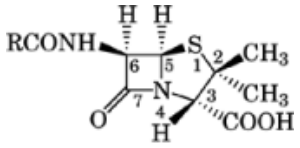
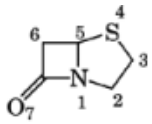
Kirk-Othmer Encyclopedia of Chemical Technology.

PENICILLINS AND OTHERS, β-LACTAMS

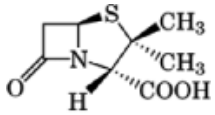
The basic structural features of the penicillin nucleus **(1)** include a β-lactam ring fused through nitrogen and the adjacent tetrahedral carbon to a second heterocycle which, in natural penicillin is a 5-membered thiazolidine ring. Biologically active penicillins are generally characterized by a functionalized amino group in the 6β-position of the β-lactam ring and a carboxyl group in the 3-position in the thiazolidine ring.



(1)



(2)



(3)

In general, penicillins exert their biological effect, as do the other β-lactams, by inhibiting the synthesis of essential structural components of the bacterial cell wall. These components are absent in mammalian cells so that inhibition of the synthesis of the bacterial cell wall structure occurs with little or no effect on mammalian cell metabolism. Additionally, penicillins tend to be irreversible inhibitors of bacterial cell-wall synthesis and are generally bactericidal at concentrations close to their bacteriostatic levels. Consequently penicillins have become widely used for the treatment of bacterial infections and are regarded as one of the safest and most efficacious classes of antibiotics.

1. Nomenclature

Chemical Abstracts indexes most penicillins as 4-thia-1-azabicyclo[3.2.0]heptane-7-ones **(2)**. Using this system, penicillin G [161-33-6] (**1**, R = $C_6H_5CH_2$), $C_{16}H_{18}N_2O_4S$, is 6-(2-phenyl-acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. The unsubstituted bicyclic ring system of the penicillins is designated as penam [53908-04-6], C_5H_7NOS, **(2)** (1) and the penicillins **(1)** are generally 6-acylamino-2,2-dimethylpenam-3-carboxylic acids. A further simplification is the use of the term penicillanic acid [87-53-6], $C_8H_{11}NO_3S$, to designate the penicillin ring system having the substituents indicated in **(3)**. Thus the penicillins are named as the appropriate acylaminopenicillanic acid. Because the great majority of the variations of the penicillin structure are in the acyl side chain, the carbonyl of the acyl group is included in the basic moiety name penicillin.

Landmarks in the development of penicillin are its discovery in 1929 (2) and the subsequent recognition in 1940 of the potential utility of penicillin for controlling antibacterial infections in animals (3) and shortly afterward in humans (4, 5). The realization that penicillin was a useful drug occurred during World War II (6).

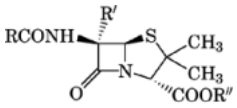
Penicillin was first obtained as a product of the fungus *Penicillium notatum*, but the early manufacture utilizing this organism was not amenable to large-scale handling. Modifications were soon introduced which improved yields and quality of the product (7). Although there was an intense effort from 1940 on, it took until 1945 before the combined results of chemical degradation and x-ray crystallography made it possible to be certain that the penicillin structure contained the β-lactam thiazolidine ring system (8).

In 1959 isolation of the penicillin nucleus, 6-aminopenicillanic acid [551-16-6] (6-APA) (**1**, RCO = H), $C_8H_{12}N_2O_3S$, from fermentations deficient in side-chain precursors was reported (9). It was soon found that 6-APA could be produced more efficiently by enzymatically removing the acyl group from various penicillins using penicillin acylases. Subsequently this intermediate has also been made by chemically removing the 6-acyl group after first protecting the C-3 carboxyl group. However, for manufacturing purposes, the majority of 6-APA is currently produced by enzymatic deacylation of penicillin G or penicillin V [87-08-1]. The isolation of 6-aminopenicillanic acid has resulted in the synthesis and biological evaluation of many thousands of penicillin analogues derived primarily by acylation of the 6-amino group. From this vast chemical investment an important range of semisynthetic penicillins have found wide clinical use (Table 1).

2. Physical Properties

Penicillins have several properties that are characteristic of β-lactam antibiotics (10). They are obtained in relatively pure form as off-white, tan, or yellow freeze-dried or spray-dried solids that are usually amorphous. Alternatively they are sometimes obtained as crystalline solids, often as hydrates. Penicillins do not usually have sharp melting points, but decompose upon heating to elevated temperatures. Most natural members have a free carboxyl group and commercial preparations are generally either supplied as salts, most frequently as sodium salts, or in zwitterionic form as hydrates, eg, amoxicillin trihydrate [61336-70-7]. The acid strength of the carboxyl group in aqueous solution varies from $pK_{a1} = 2.73$ for oxacillin to $pK_{a1} = 3.06$ for carbenicillin. For zwitterionic penicillins amoxicillin, having $pK_{a1} = 2.67$ and $pK_{a2} = 7.11$, is typical (11).

Table 1. Penicillins[a] in Clinical Use



(4)

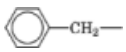
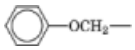
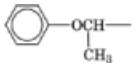
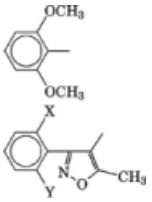
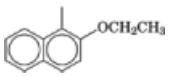
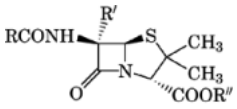
Name	CAS Registry Number	Molecular formula	Structure Reference number	R	R′	R″[b]	Administration Route[c]	Administration Av dose, g/d
			Limited spectrum					
benzyl penicillin (penicillin G)[b]	[61-33-6]	$C_{16}H_{18}N_2O_4S$	**(4)**		H	H	iv im po	3–12[d] 1–7[e] 0.6–6[f]
phenoxymethyl penicillin (penicillin V)	[87-08-1]	$C_{16}H_{18}N_2O_5S$	**(4)**		H	H	po	0.3–6
phenethicillin	[132-93-4]	$C_{17}H_{20}N_2O_5S{\cdot}K$	**(4)**		H	K	po	0.5–1
			β-Lactamase stable					
methicillin	[132-92-3]	$C_{17}H_{20}N_2O_6S{\cdot}Na$	**(4)**		H	Na	im iv	6–12 4–6
oxacillin	[66-79-5]	$C_{19}H_{19}N_3O_5S$		X = H, Y = H	H	H	po, im, iv	1–6
cloxacillin	[61-72-3]	$C_{19}H_{18}ClN_3O_5S$		X = H, Y = Cl	H	H	po	1–6
dicloxacillin	[3116-76-5]	$C_{19}H_{17}Cl_2N_3O_5S$		X = Cl, Y = Cl	H	H	po	1–6
flucloxacillin	[5250-39-5]	$C_{19}H_{17}ClFN_3O_5S$		X = Cl, Y = F	H	H	po	1–6 1–2
nafcillin	[985-16-0]	$C_{21}H_{22}N_2O_5SNa$	**(4)**		H	Na	po	
			Broad spectrum					

Table 1. ***Continued***



(**4**)

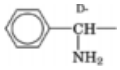
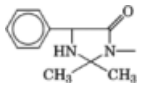
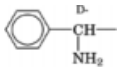
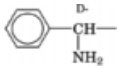
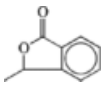
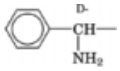
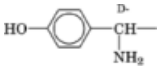
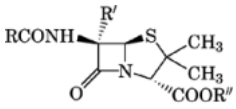
Name	CAS Registry Number	Molecular formula	Structure Reference number	R	R′	R″[b]	Administration Route[c]	Administration Av dose, g/d
ampicillin	[69-53-4]	$C_{16}H_{19}N_3O_4S$	**(4)**		H	H	po, iv, im	1–4
hetacillin[g]	[3511-16-8]	$C_{19}H_{23}N_3O_4S$	**(4)**		H	H		1–4
pivampicillin	[33817-20-8]	$C_{22}H_{29}N_3O_6S$	**4**		H	$CH_2OCOC(CH_3)_3$		1–4
talampicillin	[47747-56-8]	$C_{24}H_{23}N_3O_6S$	**4**		H			1–4
bacampicillin	[50972-17-3]	$C_{21}H_{27}N_3O_7S$	**4**		H		po, iv, im	1–4
ciclacillin	[3485-14-1]	$C_{15}H_{23}N_3O_4S$	**(4)**		H	H	po, iv	1–4
amoxicillin	[26787-78-0]	$C_{16}H_{19}N_3O_5S$	**(4)**		H	H	po	0.75–3

Table 1. ***Continued***



(**4**)

