Tetrahedron. Vol. 24, pp. 1275 to 1281. Pergamon Press 1968. Printed in Great Britain

STEREOCHEMISTRY IN THE β-LACTAM SERIES—III*

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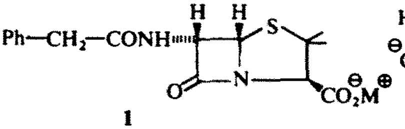
(*Received in UK 26 June 1967; accepted for publication 24 July 1967*)

Abstract—X-ray analysis of β-lactams **5** and **6** confirms the *cis* configuration assigned before on the basis of their NMR spectra. The valence bonds of nitrogen form a very flat pyramid and the dihedral angle between the Ar_2 phenyl and the β-lactam ring, which is planar, is very small. These results are compared with the data given by spectral methods applied to various β-lactams.

MOLECULES containing a β-lactam ring have been investigated by several physical methods. The structures of antibiotics like benzylpenicillin **1**[3] and cephalosporin *C* **2**[4] have been determined by X-ray methods. More recently, the NMR technique has revealed new data concerning (1) the structure of N-phenyl or N-benzyl azetidinones, and (2) the nature of the amide bond in homologous series of lactams.[1, 5, 6]



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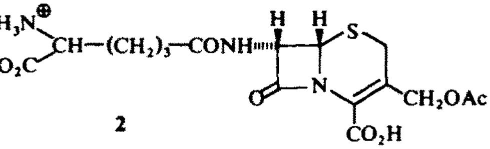

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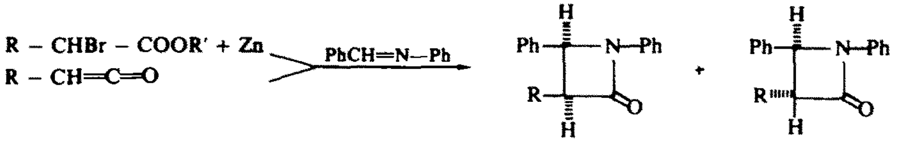
The interest of β-lactams has been enhanced since it has been shown that they possess various biological properties.[7] A series of β-lactams has been prepared by the Reformatsky reaction,[1] or by condensation of a ketene with a Schiff base.[9] These reactions yield two diastereoisomers (*cis-trans* pair) the formation of which has been studied.



R = Me, Et, i-Pr, t-Bu, Ph

3 **4**

The NMR spectra of these substances[1] suggest the assignment of the configurations **3** and **4** to the epimers. In order to confirm these assignments and to test the associated hypotheses, the X-ray technique has been employed.

The bromo and chloro derivatives (**5** and **6** respectively) were subjected to X-ray

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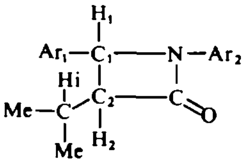
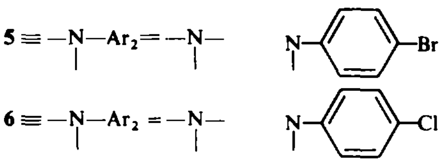
[*] For I and II, see Refs. 1 and 2.

Main paper covering a part of the thesis in organic chemistry (doctorat d'Etat) to be presented by J. L. Luche before the Faculty of Sciences, Paris.

analysis, the photographic techniques being employed for **5** and the scintillation-counter technique for **6**.





In the following two sections, the main results obtained by the NMR and the X-ray studies are given and in the last section, the results obtained by chemical and physical methods, and their implications regarding the stereochemistry of N-containing rings are discussed. In particular, there are four stereochemical problems: (a) The planarity of the 4-membered ring; (b) The dihedral angles between the 4-membered ring and the two Ph groups; (c) The conformation of the isopropyl group with respect to the lactam ring and the Ar₁ group and (d) The geometry of the Aryl-N—C=O system (resonance).

NMR spectra of derivatives **3** *and* **4**

The β-lactams we prepared can be classified with respect to their NMR spectra: in type **3**, the coupling constant J_{H1-H2} is about 6 c/s and for type **4**, about 2·5 c/s. The chemical shift, δ, of the protons of R for type **3** is always smaller than the corresponding δ in **4**.

