Tetrahedron. Vol. 24, pp. 1237 to 1245. Pergamon Press 1968 Printed in Great Britain

STUDIES ON LACTAMS—VIII[1]

THE CONFORMATION OF N-ARYL LACTAMS[2]

M. S. MANHAS, S. JENG and A. K. BOSE

Department of Chemistry and Chemical Engineering,
Stevens Institute of Technology, Hoboken, New Jersey 07030

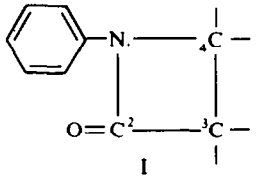
(*Received in USA* 6 *April* 1967; *accepted for publication* 4 *July* 1967)

Abstract—N-Aryl-β-lactams have been found to be characterized by strong UV maxima at about 250 mμ. Some N-aryl γ-lactams also show similar absorption max but heavily substituted γ-lactams or N-phenyl δ-lactam display only low absorption in this region.

A study of UV and NMR spectra indicates that in N-aryl β-lactams, the heterocyclic ring and the three valences of nitrogen are planar and the N-aryl ring lies in the plane of the β-lactam. This planarity as well as the strong UV absorption are the result of an extended conjugation between the aryl ring and the amide function. *Ortho* substitution on the aryl ring causes a slight departure from this planarity and reduces the intensity of the UV absorption. In case of N-aryl γ-lactams, *ortho* substitution on the aryl ring causes enough departure from planarity to eliminate altogether the absorption max near 250 mμ.

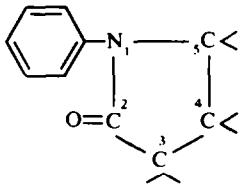
THE characteristic carbonyl absorption in the IR has been used extensively for distinction between β-, γ- and δ-lactams.[3] Several isolated reports on the UV absorption of amides,[4] lactams[5] and unsaturated lactams[6] have appeared in the literature, but the structural and stereochemical features of cyclic amides have not been related to their electronic spectra. We have investigated a large number of lactams and have discovered a correlation between the UV spectra of N-aryl lactams and their structure and stereochemistry.

N-Phenyl-β-lactams (I) with various substituents on the heterocyclic ring were found to show a strong max near 250 mμ (Table 1). The position of this max undergoes a bathochromic shift on the *p*-substitution of a halogen or methoxy group on the N-phenyl ring.[2] A change in the steric disposition of groups at C_3 and C_4 does not introduce any appreciable change in the position of the absorption maxima.

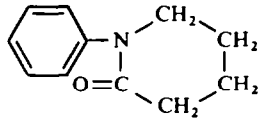


I

N-Aryl γ-lactams (II) are also characterized by a strong UV max near 250 mμ (Table 2). However, substitution on the heterocyclic ring eliminates this absorption. For example, 1-phenylpyrrolidin-2-one shows an absorption max at 246 mμ (ε 17,200) whereas 1-phenyl-5,5-dicarbomethoxypyrrolidin-2-one shows no max above 210 mμ. Even the simplest N-phenyl-δ-lactam (III) fails to display any strong UV max.



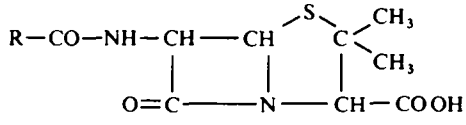
II



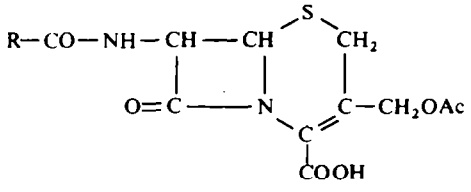
III

λ_{max} 230 mμ (ε 5200)