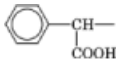
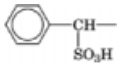
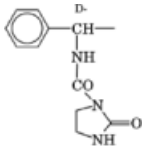
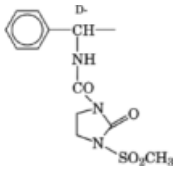
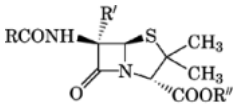
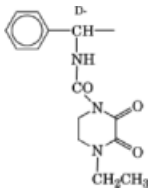
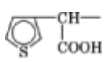
Name	CAS Registry Number	Molecular formula	Structure Reference number	R	R′	R″[b]	Administration Route[c]	Administration Av dose, g/d
carbencillin[h]	[4697-36-3]	$C_{17}H_{18}N_2O_6S$	**(4)**		H	H	iv	to 30
ticarcillin	[34787-01-4]	$C_{15}H_{16}N_2O_6S_2$	**(4)**		H	H	iv	to 20
sulbenicillin	[41744-40-5]	$C_{16}H_{18}N_2O_7S_2$	**(4)**		H	H	iv	to 20
azlocillin	[37091-66-0]	$C_{20}H_{23}N_5O_6S$	**(4)**		H	H	iv	to 20
mezlocillin	[51481-65-3]	$C_{21}H_{25}N_5O_8S_2$	**(4)**		H	H	iv	to 20

Table 1. ***Continued***



(4)

Name	CAS Registry Number	Molecular formula	Structure Reference number	R	R′	R″[b]	Administration Route[c]	Av dose, g/d
piperacillin	[61477-96-1]	$C_{23}H_{27}N_5O_7S$	**(4)**		H	H	iv	to 20
			Directed spectrum β-lactamase stable					
temocillin	[66148-78-5]	$C_{16}H_{18}N_2O_7S$	**(4)**		OCH_3	H	iv	to 20

[a] Structure (**4**) where R, R′, and R″ are as indicated.
[b] Whereas the carboxylic acid is shown for many of these compounds, the majority of the commercial penicillins are sodium salts. Penicillin G is available as the calcium salt [973-53-5], $C_{16}H_{17}N_2O_4S{\cdot}1/s\,Ca$, and as the potassium salt [113-98-4], $C_{16}H_{17}N_2O_4S{\cdot}K$.
[c] Where iv = intravenously, im = intramuscularly, and po = orally.
[d] Corresponds to 5–20 million units.
[e] Corresponds to 2–12 million units.
[f] Corresponds to 1–10 million units.
[g] The R group given is equivalent to the RCONH of **(4)** and attaches directly to the C-6 of the penam ring **(2)**.
[h] Also available as the indanyl ester [26605-69-6], $C_{26}H_{26}N_2O_6SNa$.

2.1. Spectral Characteristics

The infrared stretching frequency of the penicillin β-lactam carbonyl group normally occurs at relatively high frequencies ($1770 - 1815\ cm^{-1}$) as compared to the absorptions for the secondary amide ($1504 - 1695\ cm^{-1}$) and ester ($1720 - 1780\ cm^{-1}$) carbonyl groups. There is little difference between solution and KBr spectra. The nuclear magnetic resonance spectrum of penicillins invariably provides information about the integrity of the ring, attachments to the ring, and the stereochemistry of those attachments. The disposition of the C-5 and C-6 resonances are also characteristic. Thus the proton on the amide-bearing carbon appears as a quartet that collapses to a doublet on D_2O exchange, where $\delta = 5.42 - 6.15$ ppm and $J_{AB}(cis) = 4 - 5$ Hz; $J_{AB}(trans) = 1.5 - 2$ Hz. The proton on the bridgehead carbon appears as a doublet, $\delta = 4.66 - 5.60$; the C-3 proton absorbs in the range $\delta = 3.88 - 4.58$ (10, 12). More recently nmr spectroscopy has also proved to be a valuable tool for detecting and characterizing penicillin metabolites in biofluids (13).

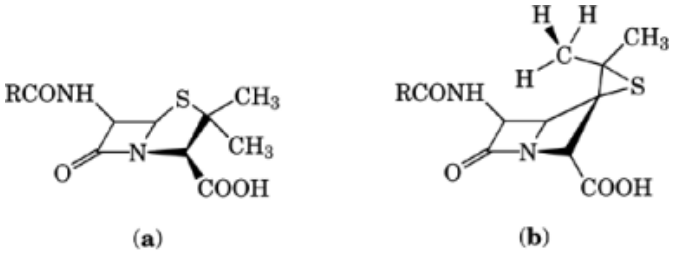


Fig. 1. The penicillin thiazolidine ring: (**a**) open conformation; (**b**) closed conformation.

The carbon-13 nmr features of penicillins have been studied and documented (10, 14). The four sp^3 ring carbons give rise to resonances in order of decreasing chemical shift, C-3, C-5, C-2, and C-6. For C-3 the chemical shift ranges are 73.5–74.4 ppm for alkali metal salts in D_2O and 70.9–71.6 ppm for HCl salts having nonionizable carboxylate functions. The C-5 resonance ranges from 66.0 to 68.7 ppm, and the C-6 resonance from 57.4 to 59.1 ppm, or 60.0 to 64.6 ppm for examples with protonated side chains. The C-2 ranges from 63.9 to 66.0 ppm. The range for the 2α,2β-methyl signals are both narrow: for the high field 2-methyl the range is 26.5–28.0 ppm; and for the low field 2-methyl the range is 29.6–32.5 ppm. The carbonyl carbons give rise to resolved signals in most spectra in the range 167–176 ppm.

The analysis of penicillins by mass spectrometry (qv) has developed with the advent of novel techniques such as fast atom bombardment. The use of soft ionization techniques has enabled the analysis of thermally labile nonvolatile compounds. These techniques have proven extremely valuable in providing abundant molecular weight information from underivatized penicillins, both as free acids and as metal salts (15).

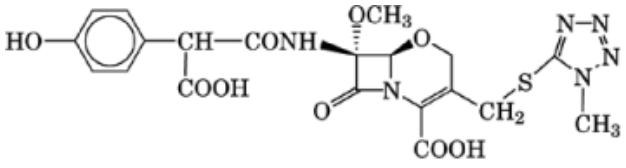
2.2. Stereochemistry

The absolute stereochemistry of the penicillins is 3(*S*):5(*R*):6(*R*) and the stereochemistry of the substituents attached to the ring is designated by the α and β-notations. Thus the β-lactam hydrogens are α, the acylamino group is β, and the penicillin carboxyl is α as in **(1)**. A study of derivatives for which crystal structures have been determined has shown that the derivatives belong to two classes, either open or closed, depending on the conformation of the thiazolidine ring as shown in Figure 1 (16). In both cases puckering of the ring system is relatively pronounced and it is suggested that changes in the nature of the conformation influence biological activity.

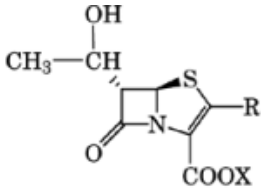
3. Chemical Properties

3.1. Penicillin to Other β-Lactam Conversions

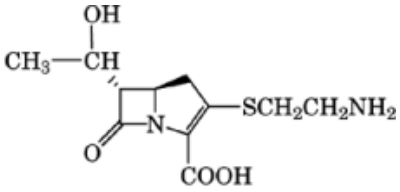
Penicillin G (**1**, R = $C_6H_5CH_2$), penicillin V (**1**, R = $C_6H_5OCH_2$), and 6-APA (**1**, RCO = H) have proven to be cheap and versatile starting materials for a number of conversions to novel β-lactam containing systems. The commercial process for the preparation of 7-aminodeacetoxycephalosporanic acid (7-ADCA) and the deacetoxycephalosporins, cephalexin and cephradine, utilizes penicillin V (17) and the processes for conversion of penicillins into cephalosporins are well documented (18). Moxalactam [64952-97-2] **(5)** and related oxacephems are similarly derived from 6-APA (19).



(5)



(6)



(7)

Synthesis of the penem ring system **(6)** from 6-APA has been described (20) and subsequently syntheses of novel penems having potential biological utility such as FCE 22101 (**6**, R = CH_2OCONH_2, X = Na) [84845-58-9] (21), SCH 29482 (**6**, R = SCH_2CH_3, X = Na) [77646-84-5], and SCH 34343 (**6**, R = $SCH_2CH_2OCONH_2$, X = Na) [94392-35-5] (22) have been documented. Similarly, synthesis of the carbapenem antibiotic thienamycin [59995-64-1] **(7)**, $C_{11}H_{16}N_2O_4S$, has been achieved from 6-APA (23).

4. Synthesis

The only penicillins used in their natural form are benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V). The remainder of penicillins in clinical use are derived from 6-APA and most penicillins having useful biological properties have resulted from acylation of 6-APA using standard procedures.

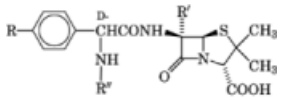
A variety of coupling methods have been employed including: acid chlorides, mixed anhydrides, mixed sulfonic acid anhydrides, *N,N*-dicyclohexylcarbodiimide and similar condensing agents, activated esters with *N*-hydroxysuccinimide, and *N*-hydroxybenzotriazole together with other acylating agents commonly used in peptide synthesis. The choice of coupling reaction is invariably dependent on the side chain. The efficiency of the reaction varies considerably between side chains so that optimization of the coupling procedure is often a matter of trial and error.

