SYNTHESIS OF PIVALOYLOXYMETHYL ESTERS OF PENICILLINS AND THEIR CONVERSION TO DEACETOXYCEPHALOSPORINS

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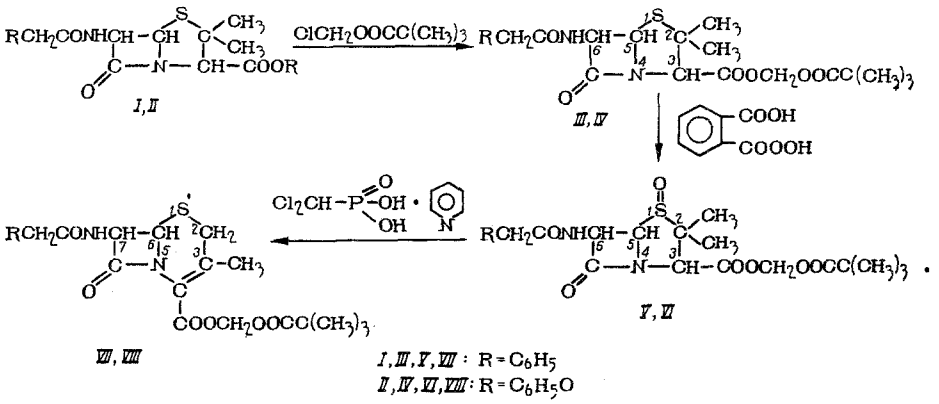
The chemical transformation of penicillins is an important method of obtaining compounds of the cephalosporin series, and has already found practical use in the production of cephalosporin preparations such as cephalexin and cephradin [1, 2]. The method of transformation which has received the most attention uses the trichloroethyl [1] and p-nitrobenzyl [3] esters of benzyl and phenoxymethyl penicillin sulfoxides. One of the defects of these methods is the difficulty of removing the ester-protecting groups from the carboxyl group in the final product. Hence, it was of interest to investigate the use of other penicillin esters for the transformation, esters which would either split more readily or would give a preparation suitable for use as an ester. The acyloxymethyl esters of penicillins [4] are compounds of this type. The possibility of using cephalosporin acyloxymethyl esters is also indicated in the literature [5].

The present work examines the possibility of converting penicillin pivaloyloxymethyl esters to the corresponding deacetoxycephalosporins, which are intermediates in the synthesis of cephalosporin preparations such as cephalexin or its esters.

The conversion of penicillins to cephalosporins involves the expansion of the five-membered thiazolidine ring to the six-membered thiazine ring, and takes place according to the scheme



The starting products for the transformation — benzylpenicillin and phenoxymethylpenicillin pivaloyloxymethyl esters (III) and (IV) — are obtained by reacting the potassium salt of benzyl or phenoxymethyl penicillin (I) or (II) with an equimolar quantity of pivaloyloxymethyl chloride in the presence of anhydrous sodium iodide. The compounds (III) and (IV) are characterized by IR, UV, and proton magnetic resonance spectra (see Tables 1 and 2). In the proton magnetic resonance spectrum of compound (III) there is a singlet in the region of aromatic proton resonance corresponding to the protons of the phenyl ring at 7.36 ppm. The amide proton appears as a wide doublet (6.49 ppm). The protons in the 5 and 6 positions and also in the methylene group of the ester radical form multiplets at 5.48-5.88 ppm, while the 5H and 6H protons of the multiplet give 2 doublets at 5.53 and 5.86 ppm

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TABLE 1. Penicillin Pivaloyloxymethyl Esters and Their Transformation Products

