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Synthesis of Analogues of GABA. XV* Preparation and Resolution of Some Potent Cyclopentene and Cyclopentane Derivatives

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Abstract

A series of cyclopentene and cyclopentane analogues of GABA has been prepared utilizing a thermal *cis–trans* isomerization of the phthalimido β,γ-unsaturated acid (10) as the key step to obtain *trans*-4-aminocyclopent-2-ene-1-carboxylic acid (7). Resolution of some of the potent GABA analogues, in particular (+)-(4*S*)- and (−)-(4*R*)-4-aminocyclopent-1-ene-1-carboxylic acid (5), has been achieved by crystallization of isopropylideneribonolactone esters or pantolactone esters of the phthalimido-protected intermediates.

Conformationally restricted analogues of the inhibitory neurotransmitter γ-aminobutyric acid [GABA, (1)] have given considerable information about active conformations of GABA at receptors and uptake sites in the nervous system.[1,2] Of the carbocyclic analogues, cyclopentane compounds such as *cis*- and *trans*-3-aminocyclopentane-1-carboxylic acid (2) and (3) are notably active.[1,3,4] Further subtle changes in conformation by the introduction of a double bond into the ring have led to (4), (5) and (6),[5] of which (5) was the most notable by acting potently on both GABA receptors and GABA uptake.[3,5] The *trans*-unsaturated compound (7) was needed to complete structure–activity studies. Furthermore, for biological testing, these racemic derivatives must necessarily be considered as a mixture of two optical isomers with potentially different actions, and resolution of the analogues is important particularly for potent derivatives such as (5). We have previously reported a synthesis of all the optical isomers of the saturated analogues (2) and (3) via keto acids or diacids which had been resolved as brucine salts.[6]

* Part XIV, *Aust. J. Chem.*, 1985, **38**, 1651.

[1] Allan, R. D., and Johnston, G. A. R., *Med. Res. Rev.*, 1983, **3**, 91.

[2] Krogsgaard-Larsen, P., *J. Med. Chem.*, 1983, **24**, 1377; Krogsgaard-Larsen, P., and Falch, E., *Mol. Cell. Biochem.*, 1981, **38**, 129.

[3] Johnston, G. A. R., Allan, R. D., Kennedy, S. M. E., and Twitchin, B., in 'GABA-Neurotransmitters' (Eds P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod) p. 149 (Munksgaard: Copenhagen 1978).

[4] Segal, M., Sims, M., and Smissman, E., *Br. J. Pharm.*, 1975, **54**, 181; Nicoll, R. A., *Br. J. Pharm.*, 1977, **59**, 303.

[5] Allan, R. D., and Twitchin, B., *Aust. J. Chem.*, 1980, **33**, 599.

[6] Allan, R. D., Johnston, G. A. R., and Twitchin, B., *Aust. J. Chem.*, 1979, **32**, 2517; Johnston, G. A. R., Allan, R. D., Andrews, P. R., Kennedy, S. M. E., and Twitchin, B., in 'Advances in Pharmacology and Therapeutics' Vol. 12: Neurotransmitters (Ed. P. Simon) p. 11 (Pergamon Press: Oxford 1978).

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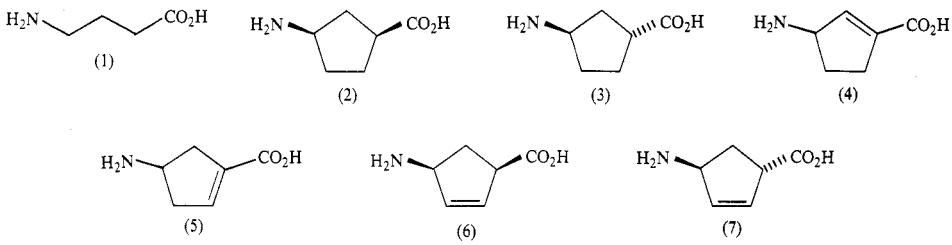
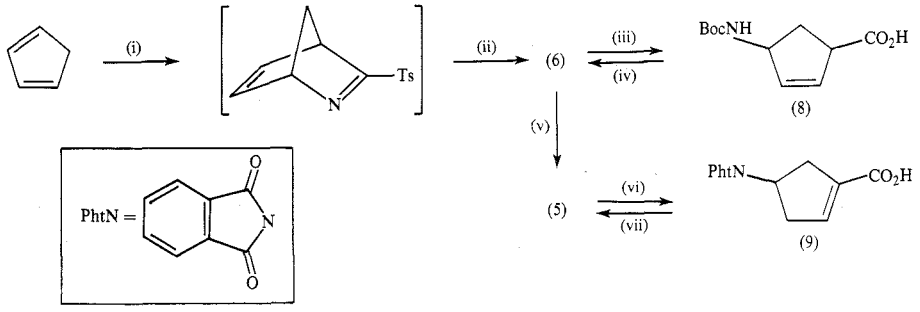
The separation of optical isomers by the formation of diastereomeric derivatives offers advantages of greater certainty of stereochemical purity, especially if the intermediate can be crystallized and the purity monitored by physical techniques such as n.m.r. spectroscopy. We report here the utility of protected ribonolactone and pantolactone esters[7] in generating easily purified diastereomeric phthalimido esters for the synthesis of optically pure GABA analogues.



