CO_2H R = Bzl
7 X = H R = Bzl (76% from 6)
47 X = Br R = Bzl (64%)
49 X = CO_2H R = Me
50 X = Br R = Me (77%)



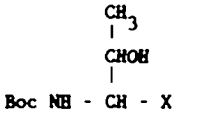
8 X = CO_2H
9 X = H (93% from 8)
51 X = Br (69%)



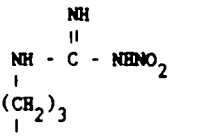
10 X = CO_2H
11 X = H (85% from 10)



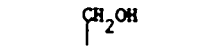
12 X = CO_2H R = S - CH_3
13 X = H R = S - CH_3 (78% from 12)
14 X = CO_2H R = CO_2Bzl
15 X = H R = CO_2Bzl (93% from 14)



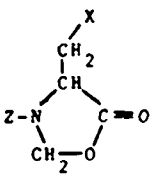
16 X = CO_2H
17 X = H (87% from 16)



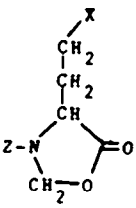
18 X = CO_2H
19 X = H (80% from 18)



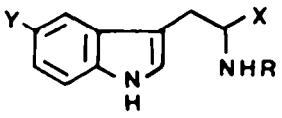
20 X = CO_2H
21 X = H (87% from 16)



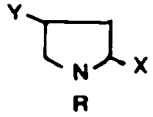
22 X = CO_2H
23 X = H (65% from 22)



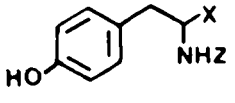
24 X = CO_2H
25 X = 4 (78% from 24)
48 X = Br (47%)



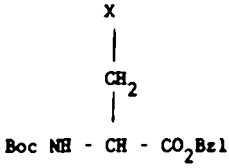
26 X = CO_2H, Y = H, R = Z
27 X = H, Y = H, R = Z (94% from 26)
28 X = CO_2H, Y = OH, R = Boc
29 X = H, Y = OH, R = Boc (61% from 28)



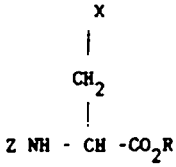
30 X = CO_2H, Y = H, R = Z
31 X = H, Y = H, R = Z (81% from 30)
32 X = CO_2H, Y = OH, R = Boc
33 X = H, Y = OH, R = Boc (69% from 32)



34 X = CO_2H
35 X = H (96% from 34)

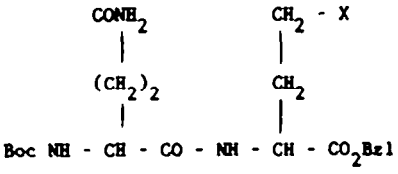


43 X = CO_2H
44 X = Br (60%)
54 X = S(2)Py (65%)

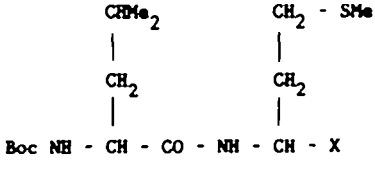


45 X = CO_2H, R = Bzl
46 X = Br, R = Bzl (60%)
53 X = S(2)Py, R = Bzl (74%)

The reduction of the tyrosine derivative 34 gave an excellent yield of 35 without interference from the phenolic hydroxyl. The failure of a number of reasonably nucleophilic groups to interfere in the formation of esters of type 3 is a reflection of the great nucleophilicity of N-hydroxy-2-thiopyridone. Other methods are, of course, available for the decarboxylation of simple amino-acids[13] although the process here reported involving disciplined radicals is probably the mildest. There is, to our knowledge, no mild procedure for the decarboxylation of polypeptides. We were able to show that both side chain decarboxylation of 36 and α-decarboxylation of 38 to give 37 and 39 respectively proceeded in excellent yield.



36 X = CO_2H
37 X = H (74% from 36)



38 X = CO_2H
39 X = H (83% from 38)

The addition of a halogen transfer reagent to our radical generating system permits the Hunsdiecker-Borodin reaction to be carried out under neutral conditions. The non-electrophilic nature of the esters 3 is advantageous,[14] especially for electron rich, sensitive molecules. Similar considérations apply in amino-acid chemistry (Table I). From the acid 4, after conversion into the derivative of type 3, and photolysis in the presence of bromotrichloromethane the bromo-compound 40 was obtained in 82% yield.