Compound	Melting point (in deg)*	$[\alpha]_D^{20}$ (c = 1, chloroform)†	R_f	Found (in %)				Empirical formula	Calculated (in %)			
				C	H	N	S		C	H	N	S
III	120—3	+101°	0,61	58,7	6,1	6,2	7,4	$C_{22}H_{28}N_2O_6S$	59,0	6,3	6,3	7,2
IV	Oil	+117°	0,67	57,2	6,1	6,2	6,7	$C_{22}H_{28}N_2O_7S$	57,0	6,1	6,0	6,9
V	131—6	+162°	0,32	56,8	6,2	6,0	6,7	$C_{22}H_{28}N_2O_7S$	57,0	6,1	6,0	6,9
VI	109—11	+168°	0,41	55,1	6,1	6,1	6,9	$C_{22}H_{28}N_2O_8S$	55,0	5,9	5,8	6,7
VII	171—4	+59°	0,56	59,5	6,0	6,2	6,9	$C_{22}H_{26}N_2O_6S$	59,2	5,8	6,3	7,2
VIII	98—101	+68°	0,62	57,5	5,8	6,4	7,1	$C_{22}H_{26}N_2O_7S$	57,2	5,7	6,1	6,9

*All substances melt with decomposition. Compound III was crystallized from methanol and V from ethyl acetate.
†For III $[\alpha]_D^{20}$ + 236° (c = 1, methanol) [13].

with constant spin—spin splitting J = 5 Hz. The proton in the 3 position and the protons of the CH_2 group of the benzyl radical appear in the spectra as singlets at 4.41 and 3.61 ppm respectively. The methyl groups in the 2 position and the methyl groups of the tert-butyl radical (ester group) appear as singlets at 1.46 and 1.20 ppm respectively. The 2-α- and 2-β-CH_3 groups might have been expected to give different chemical shifts; however, for (III) they are equivalent. In the proton magnetic resonance spectrum of compound (IV) the protons of the 2-α- and 2-β-CH_3 groups have different chemical shifts: 1.43 (α) and 1.59 (β) ppm. The protons of the phenyl group appear as two multiplets at 6.78-6.97 and 7.11-7.35 ppm. The compound (IV), compared to the CH_2 group of the benzyl radical of compound (III), is displaced towards the low-field region by 0.84 ppm; this agrees with the literature data [6, 7]. The amide proton in compound (IV) appeared as a broad signal, so that it was difficult to determine its chemical shift accurately.

Organic peracids are the most effective reagents for the oxidation of penicillin esters to sulfoxides. Thus, benzylpenicillin sulfoxide tert-butyloxycarbonyloxymethyl ester is obtained by the action of perbenzoic acid on the corresponding benzylpenicillin ester [8]. The reaction takes place at 0° in chloroform and is complete after 24 h.

We obtained benzyl and phenoxymethyl penicillin sulfoxide pivaloyloxymethyl esters (V) and (VI) by the action of a solution of monoperphthalic acid in ether on compounds (III) and (IV) respectively. The reaction takes place in chloroform at temperatures below 10° and is complete after 1-1.5 h; the process of oxidation is accompanied by the precipitation of phthalic acid. The use of excess monoperphthalic acid leads to the formation of the penicillin sulfone, although in the literature it is reported that penicillin sulfones are formed under more drastic conditions, for example the oxidation of penicillins with potassium permanganate in dioxane [9]. The disappearance of a spot of the original penicillin on a chromatogram indicates that the oxidation is complete.

Compounds (V) and (VI) were characterized by IR, UV, and proton magnetic resonance spectra (see Table 2). The proton magnetic resonance spectrum of compound (V) differs from that of the starting compound (III) in the shift in the strong-field region by 0.53 ppm for the 5H proton and by 0.15 ppm for the 6H proton. The methyl groups in 2 position also have different chemical shifts: The α-CH_3 appears at 1.23 ppm (magnetoequivalent of the methyl group of the tert-butyl radical), and the β-CH_3 group has a chemical shift of 1.65 ppm, i.e., the α-CH_3 group under the influence of the sulfoxide group is displaced in the strong-field region by 0.23 ppm, and the β-CH_3 group in the weak-field region by 0.19 ppm, which agrees with the literature data [1, 6]. In the proton magnetic resonance spectrum for compound VI the same shift is observed for the 5H and 6H protons in the strong-field region and for the 2-α- and 2-β-methyl groups. The position of the amide proton in the spectrum of V is not sharply defined.

