SILYL METHODS FOR THE MODIFICATION OF PENICILLIN AND CEPHALOSPORIN (REVIEW)

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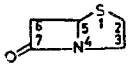
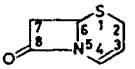
The principal pathways of modification of β-lactam antibiotics by means of silyl methods, including silylation, the preparation of N-acyl and amide analogs of penicillin and cephalosporin, the deacylation of N-protective groups, the epimerization of the side chain, the transformation of penicillin to cephalosporin, and other transformations, are examined.

The overwhelming majority of structural analogs of β-lactam antibiotics have been obtained as a result of modification of the substituents attached to penam (I) and ceph-3-eme (II)* — the heterocyclic rings of the natural antibiotics benzylpenicillin and cephalosporin C — including replacement of the hydrogen atoms in the 6 and 7 positions of the I and II molecules and the sulfur atoms by other substituents or heteroatoms [1-4].



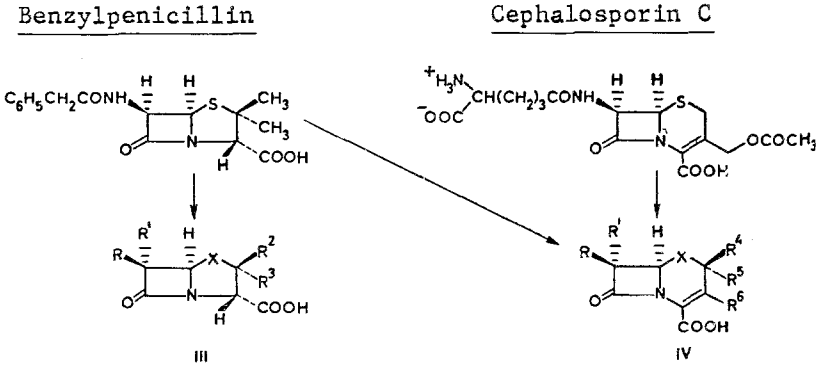
penam (I)



ceph-3-eme (II)

Despite the great diversity of the structural modifications, the principal elements that ensure retention of intensification of the antibiotic activity of III and IV are: a two-ring, condensed, heterocyclic system that contains a β-lactam ring, a nodal nitrogen atom, and a reduced sulfur atom; a β configuration of the substituents attached to the 5,6 and 6,7 carbon atoms in penam and ceph-3-eme (5R,6R and 6R,7R configurations, respectively, according to international nomenclature); a free carboxy group attached to the carbon atom adjacent to the nodal nitrogen atom.

Scheme 1. Principal Pathways of the Structural Modification of β-Lactam Antibiotics



III, IV R=R^7CONH, $R^8NHCONH$, R^9OCONH, $R^{10}-\underset{\displaystyle R^{11}}{\overset{\displaystyle R^{12}}{\underset{|}{\overset{|}{N}}}}-C=N$ etc.; R^1=H, Hal, OAlk, Alk etc.; R^2 and R^3=CH_3, H, CH_2Hal, CH_2OCOCH_3 etc.; R^4 and R^5=H, Hal, Alk etc.; R^6=CH_3, CH_2OAr, CH_2SAr, OAlk, SAlk, Hal etc.; X=CH_2, O, N, SO, SO_2

*See [4] for the generally accepted nomenclature for β-lactam antibiotics [4].

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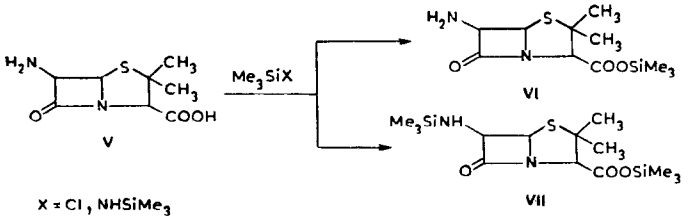
In planning the synthesis of biologically active structural modifications III and IV the requirements indicated above, as one of the principal conditions, stipulate the necessity for protection of the carboxy group and its liberation prior to their use as medicinals. Despite the large number of possible protective groupings, only a few are used in the chemistry of penicillin and cephalosporin. This is explained by the instability of penam and ceph-3-eme under the conditions of the addition and, in particular, the splitting out of most protective groups: hydrolysis in acidic and alkaline media, isomerization under the influence of nucleophilic agents, thermal instability, desulfuration during hydrogenolysis by means of Raney nickel, etc. Factors involving the technological effectiveness, the accessibility, and cost of the corresponding reagents play an important role in the selection of a suitable method, since the demand for medicinal penicillins and cephalosporins varies annually from several hundred kilograms to tens and hundreds of tons.

Silyl protective groups satisfy the requirements mentioned above to the greatest degree. By means of these groups one can successfully solve a number of problems associated with the purposeful structural transformation of natural compounds: antibiotics, nucleosides, prostaglandins, enzymes, etc. [5, 6], and substances that contain, as rule, several reaction centers that are inclined to undergo racemization, isomerization, destruction, and other undesirable transformations under the conditions of traditional chemical methods.

However, the use of silyl methods in the chemistry of β-lactam antibiotics — penicillin and cephalosporin — is characterized by, perhaps, the most significant advances from the point of view of both complexity and diversity and the practical value of the transformations realized. The experimental data accumulated with respect to their modification by means of organosilicon compounds in the nineteen sixties and seventies make it possible to reflect such data in a special review. We hope that a detailed familiarization with the structural transformations of β-lactam antibiotics will have a stimulating effect on the use of these methods in other classes of natural and synthetic heterocyclic compounds.

Silylation and Silylating Agents

The first experiments on the use of silylated 6-aminopenicillanic acids (VI, VII) as intermediates in the synthesis of semisynthetic penicillins revealed valuable synthetic and technological advantages of this method [7-10]:



First, esterification by means of trimethylchlorosilane, hexamethyldisilazane, or trimethyl(dimethylamino)silane proceeds in quantitative yield under mild conditions in a short time. The N,O-bis(silylated) acid (VII) is formed in the presence of excess silylating agent. Trimethylsilyl esters VI and VII, in contrast to the starting zwitterion form of amino acid V, are quite soluble in chloroform, methylene chloride, dioxane, tetrahydrofuran, toluene, diethyl ether, and other aprotic solvents.

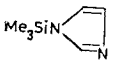
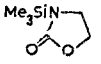
Second, splitting out of the trialkylsilyl protective group also proceeds in quantitative yield under conditions that are the most favorable for the antibiotic, viz., under the influence of an equivalent of water or lower aliphatic alcohol at or below room temperature.

Third, the presence of a trimethylsilyl group does not hinder acylation of the amino group by both the acid-chloride method and the mixed-anhydride method with yields that are not inferior to those presented in studies in which other protective groupings are used.

Fourth, the quantitative yields in the steps involving the addition and splitting out of the trimethylsilyl group exclude the necessity for isolation and purification of the intermediates, and the entire technological process for the preparation of semisynthetic penicillins III by this method is realized virtually in one step.

