Conversion of Benzyl 6-Diazopenicillanate into 6-Phenylacetylhydrazono- and 6β-Phenylacetylhydrazino-penicillanic Acid

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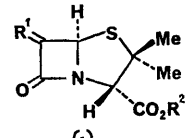
Summary Benzyl 6-diazopenicillanate (**1**; $R^1 = N_2$, $R^2 = CH_2Ph$) has been converted into 6-acetyl- and 6-phenylacetyl-hydrazonopenicillanic acid (**3**; $R^1 = Me$, $R^2 = H$ and $R^1 = PhCH_2$, $R^2 = H$) and 6β-acetyl- and 6β-phenylacetyl-hydrazinopenicillanic acid (**4**; $R^1 = Me$, $R^2 = H$ and $R^1 = PhCH_2$, $R^2 = H$); the latter is an effective antibiotic against a penicillin-resistant strain of *Staphalococcus aureus*.

THE potential of esters of 6-diazopenicillanic acid (**1**; $R^1 = N_2$)[1-3] as a source of new antibacterial agents has not yet been realised. With a view to developing stereoselective reductive methods leading to 6β-penicillanic acid derivatives, benzyl 6-diazopenicillanate (**1**; $R^1 = N_2$, $R^2 = CH_2Ph$) was prepared from penicillin G benzyl ester (**2**)[4] by a modification of the method of Hauser and Sigg,[1] in considerably improved yield.

Catalytic hydrogenation of benzyl 6-diazopenicillanate (**1**; $R^1 = N_2$, $R^2 = CH_2.Ph$) in dioxan over 5% palladium on barium sulphate gave benzyl penicillanate (**1**; $R^1 = H_2$, $R^2 = CH_2Ph$) as the only isolable product. However treatment of benzyl 6-diazopenicillanate (**1**; $R^1 = N_2$, $R^2 = CH_2Ph$) with triphenylphosphine in wet ether gave,



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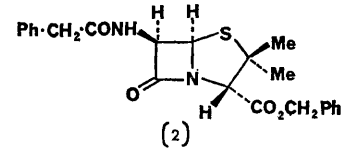

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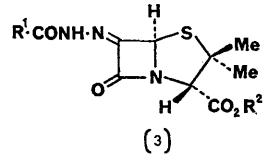

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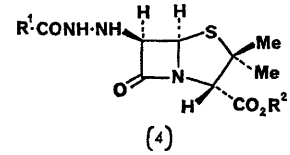

(4)

after chromatography on silica gel using chloroform as the eluant, a crystalline complex of triphenylphosphine oxide and benzyl 6-hydrazonopenicillanate, m.p. 123—125°. When penicillin G benzyl ester (**2**) was converted into the

complex without purification of the intermediates an overall yield of 27% was obtained. Unlike benzyl 6-diazopenicillanate (**1**; $R^1 = N_2$, $R^2 = CH_2Ph$) or benzyl 6-hydrazonopenicillanate (**1**; $R^1 = H_2N{\cdot}N{:}$, $R^2 = CH_2Ph$) (*vide infra*), the complex is indefinitely stable at 0°.

Although it was possible to isolate benzyl 6-hydrazonopenicillanate (**1**; $R^1 = H_2N{\cdot}N{:}$, $R^2 = CH_2Ph$) from the complex by chromatography on silica gel acylation was more satisfactorily achieved using the triphenylphosphine oxide complex. Acetylation with acetic anhydride in the presence of a catalytic amount of pyridine gave, after chromatography on silica gel, benzyl 6-acetylhydrazonopenicillanate (**3**; $R^1 = Me$, $R^2 = CH_2Ph$) which was hydrogenolysed over 10% Pd–C in ethanol to 6-acetylhydrazonopenicillanic acid (**3**; $R^1 = Me$, $R^2 = H$). Acylation of the triphenylphosphine oxide complex with phenylacetyl chloride in the presence of pyridine gave, after chromatography on silica gel, benzyl 6-phenylacetylhydrazonopenicillanate (**3**; $R^1 = PhCH_2$, $R^2 = CH_2Ph$), $[\alpha]_D^{20} + 268°$ (*c* 0·3, $CHCl_3$); λ_{max} (EtOH) 269 nm (ϵ 18,000), ν_{max} ($CHCl_3$) 1780 cm^{-1} (β-lactam); τ ($CDCl_3$), 4·0 (1H, s, 5-H). Hydrogenolysis over 10% Pd–C in ethanol gave 6-phenylacetylhydrazonopenicillanic acid (**3**; $R^1 = PhCH_2$, $R^2 = H$).

Stereoselective reduction of the benzyl 6-acylhydrazonopenicillanates was achieved by carefully controlled reduction with sodium borohydride in isopropyl alcohol to which solid carbon dioxide had been added in order to control the basicity of the solution. A single reduction product was isolated from each reaction, which were shown spectroscopically to be the benzyl 6β-acylhydrazinopenicillanates (**4**; $R^1 = Me$, $R^2 = CH_2Ph$ and $R^1 = PhCH_2$, $R^2 = CH_2Ph$). Benzyl 6β-phenylacetylhydrazinopenicillanate (**4**; $R^1 = PhCH_2$, $R^2 = CH_2Ph$), ν_{max} ($CHCl_3$) 1770 cm^{-1} (β-lactam); τ ($CDCl_3$) 5·5 (1H, q, $J_{5,6}$ 4·0 Hz, $J_{6,NH}$ 8·5 Hz, 6-H), 4·4 (1H, d, $J_{5,6}$ 4·0 Hz, 5-H) was hydrogenolysed over 10% Pd–C in ethanol to give 6β-phenylacetylhydrazinopenicillanic acid (**4**; $R^1 = PhCH_2$, $R^2 = H$).

6β-Phenylacetylhydrazinopenicillanic acid (**4**; $R^1 = PhCH_2$, $R^2 = H$) was a more effective antibiotic than 6-phenylacetylhydrazonopenicillanic acid (**3**; $R^1 = PhCH_2$, $R^2 = H$) against *Staphalococcus aureus* NCTC 6571 (Oxford strain) but considerably less effective than penicillin G. However 6β-phenylacetylhydrazinopenicillanic acid (**4**; $R^1 = PhCH_2$, $R^2 = H$) was not hydrolysed by *B. cereus* penicillinase and had a minimum inhibitory concentration of 16 μg ml^{-1} against a penicillinase producing *S. aureus*. Against the same cell inoculum, methicillin had a minimum inhibitory concentration of 4 μg ml^{-1}.

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