β-Elimination as a General Process in Penicillin Chemistry. The Stereochemistry and Mechanism of Raney Nickel Desulphurisation of Penicillin G and Penicillin V

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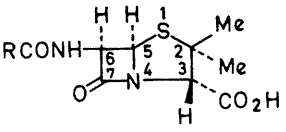
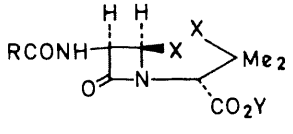
Summary The conversions of penicillin G and penicillin V into their dethio-derivatives with deuteriated Raney nickel proceed with retention of configuration at C-5 and with extensive incorporation of deuterium on the *gem*-dimethyl groups: a β-elimination mechanism is suggested to explain these results and the generality of β-elimination in penicillin chemistry is noted.

THE conversion of penicillin G (**1a**) into dethiopenicillin G (**2a**)[1] provided for the first time during the investigation of the structure of penicillins a degradation product which indicated the presence of a β-lactam ring in the skeleton of these compounds. In the course of these studies it was shown that refluxing of (**1a**) with Raney nickel for 15 min in aqueous solution produced, in addition to (**2a**), phenylacetyl-L-alanyl-D-valine (**3**) and the isobutyl-amide of phenylacetyl-L-alanine (**4**). Since the peptide (**3**) did not result from hydrogenolysis of (**2a**), it was suggested[2] that cleavage of the 1–5 and 4–5 bonds of penicillin are competitive reactions, the former leading to (**2a**), and the latter to (**3**) *via* an intermediate thiazepine. A subsequent demonstration[3] that (**5**) is converted in 97% yield into the methyl ester of phenylacetyl-D-alanyl-D-valine provides support for this pathway. The decarboxylation which produces (**4**) was not discussed and appears to be without precedent for a Raney-nickel reaction. Taking account of the decarboxylation step (**7**)→(**8**) which occurs during the rearrangement of a penicillin sulphoxide to a Δ^3-cephem[4] (**6**) → (**7**) → (**8**), an analogous scheme, *viz.*, (**1a**) → (**9**) → (**10**) → (**11**) → (**4**), can be written for the reaction of (**1a**) with Raney nickel; and if it is assumed that the step (**9**) → (**10**) [or an analogous sequence performed on (**1a**)] is reversible, it follows that more than two atoms of deuterium will be incorporated into (**2a**) when deuteriated Raney nickel is employed and that the excess of deuterium will be located on the methyl groups. Note that (**1a**), n-heptylpenicillin, 3-acetyl-5,5-dimethylthiazolidine-4-carboxylic acid, *S*-benzylpenicillamine, and biotin react with deuteriated Raney nickel to give, in each case, a dethio-compound which contains more than two atoms of deuterium.[5]

The desulphurisation of penicillins to dethiopenicillins with deuteriated Raney nickel has now been re-examined, mass spectrometry being used to study the extent and site of deuterium incorporation, and n.m.r. spectrometry to study the stereochemical course of the reaction at C-5. Penicillin G (**1a**) and penicillin V (**1b**) were converted into their dethio-derivatives (**2b**) and (**2c**)[6] on being refluxed for 15 min with Raney nickel in aqueous solution. In each case the derivatives (**2**) were isolated in analytically pure form as their methyl esters: m.p. of (**2b**), 116—117°; m.p. of (**2c**), 108—110°. The crystalline deuteriated dethiopenicillin esters (**2d**) and (**2e**) were prepared similarly in deuterium oxide solution following exchange of the Raney nickel by repeated washing with deuterium oxide. The n.m.r. data for the four compounds are summarized in Table 1. Deuteriation at C-2 in (**2d**) and (**2e**) is shown by the change in the 3-H absorption from a doublet to a singlet. The C-5 protons of (**2b**) and (**2c**) form the AB portion of an ABX system, J_{gem} 5·6 and 5·2; J_{cis} 5·6 and 5·2; J_{trans} 3·0 and 2·5 Hz,



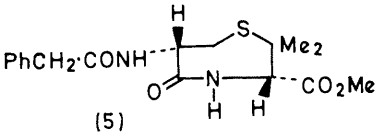


(1) a; R = $PhCH_2$
b; R = $PhOCH_2$

(2) a; R = $PhCH_2$; X = Y = H
b; R = $PhCH_2$; X = H; Y = Me
c; R = $PhOCH_2$; X = H; Y = Me
d; R = $PhCH_2$; X = D; Y = Me
e; R = $PhOCH_2$; X = D; Y = Me

$PhCH_2 \cdot CONH \cdot CH(Me)CONH \cdot CH(CHMe_2)CO_2H$
(3)

$PhCH_2 \cdot CONH \cdot CH(Me)CONH \cdot CH_2 \cdot CHMe_2$
(4)



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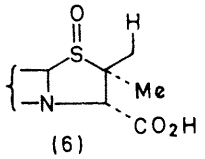

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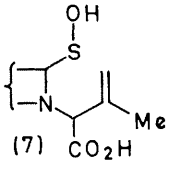

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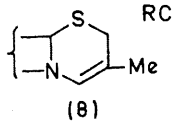

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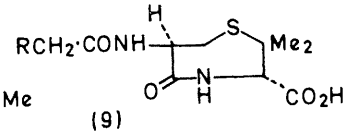

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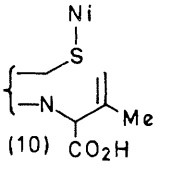

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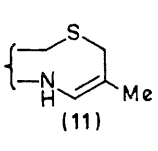

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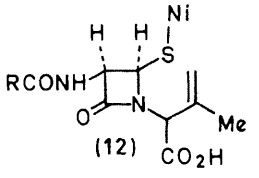

(12)

respectively. Since it is well established[7] that $J_{cis} > J_{trans}$ for β-lactam protons, it is possible in each case to assign the low-field absorption of the C-5 protons to 5α-H and the high-field absorption to 5β-H. The deuteriated compounds (**2d**) and (**2e**) retain the 5α-proton, as a doublet (because of coupling to 6-H), and the absorption of the 5β-proton is absent. This result demonstrates that the replacement of sulphur by deuterium at C-5 proceeds with retention of configuration.

