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Progress in the Chemistry of Organic Natural Products

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Recent Developments in the Chemistry of Penicillins

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I. Introduction

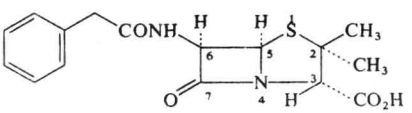
The purpose of this review is to summarize the important developments in the chemistry of the penicillin molecule which have been reported in the scientific literature during the approximate period 1964 through 1972. The penicillins were intensively studied from a chemical

point of view during the 1940's and this work is discussed in detail in the penicillin monograph (*36*). The isolation of 6-aminopenicillanic acid in 1959 (*16*) led to the preparation of large numbers of penicillin derivatives in which the side chain at the 6-position of the penicillanic acid nucleus was modified. These efforts, which have been successful in introducing a number of important changes in the biological properties of the penicillin molecule, have been reviewed by PRICE (*144*) and others (*55, 175, 72, 145, 2, 91*). This aspect of penicillin chemistry will be dealt with only briefly in this review, and then only with reference to the chemistry involved. Recently, and particularly during the last four years (1969 through 1972), there have been increasing numbers of reports in which the chemistry of the penicillanic acid nucleus itself has been investigated, and it is principally to these studies that this review will address itself (see also *81, 129, 130,* and *66*).

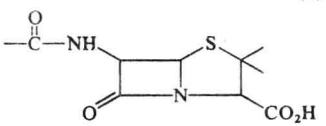
Ever since the structure of the penicillin molecule was elucidated (*36*), there have been continuing efforts directed toward the total synthesis of penicillins and penicillin analogs. These studies are outside the scope of the present review, and the reader is referred to the books by MANHAS and BOSE (*129, 130*) and the chapters by HEUSLER (*89, 86*) for summaries.

II. Nomenclature

The nomenclature which will be utilized throughout this review can be illustrated by referring to the structure of benzylpenicillin (penicillin G) (**1**). This will be designated 6-phenylacetamidopenicillanic acid and



(1)



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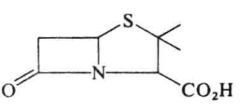


(3)

the numbering system shown in (**1**) will be used (note that the term "penicillin" refers to (**2**) except when being used as a general name for the entire class of compounds). Unless otherwise specified either in the name or the structure, the natural penicillin configuration as shown in (**1**)

will be assumed (*i.e.*, the 6-substituent β, the 3-substituent α and the 5- and 6-hydrogens *cis*). Other names which, according to other conventions, can be given to (**1**) are 2,2-dimethyl-6β-phenylacetamidopenam-3α-carboxylic acid, and (2*S*, 5*R*, 6*R*)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. The penicillanic acid nucleus (**3**) consists of fused β-lactam and thiazolidine rings—these portions of the nucleus will be referred to by these names.

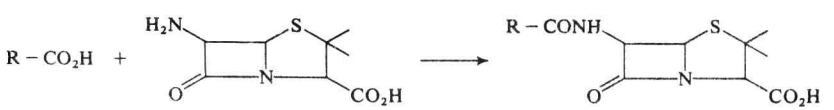
Several abbreviations will be used throughout the review: Et for ethyl, tBu for *t*-butyl, Ø for phenyl, Ac for acetyl, Ts for *p*-toluenesulfonyl, and Phth for phthaloyl.

III. Reactions at the β-Lactam Ring

Transformations which primarily involve the β-lactam portion of the penicillanic acid nucleus and its substituents will be considered under this heading. Some reactions which involve both the β-lactam and the thiazolidine ring will be dealt with in Section IV C. The chapter by KAISER and KUKOLJA (*106*) includes a discussion of many of these topics.

