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STUDIES ON LACTAMS—V[1]

3-AZIDO-2-AZETIDINONES

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Abstract A convenient synthesis of α-amino-β-lactams has been devised with the aim of preparing derivatives and analogs of penicillin and cephalosporin C. It has been found that α-azido-β-lactams can be obtained from the reaction of α-azido acid chlorides with imines in presence of triethylamine. The azido group undergoes facile catalytic reduction to afford α-amino-β-lactams. The sequence of addition of the reactants influences the stereochemistry of the azido-β-lactam formed. The slow addition of azidoacetyl chloride to a solution of benzalaniline and triethylamine in methylene chloride favors the *cis* product, while the *trans* stereochemistry is favored when triethylamine is added to a mixture of the Schiff base and azidoacetyl chloride. Prolonged heating in presence of triethylamine did not result in the interconversion of *cis*- and *trans*- 1-phenyl-3-azido-4-(p-nitrophenyl)-azetidin-2-one.

1-Cholestanyl-3,3-dimethylazetidine-2-one has been prepared as an analog of the β-lactam-substituted steroid alkaloids reported recently.

β-LACTAMS as a class had been of limited interest until the discovery that penicillin possesses this heterocyclic ring system[2] as a key feature. Further interest was aroused by the finding that the structure of the antibiotic cephalosporin C[3] also contains the α-amido-β-lactam moiety. Recently it was reported[4] that the major alkaloid of *Pachysandra terminalis* is a steroidal alkaloid carrying a β-lactam ring. Thus it is apparent that β-lactams are not quite as uncommon in nature as it was considered earlier.

In the course of his studies on the chemistry of ketenes, Staudinger[5] discovered that ketenes, in particular keto-ketenes, react with imines to produce β-lactams. The first known β-lactam, 1,3,3,4-tetraphenyl-2-azetidinone, was prepared from diphenylketene and benzylidene aniline.[6]

In connection with the total synthesis of penicillin, Sheehan and Ryan[7] allowed phthaloylglycyl chloride to react with benzylidene aniline and other Schiff bases in the presence of triethylamine and obtained 1,4-disubstituted 3-phthalimido-2-azetidinones. These phthalimido β-lactams could be converted to the corresponding 3-amino-β-lactams by hydrazinolysis. However, this approach is unsuitable for the

[1] For part IV see A. K. Bose, M. S. Manhas and R. M. Ramer, *Tetrahedron* **21**, 449 (1965) and for part VII see A. K. Bose and I. Kugajevsky, *Ibid.* **23**, 957 (1967).

[2] H. T. Clarke, J. R. Johnson and R. Robinson, *The Chemistry of Penicillin*. Princeton University Press (1949).

[3] E. P. Abraham and G. G. F. Newton, *Biochem. J.* **79**, 377 (1961).

[4] T. Kikuchi and S. Uyeo, *Tetrahedron Letters* 3473 (1965).

[5] H. Staudinger, *Die Ketene*. Ferdinand Enke, Stuggart (1912).

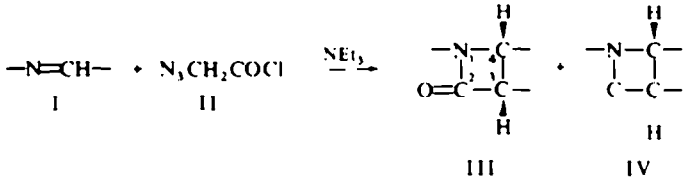
[6] H. Staudinger, *Liebigs Ann.* **356**, 51 (1907).

