Desulfurization of Penicillins

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The discovery of nocardicin[1] and more recently of sulfacezin[2] has rekindled interest in the preparation of monocyclic β-lactams. In this connection, we have reinvestigated the Raney nickel desulfurization of penicillins, since desthiopenicillins **2** are useful intermediates in the synthesis of such antibiotics. Although the Raney nickel desulfurization of penicillins has been long known[3-7], our own studies now show that in addition to desthiopenicillins **2**, previously observed as the sole products of the reaction, considerable yields of azetidinones **3** can be obtained under controlled conditions (Table).

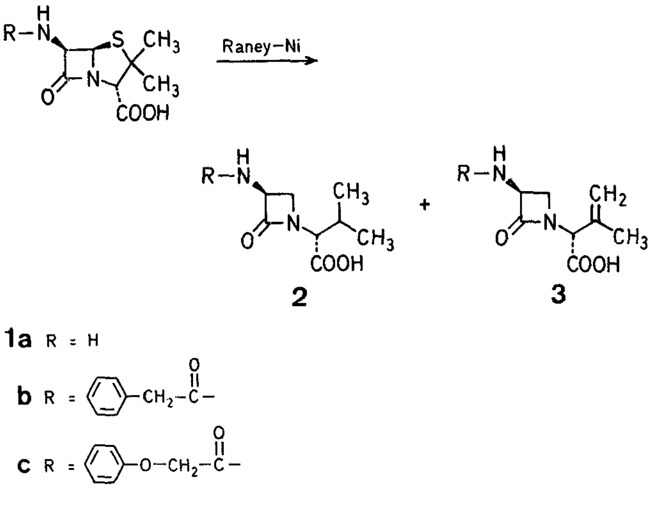


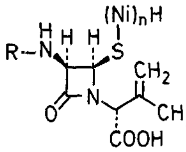
Table. Product Distribution from the Desulfurization of Penicillins **1**

Substrate	Yield [%] of **2** + **3**	Product Distribution [%]	
		2	**3**
1a	31[a]	50	50
1b	35[b]	60	40
1c	38[b]	64	36

[a] Based on *N*-benzyloxycarbonyl derivative.

[b] Based on the corresponding benzhydryl ester.

The structure of **3a** has been confirmed by X-ray crystallography[8]. The formation of **3** is not completely unexpected if one assumes the intermediacy of **4** in the described reactions. A similar intermediate has been suggested previously[6]. Compounds of type **3**, which have been prepared by multi-step syntheses[9], are versatile intermediates since their olefinic group allows various functionalizations. For example, they are converted easily to 3-acylamino-2-azetidinones (**5**)[10], which serve particularly well in the preparation of the monocyclic β-lactam antibiotics[11, 12].



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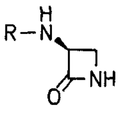

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Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. I.R. and U.V. spectra were recorded on Digilab FTS 14 and Cary Model 14 spectrophotometers, respectively. ^{1}H-N.M.R. spectra were obtained on a Varian XL-100 instrument. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Preparative high performance liquid chromatographies (H.P.L.C.) were carried out on a Waters Autoprep 500 instrument. The Raney nickel used in our experiments was of type 28 (W. R. Grace & Co.).

Desulfurization of Sodium 6-Aminopenicillanate (Sodium Salt of 1a):
A solution of 6-aminopenicillanic acid (**1a**; 64.8 g, 0.3 mol) and sodium hydrogen carbonate (25.9 g, 0.3 mol) in water (750 ml) is poured into a well stirred suspension of Raney-Ni (650 g) in water (1350 ml) and placed in a preheated bath (76 °C) with vigorous stirring for 35 min. The mixture is cooled immediately, filtered, and washed with water (100 ml). To the combined filtrate, sodium hydrogen carbonate (51.8 g, 0.62 mol) and benzyl carbonochloridate (60 ml, 0.42 mol) in acetone (60 ml) are added. The resulting mixture is stirred vigorously for 3 h, washed with dichloromethane (3 x 750 ml), acidified to pH 3 with concentrated hydrochloric acid at 0 °C, and stirred at room temperature for 1 h. Filtration of the solids gives a mixture of the *N*-benzyloxycarbonyl derivatives of **2a** and **3a**; yield: 30.2 g (31%). The derivatives ratio of **2a** : **3a** is 1 : 1, based on the ^{1}H-N.M.R. signals at $\delta = 2.00$ and $\delta = 1.20$ ppm (CDCl$_3$ solution). The mixture can be used for further reactions such as isomerization, epoxidation, or bromination without further purification.