Further of our results are summarised in Table I. In preliminary thermal experiments the use of carbon tetrachloride gave the chloride 41, whilst iodoform furnished the iodo-derivative 42.

Table I

Starting material	Product	Yield Isolated (%)
4	40	82
4	41[a]	43
4	42[a]	49
43	44	60
45	46	60
6	47	64
24	48	47
49	50	77
8	51	69

(a) thermolysis

The aspartic acid derivative 43 gave the bromide 44, without any elimination, as did derivative 45, which afforded bromide 46. In the glutamic acid series again, the derivative 6 gave the bromide 47. Another glutamic acid derivative 24 furnished bromide 48. Again the glutamic acid derivative 49 gave the bromide 50 in good (77%) yield. Tamm recently reported[15] a yield of 84% of the same crystalline bromide 50 which was an intermediate in an elegant synthesis of 1-amino-cyclopropane-1-carboxylic acid. Finally, in the aspartic acid series 8 afforded 51 in good yield.

In the absence of a radical trap, esters of type 3 rearrange with loss of carbon dioxide to give S(2)-Pyridyl derivatives. These derivatives lend themselves to further useful chemical manipulations. As expected then, several typical examples illustrated that the side chain carboxyl function could be conveniently modified in the same way (Table II).

Table II

Starting Material	Product	Yield Isolated (%)
43	54	65
4	52	48
45	53	74

From these preliminary studies it is clear that disciplined radicals have the potential to play a major role in the modification of amino-acids and peptide molecules.

The availability of the sodium salt of N-hydroxy-2-thiopyridine as a 40% aqueous solution from the Olin corporation provides an inexpensive source of N-hydroxy-2-thiopyridone (acidification with concentrated HCl) and permits large scale work.[14,15]

EXPERIMENTAL

For general Experimental see our previous papers on peptide chemistry.[5,6,7] All rotations were taken in MeOH unless specified to the contrary. In all experiments herein reported, only L-amino-acids were used as starting materials.

Synthesis of Esters 3.-

Into a three necked flask equipped with a thermometer, was added (under nitrogen or argon) N-methylmorpholine (1 mmol, 0.11 ml) and isobutyl chloroformate (1 mmol, 0.14 ml) at - 15°C to a solution of the suitably protected amino-acid (1 mmol) in dry tetrahydrofuran (5 ml). After 5 min. at - 15°C, a solution of N-hydroxy-2-thiopyridone (1.2 mmol, 152 mg) and of triethylamine (1.2 mmol, 0.17 ml) in dry tetrahydrofuran (3 ml) was added. The mixture was stirred at - 15°C under nitrogen or argon, sheltered from the light (aluminium foil), during about one hour. The required ester formation can be followed by t.l.c. (yellow spot-ethylacetate-hexane (1:1)). The precipitate of N-methylmorpholine hydrochloride was filtered and washed with more dry tetrahydrofuran under aluminium foil protection.

Reduction of Esters 3.-

The yellow filtrate was irradiated in presence of t-butyl thiol with two 100 watt tungsten lamps at room temperature under an inert atmosphere in a water bath until the yellow colour has disappeared (usually 10-20 mins). The temperature in the flask was close to room temperature. Ether was then added and the ether layer was washed with sodium hydrogen carbonate (0.1 N), water, dilute hydrochloric acid (0.5 N), water again and then with saturated brine. The product was then purified on silica gel.

Bromination.-

After filtration of N-methylmorpholine hydrochloride the tetrahydrofuran was removed in vacuo at room temperature with protection from light (aluminium foil). The residue was taken up in bromotrichloromethane and irradiated as above. The bromotrichloromethane was removed in vacuo and the product purified on silica gel.

Chlorination and Iodination.-

After removal of the tetrahydrofuran, CCl_4 or benzene-iodoform were added and the yellow solutions were heated. These were only two preliminary experiments and the photochemical method would surely give better yields.

The L benzyl ester 5.- This was obtained as an oil (78%). $[\alpha]_D$ = - 42.0° (c = 1.2) ; ν_{max} : 1760, 1680 cm^{-1} ; δ_H : 0.86 (3H, t, J = 7.9 Hz), 1.39 (9H, s), 1.69 (2H, m), 4.09 (1H, q, J = 7 Hz), 4.72 (1H, m), 4.95 (2H, s), 7.03 (5H, s) (Found : C, 65.58 ; H, 7.91 ; O, 22.10. Calc. for $C_{16}H_{23}NO_4$: C, 65.51 ; H, 7.90 ; O, 21.82).

