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STUDIES ON INDOLIC MOULD METABOLITES. TOTAL SYNTHESIS OF L-PROLYL-2-METHYLTRYPTOPHAN ANHYDRIDE AND DEOXYBREVIANAMIDE E

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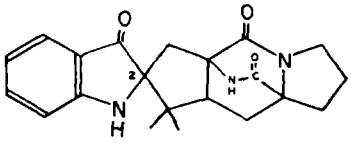
Abstract—Syntheses of L - prolyl - 2 - methyl - L - tryptophan anhydride, L -prolyl - 2 - methyl - D - tryptophan anhydride, deoxybrevianamide E, and L - prolyl - 2 - (1,1 - dimethylallyl) - D - tryptophan anhydride are described. A route for the conversion of deoxybrevianamide E into brevianamide E has also been examined.

The brevianamides constitute a group of indolic mould metabolites derived from tryptophan, proline and mevalonic acid, which were isolated by Birch and Wright[1] from *Penicillium brevi-compactum* Dierckx. Of these, brevianamide A **1**[1,2] is the major metabolite, and brevianamide B[3] is simply isomeric with brevianamide A at the indoxyl spirocyclic centre (C-2). Brevianamides C **2** and D **3** are probably artifacts, since they can be prepared by irradiation of brevianamide A, and they were not detected in *P. brevi-compactum* cultures when grown in the absence of light.[3] Brevianamide E[1] is a hydroxypyrroloindole derivative of structure **4**, and the remaining metabolite, brevianamide F **5**, is simply L -prolyl - L - tryptophan anhydride.[3]



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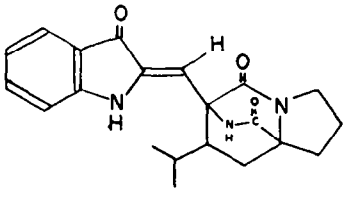

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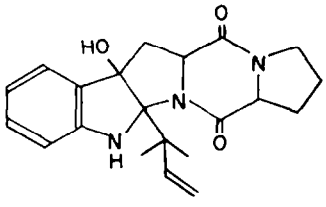
3: E isomer



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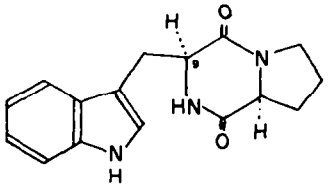

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Aside from brevianamide F, whose structure was established by direct comparison with authentic material, the structures of the brevianamides were deduced from their spectrographic properties and biogenetic considerations. Owing to lack of material extensive chemical degradation could not be undertaken, and it was therefore of interest to confirm the structures of these metabolites by total synthesis. We chose for our initial study the total synthesis of brevianamide E, partly because the molecule is simpler than that of brevianamide A, and partly because neither brevianamide E nor a close relative had been examined by the X-ray method, in contrast to brevianamide A, the 5-bromo derivative of which had been studied by Coetzer.[2] Another consideration was the fact that, in principle, brevianamide E can be approached *via* its reduction product, deoxybrevianamide E **6**, which is a natural product in its own right, since it is a constituent of *Aspergillus ustus* (Bainer) Thom and Church.[4] Our immediate objective was therefore the total synthesis of deoxybrevianamide E.[5]

As a model for the synthesis of deoxybrevianamide E attention was first directed towards the synthesis of the simpler 2-methyl analogue **7a**. The most direct route to **7a** involves alkylation of the dioxopiperazine derivative **8** by means of 2-methylgramine. The former was obtained by a conventional preparation from benzyloxycarbonyl - L - proline and aminomalonic ester; coupling by means of dicyclohexylcarbodi - imide was followed by hydrogenolysis of the benzyloxycarbonyl group, and cyclisation by boiling in toluene with 4A molecular sieves. Halpern's method[6] gave some L - prolyl - 2 - ethoxycarbonylglycine anhydride **8**, but the yield was lowered by formation of the N-formyl derivative **9**, obtained as a mixture of amide rotamers.

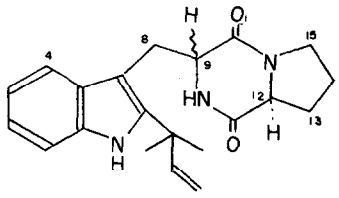
Attempted condensation of 2-methylgramine with the

dioxopiperazine derivative **8** by Kishi's method[7] failed to give a significant yield of the desired product, hence a stepwise approach to the synthesis of **7a** was adopted. Again, Kishi's conditions (sodium hydroxide in xylene) for the alkylation of the protected dipeptide **10** by means of 2-methylgramine failed, presumably as a consequence of the demonstrated instability of 10 under the reaction conditions. In contrast, alkylation of the sodium derivative of 10 by means of 2-methylgramine ethiodide[8] or, better, 2-methylgramine methosulphate, proceeded smoothly, with formation of the amide di-ester **11**. Hydrolysis and decarboxylation of **11** gave a mixture of the monocarboxylic acid **12** and the related ester **13**, which were separately converted into a mixture of the epimeric L - prolyl - 2 - methyltryptophan anhydrides, **7a** and **7b**. Anticipating a synthesis of deoxybrevianamide E, which contains an olefinic linkage, we avoided the hydrogenolytic method, and the benzyloxycarbonyl group in **12** and **13** was removed by means of hydrogen bromide in acetic acid. The aminoacid **14** was then cyclised by boiling in toluene and removing the water by means of a Dean–Stark water separator, and the monoester **15** was cyclised by treatment with a saturated solution of ammonia in ethanol[9] or by boiling a toluene solution of **15** with 4A molecular sieves. In each case a mixture of L - prolyl - 2 - methyl - L - tryptophan anhydride **7a** and L - prolyl - 2 - methyl - D - tryptophan anhydride **7b** was obtained, which was separated by chromatography on Kieselgel G, the former **7a** being obtained as colourless prisms, m.p. 131–133°, and the latter **7b** as a colourless glass.

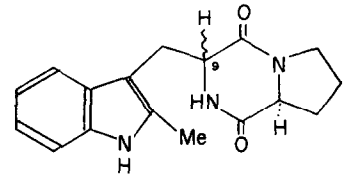
The relative stereochemistry of these two diastereoisomers was readily determined from their NMR spectra, and in particular the chemical shift of the signal owing to the hydrogen at C-12. The dioxopiperazine ring is almost planar,[10] the departure from planarity being of the order of only 5°. In the dioxopiperazine derivatives, e.g. **7**, which contain a fused 5-membered ring attached, of necessity, *via* an effectively trigonal nitrogen atom, the bicyclic assembly is particularly rigid; there is, consequently, very little conformational flexibility, and in the conformation adopted the axis of the angular C–H bond is orthogonal to the median plane of the 6,5 ring system. In **7b**, in which the hydrogen atoms at C-9 and C-12 are *trans* with respect to the dioxopiperazine ring, the C-12 proton is considerably shielded by the indolyl substituent attached to C-9, and this is reflected by the much smaller chemical shift (δ 2.53) of the quartet owing to the C-12 proton in **7b** than that (δ 4.0) of the corresponding signal in the spectrum of the *cis*-isomer **7a**. The difference in these chemical shifts is thus no less than 1.47 ppm; this is similar to the difference in chemical shifts (1.23 ppm) reported for the protons at C-12 in the compounds lacking the indole methyl group (brevianamide F **5** and its 9-epimer).[4] These differences in chemical shift are significantly greater than that observed (0.89 ppm) for the C-12 protons in the epimeric alanyltryptophan anhydrides **16a** and **16b**,[11] in which the absence of the fused pyrrolidine ring allows considerably greater conformational flexibility; in these epimers the total conformer population will include a significant proportion of conformers in which the indole ring is in a pseudoequatorial position, where its shielding effect on the proton at C-12 will almost certainly be very small indeed.

The synthesis of deoxybrevianamide E itself followed closely the route adopted for the preparation of the model compound **7a**. For this purpose the effective starting material was 2 - (1,1 - dimethylallyl) - indole **17**; this was prepared as reported earlier,[12] except that an improved method for the oxidation of the primary alcohol **18** into the corresponding aldehyde **19** was developed, which we now take the opportunity to record.