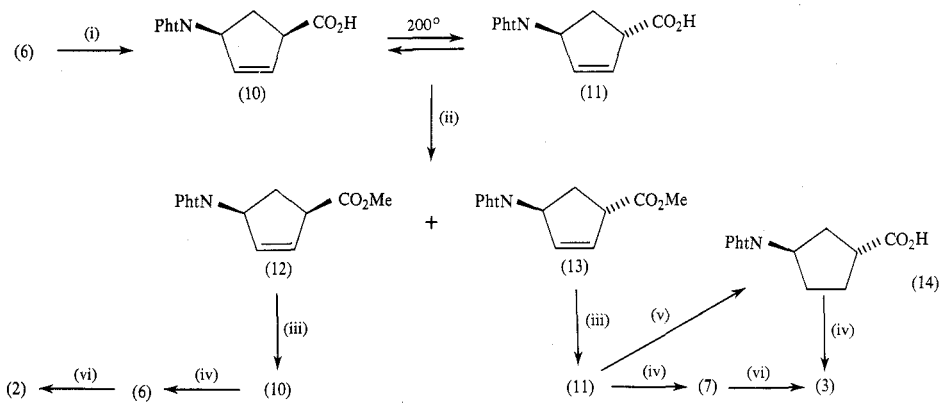
We have previously gained access to the unsaturated cyclopentane amino acids (5) and (6)[5] using the Diels–Alder addition of tosyl cyanide to cyclopentadiene.[8] However, direct purification of the crude amino acids by crystallization was liable to produce mixtures or low recoveries. Other groups have utilized this Diels–Alder addition product in the synthesis of cyclopentene amino acid derivatives,[9,10] and Kan and Oppenheimer reported the base-catalysed isomerization of the methyl ester of (6) to a *cis–trans* mixture which was separated by h.p.l.c.[9] They used the new amino acid we required (7) without characterization.

Because quantities for resolution were needed we chose to investigate crystallization of *N*-protected intermediates of (6) and (7) rather than h.p.l.c. separations. The t-butyloxycarbonyl compound (8) (Scheme 1) was found to be a convenient intermediate for the purification and regeneration of (6), and the phthalimido derivative (9) was more appropriate for the purification of (5). During these investigations it was found that a simple fusion with phthalic anhydride was far better than *N*-ethoxycarbonylphthalimide[11] for introducing the protecting group, and if the fusion temperature was 200° or greater (Scheme 2), a 1 : 1 mixture of *cis* and *trans* isomers (10) and (11) containing less than 5% of the conjugated isomer (9) resulted. The mixture could be conveniently analysed by clearly defined n.m.r. peaks at δ 3·7 and 4·2 for the α-protons of (10) and (11) respectively and δ 6·8 for the vinylic proton of (9). The two main components could be readily isolated in gram quantities by chromatography of the methyl esters (12) and (13) (Scheme 2). Deprotection with mild acid hydrolysis followed by hydrazine yielded the amino acids (6) and (7) without isomerization. As indicated in Scheme 2, the *trans* configuration of (13) was confirmed by reduction of the derived amino acid (7) to (3). Alternately, reduction of the double bond in a non-aqueous solvent was accomplished via (14), and this route may be preferable if a means of generating tritiated *trans* amino acid (3) is required.

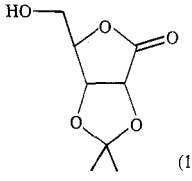
[7] Duke, C., and Wells, R. J., *Chem. Abstr.*, 1983, **98**, P198658k.
[8] Jagt, J. C., and van Leusen, A. M., *J. Org. Chem.*, 1974, **39**, 564.
[9] Kam, B. L., and Oppenheimer, N. J., *J. Org. Chem.*, 1981, **46**, 3268.
[10] Daluge, S., and Vince, R., *J. Org. Chem.*, 1978, **43**, 2311.
[11] Adriaens, P., Meesschaert, B., Janssen, G., Dumon L., and Eyssen, H., *Recl Trav. Chim. Pays-Bas*, 1978, **97**, 260.



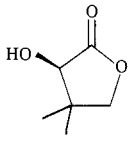
Scheme 1. Reagents: (i), TsCN (ref.[11]); (ii), H^+/H_2O; (iii), $(Boc)_2O$; (iv), HCl/EtOAc; (v), $NaOH/H_2O$; (vi), phthalic anhydride/150°; (vii), 6 M HCl/AcOH.



Scheme 2. Reagents: (i), phthalic anhydride/150°; (ii) MeOH/HCl; (iii), $H^+/AcOH/H_2O$; (iv), H_2NNH_2; (v), H_2/Pd–C/EtOAc; (vi), H_2/Pd–C/AcOH. PhtN as in Scheme 1.



(15)

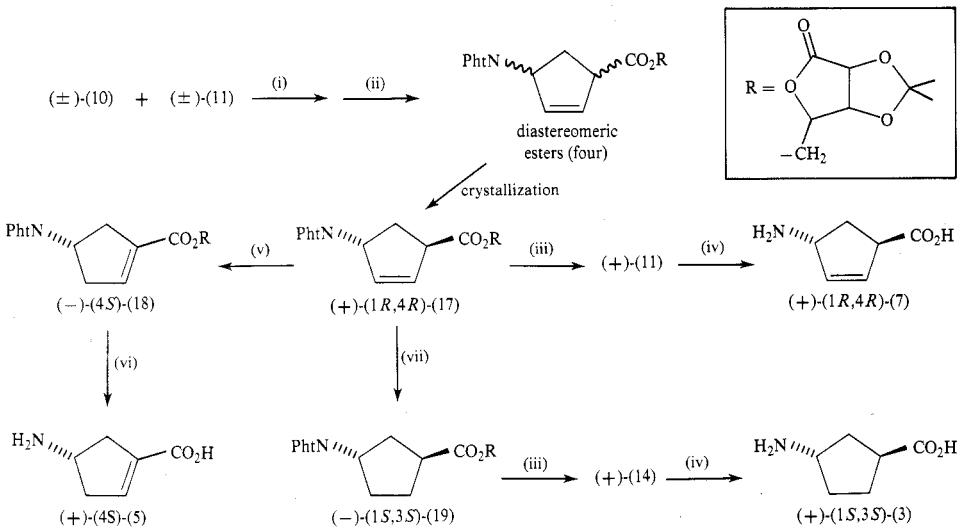


(16)

