Tetrahedron. Vol. 25, pp. 4421 to 4426. Pergamon Press 1969. Printed in Great Britain

STUDIES ON LACTAMS—XII[1]

SYNTHESIS OF SOME SPIRO-β-LACTAMS

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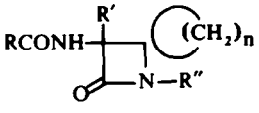
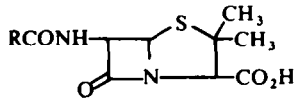
(Received in USA 7 March 1969; Received in the UK for publication 23 May 1969)

Abstract—A series of spiro-β-lactams have been prepared by the reaction of various acid chlorides with the anils of cyclohexanone, cycloheptanone and N-methylpiperidone in presence of a tertiary amine. α-Azido-β-lactams obtained by this method have been hydrogenated and acylated to give analogs of penicillin and cephalosporin C.

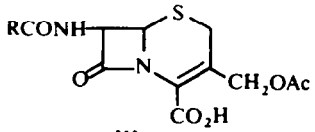
IN THE course of our studies on lactams, we were interested in the synthesis of α-amido-spiro-β-lactams of type I as analogs of penicillin (II) and cephalosporin C (III). Henery-Logan and Limburg[2] have found that N-phenaceturylaziridine-2-carboxylic acid (IV), another type of analog of these systems shows a low level of antibiotic activity.



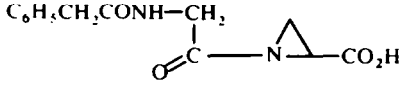
I



II

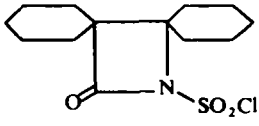


III

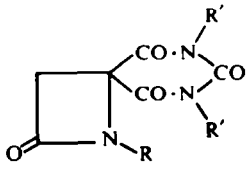


IV

Very few spiro-β-lactams have been reported in the literature. Graf[3] and Moriconi[4] have synthesized compounds of type V by the cycloaddition of an olefin with chlorosulfonylisocyanate. In this laboratory some barbiturates with a spiro-β-lactam ring (VI) were prepared by the reaction of an azetidin-2-one-4,4-dicarboxylic acid with carbodiimides.[5,6]

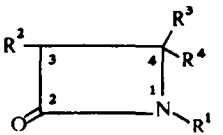


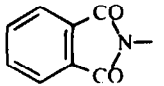
V

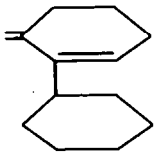
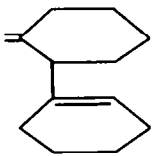


VI

TABLE 1.

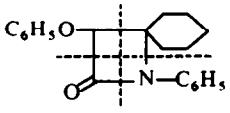


R^1	R^2	R^3 R^4	m.p. °C	Yield %	Molecular formula	Analysis*		
C_6H_{11}	N_3	$-(CH_2)_5-$	52–3	20	$C_{14}H_{22}N_4O$	C, 64·29 (64·09);	H, 8·53 (8·45);	N, 21·54 (21·36)
C_6H_{11}	$NHCOCH_2OC_6H_5$	$-(CH_2)_5-$	167–168	85	$C_{22}H_{30}N_2O_3$	C, 71·36 (71·32);	H, 7·95 (8·16);	N, 7·56 (7·56)
C_6H_5	N_3	$-(CH_2)_6-$	65–67	30	$C_{15}H_{18}N_4O$	C, 66·70 (66·65);	H, 6·75 (6·71);	N, 20·66 (20·72)
C_6H_5	$NHCOCH_2OC_6H_5$	$-(CH_2)_6-$	153–154	95	$C_{23}H_{26}N_2O_3$	C, 73·10 (72·99);	H, 6·80 (6·92);	N, 7·29 (7·40)
p-$CH_3OC_6H_4$	$NHCOCH_2OC_6H_5$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	183·5–185	68	$C_{23}H_{27}N_3O_4$	C, 67·55 (67·46);	H, 6·75 (6·65);	N, 10·09 (10·26)
C_6H_5	OCH_3	$-(CH_2)_5-$	57–58	14	$C_{15}N_{19}NO_2$	C, 73·72 (73·44);	H, 7·84 (7·81);	N, 5·64 (5·71)
C_6H_5		$-(CH_2)_5-$	282–283	33	$C_{22}H_{20}N_2O_3$	C, 73·03 (73·32);	H, 5·70 (5·59);	N, 7·60 (7·77)
$p$$CH_3OC_6H_4$	N_3	$-(CH_2)_5-$	59·5–56·0	16	$C_{15}H_{18}N_4O_2$	C, 62·44 (62·92);	H, 6·47 (6·34);	N, 19·33 (19·57)