The enumerated advantages of a trimethylsilyl protective group have promoted a significant expansion in the set of silylating reagents (Table 1) that make it possible to vary both

TABLE 1. Reagents Used for Silyl Protection of β-Lactam Antibiotics

No.	Reagent	Structure	Literature
1	Trimethylchlorosilane	Me_3SiCl	8, 11, 12
2	Methyldimethoxychlorosilane	$Me(MeO)_2SiCl$	13, 14
3	Trimethoxychlorosilane	$(MeO)_3SiCl$	14
4	Tributylchlorosilane	Bu_3SiCl	15
5	Dimethyldichlorosilane	Me_2SiCl_2	16, 17
6	Dimethoxydichlorosilane	$(MeO)_2SiCl_2$	18
7	Methylphenyldichlorosilane	$MePhSiCl_2$	19
8	Diphenyldichlorosilane	Ph_2SiCl_2	19
9	Tetrachlorosilane	$SiCl_4$	20
10	Hexamethyldisilazane	$(Me_3Si)_2NH$	7, 10—12, 21
11	Hexamethyldisilazane and bis(trimethylsilyl)sulfate	$(Me_3Si)_2NH + (Me_3Si)_2SO_4$	22
12	Trimethyl(diethylamino)silane	Me_3SiNEt_2	8
13	N-Trimethylsilylimidazole		23
14	Trimethylsilylformamide	$Me_3SiNH—CHO$	24
15	Trimethylsilylacetamide	$Me_3SiNHCOCH_3$	23, 25
16	N-Trimethylsilyl-N-methylacetamide	$Me_3SiN(CH_3)COCH_3$	25
17	Triethylsilylacetamide	$Et_3SiNHCOCH_3$	26
18	Trihexylsilylacetamide	$(C_6H_{11})_3SiNHCOCH_3$	26
19	Tribenzylsilylacetamide	$(PhCH_2)_3SiNHCOCH_3$	26
20	Dimethylphenylsilylacetamide	$Me_2PhSiNHCOCH_3$	26
21	Triphenylsilylacetamide	$Ph_3SiNHCOCH_3$	26
22	N-Trimethylsilyl-2-oxazolidinone		27, 28
23	N,N-Bis(trimethylsilyl)urea	$(Me_3SiNH)_2CO$	21, 29
24	N,N-Bis(trimethylsilyl)malonylamide	$(Me_3SiNHCO)_2CH_2$	30
25	N,N-Bis(trimethylsilyl)succinylamide	$(Me_3SiNHCOCH_2)_2$	30
26	N,O-Bis(trimethylsilyl)formamide	$Me_3SiN=CHOSiMe_3$	24
27	N,O-Bis(trimethylsilyl)acetamide	$Me_3SiN=C(CH_3)OSiMe_3$	12, 21, 23, 25, 31
28	N,O-Bis(trimethylsilyl)trifluoroacetamide	$Me_3SiN=C(CF_3)OSiMe_3$	23
29	Trimethyl(n-propylthio)silane	$Me_3SiS—C_3H_7$-n	24
30	Hexamethyldisilthian	$(Me_3Si)_2S$	24
31	Triethylsilane	Et_3SiH	32
32	Trimethylsilylethanol	$Me_3SiCH_2CH_2OH$	33

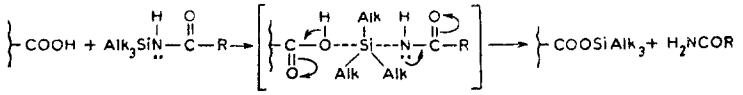
the reaction conditions and the number of silyl protective groups that can be introduced in the penicillin and cephalosporin molecules.

Of the reagents presented in Table 1, trimethylchlorosilane and hexamethyldisilazane are the most useful because of their accessibility and high reactivity. They have been used in the overwhelming majority of reactions for the preparation of semisynthetic antibiotics III and IV by this method. Trimethylchlorosilane is ordinarily used with a tertiary base (most often triethylamine) to tie up the hydrogen chloride; not only the carboxy group but also the amino group of penicillinanic and cephalosporanic acids V and IX are effectively silylated in this case. The reaction at the carboxy group takes place in the absence of a base in the case of the sodium or potassium salts of the antibiotics. The formation of the hydrochloride of the tertiary base, which in some cases hinders the isolation and purification of the desired products, is a disadvantage of this reagent.

Silylation with hexamethyldisilazane is accelerated by the addition of catalytic amounts of sulfuric or phosphoric acid. Volatile side products that are easily removable from the reaction medium by purging the system with an inert gas are formed in the reaction. However, primarily the carboxy group is silylated by hexamethyldisilazane, and this reagent is considerably inferior to trimethylchlorosilane with respect to its effectiveness in simultaneous protection of the carboxy and amino groups [7, 8]. The use of an equimolar mixture of hexamethyldisilazane and trimethylchlorosilane raises the yields of bis(silylated) 6-aminopenicillanic and 7-aminocephalosporanic acids to 92-95% [34].

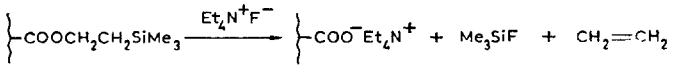
N,N-Bis(trimethylsilyl)urea, N,O-bis(trimethylsilyl)acetamide, and the structurally closely related mono- and bis(silylated) amides (Table 1) are very active silylating agents that form mono- and N,O-bis(silylated) amino acids even at room temperature. Their high

effectiveness is explained by redistribution of the electron density in the amide group of the intermediate complex, which weakens the bond between silicon and nitrogen.



The degree of silylation of the amino group in silyl esters of penicillins and cephalosporins can be determined by PMR spectroscopy by comparison of the integral intensities of the signals of the protons of the O-trimethylsilyl (0.50-0.55 ppm) and N-trimethylsilyl (0.28-0.30 ppm) groups [34].

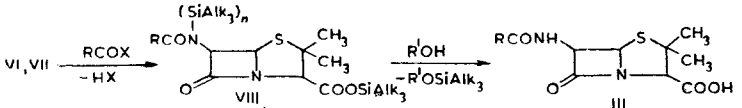
From the reagents presented in Table 1 one should single out triethylsilane and 2-trimethylsilylethanol, the reaction of which with antibiotics is realized in the first case by dehydrocondensation in the presence of palladium on carbon and in the second case by means of dicyclohexylcarbodiimide. Cephalosporin 2-trimethylsilylethyl ester is resistant to hydrolytic cleavage by water or lower alcohols. The protective group in this case is split out by tetraethylammonium fluoride [33].



Silylated antibiotics are, as a rule, difficult-to-crystallize substances. The presence of a protective group increases the thermal stability of the β-lactam ring as well as the volatilities of the compounds themselves. This has made it possible to distill 6-aminopenicillanic acid trimethylsilyl ester in a high vacuum [7] and to use gas-liquid chromatography (GLC) for the quantitative analysis of silylated aminopenicillanic and aminocephalosporanic acids [35, 36]. The use of this method has made it possible to establish the partial isomerization of the double bond in 7-aminodeacetoxycephalosporanic acid from the Δ^3 to the Δ^2 position in silylation with N,O-bis(trimethylsilyl)formamide, N-trimethylsilylimidazole, and N-trimethylsilylacetamide [35].