The L benzyl ester 7.- This (68%) had m.p. 52.0°C (Ether - Hexane). $[\alpha]_D$ = - 28.0° (c = 1.0) ; ν_{max} : 1770, 1680 cm^{-1} ; δ_H : 0.85 (3H, t, J = 8 Hz), 1.75 (2H, m), 4.35 (1H, m), 5.07 (2H, s), 5.15 (2H, s), 5.32 (1H, m), 7.27 (10H, s) (Found : C, 69.47 ; H, 6.47 ; N, 4.32 ; O, 19.78. Calc. for $C_{19}H_{21}NO_4$: C, 69.70 ; H, 6.47 ; N, 4.28 ; O, 19.55).

The L t-Butyl ester 9.- This was obtained as an oil (93%). ν_{max} : 1700 cm^{-1} ; δ_H : 1.35 (3H, d, J = 7.2 Hz), 1.39 (18H, s), 4.08 (1H, q, J = 8 Hz), 4.98 (1H, m) (Found : C, 59.04 ; H, 9.46 ; O, 26.15. Calc. for $C_{12}H_{23}NO_4$: C, 58.75 ; H, 9.45 ; O, 26.09).

The phenethylamine derivative 11.- The residue obtained after the usual washings described in Experimental was deprotected by trifluoroacetic acid (1 cm^3) in methylene chloride (1 cm^3) at room temperature for 30 mins. After addition of water, the reaction mixture was extracted with ether. The aqueous phase was made alcaline with a 17% ammonia solution and extracted with ether. This latter organic phase was washed with brine, dried on sodium sulfate, evaporated down in vacuo. The oil so obtained (85%) had I.R. and N.M.R. spectra identical with those of an authentical sample.

The methionamine 13.- This was obtained as an oil (78%). ν_{max} : 1750 cm^{-1} ; δ_H : 1.40 (9H, s), 1.75 (2H, m), 2.05 (3H, s), 2.50 (2H, t, J = 7 Hz), 3.20 (2H, q, J = 7 Hz), 4.20 (1H, m) (Found : C, 52.55 ; H, 9.33 ; N, 6.82 ; O, 15.58. Calc. for $C_9H_{19}NO_2S$: C, 52.30 ; H, 9.26 ; N, 6.56 ; O, 15.70).

The GABA derivative 15.- This (93%) had m.p. 64°C (AcOEt - Cyclohexane) ; ν_{max} : 1740, 1680 cm^{-1}; δ_H : 1.35 (9H, s), 1.81 (2H, m), 2.31 (2H, t, J = 7 Hz), 3.00 (2H, q, J = 7 Hz), 4.16 (1H, m), 4.85 (2H, s), 6.96 (5H, s) (Found : C, 65.76 ; H, 7.97 ; N, 4.91. Calc. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90 ; N, 4.78). This preparation was also repeated using anhydrous dimethylformamide as solvent (94%).

The alcohol 17.- This was obtained as an oil (87%). $[\alpha]_D$ = - 15.0° (c = 1.1) ; ν_{max} : 3460, 1750, 1700 cm^{-1} ; δ_H : 1.15 (3H, d, J = 6 Hz), 1.45 (9H, s), 3.20 (3H, m), 3.90 (1H, m), 5.25 (1H, m) (Found : C, 54.88 ; H, 9.78 ; N, 7.66 ; O, 27.54. Calc. for $C_8H_{17}NO_3$: C, 54.84 ; H, 9.78 ; N, 7.99 ; O, 27.39).

The nitroanilide 19.- This was obtained as a white powder (80%), m.p. 109°C (AcOEt) ; ν_{max} : 3380, 3300, 3160, 1690 cm^{-1} ; δ_H : 1.45 (9H, s), 1.58 (4H, m), 3.23 (4H, m), 4.67 (1H, m), 7.39 (2H, m), 8.25 (1H, m) (Found : C, 43.73 ; H, 7.43 ; O, 23.30. Calc. for $C_{10}H_{21}N_5O_4$: C, 43.62 ; H, 7.69 ; O, 23.25).

