Tetrahedron Letters No. 44, pp 4303 - 4306, 1973. Pergamon Press. Printed in Great Britain.

AZACYCLOLS FROM N-(2-BENZYLOXYCARBONYLAMINO-ACYL)-LACTAMS

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(Received in UK 10 September 1973; accepted for publication 21 September 1973)

Cyclol intermediates play an important part in several reactions connected with the chemistry and the biochemistry of peptides, cyclopeptides and cyclodepsipeptides.

The formation of these generally unstable tetrahedral intermediates containing a free OH group, has been well established in amide-amide transannular interactions[1], in aminoacyl incorporations[2,3] and has been proposed to explain the mechanism of enzymic hydrolysis[4].

Many examples of oxacyclols (hydroxy - amide interaction) have been reported since the demonstration of the cyclol structure of the alkaloid ergotamine[5]. On the other hand azacyclols (amine- or amide-amide interaction) have been found to be much more unstable and were isolated only in two cases, i.e. in a system with fused benzene ring[6] and in synthetic ergot-like peptides[7].

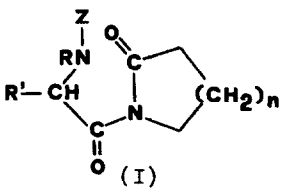
We wish to report now the observation that some simple N-protected 2-aminoacyl-lactams exist in the tautomeric structure of azacyclols.

The synthesis of the described compounds was accomplished by acylating[8] the corresponding N-trimethylsilyl-lactams with the acid chlorides of the benzyloxycarbonyl derivatives of glycine, L-alanine and N-methyl-L-alanine.

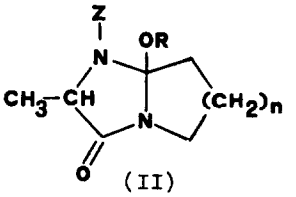
Compounds (IIa,b) were isolated in high yields and could be stored for months at -10°C after purification by preparative thin layer chromatography (silica gel, benzene-ethyl acetate). They are colourless oils which failed to crystallize (probably due to the presence of two diastereomers).

(IIa,b) are slightly soluble in water. Soluble in 0.2 N sodium hydroxide can be reprecipitated on acidification and recovered by solvent extraction

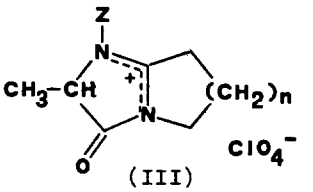
without significant decomposition. Treatment of these two compounds with excess methanol at room temperature resulted in the formation of O-methyl ethers (IIc,d) in high yields. The reaction appeared to be complete in about 24 hours in the case of (IIa) and in about 6 days in the case of (IIb). Compounds (IIc,d) could also be obtained by reacting (IIa,b) with methyl iodide and silver oxide or with an ethereal solution of diazomethane. In this latter case the reaction was however very slow.



(I)



(II)



(III)

a, R=-H;R'=-CH_3; n=1 [8]
b, R=R'=-CH_3; n=2
c, R=R'=-H; n=2 [8]

a, R=-H; n=2
b, R=-H; n=3
c, R=-CH_3; n=2
d, R=-CH_3; n=3

a, n=2
b, n=3
Z = $C_6H_5CH_2O-\overset{\overset{O}{\|}}{C}=O$

Evidence for the reverse reaction (IIc,d) ⟶ (IIa,b) could be obtained allowing (IIc,d) to stand in a $CHCl_3/H_2O$ system. Ferric hydroxamate test was positive for (Ia,b,c), negative for (IIc,d) and very weak for (IIa,b).

Treatment of (IIa,b) at room temperature with equimolecular amount of $HClO_4$ in ethanol resulted in the formation of crystalline perchlorates to which the structure of the resonance stabilized carbonium ions (IIIa,b) was assigned. Compounds (IIIa,b) allowed to stand at room temperature in excess methanol regenerated the O-methyl derivatives (IIc,d) in fairly good yields. (IIIa) m.p. 132-133°C (ethanol); ν_{max}(KBr) 1805, 1765 (>C=O), 1565 (N=$\overset{+}{C}$=N) cm^{-1}. (IIIb) m.p. 160-162°C; ν_{max}(KBr) 1795, 1770 (>C=O), 1550 (N=$\overset{+}{C}$=N)cm^{-1}.

I.r. data reported in Table I show the lack of the carbamate NH absorption (benzyloxycarbonylamino derivatives are characterized by sharp NH absorption at 3430 cm^{-1} when non bonded and examined in dilute solution of non polar solvents) and of amide II band for compounds (IIa,b,c,d).