The chromophore for the intense UV absorption must be the Aryl—N—CO— group in which the possibility exists for the overlap of the π-orbitals of the aromatic system, the *p*-orbital on the sp^2-nitrogen and the π-orbitals of the carbonyl group. This overlap is max when the valences of the nitrogen atom are planar and the aromatic ring and the C=O group are in this plane; the overlap is diminished if the aromatic ring or the carbonyl group departs from this plane or if the nitrogen atom assumes a non-planar disposition of its valencies (a possibility in γ- and δ-lactams). The difference in the UV absorption pattern in lactams of different ring size must therefore be a reflection of the shape of the ring. X-Ray studies have shown that the β-lactam ring is planar in penicillin[7] (IV) and cephalosporin C[8] (V). The strong UV absorption of the N-aryl β-lactams can be satisfactorily accounted for by assuming that the three valences of the nitrogen are in one plane and the N-aryl ring is also in the plane of the heterocyclic ring. The conformation of the δ-lactam must be such that the aryl group is substantially deflected out of the plane of the —N—CO— group. A similar situation must exist for heavily-substituted γ-lactams. But in an unsubstituted N-aryl-γ-lactam, substantial coplanarity of the chromophoric system appears feasible.



IV

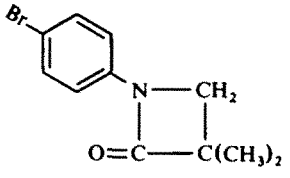


V

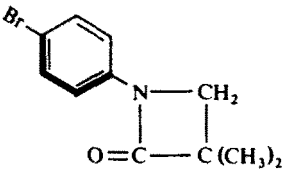
To test the validity of this assumption, N-aryl β- and γ-lactams with *p*-bromophenyl and *o*-bromophenyl substitution were examined. It was observed that N-(*o*-bromophenyl)2-azetidinone (Table 1) shows a UV absorption max with a lower intensity than its *p*-bromo isomer and that N-(*o*-bromophenyl)2-pyrrolidone (Table 2) exhibits little UV absorption in contrast with the strong max of the corresponding *p*-bromo compound. Since the *o*-bromo substituent would be expected to force the phenyl ring out of the plane of the amide group, the observed data are in agreement with our assumption regarding planarity.

Additional information on the stereochemistry of these lactams was obtained from a study of the NMR spectrum of 1-*p*-bromophenyl-3,3-dimethyl-2-azetidinone which displays a *singlet* for the two Me groups at τ 8·62 and another *singlet* for the two

methylene protons at τ 6·65. The equivalence of the Me substituents at C_3 and also of the two protons at C_4 is consistent with the planarity of the β-lactam ring and the planarity of the three valences of the N atom. This NMR spectrum alone cannot distinguish between the conformation A in which the aryl ring is in the plane of the β-lactam ring and the conformation B in which the plane of the aryl ring is at right angles but symmetrically disposed to the plane of the β-lactam ring.



A



B

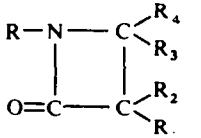
The NMR spectrum of *o*-bromophenyl-2-azetidinone also displays one singlet (τ 8·60) for the two Me groups and another singlet (τ 6·18) for the methylene group. This again reveals the planarity of the β-lactam ring. The methylene protons will be equivalent to each other if (a) the *o*-bromophenyl ring lies substantially in the plane of the β-lactam ring or if (b) the phenyl ring rotates around its axis fast enough to provide a sharp peak as the time-averaged signal for the methylene protons. Lowering of the temperature to −34° failed to resolve this methylene signal or even to broaden it.

In the NMR spectrum of *p*-bromophenyl-2-azetidinone, the C_3 methylene protons and C_4 methylene protons occur as two triplets centered at τ 6·94 and τ 6·48, respectively, again revealing the symmetry of the ring systems. The relative intensity of the peaks of the triplets are not in the 1:3:1 proportion. This may arise, at least in part, from the near identity of chemical shifts of these two methylene groups and the consequent departure from first order spectra. The corresponding *o*-bromo-β-lactam also shows two triplets centered at τ 7·01 and τ 6·01. In contrast to the C_3 methylene protons, the C_4 methylene protons have undergone a considerable downfield shift showing the strong influence of the *o*-bromine substituent on them. This influence, however, must be symmetrical with respect to the C_4 protons because the signals for the two methylene groups are close to ideal triplets. The implications of this observation are that the two protons of each methylene group are still nearly equivalent to each other. Hence, the *o*-bromophenyl ring must be rotating fast enough or its preferred conformation must not be far from the plane of the β-lactam ring so that the symmetry element has been destroyed only to a limited extent. It may be recalled that the intensity of the UV absorption of the *o*-bromo β-lactam is considerably reduced but still quite significant (λ_{max} 247 mμ, ε 8650).

