New Peptide Antibiotics, Trichopolyns I and II, from *Trichoderma polysporum*[1]

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Summary The peptide antibiotics trichopolyn I and II produced by *Trichoderma polysporum* were shown by chemical degradation and spectral analysis to have the structures (**14**) and (**15**) respectively.

THE antibiotics trichopolyn nitrate and trichopolyn hydrochloride produced by *Trichoderma polysporum* (Link *ex* Pers.) Rifai (strain TMI 60146) were reported in 1978 and named trichopolyn A and B, respectively.[2] During a structural investigation, trichopolyn was found to be a mixture of two components in a ratio of 9 : 1. The major and minor components were named trichopolyn I and II, respectively. Since the individual components were difficult to separate, the mixture was used for further detailed investigation.

Hydrolysis of trichopolyn hydrochloride (trichopolyn B) with 6 M-hydrochloric acid (110 °C, 24 h) gave (*R*)-(−)-2-methyldecanoic acid {b.p. 106 °C at 1·0 mmHg; $[\alpha]_D^{28}$ −19·4° (*c* 1·4, hexane); *cf.* *S*-acid[3]: $[\alpha]_D^{25}$ + 28°} from the ethyl acetate-soluble fraction; the aqueous fraction contained the five known amino-acids Ile, Val (very small proportion in comparison with the others), α-aminoisobutyric acid (Aib), Pro, and Ala, and three new products, trichoponamic acid (**1**), 6-epitrichoponamic acid[4] (**2**), and trichodiaminol (**7**). All the known amino-acids were demonstrated to have the L-configuration.[5,6] The structures of trichoponamic acid (**1**) {$C_{11}H_{19}NO_3$; m.p. 206—214 °C (decomp.); $[\alpha]_{589}^{21}$ 0°, $[\alpha]_{286}^{21}$ + 193°, $[\alpha]_{258}^{21}$ + 46°, $[\alpha]_{217}^{21}$ + 401° (*c* 0·20, MeOH)} and its 6-epimer (**2**) {$C_{11}H_{19}NO_3$; m.p. 197—205 °C (decomp.); $[\alpha]_{589}^{21}$ −26·5°, $[\alpha]_{286}^{21}$ −222°, $[\alpha]_{254}^{21}$ −95°,

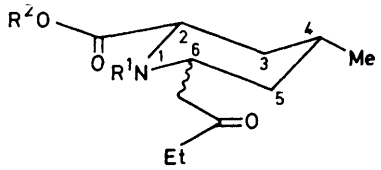
$[\alpha]_{244}^{21}$ −74°, $[\alpha]_{222}^{21}$ −18° (*c* 0·19, MeOH)} were assigned on the basis of the proton spin-decoupling studies on their methyl esters and the ^{13}C n.m.r. data of the free acids.†

The partial methanolysis product (**3**) gave the free acid (**4**) and the unsaturated acid (**5**) on treatment with 0·3 M NaOH in H_2O–MeOH (2 : 5). The latter on hydrogenation followed by hydrolysis gave the amino-acid (**10**) {m.p. 177—179 °C; $[\alpha]_D^{26}$ −17·30° (*c* 0·5, MeOH)} which was oxidised by L-amino-acid oxidase.[7] Thus the L-configuration of trichoponamic acid (**1**) and its 6-epimer (**2**) was established. The structure of (**3**) was further confirmed by hydrolysis into 2-methyldecanoic acid, L-Pro, and trichoponamic acid.

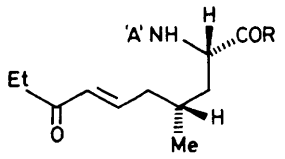
The structure of trichodiaminol (**7**) {m.p. 131—133 °C; $[\alpha]_D^{28}$ + 58° (*c* 0·5, MeOH)} was assigned on the basis of its spectral data and data for its *p*-bromobenzenesulphonate (**8**) and confirmed by independent synthesis through coupling of benzyloxycarbonyl-L-Ala(Z-L-Ala) with 2-(methylamino)-ethanol using 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline[8] giving Z-L-Ala-2-(methylamino)ethanol followed b removal of the Z group (H_2–Pd) and reduction ($LiAlH_4$).