For the particular pair with R = isopropyl, two more differences in their spectra appear: for derivative **3**, the two methyls are clearly differentiated ($\Delta\delta = 0{\cdot}8$ ppm); in derivative **4**, $\Delta\delta = 0{\cdot}1$ ppm. The coupling constant J_{H2-Hi} is about 11 c/s for **3** and 7 c/s for **4**.

Since this work has been accomplished,[1] several authors have published values for the coupling constant of neighbouring protons in some lactams: for monocyclic β-lactams, *J* (*cis*) varies between 4·9 and 5·9 c/s, *J* (*trans*) between 2·2 and 2·8 c/s[5]; for bicyclic derivatives (penicillin and cephalosporin), the corresponding values are *J* (*cis*) = 4 c/s, *J* (*trans*) = 2 c/s.[10]

A detailed study of the NMR spectra led to the following interpretation:

(a) Considering the two hydrogen atoms attached to the ring carbons, their configuration is cis *for molecules of type* **3**, trans *for* **4**.

(b) In derivative **3** with R = isopropyl, this group does not rotate freely around the C_2—C_{10} bonds (Fig. 1), but exhibits a preferential conformation for which the bonds C_2—H_2 and C_{10}—H_i are almost antiparallel; for such a conformation, the position of the two methyls of the isopropyl group with respect to the shielding cone of the Ar₁ phenyl, are not equivalent.

For derivative **4** (R = isopropyl), the NMR spectrum does not indicate any appreciable difference between the two methyls. No preferential conformation can be considered.

In order to obtain some chemical evidence regarding the above assignments, a series of epimerization experiments (*cis* → *trans*) were performed. Owing to the larger steric strains in **3** than **4**, one would expect **4** to be more stable than **3**.

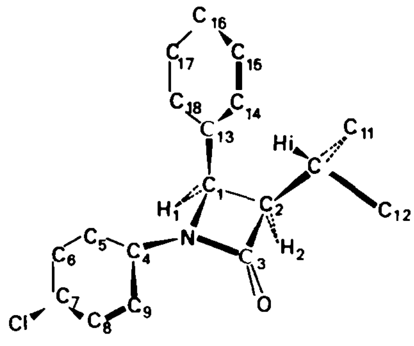
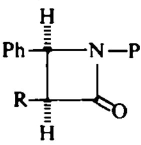


FIG. 1. Numbering of atoms perspective view

TABLE 1. EPIMERIZATION *cis* → *trans* IN t-BuOH-t-BuONa AT 75°

β-Lactam 3 	% *trans* Time of heating given in hours				
	25 hr	50 hr	75 hr	100 hr	150 hr
i-C_3H_7		55		70	75
C_6H_{11}			80		95
t-C_4H_9	95		98		98
C_6H_5*		92			

* In this experiment pure 4 (100% *trans*) was used.

An almost complete transformation of 3 to 4, under conditions specified in Table 1 was observed. These experiments are not sufficient for a precise evaluation of a stability difference between the two epimers, as the complementary epimerization experiments of 4 to 3 have not been realized. Nevertheless, a rough evaluation of ΔG *cis* → *trans* (75°) for R = t-butyl, gave an order of magnitude of 3 kcal/mole. The steric strain in 3 is also supported by mass spectroscopy experiments.[2]

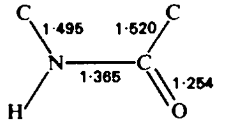
The NMR spectra of 3 and 4 gave no information about the other stereochemical problems enumerated in the introduction. However, Bose *et al.*[11] examined the conjugation in the system $\text{Ar-}\underset{|}{\text{N}}-\underset{|}{\text{C}}=\text{O}$ on the basis of UV spectra of β-lactams and stated that these spectra are compatible with a planar conformation of the system. The planarity seems associated with the presence of the aryl group: the NMR spectra of N-benzyl-β-lactams show that the two benzylic protons are not equivalent;[5] this suggests a non-planar geometry of N-atom in these compounds.