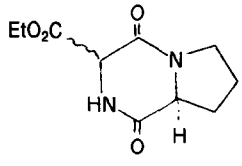
Condensation of the methosulphate of the gramine derivative **20** with the protected dipeptide **10** gave, after chromatography, the required amide di-ester **21** in 42% yield, together with some (10%) of the ether **22**; the formation of this latter product presumably reflects the lower reactivity of the intermediate derived from the gramine derivative **20** with the dipeptide **10**, as a con-



6: α-H at C-9
25: β-H at C-9



7a: α-H at C-9
7b: β-H at C-9



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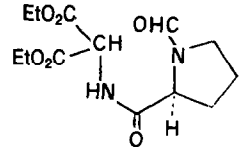

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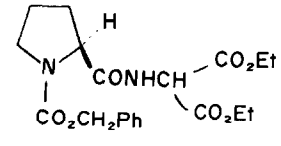

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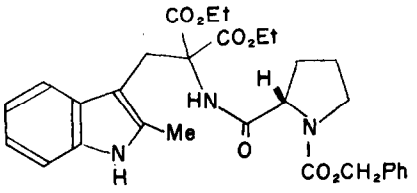

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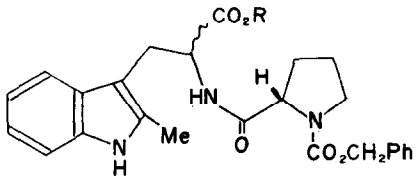
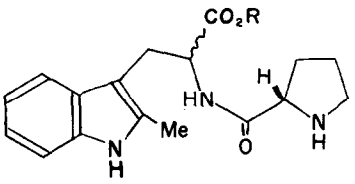
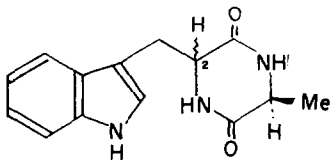


12: R = H
13: R = Et



14: R = H
15: R = Et

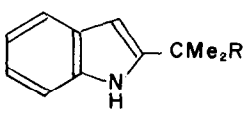


16a: α-H at C-2
16b: β-H at C-2

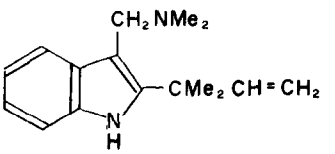
sequence of its increased steric demands. Saponification of the diester **21**, followed by decarboxylation, gave a mixture of the monoester **23** and the related carboxylic acid **24**, which was re-esterified to give a combined yield of 50% of monoester **23**. The benzyloxycarbonyl group was then removed by treatment with hydrogen bromide in acetic acid, and the free aminoester cyclised by boiling in toluene with 4A molecular sieves. Chromatography of the crude product gave L-prolyl-2-(1,1-dimethylallyl)-L - tryptophan anhydride **6** and L - prolyl - 2 - (1,1 - dimethylallyl - D - tryptophan anhydride **25** as colourless glasses, together with some N-acetyl - 2 - (1,1 - dimethylallyl) - tryptophan ethyl ester **26**.

L - Prolyl - 2 - (1,1 - dimethylallyl) - L - tryptophan anhydride **6** was shown to be identical with deoxybrevianamide E, by comparison of IR, UV, NMR and mass spectra, optical rotation and R_F values on Kieselgel G in three solvent systems with those of authentic material kindly supplied by Dr. P. S. Steyn.

As with the epimers **7a** and **7b**, evidence for the stereochemistry of **6** and **25** could be obtained from their NMR spectra. In the 60 MHz spectrum of deoxybrevianamide E **6** the signal owing to the proton at C-9 appears as a quartet at δ 4.43, and that owing to the C-12 proton as an ill-resolved multiplet at δ 4.1. In the spectrum of the LD-isomer **25** the signal owing to H-9 appears as a multiplet (quartet?) at δ 4.30, but that owing to H-12 is lost under the multiplets arising from the C-8 and C-13 methylene groups, which were responsible for complex absorption between δ 3.18 and 3.73 ppm. At 400 MHz, however, the C-9 proton appeared as a double triplet at δ 4.30, owing to coupling with the C-8 methy-



17: R = CH = CH₂
18: R = CH₂OH
19: R = CHO



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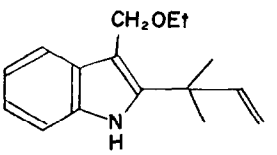

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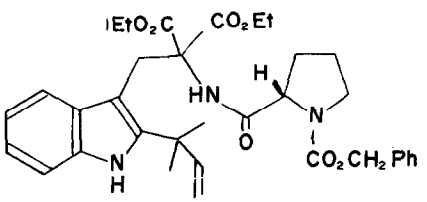

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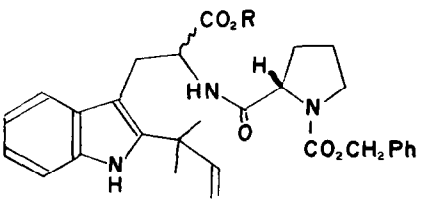
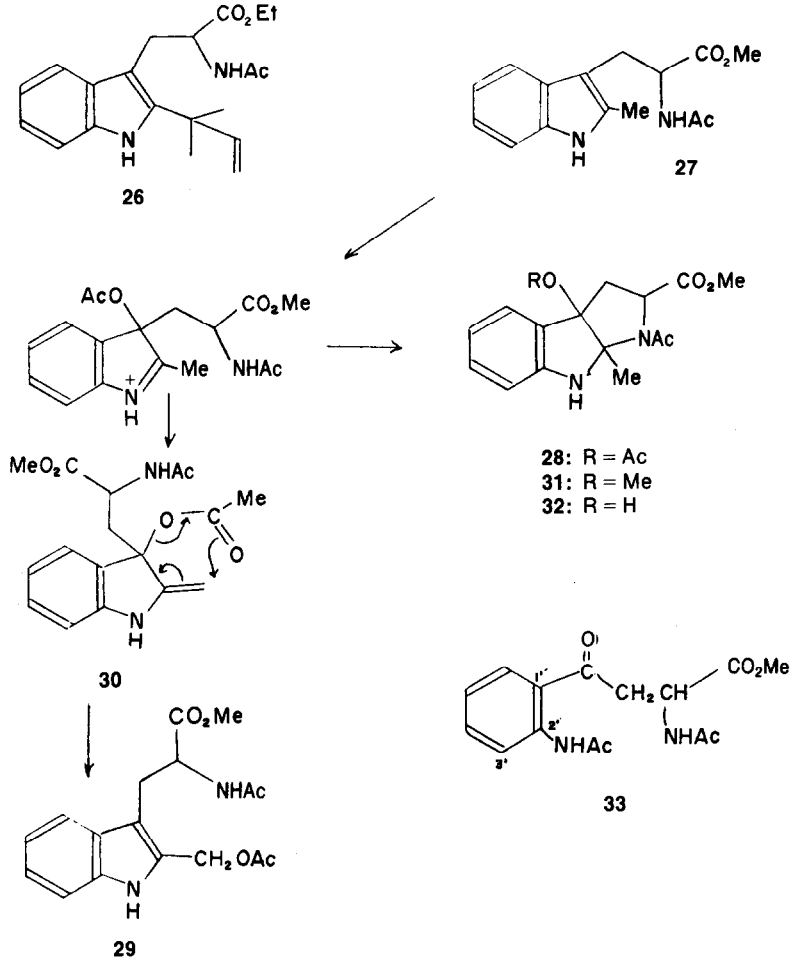


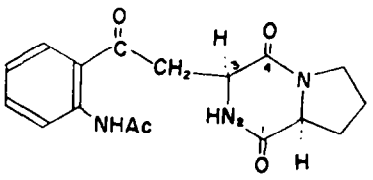
23: R = Et
24: R = H

lene group and the adjacent amide NH proton, while the C-12 proton gave rise to a double doublet centred on δ 3.71; confirmation of these assignments was obtained by double irradiation experiments. Unfortunately, by the time the 400 MHz spectrometer became available the LL - diastereoisomer (deoxybrevianamide E) had suffered aerial oxidation (*vide infra*), and no material was available for further study.