We have also examined the electronic absorption of several acyclic amides (Table 4) related to the lactams studied.* Acetanilide, dimethyl anilinomalonate and dimethyl N-acetylanilinomalonate show a strong max (ε 11,000–16,000) near 240 mμ. This

* Kagan *et al.*[9a] have studied the IR and UV spectra of enamides, a class of compounds characterized by the group $\rangle C{=}C{-}N{-}CO{-}$. This chromophoric system has been reported to have a strong absorption max at about 240 mμ (ε ~ 12,000).

TABLE 1. MONOCYCLIC β-LACTAMS



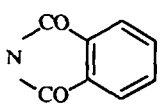
H R	R_1	R_2	R_3	R_4	λ_{max}	ε	Ref.
Ph	H	H	H	H	248	11,800	11
p-Cl—C_6H_4	H	H	H	H	254	21,000	12
p-Br—C_6H_4	H	H	H	H	254	23,400	12
					209	10,550	
p-I—C_6H_4	H	H	H	H	261	25,000	12
p-Br—C_6H_4	Me	Me	H	H	253	24,700	12
					209	10,600	
p-NO_2—C_6H_4	H	H	H	H	321	15,700	12
					224	11,500	
o-Br—C_6H_4	H	H	H	H	247	8650	12
o-F—C_6H_4		H	H	H	246	14,900	12
					Sh. 274	3600	
					Sh. 283	2620	
Ph	H	H	COOMe	COOMe	245	16,000	12
Ph	H	Ph	COOMe	COOMe	245	15,400	12
p-Me—C_6H_4	H	H	COOEt	COOEt	247	14,800	18
p-Br—C_6H_4	H	H	COOMe	COOMe	253	19,600	18
Ph	H	CH_2—C_6H_4—NO_2-*p*	COOEt	COOEt	247	17,200	15
p-Me—C_6H_4	H	H	Ph	COOEt	253	16,600	*
p-Cl—C_6H_4	H	H	Ph	COOH	302	1800	*
					255	13,700	
p-Br—C_6H_4	H	H	H	COOMe	255	22,200	12
Ph	H	H	H	Ph	248	$13,500^{20}$	4*c*
Ph	H		H	Ph	Sh. 302	1700	
					250	21,000	12
					224	42,700	

TABLE 1—*continued*

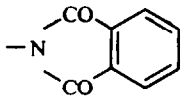
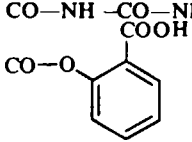
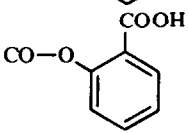
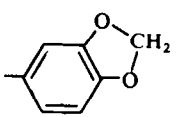
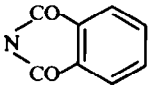
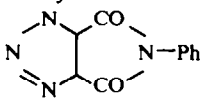
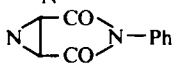
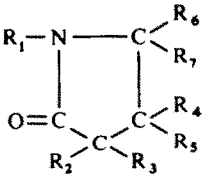
R	R_1	R_2	R_3	R_4	λ_{max}	ε	Ref.
Ph	H		Me	Ph	255 295	21,300 2520	12
Ph	H	$CH_2—C_6H_4—NO_2$-*p*	CN	Ph	Sh. 280 Sh. 270 250	9950 13,200 16,600	17
Ph	H	Ph	H	COPh	247	27,000	12
p-Me—C_6H_4	H	Ph	H	CO—Ph	249	33,700	12
p-MeO—C_6H_4	H	Ph	H	COPh	258	20,100	12
p-Br—C_6H_4	H	Ph	H	COPh	253	32,800	12
Ph	H	H	H	CO—Ph	248	27,300	12
Ph	H	H	H	CO—NH—CO—NH_2	245	13,700	*
p-Cl—C_6H_4	H	H	H	CO—NH—CO—NH_2	251	13,800	*
p-Cl—C_6H_4	H	H	H		293 254	4200 18,400	*
p-Br—C_6H_4	H	H	H		293 256	4650 22,200	*
Ph	H	N_3	H	Ph	250 252	17,000 18,200	*trans* 12 *cis* 12
Ph	H	NH—CO—CH_2—Ph	H	Ph	248 248	20,800 19,100	*trans* 12 *cis* 12
Ph	H	NH_2	H	Ph	249 249	16,400 19,300	*trans* 12 *cis* 12
p-Br—C_6H_4	H	N_3	H		260 262	24,000 22,300	*trans* 12 *cis* 12