A. Acylation of the 6-Amino Group

Most of the common methods for forming amide bonds have been applied to the coupling of an organic acid with the amino group of 6-aminopenicillanic acid (**4**) (henceforth, 6-APA) (*Chart 1*). This aspect



(4)

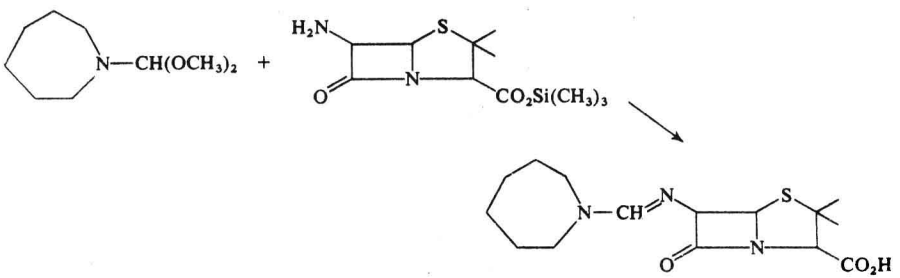
Chart 1. Acylation of 6-APA

of penicillin chemistry has been reviewed (*135*), and the reader is directed to the references cited in reviews such as the one by PRICE (*144*) for examples of a variety of penicillins and the methods used in their synthesis. Some of the coupling methods which have been described in recent years include the use of coupling reagents such as 1,1′-carbonyldiimidazole (*133*), N,N′-dicyclohexylcarbodiimide (*7*), and N,N-dimethylchloroformiminium chloride (*140*), the use of esters of *p*-nitro- and 2,4-dinitrophenol (*147*), the use of N-carboxy-α-amino acid anhydrides (*76*), and the use of mixed anhydrides with pivalic acid (*53*).

When the acid which is to be coupled to 6-APA also contains an amino group, it is generally necessary to block this amino group to prevent its acylation. A variety of protecting groups which can be removed without destroying the penicillanic acid ring system have been described: the proton (*82*), the carbobenzyloxy group (*126*), the *p*-nitrocarbobenzyloxy group (*146*), the enamine derived from methyl acetoacetate and other β-dicarbonyl compounds (*159*, *53*, *126*), the 2-methyl-2-(*o*-nitrophenoxy)-propionyl group (*103*), the *o*-nitrophenylsulfenyl group (*59*) and the trityl group (*111*). In addition, an amine precursor such as azide can be substituted for the amine (*58*). Various protecting groups have been employed to block the amine of 6-APA. These have included the trityl group (*20*, *21*, *138*), Schiff bases such as the *p*-nitrobenzylidene group (*e.g.*, *104*), and the 2,2,2-trichloroethoxycarbonyl group (*62*). With the advent of the chemical cleavage of penicillin side chains, however (see *Chart 5*), most secondary amides at the 6-position can serve as blocking groups.

Carboxylic acid blocking groups have frequently been useful in a variety of chemical manipulations involving the penicillanic acid nucleus. These can be applied either to a carboxylic acid in the side chain or to the acid at the 3-position of 6-APA, and have included benzyl esters (*85*, *26*, *125*, *164*), *p*-nitrobenzyl esters (*1*), methoxymethyl esters (*96*), silyl esters (*187*, *68*), stannous esters (*7*), phenacyl esters (*6*), trityl esters (*93*), 3,5-di-*t*-butyl-4-hydroxybenzyl esters (*93*), esters of (*E*)-oximes of benzaldehyde and 2-furaldehyde (*67*), mixed anhydrides with acetic acid (*32*), and amides of N, N′-diisopropylhydrazine (*11*).

In general, it has been necessary to have a carboxamido group at the 6-position of the penicillanic acid nucleus in order to have significant antimicrobial activity. A recent notable exception has been the preparation of several 6-amidino derivatives. One of these, FL-1060 (*Chart 2*), has been reported to have outstanding activity against certain Gram-negative organisms (*128*).



FL-1060

Chart 2. A 6-amidinopenicillin

B. Alkylation of the 6-Amino Group

6-Aminopenicillanic acid has been alkylated either by formation of the Schiff base followed by reduction (*122*) or by reaction with a diazoalkane (*57*, *134*) (*Chart 3*).