These data show that in the LD - isomer **25** H-12 absorbs at higher field than H-12 in deoxybrevianamide E **6**; the difference is 0.39 ppm, consistent with some shielding of this proton in **25** by the indole ring system. That the extent of this shielding is considerably less than that observed in **7b** is predictable, since the rotamers of **25** in which the C-12 proton experiences shielding by the indole ring are considerably destabilised by non-bonded interactions between the bulky dimethylallyl substituent and the dioxopiperazine ring. The rotamer of **25**, which involves the smallest non-bonded interactions appears to be one in which the hydrogen atoms attached to C-4 and C-9 are in close proximity. That such a rotamer makes a substantial contribution to the total population is confirmed by a NOE enhancement of the signal at δ 7.53, owing to the C-4 proton, on irradiation at the frequency of the C-9 proton signal.

The conversion of deoxybrevianamide E into brevianamide E requires an oxidation at the β-position of the indole nucleus, a reaction which is unexceptional in principle, and in fact such an oxidation has been achieved by Kishi *et al.*[13] in their total synthesis of sporidesmin, through the agency of iodosobenzene diacetate. When this reagent was applied to the simple model, N - acetyl - 2 - methyltryptophan methyl ester **27**, in either acetonitrile/dimethyl sulphide, or glacial acetic acid solution, an indolic product was obtained which was isomeric with the desired oxidation product **28**, and which proved, on examination of its spectra, to be the 2 - acetoxymethyltryptophan derivative **29** formed, presumably, by normal acetoxylation of **27** at the indole β-position, followed by proton exchange, and rearrangement of the allylic acetate function in the intermediate **30** so formed. This result was encouraging since, if this mechanism for the formation of **29** is correct, the desired oxidation at the indole β-position has initially occurred; and in connection with the synthesis of brevianamide E the proton exchange, which leads to an isomer of type **30** and thence to **29**, is not possible, since the carbon atom attached to the 2-position of the indole ring in deoxybrevianamide E is fully substituted. Nevertheless it was desirable to isolate an oxidation product which contained an oxygenated substituent at the β-position of the indole ring, and this was eventually achieved by oxidation of **27** with iodosobenzene diacetate in methanol solution; the product was the methoxy-pyrroloindole derivative **31**, and none of the corresponding acetoxy compound **28** could be detected in the reaction mixture. An obvious next step was to carry out the oxidation in the presence of water; and in fact, in aqueous acetonitrile the desired hydroxy-pyrroloindole derivative **32** was obtained, together with the





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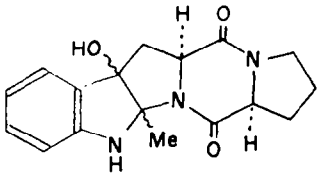

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amido ketoester derivative **33**, formed by oxidative fission of the indole double bond. Unfortunately when the same oxidising agent was applied to the oxidation of **7a** the ring-cleaved amidoketone derivative **34** was the only product isolated, and no trace of the required hydroxy-pyrroloindole derivative **35** could be found. Evidently, further oxidation of the hydroxy-indolenine derivative initially formed from **7a** competed successfully with intramolecular ring closure, a result that did not augur well for the attempted conversion of deoxybrevianamide E into brevianamide E. However, this oxidation, also with iodosobenzene diacetate, gave a mixture of two products of very similar R_F values which, in spite of repeated attempts, could not be separated by chromatography on Kieselgel G_F 254 using a variety of solvents. The mass spectrum of the mixture contained a peak owing to a molecular ion at *m/e* 367, which indicated that some material of the required relative molecular mass, i.e. brevianamide E or a stereoisomer, had been formed. The NMR spectrum of the mixture was naturally extremely complex, but it was possible to identify the absorptions expected[1] if brevianamide E were present, from which we conclude that the mixture contained some brevianamide E. It is of interest that no amidoketone derivative analogous to **34** appears to have been formed in this oxidation. Tentatively, we suggest that further oxidation of the intermediate hydroxyindolenine derivative formed from deoxybrevianamide E is hindered by the bulky dimethylallyl substituent, and therefore, in contrast to the behaviour of the 2-methyl analogue, intramolecular cyclisation to give brevianamide E or a stereoisomer occurs preferentially.

At this stabe, owing to lack of material, our investigations had to be suspended. However, Dr. Steyn[14] has kindly informed us that deoxybrevianamide E appears to be slowly converted into brevianamide E by aerial oxidation, in which case brevianamide E may be an artifact. It is relevant to note that Birch and Wright isolated only brevianamide E from *Penicillium brevicompactum*, and it may be speculated that it was formed by aerial oxidation of deoxybrevianamide E without the benefit of enzyme mediation during the time of culture (four to five weeks).

In view of this facile aerial oxidation the total synthesis of deoxybrevianamide E also constitutes, in a formal sense, the synthesis of brevianamide E. Recently, a second synthesis of deoxybrevianamide E has been reported by Kametani *et al.*,[15] who have also contributed the first satisfactory laboratory synthesis of brevianamide E, which was achieved by photochemical oxidation of deoxybrevianamide E; essentially a refinement of the aerial oxidation in the presence of light.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. U.V. spectra (determined in ethanol solution) were measured on a Unicam SP800A Spectrometer, and optical rotations on a Perkin Elmer 141 Polarimeter. IR spectra were determined on a Perkin Elmer 157G Spectrometer; NMR spectra were measured on Varian Associates A60A, Bruker 90 MHz and 400 MHz, Perkin Elmer R12 and R32 spectrometers. The mass spectra were determined on an Associated Electrical Industries MS902 instrument.

Diethyl N-*benzyloxycarbonyl* - L - *prolylaminomalonate* **10**

N-Benzyloxycarbonyl - L - proline[16] (7.12 g), diethyl aminomalonate (5.0 g), and dicyclohexyl carbodi-imide (7.22 g) were dissolved in dry tetrahydrofuran (200 ml) and the solution was left overnight at room temp. Dilute acetic acid was added to decompose excess of reagent and the precipitate of dicyclohexylurea filtered off. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate. The solution was washed with dilute hydrochloric acid, sodium bicarbonate solution and water, and then dried ($MgDO_4$). The ethyl acetate was removed under reduced pressure to yield an oil which crystallised on trituration with ethyl acetate. Diethyl N - benzyloxycarbonyl - L - prolylaminomalonate (8.85 g, 76%) was obtained from ethyl acetate-light petroleum (b.p. 60–80°C) as colourless needles, m.p. 74–75°; ν_{max} (Nujol) 3 300 (NH), 1755, 1740 (CO_2Et), 1715, 1690, 1660, 1540 cm^{-1} (amide bands); λ_{max} 209 (ϵ 9340), 264 (ϵ 1680 and 268 (ϵ 1680), δ ($CDCl_3$) 1.27 (6H, t, J 7Hz, $2\times CO_2CH_2\underline{Me}$), 1.77–2.38 (4H, m, $\rangle NCH_2\underline{CH_2}\underline{CH_2}CH\langle$), 3.40–3.70 (2H, m, $\rangle N\underline{CH_2}$–), 4.26 (4H, q, J 7 Hz, $2\times CO_2\underline{CH_2}Me$), 4.30–4.53 (1H, m, $\rangle NC\underline{H}CH_2$), 5.12 (1H, d, J 7 Hz, $\rangle C\underline{H}NH$), 5.21 (2H, s, $PhC\underline{H_2}O$), 7.37 (5H, s, aromatic H) and 7.3 (1H, br, NH) (Found: C, 58.90; H, 6.40; N, 6.85. $C_{20}H_{26}N_2O_7$ requires C, 58.90; H, 6.40; N, 6.85%).