[7] J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.* **73**, 1204, 4367 (1951).

synthesis of penicillin because of the instability of the β-lactam ring in penicillin to hydrazine.[2]

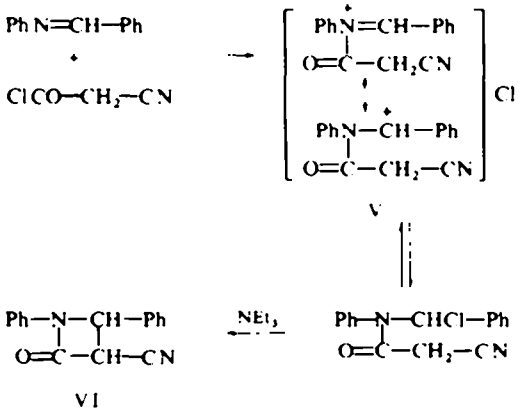
The facile conversion of the azido group to the amino function under mild conditions, such as catalytic hydrogenation, is well known. In view of this, α-azido-β-lactams appeared to us to be desirable intermediates for the synthesis of penicillin and cephalosporin C derivatives and analogs.

Azidoacetyl chloride and its homologs can be conveniently prepared.[8] We have found that the reaction of Schiff bases (I) with azidoacetyl chloride (II) in presence of triethylamine in benzene affords two isomeric α-azido-β-lactams (III and IV). The stereochemistry of these isomers was deduced from the size of the vicinal coupling of the protons at C_3 and C_4. The relative proportions of the *cis* (J = 5·6 c/s) and *trans* (J = 2·0 2·5 c/s) isomers[9] were found to depend on the sequence of addition of reactants.



When a methylene chloride solution of azidoacetyl chloride was added dropwise to a solution of benzalaniline and triethylamine in the same solvent at room temperature or below, *cis* to *trans* ratio of the resulting β-lactam was approximately 3:1. However, when triethylamine was added to a solution of the Schiff base and acid chloride, the relative proportions of *cis* and *trans* isomers were reversed and were found to be about 1:3. This indicates that a certain degree of steric control can be exercised on the product of this reaction by changing the sequence of addition of the reactants.

The possibility of interconversion of *cis*- and *trans*- isomers was examined. Each pure isomer of 1-phenyl-3-azido-4-(p-nitrophenyl)azetidin-2-one was dissolved separately in deuterated chloroform to which an excess of triethylamine was added.



[8] A. Bertho and J. Maier, *Liebigs Ann* **498**, 52 (1932)

[9] H. B. Kagan, J. J. Basselier and J. L. Luche, *Tetrahedron Letters* 941 (1964).

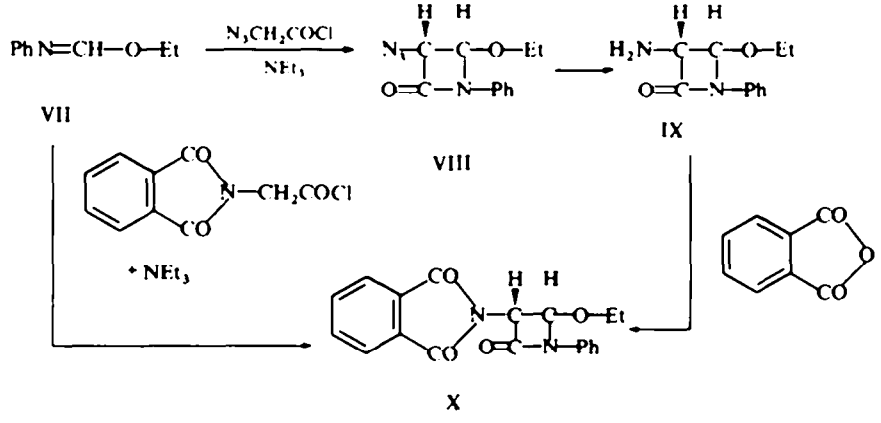
These solutions were sealed in NMR tubes and heated in a steam bath for two days. Periodic recording of NMR spectra demonstrated the complete stability of both isomers under these conditions. In the synthesis of these β-lactams, methylene chloride was used as a solvent and the reaction temperature did not exceed room temperature. Hence, the change in the relative proportion of *cis*- and *trans*- β-lactams discussed above must be ascribed to steric control of cyclization rather than equilibration.