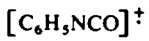
18K	p-$CH_3OC_6H_4$	NH_2	$-(CH_2)_5-$	98–99	35	$C_{15}H_{20}N_2O_2$	C, 69·37 (69·20);	H, 7·86 (7·69).
	p-$CH_3OC_6H_4$	$NHCOCH_2OC_6H_5$	$-(CH_2)_5-$	157–158	80	$C_{23}H_{26}N_2O_4$	C, 69·91 (70·03);	H, 6·62 (6·64); N, 7·08 (7·10)
	p-$CH_3C_6H_4$	N_3	$-(CH_2)_5-$	88–90	30	$C_{15}H_{18}N_4O$	C, 66·85 (66·64);	H, 6·72 (6·71); N, 20·42 (20·73)
	p-$CH_3C_6H_4$	NH_2	$-(CH_2)_5-$	103–104	20	$C_{15}H_{20}N_2O$	C, 73·48 (73·73);	H, 8·48 (8·25); N, 11·42 (11·47)
	p-$CH_2C_6H_5$	$NHCOCH_2OC_6H_5$	$-(CH_2)_5-$	174·5–175	85	$C_{20}H_{26}N_2O_3$	C, 72·88 (72·99);	H, 6·95 (6·93)
	p-ClC_6H_4	N_3	$-(CH_2)_5-$	80·5–81·5	14	$C_{14}H_{15}ClN_4O$	C, 57·74 (57·83);	H, 5·27 (5·20); N, 19·03 (19·27)
	o-$CH_3C_6H_4$	N_3	$-(CH_2)_5-$	82·5–83	31	$C_{15}H_{18}N_4O$	C, 66·42 (66·65);	H, 6·86 (7·71); N, 20·66 (20·72)
	o-CHCH	$NHCOCH_2OC_6H_5$	$-(CH_2)_5-$	157–158	40	$C_{23}H_{26}N_2O_3$	C, 73·15 (72·99);	H, 6·91 (6·92); N, 7·34 (7·40)
	p-BrC_6H_4	N_3		162–163	—	$C_{20}H_{23}BrN_4O$	C, 57·62 (57·83);	H, 5·72 (5·58); N, 13·27 (13·49)
	p-BrC_6H_4	N_3		165–166	—	$C_{20}H_{23}BrN_4O$	C, 57·62 (57·83);	H, 5·88 (5·58); N, 13·22 (13·49)

* Figures in brackets refer to the calculated values.

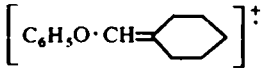
A standard method for the preparation of β-lactams consists in the addition of a ketene[7] (or an acid chloride and a base[8–12]) to a Schiff base. Standinger[13] had found that diphenylketene was the most reactive of ketenes for the cycloaddition reaction. However, we could not detect any β-lactam formation in the reaction between cyclohexanone anil and diphenylacetyl chloride or phenylacetyl chloride in presence of triethylamine. But when phenoxyacetyl chloride and tripropyl amine were used, the IR spectrum of the crude product showed the characteristic absorption of the β-lactam carbonyl. Chromatography on silica gel led to the isolation of 1-phenyl-3-phenoxy-4,4-spirocyclohexylazetidin-2-one (VII) in 48% yield. The NMR and mass spectral data were consistent with the structure assigned. Thus, prominent peaks corresponding to the expected fragments VIII, IX, X and XI were observed in the mass spectrum of VII.



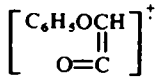
VII



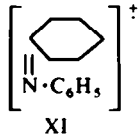
VIII



IX

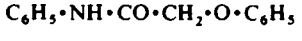


X

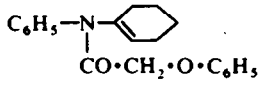


XI

The other products from this reaction were N-phenyl-phenoxyacetamide (XII; 23%), a still unidentified compound (0·5%) of mol wt 370 (mass spec) displaying IR absorption peaks at 2·95 and 5·72 μ and N-phenyl-N-(1-cyclohexenyl)-phenoxy-acetamide (XIII). The structure of XIII was deduced on the basis of IR, NMR and mass spectra.