In the u.v. spectra, (IIa,b) do not show maxima in the 215 nm region as expected for acyl-lactams[9] and as found for (Ia,b).

N.m.r. spectra (60 MHz, δ p.p.m., J values in Hz) of (IIa,b) show that a

new asymmetric center is formed and that the cyclization is not stereoselective. CH_3- signals are clearly seen as two doublets and -OH signals as two sharp singlets. (IIa), DMSO-d_6 1.32, 1.41 (two d, 3H, J=6.5, $\underline{CH_3}\text{-}\underline{C}H$-), 4.05 (two q, 1H, J=6.5, $CH_3\text{-}\underline{C}H$-), 6.83, 6.86 (two s, 1H, -OH exchangeable).

Table I. $\nu_{max/cm^{-1}}$ (CCl_4 1%).

	OR	NH	Amide I	Amide II
(Ia)		3430 (3320)*	1745,1725, 1690	1495 (1540)*
(Ib)			1715-1685	
(Ic)		3430	1728,1720, 1695	1495
(IIa)	3520--3340		1715,1690	
(IIb)	3520--3340		1715,1690	
(IIc)	2810		1720-1705	
(IId)	2810		1720-1705	

*In KBr.

(IIb), DMSO-d_6 1.33, 1.41 (two d, 3H, J=7.0, $\underline{CH_3}\text{-}\underline{C}H$-), 4.07, 4.10 (two q, 1H, J=7.0, $CH_3\text{-}\underline{C}H$-), 6.84, 6.88 (two s, 1H, -OH exchangeable).

The relative intensity of the two methyl doublets corresponds to that of the two -OH singlets. From these data a relative proportion of 3:2 and 4:1 could be determined for the two diastereomers in (IIa) and (IIb) respectively[10]. The chemical shifts of the two O-methyl groups for compounds (IIc,d) are in good agreement with the values reported for analogous systems[7,11]. (IIc), $CDCl_3$ 2.95, 3.11 (two s, 3H, $-OCH_3$); (IId), $CDCl_3$ 2.88, 3.04 (two s, 3H, $-OCH_3$).

Mass spectra of (Ia,b) show intense molecular peaks and also peaks corresponding to ions $C_6H_5\text{-}CH_2\text{-}OCO\overset{+}{N}(R)=CH\text{-}CH_3$ (1), $\left[C_6H_5\text{-}CH_2\text{-}OCON(R)C(CH_3)=C=O\right]^{+}$ (2), and m^{*} (1) $\longrightarrow$ $C_6H_5\text{-}CH_2\text{-}\overset{+}{N}(R)=CH\text{-}CH_3$. (Ia) gives also rise to a significant peak at m/e 112 which can be due to the ion $\underset{\frown}{CO\text{---}N}\text{-}C\equiv O^{+}$ (3). Analogous cleavage is observed in the case of (Ib). Fragment (1) is characteristic of benzyloxycarbonyl derivatives of linear peptides[12].

Compounds (IIa,b) do not show a molecular peak and the highest mass peak is M^+-18. Methyl ethers (IIc,d) on the other hand show a weak M^+ (for compound (IId) the abundance ratio m/e 300 : m/e 332 is 25 : 1) in addition to abundant M^+-31 and M^+-32 peaks. In the case of compounds (IIa,b,c,d) ions corresponding to the species (1), (2) and (3) are not observed or are of much lower abundance One of the principal fragmentation routes involves successive elimination of carbon dioxide and carbon monoxide from the M^+-ROH ion.

Two factors seem to influence azacyclols formation and are in accordance with data on oxacyclols and aminoacyl incorporation: (i) the size of the lactam ring [(Ia) is stable in the open form and no evidence of intramolecular interaction was found. Furthermore no M^+-18 ion was observed in the mass spectrum]. (ii) the alkyl substitution on the 2-carbon atom of the 2-aminoacyl residue [glycyl derivative (Ic) was isolated in the open form, whereas alanyl derivative (IIa) in cyclol form. It should be noted however that compound (Ic) shows clear evidence of intramolecular interaction in the mass spectrum: the abundance ratio M^+ : M^+-18 is 1:1].

FOOTNOTES AND REFERENCES

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10) No attempts were made to separate the two diastereomers for compounds (IIa,b,c,d).Careful t.l.c. examination showed two components with very close Rf values in the case of (IIb,c,d). Only one component could be evidenced for (IIa).
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13) All new compounds gave correct elemental analyses.