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THE PREPARATION AND PROPERTIES OF 6-PHENYLACETAMIDO- AND 6-PHENOXYACETAMIDOPENICILLAN-3-ACETIC ACIDS ("HOMOPENICILLINS")

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6-Phenylacetamido- and 6-phenoxyacetamidopenicillan-3-acetic acids ("homopenicillins") have been obtained from benzyl- and phenoxymethylpenicillins respectively, via their diazoketones. In these compounds, the carboxyl group is separated from the basic thiazolidine-β-lactam ring of the penicillins by a methylene group, The homopenicillins, which were characterized as their anilides, possess low antibacterial activity and are powerful penicillinase inducers.

One of the most complex problems in the study of penicillins is that of the relationship between structure and biological activity. As a result of a large number of investigations (for a summary see [1, 2]), it has been found that, apart from the side-chain and the methylene group, the penicillin molecule is extremely specific. However, until recently the significance of the carboxyl group in the 3-position had not been examined. It had earlier been shown that esters and substituted amides of penicillins were completely inactive, while unsubstituted amides, nitriles and phenylhydrazides possessed low activity. It was therefore thought that it would be of interest to synthesize penicillin analogues possessing modified carboxyl groups. We describe here the synthesis, from benzyl- and phenoxymethylpenicillin, of their homologues, in which the carboxyl group is separated from the basic ring of the penicillins by a single methylene group.

The intermediate diazoketones (I) were obtained by the reaction of penicillin salts with thionyl chloride, followed by treatment of the reaction product with diazomethane.

The IR spectra of the diazoketones showed the presence of the β-lactam ring (bands at 1788–1790 cm^{-1}), absorption bands in the 2110–2115 cm^{-1} region corresponding to the stretching frequency of the $C=\overset{-}{N}=\overset{+}{N}$ group, and valency stretching bands of the carbonyl group of the diazoketone at 1645–1670 cm^{-1}. As reference compounds, the diazoketones from benzoic, phenylacetic and sebacic acids [3, 4] were prepared. The IR spectra of these compounds showed valency stretching bands of the diazo-group (2197–2115 cm^{-1}) and the α-diazo-substituted carbonyl group (1620–1626 cm^{-1}). The literature values are 2040–2130 and 1640 cm^{-1} respectively [5].

The Antibacterial Activity of Homopenicillins and Penicillins

Test organism	Suppressant activity, μg/ml			
	Phenoxymethyl penicillin	Homophenoxymethylpenicillin	Potassium benzylpenicillin	Homobenzylpenicillin
Staphylococcus aureus 209P	0.005	2	0.005	0.5
Sarcina lutea	0.005	1.5	0.005	0.5
Bacillus subtilis	0.004	1.5	0.005	0.3

The progress of the purification of the diazoketones (I) was followed by the changes in the intensity of the bands at 2110–2115 cm^{-1}. The structure of the diazoketones I is also supported by their PMR spectra.

Both of the diazoketones obtained possess significant biological activity (for instance, the diazoketone derived from benzylpenicillin suppresses Staphylococcus aureus 209P at a concentration of the order of 1 γ/ml); they are of course many times less active than the parent penicillins, but they are comparable in activity with several widely-used antibiotics.

Numerous methods for converting diazoketones to the corresponding homoacids are known, but the majority of these are not applicable to compounds of the penicillin series. Use of the Arndt-Eistert method [6] gave a product which did not possess a β-lactam ring. Attempts to convert the diazoketone from benzylpenicillin into the methyl ester

of the corresponding homoacid by the use of silver benzoate as catalyst in a homogeneous medium were also unsuccessful [7]. In this case also, the β-lactam ring was opened.