L-*Prolyl-2-ethoxycarbonylglycine anhydride* **8**

(a) A stream of hydrogen was passed through a solution of diethyl N - benzyloxycarbonyl - L - prolylaminomalonate (1.5 g) in ethanol (50 ml) containing a suspension of 5% palladised charcoal catalyst (500 mg) at room temperature. After two hours the catalyst was removed by filtration and the filtrate evaporated under reduced pressure to yield the crude aminodiester as an almost colourless oil. Formic acid (10 ml) was added, and the resulting solution kept at room temperature for one hour. The excess of formic acid was removed under reduced pressure below 30° and the residue dissolved in butan - 2 - ol:toluene (4:1). The solution was boiled under reflux for two hours, then the solvent was distilled off slowly during one hour, the volume of solvent being kept constant by addition of further butan - 2 - ol:toluene solvent mixture. The solvent was finally removed under reduced pressure and the residue chromatographed on Kieselgel G using chloroform-5% methanol as eluant. Diethyl N - formyl - L - prolylaminomalonate **9** (380 mg, 27%) was obtained as a colourless oil, which decomposed on attempted distillation under reduced pressure; ν_{max} (film) 3280 (broad, NH) 1750 (CO_2Et), 1670, 1525 cm^{-1} (amide bands), δ ($CDCl_3$) 1.32 (6H, t, J 7 Hz, $2\times CO_2CH_2\underline{Me}$), 1.68–2.65 (4H, m, $\rangle NCH_2(\underline{CH_2})_2CH\langle$), 3.36–3.78 (2H, m, $\rangle NCH_2$–), 4.28 (4H, q, J 7 Hz, $2\times CO_2\underline{CH_2}Me$), 4.62 (1H, m, $\rangle N$–$C\underline{H}CH_2$–), 5.16 (1H, dd, J 7 Hz, $NHC\underline{H}(CO)_2$), 7.70 and 7.93 (1H, br, dd, J 7 Hz, NH), 8.29 and 8.33 (1H, 2s, CHO) (Found: M^+, *m/e* 300.131520. $C_{13}H_{20}N_2O_6$

requires *m/e* 300.132126). L - Prolyl - 2 - ethoxycarbonylglycine anhydride **8** (300 mg, 36%) was obtained from ethyl acetate–light petroleum (b.p. 60–80°) as colourless needles, m.p. 102–105°; ν_{max} (Nujol) 3110 (NH), 1730 (CO_2Et), 1690, 1675, 1440 cm^{-1} (amide bands), δ ($CDCl_3$) 1.34 (3H, t, J 7 Hz, $CO_2CH_2CH_3$), 1.68–2.60 (4H, m, $\rangle NCH_2CH_2CH_2CH\langle$), 3.40–3.75 (2H, m, $-CH_2N\langle$), 4.30 (2H, q, J 7 Hz, $CO_2CH_2CH_3$), 4.37 (1H, m, $\rangle NCHCH_2-$), 4.71 (1H, d, J 4 Hz, NHCHCO) and 8.8 (1H, br. d, J 4 Hz, NH) (Found: C, 53.25; H, 6.3; N, 12.65. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%).

(b) A stream of hydrogen was passed through a solution of N - benzyloxycarbonyl - L - prolylaminomalonate (4.0 g) in ethanol (100 ml) containing a suspension of 5% palladised charcoal catalyst (2.0 g) at room temp. After 2 hr the catalyst was removed by filtration and the filtrate evaporated under reduced pressure to yield the crude aminodiester as a colourless oil. Toluene (50 ml) was added and the resulting solution boiled under reflux with 4A molecular sieves for two hours. The solvent was removed under reduced pressure to yield a colourless gum which crystallised on trituration with ethyl acetate. The crude product was recrystallised from ethyl acetate–light petroleum (b.p. 60–80°) to give L - prolyl - 2 - ethoxycarbonylglycine anhydride (1.23 g, 56%), identical with material prepared by method (a).

3 - [2 - (N - *Benzyloxycarbonyl* - L - *prolylamido*) - 2,2 - *diethoxycarbonylethyl*] - 2 - *methylindole* **11**

(a) Diethyl N - benzyloxycarbonyl - L - prolylaminomalonate (300 mg) and 2-methylgramine[17] (140 mg) in ethanol (20 ml) were added to a stirred solution of sodium in ethanol (15 ml) in a N_2 atmosphere. The mixture was boiled under reflux and ethyl iodide (192 mg) in ethanol (5 ml) was added. The mixture was boiled under reflux overnight and the ethanol removed under reduced pressure. The residue was dissolved in water and chloroform, the organic layer washed with dilute hydrochloric acid and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a brown glass which was chromatographed on Kieselgel G using chloroform as eluant.

3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2,2 - diethoxycarbonylethyl] - 2 - methylindole (220 mg, 57%) was obtained as a colourless glass; $\nu_{max.}$ ($CHCl_3$) 3470 (indole NH), 3410 (amide NH), 1735 (ester CO) and 1710–1680, 1510 cm^{-1} (amide bands), $\lambda_{max.}$ 224 (ϵ 32400), 280 (ϵ 9430) and 290 nm (ϵ 7720), δ ($CDCl_3$) 1.22 (6H, t, J 7 Hz, $CO_2CH_2CH_3$), 1.55–2.30 (4H, m, $\rangle NCH_2CH_2CH_2CH$), 2.24 (3H, s, Me), 3.22–3.53 (2H, m, $CH_2N\langle$), 3.81 (2H, s, indole benzylic protons), 3.95–4.48 (5H, m, $2\times CO_2CH_2CH_3 + \rangle NCHCH_2-$), 4.99 and 5.04 (2H, 2×s, $PhCH_2O$), 6.85–7.68 (10H, m, aromatic protons and NH) and 8.12 (1H, br. NH) (Found: M^+, *m/e* 531.271705. $C_{30}H_{35}N_3O_7$ requires *m/e* 531.273304).

(b) Diethyl N - benzyloxycarbonyl - L - prolylaminomalonate (300 mg) and 2-methylgramine (140 mg) in ethanol (20 ml) were added to a stirred solution of sodium (19 mg) in ethanol (15 ml) in a nitrogen atmosphere at room temp. After 30 min dimethyl sulphate (155 mg) in ethanol (5 ml) was added and the mixture left at room temp overnight. The reaction mixture was worked up as in (a) to give a pale brown glass which was shown to be virtually pure by tlc on Kieselgel G using chloroform as eluant. Chromatography on Kieselgel G using chloroform as eluant gave 3 - [2 - (N - benzyloxycarbonyl - L - prolylamido) - 2,2 - diethoxycarbonylethyl] - 2 - methylindole (348 mg, 86%) as a colourless glass, identical with that prepared in method (a).

3 - [2 - (*N - Benzyloxycarbonyl* - L - *prolylamido*) - 2 - *ethoxycarbonylethyl*] - 2 - *methylindole* **15** *and the corresponding acid* **14**

3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2,2 - diethoxycarbonylethyl] - 2 - methylindole (1.10 g) was stirred in a solution of 2M sodium hydroxide solution (2.4 ml) and ethanol (15 ml) in a nitrogen atmosphere for 24 hr. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate and water. The aqueous layer was washed with ethyl acetate, acidified to Congo Red with 2M hydrochloric acid, and the organic layer washed with water and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give a colourless glass to which water (50 ml) was added. The mixture was heated to 100° for 2 hr in a stream of nitrogen. When cold, the aqueous layer was extracted with ethyl acetate, and the organic layer washed with sodium bicarbonate solution and water, and dried ($MgSO_4$). Evaporation of the solvent yielded a glass which was chromatographed on Kieselgel G using benzene-40% ether as eluant. 3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2 - ethoxycarbonylethyl] - 2 - methylindole (547 mg, 58%) was obtained as a colourless glass, ν_{max} (film) 3400–3300 (NH) 1740 (ester CO) and 1700–1650, 1515 cm^{-1} (amide bands), λ_{max} 224 (ϵ 29400), 284 (ϵ 5940) and 290 nm (ϵ 5210), δ ($CDCl_3$) 1.05 (3H, t, J 7 Hz, $CO_2CH_2CH_3$), 1.38–2.15 (4H, m, $\rangle NCH_2CH_2CH_2CH-$), 2.23 (3H, s, Me), 3.0–3.5 (4H, m, $\rangle NCH_2-$ and indole benzylic protons), 3.99 (2H, q, J 7 Hz, $CO_2CH_2CH_3$), 4.16 (1H, m, $\rangle NCHCH_2-$), 4.50–5.10 (3H, m, $PhCH_2O$ and CH_2CHNH-), 6.85–7.54 (10H, m, aromatic protons and NH) and 8.80 (1H, s, NH) (Found: M^+, *m/e* 477.226344. $C_{27}H_{31}N_3O_5$ requires *m/e* 477.226356).