The alcohol 21.- This (79%) was obtained as white needles and had m.p. 61°C (AcOEt - Cyclohexane); ν_{max} : 1690 cm^{-1} ; δ_H : 2.90 (1H, s), 3.35 (2H, m), 3.70 (2H, m), 5.30 (2H, s), 5.40 (1H, m), 7.35 (5H, s) (Found : C, 61.29 ; H, 6.67 ; N, 7.31 ; O, 24.53. Calc. for $C_{10}H_{13}NO_3$ C, 61.52 ; H, 6.71 ; N, 7.18 ; O, 24.59).

The L lactone 23.- This (65%) had m.p. 87°C (Ether - Cyclohexane) ; $[\alpha]_D$ = + 63.0° (c = 1) ; ν_{max} : 1780, 1690 cm^{-1} ; δ_H : 1.50 (3H, d, J = 7 Hz), 4.12 (1H, q, J = 7 Hz), 4.90 (2H, s), 5.05 - 5.25 (2H, 2d, J = 7 Hz), 7.06 (5H, s) (Found : C, 61.31 ; H, 5.67 ; O, 27.02 ; Calc. for $C_{12}H_{13}NO_4$: C, 61.27 ; H, 5.57 ; O, 27.21).

The L lactone 25.- This was obtained as an oil (78%). $[\alpha]_D$ = + 58.0° (c = 0.8) ; ν_{max} : 1810, 1720 cm^{-1} ; δ_H : 0.95 (3H, t, J = 8 Hz), 2.00 (2H, m), 4.30 (1H, t, J = 5 Hz), 5.18 (2H, s), 5.25-5.52 (2H, 2d, J = 7 Hz), 7.40 (5H, s) (Found : C, 62.84 ; H, 6.06 ; O, 25.93. Calc. for $C_{13}H_{15}NO_4$: C, 62.64 ; H, 6.07 ; O, 25.68).

The tryptamine derivative 27.- This was obtained as a yellow solid (94%) and had m.p. 85-86°C (AcOEt - Petroleum Ether) ; ν_{max} (Nujol) : 3390, 3270, 1710, 1680 cm^{-1} ; δ_H : 2.92 (2H, t, J = 8 Hz), 3.50 (2H, q, J = 7 Hz), 4.92 (1H, m), 5.12 (2H, s), 7.32 (5H, s), 6.75 - 7.75 (5H, m), 8.17 (1H, m) (Found : C, 73.19 ; H, 6.10 ; N, 9.59 ; O, 10.92. Calc. for $C_{18}H_{18}N_2O_2$: C, 73.45 ; H, 6.16 ; N, 9.52 ; O, 10.87).

The 5-hydroxytryptamine derivative 29.- This was obtained as an oil (61%). ν_{max} : 1685, 1630, 1580 cm^{-1} ; δ_H : 1.42 (10H, s), 2.74 (2H, t, J = 7 Hz), 3.31 (2H, q, J = 7 Hz), 4.69 (1H, m), 6.62-7.20 (4H, m), 8.17 (1H, m) (Found : C, 64.93 ; H, 7.28 ; O, 17.41. Calc. for $C_{15}H_{20}O_3N_2$: C, 65.19 ; H, 7.29 ; O, 17.37).

The pyrrolidine derivative 31.- This was obtained as an oil (81%). ν_{max} : 1750 cm^{-1} ; δ_H : 1.81 (4H, m), 3.33 (4H, m), 5.10 (2H, s), 7.16 (5H, s) (Found : C, 69.98 ; H, 7.45 ; O, 15.45. Calc. for $C_{12}H_{15}NO_2$: C, 70.22 ; H, 7.37 ; O, 15.59).

The hydroxy pyrrolidine 33.- This (69%) had m.p. 58°C (AcOEt - Cyclohexane). $[\alpha]_D$ = - 30.0° (c = 0.5) ; ν_{max} (Nujol) : 3320, 1690 cm^{-1} ; δ_H : 1.38 (9H, s), 1.88 (2H, m), 3.08 (5H, m), 4.26 (1H, m) (Found : C, 57.58 ; H, 8.90 ; N, 7.50. Calc. for $C_9H_{17}NO_3$: C, 57.77 ; H, 9.15 ; N, 7.48). In our preliminary communication[8] the rotation of this compound was uncorrectly reported to be - 15°.