Böhme *et al.*[10] have studied the reaction mechanism of β-lactam formation using cyanoacetyl chloride. According to these workers the intermediate in this reaction is the salt V which undergoes dehydrohalogenation in the presence of triethylamine to afford the β-lactam VI.

Another possible pathway is the formation of a ketene intermediate resulting from the reaction of acid chloride with triethylamine which subsequently forms a β-lactam *via* cycloaddition with the Schiff base. Since the reaction that we have studied gives both isomers irrespective of the sequence of addition of the reagents and the relative proportion of the products is dependent upon the reaction conditions, more than one reaction pathway may be operative. It is quite possible that both mechanisms are involved at the same time but at different reaction rates.

We have extended this synthesis of β-lactams by using substituted azidoacetyl chlorides. α-Methyl-, α-ethyl- and α-phenylazidoacetyl chloride were also found to react with Schiff bases to give the corresponding α-substituted α-azido-β-lactams (Table 1), although in smaller yields. Under these reaction conditions the azidoacetyl chlorides are converted to nitriles (e.g. α-phenylazidoacetyl chloride affords benzonitrile[11]).

Imines other than Schiff bases, e.g. imidates[12] also undergo reaction with azidoacetyl chloride in the presence of triethylamine to give β-lactams. Thus, ethyl N-phenylformimidate (VII) reacted with azidoacetyl chloride in the presence of triethylamine to form the β-lactam VIII. The NMR spectrum of the crude product showed the exclusive formation of the *trans* isomer. Since the β-lactam VIII did not lend itself to easy purification, it was catalytically reduced using Adams catalyst to

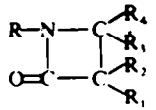


[10] H. Böhme, S. Ebel and K. Hartke, *Chem. Ber.* **98**, 1463 (1965).

[11] Similar observations have been made by Dr. G. Smolinsky of Bell Telephone Laboratories.

[12] Since the completion of this phase of our work, the reaction of phthalyl glycyl chloride with imidates has been reported by L. Paul, A. Draeger and G. Hilgetag, *Chem. Ber.* **99**, 1957 (1966).

TABLE 1. MONOCYCLIC β-LACTAMS



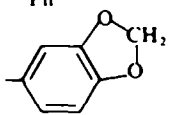
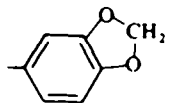
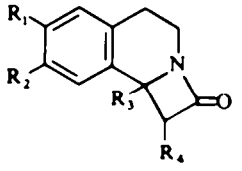
R	R_1	R_2	R_3	R_4	Stereochemistry ($J_{3,4}$ c/s)	m.p. °C	Yield %	Formula	Analysis Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
Ph	H	N_3	H	Ph	*cis* (5·5)	132–134	35–45	$C_{15}H_{12}N_4O$	67·96	4·61	21·15	68·17	4·58	21·20
Ph	H	N_3	H	Ph	*trans* (2)	81–83	50	$C_{15}H_{12}N_4O$	68·04	4·34	21·33	68·17	4·58	21·20
Ph	H	N_3	H	*p*-NO_2-C_6H_4	*cis* (5·5)	135	35	$C_{15}H_{11}N_5O_3$	58·46	3·51	22·65	58·25	3·59	22·65
Ph	H	N_3	H	*p*-MeO C_6H_4	*cis* (5·5)	125	25–30	$C_{16}H_{14}N_4O_2$	65·25	4·84	18·92	65·29	4·80	19·04
Ph	H	N_3	H	*p*-MeO C_6H_4	*trans* (2)	96–97	53	$C_{16}H_{14}N_4O_2$	65·11	4·91	18·99	65·29	4·80	19·04
p-Br C_6H_4	H	N_3	H	Ph	*cis* (5·2)	153–154	30	$C_{15}H_{11}N_4OBr$	52·52	3·43	16·12	52·48	3·21	16·33
p-Br—C_6H_4	H	N_3	H	Ph	*trans* (2)	108	65	$C_{15}H_{11}N_4OBr$	52·57	3·12	16·30	52·48	3·21	16·33
p-Br C_6H_4	H	N_3	H		*cis* (5·5)	165–167	30–35	$C_{10}H_{11}N_4O_3Br$	49·97	2·97	14·74	49·61	2·84	14·47
p-Br C_6H_4	H	N_3	H		*trans* (2)	123–124	31	$C_{16}H_{11}N_4O_3Br$	49·76	3·05	14·30	49·61	2·84	14·47
Ph	H	N_3	H	OEt	*trans* (1·5)	–		Characterized as phthalimido deriv.						