The bicarbonate washings were acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and dried. Evaporation of the solvent gave 3 - [2 - N - benzyloxycarbonyl - L - prolylamido) - 2 - carboxyethyl] - 2 - methylindole (214 mg, 24%) as a colourless glass, δ ($CDCl_3$) 1.38–2.1 (4H, m, $\rangle N-CH_2CH_2CHCH-$), 2.21 (3H, s, Me), 2.96–3.42 (4H, m, $\rangle NCH_2-$ and indole benzylic protons), 4.17 (1H, br, $\rangle NCHCH_2$), 4.60–5.05 (3H, m, $PhCH_2O$ and $-CH_2CHNH-$), 6.70–7.58 (10H, m, aromatic protons and NH), 8.34 (1H, br, s, NH), 9.25 (1H, br, s, CO_2H). The material was homogeneous by tlc and was used in the next stage without further purification.

L - *Prolyl* - 2 - *methyltryptophan anhydride* **7a** and **7b**

(a) 3 - [2 - (N - Benzyloxycarbonyl - L prolylamido) - 2 - carboxyethyl] - 2 - methylindole (214 mg) was treated with 2M hydrogen bromide in glacial acetic acid (3 ml) at room temp in a nitrogen atmosphere. After 2 hr, tlc indicated hydrolysis to be complete, and the acetic acid was removed at 0.1 mm Hg pressure at room temp to yield the crude aminoacid hydrobromide. The salt was dissolved in methanol (3 ml) and Amberlite IRA-400 ion exchange resin (2 ml) in the hydroxide form was added. The resin was filtered off, washed with methanol and the solvent removed from the combined methanol solutions under reduced pressure. Water was removed by azeotropic distillation with benzene–ethanol, and the residue boiled under reflux in a Dean–Stark apparatus for 48 hr in a nitrogen atmosphere. Evaporation of the solvent yielded a glass which was chromatographed on Kieselgel G using ethyl acetate-5% methanol as eluant. L - Prolyl - 2 - methyl - L - tryptophan anhydride **7a** (25 mg, 17%) was eluted first, and was obtained from methanol as colourless needles, m.p. 131–133°, $[\alpha]_D^{20} - 30.3°$ ($CHCl_3$), ν_{max} ($CHCl_3$) 3470 (indole NH), 3360 (amide NH), 1665 and 1460 (amide bands), λ_{max} 224 (ϵ 34600), 282 (ϵ 6530) and 289 nm (ϵ 5500), δ ($CDCl_3$) 1.55–2.2 (4H, m $\rangle NCH_2CH_2CH_2CH$), 2.31 (3H, s, Me), 2.92 (1H, q, J 15 and 10 Hz, β-ind. $CHHCH\langle$), 3.58 (2H, m, NCH_2), 3.62 (1H, q, J 15 and 5 Hz, β-ind. CHHCH-), 4.0 (1H, m, $\rangle NCHCH_2$), 4.34 (1H, q, J 10 and 5 Hz, β-ind. CHH.CH–), 5.82 (1H, br. s, NH), 6.93–7.6 (4H, m, aromatic protons) and 8.68 (1H, br. s, NH) (Found: C, 68.2; H, 6.30; N, 14.1%. M^+, *m/e* 297.146755. $C_{17}H_{19}N_3O_2$ requires C, 68.6; H, 6.40; N, 14.1%. M, 297.147718).

Further elution gave L - prolyl - 2 - methyl - D - tryptophan anhydride **7b** (16 mg, 11%) as a colourless glass, $[\alpha]_D^{20} - 93°$ ($CHCl_3$), ν_{max} ($CHCl_3$) 3460 (indole NH), 3390 (amide NH), 1650 and 1450 cm^{-1} (amide bands), λ_{max} 224 (ϵ 34700), 282 (ϵ 6820) and 289 nm (ϵ 5500), δ ($CDCl_3$) 1.4–2.1 (4H, m, $\rangle NCH_2\underline{CH_2}\underline{CH_2}CH-$), 2.32 (3H, s, Me), 2.53 (1H, m, $\rangle NC\underline{H}CH_2$), 2.95–3.6 (4H, m, $\rangle NCH_2$ and β-ind. CH_2CH-), 4.20 (1H, m, β-ind. $CH_2\underline{CH}-$), 6.78 (1H, br. s, NH), 6.9–7.6 (4H, m, aromatic protons) and 8.85 (1H, br. s, NH) (Found: M^+, *m/e* 297.147052).

(b) 3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2 - ethoxycarbonyl] - 2 - methylindole (1.0 g) was treated with 2M hydrogen bromide in glacial acetic acid (9 ml) at room temp under a nitrogen atmosphere. After 2 hr the acetic acid was removed at 0.1 mm Hg pressure at room temp and the residue suspended in toluene (30 ml). Triethylamine (0.025 ml) was added and the stirred mixture boiled under reflux with 4A molecular sieves for 18 hr. The solvent was removed under reduced pressure and the residue chromatographed on Kieselgel G using ethyl acetate–5% methanol as eluant. L - Prolyl - 2 - methyl - L - tryptophan anhydride and L - prolyl - 2 - methyl - D - tryptophan anhydride, identical to the diastereoisomers prepared by method (a), were eluted in 27% and 22% yield, respectively.

2 - (*Indol - 2 - yl*) - 2 - *methylpropanal* **19**

2 - (Indol - 2 - yl) - 2 - methylpropan - 1 - ol[12] (8.0 g) was dissolved in dry benzene (140 ml) and dry dimethyl sulphoxide (140 ml) was added. Anhydrous pyridine (3.0 ml) was added, followed by trifluoroacetic acid (1.28 ml) and dicyclohexyl carbodi-imide (21.4 g). The flask was stoppered and allowed to stand at room temp overnight. Benzene (300 ml) was added and the dicyclohexylurea filtered off. The filtrate and washings were extracted with water (3 × 300 ml) to remove dimethyl sulphoxide and the organic layer was dried ($MgSO_4$). The benzene was removed under reduced pressure to yield an oil which was chromatographed on Kieselgel G using benzene as eluant. 2 - (Indol - 2 - yl) - 2 - methylpropanal (6.35 g, 80%) was obtained from benzene–light petroleum (b.p. 60–80°) as colourless needles, m.p. 68–69° (lit.[12] m.p. 68–70°).

3 - [2 - (N - *Benzyloxycarbonyl - L - prolylamido*) - 2,2 - *diethoxycarbonylethyl*] - 2 - (1,1 - *dimethylallyl*) - *indole* **21**