The field-desorption mass spectrum of trichopoly hydrobromide showed peaks at *m/e* 1206 [M_I ($C_{61}H_{111}N_1$ O_{13}) + H], 1192 [M_{II} ($C_{60}H_{109}N_{11}O_{13}$) + H], 1188 ($M_I$ H − H_2O), and 1174 (M_{II} + H − H_2O), suggesting th trichopolyn is a mixture comprising trichopolyns I and I the former containing Ile instead of the Val in the latte The results of the foregoing acid hydrolysis also support thi

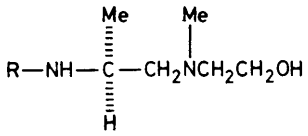
A ^1H n.m.r. (200 MHz; CD_3COCD_3) spin-decouplir experiment on trichopolyn hydrochloride showed tl presence of the partial structure (**11**). Partial methanoly (12 M-HCl–MeOH, 1 : 1; 37 °C; 15 h) of trichopolyn hydr chloride gave the methyl ester (**3**) and (*R*)-(−)-2-methy decanoyl-L-Pro-OMe from the chloroform-soluble fracti and fragment (**9**) from the water-soluble fraction. C hydrolysis, the hydrochloride of (**9**) {m.p. 153—155 °($[\alpha]_D^{22}$ + 5·8° (*c* 1·0, MeOH); *N*-terminal: Ala} afford



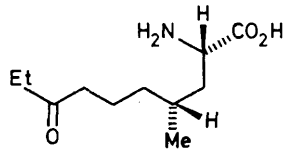
(1) $R^1 = R^2 =$ H, 6_α-H
(2) $R^1 = R^2 =$ H, 6_β-H
(3) $R^1 =$ 'A', $R^2 =$ Me
(4) $R^1 =$ 'A', $R^2 =$ H



(5) R = OH
(6) R = 'B' NHCH(Me)CH_2N(Me)CH_2CH_2OAc



(7) R = H
(8) R = *p*-$BrC_6H_4SO_2$
(9) R = H 'B'



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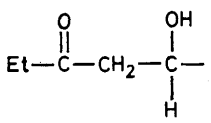
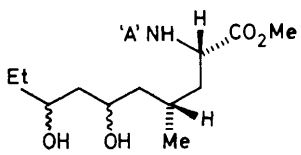


(11)



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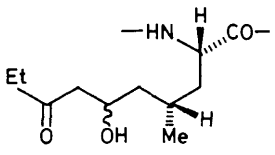

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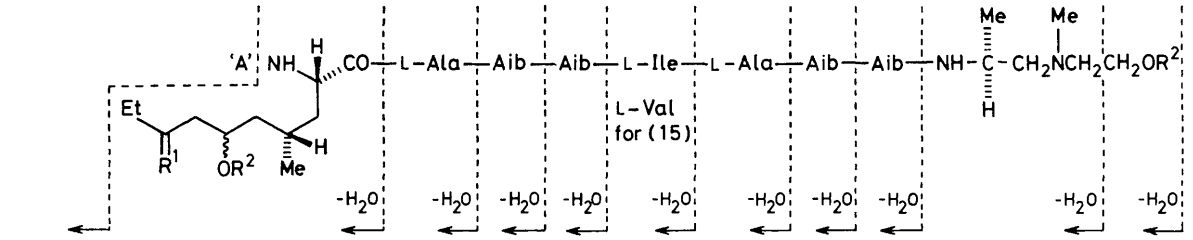

(14)	266	461	532	617	702	815	886	971	1056	1156	1187
(15)	266	461	532	617	702	801	872	957	1042	1142	1173

(14) (15) $R^1 = O$, $R^2 =$ H
(16) $R^1 =$ H, OH, $R^2 =$ H
(17) $R^1 = O$, $R^2 =$ Ac

'A' = (*R*)-2-methyldecanoyl-L-Pro-
'B' = -L-Ala-$(Aib)_2$-L-Ile-L-Ala-$(Aib)_2$-

† Satisfactory analytical and spectral data have been obtained for all the new compounds.

trichodiaminol (**7**). The mass spectrum of the hydrochloride of (**9**) showed a fragmentation pattern supporting its structure.

Trichopolyn hydrochloride on $NaBH_4$ reduction gave the triol (**16**) hydrochloride {m.p. 123·5—125 °C; $[\alpha]_D^{28}$ −35° (*c* 1·0, MeOH); triacetate: m.p. 109—112 °C} which on methanolysis gave the diol methyl ester (**12**). Thus trichopolyn contained no pipecolic acid unit. The pipecolic acid derivatives (**1**), (**2**), and (**3**) must be generated from the partial structure comprising the 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid residue (**13**) *via* dehydration followed by Michael addition during the hydrolysis or the methanolysis of trichopolyn.

The order of linkage of the foregoing components was established by in-beam mass spectrometry[9] on trichopolyn, and the structures of trichopolyns I and II can be represented as (**14**) and (**15**), respectively. The mass spectral fragmentation is indicated below their formulae. The structures (**14**) and (**15**) account for the fact that trichopolyn hydrochloride on acetylation with acetic anhydride and pyridine gave the anhydromonoacetate (**6**) hydrochloride (m.p. 107—110 °C), while it gave the diacetate (**17**) hydrochloride (m.p. 104—107 °C) on treatment with acetic anhydride and BF_3–Et_2O.

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