The tyramine derivative 35.- This (96%) had m.p. 100°C (Ether - Cyclohexane). ν_{max} (Nujol) : 3330, 1690, 1600 cm^{-1} ; δ_H : 2.50 (1H, s), 2.60 (2H, t, J = 6 Hz), 3.23 (2H, q, J = 6.2 Hz), 4.62 (1H, m), 4.88 (2H, s), 6.47 (2H, d, J = 7.9 Hz), 6.70 (2H, d, J = 7.9 Hz), 6.93 (5H, s) (Found : C, 70.77 ; H, 6.35 ; O, 17.96. Calc. for $C_{16}H_{17}NO_3$: C, 70.83 ; H, 6.32 ; O 17.69).

The L,L dipeptide derivative 37.- This (74%) had m.p. 126-127°C (AcOEt - Cyclohexane) ; $[\alpha]_D$ = -35° (c = 1) ; ν_{max} (Nujol) : 3500, 3430, 3310, 1780, 1710, 1690 cm^{-1} ; δ_H : 0.95 (3H, t, J = 8 Hz), 1.45 (9H, s), 2.1 (2H, m), 2.40 (4H, m), 4.30 (1H, m), 4.65 (1H, m), 5.25 (2H, s), 6.00 (1H, m), 6.40 (1H, m), 7.40 (5H, s), 7.70 (2H, m). (Found : C, 59.80 ; H, 7.34 ; O, 22.81. Calc. for $C_{21}H_{31}N_3O_6$ C, 59.84 ; H, 7.41 ; O 22.78).

The L dipeptide derivative 39.- This (83%) obtained as a white powder had m.p. 69-70°C (Ether - Cyclohexane). $[\alpha]_D$ = - 28.0° (c = 1.2) ; ν_{max} (Nujol) : 3300, 1680, 1650 cm^{-1} ; δ_H : 0.89 (6H, d, J = 6 Hz), 1.39 (9H, s), 1.48 (1H, m), 1.78 (4H, m), 1.98 (3H, s), 2.40 (2H, t, J = 8 Hz), 3.30 (2H, q, J = 7 Hz), 3.89 (1H, m), 4.90 (1H, m), 6.77 (1H, m) (Found : C, 56.82 ; H, 9.59 ; N, 8.69; O, 14.98. Calc. for $C_{15}H_{30}NO_3S$: C, 56.57 ; H, 9.49 ; N, 8.80 ; O, 15.07).

The L bromo ester 40.- This (82%) had m.p. 53°C (Pentane). $[\alpha]_D$ = - 34.0° (c = 1.0) ; ν_{max} (Nujol) : 3370, 1770, 1685 cm^{-1} ; δ_H : 1.45 (9H, s), 2.32 (2H, m), 3.40 (2H, t, J = 7 Hz), 4.47 (1H, m), 5.10 (1H, m), 5.22 (2H, s), 7.42 (5H, s) (Found : C, 51.53 ; H, 5.96 ; N, 3.85 ; O, 16.94. Calc. for $C_{16}H_{22}BrNO_4$: C, 51.62 ; H, 5.96 ; N, 3.76 ; O, 17.19).

The L chloro derivative 41.- This (43%) had m.p. 42-43°C (Petroleum Ether). $[\alpha]_D$ = - 36.2° (c = 1.3) ; ν_{max} : 3400, 1730, 1700 cm^{-1} ; δ_H : 1.42 (9H, s), 2.27 (2H, m), 3.59 (2H, t, J = 7 Hz), 4.47 (1H, m), 5.15 (1H, m), 5.20 (2H, s), 7.30 (5H, s) ; m/e : 327 (M^+), 227 (M^+-Boc).

The L iodo derivative 42.- This (49%) had m.p. 54°C (Pentane). $[\alpha]_D$ = - 33.0° (c = 1.0) ; ν_{max} (Nujol) : 3300, 1765, 1685 ; δ_H : 1.40 (9H, s), 2.20 (2H, q, J = 8 Hz), 3.03 (2H, t, J = 8 Hz), 4.20 (1H, m), 5.00 (1H, m), 5.20 (2H, s), 7.25 (5H, s) (Found : C, 45.63 ; H, 5.25 ; N, 3.40 Calc. for $C_{16}H_{22}INO_4$: C, 45.83 ; H, 5.29 ; N, 3.34).