Diethyl N - benzyloxycarbonyl - L - prolylaminomalonate (4.20 g) and 2 - (1,1 - dimethylallyl) gramine[11] (2.50 g) in ethanol (50 ml) were added to a stirred solution of sodium (210 mg) in ethanol (50 ml) at room temp in a nitrogen atmosphere. After 30 min, dimethyl sulphate (1.96 ml) in ethanol (5 ml) was added and the mixture allowed to stand at room temp overnight. The reaction mixture was then boiled under reflux for 2 hr, and the solvent was then removed under reduced pressure. The residue was taken up in ethyl acetate and water, the organic layer washed with dilute hydrochloric acid and brine, and dried ($MgSO_4$). Evaporation of the solvent yielded a brown oil which was chromatographed on Kieselgel G using benzene initially, then benzene–ether (3:1) as eluant. Benzene eluted 2 - (1,1 - dimethylallyl) - 3 - ethoxymethylindole **22**, and benzene–ether eluted 3 - [2 - (N - benzyloxycarbonyl - L - prolylamido) - 2,2 - diethoxycarbonylethyl] - 2 - (1,1 - dimethylallyl) - indole **21**. 2 - (1,1 - Dimethylallyl) - 3 - ethoxymethylindole **22** (234 mg, 10%) was obtained as a yellowish glass, ν_{max} ($CHCl_3$) 3460 (NH), 1080 (ether C–O) and 1005, 920 cm^{-1} ($CH=CH_2$), λ_{max} 226 (ϵ 29850), 275 (ϵ 7250), 283 (ϵ 7820) and 291 nm (ϵ 7040), δ ($CDCl_3$) 1.20 (3H, t, J 7 Hz, CH_3CH_2O-), 1.54 (6H, s, CMe_2), 3.53 (2H, q, J 7 Hz, OCH_2CH_3), 4.73 (2H, s, ind. CH_2-O), 5.13 (2H, dq, J 1.5, 18 and 10 Hz, $-CH=CH_2$), 6.18 (1H, q, J 18 and 10 Hz, $-CH=CH_2$), 7.0–7.8 (4H, m, aromatic protons), and 8.0 (1H, br. NH) (Found: M^+, *m/e* 243.162489. $C_{16}H_{21}NO$ requires *m/e* 243.162306). 3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2,2 - diethoxycarbonylethyl] - 2 - (1,1 - dimethylallyl) - indole **21** (2.44 g, 42%) was obtained as a colourless glass, ν_{max} (film) 3400 br (NH), 1740 (ester CO), 1710, 1690, 1500 (amide bands) and 1015, 920 cm^{-1} ($CH=CH_2$). λ_{max} 224 (ϵ 34500), 284 (ϵ 8840) and 290 nm (ϵ 7750), δ ($CDCl_3$) 1.09 (6H, t, J 7 Hz, $2\times CO_2CH_2\underline{CH_3}$), 1.54 [6H, s, $-C(\underline{CH_3})_2$], 1.35–2.2 (4H, m, $\rangle NCH_2\underline{CH_2}\underline{CH_2}CH-$), 3.05–3.45 (2H, m, $NC\underline{H}CH_2$), 3.85–4.5 (7H, m, β-ind.$\underline{CH_2}$, $2\times CO_2\underline{CH_2}CH_3$, and $\rangle NC\underline{H}CH_2-$), 4.9–5.33 (4H, m, $PhCH_2O$ and $CH=\underline{CH_2}$), 6.19 (1H, q, J 10 and 18 Hz, $-\underline{CH}=CH_2$), 6.88–7.78 (10H, m, aromatic protons and NH) and 8.62 (1H, br. s, NH) (Found: M^+, *m/e* 603.294141. $C_{34}H_{41}N_3O_7$ requires *m/e* 603.294431.

3 - [2 - (N - *Benzyloxycarbonyl - L - prolylamido*) -2 - *ethoxycarbonylethyl*] - 2 - (1,1 - *dimethylallyl*) - *indole* **23**

3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2,2 - diethoxycarbonylethyl] - 2 - (1,1 - dimethylallyl) - indole (1.48 g) was stirred in a solution of 2M sodium hydroxide solution (1.25 ml) in ethanol (50 ml) at room temp overnight in a nitrogen atmosphere. The ethanol was removed under reduced pressure and the residue taken up in ethyl acetate and water. The aqueous layer was washed with ethyl acetate, acidified to Congo red with 2M hydrochloric acid, extracted with ethyl acetate, and the organic layer washed with water and dried ($MgSO_4$). Evaporation of the solvent gave a colourless glass to which water (25 ml) was added. The mixture was heated at 100° for 2 hr in a stream of nitrogen. When cold, the aqueous mixture was extracted with ethyl acetate, washed with sodium bicarbonate solution and water, and dried ($MgSO_4$). Evaporation of the solvent gave the crude monoester **23** as a glass (50 mg). The bicarbonate washings were acidified to Congo red with 2M hydrochloric acid, extracted with ethyl acetate, and the organic extract washed with water and dried ($MgSO_4$). Removal of the solvent gave the crude monocarboxylic acid **24**. The acid was re-esterified without further purification by adding thionyl chloride (0.03 ml) to a solution of the acid in dry ethanol (5 ml) at − 10° and allowing the resulting solution to stand at room temp overnight. The solvent was then removed under reduced pressure and the residue taken up in ethyl acetate and water. The organic layer was washed with sodium bicarbonate solution and water, and dried ($MgSO_4$). Evaporation of the solvent gave the monoester as a colourless glass which was combined with the material prepared as above. The combined samples were chromatographed on Kieselgel G using benzene–40% ether as eluant to give 3 - 2 - (N - benzyloxycarbonyl - L - prolylamido) - 2 - (ethoxycarbonylethyl - 2 - (1,1 - dimethylallyl) - indole (700 mg, 52%) as a colourless glass, ν_{max} (film) 3340 br. (NH) 1740 (ester CO), 1710–1670 br, 1510 (amide bands) and 1015, 915 cm^{-1} ($CH=CH_2$), λ_{max} 225 (ϵ 32100), 284 (ϵ 7070) and 291 nm (ϵ 6380), δ ($CDCl_3$) 0.98, 1.03 (3H, dt, J 7 Hz, $CO_2CH_2\underline{CH_3}$), 1.54 [6H, s, $C(\underline{CH_3})_2$], 1.54–2.15 (4H, m, $\rangle N\text{-}CH_2\underline{CH_2}\underline{CH_2}CH$), 2.85–3.6 (4H, m, β-ind.$\underline{CH_2}$ and $\rangle N\text{-}\underline{CH_2}\text{-}CH_2$-), 3.75–4.35 (3H, m, $\rangle N\text{-}C\underline{H}CH_2$- and $CO_2\underline{CH_2}CH_3$), 4.9 (1H, m, ind.$CH_2\underline{CH}$-), 5.16 (2H, s, $PhCH_2$), 5.18 (2H, dq, J 1.5, 10 and 18 Hz, $-CH=CH_2$), 6.18 (1H, q, J 10 and 18 Hz, $-\underline{CH}=CH_2$), 6.85–7.6 (10H, m, aromatic protons and NH) and 8.22 (1H, br.. s, NH), (Found: M^+, *m/e* 549.246258. $C_{30}H_{37}N_3O_7$ requires *m/e* 549.247483).

L - *Prolyl* - 2 - (1,1 - *dimethylallyl*) - *tryptophan anhydride* **6** *and* **25** 3 - [2 - (N - Benzyloxycarbonyl - L - prolylamido) - 2 - ethoxycarbonylethyl] - 2 - (1,1 - dimethylallyl) - indole (568 mg) was treated with 2M hydrogen bromide in acetic acid (10 ml) at room temp in a N_2 atmosphere. After 2 hr tlc indicated hydrolysis to be complete and the acetic acid was removed at 0.1 mm Hg pressure at room temp. The residue was suspended in toluene (25 ml), triethylamine (0.03 ml) was added, and the stirred mixture boiled under reflux through 4A molecular sieves for 18 hr. The solvent was then removed under reduced pressure, and the residue chromatographed on Kieselgel G using ethyl acetate–5% methanol as eluant. Three products were eluted. The first to be eluted was purified further by preparative tlc on Kieselgel G_F 254 using benzene–ether (2:1) as eluant and identified as N - acetyl - 2 - (1,1 - dimethylallyl) - tryptophan ethyl ester. The remaining two products were purified by preparative tlc on Kieselgel G_F 254