TABLE 1. *continued*

Ph	H	NH_2	H	Ph	*cis* (5·5)	176–178	—	$C_{15}H_{14}N_2O$	75·59	6·02	11·93	75·60	5·92	11·76
Ph	H	NH—CO CH_2 Ph	H	Ph	*cis* (5·5)	178 180	-	$C_{23}H_{20}N_2O_2$	77·42	5·79	7·99	77·50	5·66	7·86
p-F—C_6H_4	H	N_3	H	Ph	*cis* (5)	113 114	23	$C_{15}H_{11}FN_4O$	63·53	4·09	19·68	63·81	3·93	19·85
Ph	H	N_3	H	*p*-Br C_6H_4	*cis* (5)	141 143	30	$C_{15}H_{11}BrN_4O$	52·64	3·22	16·15	52·49	3·23	16·32
Ph	H	N_3	H	*p*-F C_6H_4	*cis* (5·3)	142 143	19	$C_{15}H_{11}FN_4O$	63·68	4·13	19·62	63·81	3·93	19·85
Ph	H	N_3	Me	Ph			30	Characterized as phthalimido deriv.						
Ph	H	N_3	Ph	Ph		121 122	60	$C_{21}H_{16}N_4O$	74·11	4·75	16·42	74·10	4·74	16·46
Ph	Me	N_3	H	Ph	-	130 132	10	$C_{16}H_{14}N_4O$	69·16	5·06	20·23	69·05	5·07	20·13
Ph	Et	N_3	H	Ph	-	115 117	9	$C_{17}H_{16}N_4O$	70·05	5·42	19·14	69·84	5·52	19·17
Ph	Ph	N_3	H	Ph		160 161	5·7	$C_{21}H_{16}N_4O$	73·94	4·90	16·48	74·10	4·74	16·46

TABLE 2. FUSED β-LACTAMS

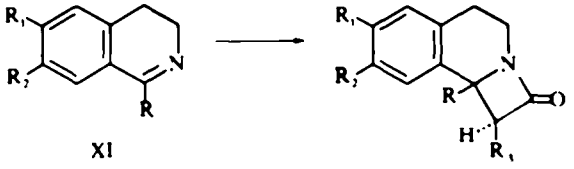


R_1	R_2	R_3	R_4	m.p. °C	Yield %	Formula	Analytical data: Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
H	H	Ph	N_3	123–125°d	66	$C_{17}H_{14}N_4O$	70·54	4·78	19·38	70·83	4·86	19·30
H	H	*p*-NO_2—C_6H_4	N_3	157°d	77	$C_{17}H_{13}N_5O_3$	60·86	4·02	20·95	60·89	3·91	20·89
OMe	OMe	*p*-NO_2 C_6H_4	N_3	137°d	73	$C_{19}H_{17}N_5O_5$	57·35	4·73	17·56	57·72	4·33	17·72
H	H	Ph	NH_2	184	75 80	$C_{17}H_{16}N_2O$	77·13	5·91	10·42	77·25	6·10	10·60
H	H	Ph	NH CO CH_2—Ph	167 168	82	$C_{25}H_{22}N_2O_2$	78·46	5·67	7·26	78·51	5·80	7·33

the corresponding amino-β-lactam (IX) which was subsequently converted to the crystalline phthalimido β-lactam (X). The same β-lactam X was also prepared by reacting phthaloylglycyl chloride with VII in the presence of triethylamine.