TABLE 1—*continued*

R	R_1	R_2	R_3	R_4	λ_{max}	ε	Ref.
Ph	H		H	OEt	295	1990	
					240	27,700	*trans* 12
					223	34,200	
p-Br—C_6H_4	H	Cl	H	C_6H_4—OMe-*p*	264	20,000	*trans* 12
					233	18,200	
p-Br—C_6H_4	H	N_3	H	Ph	260	23,000	12
Ph	H	N_3	H	OEt	247	15,000	12
Ph	H	N_3	H	C_6H_4—OMe-*p*	254	19,000	12
					235	23,100	
p-Br—C_6H_4	H	N_3	H	Ph	260	22,000	12
Ph	H	N_3	H	C_6H_4—Br-*p*	252	16,200	12
					230	18,500	
Ph	H	N_3	H	C_6H_4—F—*p*	251	17,000	12
Ph	Me	N_3	H	Ph	252	16,900	12
Ph	Ph	N_3	H	Ph	255	16,750	12
Ph	Et	N_3	H	Ph	253	15,700	12
Ph	H	N_3	Ph	Ph	255	14,100	12
p-F—C_6H_4	H	N_3	H	Ph	251	19,000	12
Ph	H	N_3	H	C_6H_4—NO_2-*p*	256	23,700	12
Ph	H		H	Ph	252	21,800	12
Ph	H		H	Ph	252	17,400	12
H	Me	Ph	H	H	264	137	13
					258	185	
					252	157	
					Sh. 247	112	
H	Ph	Ph	H	H	Sh. 268	256	14, 15
					Sh. 264	338	
					259	437	
					253	380	
					Sh. 248	310	
H	Et	C_6H_4—NO_2-*p*	H	H	273	11,100	16

* Samples kindly supplied by Dr. B. G. Chatterjee, Indian Institute of Technology, Kharagpur, India.
* Henery-Logan and Rodricks have reported λ_{max} 247 mμ (ε 1300) for this compound. See Ref. 6c.

TABLE 2. γ-LACTAMS

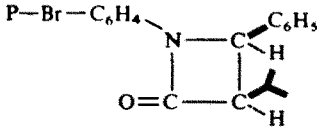


	λ_{max}	ε	Ref.
R_1 = Ph, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	246	17,200	*
R_1 = R_5 = Ph, R_2 = R_3 = R_4 = H, R_6 = R_7 = COOMe	Sh. 256	842	*
R_1 = R_6 = Ph, R_2 = R_7 = H, R_3 = *p*-NO_2—C_6H_4—CH_2,	267	12,700	17
R_5 = R_4 = COOMe	Sh. 218	16,300	
R_1 = Ph, R_2 = R_3 = R_4 = R_5 = H, R_6 = R_7 = COOMe	no peak or shoulder above 210 mμ		
R_1 = Me, R_2 = R_3 = Ph, R_4R_5 = CH—Me, R_6 = R_7 = H	Sh. 270	212	**
	266	356	
	259	465	
	253	423	
R_1 = *p*-Cl—C_6H_4, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	252	15,700	*
R_1 = *p*-Br—C_6H_4, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	254	18,100	*
	209	10,500	*
R_1 = *p*-I—C_6H_4, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	257	23,000	*
R_1 = *p*-Me—C_6H_4, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	256	20,500	*
R_1 = *o*-Br—C_6H_4, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	Sh. 293	190	*
	Sh. 273	350	
	Sh. 267	425	
R_1 = *o*-F—C_6H_4, R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = H	Sh. 268	691	*
	230	3304	

