A Convenient Nomenclature for Fused β-Lactams

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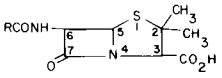
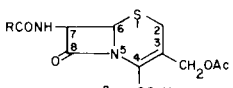
A new nomenclature is proposed which provides a convenient stereo-description of diverse types of fused β-lactams appearing in the literature in recent years.

An examination of the current literature shows that β-lactams including penicillins **1** and cephalosporins **2** are attracting the attention of various types of chemists. Industrial as well as academic laboratories are reporting large numbers of fused β-lactams some of which are close analogs of penicilins or cephalosporins and some are *distant* analogs. Monocyclic β-lactams derived from naturally occuring antibiotics or obtained by synthesis have assumed importance as key intermediates for the prepration of cephalosporins, penicillins and analogs (2). It is obviously advantageous to be able to recognize easily the close relationship between these various monocyclic and fused β-lactams.

Sheehan (3) coined the trivial name 'penam' for the fused β-lactam system in penicillin and used the numbering system shown in **1**. The analogous trivial name 'cepham' with the numbering system as in **2** was later assigned by Morin *et al.*, (4) to the bicyclic skeleton of cephalosporins.

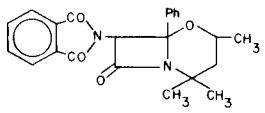


1



2

The penam-cepham nomenclature has been widely used in the past for naming derivatives and close analogs of penicillins and cephalosporins. But, this nomenclature becomes cumbersome when the sulfur atom in penicillins and cephalosporins is placed at a different location or replaced by some other atom; for example, **3** should be termed 1-dethia-1-oxacepham although Sheehan and Dadic (5) have suggested the abbreviation *O*-cepham; (**4**) (6) should be designated as 1-dethia-2-thiapenam. This nomenclature cannot be conveniently broadened to apply to distant analogs and homologs of penicillins and cephalosporins which have already been reported or will appear in the literature in coming years.



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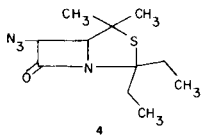
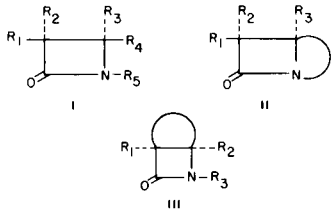


4

Designation according to the rules of Chemical Abstracts, no matter how complicated, are necessary for keeping formal records. But for less formal purposes, trivial names play a useful role. We wish to propose here a nonemclature and stereodescription which puts primary emphasis on the β-lactam part of the molecule in fused β-lactams of diverse types. The universally accepted conventions in the field of steroid chemistry have served to some extent to quide our proposal.

The Nomenclature and Stereodescription.

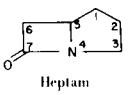
1) To bring uniformity in a field that is rapidly growing and where the β-lactam ring has been depicted in different ways by different authors, we propose that the monocyclic and the two fused β-lactam systems be represented exclusively by the stereodescriptors I, II, and III.

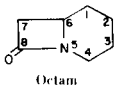


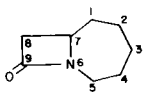
I II III

2) The fused β-lactams **5-8** of type II containing 7, 8, 9, and 10 atoms in the bicyclic system are given generic names (with the self-evident mnemonic) heptam, octam, nonam, and decam, respectively. Larger rings can be named similaryl using Latin roots.

3) The numbering system is chosen to conform to the


Heptam
5


Octam
6


Nonam
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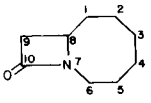
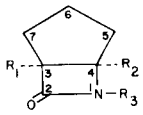
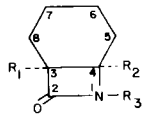

Decam
8

convention that has found acceptance for penicillins **1** and cephalosporins **2**.

4) Fused β-lactams of type III, for example, **20** and **21**, have gained attention in recent years as intermediates for the total synthesis of cephalosporins or the conversion of penicillins to cephalosporins. The bicyclic β-lactams **9**. **10** of type III containing 7 and 8 atoms in the rings are given the generic names neophptam and neooctam, respectively. Larger rings can be named similarly. The numbering of the ring atoms is an extension of the usual numbering of monocyclic β-lactams (2-azetidinones).