Attempts to resolve the *N*-protected acids (8), (10) and (11) with a wide range of resolving bases, including arginine,[12] failed. Wells and Duke[7] have developed the technique of using protected sugar alcohols such as 2,3-isopropylidine-D-(+)-ribonic acid-1,4-lactone (15) and D-(−)-pantolactone (16) to give diastereomeric esters which could be separated by crystallization or chromatography. Application of this technique to the *trans* phthalimido acid (11) gave a mixture from which one isopropylidineribonolactone ester crystallized readily. Indeed, pure (17) could be

[12] Allan, R. D., Johnston, G. A. R., and Twitchin, B., *Aust. J. Chem.*, 1981, **34**, 2231.

readily obtained from the crude *cis–trans* isomerization product, crystallizing from a mixture of four diastereomeric esters as shown in Scheme 3. The yield of (17) from the crude *cis*-phthalimido acid (10) was 8·7%. The protected ribonolactone ester function was readily hydrolysed without isomerization to give (+)-(1*R*,4*R*)-(7) ($[\alpha]_D$ +332°) or, after conjugation of the double bond, (+)-(4*S*)-(5) ($[\alpha]_D$ +28·0°) (Scheme 3). The absolute stereochemistry was shown to be as indicated by reduction to (19) and subsequent deprotection to the known potent GABA agonist (+)-(1*S*,3*S*)-(3) with $[\alpha]_D$ +23·1° compared with $[\alpha]_D$ +24° reported previously.[6]

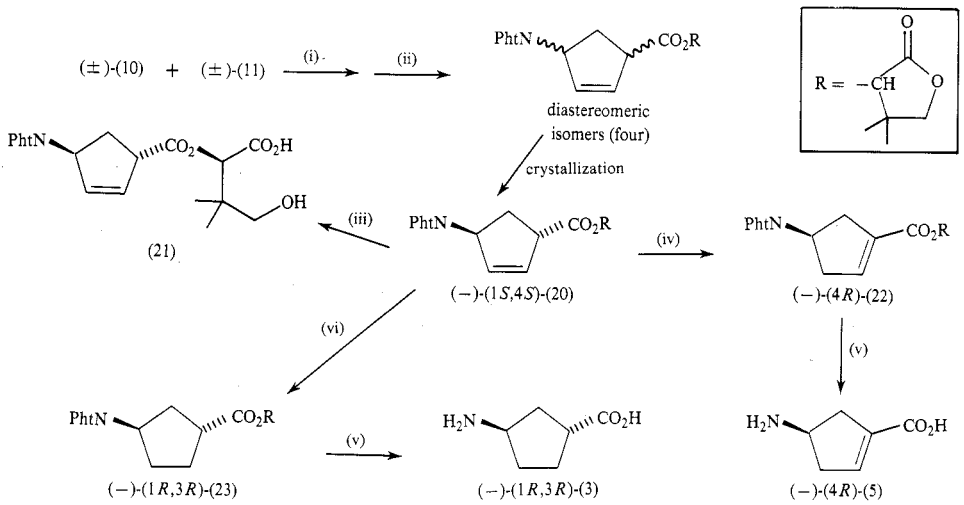


Scheme 3. Reagents: (i), $(COCl)_2$/benzene; (ii), (15)/pyridine/tetrahydrofuran; (iii), 1 M HCl/AcOH; (iv), H_2NNH_2; (v), 1,5-diazabicyclo[4.3.0]non-5-ene; (vi), 6 M HCl/AcOH; (vii), H_2/Pd–C/EtOAc. PhtN as in Scheme 1.

It was particularly important for structure–activity studies on GABA receptors and GABA uptake to prepare the enantiomeric conjugated amino acid (−)-(4*R*)-(5) which was not readily forthcoming from the mother liquors of (17). One direct route would be to use the enantiomeric 2,3-isopropylidine-L-(−)-ribonic acid-1,4-lactone but this material is not available in reasonable quantity. This problem was circumvented by the discovery that the pantolactone ester of 1*S*,3*S* (11) could also be readily crystallized from a mixture of four diastereomeric esters (Scheme 4). As with the ribonolactone esters, the purity of the ester (20) could be readily monitored by ^{13}C n.m.r. spectroscopy and shown to be greater than 99% pure. Because the conditions used in subsequent transformations do not epimerize the amino substituent, the optical purity of the resultant amino acids must be at least 99%. This independent assessment of optical purity is particularly important in cases such as these where the specific rotations are comparatively low for all the amino acids except (7), and minor contamination by an active enantiomer can have a marked effect on the biological activity of a sample.

Unfortunately, mild acid hydrolysis only opened the pantolactone ester to give the hydroxy acid (21) (Scheme 4), and harsher conditions resulted in a *cis–trans* isomerization during ester hydrolysis to give an amino acid mixture. This was not a problem with the conjugated ester (22) or with the reduced ester (23) where the

activating effect of the double bond had been removed. Deprotection to the amino acid was accomplished in one step (Scheme 4) to (−)-(4*R*)-(5) ($[\alpha]_D$ −28·1°) and (−)-(1*R*,3*R*)-(3) ($[\alpha]_D$ −22·3°) respectively. The minor discrepancies in the specific rotations of (+)- and (−)-(3) are most likely due to inaccuracies in measurement of optical rotations since all the isolated amino acids were shown to be free of impurities by g.l.c. of the *N*-trifluoroacetyl methyl esters at a detection limit of 1%.



Scheme 4. Reagents: (i), $(COCl)_2$/benzene; (ii), (16)/pyridine/tetrahydrofuran; (iii), 6 M HCl/AcOH/1 h; (iv), 1,5-diazabicyclo[4.3.0]non-5-ene; (v), 6 M HCl/AcOH/5 h; (vi), H_2/Pd–C/EtOAc. PhtN as in Scheme 1.