The use of protecting groups is common in penicillin chemistry: the amino function is normally protected by a trityl, benzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, trichloroethyloxycarbonyl, or trimethylsilyl group; and the carboxylic acid is usually protected as a benzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, or trichloroethyl ester. Acylations may thus be carried out in aqueous or nonaqueous media with subsequent removal of the protecting group as required. Use of a tertiary base such as triethylamine is common in anhydrous reactions. Aqueous

systems frequently utilize acetone–water mixtures in the presence of sodium bicarbonate. The resulting penicillins are usually isolated by the partitioning of the product as its free acid into a water-immiscible organic solvent and the salts or other impurities into water. The penicillins can be precipitated from organic solution as amine salts, or as alkali metal salts. Potassium or sodium ethylhexanoate dissolved in lower aliphatic alcohols may be used to effect purification. Alkali metal salts may be further purified by use of ion-exchange resins, eg, Diaion HP-20SS, and the final product isolated by freeze-drying (lyophilization), spray-drying, precipitation, or occasionally by crystallization.

After the influx of several α-amino penicillins such as ampicillin (Table 1) and related analogues, and the β-lactamase stable isoxazolyl penicillins in the 1950s and early 1960s, attention turned to identifying derivatives having a broader spectrum of activity. Carbenicillin and later, ticarcillin, reached the marketplace by the early 1970s. Effort then focused on the acyl and ureido ampicillin derivatives and culminated in the commercialization first of azlocillin and mezlocillin, then of piperacillin. Many thousands of derivatives were synthesized and some of the more active examples that have made little or no commercial impact are shown in Tables 2 and 3.

Table 2. α-Amino, Acyl, or Ureido Penicillins[a] Under Investigation or Exhibiting Limited Clinical Utility



(8)

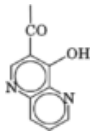
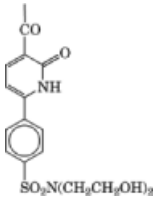
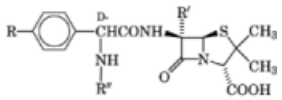
Name	CAS Registry Number	Molecular formula	R	R′	R″	Originating company	Status[b]	Structure Reference Number
apalcillin	[63469-19-2	$C_{25}H_{23}N_5O_6S$	H	H		Sumitomo	C	**(8)**
piridacillin (Cl-867)	[69414-41-1]	$C_{32}H_{35}N_5O_{11}S_2$	OH	H		Warner-Lambert	N	**(8)**

Table 2. ***Continued***



(8)

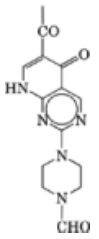
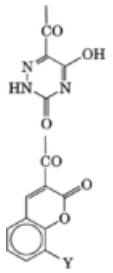
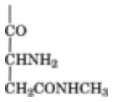
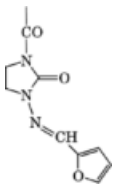
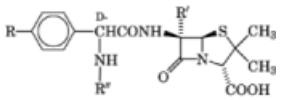
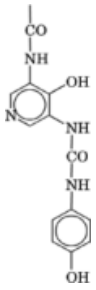
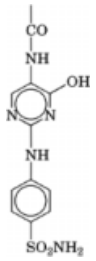
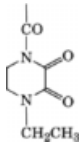
Name	CAS Registry Number	Molecular formula	R	R′	R″	Originating company	Status[b]	Structure Reference Number
PL-385	[85550-66-9]	$C_{29}H_{30}N_8O_8S$	OH	H		Dianippon	N	**(8)**
BLP-1908	[65742-38-3]	$C_{20}H_{20}N_6O_8S$	OH	H		Bristol	N	**(8)**
TEI 1194	[67609-13-6]	$C_{26}H_{23}N_3O_7S{\cdot}Na$	H	H	Y = H	Teijin	N	
TEI 2012	[71344-34-8]	$C_{26}H_{23}N_3O_8S{\cdot}Na$	H	H	Y = OH	Teijin	N	
aspoxicillin (TA058)	[63358-49-6]	$C_{21}H_{27}N_5O_7S$	OH	H		Tanabe	I	**(8)**
furazlocillin	[66327-51-3]	$C_{25}H_{26}N_6O_8S$	H	H		Bayer	C	**(8)**

Table 2. ***Continued***



(8)

Name	CAS Registry Number	Molecular formula	R	R′	R″	Originating company	Status[b]	Structure Reference Number
EMD 39734		$C_{29}H_{29}N_7O_9S$	OH	H		E. Merck	N	**(8)**
VX-VC-43	[82509-56-6]	$C_{27}H_{28}N_8O_9S_2$	H	H		Thomae	N	**(8)**
lenampicillin[c]	[86273-18-9][c]	$C_{21}H_{23}N_3O_7S$[c]	H	H	H	Kanebo	C	
formidacillin (BRL 36650)	[94425-13-5]	$C_{24}H_{28}N_6D_{10}S{\cdot}Na$	3,4 di-OH	NHCHO		Beecham	N	**(8)**

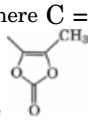
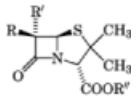
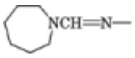
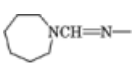
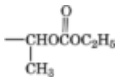
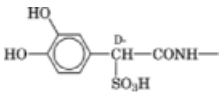
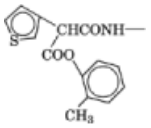
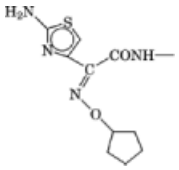
[a]Structure **(8)** where R, R′, and R″ are as indicated.
[b]Drug status where C = in clinical use, I = investigational, and N = not progressed.
[c]Represents the  ester.

Table 3. Other Penicillins[a] Under Investigation or Exhibiting Limited Clinical Utility



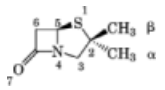
(9)

Name	CAS Registry Number	Molecular formula	R	R′	R″	Originating company	Status[b]	Structure Reference Number
mecillinam	[32887-01-7]	$C_{15}H_{23}N_3O_2S$		H	H	Leo	C	**(9)**
bacmecillinam	[50846-45-2]	$C_{20}H_{31}N_3O_6S$		H		Kyowa	I	**9**
BRL 28917	[85621-68-7]	$C_{17}H_{20}N_2O_{10}S_2$		OCH_3	H	Beecham	N	**(9)**
BRL 20330	[78968-21-5]	$C_{23}H_{24}N_2O_7S_2$		OCH_3	H	Beecham	N	**(9)**
BRL 44154	[110717-44-7]	$C_{19}H_{24}N_5O_6S_2$		H	H	Beecham	I	**(9)**

[a]Structures **(9)**, where R, R′, and R″ are as indicated.
[b]Drug status where C = in clinical use, I = investigational, and N = not progressed.

Examples of the acyl ampicillin series found in Table 2 are apalcillin (24), piridacillin (25), PL-385 (26), BLP-1908 (27), the Teijin examples TEI 1194 and TEI 2012 (28), and aspoxicillin (29). Other members of the ureido series of penicillins, of which azlocillin, mezlocillin, and piperacillin (Table 1) are commercial examples, are furazlocillin, EMD 39734 (30), and VX-VC-43 (31). During the 1970s the amidino penicillin mecillinam (Table 3), which possesses an unusual nonacyl side-chain substituent and a spectrum of activity limited to gram-negative organisms, was prepared. More recently a further example of a different type of acylated β-lactamase stable 6-APA derivative, BRL 44154, has been documented (32). BRL 44154 exhibits high activity against gram-positive organisms and methicillin-resistant staphylococci (MRSA).

