Synthesis of Cyclols from Some Small Peptides *via* Amide–Amide Reaction

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Summary The synthesis of cyclols from *p*-nitrophenyl esters of some small peptides, *via* amide–amide reaction in aqueous alkaline medium, is reported.

THERE is a long-standing suggestion that unusual bonding of amino-acids in natural products may also arise through intramolecular reactions involving amide groups.[1]

Though cyclol intermediates have been suggested,[2–4] only a few examples of well established cyclol structures have been reported.[4,5] The cyclols known so far result from reaction between an amide and an alcoholic, amino-, or thiol group and only some of them are of the peptide type. Although cyclol intermediates resulting from amide–amide reaction have been suggested,[3] cyclols of this type have not yet been isolated or characterised.

We report the synthesis of cyclols resulting from an amide–amide reaction. These compounds were obtained from *p*-nitrophenyl esters of small peptides such as (1), on mild treatment in an alkaline medium.† The cyclol system derives from an amide–amide reaction in an intermediate of the acylalanyl-diketopiperazine type (6) or of the cyclopeptide type (7).

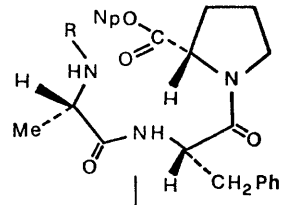
N-Benzyloxycarbonyl-L-alanyl-L-phenylalanylhydrazide[7] was prepared from the corresponding methyl ester; after conversion into the azide, it was condensed with L-proline to give *N*-benzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-

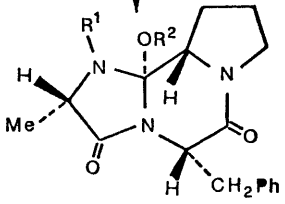
† Goodman and his co-workers have prepared *N*-benzyloxycarbonylglycylprolyl-diketopiperazine starting from the *p*-nitrophenyl ester of *N*-benzyloxycarbonylglycylproline.[6]

proline‡ m.p. 174—176°; $[\alpha]_D^{20}$ −45° (*c* 1·5, $CHCl_3$). The *p*-nitrophenyl ester (1), m.p. 109—111°, $[\alpha]_D^{20}$ −48° (*c* 0·5, ethyl acetate), prepared using *p*-nitrophenyl sulphite, was added to a dioxan–aqueous buffer§ solution (1 : 1) and was left at room temperature for 1 h; we attribute the structure (3) to the compound so formed, m.p. 183—185°, $[\alpha]_D^{20}$ −32° (*c* 1·0, ethanol). The i.r. spectrum showed no amide II band; in the mass spectrum the molecular peak at *m/e* 449 and the peak at $M^+ - 18$ (loss of water) are in agreement with structure (3); n.m.r. ($CDCl_3$) δ 1·30 (d, 3H, *J* 6·5 Hz Me), 2·30—1·55 (m, 4H, $CH_2 \cdot CH_2$), 3·75—3·0 [5H, AB part of the ABX system $PhCH_2 \cdot CH$ superimposed on $CH_2 \cdot N$

(1) R = $PhCH_2 \cdot O \cdot CO$; Np = $p\text{-}NO_2 \cdot C_6H_4$

(2) R = $p\text{-}Br \cdot C_6H_4 \cdot CH_2 \cdot O \cdot CO$; Np = $p\text{-}NO_2 \cdot C_6H_4$

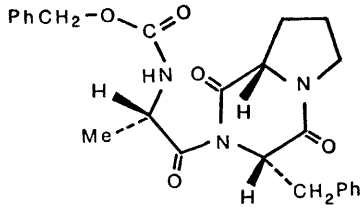




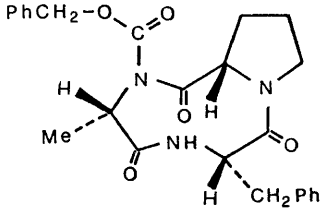
(3) R^1 = $PhCH_2 \cdot O \cdot CO$; R^2 = H

(4) R^1 = $p\text{-}Br \cdot C_6H_4 \cdot CH_2 \cdot O \cdot CO$; R^2 = H

(5) R^1 = $PhCH_2 \cdot O \cdot CO$; R^2 = Me



(6)



(7)

‡ All new compounds had satisfactory microanalytical and spectral properties.

§ Equal volumes of 0·1 M $NaHCO_3$ and Na_2CO_3 solutions.

multiplets and C(OH)·*CH*·N], 3·95 (q, 1H, *J* 6·5 Hz Me*CH*), 4·57 (broad s, 1H, exchangeable with D_2O, OH), 4·84 (1H, X part of the ABX system $PhCH_2$·*CH*), 5·16 (s, 2H, $PhCH_2$·O·CO), and 7·5—7·0 (m, 10H, aromatic H). Compound (3) has acidic properties (it is soluble in 1N-NaOH from which it is reprecipitated on acidification) and reacts with CH_3I–Ag_2O giving the corresponding *O*-methyl ether (5), m.p. **143—144°**, $[\alpha]_D^{20}$ −23° (*c* 1·0, $CHCl_3$); n.m.r. ($CDCl_3$) 3·02 (s, 3H, OMe).

To confirm the structure, we prepared *p*-bromobenzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline from L-alanyl-L-phenylalanyl-L-proline[8] on acylation with *p*-bromobenzyloxycarbonyl chloride. On treatment as for compound (1), the *p*-nitrophenyl ester (2), m.p. **165—166°**, $[\alpha]_D^{20}$ −49° (*c* 1·0, dioxan), gave a product m.p. **167—168°**, $[\alpha]_D^{20}$ −23° (*c* 1·5, $CHCl_3$), to which the cyclol structure (4) was assigned, on the basis of chemical and spectral properties, analogous to that of cyclol (3). This structure was further confirmed by *X*-ray analysis.[9]

Compounds (3) and (4) were obtained in 70% and 50% yield respectively.

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