The activity of the amino acids as GABA mimetic agents will be discussed in detail elsewhere[13] but a major finding is that the action of racemic (5) on both GABA receptors and GABA uptake systems can be separated. The (+)-(4*S*)-isomer of (5) is about 600 times more active than its enantiomer as a GABA agonist with respect to the transient contraction of the guinea-pig ileum, whereas (−)-(4*R*)-(5) is at least 100 times more potent than the (+)-(4*S*)-isomer at inhibiting the uptake of [^{3}H]-GABA into rat brain slices.

Experimental

^{1}H N.m.r. spectra were obtained on a Varian EM-360A spectrometer in either $CDCl_3$ or D_2O (for amino acids) with tetramethylsilane as internal or external standard, respectively, and ^{13}C n.m.r. spectra were recorded at 20 MHz on a Jeol FX90Q spectrometer in $CDCl_3$ relative to tetramethylsilane. I.r. spectra were taken from Nujol mulls on a Perkin–Elmer 177 spectrometer. Melting points (uncorrected) were measured on a Reichert hot-stage apparatus. Microanalyses were determined by the Australian Microanalytical Service, Melbourne. R_F values for thin-layer chromatography (t.l.c.) on Merck Kieselgel 60 precoated t.l.c. plates refer to the following solvents: (A) light petroleum/diethyl ether, 1 : 2; (B) dichloromethane/acetone, 1 : 1; (C) n-butanol/acetic acid/water, 4 : 1 : 1. Chromatographic separations were accomplished by the technique of collecting appropriate fractions from a column packed dry or wet with t.l.c. grade Kieselgel 60H silica gel to form a bed up to 6 cm high in a filter funnel of diameter 3 to 10 cm. The elution rate was increased by applying a vacuum via a Buchner flask, the only constraint on

[13] Allan, R. D., Dickenson, H. W., and Fong, J., *Eur. J. Pharmacol.*, 1986, **122**, 339.

the rate being that the top of the column should be kept wet with appropriate solvent. The purity of the amino acid products was analysed by gas chromatography of *N*-trifluoroacetyl methyl ester derivatives on SE30 on Chromosorb W as reported elsewhere.[6] Typical comparative retention times for the derivatives were (in min, s) (6) 2·13, (2) 2·35, (7) 2·40, (3) 2·55, (5) 3·33. All organic extracts were dried with sodium sulfate before rotary evaporation of the solvent. All compounds isolated, including the amino acids, were subjected to chemical ionization mass spectrometry on a Finnegan 2300E instrument and gave spectra consistent with the structural assignments.

cis-*4-(t-Butyloxycarbonyl)aminocyclopent-2-ene-1-carboxylic Acid (8)*

Cyanogen chloride (125·8 g, 2·0 mol) was bubbled into a solution of sodium *p*-toluenesulfinate (332 g, 1·86 mol) in water (2 l) according to the procedure of Daluge and Vince.[10] This tosyl cyanide product was added to freshly cracked cyclopentadiene at 0°C to yield the intermediate *N*-tosyl-2-azabicyclo[2·2·1]-hept-5-en-3-one which was hydrolysed with cold glacial acetic acid (500 ml) for 15 min and then with 4 M HCl (600 ml) at room temperature under nitrogen for 16 h. After evaporation of the solvent, this crude *cis* amino acid product (287 g) could be stored at 0°, and portions used to generate the neutral *cis* amino acid as required by absorbing onto a column of Dowex 50W (H^+) and eluting with 1 M pyridine.

This crude amino acid (6) (1·27 g, 10 mmol) was dissolved in 2·5 M sodium hydroxide (20 mmol, 8 ml) and t-butyl alcohol (15 ml). Following the addition of di-t-butyl dicarbonate (2·72 g, 12·5 mmol) a precipitate was observed after 2 min and rapid stirring was continued for 1·5 h. Water (30 ml) was added and the product was washed with hexane (2×20 ml), acidified with 6 M HCl and extracted into ethyl acetate (2×25 ml). Evaporation yielded a crude product (1·93 g, 85%) which was recrystallized from ethyl acetate to give the *N-Boc amino acid* (8), m.p. 108–113°, solidify 115°, remelt 129–130° (Found: C, 58·1; H, 7·6; N, 6·1. $C_{11}H_{17}NO_4$ requires C, 58·1; H, 7·5; N, 6·2%). I.r. ν_{max} 3340, 1688 cm^{-1}. ^1H n.m.r. δ 5·95, m, 2H, =CH; 5·0–4·50, m, CHN; 3·54, dd, *J* 3, 4·2 Hz, $CHCO_2$; 2·9–1·7, m, CH_2; 1·5, s, t-Bu. R_F(A) 0·70.

cis-*4-Aminocyclopent-2-ene-1-carboxylic Acid Hydrochloride (6).HCl*

Anhydrous HCl was passed through a solution of (8) (295 mg, 0·14 mmol) in ethyl acetate (10 ml) for 30 min. The white precipitate was filtered and washed with ethyl acetate to give the *amino acid* (6).HCl, m.p. 172–174° (lit.[5] 167–170°) (Found C, 44·1; H, 6·2; N, 8·6. $C_6H_{10}ClNO_2$ requires C, 44·0; H, 6·2; N, 8·6%). I.r. ν_{max} 3080, 1705, 780, 765 cm^{-1}. ^1H n.m.r. δ (for neutral amino acid) 6·79, m, 1H, =CH; 6·47, m, 1H, =CH; 5·02–4·69, m, CHN; 4·18–3·83, m, $CHCO_2$; 3·30–2·26, m, CH_2. R_F(C) 0·31.