Semisynthetic Penicillins and Cephalosporins

The use of mono- and N,O-bis(silylated) 6-aminopenicillanic acid (VI, VII) as intermediates has made it possible to develop an extremely effective method for the acylation of their amino groups, which leads to the preparation of the so-called semisynthetic penicillins III [7-10]. This method was subsequently successfully extended to the preparation of N-acyl derivatives of amino acids of not only the penicillin series but also the cephalosporin series IX (see Table 2).



More than 200 papers and patents with descriptions of examples of the preparation by this method of the most diversely constructed N-acyl synthetic analogs of penicillin and cephalosporin (III and IV) were published in 1964-1980. One should note the recent publication of patents dealing with the use in the acid-chloride method of excess silylating agent, viz., N,O-bis(trimethylsilyl)acetamide, N,N-bis(trimethylsilyl)urea, and other silylated amides, to tie up the resulting hydrogen chloride, which substantially simplifies the isolation and purification of the desired antibiotics [12, 47, 48].

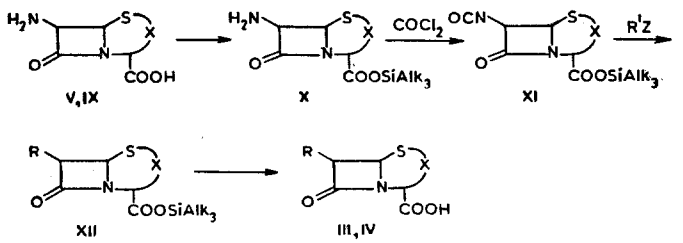
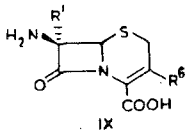
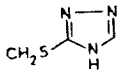
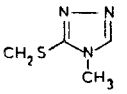
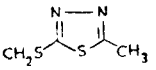


TABLE 2. Structural Modifications of 7-Aminocephalosporanic Acid Acylated by the Silyl Protective Method



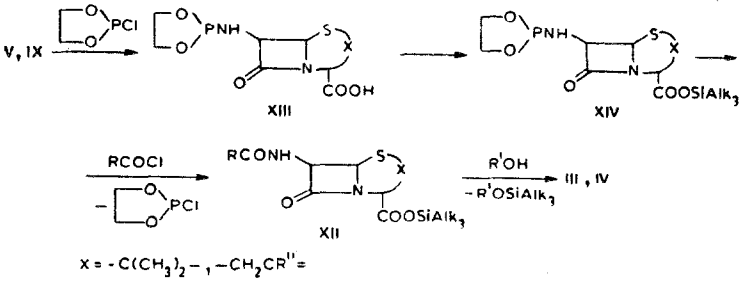
IX

No.	R^1	R^6	Literature
1	H	CH_3	37, 38
2	H	CH_2OCOCH_3	15, 24, 39, 40
3	H	CH_2OCONH_2	41
4	H	$CH_2Alk(Ar)$	15
5	H	Cl	42
6	H	OCH_3	42
7	H		21
8	H		43, 44
9	H		45
10	OCH_3	CH_3	46
11	OCH_3	CH_2OCOCH_3	46

A widely used method for the preparation of semisynthetic penicillins and cephalosporins is based on the conversion of trimethylsilyl esters of acids V and IX by means of phosgene to the corresponding 6-isocyanatopenicillanic and 7-isocyanatocephalosporanic acid esters (XI), which react with carboxylic acids, organometallic compounds, sulfinic acids, amines, amidines, and alcohols to give N-acyl derivatives of antibiotics III and IV of the amide, sulfinamide, ureylene, and urethane types [17, 49-54].

A 6-isothiocyanatopenicillanic acid ester was obtained by similar treatment of the trimethylsilyl ester of acid V with thiophosgene at —55°C [55].

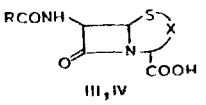
A method for the preparation of semisynthetic β-lactam antibiotics based on the acylation of intermediate trimethylsilyl esters of 6-(2-phospha-1,3-dioxolan-2-yl)aminopenicillanic and 7-(2-phospha-1,3-dioxolan-2-yl)aminocephalosporanic acids (XIV) has also been developed [56-58].



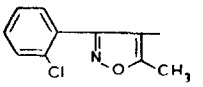
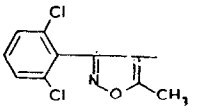
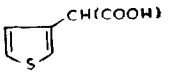
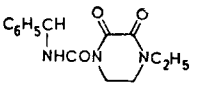
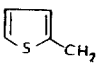
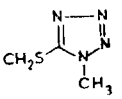
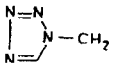
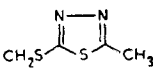
Various methods for the acylation of trialkylsilyl esters of acids V and IX have made it possible to substantially improve the technology in the preparation of semisynthetic β-lactam antibiotics, primarily those that have been widely used in medical practice as effective antibacterial preparations (see Table 3).

In addition to aminopenicillanic and aminocephalosporanic acids V and IX, some other subjects of chemical modification designed to obtain new N-acyl derivatives are semisynthetic penicillins and cephalosporins that contain a free amino group in the side chain — most often the preparations ampicillin, amoxicillin, cephalexin, etc. (see Table 3). In this case also

TABLE 3. Medicinal Semisynthetic Penicillins and Cephalosporins Obtained by the Silyl Protective Method



III, IV

No.	Preparation	R	X	R^6	Literature
1	Phenoxymethylpenicillin	$C_6H_5CH_2$	$-C(CH_3)_2-$		56, 59
2	Ampicillin	$C_6H_5CH(NH_2)$	$-C(CH_3)_2-$		8, 37, 41
3	Amoxicillin	*p*-$HOC_6H_5CH(NH_2)$	$-C(CH_3)_2-$		31, 60, 61
4	Carbenicillin	$C_6H_5CH(COOH)$	$-C(CH_3)_2-$		44, 62, 63
5	Cloxacillin		$-C(CH_3)_2-$		25
6	Dicloxacillin		$-C(CH_3)_2-$		25
7	Sulfocillin	$C_6H_5CH(SO_3H)$	$-C(CH_3)_2-$		25
8	Thicarcillin		$-C(CH_3)_2-$		44
9	Piperacillin		$-C(CH_3)_2-$		66
10	Cephalothin		$-CH_2CR^6=$	CH_2OCOCH_3	41, 59
11	Cephaloglycin	$C_6H_5CH(NH_2)$	$-CH_2CR^6=$	CH_2OCOCH_3	37
12	Cephacetrile	$NC-CH_2$	$-CH_2CR^6=$	CH_2OCOCH_3	33, 41
13	Cephalexin	$C_6H_5CH(NH_2)$	$-CH_2CR^6=$	CH_3	37, 41
14	Cephamandol	$C_6H_5CH(OH)$	$-CH_2CR^6=$		65
15	Cephazolin		$-CH_2CR^6=$		67

the synthesis of new derivatives is simplified substantially when a silyl protective group is used with subsequent acylation of the amino group by the acid-chloride and isocyanate methods or by the mixed-anhydride method [68-71].