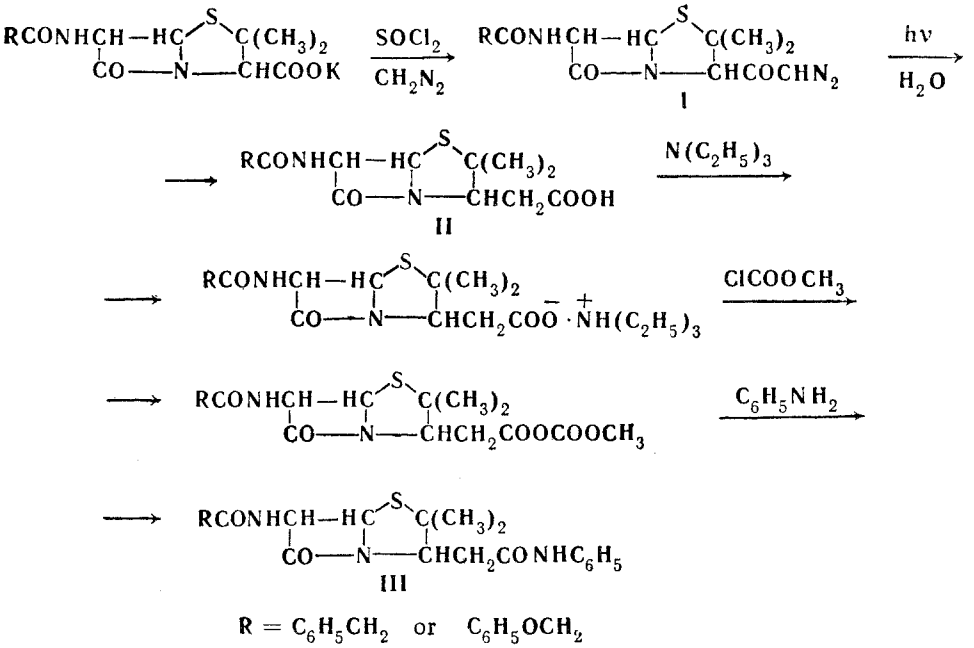
Irradiation of aqueous-dioxane solutions of the diazoketones from phenoxymethylpenicillin and benzylpenicillin with BUV-15 lamps gave small yields of homophenoxymethylpenicillin and homobenzylpenicillin (II). The homopenicillins were active, but in comparison with the parent penicillins their activity was small (cf. table).

It is interesting that the homopenicillins are very powerful promoters of penicillinase formation, being comparable with methicillin and much more effective than benzyl- and phenoxymethylpenicillin in this respect (according to the results of S. M. Chaikovskii).

The homopenicillins were characterized as their anilides (III), which were prepared by the action of aniline on the mixed anhydrides obtained from the triethylamine salts of the homopenicillins and chloroformate esters, according to the method described for the amides of phenoxymethylpenicillin [8]. The structure of the homopenicillin anilides was confirmed by their PMR spectra.

The presence in the IR spectrum of homophenoxymethylpenicillin anilide of a band at 1785 cm^{-1}, and in the spectrum of homobenzylpenicillin anilide at 1780 cm^{-1}, (in chloroform) shows the presence of the β - lactam ring. Further evidence of the presence of this ring is provided by iodometric titration. It is of interest that when the IR spectra are recorded in the crystalline state, as in the case of phenoxymethylpenicillin, the absorption frequency of the β-lactam carbonyl group is shifted somewhat, to 1747 cm^{-1} in the case of homophenoxymethylpenicillin anilide, and to 1750 cm^{-1} in the case of homobenzylpenicillin anilide.

All the chemical reactions described in this paper are represented by the following scheme:



Experimental

Diazoketones (I). A chloroform solution of thionyl chloride was added in equimolar amount, with stirring, to a suspension of the dry potassium salt of benzylpenicillin in pure, dry chloroform at −5° to −8° C. The reaction mixture was kept for a further 30 min at this temperature, then added dropwise with stirring at room temperature to a chloroform solution of diazomethane (6–8 mole per mole of penicillin), nitrogen being evolved and the solution becoming cloudy. After standing for 40 hr at room temperature the mixture was filtered and vacuum-evaporated at a temperature not exceeding 30°. The resulting oil was dissolved in benzene, the insoluble portion discarded, and ether added to the benzene solution. The precipitate which formed was discarded, and the benzene-ethereal solution vacuum-evaporated at 30° to give an oily solid which was dissolved in chloroform and washed successively with an 0.2 M solution of Na_2HPO_4, water, 0.2 M citric acid, water, dried over anhydrous sodium sulfate and vacuum-evaporated at 30°. The residue was dissolved in benzene, ether added, the resulting precipitate removed, and the ethereal-benzene solution vacuum-evaporated. The residue on trituration with light petroleum gave a yellow powder. Yield 50%. Found: C 56.92, 57.07; H 5.56, 5.39; S 8.97, 9.19%. Calculated for $C_{17}H_{18}N_4O_3S$: C 56.96; H 5.06; S 8.92%.

The diazoketone from phenoxymethylpenicillin was prepared similarly.

Homophenoxymethylpenicillin and homobenzylpenicillin (II). The diazoketone from phenoxymethylpenicillin (1.5 g, 0.004 mole) was dissolved in 25 ml of pure dioxane and 10 ml of water. The solution was irradiated with BUV-15 lamps, with internal water cooling, agitation being effected by passage of a stream of inert gas. When the reaction was complete, the solution was acidified with 10% H_2SO_4 to pH ~2 and extracted 5 times with 5 ml of chloroform. The acid was removed from the chloroform layer by extraction with 8 × 5 ml of 5% sodium carbonate. The sodium carbonate extract was acidified to pH ~2 with 10% H_2SO_4, and extracted with 5 × 5 ml of chloroform. The residue after removal of the solvent was dried by repeated evaporation with benzene. Yield, 280 mg (19%) of homophenoxymethylpenicillin. Homobenzylpenicillin was obtained similarly, after irradiation for 18 hr, in the same yield.

The homophenoxymethylpenicillin was twice purified, as follows: it was dissolved in 15 ml of 5% $NaHCO_3$, the solution filtered, shaken with activated charcoal, again filtered, and acidified with 10% H_2SO_4 to pH ~ 2. The material which separated was dissolved in 15 ml of chloroform, the chloroform solution washed twice with 10 ml of water and vacuum-evaporated at ~30°. The resulting oily solid was dried by repeated evaporation with benzene, and on trituration with ether it solidified.

Homophenoxymethylpenicillin and homobenzylpenicillin anilides (III). Homophenoxymethylpenicillin (280 mg; 0.76 mM) was dissolved in 10 ml of pure, dry chloroform, cooled at 5° C, and 0.38 ml of a 2 M solution of triethylamine in chloroform (9.76 mM) added. After 30 min at 5°, 0.38 ml of a 2 M solution of methyl chloroformate in chloroform (0.76 mM) was added and the mixture kept for a further 30 min at 5°. 0.38 ml of a 2 M solution of aniline in chloroform was added to the resulting solution (9.76 mM), and after 1 hr the solution was washed successively with 25 ml of distilled water, 20 ml of an 0.2 M solution of citric acid, 20 ml of an 0.2 M solution of Na_2HPO_4, and twice with 25 ml of distilled water; after drying over calcined sodium sulphate the solution was filtered and vacuum-evaporated. The product (240 mg; 71%) was dissolved in 6 ml of ethanol, the insoluble material discarded, the solvent vacuum-distilled off and the residue recrystallized from ethanol to give needles, mp 206°-209° (Kofler block). Found: C 62.60; H 5.71; N 9.84; S 7.22%. Calculated for $C_{23}H_{25}N_3O_4S$: C 62.85; H 5.73; N 9.56; S 7.29%.

The anilide of homobenzylpenicillin was obtained similarly in 78% yield. After two recrystallizations from ethanol it melted at 211.5°-213° (Kofler block). Found: C 64.98, 65.18; H 5.75, 5.92; N 9.91, 9.96; S 7.25, 7.55%. Calculated for $C_{23}H_{25}N_3O_3S$: C 65.22; H 5.95; N 9.92; S 7.75%.

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