4-Phthalimidocyclopent-1-ene-1-carboxylic Acid (9)

The crude amino acid (6) (17·6 g) was conjugated with hot aqueous 2 M sodium hydroxide[5] to give a crude sample of (9) (16 g). This material (5·84 g, 46 mmol) and phthalic anhydride (7·15 g, 48 mmol) were powdered together and heated to a melt at 150° for 15 min with magnetic stirring under nitrogen. The crude product was cooled to about 80° and boiling glacial acetic acid (40 ml) was added with activated charcoal. After filtering through Celite and concentrating, the *phthalimido amino acid* (9) crystallized slowly (6·08 g, 91%), m.p. 220° (Found: C, 65·5; H, 4·5; N, 5·3. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·4%). I.r. ν_{max} 1766, 1705, 1680, 717 cm^{-1}. ^1H n.m.r. δ ($CDCl_3/CD_3SOCD_3$) 7·79, m, ArH; 6·80, m, sharp, =CH; 5·45–4·77, m, apparent q, *J* 9 Hz, CHN; 3·06, m, 1H, CH_2; 2·92, m, 1H, CH_2. R_F(B) 0·55.

4-Aminocyclopent-1-ene-1-carboxylic Acid (5)

(9) (1·95 g) was refluxed with 6 M HCl (50 ml) and acetic acid (20 ml) for 16 h and the solvents were removed. Water was added and insoluble material was removed by filtration through Celite. After absorption on a Dowex 50W (H^+) ion-exchange column (40 ml) and elution with 1 M pyridine, crystallization from aqueous ethanol gave the *amino acid* (5) (0·7 g, 72%), m.p. 281–285° (dec.). ^1H n.m.r. δ 6·93, m, sharp, =CH; 4·85–4·35, m, CHN; 3·87–2·47, m, 4H, CH_2. R_F(C) 0·34.

Methyl cis- *and* trans-*4-Phthalimidocyclopent-2-ene-1-carboxylate (12) and (13)*

The crude *cis* amino acid (6) (76·2 g, 0·64 mol) and phthalic anhydride (95 g, 0·64 mol) were powdered together and heated to a melt at 200° under nitrogen with stirring for 30 min. The crude product was refluxed in ethyl acetate (400 ml) with activated charcoal (2 g) and filtered through Celite. The filtrate was concentrated to yield a crystalline mixture of (10) and (11) (134 g, 87%). A portion of this mixture (16·9 g) was refluxed in methanolic HCl (80 ml) for 20 min. After removal of the solvent, the brown gum was dissolved in ether/light petroleum (30 : 60 ml) and passed down a quick column (10 cm by 6 cm). After dimethyl phthalate, subsequent fractions gave crystalline (13) (2·95 g, 17%), a 1 : 1 mixture of (12) and (13) containing 5% of the conjugated ester (5·9 g), and crystalline (12) (2·6 g, 15%). Recrystallization from chloroform gave:

Ester (12), m.p. 91–92° (Found: C, 66·1; H, 4·8, N, 5·0. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·2%). I.r. ν_{max} 1770, 1736, 1710, 742, 718 cm^{-1}. ^1H n.m.r. δ 7·88, m, ArH; 6·26, m, 1H, =CH; 5·93, m, 1H, =CH; 5·65–5·15, m, CHN; 4·17–3·45, m, $CHCO_2$; 3·85, s, CH_3; 2·95–2·35, m, CH_2. R_F(A) 0·44.

Ester (13), m.p. 84–85° (Found: C, 66·1; H, 4·7; N, 5·4. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·2%). I.r. ν_{max} 1765, 1730, 1705, 760, 722 cm^{-1}. ^1H n.m.r. δ 7·82, m, ArH; 6·18, m, 1H, =CH; 5·80, m, 1H, =CH; 5·70–5·35, m, CHN; 4·40–3·98, m, $CHCO_2$; 3·77, s, CH_3; 3·05–2·10, m, CH_2. R_F(A) 0·55.

cis- *and* trans-*4-Phthalimidocyclopent-2-ene-1-carboxylic Acid (10)* and *(11)*

(12) (346 mg) was refluxed in a solution of 0·5 M HCl (4 ml) and glacial acetic acid (4 ml) for 30 min. The solvent was removed and the product recrystallized from ethyl acetate (2 ml) at 4° to yield the *phthalimido amino acid* (10) (162 mg), m.p. 170–172° (Found: C, 65·2; H, 4·4; N, 5·2. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·4%). I.r. ν_{max} 1797, 1770, 1700, 720 cm^{-1}. ^1H n.m.r. δ 7·90, m, ArH; 6·26, m, 1H, =CH; 5·92, m, 1H, =CH; 5·69–5·25, m, CHN; 4·03–3·52, m, $CHCO_2$; 3·19–2·35, m, CH_2. R_F(B) 0·58.

Similarly (13) gave the *phthalimido amino acid* (11) (68%), m.p. 143–145° (Found: C, 65·4; H, 4·4; N, 5·4. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·4%). I.r. ν_{max} 1765, 1700, 765, 715 cm^{-1}. ^1H n.m.r. δ 7·87, m, ArH; 6·27, m, 1H, =CH; 5·85, m, 1H, =CH; 5·80–5·45, m, CHN; 4·50–4·10, m, $CHCO_2$; 3·08–2·08, m, CH_2. R_F(B) 0·65.

trans-*4-Aminocyclopent-2-ene-1-carboxylic Acid (7)*

(11) (392 mg, 1·5 mmol) was refluxed in methanol (10 ml) and hydrazine (0·75 ml, 15 mmol) for 30 min and the solvent was removed under vacuum. To this gum was added 6 M HCl (3 ml) and the precipitate was removed by filtering through Celite. The neutral amino acid was isolated from a column of Dowex 50W (H^+) (25 ml) with 1 M pyridine elution, and crystallized from ethanol (1·5 ml)/water (0·5 ml) to give the *amino acid* (7), m.p. 256–260° (dec.) (Found: C, 56·4; H, 6·9; N, 11·0. $C_6H_9NO_2$ requires C, 56·7; H, 7·1; N, 11·0%). I.r. ν_{max} 2160, 1628, 1555br, 772, 752 cm^{-1}. ^1H n.m.r. δ 6·80, m, 1H, =CH; 6·48, m, 1H, =CH; 5·29–4·80, m, CHN; 4·48–4·04, m, $CHCO_2$; 3·49–2·20, m, CH_2. R_F(C) 0·35.