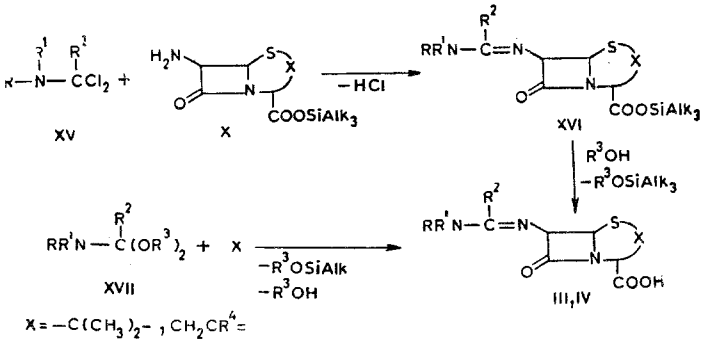
In the synthesis of semisynthetic β-lactam antibiotics by the silyl protective method the trialkylsilyl group is also used to protect the carboxy, hydroxy, amino, and imino groups included in the composition of the polyfunctional carboxylic acids used as acylating agents [51, 57, 62, 66, 72]. After acylation is complete, all of the protective groups are split out simultaneously.

Amidine and Imidoyl Chloride Derivatives of Penicillin and Cephalosporin

A new promising class of biologically active analogs of penicillin and cephalosporin, viz., derivatives of 6-amidinopenicillanic and 7-amidinocephalosporanic acids III and IV

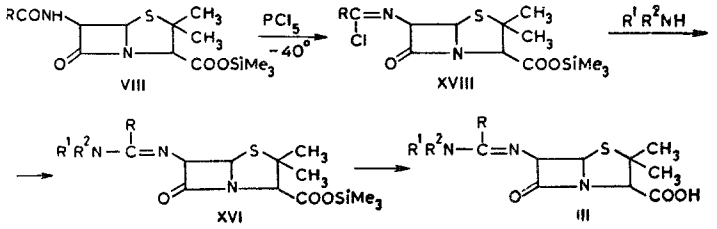
$(R=R^{10}-\underset{\displaystyle R^{11}}{\overset{\displaystyle R^{12}}{N-C}}=N)$, was discovered in the early nineteen seventies (see Scheme 1) [73, 74].

In this case also trialkylsilyl esters of 6-aminopenicillanic and 7-aminocephalsoporanic acids (X) have been successfully used in the alkylation of the amino group of N,N-disubstituted amides with an activated carbonyl group in the form of the dichloride (XV) or the diacetal (XVII):

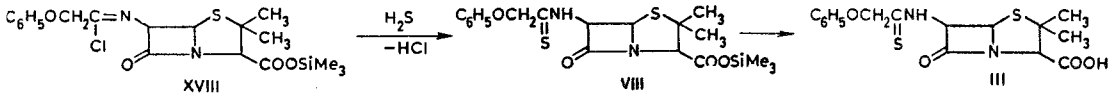


When amide diacetals (XVII) are used as the starting substances, splitting out of the trialkylsilyl protective grouping from the desired antibiotic takes place during condensation, which is accompanied by the formation of two molecules of alcohol. Special selection of the solvents and the temperature conditions has made it possible to use this property in such a way that the resulting amidine antibiotic precipitates in crystalline form and thus is easily separated from the impurities, which remain in solution [73, 75, 76].

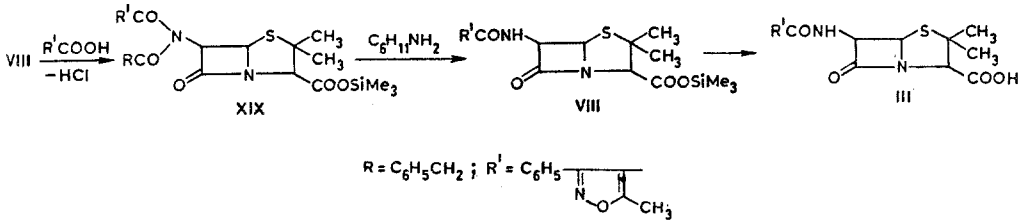
Amidine analogs of antibiotics can also be obtained by transformation of the side chain in trimethylsilyl esters of natural and semisynthetic penicillins, viz., by conversion of the exocyclic amide group under the influence of phosphorus pentachloride to an imidoyl chloride group and treatment of the latter with secondary amines [77].



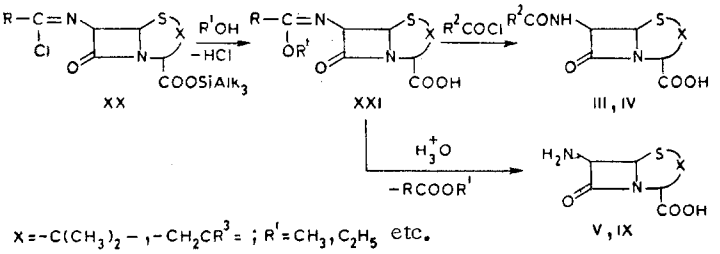
The development of a method for the preparation of the trimethylsilyl ester of the imidoyl chloride derivative of natural and semisynthetic β-lactam antibiotics XVIII has made it possible to synthesize a thioamide derivative of phenoxymethylpenicillin (III) [78] and to carry out replacement of the side chain of benzylpenicillin by a new N-acyl grouping by conversion



of imidoyl chloride derivative XVIII by means of the carboxylic acid to the trimethylsilyl ester of diacylated 6-aminopenicillanic acid (XIX) with subsequent selective splitting out of the phenylacetyl group with cyclohexylamine [79]:



Another more universal transacylation method consists in treatment of the imidoyl chloride group in compounds of the XX type with a lower alcohol and the action of a carboxylic acid chloride on intermediate imido ester derivative XXI [80, 81]:

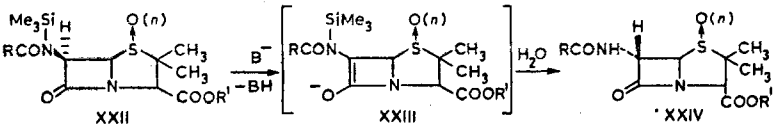


However, the chief goal in the preparation of silyl esters of imidoyl derivatives of natural and semisynthetic penicillins and cephalosporins is splitting out of the N-acyl side chain. For this, imido ester XXI is treated with a weakly acidic aqueous solution, which leads to cleavage of the double bond and the formation of 6-aminopenicillanic or 7-aminocephalosporanic acid (V, IX) [82-87].