The method commonly described in the literature for the transformation of penicillin sulfoxide esters involves boiling the ester in neutral solvent (benzene, toluene, dioxane) in the presence of an acid catalyst. The yield of deacetoxycephalosporinic ester and the amount of secondary products formed depend on the catalyst, temperature, and duration of the reaction. When benzylpenicillin sulfoxide methyl ester is boiled in benzene in the presence of acetic anhydride for 21 h, in addition to 7-phenylacetamido-3-methylcephem-3-

TABLE 2. Spectral Characteristics of Penicillin Pivaloyloxymethyl Esters and Their Transformation Products

Compound	UV spec.		IR spectrum CO (cm^{-1})			Proton magnetic resonance spectrum (δ, ppm)†									
	λ_{max} (in nm)	lg ε	β-lactam	ester	amide	C $(CH_3)_2$	2-CH_3 α	2-CH_3 β	2-CH_2	3-H	5-H	6-H	7-H	$-COOCH_2-$	CH_2	NH	C_6H_5
III	252*	2,47	1780	1765	1685	1,20s	1,46s	1,46s	—	4,41s	5,53d I=5 Hz	5,86d I=5 Hz	—	5,48—5,88 m	3,61s	6,49d I=9Hz	7,36s
	258	2,40															
	265	2,25															
IV	263	3,03	1780	1750	1685	1,13s	1,43 s	1,53s	—	4,40s	5,47d I=5 Hz	5,72 d I=5 Hz	—	5,58—5,83 m	4,45s	—	6,78—6,97m 7,11—7,35m
	269	3,17															
	276	3,06															
V	252*	2,38	1790	1755	1690	1,23s	1,23s	1,65s	—	4,66s	5,00d I=5 Hz	5,71d I=5 Hz	—	5,93—6,10 m	3,60s	—	7,31s
	258	2,35															
	265	2,22															
VI	263	3,03	1800	1758	1694	1,14s	1,14s	1,62s	—	4,61s	5,00d I=5 Hz	5,63d I=5 Hz	—	5,86—6,10 m	4,45s	8,15d I=10 Hz	6,81—7,29m
	269	3,16															
	276	3,08															
	253*	3,84															
VII	258	3,87		1752—1762	1685	1,22s	2,11s‡		3,31q I=17Hz	—	—	4,93d I=5Hz	—	5,09—5,88 m	3,62s	6,64d I=9Hz	7,32s
	265	3,86															
VIII	262	3,89		1755—1770	1675	1,15s	2,05s‡		3,31 d I=17 Hz	—	—	4,92d I=5Hz	—	4,69—5,88m	4,45s		6,79—7,36m
	269	3,90															
	275	3,85															

*Shoulder.
†Abbreviations: s — singlet, d — doublet, q — quartet, m — multiplet.
‡ Methyl group in the 3 position.

carboxylic acid methyl ester, six secondary products are also formed [9]. The best procedure for this conversion uses organic derivatives of phosphonic acid as catalyst and absolute dioxane as solvent; this method guarantees a high yield (up to 80%) [1, 7]. Monopyridine salt of dichloromethylphosphonic acid (IX) was used as a catalyst for the conversion in the present work. The pivaloyloxymethyl esters of 7-phenylacetamido- (VII) and 7-phenoxyacetamido-3-methylcephem-3-carboxylic-4 acids (VIII) were obtained by boiling (V) and (VI) in absolute dioxane in the presence of (IX). Completion of the reaction was determined by the disappearance on a chromatogram of a spot of the original penicillin sulfoxide ester. The compounds (VII) and (VIII) were characterized by IR, UV, and proton magnetic resonance spectra (see Table 2). The proton magnetic resonance spectra of compounds (VII) and (VIII) differ from those of the corresponding sulfoxides by the appearance at 3.27-3.31 ppm of a quartet corresponding to the 2-CH_2 group and the disappearance of the signal corresponding to the methyl groups in the 2 position of the penicillin molecule.

