SYNTHESIS OF 2-[N-(2-METHYLPROPANOYL]-N-PHENYL-ETHYLGLUTARIMIDE

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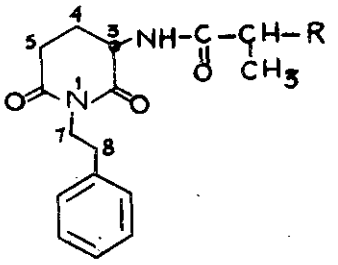
The structure of the glutarimide peptide (I) isolated from Croton humilis has been confirmed by synthesis.

Recently we reported the isolation of a 1:1 mixture of $C_{17}H_{22}N_2O_3$ and $C_{18}H_{24}N_2O_3$ compounds from Croton humilis, and on the basis of spectral and degradative studies proposed the structures (I) and (II) respectively.[1]



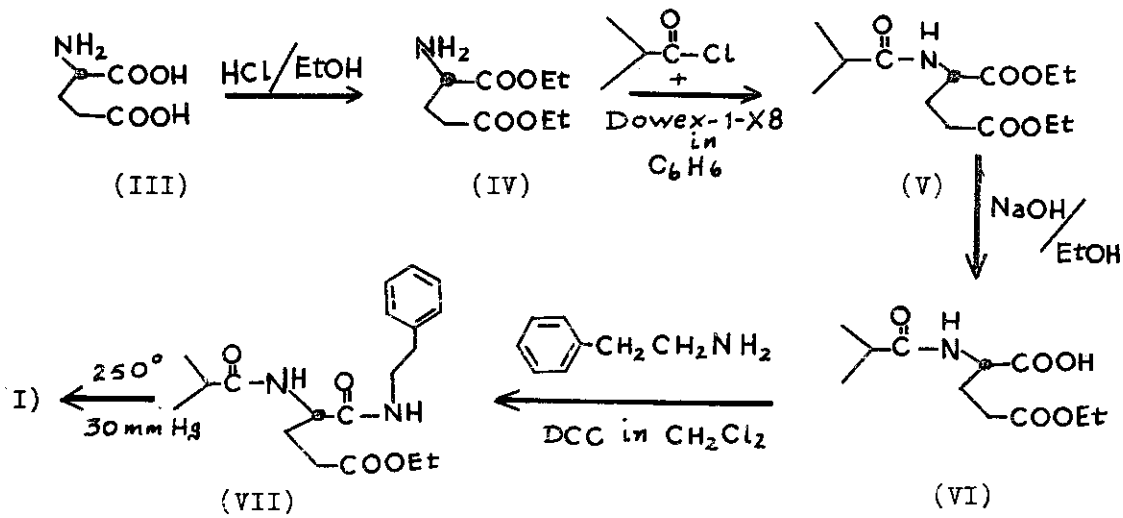
[(I), R = CH_3; (II), R = CH_2CH_3].

We have now been successful in separating these compounds. The $C_{17}H_{22}N_2O_3$ glutarimide had m.p. 148-155°, $[\alpha]_D$ + 11°, ($CHCl_3$), λ_{max}^{EtOH} 210 nm (ε 17,560), ν_{max}($CHCl_3$) 3390 (amide), 2899, 1724 (glutarimide), 1681, 1493, 1339, 1156, 1148 $cm.^{-1}$. ORD (c, 0.48 in MeOH): $[\alpha]_{589}$ + 16.8°, $[\alpha]_{500}$ + 16.4°, $[\alpha]_{400}$ + 16.0°, $[\alpha]_{350}$ + 12.5°

$[\alpha]_{300}$ + 10°, $[\alpha]_{250}$ + 3.0°. The NMR (60 M Hz in $CDCl_3$) showed signals at δ 7.27, (s, 5H; aromatic), 6.37 (bs, 1H; NH), 4.45 (m, 1H; C-3), 4.05 (m, 2H; C-7), 2.62 to 2.97 (m, 2H; C-8), 2.75 to 1.4 (5H; C-4, C-5 and isopropyl-CH), 1.15 (d, 6H, J = 7.5 Hz; isopropyl methyl groups); M^+ 302.162 (9%): Calculated for $C_{17}H_{22}N_2O_3$, 302.163.

The $C_{18}H_{24}N_2O_3$ homolog, had m.p. 121-122°, $[\alpha]_D$ + 7.3° ($CHCl_3$), λ_{max}^{EtOH} 210 nm (ε 18,540), ν_{max}($CHCl_3$), 3390, 2899, 1724, 1681, 1493, 1342, 1156, 1148 cm^{-1}; M^+ 316.180 (66%), $C_{18}H_{24}N_2O_3$ requires 316.179.

We have been able to make configurational assignments on the basis of acid degradation and ORD measurements.[2] Structural confirmation is now reported by way of the synthesis of (I), which was identical in all respects with the natural product. (m.p., $[\alpha]_D$, t.l.c., IR). By starting with L-(+)-glutamic acid (III), the synthesis was achieved in an overall yield of 2.5% and is shown schematically below.[3]



(III) (IV) (V) (VI) (VII)

There is only one other case reported of the presence of a glutarimide from a plant source.[4] This compound, julocrotine, $C_{18}H_{24}N_2O_3$, is diasterioisomeric with (II), and occurs in Julocroton montevidensis Klotzsch.

Acknowledgement

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REFERENCES

1. J.P. Kutney, F.K. Klein, G. Eigendorf, D. McNeill and K.L. Stuart, Tetrahedron Letters, 1971, 4973; ibid 1972, 250.

2. K.L. Stuart, D. McNeill, J.P. Kutney, F.K. Klein and G. Eigendorf, Tetrahedron, submitted.

3. Satisfactory analytical data were obtained for key compounds reported.

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