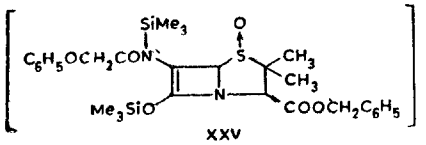
This reaction has made it possible to solve the complex technological problem of the chemical preparation of amino acids V and IX from acylated antibiotics; whereas in the case of benzylpenicillin an alternative method of enzymatic deacylation of the side chain also existed prior to the discovery of this method at the end of the nineteen sixties, the lack of a similar specific acylase for cephalosporin C substantially retarded the creation of medicinal cephalosporins. A valuable feature of this method is its universality with respect to N-acyl groupings with the most diverse structures, as well as the fact that all of the chemical transformations, commencing with the silylation of the carboxy group of the antibiotic and terminating with cleavage of the imido ester bond, are realized without isolation of the intermediates. The yield of 6-aminopenicillanic acid (V) obtained from benzylpenicillin by this method reaches 98% [82], while the yield of 7-aminocephalosporanic acid obtained from cephalosporin C reaches 91% [18, 83, 88, 89].

Epimerization of the Side Chain of Penicillin

Replacement of the amide proton by a trimethylsilyl group in the side chain of benzyl- and phenoxymethylpenicillin, as well as their sulfoxides, by means of N,O-bis(trimethylsilyl)-acetamide facilitated the successful inversion of the configuration of the substituents attached to the C_6 atom [90, 91]:



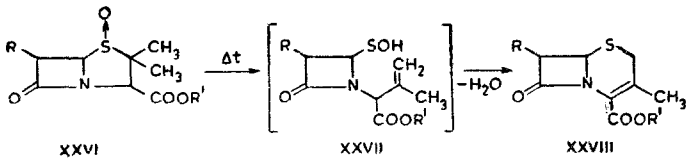
The most effective epimerization catalyst is 1,5-diazabicyclo[4.3.0]non-5-ene, which promotes detachment of a proton from the C_6 atom and enolization of the β-lactam carbonyl group. However, the benzyl ester of phenoxymethylpenicillin sulfoxide undergoes 68% epimerization by N,O-bis(trimethylsilyl)acetamide itself as a result of the formation of intermediate silyl enol XXV:



Taking into account the reversibility of the reaction indicated above, N,O-bis(trimethylsilyl)acetamide has been used successfully for the conversion of the α epimers of penicillin XXIV to biologically active β epimers XXII [92].

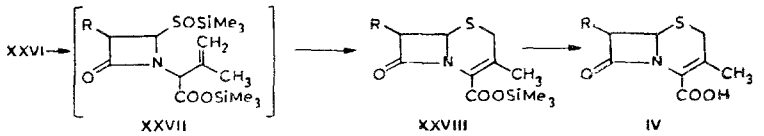
Conversion of Penicillin to Deacetoxycephalosporin

Another important pathway in the chemical transformation of β-lactam antibiotics that is of practical value is the thermal rearrangement of esters of penicillin sulfoxide to the corresponding esters of deacetoxycephalosporin [93]:



XXVI XXVII XXVIII

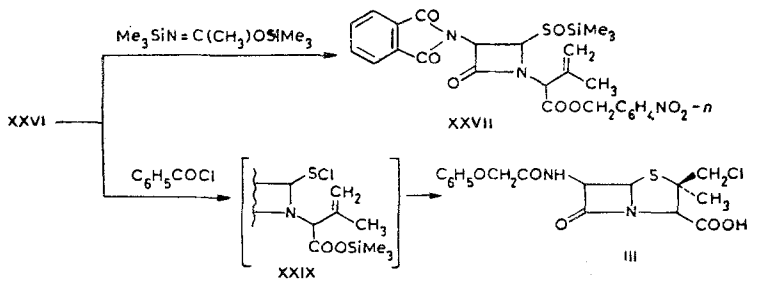
The discovery of this reaction has created practicable prerequisites for the utilization of the cheap and accessible benzylpenicillin as the starting material for the preparation of semisynthetic cephalosporins. A study of the rearrangement mechanism has revealed the necessity of obligatory protection of the carboxy group from decarboxylation. It was established that conversion of the sulfene group in intermediate azetidinone XXVII to the anhydride or ester promotes its intramolecular electrophilic addition to the double bond of the butene-3-carboxylic acid ester fragment in XXVII with cyclization to deacetoxycephalosporin XXVIII [4]. In this case also the silylating agents N,O-bis(trimethylsilyl)acetamide and N,N-bis(trimethylsilyl)urea proved to be the most suitable reagents for ensuring all of the enumerated conditions, and this made it possible to develop methods for the preparation of the desired modified cephalosporins IV in greater than 80% yields [94-98]:



XXVII XXVIII IV

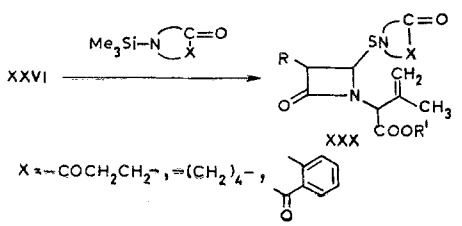
R = $C_6H_5CH_2CONH$, $C_6H_5OCH_2CONH$

An azetidinone silylated at the sulfene group (XXVII) and β-chloromethylpenicillin III were isolated and characterized during a study of this reaction by means of trimethylsilyl protective methods, and this confirmed the rearrangement mechanism [99, 100]:



XXVII XXIX III

In addition, azetidinone-4-sulfenoimides XXX, which are intermediates in the synthesis of cephalosporin, were obtained by cleavage of the S_1—C_2 bond in esters (including the trimethylsilyl ester) of penicillin sulfoxide XXVI with N-trimethylsilylsuccinimide, N-trimethylsilylphthalimide, or N-trimethylsilylcaprolactam [101-103]:



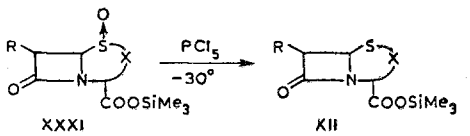
XXX

X = $-COCH_2CH_2-$, $=(CH_2)_4-$,

Other Silyl Methods for the Modification of Penicillin and Cephalosporin

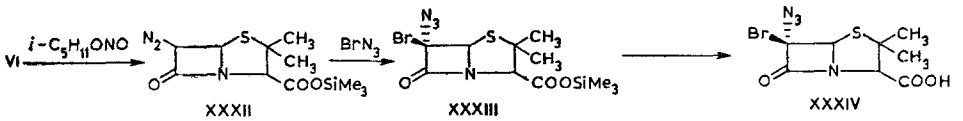
Trimethylsilyl protection of the carboxy group of β-lactam antibiotics has been sucessfully used for a number of other modifications:

a) reduction of the sulfoxide group in penicillins and cephalosporins to a sulfide group [104]:



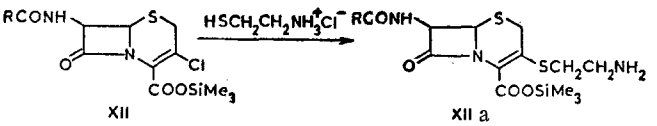
XXXI XII

b) diazotization of the amino group of 6-aminopenicillanic acid with isoamyl nitrite in the presence of trifluoroacetic acid and subsequent preparation of 6-α-azido-6-β-bromopenicillanic acid [105]:



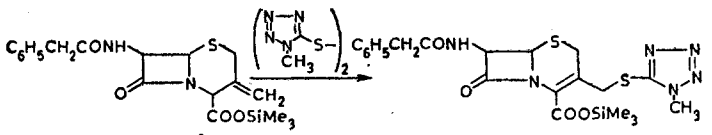
XXXII XXXIII XXXIV

c) nucleophilic substitution of a chlorine atom in the 3 position of cephalosporin by means of mercaptoethylamine [106]:



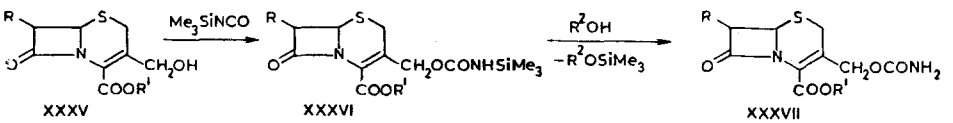
XII XII a

d) addition of a heterocyclic disulfide to the double bond of 3-methylenecepham-4-carboxylic acid [107]:



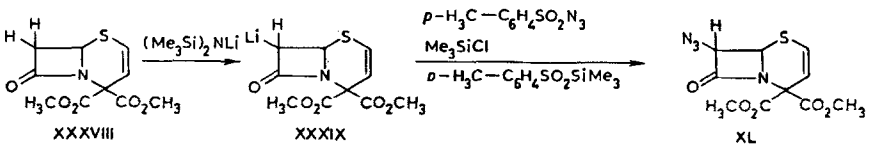
XII b XII c

A new direction in the modification of β-lactam antibiotics, which consists in transformation of the functional groupings in penicillin and cephalosporin by special silicon-containing reagents, has recently been developed. Thus the hydroxymethyl group in cephalosporin XXXV has been converted to a carbamoylmethyl group by the action of trimethylsilyl isocyanate [108]:



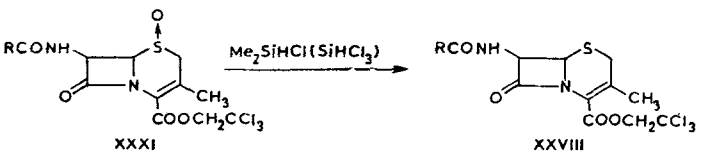
XXXV XXXVI XXXVII

The use of lithium bis(trimethylsilyl)imide has made it possible to replace the hydrogen atom in the 7 position of the synthetic analog of cephalosporin by a lithium atom, which in turn was replaced by an azido group by means of p-toluenesulfenyl azide and trimethylchlorosilane [109]:



XXXVIII XXXIX XL

The sulfoxide group in deacetoxycephalosporin ester XXXI has been successfully reduced to a sulfide group by means of dimethylchlorosilane or trichlorosilane [110]:



XXXI XXVIII

The silylation of penicillins and cephalosporins is also being used as a technological method to remove impurities from them or to obtain antibiotics that do not contain crystallization water. Thus treatment of trimethylsilyl esters III and IV with an equimolar mixture of water and the sodium (or potassium) salt of α-ethylcaproic acid has made it possible to obtain the corresponding salts of the antibiotics that are virtually free of impurities [111, 112]. Cleavage of the trimethylsilyl ester of ampicillin (see Table 3) with isopropyl alcohol was the most convenient method for the preparation of the anhydrous antibiotic [113]. In

the case of the cephalosporin preparation cephamandol (see Table 3) its bis(trimethylsilyl) derivative with respect to the carboxy and hydroxy groups has been found to be an extremely stable and easily crystallizable compound, and this derivative has been used for its purification [66].

Despite the great structural diversity of the side chain of the semisynthetic penicillins and cephalosporins, virtually no systematic research dealing with the synthesis and biological study of compounds that contain a silicon atom in the side chain in order to study its effect on the biological activity of antibiotics has been carried out. However, the published data indicate the presence of antibiotic activity, including activity with respect to microorganisms that are resistant to benzylpenicillin, in silicon-containing penicillins and cephalosporins [114-116].

In summing up the chemical modifications of β-lactam antibiotics based on the use of silyl methods one should note that, in addition to silicon, another element of the fourth group, viz., tin, has been used for this purpose. The tributylstannyl group, like the trialkylsilyl group, simplifies the technology involved in the preparation of semisynthetic penicillins and cephalosporins. However, it is considerably more resistant to hydrolysis and is usually split out with sodium thiophenoxide in dimethylformamide [17, 117-119]. A tributylstannyl protective group has also been used successfully in the synthesis of 6-aminopenicillanic acid by chemical deacylation of the side chain of the antibiotic through the intermediate imidoyl chloride [120] and epimerization of the side chain in 6-β-benzylideneaminopenicillanic acid [121].

LITERATURE CITED

1. E. H. Flynn, Cephalosporins, Chemistry and Biology, Academic Press, New York (1972).
2. J. H. C. Nayler, Adv. Drug Res., 7, 1 (1973).
3. A. K. Mukerjee and A. K. Singh, Synthesis, 9, 547 (1975).
4. R. J. Stoodley, Tetrahedron, 31, 2325 (1975).
5. B. E. Cooper, Process Biochem., 9 (1980).
6. É. Ya. Lukevits, A. E. Zablotskaya, and I. I. Solomennikova, Usp. Khim., 43, 370 (1974).
7. K. W. Glombitza, Lieb. Ann., 673, 166 (1964).
8. B. O. Sjoberg and A. B. Ekstrom, BE Patent No. 628231; Chem. Abstr., 61, 1870 (1964).
9. Chemie Grunenthal G.m.b.H., BE Patent No. 615344; Chem. Abstr., 59, 5173 (1963).
10. L. Birkofer, BE Patent No. 615401; Chem. Abstr., 59, 2826 (1963).
11. S. Herrling and H. Muecter, US Patent No. 3249622; Chem. Abstr., 65, 3884 (1966).
12. G. Palladino and E. Paolinich, GB patent No. 2001985; Chem. Abstr., 91, 211428 (1979).
13. T. Ishimary and Y. Codama, JA Patent No. 738690; Chem. Abstr., 80, 37131 (1974).
14. T. Ishimary and Y. Codama, DT Patent No. 2151531; Chem. Abstr., 77, 34502 (1972).
15. P. Crooij and A. Colinet, US Patent No. 3912728; Chem. Abstr., 84, 440986 (1976).
16. S. Herrling, DT Patent No. 2115542; Chem. Abstr., 78, 84400 (1973).
17. J. Werweij, DT Patent No. 2166561; Chem. Abstr., 81, 152216 (1974).
18. N. Asako, T. Soma, and C. Harukawa, Jpn. Patent No. 7748991; Chem. Abstr., 89, 215417 (1978).
19. C. A. Robinson, DT Patent No. 1931624; Chem. Abstr., 72, 43665 (1970).
20. T. Ishimary, Jpn. Patent No. 7612637; Chem. Abstr., 86, 121324 (1977).
21. S. P. A. Procter, GB Patent No. 1459807; Chem. Abstr., 87, 39508 (1977).
22. B. E. Cooper and D. W. Butler, DT Patent No. 2649536; Chem. Abstr., 87, 135894 (1977).
23. W. J. Wheeler, US Patent No. 4035361; Chem. Abstr., 87, 135371 (1977).
24. T. Tamura, T. Ishimary, and T. Shinuchi, Jpn. Patent No. 77125186; Chem. Abstr., 88, 170166 (1978),
25. M. Croci and G. Gotti, DT Patent No. 2701406; Chem. Abstr., 87, 135309 (1977).
26. B. G. Jackson, DT Patent No. 1942454; Chem. Abstr., 74, 125836 (1971).
27. C. A. Gema, DT Patent No. 2462383; Chem. Abstr., 86, 140067 (1977).
28. A. L. C. Palomo, DT Patent No. 2408171; Chem. Abstr., 81, 152210 (1974).
29. P. Renato and F. Marco, ES Patent No. 448741; Chem. Abstr., 88, 105387 (1978).
30. K. Ishibashi, H. Ishiguro, Y. Miyaji, and K. Moshizuki, Jpn. Patent No. 7859689; Chem. Abstr., 89, 146917 (1978).
31. K. Shimizy, H. Asai, and S. Kuroyanagi, Jpn. Patent No. 7882791; Chem. Abstr., 90, 103979 (1979).
32. L. Birkofer and A. Ritter, DT Patent No. 1770855; Chem. Abstr., 81, 13501 (1974).
33. P. Sieber, DT Patent No. 2706490; Chem. Abstr., 88, 23391 (1978).
34. F. Bortesi, S. Cavalli, and A. Mangia, J. Pharm. Sci., 66, 1767 (1977).