The L bromo ester 44.- This (64%) obtained as white needles had m.p. 66°C (Ether - Pentane). $[\alpha]_D$ = - 22.0° (c = 1.4) ; ν_{max} (Nujol) : 1735, 1685 cm^{-1} ; δ_H : 1.40 (9H, s), 3.71 (2H, t, J = 4 Hz), 4.71 (1H, m), 5.20 (2H, s), 5.43 (1H, m), 7.36 (5H, s) (Found : C, 50.47 ; H, 5.62 ; N, 4.09; O, 17.67. Calc. for $C_{15}H_{20}BrNO_4$: C, 50.29 ; H, 5.63 ; N, 3.91 ; O, 17.87).

The L bromo ester 46.- This (60%) obtained as white needles had m.p. 84-85°C (Ether - Pentane). $[\alpha]_D$ = - 18.1° (c = 1.0) ; ν_{max} (Nujol) : 1745, 1685 cm^{-1} ; δ_H : 3.77 (2H, m), 4.81 (1H, m), 5.12 (2H, s), 5.21 (2H, s), 5.75 (1H, m), 7.37 (10H, s) (Found : C, 55.20 ; H, 4.63 ; N, 3.51 ; O, 16.25. Calc. for $C_{18}H_{18}BrNO_4$: C, 55.12 ; H, 4.62 ; N, 3.57 ; O, 16.32).

The L bromo ester 47.- This (64%) obtained as a white solid had m.p. 64°C (Ether - Cyclohexane). $[\alpha]_D$ = - 35.0° (c = 1.0) ; ν_{max} (Nujol) : 1740, 1690 cm^{-1} ; δ_H : 2.45 (2H, q, J = 8 Hz), 3.4 (2H, t, J = 7 Hz), 4.57 (1H, q, J = 6 Hz), 5.12 (2H, s), 5.20 (2H, s), 5.50 (1H, m), 7.63 (10H, s) (Found : C, 56.00 ; H, 5.12 ; N, 3.16 ; O, 15.51. Calc. for $C_{19}H_{20}BrNO_4$: C, 56.17 ; H, 4.96 ; N, 3.45 ; O, 15.75).

The L bromo lactone 48.- This (73%) obtained as a white solid had m.p. 66°C (Cyclohexane). $[\alpha]_D$ = + 54.0° (c = 0.9) ; ν_{max} (Nujol) : 1780, 1720, 1500 cm^{-1} ; δ_H : 2.50 (2H, q, J = 7 Hz), 3.47 (2H, t, J = 8 Hz), 4.47 (1H, t, J = 6 Hz), 5.25 (2H, s), 5.32 (1H, d, J = 7 Hz), 5.60 (1H, d, J = 7 Hz), 7.42 (5H, s) (Found : C, 47.58 ; H, 4.25 ; N, 4.12 ; O, 19.76. Calc. for $C_{13}H_{14}BrNO_4$: C, 47.58 ; H, 4.30 ; N, 4.27 ; O, 19.50).

The L bromo methyl ester 50.- This (77%) had m.p. 63-64°C (Petroleum Ether). $[\alpha]_D$ = - 40.8° (c = 1.0, DMF) Lit.[10] m.p. 62-64°C and $[\alpha]_D$ = - 41.2° (c = 0.5, DMF) (Lit.[15] 60-61°C) ; ν_{max} : 1730 cm^{-1} ; δ_H : 2.21 (2H, m), 3.40 (2H, t, J = 6 Hz), 3.74 (3H, s), 4.52 (1H, m), 5.14 (2H, s), 5.55 (1H, m), 7.39 (5H, s) (Found : C, 47.43 ; H, 4.90. Calc. for $C_{13}H_{16}BrNO_4$: C, 47.49 ; H, 4.44).

The L bromo t-butyl ester 51.- This (69%) had m.p. 64-65°C (Ether - Cyclohexane). $[\alpha]_D$ = - 9.0° (c= 1.0) ; ν_{max} (Nujol) : 1720 cm^{-1} ; δ_H : 1.46 (9H, s), 1.50 (9H, s), 3.75 (2H, m), 4.57 (1H, m), 5.32 (1H, m) (Found : C, 44.50 ; H, 6.91 ; N, 4.15 ; O, 19.90. Calc. for $C_{12}H_{22}BrNO_4$: C, 44.45 ; H, 6.83 ; N, 4.32 ; O, 19.74).