* Prepared in this laboratory, to be described elsewhere. For 1-phenylpyrrolidin-2-one. see[19]
**Sample kindly supplied by Dr. C. D. Lunsford of A. H. Robins Company.

max disappears in the N-chloro-acetyl- and N-(β-bromopropionyl)anilinomalonates. That this change in the UV absorption is caused by steric factors and not the presence of a halogen atom was demonstrated by the observation that dimethyl N-isobutryl-anilinomalonate displays little absorption in the 240 mμ region. Obviously a bulky N-aryl group interferes with the preferred conformation in which the aryl group, the nitrogen and the amide carbonyl are in the same plane.

X-Ray studies by Kagan *et al.*[10] have demonstrated that in VI, in the crystalline state, the valencies of nitrogen are very nearly planar and the N-aryl ring is indeed in the same plane as the β-lactam ring. Our spectral observations indicate that the same conformation is preferred even in solution. However, in a δ-lactam or in a heavily substituted γ-lactam, the tendency for the coplanarity of the aryl—N—CO— system due to conjugation is superseded by the steric requirements of the rest of the ring.



VI

TABLE 3. AMIDES

No.	Compound	λ_{max}	ε
1.	Ph—NH—CO—Me[2]	Sh. 279	490
		241	15,700
*2.	Ph—NH—CH(CO_2Me)$_2$	288	1800
		239	11,100
3.	Ph—NH—CH(CO_2Me)$_2$	285	2200
	CO—Me	237	14,300
4.	Ph—N—CH(CO_2Me)$_2$	Sh. 267	545
		Sh. 262	657
	CO—CH_2—Me	Sh. 258	726
		Sh. 225	4500
5.	Ph—N—CH(CO_2Me)$_2$	Sh. 267	250
		Sh. 264	265
	CO—$CHMe_2$	Sh. 262	289
		Sh. 260	313
		Sh. 257	342
6.	Ph—N—CH(CO_2Me)$_2$	Sh. 266	400
		Sh. 260	615
	CO—CH_2—Cl	Sh. 225	5420
7.	Ph—N—CH(CO_2Me)$_2$	Sh. 267	244
		Sh. 260	392
	CO—CH_2—CH_2—Br		
8.	*p*-Br—C_6H_4—N—CH(CO_2Me)$_2$	227	13,900
	CO—CH_2—CH_2—Br		
9.	*p*-Me—C_6H_4—N—CHPh—CO_2Et	Sh. 264	650
		Sh. 269	488
	CO—CH_2—Cl		
10.	Ph—N—CH_2—COPh	Sh. 289	1270
		238	22,200
	CO—CH(Cl)Ph		
*11.	Ph—NH—CH_2—CO—Ph	285	3250
		245	21,400
12.	Ph—NH—CO—CMe_2Br	285	2400
		234	12,000
13.	Ph—NH—CO$(CH_2)_4$Br	242	14,400
14.	*p*-Br—C_6H_4—CO—CMe_2—CH_2Cl	249	16,500

* Starting materials for some amides. These compounds have been included for the sake of comparison.

EXPERIMENTAL

The UV spectra were recorded on a Beckman-DK-2A spectrometer in 95% EtOH soln at room temp (~25°).

Dimethylanilinomalonate, m.p. 66°, was prepared according to procedure of Blank.[20] The amides 3–10 and 12–14 (Table 4) were prepared by acylation of the corresponding amino compounds with the appropriate acid.[21] Anilinoacetophenone (compound 11, Table 4) was prepared as described by Verkade and Janetzky.[22] All the compounds were characterized by satisfactory elemental analysis of their mass spectral fragmentation.