35. S. Silingardi, M. Di Bitetto, and A. Mangia, J. Pharm. Sci., 66, 1769 (1977).
36. H.-L. Wu, M. Masada, and T. Uno, J. Chromatogr., 137, 127 (1977).
37. L. Doub and J. S. Kalterbronn, US Patent No. 3948903; Chem. Abstr., 85, 21348 (1976).
38. H. H. Silvestri, US Patent No. 3862186; Chem. Abstr., 83, 48198 (1975).
39. E. Kisewetter and S. Herrling, US Patent No. 3926954; Chem. Abstr., 85, 33042 (1976).
40. T. Ishimary and Y. Kodama, DT Patent No. 2163514; Chem. Abstr., 79, 78862 (1973).
41. P. Borrevang, P. Faarup, E. Guddal, J. K. Nielsen, and H. B. Petersen, DT Patent No. 2612523; Chem. Abstr., 86, 89853 (1977).
42. R. Wiederkehr and H. Bickel, DT Patent No. 2636962; Chem. Abstr., 87, 85015 (1977).
43. B. Bouzard and A. Weber, GB Patent No. 1484120; Chem. Abstr., 88, 105365 (1978).
44. P. Crooij and G. Simonet, DT Patent No. 2615091; Chem. Abstr., 86, 89905 (1977).
45. R. D. G. Cooper, G. V. Kaiser, C. F. Murphy, E. M. van Heyningen, and J. A. Webber, DT Patent No. 1940080; Chem. Abstr., 74, 22863 (1971).
46. B. G. Kristensen, USSR Inventor's Certificate No. 450413; Byull. Izobret., No. 42, 154 (1974).
47. K. Shimizu and A. Asai, Jpn. Patent No. 78124289; Chem. Abstr., 90, 152173 (1979).
48. K. Shimizu and H. Terai, Jpn. Patent No. 7884988; Chem. Abstr., 90, 6393 (1979).
49. P. W. Henniger, GB Patent No. 1339708; Chem. Abstr., 80, 95937 (1974).
50. P. M. Smid and J. Calter, DT Patent No. 2264602; Chem. Abstr., 81, 49675 (1974).
51. J. H. Sellstedt and S. C. Bell, US Patent No. 3714150; Chem. Abstr., 78, 124608 (1973).
52. P. W. Henniger and J. K. van der Drift, DT Patent No. 2235390; Chem. Abstr., 78, 124608 (1973).
53. J. H. Sellstedt, D. M. Teller, and C. J. Guinosso, US Patent No. 3720666; Chem. Abstr., 79, 5329 (1973).
54. P. Grooji and A. Colinet, US Patent No. 3994887; Chem. Abstr., 86, 106624 (1977).
55. Koninklijke Nederlandishe, DT Patent No. 2062297; Chem. Abstr., 75, 98565 (1971).
56. P. Borrevang, E. Guddal, H. B. Petersen, P. Faarup, and J. K. Nielsen, DT Patent No. 2364759; Chem. Abstr., 83, 10064 (1975).
57. E. Guddal, DT Patent No. 2626280; Chem. Abstr., 86, 140072 (1977).
58. P. Borrevang, P. Faarup, E. Guddal, J. K. Nielsen, and H. B. Petersen, DT Patent No. 2612523; Chem. Abstr., 86, 89853 (1977).
59. E. Kiesewetter and S. Herrling, US Patent No. 3926954; Chem. Abstr., 85, 33042 (1976).
60. J. H. Grossman and G. A. Hardcastle, DT Patent No. 2611286; Chem. Abstr., 86, 16664 (1977).
61. D. A. Love, GB Patent No. 1339605; Chem. Abstr., 80, 108507 (1974).
62. J. M. Goldman, DT Patent No. 2334343; Chem. Abstr., 80, 120917 (1974).
63. P. Feyen, DT Patent No. 2622456; Chem. Abstr., 88, 89622 (1978).
64. S. Morimoto, H. Nomura, T. Fugonono, K. Takeshi, and J. Ishigura, DT Patent No. 1966850; Chem. Abstr., 81, 136135 (1974).
65. J. Saikawa, S. Takano, H. Imaizumi, I. Takakura, H. Ochiaki, T. Yasuda, H. Taki, M. Tai, and Y. Kodama, DT Patent No. 2831568; Chem. Abstr., 90, 186980 (1979).
66. W. J. Wheeler, US Patent No. 4035361; Chem. Abstr., 87, 135371 (1977).
67. K. Kariyone, M. Kurita, H. Yasawa, and T. Oku, DT Patent No. 2262262; Chem. Abstr., 79, 92244 (1973).
68. L. Doub, J. S. Kalternborn, and D. Shweiss, US Patent No. 3595734; Chem. Abstr., 85, 108863 (1976).
69. L. Doub and J. S. Kalternborn, US Patent No. 3873523; Chem. Abstr., 83; 58807 (1975).
70. A. E. Alburn and W. Dwonch, US Patent No. 3932321; Chem. Abstr., 85, 32998 (1976).
71. T. H. Cronin, US Patent No. 3847900; Chem. Abstr., 82, 57681 (1975).
72. C. Palomo and L. Antonio, DT Patent No. 2408171; Chem. Abstr., 81, 152210 (1974).
73. F. Lund and L. Tybring, Nature, New Biol., 236, 153 (1972).
74. F. Lund, DT Patent No. 2430375; Chem. Abstr., 83, 58850 (1975).
75. G. A. Veinberg, K. I. Dikovskaya, E. M. Belevich, S. A. Giller, and A. S. Khokhlov, USSR Inventor's Certificate No. 516691; Byull. Izobret., No. 21, 89 (1976).
76. I. Busko-Oszczapowich and J. Cieslak, Acta Pol. Pharm., 30, 43 (1973).
77. I. Busko-Oszczapowich and J. Cieslak, GB Patent No. 1312030; Chem. Abstr., 79, 18700 (1973).
78. R. G. Micetich, C. G. Chin, and R. B. Morin, Tetrahedron Lett., No. 13, 967 (1976).
79. R. D. Carrol, D. K. Pirie, W. M. Welch, and E. S. Hamanaka, DT Patent No. 2253781; Chem. Abstr., 79, 42490 (1973).
80. R. Gericke, E. Poetsch, H. Juraszuk, J. Suebert, W. Strehlow, and R. Gottschlich, DT Patent No. 2626026; Chem. Abstr., 88, 105383 (1978).