using ether as eluant, and identified as the two diastereoisomers of L - prolyl - 2 - (1,1 - dimethylallyl) - tryptophan anhydride (**6** and **25**). N - Acetyl - 2 - (1,1 - dimethylallyl) - tryptophan ethyl ester **26** (43 mg, 11%) was obtained as a colourless glass, ν_{max} ($CHCl_3$) 3480, 3450 sh, 3440 (NH), 1735 (ester CO), 1670, 1510 (amide bands), and 1010, 920 cm^{-1} ($CH{=}CH_2$) λ_{max} 226 (ϵ 24200), 275 sh (ϵ 5500), 284 (ϵ 5800) and 293 nm (ϵ 5500), δ ($CDCl_3$) 1.00 (3H, t, J 7 Hz, $CO_2CH_2CH_3$), 1.58 [6H, s, $C(CH_3)_2$], 1.85 (3H, s, $NHCOCH_3$), 3.29 (2H, d, J 7.5 Hz, β-ind.CH_2–), 4.00 (2H, q, J 7 Hz, $CO_2CH_2CH_3$), 4.86 (1H, q, J 7.5 Hz, $-CH_2CHNH-$), 5.21 (2H, dq, J 1.5, 10 and 18 Hz, $-CH{=}CH_2$), 6.22 (1H, q, J 10 and 18 Hz, $-CH{=}CH_2$), 6.19 (1H, br. d, J 7.5 Hz, $-CH-NH-$), 7.00–7.68 (4H, m, aromatic protons) and 8.28 (1H, br. s, indole NH) (Found: M^+, *m/e* 342.194101. $C_{20}H_{26}N_2O_3$ requires *m/e* 342.194331). L - Prolyl - 2 - (1,1 - dimethylallyl) - L - tryptophan anhydride (deoxybrevianamide E) (**6**) (85 mg, 20%) was obtained as a colourless glass, $[\alpha]_D^{22}$ – 58° ($CHCl_3$), ν_{max} ($CHCl_3$) 3480, 3450 (indole NH), 3360 (amide NH), 1665 br (CO), 1000, 918 cm^{-1} ($CH{=}CH_2$), λ_{max} 225 (ϵ 32400), 284 (ϵ 8140) and 291 nm (ϵ 7080), δ ($DCDl_3$) 1.53 [6H, s, $C(CH_3)_2$], 1.75–2.4 (4H, m, $\rangle N-CH_2CH_2CH_2CH$), 3.16 (1H, q, J 11 and 15 Hz, β-ind. $CHH-CH-$), 3.76 (1H, q, J 4 and 15 Hz, β-ind. $CHH-CH-$), 3.5–3.8 (2H, m, $\rangle NCH_2CH_2$), 4.10 (1H, m, C-12H), 4.43 (1H, q, J 11 and 4 Hz, β-ind. CH_2CHNH), 5.12 (2H, dq, J 1, 10 and 18 Hz, $-CH{=}CH_2$), 5.73 (1H, br. s, NH), 6.15 (1H, q, J 10 and 18 Hz, $-CH{=}CH_2$), 7.0–7.65 (4H, m, aromatic protons) and 8.7 (1H, br. s, NH) (Found: M^+, *m/e* 351.194517. $C_{21}H_{25}N_3O_2$ requires *m/e* 351.194666). L - Prolyl - 2 - (1,1 - dimethylallyl) - L - tryptophan anhydride showed identical UV, IR, NMR and mass spectra, optical rotation, and R_F values on Kieselgel G in ether, ethyl acetate–4% methanol, and chloroform–4% methanol to those shown by natural deoxybrevianamide E.[18]

L-Prolyl - 2 - (1,1 - dimethylallyl) - D- tryptophan anhydride **25** (53 mg, 14%) was obtained as a colourless glass, $[\alpha]_D^{22}$ – 30° ($CHCl_3$), ν_{max} ($CHCl_3$) 3450 (indole NH), 3390 (amide NH), 1660 (CO) and 1020, 920 cm^{-1} ($CH{=}CH_2$), λ_{max} 225 (ϵ 32200), 284 (ϵ 8120) and 291 nm (ϵ 7000), δ ($CDCl_3$) (400 MHz) 1.53, 1.54 (6H, 2s, Me_2C), 1.75, 1.95 (3H, m, $\rangle NCH_2CH_2CHH-$), 2.3 (1H, m, $\rangle NCH_2CH_2CHH-$), 3.3 (1H, dd, J 9.5 and 14.5 Hz, β-ind. $CHH-CH$), 3.47 (2H, q + m, J 4 and 14.5 Hz, β-ind.$CHH-$ and $\rangle NCHH-CH_2-$), 3.65 (1H, m, $\rangle NCHH-CH_2-$), 3.71 (1H, dd, J 6.5 and 10.5 Hz, C-12H), 4.3 (1H, dt, J 4 and 9.5 Hz, β-ind. CH_2CH), 5.18 (2H, dq, J 1, 10 and 17 Hz, $CH{=}CH_2$), 5.84 (1H, d, J 4 Hz, NHCO), 6.14 (1H, dd, J 10 and 17 Hz, $CH{=}CH_2$), 7.07–7.20 (2H, m, aromatic H), 7.29 (1H, m, aromatic H), 7.53 (1H, dt, J 0.5, 0.5 and 8 Hz, C-4H), and 8.1 (1H, s, indole NH) (Found: M^+, *m/e* 351.194166. $C_{21}H_{25}N_3O_2$ requires *m/e* 351.194666).

N - Acetyl - 2 - methyltryptophan methyl ester **27**

N - Acetyl - 2 - methyltryptophan[17] (600 mg) was dissolved in dry methanol (6 ml) and thionyl chloride (0.40 ml) added dropwise to the stirred solution at – 10°. The resulting solution was left at room temp for 48 hr. Evaporation of the solvent gave a glass which was chromatographed on silica gel using chloroform–3% ethanol as eluant. N - Acetyl - 2 - methyltryptophan methyl ester (278 mg, 46%) was obtained from methanol as colourless plates, m.p. 176–178°, ν_{max} ($CHCl_3$) 3470, 3425 (NH), 1740 (ester CO), 1670, 1510 cm^{-1} (amide bands), λ_{max} 225 (ϵ 31300), 283 (ϵ 6470) and 290 nm (ϵ 5050), δ ($CDCl_3$) 1.88 (3H, s, $NHCOCH_3$), 2.27 (3H, s, α-ind. CH_3), 3.21 (2H, d, J 5 Hz, β-ind. CH_2CH), 6.20 (1H, br. d, J 8 Hz, CONH) 6.93–7.55 (4H, m, aromatic protons) and 8.6 (1H, br. s, indole NH) (Found: C, 65.95; H, 6.55; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%).

Oxidation of N - Acetyl - 2 - methyltryptophan methyl ester **27**

(a) *2 - Acetoxymethyl - N - acetyl - 2 - methyltryptophan methyl ester* **29**. Iodosobenzene diacetate (354 mg) was dissolved in a solution of dimethyl sulphide (69 mg) in acetonitrile (10 ml). The apparatus was flushed out with N_2, the solution was stirred, and a solution of N - acetyl - 2 - methyltryptophan methyl ester (274 mg) in acetonitrile was added. The mixture was allowed to stand overnight, water (50 ml) was added, and the resulting solution extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent yielded a brown oil which was purified by preparative plate chromatography on Kieselgel G_F 254 using chloroform–3% methanol as eluant. 2 - Acetoxymethyl - N - acetyl - 2 - methyltryptophan methyl ester **29** (83 mg, 25%) was obtained from ethyl acetate–light petroleum (b.p. 60–80°) as colourless prisms, m.p. 144–145°, ν_{max} (Nujol) 3370 (indole NH), 3240 (amide NH), 1745, 1730 (ester CO), and 1665, 1530 cm^{-1} (amide bands), λ_{max} 224 (ϵ 30800), 278 (ϵ 7900), 284 (ϵ 8050) and 292 nm (ϵ 6300), δ ($CDCl_3$) 1.92 (3H, s, $NHCOCH_3$), 2.08 (3H, s, $OCOCH_3$), 3.31 (2H, d, J 5.5 Hz, β-ind. CH_2CH), 4.90 (1H, m, β-ind. CH_2CHNH), 5.18 (2H, d, J 1 Hz, α-ind. CH_2–O), 6.23 (1H, d, J 8 Hz, amide NH), 6.97–7.62 (4H, m, aromatic protons), 8.80 (1H, br., indole NH) (Found: C, 61.35; H, 5.95; N, 8.2. $C_{17}H_{20}N_2O_5$ requires C, 61.4; H, 6.2; N, 8.4%).

(b) When the preparation described in (a) was repeated using acetic acid (20 ml) as solvent instead of dimethyl sulphide–acetonitrile, work-up in the normal manner followed by chromatography on Kieselgel G_F 254 gave 2 - acetoxymethyl - N - acetyl - 2 - methyltryptophan methyl ester **29** (65% yield, m.p. 144–146°, identical to that obtained as in (a) above.