Imines in which the $\cdots C{=}N-$ moiety is a part of a ring system, e.g. in 3,4-dihydroisoquinolines XI, react with azidoacetyl chloride to give fused α-azido-β-lactams (XII–XIV) in good yield. The azido-β-lactam XII could be catalytically reduced to amino β-lactams (XV) and subsequently acylated (XVI) (Table 2).

This method for the synthesis of α-acylamino-β-lactams has been extended to the preparation of some structures closely related to penicillin and cephalosporin C.[13] Further work along these lines is in progress.

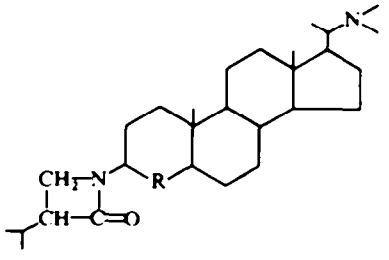


XI

X: R = Ph, $R_1 = R_2 = H$, $R_3 = N_3$
XI: R = *p*-NO_2 C_6H_4, $R_1 = R_2 = H$, $R_3 = N_3$
XII: R = *p*-NO_2-C_6H_4, $R = R_2 = OMe$, $R_3 = N_3$
XIII: R = Ph, $R_1 = R_2 = H$, $R_3 = NH_2$

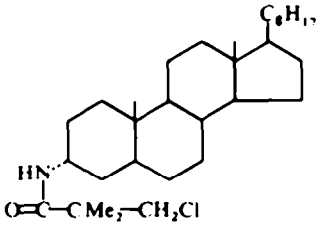
XIV: R = Ph, $R_1 = R_2 = H$, $R_3 = PhCH_2CNH$

We have also prepared an analog (XX) of the recently discovered steroidal alkaloids,[4] pachystermine-A (XVII) and pachystermine-β (XVIII), by the cyclization[14] of the β-chloroamide XIX from 3α-aminocholestane.

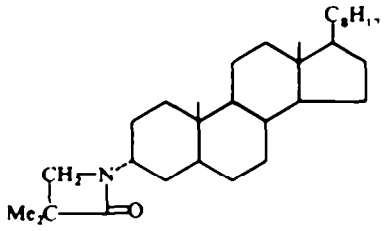


XVII: Pachystermine A; R, C=O
XVIII: Pachystermine B; R, CHOH

[13] A. K. Bose and B. Anjaneyulu, *Chem. & Ind.* 903 (1966).
[14] I. L. Knunyants, E. E. Rytslin and N. P. Gambaryan, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk* 1037 (1955); M. S. Manhas and S. J. Jeng, *J. Org. Chem.* **32**, 1246 (1967).



XIX



XX

EXPERIMENTAL[15]

Azidoacetyl chloride and α-azidopropionyl chloride were prepared by the method described by Bertho and Maier[8]

α-Azidophenyl chloride[16] A soln of 21 g α-azidophenylacetic acid in 30 ml benzene and 18 ml $SOCl_2$ was refluxed for 3 hr After removing benzene and the excess $SOCl_2$ the residue was distilled The fraction distilling at 98–102° 4 mm (16·8 g) was the title compound.