Table 4. Chemical Modification of Penicillins



		Modification
Position	From	To
1	S	SO, SO_2, $\overset{+}{S}CH_3$
2	$(CH_3)_2$	$(H)_2$, cycloalkyl, 4-piperidinyl, $=CH_2$ α-CH_2 halogen, β-CH_2 halogen, α-CHF_2, β-CHF_2 β-$COCH_3$, β-CH_2OR, β-CH_2OH, β-CHO, β-vinyl β-CON$(CH_3)_2$, β- CH, β-CH=CHCOOR $\beta-CH=CHCN$, $\beta-CH=CH-$ tetrazole
3	COOH	H, COOR, $COOCH_2OCOR$, COR, COOOCOR, CO_2SiR_3, CON_3, CH_2OH, CH_2OR, CH_2COOH, $COCHN_2$, CN, $PO(OCH_3)OH$, $PO(OCH_3)_2$, CHO, OH, NCO, CH_2N_3, CH_2NR_2, COSH, CH_2COOH, CH_2CH_2COOH, tetrazolyl, diketopiperazinyl
2,3		cyclopropyl
6β	RCONH	H, NH_2, R′CONH, $R''N=C=N$, $ArC=N$, R_2N, RNH, $CH(OH)CH_3$, CH_2OH, CH_2NH_2, OH, halogen, 6-oxopenam
6α	H	CH_3 OCH_3, NH_2, RCONH, OH, CH_2OH, CH_2Cl, CH_2F, D, CH(OH)F, CH_2NH_2, SCH_3, $S(O)CH_3$, $CH_2CO_2CH_3$, CH_2Ar, COOH, COOR, NC, $NHCH_3$, $CH=CH_2$, CN, OCH_2CH_3, $CH=CH-CN$, $CH=CHCHO$, NHC_6H_5, $NHNHCOOCH_3$, $NHOCH_3$, N(CHO)NHCHO, $NHCOOCH_3$, $NHCOCF_3$, $NHSO_2CH_3$, $N(OCH_3)CHO$, $NHCONHCH_3$, $N(CH_3)_2$, $N(CH_3)CHO$, NHNHCHO, $N(OH)CH_3$, $COCH_3$, CH_2OCH_3, $CH_2OSO_2CH_3$, CHO, ONHCHO, ONH_2, C_6H_5, tetrazolyl, succinimido-oxy, $CH(OH)OCH_3$, $CONH_2$, CH(OH)Ar, CH_2CH_2CN
7	O	S

4.1. Chemical Modification

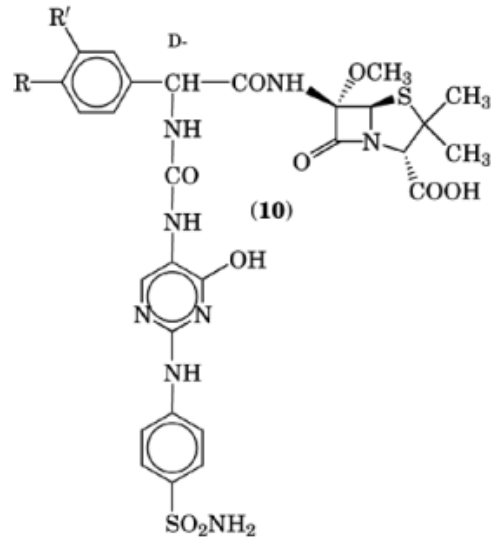
Chemical modification of most positions in the penicillin nucleus have been carried out and these are summarized in Table 4. Apart from acylation of 6-APA, few of these modifications have proven profitable in terms of improving the biological properties of the derived penicillins. However, one of the modifications that has led to beneficial properties is substitution at the 6α-position.

4.1.1. 6α-Substituents

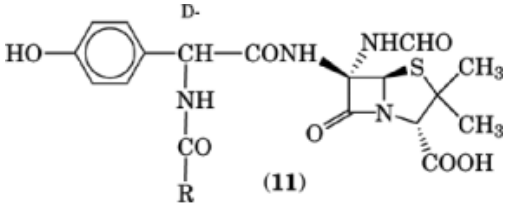
In the early 1970s the discovery of the cephamycins, stabilized to attack by β-lactamase through the presence of 7α-methoxy substituents, stimulated a parallel investigation of penicillins substituted by methoxy at the 6α-position (33). This study led to the identification of the directed spectrum β-lactamase stable temocillin, (Table 1) (34), the stability of which results from the combination of the 6α-methoxy group and the dicarboxylic acid functionality. Temocillin possessed high and prolonged serum levels in human volunteers but was directed in its spectrum of activity to gram-negative organisms. Whereas temocillin was active only by the parenteral route, the *o*-methylphenyl ester prodrug BRL 20330 (Table 3) was found to be absorbed orally (35). Replacement of the side-chain carboxylic acid by sulfonic acid led to BRL 28917 (Table 3), a β-lactamase stable penicillin with high activity against *Pseudomonas sp.* (36).

Substitution of penicillins by 6α-methoxy was found to be compatible with an α-acidic side chain in terms of antibacterial activity, but less beneficial when the side chain contained an α-acyl or α-ureido substituent.

However, analogues of the ureido penicillin VX-VC-43 (Table 2) containing a 6α-methoxy substituent **(10)** were found to combine good stability to β-lactamase and relatively high antibacterial activity (37). Following an extensive program to identify other 6α-substituents that would stabilize the acyl and ureido series of penicillins, the 6α-formamido series **(11)** represented by formidacillin (BRL 36650) (Table 2) was developed (38).

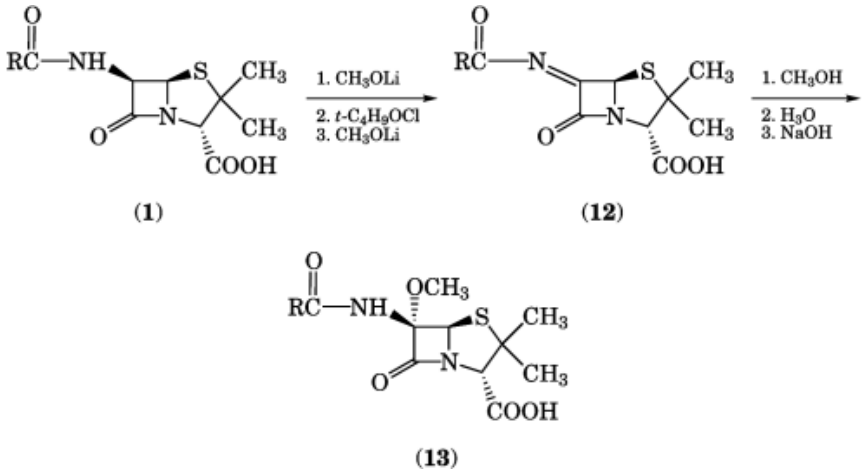


(10)



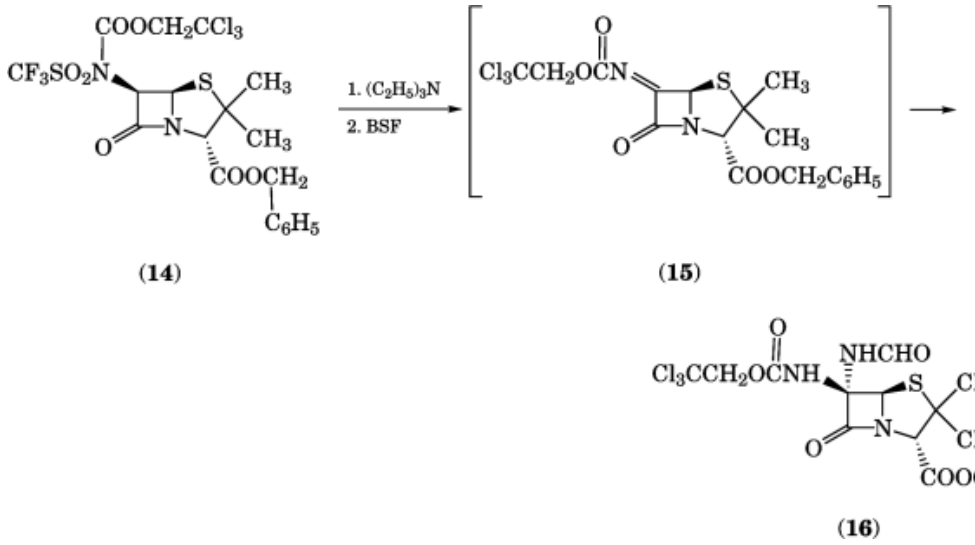
(11)

The early chemistry leading to these derivatives was originally carried out via the 6α-(methylthio) derivative **(17)** which was prepared by way of a Schiff's base (39). The 6α-thiomethyl group could then be displaced by various nucleophiles giving rise to 6α-methoxy or other 6α-substituted penicillins. A stereo-specific one-step introduction of a methoxy group at C-6 in penicillins provided a simple entry to 6α-methoxy penicillins (40) in yields ranging from 50–62%.