(c) *Methyl - 1 - acetyl - 3a - methoxy - 8a - methyl - 2,3,3a,8a - tetrahydropyrrolo - [2,3,b] - indole - 2 - carboxylate* **31**. A solution of iodosobenzene diacetate (177 mg) in methanol (10 ml) was stirred in a nitrogen atmosphere, and a solution of N - acetyl - 2 - methyltryptophan methyl ester (137 mg) in methanol (5 ml) was added. The resulting mixture was stirred at room temp overnight and the methanol was then removed under reduced pressure. The residue was taken up in water and ether, and the organic layer dried ($MgSO_4$). Evaporation of the solvent yielded an oil which was purified by preparative plate chromatography on Kieselgel G_F 254 using chloroform–3% methanol as eluant. Starting material (72 mg) was recovered, together with a product which crystallised on trituration with chloroform. Methyl 1 - acetyl - 3a - methoxy - 8a - methyl - 2,3,3a,8a - tetrahydropyrrolo - [2,3,*b*] - indole - 2 - carboxylate **31** (71 mg, 46%) was obtained from light petroleum (b.p. 60–80°) as colourless plates, m.p. 123–126°, ν_{max} ($CHCl_3$) 3445 (NH), 1745 (ester CO) and 1640 cm^{-1} (amide band), λ_{max} 243 (ϵ 7400) and 306 nm (ϵ 2270), δ ($CDCl_3$) 1.72 (3H, s, C-CH_3), 1.85 (3H, s, $\rangle NCOCH_3$), 2.56 (1H, q, J 8 and 13 Hz, $-CHH-CH-$), 2.92 (1H, q, J 2 and 13 Hz, $-CHH-CH-$), 3.05 (3H, s, OCH_3), 3.18 (3H, s, CO_2CH_3), 4.38 (1H, q, J 2 and 8 Hz, $-CHH-CH$), 6.11 (1H, br. s, NH) and 6.55–7.24 (4H, m, aromatic protons) (Found: C, 63.05; H, 6.45; N, 8.9. $C_{16}H_{20}N_2O_4$ requires C, 63.2; H, 6.6; N, 9.2%).

(d) N - Acetyl - 2 - methyltryptophan methyl ester (137 mg) in acetonitrile (5 ml) was added to a solution of iodosobenzene diacetate (177 mg) in acetonitrile (5 ml) and water (5 ml) under N_2, and the mixture allowed to stand at room temp overnight. The mixture was then diluted with water (30 ml), and twice extracted with ether. The combined ethereal extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent yielded an oil which was purified by preparative plate chromatography on Kieselgel G_F 254 using chloroform–3% methanol as eluant. Starting material (48 mg) was recovered together with two major products.

Methyl - 2 - acetamido - 4 - (2' - acetamidophenyl) - 4 - oxobutanoate **33** (20 mg, 13%) was obtained from ethyl acetate–light petroleum (b.p. 60–80°) as colourless needles, m.p. 134–136°, ν_{max} (Nujol) 3300, 3240 br (NH), 1728 (ester CO), 1690 (ketone CO) and 1660, 1645, 1535 cm^{-1} (amide bands), λ_{max} 230 (ϵ 27300), 234 (ϵ 27300), 259 (ϵ 10500), 266 (ϵ 8720) and 324 nm (ϵ 4800), δ ($CDCl_3$) 2.02, 2.22 (2 × 3H, s, 2 × $HNCOCH_3$), 3.6–3.8 (2H, m, $-CH_2CO$), 3.74 (3H, s, $-OCH_3$), 4.92 (1H, m, $-CH-CO$), 6.54 (1H, d, J 8 Hz, NHCH), 7.11 (1H, dt, J 1.5 and 8 Hz, C-5'H), 7.59 (1H, dt, J 1.5 and 8 Hz, C-4'H), 8.7 (1H, br. d, J 8 Hz, C-3'H), 7.9 (1H, dd, J 1.5 and 8 Hz, C-6'H), 11.4 (1H, br. s, NH) (Found: M^+, *m/e* 306.11943. $C_{15}H_{18}N_2O_5$ requires *m/e* 306.12156).

Methyl 1 - acetyl - 3a - hydroxy - 8a - methyl - 2,3,3a,8a, - tetrahydropyrrolo - [2,3,*b*] - indole - 2 - carboxylate **32** (39 mg, 43%) was obtained from ethyl acetate–light petroleum (b.p. 60–80°) as colourless plates, m.p. 191–194°, ν_{max} (Nujol) 3375 br. (OH and NH), 1730 (ester CO), 1635 cm^{-1} (amide band), λ_{max} 243 (ϵ 6950) and 304 nm (ϵ 2200), δ ($CDCl_3$) 1.66 (3H, s, –C–CH_3), 1.84 (3H, s, $COCH_3$), 2.45–2.85 (1H, br. OH), 2.58 (1H, q, J 13 and 8 Hz, –CHH–CH–), 2.89 (1H, q, J 13 and 1.5 Hz, –CHH–CH), 3.18 (3H, s, CO_2CH_3), 4.35 (1H, q, J 1.5 and 8 Hz, –CHH–CH–), and 6.45–7.32 (5H, m, aromatic protons and NH) (Found: C, 61.8; H, 6.2; N, 9.8. $C_{15}H_{18}N_2O_4$ requires C, 62.1; H, 6.2; N, 9.7%).

3 - [2 - (2′ - *Acetamidophenyl* - 2 - *oxoethyl*] - *pyrrolo* - [1,2,*a*] - *pyrazine* - 1,4 - *dione* **34**

L - Prolyl - 2 - methyl - L - tryptophan anhydride (230 mg) in acetonitrile (5 ml) was added to a solution of iodosobenzene diacetate (275 mg) in acetonitrile (5 ml) and water (5 ml) under N_2 and the mixture allowed to stand at room temp overnight. The mixture was then diluted with water (30 ml) and extracted with ether. The ethereal extract was washed with water, and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was purified by preparative plate chromatography on Kieselgel G_F 254 using chloroform–3% methanol as eluant. Starting material (120 mg) was recovered, followed by 3 - [2 - (2′ - acetamidophenyl - 2 - oxoethyl] - pyrrolo[1,2,*a*] - pyrazine 1,4 - dione **34** (20 mg, 9%), which was obtained from ethyl acetate as colourless needles, m.p. 233–234°, ν_{max} (Nujol) 3250 br (NH), 1700, 1670, 1650, 1630 cm^{-1} (amide bands), λ_{max} 230 (ϵ 26300), 235 (ϵ 25000), 261 (ϵ 10900), 268 (ϵ 9900) and 327 nm (ϵ 3830), δ ($CDCl_3$) 2.24 (3H, s, $NHCOCH_3$), 1.8–2.5 (4H, m, $\rangle NCH_2CH_2CH_2CH$–), 3.23 (1H, q, J 10 and 18 Hz, CO–CHH–CH–), 3.65 (2H, m, $\rangle NCH_2$–), 4.19 (1H, q, J 3 and 18 Hz, –CO–CHH–CH–), 4.2 (1H, m, $\rangle NCHCH_2$–), 4.62 (1H, br. d, J 10 Hz, –$COCH_2CH$–), 6.6 (1H, s, NH), 7.10 (1H, dt, J 7.5 and 1.5 Hz, C–5′H), 7.57 (1H, dt, J 7.5 and 1.5 Hz, C–4′H), 7.95 (1H, dd, J 1.5 and 8 Hz, C–6′H), 8.7 (1H, br. d, J 8 Hz, C–3′H) and 9.5 (1H, s, NH) (Found: M^+, *m/e* 329.1316. $C_{17}H_{19}N_3O_4$ requires *m/e* 329.13755).

Oxidation of Deoxybrevianamide E

Deoxybrevianamide E (60 mg) in acetonitrile (5 ml) was added to a solution of iodosobenzene diacetate (55 mg) in acetonitrile (5 ml) and water (5 ml) under a nitrogen atmosphere, and the mixture allowed to stand at room temp for 72 hr. The mixture was then diluted with water (30 ml), and extracted with ether. The ethereal extract was washed with water, and dried ($MgSO_4$). Evaporation of the solvent yielded an oil which was chromatographed on Kieselgel G_F 254 using ether as eluant. Starting material (20 mg) was recovered, together with a product (10 mg), which consisted of two compounds of closely similar R_F value. The two components of this mixture could not be separated on preparative tlc using a variety of eluting solvents.

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