Neoheptam
9

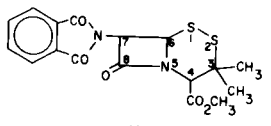

Neooctam
10

5) The "α", "β" stereodescription is used for designating configuration. As in steroid nomenclature, "β" indicates a substituent above the plane of the β-lactam ring drawn according to the convention stated in articles 1 and 4 above. Unless stated to the contrary, the ring junction substituent R_3 in II and R_1 and R_2 in III are to be considered below the plane of the fused ring system. In the case of naturally occuring antibiotics, such as penicillins, cephalosporins and cephamycins, the stereostructures so depicted coincide with their absolute configuration. In dealing with racemic compounds, such stereostructures reflect the relative configuration only.

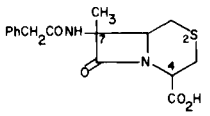
In this nomenclature penam is 1-thiaheptam and cepham is 1-thiaoctam; therefore the penam and cepham terminology is compatible with the proposed nomenclature and will not cause confusion.

Illustrative Examples.

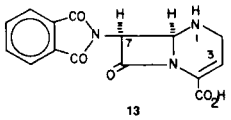
A few bicyclic β-lactams **11-16** from the recent literature, some of which are distant analogs of penicillins and cephalosporins, are named here according to the new nomenclature.


11

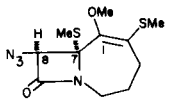
4-Carbomethoxy-3,3-dimethyl-7-phthalimido-1,2-dithiaoctam (7).


12

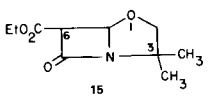
7-Methyl-7-phenylacetamido-2-thiaoctam-4-carboxylic acid (8).


13

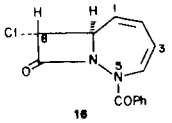
7-β-Phthalimido-1-aza-3-octem-4-carboxylic acid (9).


14

8-β-Azido-2,7α-dimethylthio-1-methoxy-1-nonem (10).

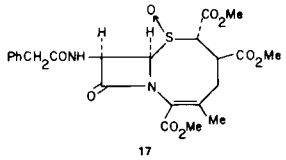

15

Ethyl 3,3-Dimethlyl-1-oxaheptam-6-carboxylate (11).


16

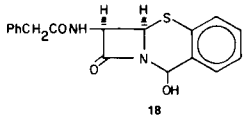
5-Benzoyl-8α-chloro-5-azanonam-1,3-diene (12).

The compound **17** obtained from natural penicillin by bishomologation is named here so as to indicate its absolute configuration.

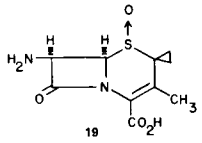

17

Trimethyl 5-methyl-9β-(phenylactamido)-1-thia-5-decem-1-oxide-2α,3β,6-tricarboxylate (13).

Tricyclic system such as **18** can also be named easily according to our nomenclature. The more complicated policyclic structures, for example, **19** will have cumbersome designation in any system of nomenclature.


18

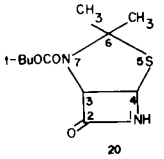
4-Hydroxy-7β-(phenylactamido)-2,3-benzo-1-thiaoctem (14).



19

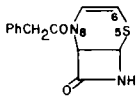
7β-Amino-2,2-ethylene-3-methyl-1-thia-3-octem-1-oxide-4-carboxylic acid (15).

Two examples **20**,**21** of fused β-lactams of type III are provided here from recent literature.



20

7-(*t*-Butoxycarbonyl)-6,6-dimethyl-5-thia-7-aza-neoheptam (16).



21

8-(Phenylacetyl)-5-thia-8-aza-6-neooctem (17).

Advantages of the Nomenclature.

In view of the strikingly high level of research activity that is in progress in the β-lactam field, it is opportune now to consider a new nomenclature. Designations such as penams and cephams will probably find continued favor with those who have been dealing with minor structural variants of penicillins and cephalosporins; but for others, in particular for new entrants (18) to the β-lactam field, the nomenclature proposed here provides a convenient and logical system of trivial names.

Acknowledgment.

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(18) For example, Luttringer and Streith have already used our nomenclature to name a series of novel bicyclic β-lactams, see Reference 12.