Acknowledgement—We wish to thank Drs. E. Testa, B. G. Chatterjee, B. N. Ghosh-Mazumdar, B. Anjaneyulu, S. K. Bhattacharya and C. D. Lunsford and J. S. Chib for the samples of some β- and γ-lactams and the U.S. Public Health Service for the support of this research through a grant (MH-03930).

REFERENCES

[1] For Part VII, see A. K. Bose and I. Kugajevsky, *Tetrahedron* **23**, 957 (1967).
[2] Presented in part at The First Middle Atlantic Regional Meeting at Philadelphia, Pa., February (1966).
[3] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* (2nd Edition); p. 213. Wiley, New York (1960).
[4] H. E. Ungnade, *J. Am. Chem. Soc.* **76**, 5133 (1954).
[5] [a] S. Sunagawa and N. Yoshida, *Yakugaku Zasshi* **82**, 826 (1962).
[b] M. Perelman and S. A. Mizsak, *J. Am. Chem. Soc.* **84**, 4988 (1962).
[c] E. J. Moriconi and P. H. Mazzocchi, *J. Org. Chem.* **31**, 1372 (1966).
[6] [a] O. E. Edwards and T. Singh, *Canad. J. Chem.* **32**, 683 (1954).
[b] R. H. Mazur, *J. Am. Chem. Soc.* **81**, 1454 (1959).
[c] K. R. Henery-Logan and J. V. Rodricks, *Ibid.* **85**, 3524 (1963).
[7] D. Crowfoot and B. W. Rogers-Low, *The Chemistry of Penicillin* (Edited by H. T. Clarke, J. R. Johnson and R. Robinson) p. 310–366. Princeton University Press, Princeton, N.J. (1949). See also D. Crowfoot, *Ann. Rev. Biochem.* **17**, 115 (1948).
[8] D. C. Hodgkin and E. N. Maslen, *Biochem. J.* **79**, 393 (1961).
[9] [a] Y. H. Suen and H. B. Kagan, *Bull. Soc. Chim.* 1460 (1966).
[b] P. Rouillier, J. Delman, J. Duplan and C. Nofre, *Tetrahedron Letters* 4189 (1966).
[10] H. B. Kagan, J. L. Luche, J. J. Basselier, G. Tsoucaris, C. de Rango and C. Zelver, *Bull. Soc. Chim.* France, (1967).
[11] J. C. Sheehan and P. T. Izzo, *J. Am. Chem. Soc.* **70**, 1985 (1948); **71**, 4059 (1949).
[12] Prepared in this laboratory, to be described elsewhere.
[13] E. Testa, B. J. R. Nicolaus, E. Bellasio and L. Mariconi, *Liebigs Ann.* **673**, 71 (1964).
[14] I. L. Kunyants, E. E. Rytslin and N. P. Gambaryan, *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk* 83 (1961).
[15] E. Testa, L. Fontanella and F. Fava, *Il. Farmaco Ed. Sci.* **13**, 152 (1958).
[16] L. Fontanella and E. Testa, *Liebigs Ann.* **622**, 117 (1959).
[17] A. K. Bose, M. S. Manhas and R. M. Ramer, *Tetrahedron* **21**, 449 (1965).
[18] B. G. Chatterjee, V. V. Rao and B. N. Ghosh-Mazumdar, *J. Org. Chem.* **30**, 4101 (1965).
[19] G. R. Proctor and R. H. Thomson, *J. Chem. Soc.* 2303 (1957).
[20] R. Blank, *Ber. Dtsch. Chim. Ges.* **31**, 1815 (1898).
[21] A. K. Bose and M. S. Manhas, *J. Org. Chem.* **27**, 1244 (1962).
[22] P. E. Verkade and E. F. J. Janetzky, *Rec. Trav. Chim.* **62**, 763 (1943). *Chem. Abstr.* **38**, 6284 (1944).