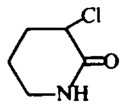
It is important to emphasize that the interpretation of the NMR spectra of all the β-lactams considered in this work is based on two stereochemical hypotheses: (a) that the 4-membered ring is planar, and (b) that the Ar_1 phenyl is nearly perpendicular to the β-lactam ring.

In order to test these assumptions and the results obtained by NMR spectroscopy, we determined by X-ray analysis the structures of two β-lactam derivatives, keeping in mind that the conformation may be not necessarily the same in solution as in the crystal.

X-ray analysis of β-lactam 5 and 6

We prepared the two racemic *cis* compounds **5** (m.p. = 175°) and **6** (m p. = 168°). Their NMR spectra are identical to that of **3** (R = isopropyl) which has been discussed above. The space group is $P2_1/c$ with 4 molecules per unit cell; the two derivatives are true racemates. For derivative **5**, the X-ray pattern was recorded with a Weissenberg camera using the multiple film technique. The heavy-atom method yielded a molecular model which has undoubtedly the *cis* configuration. The crystallographic "R-factor" (which is in some extent an inverse measure of the precision) is 0·19 for this model. No detailed refinement has been carried out, as derivative **6** was studied simultaneously by the counter method (General Electric Diffractometer XRD-5). The R-factor for **6** is 0·04. The detailed discussion of bond-lengths and valence angles has been given in a separate paper.[8] A recent determination[17] of a δ-lactam (α-chloro-δ-lactam) showed almost identical values for the interatomic distances, with one exception (see Fig. below) dC=O = 1·254 for the δ-lactam, instead of 1·210 for the β-lactam in the present work. (Fig. 2).





Here, the stereochemical aspects indicated in the introduction in conjunction with chemical and NMR evidence are discussed. The approximate shape of the molecule and the numbering of atoms are given in Fig. 1. Bond distances and valence angles are given in Fig. 2.

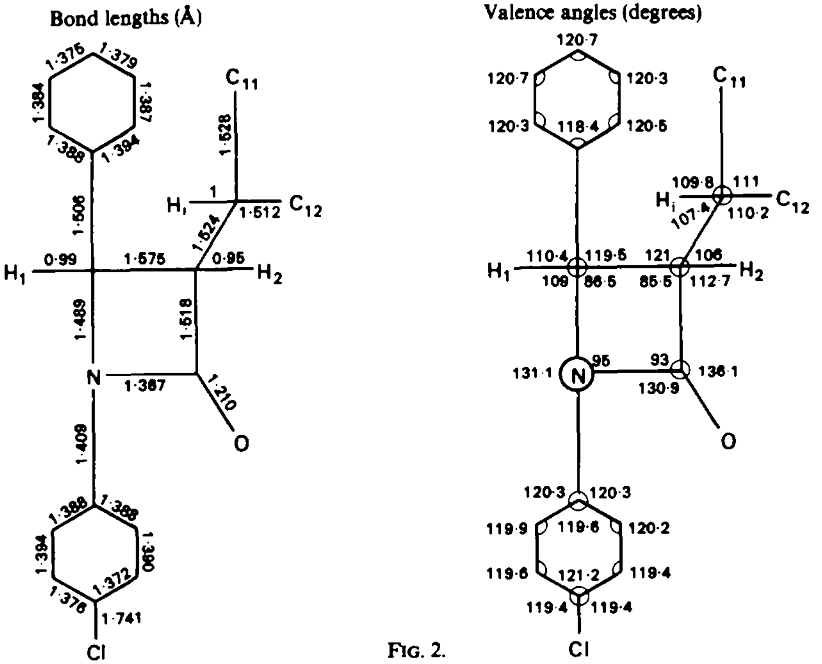


Fig. 2.

In **6**, the standard deviation is $\sigma_d = 0{\cdot}005$ Å for C—C bonds and $\sigma_\alpha = 0{\cdot}3°$ for valence angles. Crystallographers usually consider that, when two magnitudes are compared with a standard deviation for each of them, differences higher than 2·5 σ are quite significant. In **5**, the corresponding values are $\sigma_d = 0{\cdot}04$ Å and $\sigma_\alpha = 2°$.