For analytical purposes, *2-(3-benzyloxycarbonylamino-2-oxo-1-azetidinyl)-3-methyl-3-butenoic acid* (derivative of **3a**) is obtained by crystallization of the mixture from methanol/water and then repeated recrystallization from chloroform; m.p. 151–152 °C; $[\alpha]_D^{25}$: $-129.40°$ (*c* 1.9728, DMSO); purity: 97% (according to ^{1}H-N.M.R.).

$C_{16}H_{18}N_2O_5$	calc.	C 60.37	H 5.70	N 8.80
(318.3)	found	60.10	5.81	8.80

I.R. (KBr): $\nu = 1757$ cm^{-1} (β-lactam C=O).

^{1}H-N.M.R. (DMSO-d_6/TMS): $\delta = 1.80$ (s, 3H, CH$_3$); 3.26 (dd, 1H, $J = 5.2$ Hz, 2.5 Hz, 4-H); 3.72 (t, 1H, $J = 5.2$ Hz, 4-H); 4.7 (m, 1H, 3-H); 4.78, 4.98 (2s, 2H, =CH$_2$); 5.06 (s, 2H$_{\text{benzylic}}$); 5.07 (s, 1H, >CH–COOH); 7.35 (m, 5H$_{\text{arom}}$); 8.06 ppm (d, 1H, $J = 8$ Hz, NH).

Desulfurization of Potassium 6-Phenylacetamidopenicillanate (Potassium Salt of 1b):
To a solution of potassium 6-phenylacetylaminopenicillanate (11.5 g, 0.03 mol) in water (600 ml) is added Raney Ni (72 g). The mixture is placed in a preheated oil bath (165 °C), vigorously stirred for 15 min, then cooled immediately, filtered, and the filter residue washed with water (50 ml). The combined filtrates are acidified to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 200 ml). The extract is washed with water (2 x 50 ml), dried with sodium sulfate, and evaporated in vacuo to leave an oil; yield: 6.4 g.

T.L.C. (silica gel; 60 : 3 : 1 ethyl acetate/acetic acid/water): two major spots with $R_f = 0.31$ (**2b**) and $R_f = 0.18$ (**3b**).

The mixture of **2b** and **3b** is dissolved in chloroform (60 ml) and a solution of diphenyldiazomethane (4,9 g, 0.025 mol) in dichloromethane (100 ml) is added in portions until the purple color persists. The mixture is stirred at room temperature for 3 h, excess diphenyldiazomethane is decomposed by addition of acetic acid (2 ml), the organic phase is washed with 5% sodium hydrogen carbonate solution (2 x 50 ml), water (2 x 50 ml) dried with sodium sulfate, and evaporated to dryness. The oily residue is purified by preparative H.P.L.C. (silica gel; 1 : 1 ethyl acetate/hexane; $R_f = 0.14$) and recrystallized from 1 : 1 ethyl acetate/hexane to give an inseparable 6 : 4 mixture (by ^{1}H-N.M.R.) of the benzhydryl esters of **2b** and **3b**. These esters can be used directly for subsequent reactions such as isomerization, epoxidation, or bromination to give separable products and the unreacted benzhydryl ester of **2b**.

Desulfurization of Potassium 6-Phenoxyacetamidopenicillanate (Potassium Salt of 1c):
The desulfurization method described above for potassium 6-phenylacetylpenicillanate is followed using potassium 6-phenoxyacetylaminopenicillanate (12.03 g, 0.03 mol) and Raney nickel (72 g) to give an inseparable 6.4 : 3.6 mixture of the benzhydryl esters of **2c** and **3c**; yield: 5.7 g (38%).

T.L.C. (silica gel; 1 : 1 ethyl acetate/hexane): $R_f = 0.22$.

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