β-Chloropivalyl chloride[17] A mixture of β-chloropivalic acid (13 g), $SOCl_2$ (18 g) and benzene (10 ml) was stirred for 1 hr and then refluxed for 2 hr The acid chloride (9·4 g) was obtained by distillation as the fraction b.p. 88–90°/60 mm

N-Cholestanyl β-chloropivalylamide. A soln of 4 g 3α-aminocholestane[18] in 200 ml benzene and 3·5 g β-chloropivalyl chloride were refluxed for 4 hr. The reaction mixture was washed successively with water, $NaHCO_3$ aq and water. The solvent was removed from the organic layer after drying over $MgSO_4$ and the residue was crystallized from EtOH to give 4·7 g (90%) of the amide, m.p. 144–145°. λ_{max}^{Nujol} 3 μ (NH), 6·13 μ (amide carbonyl). (Found: C, 75·77; H, 10·97; N, 2·40. Calc for $C_{32}H_{56}ClNO$: C, 75·91; H, 11·15; N, 2·76.)

1-Cholestanyl 3,3-dimethylazetidine-2-one. N-Cholestanyl-β-chloropivalylamide (7 g), potassium t-butoxide (2·5 g) and benzene (300 ml) were refluxed for 3 hr. The reaction mixture was washed with water The organic layer dried over $MgSO_4$. Removal of the solvent from this soln left a white solid which was crystallized from acetone to give 3·7 g (57%) of the β-lactam, m.p. 101–103°, λ_{max}^{Nujol} 5·7 μ (β-lactam carbonyl). (Found: C, 81·81; H, 11·50; N, 3·06. Calc. for $C_{32}H_{55}NO$: C, 81·81; H, 11·80; N, 2·98.)

p-Fluorobenzalaniline. A mixture of 6 g aniline and 8 g *p*-fluorobenzaldehyde was refluxed on a steam bath for 1 hr Distillation of the reaction mixture afforded 13 g of the Schiff base (b.p. 140–145°/3 mm) (Found: C, 78·14; H, 5·42; N, 6·87. Calc. for $C_{13}H_{10}FN$: C, 78·37; H, 5·05; N, 7·03%.)

Below are given typical procedures for preparing β-lactams by the reaction of a Schiff bases with azido acid chlorides in presence of Et_3N. The sequence of addition of the acid chloride and Et_3N to the Schiff bases determined the preponderance of the *cis* or the *trans* β-lactams. Method A afforded the *cis* isomer and Method B yielded the *trans* isomer as the major product

Method A. A soln of 2·26 g (10 mmoles) *p*-nitrobenzalaniline and 1·4 ml (10 mmoles) Et_3N in 60 ml dry CH_2Cl_2 was cooled to 0°. To this was added with stirring, over a period of 45 min a soln of 1·2 g (10 mmoles) azidoacetyl chloride in 30 ml CH_2Cl_2. The mixture was then stirred for 1 hr at 0° and an additional 1 hr at room temp. The reaction mixture was washed with water. The organic layer was dried over $MgSO_4$. Removal of the solvent afforded a brown residue which on crystallization from alcohol give the *cis* β-lactam, m.p. 135° (yield 35%).

Method B. To a soln of 1·3 g (5 mmoles) benzal-*p*-bromoaniline and 0·6 g (5 mmoles) azidoacetyl chloride in 25 ml dry CH_2Cl_2 at 0° was added dropwise with stirring over a period of 45 min a soln of 0·7 ml (5 mmoles) Et_3N in 25 ml CH_2Cl_2. This soln was stirred for ½ hr more and worked up in the usual

[15] All m.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer infracord. The NMR spectra were recorded on a Varian A-60A spectrometer and mass spectra were taken on a 21–103C CEC mass spectrometer. The microanalysis of the compounds reported were performed by A. Bernhardt at Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

[16] A. Darapsky, *J. Prakt. Chem.* **99**, 179 (1919).

[17] M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.* **62**, 925 (1940).

[18] W. R. Hertler and H. J. Corey, *J. Org. Chem.* **23**, 1221 (1958).

way. The crude product was chromatographed over 20 g neutral alumina. Benzene eluates afforded 0·54 g (65%) pure *trans* β-lactam, m.p. 108° (EtOH).

Acknowledgement—This research was supported in part by grants from the U.S. Public Health Service (MH-03930) and from Stevens Institute of Technology.