DISCUSSION

(a) *Planarity of the 4-membered ring.* The distances of each atom to the mean plane of the ring are given below. For both derivatives, all distances are not significant, and, therefore, within the experimental error, the ring is planar, and the carbonyl lies in the plane of the ring.

	Distances in Å to the mean plane				
	O	N	C_1	C_2	C_3
5, X = Br	−0·007	−0·013	+0·036	−0·025	+0·011
6, X = Cl	+0·018	−0·001	+0·004	−0·009	+0·006

The planarity of the β-lactam ring is not necessarily a direct consequence of the presence of the —N—C═O group as several cyclobutane derivatives exhibit also a planar configuration.[12]

(b) *Angles between the 4-membered ring and, respectively, the* Ar_1 *and* Ar_2 *groups.* The angle between the lactam ring and Ar_1 is 79 ± 2° in **6** and 80 ± 2° in **5**. The corresponding angle for Ar_2 is 8 ± 1° in **6** and 5 ± 1° in **5**. These last values will be discussed in Section (d).

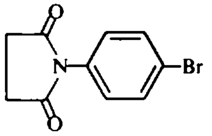
(c) *Conformation of the isopropyl group.* The relative configuration of the isopropyl and Ar_1 groups is *cis*. The dihedral angle between the $C_{10}C_2C_1$ and $C_2C_1C_{13}$ planes is 0 ± 1°. The corresponding angle for a *trans* configuration would be about 125°. Between the isopropyl and Ar_1 groups, which are eclipsed, no steric hindrance occurs, despite the fact that they are both large substituents.[13] The distance $C_{10}C_{13}$ is 3·4 Å, definitely larger than the 1,3-diaxial distance (2·5 Å) in cyclohexane compounds. The C_{10} and C_{13} atoms are the closest atoms of the isopropyl and Ar_1 groups.

The rotational conformation of isopropyl is such that the planes $H_1C_{10}C_2$ and $C_{10}C_2H_2$ make a dihedral angle of about 180°. It is important to emphasize that these values are identical with those postulated[1] in order to explain the NMR spectra.

(d) *Stereochemistry of the nitrogen atom.* The main problem is to determine whether, and under which conditions, the geometry of the three valence bonds issuing from the N-atom is planar or pyramidal. For derivatives **5** and **6**, the three valences of N are almost coplanar: the angle between the N—C_4 bond and the mean β-lactam ring is 9·3°.

The same order of magnitude has been found for two other N-containing rings, studied by X-ray analysis: *p*-bromophenylsuccinimide 7[14] and the dimer of phenylisocyanate, 8[15] as shown in Table 2.

Table 2 gives the dihedral angle between the plane of the Ar_2 phenyl and the plane of the N-containing ring. The value of this angle for the *p*-bromophenylsuccinimide **7** which contains a 5-membered ring, is very different (65°) from the values (<10°) for the molecules containing 4-membered rings. It very likely is that this difference is not the result of the different packing of molecules in the crystal, but it is probably a molecular characteristic: the conformation of the phenyl ring with respect to the N-containing ring is subjected to two opposing factors, viz: conjugation in the Aryl-N—C=O system which tends to produce coplanarity; and steric hindrance between the *ortho* hydrogens of phenyl and the oxygen of carbonyl which tends to hinder coplanarity.



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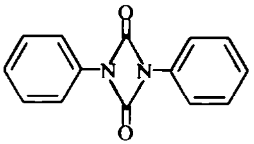

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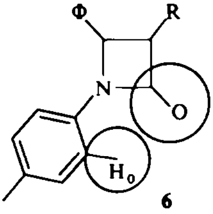
TABLE 2.