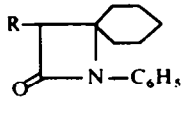


XII



XIII

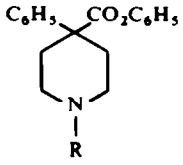
Azidoacetyl chloride was found to be even more reactive than phenoxyacetyl chloride in the cycloaddition reaction, the azido-β-lactam (XIV) was obtained in 54% yield. The azido group was easily reduced by catalytic hydrogenation in presence of Adams catalyst. Acylation with phenoxyacetyl chloride of the amine (XV) afforded the desired α-amido-spiro-β-lactam (XVI) in nearly quantitative yield.



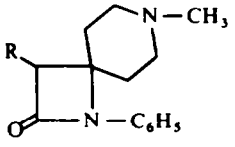
XIV: R = N_3
XV: R = NH_2
XVI: R = $NH{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}C_6H_5$

The sequence of addition of an acid chloride, triethylamine and anil had a marked influence on the course of this reaction.[12] When the base was added to a mixture of an acid chloride and the anil, only amides with carbonyl absorption at 6 μ were obtained. The absence of any absorption at 5·6–5·70 μ indicated that no β-lactam had been formed. The desired β-lactam was obtained in about 50% yield by the addition of the acid chloride to a mixture of the anil and the organic base. The mechanism(s) of this reaction is under investigation and will be reported separately.

Piperidine derivatives of type XVII such as anileridine (XVIIa) and piminodine (XVIIb) are known for their analgesic activity.[14] It was of interest, therefore, to prepare a spiro-β-lactam containing a piperidine ring. The anil from N-methyl-4-piperidone was used as the starting material and the azido-β-lactam XVIII was obtained in moderate yield. Reduction and acylation using conditions similar to that for the synthesis of XVI led to the desired spiro-β-lactam XIX. Various other spiro-β-lactams prepared by this method and their derivatives are listed in Table 1.



XVIIa: R = CH_2—CH_2—C_6H_4—NH_2(*p*)
b: R = CH_2—CH_2—CH_2—NH—C_6H_5



XVIII: R = N_3
XIX: R = —NH CO $CH_2OC_6H_5$

EXPERIMENTAL

All the m.ps are uncorrected. Microanalyses were performed by Alfred Bernhardt at the Max-Planck Institute in West Germany and MHW Laboratories in Garden City, Michigan. The IR spectra were recorded on a Perkin–Elmer Infracord, the NMR spectra on an A-60A Varian Spectrometer and the mass spectra on a 21-103C CEC mass spectrometer.

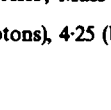
1-*Phenyl-3-phenoxy-4,4-spirocyclohexylazetidin-2-one* (VII). A soln of cyclohexanone anil (1·73 g) and tripropylamine (1·46 g) in 200 ml freshly distilled CH_2Cl_2 was cooled in a freezing mixture. Dropwise addition of a soln of phenoxyacetyl chloride in 100 ml of the same solvent was carried out under anhydrous conditions over a period of 3 hr. The reaction mixture was stirred for another hr and then subjected to the usual work up when 2·64 g of the crude product was obtained. TLC of this product showed four spots when C_6H_6—CH_2Cl_2 (1:1) was used.

The total crude product was chromatographed on a silica gel (75 g) column and four fractions were collected.

Fraction 1 (700 ml CH_2Cl_2—C_6H_6 (4:1) eluant) contained VII in 48% yield, m.p. 95–97° (CH_2Cl_2–pet. ether); λ_{max}^{Nujol} 5·7 μ (β-lactam CO); λ_{max}^{EtOH} 255 mμ (ε 13,900) (N-aryl-β-lactam[15]); NMR ($CDCl_3$) τ: 2·6 (m, 10H, aromatic protons), 5·05 (s, 1H, —C<u>H</u>·O·C_6H_5), 8·2 (m, broad, 10H, —$(CH_2)_5$—). Mass spectrum, M^+ at *m/e* 307. (Found: C, 78·26; H, 6·94; N, 4·74. Calc. for $C_{20}H_{21}O_2N$: C, 78·14; H, 6·89; N, 4·56%).