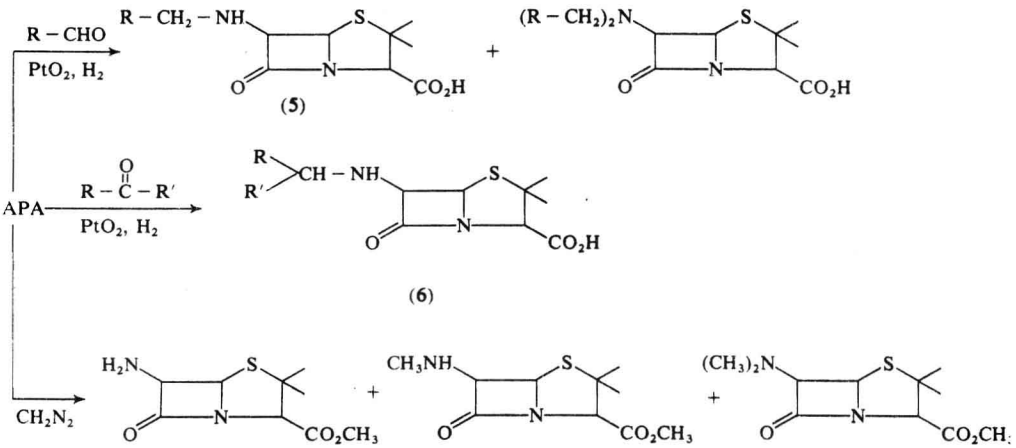


Chart 3. Alkylation of 6-APA

Acylation of compounds of the type (**5**) did not afford derivatives with interesting biological properties; (**6**) ($R = R' = CH_3$) could not be acylated.

A special form of N-alkylation is involved in the formation of hetacillin (**8**) by treatment of ampicillin (**7**) with acetone under basic conditions (*Chart 4*) (*82*). The unique imidazolidinone structure has been confirmed

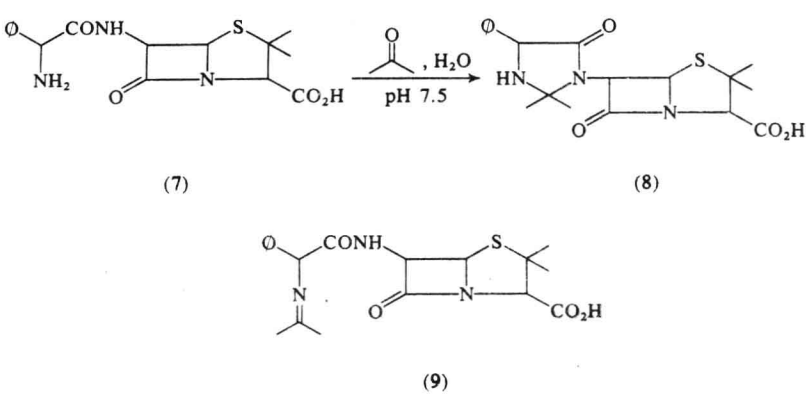


Chart 4. Hetacillin

by X-ray structural analysis. Compared to (**7**), (**8**) has a lower isoelectric point, and the β-lactam is less susceptible to opening with acid, 2,4-dinitrophenylhydrazine, and by way of polymerization reactions (*113*). The stability (*162*, *113*), microbiological (*179*, *171*), and pharmacological (*179*) properties of (**8**) have been interpreted in terms of an equilibrium between (**7**) and (**8**), possibly involving the Schiff base (**9**) as an intermediate (*56*).

C. Hydrolysis of the 6-Amido Group

Because the cleavage of a penicillin to 6-APA requires the hydrolysis of the more stable 6-carboxamido group in the presence of the labile β-lactam, it would be reasonable to suppose that only the high specificity afforded by an enzymatic reaction would be successful for this conversion (*92*). Weissenberger and van der Hoeven (*187*), however, took advantage of the fact that the 6-carboxamido function is a secondary amide, and were able to convert penicillin G to 6-APA in 91% overall yield by blocking the carboxylic acid as a silyl ester, then converting the 6-carboxamido group to a readily hydrolyzed imino ether by treatment with PCl_5 and l-butanol (*Chart 5*). Similar conversions have been carried out using the

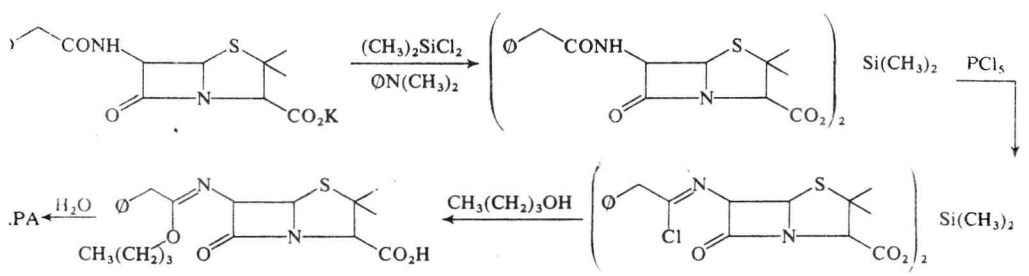


Chart 5. 6-APA from penicillin G

mixed anhydride with acetic acid (*32*) or the ester with the (*E*)-oximes of benzaldehyde or 2-furaldehyde (*67*) to block the carboxylic acid.