(1) (12) (13)

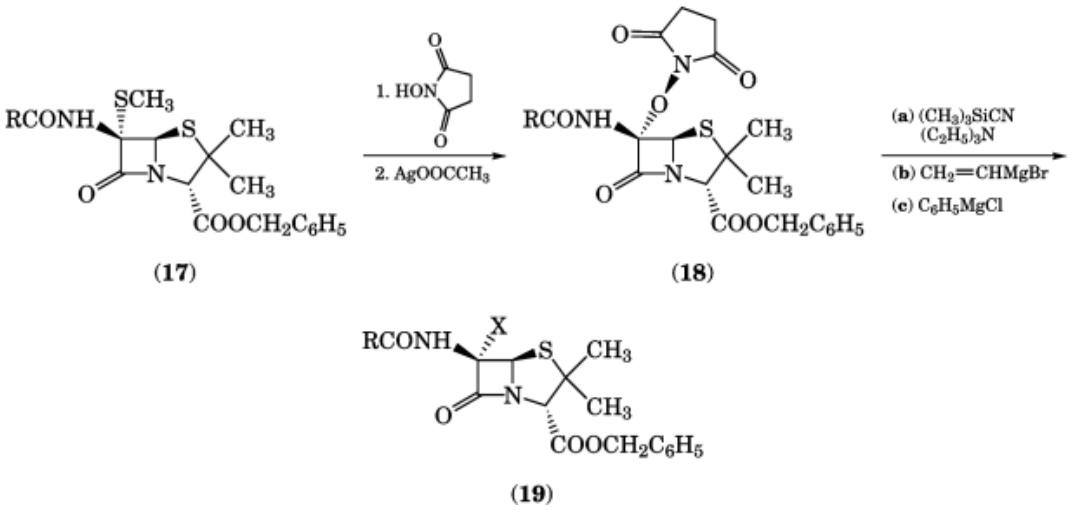
After formation of the acylimine **(12)**, methanol adds to the less sterically hindered α-face of the molecule with high selectivity to provide **(13)**. A further direct incorporation of a 6α-methoxy group (41) and subsequently a 6α-formamido group into penicillin has been achieved using trifluoromethanesulfonamides of type **(14)** (42).



(14) (15) (16)

Preparation of **(14)** and treatment with *N,N*-bis(trimethylsily)formamide (BSF) and triethylamine provided **(16)** in 84% yield via the putative imine intermediate **(15)**. The trifluoromethyl group could be replaced by other moieties such as 2,4,5 trichlorophenyl, pentafluorophenyl, or nonafluorobutyl with increasing effectiveness.

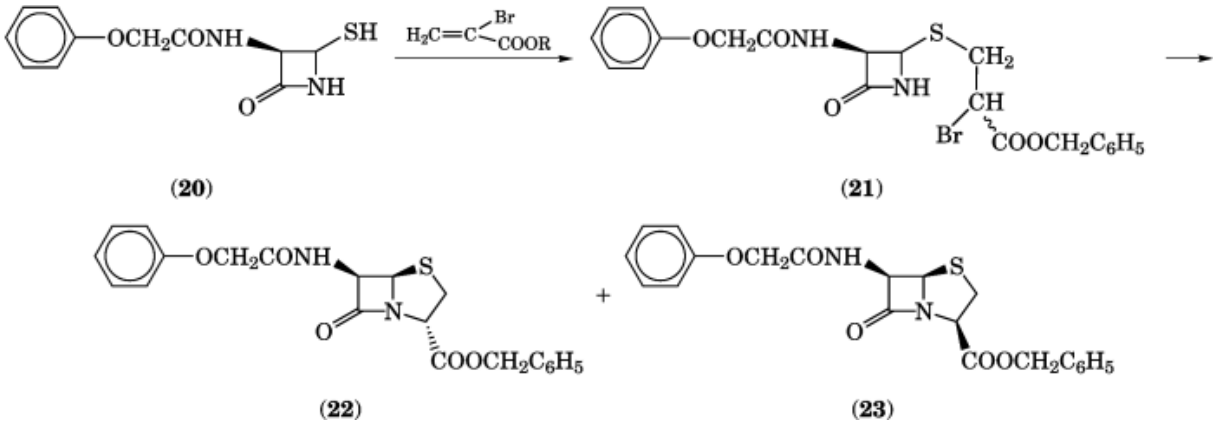
Further versatility was added to the range of substituents available for introduction into the 6α-position by use of the 6α(succinimido-oxy) derivative **(18)** prepared by treatment of the 6α-(methylthio) derivative **(17)** with *N*-hydroxy-succinimide and silver(I) acetate in dimethylformamide in virtually quantitative yield. In this way the 6α-cyanopenicillin (**19**, X = CN), 6α-vinylpenicillin (**19**, X = $CH{=}CH_2$) and 6α-phenylpenicillin (**19**, X = C_6H_5) could be prepared in high yield (43).



(17) (18) (19)

4.1.2. 2α-2β-Substituents

Modifications at the 2-position of the penicillin nucleus has led to benefits in the biological properties of the modified penicillins. The series that has generated the most interest is the bisnorpenicillins depicted by **(22)**. Synthesis of these derivatives employs as a key intermediate the 4-mercaptoazetidin-2-one **(20)** which in turn is generated from penicillin V (**1**, R = $C_6H_5OCH_2$) (44).



(20) (21) (22) (23)

Reaction of **(20)** with ethyl 2-bromoacrylate in hexamethylphosphorous triamide (HMPT) in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) yielded **(22)** in moderate yield. Use of potassium carbonate in DMF afforded a mixture of C-3 epimeric bisnorpenicillanates **(22)** and **(23)** (45). Removal of the phenoxyacetyl side chain was effected by Delft cleavage namely, treatment with phosphorus pentachloride in methylene chloride containing *N*-methylmorpholine followed by methanol and water. Acylation was then carried out using standard procedures. Bisnorampicillin was found to be less active than ampicillin, but bisnorpiperacillin proved to be similar in activity to piperacillin. Bisnorpiperacillin possesses a slightly broader spectrum of activity than the unmodified compound because of increased stability towards bacterial β-lactamases (46). Studies have shown that enhanced β-lactamase stability is a general property of acyl and ureido bisnorpenicillin derivatives (47). Synthesis of cycloalkanespiro-2-bisnorpenicillins led to a further series of nuclear modified penicillins:

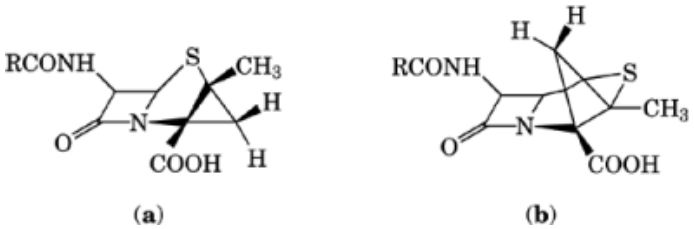


Fig. 2. Structures of (**a**) (2,3)-α-methylenepenams, and (**b**) (2,3)-β-methylenepenams.

spirocyclohexane, spirocyclopentane, spirocyclobutane, and spirocyclopropane analogues have been prepared. Only those containing the spirocyclopropane ring system provided analogues that had antibacterial properties comparable to those of the corresponding penicillins (48). Other modifications of the C-2 position are shown in Table 4.

4.1.3. 2,3-Methylenepenams

The penam nucleus is also able to assume both of the ring conformations depicted in Figure 1 and the (2,3)-α-and (2,3),-β-methylenepenams shown in Figure 2 may be regarded as penicillin analogues (49). Studies involving the (2,3)-methylenepenams, when R = $CH_2C_6H_5$, and analogues revealed that the (2,3)α-methylenepenam penetrated the outer membrane of *E. coli* more readily than did the penicillin G analogue (50). Intrinsically, the alpha compound was found to have similar activity to that of penicillin G. By comparison the β-methylene analogue had poor activity.