trans-*3-Phthalimidocyclopentane-1-carboxylic Acid (14)*

(13) was hydrogenated at atmospheric pressure over 10% palladium on carbon (40 mg) in ethyl acetate (20 ml) at room temperature overnight. The product was filtered through Celite and the solvent removed to give the *phthalimido amino acid* (14) (253 mg, 98%), m.p. 159–160° (Found: C, 64·7; H, 4·9; N, 5·4. $C_{14}H_{13}NO_4$ requires C, 64·8; H, 5·0; N, 5·4%). I.r. ν_{max} 1765, 1735, 1680br, 718 cm^{-1}. ^1H n.m.r. δ 7·90, m, ArH; 5·28–4·60, m, apparent q, *J* 9 Hz, CHN; 3·65–3·12, m, CHN; 2·66–1·70, m, 6H, CH_2. R_F(B) 0·72.

trans-*3-Aminocyclopentane-1-carboxylic Acid (3)*

(*a*) (14) (257 mg) was treated with hydrazine in methanol as above and recrystallized from methanol to give the *amino acid* (3) (84 mg, 78%), m.p. 238–242° (dec.) (lit.[14] 235–236°). I.r. ν_{max} 2210, 1703, 1630, 1525br, 760 cm^{-1}. ^1H n.m.r. δ 4·58–3·97, m, CHN; 3·64–3·09, m, $CHCO_2$; 3·09–1·68, m, 6H, CH_2. R_F(C) 0·42.

[14] Berger, H., Paul, H., and Hilgetag, G., *Chem. Ber.*, 1968, **101**, 1525.

(*b*) (7) (38 mg) was hydrogenated at atmospheric pressure over 10% palladium on carbon (20 mg) at room temperature in glacial acetic acid (5 ml). The product was filtered through Celite and the solvent removed to yield the *amino acid* (3) (35 mg, 90%) after crystallization from ethanol.

cis-*3-Aminocyclopentane-1-carboxylic Acid (2)*

(6) (49 mg) was reduced as for (7) above to give the *amino acid* (2) (40 mg, 81%), m.p. 240–243°. I.r. ν_{max} 2240, 1585, 1566, 1530 cm^{-1}. ^1H n.m.r. δ 4·52–3·97, m, CHN; 3·70–3·07, m, $CHCO_2$; 3·07–1·86, m, 6H, CH_2. R_F(C) 0·37.

*2,3-Isopropylidene-*D*-ribonolactone Ester of (+)-*trans*-(1*R*,4*R*)-4-Phthalimidocyclopent-2-ene-1-carboxylate (+)-(17)*

(10) (43·7 g, 0·17 mol) was heated to a melt at 200° under nitrogen for 20 min with vigorous stirring and cooled before anhydrous benzene (170 ml), oxalyl chloride (14·8 g, 0·17 mol) and anhydrous dimethylformamide (1 drop) was added. The gum dissolved over 30 min with vigorous stirring. More oxalyl chloride (7·4 g) was added and the solution was warmed to 60° for 10 min. The excess oxalyl chloride was removed under vacuum with anhydrous benzene (3×50 ml). To this acid chloride in anhydrous tetrahydrofuran (170 ml) were added 2,3-isopropylidene-D-ribonolactone (32 g, 0·17 mol) and anhydrous pyridine (13·7 ml, 0·17 mol). The solution rapidly gave a crystalline suspension and was stirred at room temperature for 2 h. More anhydrous pyridine (13·7 ml) was added and the mixture was stirred overnight. All solvents were removed under vacuum and the product was extracted into ethyl acetate (2×150 ml) from the aqueous layer which had been neutralized with 6 M HCl (30 ml). The organic layer was dried and the solvent removed to yield the crude product (65·1 g, 90%) which was dissolved in dichloromethane/light petroleum, 80 : 100 ml. The solution was divided into three portions and each was chromatographed on a filter funnel column (10 cm by 7 cm) with dichloromethane/ethyl acetate mixtures. The relevant fractions (43·7 g) gave 20·3 g of solid on trituration with ether and after recrystallization, fractions with $[\alpha]_D$ +150° to +180° were combined and recrystallized to give the pure *ribonolactone ester* (+)-(17) (5·6 g, 8·7%), m.p. 204–206°, $[\alpha]_D$ +216° (Found: C, 61·5; H, 5·0; N, 3·2. $C_{22}H_{21}NO_8$ requires C, 61·8; H, 5·0; N, 3·3%). I.r. ν_{max} 1784, 1746, 1708, 750, 719 cm^{-1}. ^1H n.m.r. δ 7·85, m, ArH; 6·10, m, 1H, =CH; 5·82, m, 1H, =CH; 5·75–5·35, m, CHN; 4·82, m, 3H, CH_2O or CHO; 4·50, m, 2H, CH_2O or CHO; 4·34–4·00, m, $CHCO_2$; 2·95–2·17, m, CH_2; 1·52, s, CH_3; 1·43, s, CH_3. ^{13}C n.m.r. δ phthalimido: 173·1, 133·1, 134·0, 123·2; cyclopentene: 50·8, 131·3, 132·7, 55·4, 31·6, 172·6; lactone: 167·7, 79·7, 75·3, 77·8, 64·0, 113·9, 26·7, 25·6. R_F(A) 0·21.

*(+)-*trans*-(1*R*,4*R*)-4-Phthalimidocyclopent-2-ene-1-carboxylic Acid (+)-(11)*

(+)-(17) (1·63 g,) was refluxed in glacial acetic acid (30 ml) and 1 M HCl (8 ml) for 1 h. The solvent was removed and the product extracted into ethyl acetate, washed with water and recrystallized from ethyl acetate/cyclohexane to yield the *phthalimido amino acid* (+)-(11) (825 mg, 84%), m.p. 146–147°, $[\alpha]_D$ +326° (Found: C, 65·0; H, 3·9; N, 5·3. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·4%).