A less general method of side chain cleavage was employed to remove the phenylglycyl residue from 6-epihetacillin (*Chart 6*) to afford 6-epiAPA (**10**) (*100*).

References, pp. 53—62

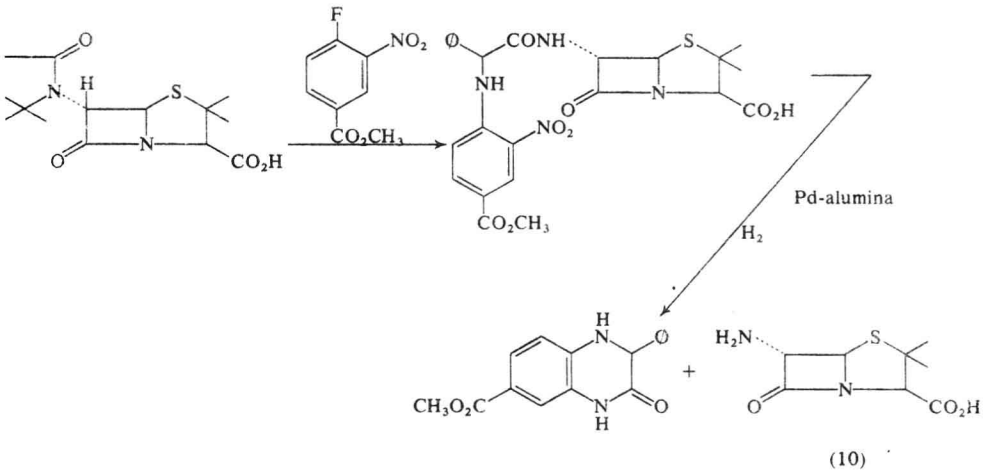


Chart 6. 6-EpiAPA from 6-epihetacillin

Several procedures have been devised which will allow the exchange of one acyl function on the 6-amino group of 6-APA for another, without involving 6-APA as an intermediate. An early example of this type of conversion has been described by SHEEHAN (*164*) and is shown in *Chart 7*. A more general exchange reaction is illustrated in *Chart 8* (*1*). Treatment

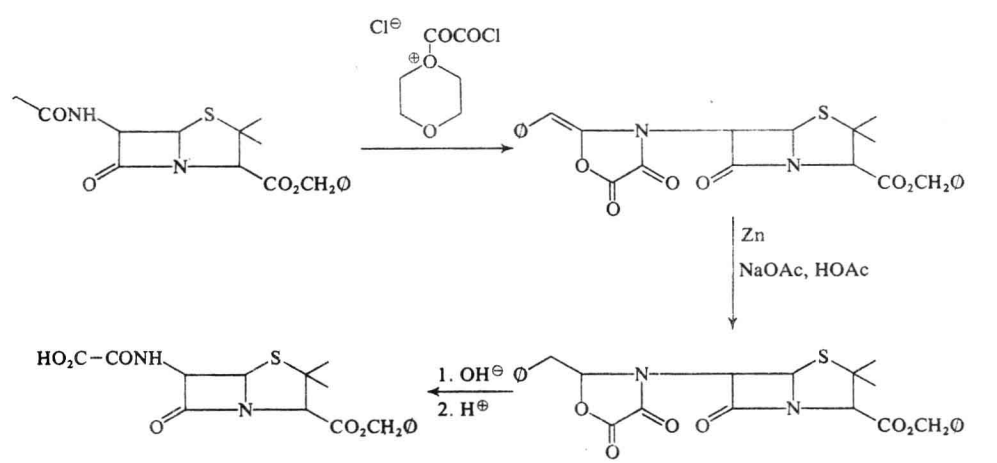


Chart 7. Benzyl 6-oxamidopenicillanate from penicillin G benzyl ester