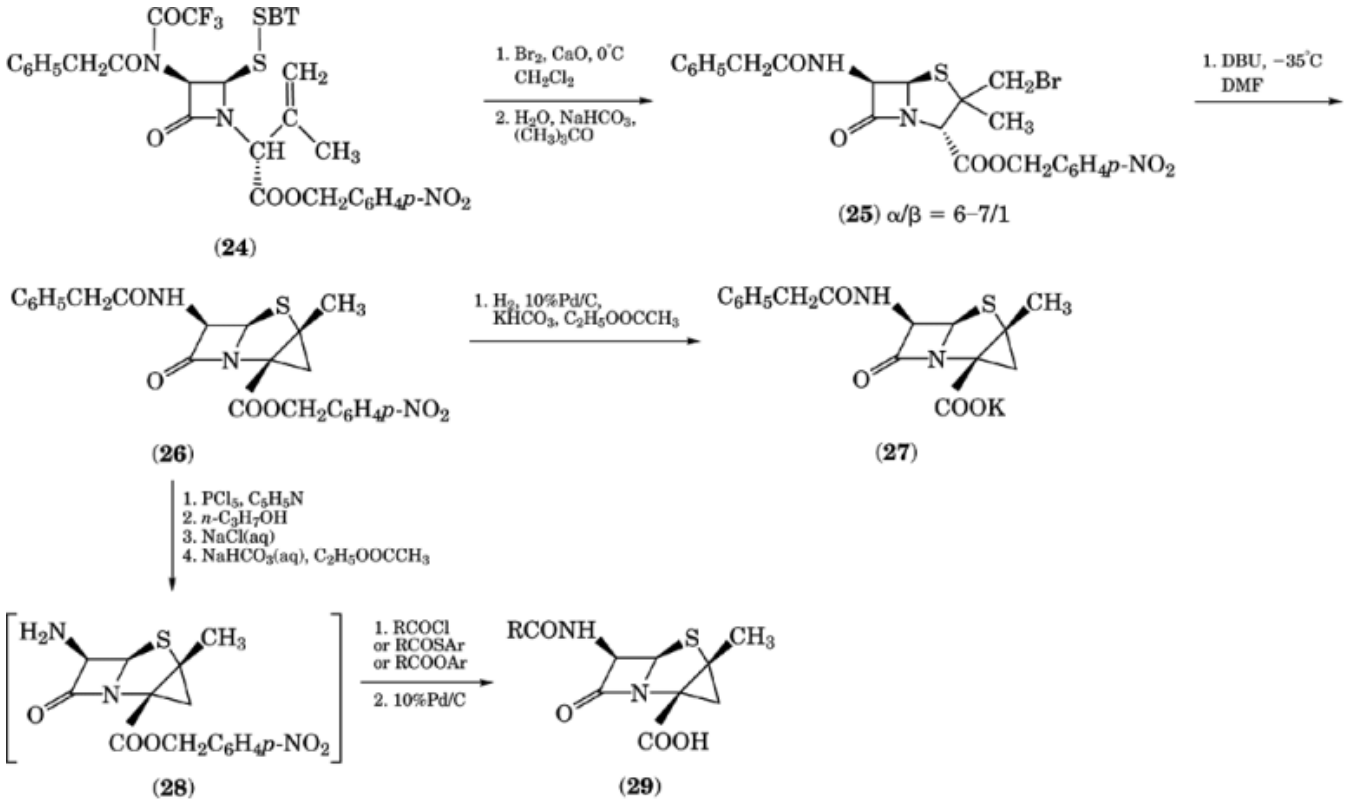
Later investigations led to improved synthetic routes and analogues such as those shown in Figure 3 (51). Conversion of the mixed imide (**24**) to the bromide (**25**) provided a mixture of α- and β-bromomethylpenicillins in which the α-isomer predominated. 1,8-Diazabicyclo[5,4,0]undec-7-ene(DBU)-mediated cyclization led to the (2,3)-methylenepenicillanic acid (**26**) which was converted by catalytic hydrogenation followed by reverse phase chromatography to the potassium salt (**27**). The preparation of analogues (**29**) was carried out by reaction of (**26**) with 1.1 equivalents of PCl_5 and 1.9 equivalents of dry pyridine in chloroform followed by treatment with *n*-propanol and saturated aqueous sodium chloride solution. The resulting amine (**28**) was used without further purification and then transformed into derivatives (**29**) using suitably activated acids followed by hydrogenolysis using 10% palladium on carbon.

In general the (2,3)-α-methylenepenams were found to be chemically reactive and biologically active in contrast to the β-methylene counterparts supporting the hypothesis that the open conformation of penicillins is the biologically active form. In (2,3)-α-methylenepenams the absolute configuration at C-2 is opposite that of the naturally occurring penicillins placing the carboxyl group in a position more akin to that found in the cephalosporins. The compounds were found to be more susceptible to cephalosporinase than penicillinase. The (2,3)-α-methylene penicillin G analogue was found to be more selective in the inhibition of PBP 3 than was the β-analogue. It also bound more effectively to PBP 2 of *S. aureus* than the β-isomer (52).

Biochemical studies showed that the α-aminoadipoyl analogue derived from (2,3)-β-methylenepenam was not a substrate for expandase activity but rather, it was a potent reversible inhibitor of the ring expansion of α-aminoadipoyl-penicillin into deacetoxycephalosporanic acid by the expandase enzyme (53).

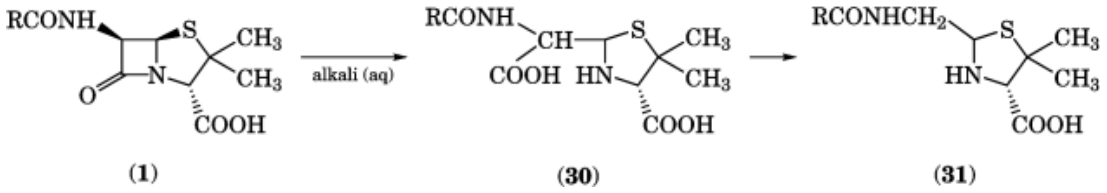
4.2. Degradation

Penicillins are rapidly hydrolyzed by aqueous alkali to the corresponding penicilloic acids **(30)** which are stable as salts, but which decarboxylate on acidification to yield penilloic acids **(31)**.



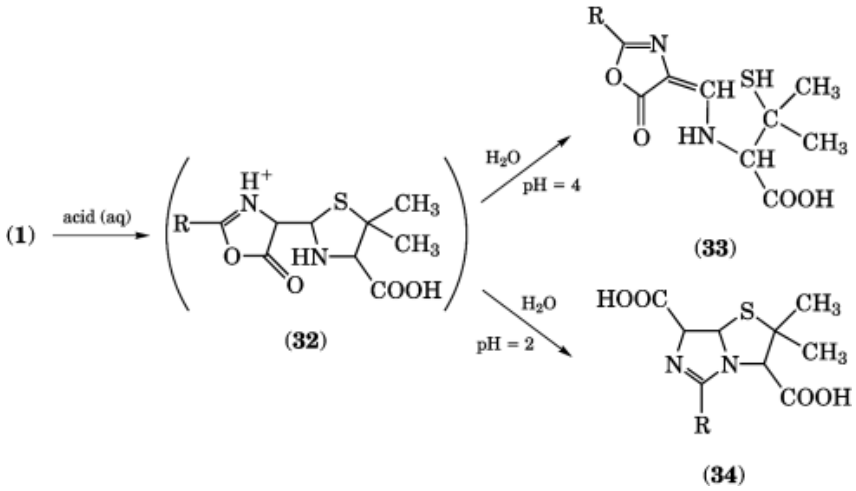
(24) (26) (27) (28) (29)

Fig. 3. Reaction scheme for the synthesis of (2,3)-α-methylenepenams where BT is 2-benzthiazolyl, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.



(1) (30) (31)

Penicillins are also degraded by aqueous acids via initial reaction of the sidechain carbonyl group with the β-lactam. Penicillenic acids **(33)** are obtained when hydrolysis is carried out at pH 4, penillic acids **(34)** at pH 2.



Electron-withdrawing groups at the α-position of the 6-acyl substituent stabilize the compounds to attack by acids. Thus phenoxymethylpenicillin and ampicillin are more stable to acid and more efficiently absorbed by the oral route than is benzyl penicillin. Degradation of temocillin (Table 1), a 6α-methoxy-penicillin, occurs in a way similar to that shown for **(31)**, **(33)**, or **(34)**. Although temocillin exhibits good stability in mild aqueous acid or base, in stronger acid the corresponding methoxypenillic acid is formed and under alkaline conditions the methoxypenicilloic acid is generated together with the C-5 epimer (54). Degradation of BRL 36650 (**35**) shown in Figure 4, containing a 6α-formamido substituent, occurs quite readily under mildly acidic aqueous conditions. Cleavage of the C-5–C-6 bond leads to two fragments, the formamido acid (**39**) and *N*-formyl penicillamine (**40**) presumably generated via the putative penicillenic acid intermediate (**36**) (55). The presence of the electron-withdrawing 6α-formamido group serves to accelerate degradation and leads to products that have been detected for penicillins in aqueous solution left over a longer period of time.

5. Biological Properties

5.1. Structure-Activity Relationships

Biological evaluation of penicillins yields information such as *in vitro* and *in vivo* antibacterial activities, minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), protective effectiveness in laboratory animals (PD_{50}), and pharmacokinetic characteristics including efficiency of absorption, serum levels, tissue distribution, urinary excretion, metabolism, serum binding, serum and tissue activation, biliary excretion, recycling, etc. Penicillins are also tested for ability to resist inactivation by β-lactamase produced by both gram-positive and gram-negative bacteria.

Table 5 gives a range of activities for some modified penicillins. Penicillin G remains probably the most active penicillin against gram-positive organisms. However, the majority of *Staphylococcus aureus* strains are resistant to penicillin by virtue of β-lactamase production. The β-lactamase resistant penicillins such as oxacillin, cloxacillin, flucloxacillin, and nafcillin are active against most penicillin-resistant *Staphylococci* but lack activity against methicillin-resistant *Staphylococci* (MRSA) and the majority of gram-negative organisms.