*(+)-*trans*-(1*R*,4*R*)-4-Aminocyclopent-2-ene-1-carboxylic Acid (+)-(7)*

(+)-(11) was deprotected as for the racemic material and recrystallized from aqueous ethanol to give the *amino acid* (+)-(7) (74%), m.p. 248–252°, $[\alpha]_D$ +332° (Found: C, 56·8; H, 7·0; N, 11·2. $C_6H_9NO_2$ requires C, 56·7; H, 7·1; N, 11·0%). R_F(C) 0·35.

*(−)-Isopropylidene-*D*-ribonolactone Ester of (4*S*)-4-Phthalimidocyclopent-1-ene-1-carboxylic Acid (−)-(18)*

(+)-(17) (2·14 g, 5 mmol) was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (186 mg, 1·5 mmol) at room temperature for 2 days. After washing with 1 M HCl (20 ml), solvent removal gave a product which contained a trace of conjugated material. Crystallization from ethyl acetate/hexane (20 ml) yielded the *ribonolactone ester* (−)-(18), m.p. 169°, $[\alpha]_D$ −5·3° (Found: C, 61·8; H, 5·0; N, 3·2. $C_{22}H_{21}NO_8$ requires C, 61·8; H, 5·0; N, 3·3%). I.r. ν_{max} 1786, 1705, 718 cm^{-1}. ^1H n.m.r. δ 7·82, m, ArH; 6·82, m, sharp, =CH; 5·32–4·68, m, apparent

q *J* 9 Hz, CHN; 4·85, m, 3H, CH_2O or CHO; 4·42, m, 2H, CH_2O or CHO; 3·08, m, 1H, CH_2; 2·92, m, 1H, CH_2; 1·52, s, CH_3; 1·43, s, CH_3. ^{13}C n.m.r. δ phthalimido: 173·4, 133·4, 134·1, 123·2; cyclopentene: 131·9, 142·8, 37·9, 47·8, 35·8, 163·0; lactone: 167·9, 79·7, 75·2, 77·9, 63·4, 113·7, 26·7, 25·6. R_F(A) 0·23.

(+)-(4S)-4-Aminocyclopent-1-ene-1-carboxylic Acid (+)-(5)

(−)-(18) (1·0 g) was refluxed in glacial acetic acid (10 ml) and 6 M HCl (20 ml) for 5 h and the solvents were removed. Water (2 ml) was added and the by-product removed by filtering through Celite. After purifying on an ion-exchange column of Dowex 50W (H^+) (15 ml) and eluting with 1 M pyridine, the crude product (220 mg, 74%) was recrystallized from ethanol to give the *amino acid* (+)-(5) (165 mg), m.p. 276–280°, $[\alpha]_D$ +28·0° (Found: C, 56·5; H, 7·0; N, 11·0. $C_6H_9NO_2$ requires C, 56·7; H, 7·1; N, 11·0%).

(−)-2,3-Isopropylidine-D-ribonolactone Ester of
trans-(1S,3S)-3-phthalimidocyclopentane-1-carboxylate (−)-(19)

(+)-(17) (213 mg, 0·5 mmol) was hydrogenated as for the phthalimido acid (11) and the product recrystallized from ethyl acetate/hexane to yield the *ribonolactone ester* (−)-(19) (193 mg, 90%), m.p. 140–141°, $[\alpha]_D$ −10·4° (Found: C, 61·5; H, 5·4; N, 3·2. $C_{22}H_{23}NO_8$ requires C, 61·5; H, 5·4; N, 3·3%). I.r. ν_{max} 1785, 1726, 1704, 718 cm^{-1}. ^1H n.m.r. δ 7·90, m, ArH; 5·10–4·60, m, CHN; 4·85, m, 3H, CHO or CH_2O; 4·42, m, 2H, CHO or CH_2O; 3·70–3·05, m, $CHCO_2$; 2·75–1·75, m, 6H, apparent q, *J* 9 Hz; 1·52, s, CH_3; 1·43, s, CH_3. ^{13}C n.m.r. δ phthalimido: 173·4, 131·9, 134·0, 123·1; cyclopentane: 43·0, 29·8, 30·1, 49·6, 32·7, 174·4; lactone: 168·1, 79·7, 75·2, 77·8, 63·6, 113·8, 26·7, 25·6. R_F(A) 0·22.

(+)-trans-(1S, 3S)-3-Phthalimidocyclopentane-1-carboxylic Acid (+)-(14)

(−)-(19) (1·0 g) was refluxed in glacial acetic acid (25 ml) and 1 M HCl (7 ml) for 1 h. Normal workup and crystallization from ethyl acetate gave the *phthalimido amino acid* (+)-(14) (596 mg, 98%), m.p. 174–175°, $[\alpha]_D$ +31·4° (Found: C, 64·7; H, 4·9; N, 5·2. $C_{14}H_{13}NO_4$ requires C, 64·8; H, 5·0; N, 5·4%).

(+)-trans-(1S,3S)-3-Aminocyclopentane-1-carboxylic Acid (+)-(3)

(*a*) (+)-(14) (562 mg) was deprotected as for the racemic compound and recrystallized from methanol to give the *amino acid* (+)-(3) (196 mg, 70%), m.p. 264–266° (dec.) (lit.[6] 245–250°), $[\alpha]_D$ +23·1° (lit.[6] $[\alpha]_D$ +24°).

(*b*) (+)-(7) (68 mg) was reduced as for the racemic compound and recrystallized from aqueous ethanol to give the *amino acid* (+)-(3) (41·4 mg, 60%), $[\alpha]_D$ +23°.