	Angle between the N-containing ring and	
	the N—Ar_2 bond	the plane of Ar_2
β-lactam **5**	8·5°	5·6°
β-lactam **6**	9·3°	8·0°
Isocyanate dimer **8**	9·0°	9·5°
Succinimide **7**	10°	65°

In all 4-membered ring derivatives like **6**, there is no such steric interference, as the distance H°—O (about 2·66 Å) is larger than the sum of the van der Waals' radii (about 2·4 Å) (Fig. 3). In these molecules, conjugation occurs, and this is supported by the values of the interatomic distances.[8]

In the succinimide derivative **7**, however, it has been shown[14] that coplanarity would necissitate an interpenetration of the van der Waals' radii of 0·7 Å. This serves to rationalize the value of 65° for the angle between the two rings; here, conjugation is appreciably decreased.



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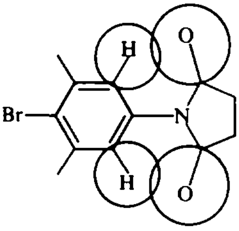

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FIG. 3.

CONCLUSION

A very accurate X-ray analysis of a crystal of **6**[8] provided values of all intramolecular interatomic distances and bond angles. The molecular structure of a crystal of **5** determined with a lower accuracy, is essentially the same. On the other hand, the studies of NMR spectra of a series of β-lactams including **5** and **6** produced evidence about the molecular conformation in solution. Three main aspects are discussed:

(1) *Planarity of the β-lactam ring.* This hypothesis, which is the basis for the explanation of the NMR spectra, has been confirmed by the X-ray analysis.

(2) *Configuration of the isopropyl and phenyl groups.* The NMR spectra showed that molecules of type **3** are *cis*; molecules of type **4** are *trans*.

The conformation in the crystal of the isopropyl group, which could rotate around the C_2—C_{10} bond, is such that the C_2—H_2 and C_{10}—H_1 bonds are antiparallels. The NMR spectra provided evidence that such a preferential conformation occurs in solution.

(3) *Geometry of the* $\mathrm{Ar{-}\underset{|}{N}{-}\underset{|}{C}{=}O}$ *system.* The geometry of the three valence bonds of N is much closer to the planar than to the pyramidal one. The phenyl and the β-lactam rings are almost coplanar. It seems that this last point is a characteristic of the β-lactam ring.

The planarity of the group is associated with conjugation, which is also supported by interatomic distances.

UV spectra[11] support the assumption that this nearly planar configuration is preferred in solution.

EXPERIMENTAL

Preparation of β-lactams 5 and 6. In accordance with Reformatsky reaction using Zn, methyl α-bromoisovalerate and N-benzylidene-*p*-halo aniline were heated under reflux in THF for 2 hr, according to the procedure of Gilman and Speeter.[16] Yielding the crude product (95% yield). After two recrystallizations from MeOH, compounds 5 (m.p. 175–176°) and 6 (m.p. 168–169°) were obtained as white needles. (Found for **5** ($C_{18}H_{18}NOBr$, mol. wt. 344·25): C, 62·62; H, 5·36. Calc: C, 62·80; H, 5·77%; for **6** ($C_{18}H_{18}NOCl$, mol. wt. 299·75): C, 72·12; H, 6·10; calc: C, 72·14; H, 6·01%.) IR spectra in $CHCl_3$ soln and in Nujol suspension were identical and show a characteristic absorption at 1735 cm^{-1}; UV spectra: $\lambda_{max} = 260$ mμ; $\varepsilon = 2 \cdot 10^4$; NMR spectra: identical to the spectra of 3 (R = isopropyl).

Epimerization of the β-lactams (Table 1). 1/1000 mole β-lactam 3, 5 mg (0·2 equiv) NaH (i.e. 10 mg of a 50% dispersion of NaH in mineral oil) and 10 ml of dry t-BuOH were placed in a gas tight stoppered flask and heated at 75° in an oil bath. When the reaction stopped, 20 ml ether were added and the mixture washed with 1N HCl then with 1N NaOH, dried with Na_2SO_4 and the solvent distilled off. The remaining oil was submitted to NMR analysis. In the case of 3 (R = Me), the epimerization was difficult. The higher percentage of **4** was about 42% after 50 hr at 75°. If heating was continued, side reactions occurred, and the percentage of **4** decreased. In this case, it was not possible to determine if the equilibrium had been reached.

Acknowledgement—The authors wish to thank Professor D. Harker for his interest.

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