Ampicillin and its congeners amoxicillin, bacampicillin, and ciclacillin, have largely similar antibacterial spectra, exhibiting activity against both penicillin sensitive gram-positive and gram-negative microorganisms. The susceptibility of ampicillin or amoxicillin to β-lactamase may be overcome by combination with

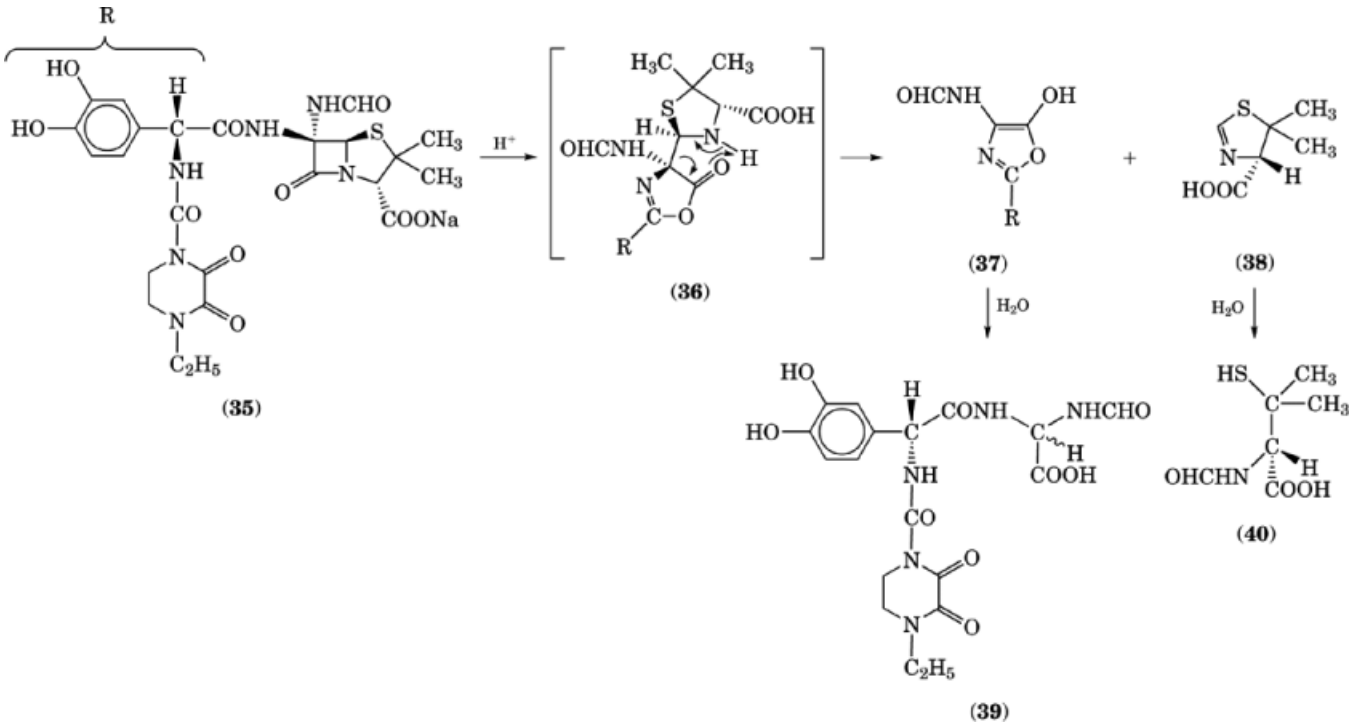


Fig. 4. Acid degradation of BRL 36650.

aβ-lactamase inhibitor. Clavulanic acid and sulbactam are two such β-lactamase inhibitors in clinical use. The products Augmentin, a combination of clavulanic acid and amoxycillin for oral use primarily, and Unasyn, a combination of sulbactam and ampicillin for use by injection, are highly active against both gram-positive aerobic and anaerobic organisms in addition to many important gram-negative pathogens. Carbenicillin and ticarcillin possess moderate broad-spectrum activity and were the first penicillins to show activity against *Pseudomonas* species. Azlocillin, mezlocillin, and piperacillin possess largely the same characteristics but have slightly greater potency against many gram-negative species. Temocillin is the first penicillin to possess a high level of activity against gram-negative organisms, notably the *Enterobacteriaceae*, as well as excellent β-lactamase stability. The introduction of the *6α-methoxy* group and the concomitant β-lactamase stability compromises activity against both gram-positive organisms and *Pseudomonas* species. Similarly BRL 36650, having the 6α-formamido substituent, exhibits high bacterial β-lactamase stability. Some activity is retained against most species of *Streptococci* but the compound is inactive against *Staphylococci*. BRL 36650 is highly potent against most gram-negative organisms including refractory gram-negative species such as *Acinetobacter* and *Pseudomonas*. The level of potency is much greater than either that of ticarcillin or piperacillin (56).

The pharmacology of penicillins differs markedly from compound to compound but has been well reviewed (57). The majority of derivatives, including penicillin G and the antipseudomonal penicillins, are unstable in gastric acid and are not available orally. The isoxazolyl penicillins are relatively acid stable but not consistently well absorbed by the oral route. Nafcillin and oxacillin are poorly absorbed orally; cloxacillin, dicloxacillin, and flucloxacillin are more reliable. Penicillin V, ampicillin, and particularly amoxicillin are relatively well absorbed orally. Esters of ampicillin such as bacampicillin, pivampicillin, and talampicillin improve the level of oral absorption of ampicillin to that achieved by amoxicillin. Absorption can be diminished by food after oral

Table 5. Antibacterial Activity[a] of Modified Penicillins

Organism	Penicillin G	Ampicillin	Amox + clav[b]	Ox/Naf[c]	BRL 44154	Carb/Ticar[d]	Azlo/Mezlo/Piper[e]	Temocillin	BRL 36650
				Gram-positive					
Staphylococcus (−)[f]	++	++	++	++	++	+	++	−	−
Staphylococcus (+)[g]	−	−	++	++	++	−	−	−	−
Staphylococcus (MRSA)[h]	−	−	−	−	+	−	−	−	−
Streptococcus pyogenes	++	++	++	+	++	+	++	−	+
Streptococcus pneumoniae	++	++	++	+	++	+	++	−	+
Enterococcus	++	++	++	−	−	+	++	−	−
Bacterioides fragilis	−	+	++	−	−	+	+	−	−
other anaerobes	−	+	++	−	−	+	+	−	−
				Gram-negative					
E. coli	−	+	++	−	+	+	++	++	++
Klebsiella	−	−	++	−	−	−	+	++	++
Proteus mirabilis	−	++	++	−	++	++	++	++	++
other Proteus	−	−	−	−	−	+	++	++	++
Enterobacter	−	−	−	−	−	+	++	++	++
Pseudomonas aeruginosa	−	−	−	−	±	+	±	−	++
other Pseudomonas species	−	−	−	−	−	−	+	−	++

[a] ++ = very active at low concentrations; + = moderately active against most strains or active only at high concentrations; and − = inactive against the majority of strains.
[b] A mixture of amoxicillin and clavulanic acid.
[c] Activity represents that of both oxacillin and nafcillin.
[d] Activity represents that of both carbenicillin and ticarcillin.
[e] Activity represents that of azlocillin, mezlocillin, and piperacillin.
[f] *Staphylococcus* (−) = β−lactamase negative.
[g] *Staphylococcus* (+) = β−lactamase positive.
[h] *Staphylococcus* (MRSA) = methicillin − resistant *Staphylococcus aureus*.

administration, however, and peak blood levels, usually achieved after 1 to 2 h, are somewhat delayed after ingestion of food.

Parenteral penicillins generally are virtually 100% available and half-lives vary from one-half hour for nafcillin and oxacillin to over an hour for amoxicillin and ticarcillin. The exception to this rule is temocillin which has an unusually long half-life of 4.5–5 h. Long-acting preparations of penicillin G are available as the procaine and benzathine derivatives. When these derivatives are administered intramuscularly, they provide effective serum levels for 12–24 and 3–4 weeks, respectively. Penicillins are eliminated by active secretion by renal tubular epithelial cells. This secretion can be blocked by probenicid [57-66-9], $C_{13}H_{19}NO_4S$, resulting in higher blood levels and prolonged serum half-lives. Most penicillins distribute well to body cavities and kinetics are usually linear. Urinary concentrations of penicillins are normally high, even in the presence of renal failure. Intracellular penetration of penicillins because of their lipid insolubility is invariably low. They also penetrate poorly into the central nervous system and the eye. Biliary concentrations of penicillins generally exceed serum concentrations in the presence of adequate bile flow.