D-Pantolactone Ester of trans-(1S,4S)-4-Phthalimidocyclopent-2-ene-1-carboxylic Acid (−)-(20)

This ester was prepared following the procedure for the preparation of (+)-(17), starting with racemic (10) (63·7 g, 0·25 mol) and D-pantolactone (32·3 g, 0·25 mol). The combined ester fractions from chromatography (59·5 g, 70%) gave crystalline (10) (11·3 g) on trituration with ether. One recrystallization from ethyl acetate produced the pure *pantolactone ester* (−)-(20) (7·89 g) and the optical rotation did not change on further recrystallization, m.p. 201–202°, $[\alpha]_D$ −281° (Found: C, 65·3; H, 5·0; N, 3·6. $C_{20}H_{19}NO_6$ requires C, 65·0; H, 5·2; N, 3·8%). I.r. ν_{max} 1780, 1738, 1700, 763, 721 cm^{-1}. ^1H n.m.r. δ 7·85, m, ArH; 6·20, m, 1H, =CH; 5·83, m, 1H, =CH; 5·72–5·40, m, CHN; 5·48, s, CHO; 4·60–4·10, m, $CHCO_2$; 4·10, s, OCH_2; 3·08–2·00, m, CH_2; 1·24, s, CH_3; 1·17, s, CH_3. ^{13}C n.m.r. δ phthalimido: 172·6, 132·1, 134·0, 123·2; cyclopentene: 50·8, 131·3, 132·9, 55·4, 31·6, 172·0; lactone: 167·8, 74·4, 40·2, 76·3, 23·2, 19·9. R_F(A) 0·30.

Hydroxy Acid (−)-(21)

By the same hydrolysis procedure as for the preparation of (+)-(11), or with 6 M HCl/glacial acetic acid (−)-(20) the *hydroxy acid* (−)-(21), m.p. 135–140°, was obtained. I.r. ν_{max} 3170br, 1740, 1670, 720 cm^{-1}. ^1H n.m.r. δ 7·85, m, ArH; 7·0, bs, 2H, OH; 6·22, m, 1H, =CH; 5·80, m, 1H, =CH; 5·70, m, CHO; 5·75–5·35, m, CHN; 4·35–4·0, m, $CHCO_2$; 4·02, s, CH_2O; 2·9–2·1, m, CH_2; 1·28, m, CH_3; 1·09, m, CH_3. R_F(A) 0·22.

D-*Pantolactone Ester of (4*R*)-4-Phthalimidocyclopent-1-ene-1-carboxylic Acid (−)-(22)*

By a similar conjugation procedure to that above, (−)-(20) (2·95 g) was converted into the *pantolactone ester* (−)-(22) (from ethyl acetate/hexane) (2·53 g, 86%), m.p. 166°, $[\alpha]_D$ −12·7° (Found: C, 65·0; H, 5·3; N, 3·8. $C_{20}H_{19}NO_6$ requires C, 65·0; H, 5·2; N, 3·8%). I.r. ν_{max} 1790, 1705, 714 cm^{-1}. ^1H n.m.r. δ 7·89, m, ArH; 7·09, m, sharp, =CH; 5·53, s, CHO; 5·50–4·85, m, apparent q, *J* 9 Hz, CHN; 4·10, s, CH_2O; 3·15, m, 1H, CH_2; 3·05, m, 1H, CH_2; 1·26, s, CH_3; 1·15, s, CH_3. ^{13}C n.m.r. δ phthalimido: 172·3, 133·4, 134·1, 123·2; cyclopentene: 131·9, 143·6, 37·4, 48·2, 35·3, 162·8; lactone: 167·9, 75·0, 40·3, 76·2, 23·0, 19·9. R_F(A) 0·27.

*(−)-(4*R*)-4-Aminocyclopentane-1-carboxylic Acid (−)-(5)*

(−)-(22) (2·22 g) was hydrolysed as for (18). Crystallization from ethanol gave the *amino acid* (−)-(5) (552 mg, 72%), m.p. 274–278° (dec.), $[\alpha]_D$ −28·1° (Found: C, 56·5; H, 7·0; N, 11·2. $C_6H_9NO_2$ requires C, 56·7; H, 7·1; N, 11·0%).

D-*Pantolactone Ester of* trans-*(1*R*,3*R*)-3-Phthalimidocyclopentane-1-carboxylic Acid (−)-(23)*

(20) (1·11 g) was reduced following the procedure for (14) and crystallized from ether to give the *pantolactone ester* (−)-(23) (857 mg, 77%), m.p. 112–113°, $[\alpha]_D$ −20·1° (Found: C, 64·5; H, 5·8; N, 3·7. $C_{20}H_{21}NO_6$ requires C, 64·7; H, 5·7; N, 3·8%). I.r. ν_{max} 1797, 1736, 1700, 720 cm^{-1}. ^1H n.m.r. δ 7·90, m, ArH; 5·52, s, CHO; 5·25–4·49, m, apparent q, *J* 9 Hz, CHN; 4·17, s, CH_2; 3·85–3·19, m, apparent q, *J* 9 Hz, $CHCO_2$; 2·75–1·80, m, 6H, CH_2; 1·28, s, CH_3; 1·19, s, CH_3. ^{13}C n.m.r. δ phthalimido: 172·3, 131·9, 134·0, 123·1; cyclopentane: 43·0, 29·8, 30·1, 49·8, 32·9, 174·4; lactone: 168·1, 74·9, 40·1, 76·2, 23·1, 19·9. R_F(A) 0·29.

*(−)-*trans-*(1*R*,3*R*)-3-Aminocyclopentane-1-carboxylic Acid (−)-(3)*

(−)-(23) (786 mg) was hydrolysed following the procedure for (18) and the product crystallized from ethanol to give the *amino acid* (−)-(3) (240 mg, 88%), m.p. 253–256° (dec.), $[\alpha]_D$ −22·3° (lit.[6] −23°).

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