Fraction 2 (600 ml CH_2Cl_2 eluant) was identified as N-phenyl-phenoxy-acetamide (23%), m.p. 99–101° (lit.[16] m.p. 101·5°).

Fraction 3 (200 ml $CHCl_3$ eluant) was obtained in about 0·5% yield as a single spot material which could not be characterized. The IR spectrum of this compound showed a minor peak at 2·95 μ and an intense peak at 5·72 μ. It showed the molecular ion at *m/e* 370 in the mass spectrum.

Fraction 4 (300 ml $CHCl_3$ eluant) was characterized as XIII; Mass spectrum: M^+ at *m/e* 307; λ_{max}^{Nujol} 6 μ (amide CO); NMR ($CDCl_3$) τ: 3 (m, 10H, aromatic protons), 4·25 (broad, 1H, ), 5·42 (S, 2H, OC—CH_2—), 8·1 (broad, 8H, —$(CH_2)_4$—).

1-Phenyl-3-azido-4,4-spirocyclohexylazetidin-2-one (XIV). A CH_2Cl_2 soln of azidoacetyl chloride[17,18] (3·5 g in 50 ml) was added dropwise under anhydrous conditions to an ice cold soln containing 5·09 g cyclohexanone anil and 2·97 g Et_3N in 200 ml CH_2Cl_2 with stirring over a period of 3 hr. The reaction mixture was stirred for an additional hr. The crude product isolated by the usual work-up was dissolved in CH_2Cl_2 and chromatographed over a silica gel column. There was obtained the title compound (4 g) in 54% yield, m.p. 84–86° (CH_2Cl_2–pet. ether); λ_{max}^{Nujol} 4·67 μ (azide), 5·62 μ (β-lactam CO); λ_{max}^{EtOH} 255 μ (ε 13,400) (N-aryl β-lactam). NMR ($CDCl_3$) τ: 2·6 (m, 5H, aromatic protons), 5·7 (S, 1H, —CH·N_3), 8·25 (m, 10H, —$(CH_2)_5$—); mass spectrum: M^+ at *m/e* 256. (Found: C, 65·62; H, 6·58; N, 21·97. Calc. for $C_{14}H_{16}N_4O$: C, 65·61; H, 6·29; 21·86%).

1-Phenyl-3-amino-4,4-spirocyclohexylazetidine-2-one (XV). An EtOAc soln of XIV (0·35 g) containing 0·35 g PtO_2 was shaken in the presence of H_2 (38 psi) for 18 hr. Removal of the solvent and the catalyst gave the corresponding amino compound, m.p. 73–75° in 78% yield; λ_{max}^{Nujol} 2·85 μ and 2·95 μ (NH_2), 5·65 μ (β-lactam CO); mass spectrum: M^+ at *m/e* 230. (Found: C, 78·27; H, 7·95; N, 12·99. Calc. for $C_{14}H_{18}N_2O$: C, 78·46; H, 8·47; N, 13·07%).

1-Phenyl-3-phenoxyacetamido-4,4-spirocyclohexylazetidin-2-one (XVI). To a soln containing 0·625 g of XV and 0·293 g Et_3N in 100 ml CH_2Cl_2 at 0° was added with constant stirring 0·52 g phenoxyacetyl chloride in CH_2Cl_2 (50 ml) over a period of 2 hr. The stirring was continued for 1 hr more. After removing the solvent from the reaction mixture the residue was extracted with ether. The usual work-up of the ether soln gave nearly quantitative yield of the amide, m.p. 145–146°; λ_{max}^{Nujol} 3·08 μ (NH), 5·63 μ (β-lactam CO), 6 μ (amide CO); mass spectrum: M^+ at *m/e* 364; NMR ($CDCl_3$) τ: 2·65 (m, 11H, aromatic protons, and —CO—NH—), 5·0 (d, 1H, —N J = 9·5 c/s), 5·42 (S, 2H, —CO—CH_2—O—), 8·35 (m broad, 10H, Cyclohexyl).

The spiro-β-lactams described in Table 1 were synthesized by the method described above. The α-azido-β-lactams were reduced using Adams catalyst to the amino derivatives and subsequently acylated.

Acknowledgement—This research was supported in part by a grant (MH-03930) from the National Institute of Mental Health of the U.S. Public Health Service.

[1] For Part XI, see A. K. Bose, V. Sudarsanam, B. Anjaneyulu and M. S. Manhas, *Tetrahedron* **25**, 1191 (1969).
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