EXPERIMENTAL METHOD

The IR spectra were measured in mineral oil for (IV) and as potassium bromide pellets on a VR-10 apparatus. The UV spectra were recorded on an SF-4A apparatus. The proton magnetic resonance spectra (III), (V), and (VII) were taken on a Varian XL-100 apparatus using tetramethylsilane as internal standard. The proton magnetic resonance spectra (IV), (VI), and (VIII) were taken on a "Varian XA-100" apparatus, internal standard — hexamethyldisiloxane. The angles of rotation were measured on a "Roussel Jouan" apparatus. Thin layer chromatography was carried out with "Silufol" plates, the solvent system was benzene—ethyl acetate (2:1). Column separation was performed using silica gel "L 100/250 μ," elution was carried out with a benzene—ethyl acetate (4:1) system.

Benzylpenicillin Pivaloyloxymethyl Ester (III). A solution of I (7.45 g), anhydrous sodium iodide (0.75 g), and pivaloyloxymethyl chloride (3.01 g) [10] in absolute dimethylformamide (100 ml) is stirred for 36 h at 20°. It is poured into ethyl acetate (500 ml), washed in turn with cooled water (500 ml), sodium carbonate solution (200 ml, 3%) and water (2 × 150 ml). The ethyl acetate solution is separated, dried, and concentrated to dryness. The residue is washed on the filter with cooled ether, and dried. Yield 6.42 g III (73%).

Phenoxymethylpenicillin Pivaloyloxymethyl Ester (IV). This is obtained in 55% yield in the same way as (III) from 7.5 g of (II). After concentration of the ethyl acetate solution IV is obtained as a yellow oil which is dissolved in an equal volume of benzene, applied to a silica gel column, and then eluted. The eluate is concentrated and (IV) is obtained as a colorless oil.

Benzylpenicillin Sulfoxide Pivaloyloxymethyl Ester (V). To a solution of (III) (4.5 g) in dry chloroform (75 ml) at a temperature below 10° are added portions of a freshly prepared solution of monoperphthalic acid [11]. Completion of the reaction is determined chromatographically. The precipitate is separated, the solution treated with cooled 3% solution of sodium bicarbonate (2 × 40 ml), and water (2 × 40 ml). The organic layer is separated, dried and concentrated. The resulting oil is triturated with ether, the residue separated, washed with ether and dried. Yield 4.27 g (V) (92%).

Phenoxymethylpenicillin Sulfoxide Pivaloyloxymethyl Ester (VI). This is obtained in the same way as (V) as an oil in 67% yield. The oil as a 30% solution in benzene is applied to a silica gel column, eluted, and the eluate concentrated. The remaining oil is dissolved in a minimum quantity of dry ether. On standing, crystals of (VI) separate from the ether solution, they are removed and dried.

7-Phenylacetamido-3-methylcephem-3-carboxyl-4 Acid Pivaloylmethyl Ester (VII). A solution of (V) (4.65 g), (IX) (0.1 g) [12], dry pyridine (0.033 ml) in absolute dioxane (25 ml) is boiled for 12 h, completion of the reaction is determined chromatographically. The resulting dark brown solution is concentrated, the amorphous precipitate recyrstallized from ethanol. Yield 2.99 g (VII) (67%) as a white crystalline substance.

7-Phenoxyacetomido-3-methylcephem-3-carboxylic-4 Acid Pivaloyloxymethyl Ester (VIII). A solution of (VI) (1.94 g), (IX) (0.04 g) and dry pyridine (0.013 ml) in absolute dioxane (20 ml) is boiled for 11 h. Completion of the reaction is determined chromatographically. The resulting dark brown solution is concentrated, the remaining oil applied as 40% benzene solution to a silical gel column and eluted. The eluate is concentrated, and the colorless oil dissolved in a minimum quantity of dry ether. On standing, crystals form in the ether solution and are separated and dried. Yield 0.87 g (VIII) (47%).

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