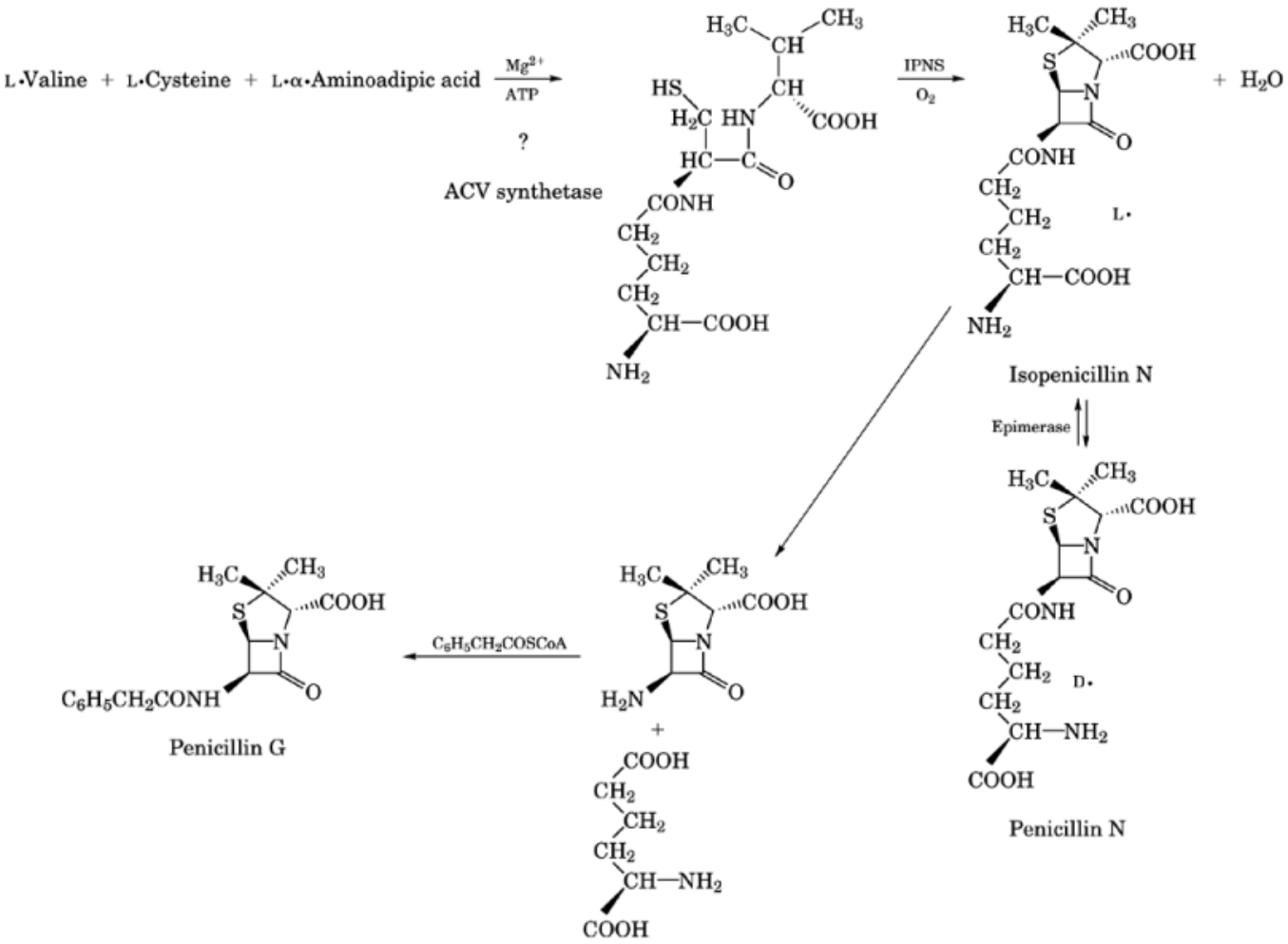


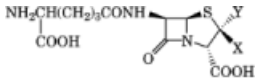
Fig. 5. Biosynthesis of penicillins when ACV is aminoadipoly cysteinyl valine and IPNS is isopenicillin N synthase and $C_6H_5CH_2COSCoA$ represents benzyl coenzyme A. ACV synthetase is thought to catalyze the first step of this reaction sequence.(Courtesy of J. E. Baldwin, Royal Society of Chemistry.)

The penicillins in general, are renowned for their lack of toxicity. The most common adverse effect of the use of penicillins is an allergic reaction which can change from a mild rash to fatal anaphylactic shock in rare cases. All penicillins cross the placenta and are excreted in maternal milk. However, the relative freedom from toxicity renders these compounds valuable agents during pregnancy and lactation.

5.2. Biosynthesis

The microbial synthesis of penicillins from eukaryotes such as *C. acremonium* and *P. chrysogenum* has been comprehensively reviewed (58). In essence the biosynthesis of penicillins is described in Figure 5 although certain stages have yet to be fully characterized. Products are isopenicillin N, penicillin G, and penicillin N [525-94-0], $C_{14}H_{21}N_3O_6S$.

Table 6. Modified Penicillins[a] Prepared Using IPNS[b]



(42)

X	Y	X	Y
CH_3	H	CH_3	CH_2OH
H	CH_3	H	CH_2OH
CH_3	C_2H_5	CH_3	OCH_3
C_2H_5	CH_3		
—CH=CH_2	H	H	C_2H_5
H	—CH=CH_2	H	
CH_3	—CH=CH_2	H	—C=C=CH_2

[a] Structure **(42)** where X and Y are as indicated.
[b] Ref. 58.

The key enzyme in this sequence, isopenicillin N synthase (IPNS), has been purified from *E. coli* (59) and the recombinant enzyme shown to be a single polypeptide of 336 amino acids containing two cysteines, numbers 106 and 255 from the *N*-terminus, and probably a ferrous ion in a nonheme environment. The enzyme has been crystallized and studies undertaken to obtain suitably sized crystals for diffraction studies.

The IPNS enzyme has also been shown to recognize modified tripeptides. The synthesis of a range of tripeptides, other than aminoadipoyl cysteinyl valine (ACV) (Table 6), has given rise to a selection of modified penicillins using IPNS as a means of cyclizing the tripeptide (58).

5.3. Mode of Action

Penicillins exert their antibacterial effect by inhibiting the high molecular weight penicillin binding proteins (PBPs) that are implicated in the final stages of peptidoglycan synthesis (60). These PBPs have been extensively studied in *E. coli* in terms of the relative affinity of the drug for the three physiologically important proteins. Inhibition of PBP-1 causes rapid cell lysis whereas inhibition of PBP-2 and PBP-3 results in the formation of spherical and filamentous cells, respectively. PBP-1 may be further subdivided into PBPs 1*a* and 1*b*. PBP-1*a* is usually highly sensitive to penicillins and it is the effective inhibition of PBP-1*b* that is regarded as the more crucial stage leading to cell lysis. The low molecular weight PBPs 4, 5, and 6 of *E. coli* are believed to be nonessential for cell survival and therefore not considered of major importance in the killing mechanism of penicillins (61).

The changes that occur when an organism is exposed to different concentrations of penicillin provides a characteristic morphological response that can be particularly well demonstrated in the scanning electron microscope. Penicillin G binds preferentially to PBP 3 causing filamentation. Most penicillins bind principally to PBPs 1 and 3 leading to filamentous forms. Exceptions are amoxicillin and mecillinam. Amoxicillin binds to PBPs 1 and 3 but at low concentrations forms spheroplasts and at higher concentrations, filaments. Mecillinam binds only to PBP 2 producing ovoid and later spherical cells. The novel penicillin BRL 44154 has been shown to bind to PBPs 1 and 3 and also to PBP 2′, the protein responsible for the resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) (62).

Rapid progress is being made in the protein crystallography of low molecular weight PBPs and demonstration of the feasibility of obtaining water-soluble forms of high molecular weight PBPs suggests that crystallization of the latter proteins can be achieved. These enzymes are inserted into the cytoplasmic membrane only

at their amino termini and water-soluble forms are expected to be suitable for crystallization and x-ray analysis (57). Preliminary investigations involving a β-lactam-sensitive, bifunctional D-alanyl-carboxypeptidase–transpeptidase (C Pase–T Pase)from *Streptomyces* R61 have identified the three-dimensional structure and catalytic site of interaction with penicillins (63).

6. Production, Manufacture, and Processing

Most methods used for the production of the commercially important α-amino penicillins, such as ampicillin and amoxicillin, are based on modifications of an enamine process employing the appropriate phenylglycine and methylacetoacetate followed by coupling with 6-APA (64). Other aspects of the fermentation, strain maintenance, equipment, inoculum development, media, and procedures used in the production of penicillin are well covered in previous editions of the *Encyclopedia.* Developments in these areas have been reviewed (65).

7. Economic Aspects

Worldwide retail antibiotic sales in 1986 were approximately $11 billion of which penicillins comprised approximately $2.5 billion (66). Preparations containing ampicillin are estimated at $800 million whereas those containing amoxicillin are estimated at $1,020 million. Total sales include sales of ampicillin esters and the ureidopenicillins derived from ampicillin. Total sales of penicillins, including semisynthetic penicillins in the United States in 1987, were $25 million (67). Sales of amoxicillin, the largest single selling penicillin, were approximately $350 million.

The volume of bulk ampicillin produced was 3,700 t, valued at $260 million, and of bulk amoxicillin, 2,200 t valued at $190 million, both as the trihydrate. It was predicted that the market for bulk ampicillin was growing at 3% annually and would reach 4,160 t by 1990. Sales of amoxicillin, growing at 10% annually were predicted to reach a consumption of 2,800 t in 1990 with an average growth rate of 8%. The demand for both products is expected to reach 4,500 t by 2000 (68).

The cost of 6-APA, ampicillin, and amoxicillin is invariably linked to that of penicillin G. 6-APA remains one of the cheapest raw starting materials available for the preparation of semisynthetic penicillins and other related β-lactam antibiotics.

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