The L pyridine derivative 52.- This was obtained as an oil (48%). $[\alpha]_D$ = - 39.5° (c = 1.0) ; ν_{max} : 3360, 1750, 1715 cm^{-1} ; δ_H : 1.45 (9H, s), 2.22 (2H, m) ; 3.20 (2H, t, J = 8 Hz), 4.45 (1H, m), 5.17 (2H, s), 5.82 (1H, m), 7.32 (5H, s), 6.85, 8.45 (4H, m) (Found : C, 62.60 ; H, 6.41 N, 7.21 ; O, 15.69. Calc. for $C_{21}H_{26}N_2O_4S$: C, 62.66 ; H, 6.51 ; N, 6.96 ; O, 15.90).

The L pyridine derivative 53.- This was obtained as an oil (74%). $[\alpha]_D$ = - 45.5° (c = 1.4) ; ν_{max} : 1740, 1700 cm^{-1} ; δ_H : 3.61 (2H, d, J = 7 Hz), 4.65 (1H, m), 5.06 (2H, s), 5.11 (2H, s), 7.27 (14H, m) (Found : C, 65.52 ; H, 5.22 ; N, 6.60 ; O, 15.22. Calc. for $C_{23}H_{22}N_2O_4S$: C, 65.36 H, 5.25 ; N, 6.66 ; O, 15.14).

The L pyridine derivative 54.- This (65%) had m.p. 51-52°C (Pentane). $[\alpha]_D$ = - 37.5° (c = 1.0) ; ν_{max} : 1750, 1720 cm^{-1} ; δ_H : 1.40 (5H, s), 3.65 (2H, d, J = 6 Hz), 4.64 (1H, m), 5.15 (2H, s), 6.29 (1H, m), 7.35 (9H, m) (Found : C, 62.09 ; H, 6.17 ; N, 7.16 ; O, 16.42. Calc. for $C_{20}H_{24}N_2O_4S$: C, 61.83 ; H, 6.23 ; N, 7.21 ; O, 16.47).

REFERENCES

1. D.H.R. Barton, D. Crich and W.B. Motherwell, J. Chem. Soc. Chem. Comm., 1983, 939 ; D.H.R. Barton, D. Crich and W.B. Motherwell, Tetrahedron, 1985, 41, 3901.
2. M. Newcomb and S.U. Park, J. Am. Chem. Soc., 1986, 108, 4132.
3. M. Newcomb, S.U. Park, J. Kaplan and D.J. Marquardt, Tetrahedron Lett., 1985, 26, 5651 ; M. Newcomb and T.M. Deeb, J. Am. Chem. Soc., 1987, 109, 3163.
4. D.H.R. Barton, H. Togo and S.Z. Zard, Tetrahedron, 1985, 41, 5507.
5. D.H.R. Barton, Y. Hervé, P. Potier and J. Thierry, Tetrahedron, 1987, 43, 4297.
6. D.H.R. Barton, D. Crich, Y. Hervé, P. Potier and J. Thierry, Tetrahedron, 1985, 41, 4347.
7. D.H.R. Barton, D. Bridon, Y. Hervé, P. Potier, J. Thierry and S.Z. Zard, Tetrahedron, 1986, 42, 4983.
8. D.H.R. Barton, Y. Hervé, P. Potier and J. Thierry, J. Chem. Soc. Chem. Comm., 1984, 1298.
9. G.W. Anderson, J.E. Zimmermann and F.M. Callahan, J. Am. Chem. Soc., 1967, 89, 5012.
10. B.D. Harris, K.L. Bhat and M.M. Joullié, Synthetic Communications, 1986, 16, 1815.
11. K.L. Bhat, D.M. Flanagan and M.M. Joullié, Synthetic Communications, 1985, 15, 587.
12. P. Renaud and D. Seebach, Synthesis, 1986, 424.
13. M. Hashimoto, Y. Eda, Y. Osanai, T. Iwai and S. Aoki, Chem. Lett., 1986, 893, and references there cited.
14. For example see E.W. Della and J. Tsanaktsidis, Aust. J. Chem., 1986, 39, 2061 ; G. Quinkert, V.M. Billhardt, H. Jakob, G. Fischer, J. Glenneberg, P. Nagler, V. Autze, N. Heim, M. Wacher, T. Schwalbe, Y. Kurth, J.W. Bats, G. Dürner, G. Zimmermann and H. Kessler, Helv. Chim. Acta, 1987, 70, 771.
15. P. Strazewski and C. Tamm, Synthesis, 1987, 298.
16. K. Jost and J. Rudinger, Coll. Czech. Chem. Comm., 1967, 32, 2485.