81. V. Henri and V. Lunn, USSR Inventor's Certificate No. 686621; Byull. Izobret., No. 34, 244 (1979).
82. H. W. O. Weissenburger and M. G. van der Hoeven, Rec. Trav. Chim., 89, 1081 (1970).
83. E. Visher, Helv. Chim. Acta, 51, 1108 (1968).
84. D. A. Johnson, S. P. Brundidge, A. L. Vulkano, C. Sapino, Jr., H. Mahan, and J. G. Grossman, US Patent No. 3932392; Chem. Abstr., 85, 33039 (1976).
85. T. Ishimary and Y. Codama, DT Patent No. 2151530; Chem. Abstr., 77, 34544 (1972).
86. E. Bauershmidt, D. Bormann, and M. Worn, DT Patent No. 2243242; Chem. Abstr., 80, 1146184 (1974).
87. K. Hattori, J. Ueda, K. Endo, D. Morino, A. Morimoto, K. Kauyone, M. Kurita, M. Hashimoto, and O. Nishiwaki, DT Patent No. 2332045; Chem. Abstr., 80, 95981 (1974).
88. N. Asako, T. Soma, and C. Harukawa, Jpn. Patent No. 7748991; Chem. Abstr., 89, 21547 (1978).
89. T. Ishimary and M. Kawabata, DT Patent No. 2523280; Chem. Abstr., 84, 135692 (1976).
90. P. Claes, A. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, J. Chem. Soc., Perkin Trans. I, No. 9, 932 (1973).
91. A. Vlietinck, E. Roels, P. Claes, G. Jassen, and H. Vanderhaeghe, J. Chem. Soc., Perkin Trans. I, No. 9, 937 (1973).
92. R. E. Gutowski, US Patent No. 3719667; Chem. Abstr., 78, 147944 (1973).
93. R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavangino, W. B. Scanlon, and S. L. Andrews, J. Am. Chem. Soc., 91, 1401 (1969).
94. T. S. Chou, DT Patent No. 2323395; Chem. Abstr., 80, 48013 (1974).
95. T. S. Chou, Tetrahedron Lett., No. 9, 725 (1974).
96. J. J. de Coning, J. H. Kooreman, H. S. Tan, and J. Werweij, J. Org. Chem., 40, 1346 (1975).
97. Koninklijke Nederlandishe Gist-en Spiritus-Fabriek N. V., DT Patent No. 2107650; Chem. Abstr., 76, 3879 (1972).
98. J. Werweij, H. S. Tan, and J. H. Kooreman, DT Patent No. 2240224; Chem. Abstr., 78, 136314 (1973).
99. T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and C. P. Kukolja, J. Am. Chem. Soc., 95, 1609 (1974).
100. H. Tanida and T. Tsuji, DT Patent No. 2333256; Chem. Abstr., 80, 95976 (1974).
101. J. Werweij and H. S. Tan, DT Patent No. 2406165; Chem. Abstr., 81, 152253 (1974).
102. J. Werweij and H. S. Tan, DT Patent No. 2505280; Chem. Abstr., 83, 193062 (1975).
103. R. Broggi and M. Falciani, DT Patent No. 2724286; Chem. Abstr., 88, 89696 (1978).
104. H. Ishimary, Jpn. Patent No. 79112891; Chem. Abstr., 92, 41435 (1980).
105. B. G. Christensen and L. D. Cama, US Patent No. 4071529; Chem. Abstr., 89, 6318 (1978).
106. T. R. Beattie, L. D. Cama, B. G. Christensen, and F. P. Dinnino, US Patent No. 4150156; Chem. Abstr., 91, 57041 (1979).
107. W. A. Slusarchuk, E. M. Gordon, and W. H. Koster, DT Patent No. 2754742; Chem. Abstr., 90, 103977 (1979).
108. F. E. Roberts, USSR Inventor's Certificate No. 608477; Byull. Izobret., No. 19, 172 (1978).
109. K. Kuetlein and H. Jensen, DT Patent No. 2337443; Chem. Abstr., 82, 171002 (1975).
110. R. D. G. Cooper, G. V. Kaiser, C. F. Murphy, E. M. van Heyningen, and J. A. Webber, DT Patent No. 1940080; Chem. Abstr., 74, 22863 (1971).
111. E. Keisewetter and S. Herrling, DT Patent No. 2026508; Chem. Abstr., 76, 99650 (1972).
112. E. Keisewetter and S. Herrling, US Patent No. 3926954; Chem. Abstr., 85, 33042 (1976).
113. A. C. Adams, US Patent No. 3479338; Chem. Abstr., 72, 31783 (1970).
114. T. M. Vorozhkina, I. T. Strukov, and M. F. Shostakovskii, Zh. Obshch. Khim., 34, 1464 (1964).
115. G. A. Veinberg, É. P. Popova, A. M. Kats, and É. Ya. Lukevich, Khim.-farm. Zh., No. 10, 48 (1980).
116. G. Nannini, G. Molgora, G. Biasoli, P. Cozzi, F. Casabuona, G. Galli, D. Saverino, L. Sala, C. Confalonieri, P. N. Gicaldi, G. Vita, J. Decarneri, G. Meinardi, G. Monti, and A. Bianchi, Arzneim. — Forsch.-Drug Res., 27, 343 (1977).
117. P. Bamberg, B. A. Ekstrom, and B. O. H. Sjoberg, Acta Chem. Scand., 22, 367 (1968).
118. P. Bamberg, B. A. Ekstrom, and B. O. N. Sjoberg, FR Patent No. 1507866; Chem. Abstr., 70, 47434 (1969).
119. L. P. Puigdellivol, ES Patent No. 470902; Chem. Abstr., 91, 140851 (1979).
120. A. P. Da Luz, ZA Patent No. 7301720; Chem. Abstr., 83, 58805 (1975).
121. R. J. Stoodley, DT Patent No. 2202725; Chem. Abstr., 77, 126614 (1972).