From the mass spectra of the four compounds the following fragments were used to locate the deuterium atoms: M, $M - 59$ (loss of CO_2Me), $M - 87$ (loss of CO_2Me and the β-lactam carbonyl group), $RCONHCH{=}CH_2$ (cleavage of the β-lactam ring by reverse cycloaddition, R denoting the side chain), R, RCO, RNCO. In the deuteriated compounds the patterns at M, $M - 59$, and $M - 87$ revealed that extensive incorporation of deuterium had occurred. For both (**2b**) and (**2d**), peaks were observed at *m/e* 91 ($C_7H_7^+$), 118 ($PhCHCO^{+\cdot}$), 119 ($PhCH_2CO^+$), and 133 ($PhCH_2NCO^{+\cdot}$). For both (**2c**) and (**2e**), peaks were observed at *m/e* 77 (Ph^+), 94 ($PhOH^{+\cdot}$), 107 ($PhOCH_2^+$), and 149 ($PhOCH_2NCO^{+\cdot}$). These results show that deuterium is not incorporated in either case into the benzene ring or the side-chain methylene group, in contrast to an earlier finding.[5] The ions $[RCONH{\cdot}CH{=}CH_2]^{+\cdot}$, which appear at *m/e* 161 in (**2b**) and 177 in (**2c**) were shifted in (**2d**) and (**2e**) to 162 and 178, respectively. Therefore, each contains one deuterium, as expected for the incorporation of one deuterium at C-5 in the dethiopenicillins, already demonstrated; deuterium is not incorporated into (**2d**) and (**2e**) at C-6. Since deuterium is not present in the methoxycarbonyl group (introduced following the reaction), or at C-3 (from the n.m.r. data), the total amount of deuterium in (**2d**) and (**2e**) must be ascribed to the one deuterium at C-5, the one deuterium at C-2, and the total amount of deuterium introduced into the *gem*-dimethyl groups.

TABLE 1

The n.m.r. spectra of the methyl dethiopenicillinates (**2a**)—(**2d**)

Compound	2-H	Methyl groups	3-H	5α-H	5β-H	6-H	CH_2	OMe	Phenyl
				Assignment[a]					
(**2a**)	7·4—8·15 (m)	9·02 (d, 6·4 Hz)	5·8 (d, 7·6 Hz)	6·1 (t, 5·2 Hz)	6·57 (q, 5·2, 2·5 Hz)	5·04—5·37 (m)	6·44	6·27	2·74
(**2b**)	[b]	9·04 (s)	5·79 (s)	6·14 (d, 5·0 Hz)	[b]	5·02—5·44 (m)	6·42	6·27	2·67
(**2c**)	7·77—8·17 (m)	9·00 (d, 6·8 Hz) 9·03 (d, 6·8 Hz)	5·75 (d, 7·6 Hz)	6·05 (t, 6·5 Hz)	6·47 (q, 5·6, 3·0 Hz)	4·84—5·24 (m)	5·54	6·27	2·44—3·19 (m)
(**2d**)	[b]	8·99(s) 9·02(s)	5·75 (s)	6·1 (d, 5·4 Hz)	[b]	4·8—5·0 (m)	5·54	6·29	2·5—3·1 (m)

[a] Chemical shift values are reported in τ units; the chemical shifts of the NH protons are not shown.
[b] Not observed.

unsuccessful,[8] and it is generally accepted that the reaction proceeds *via* radical intermediates. Elimination–addition processes would then account for the incorporation of the excess of deuterium when this mechanism applies. However, a radical mechanism cannot account for the present results for three reasons: the excess of deuterium is introduced only on one side of the original sulphur atom; the reaction is stereoselective; the stereoselectivity is such that the thermodynamically less stable product is obtained.[9] At present a sequence (**1**) ⇄ (**12**) → (**2**) appears necessary to account for the results; the nature of the bonding to nicke in (**12**) is unknown, but the analogy to the hydrogenolyses of some benzylic alcohols, for which retention of configuration with Raney-nickel catalysts is also observed,[10] should be noted.

TABLE 2

Deuterium content of (**2d**) *and* (**2e**)

Compound	$^2H_0$	$^2H_1$	$^2H_2$	$^2H_3$	$^2H_4$	$^2H_5$	$^2H_6$	$^2H_7$	$^2H_8$
	Percentage deuterium (total)								
(**2d**)	9·0	11·5	16·9	24·7	12·6	11·3	6·5	4·0	3·4
(**2e**)	3·3	7·8	14·1	27·4	16·0	15·3	6·1	5·4	4·7

The Raney nickel used in the present work[1] is slightly more active than the W-2 catalyst used by most investigators,[11] but it seems unlikely that our results are due solely to differences in the catalyst. This point and the role of β-elimination in the desulphurisation of penicillin sulphoxides and sulphones are under investigation. In penicillin, sulphur and the hydrogen atoms β to it at several different sites facilitate a variety of cleavage reactions of the thiazolidine ring, by an appropriate β-elimination. The examples now include rearrangement of penicillins to anhydropenicillins (loss of 3-H [12]), rearrangement of penicillin sulphoxides to Δ^3-cephems [loss of a methyl proton; *cf.* (**6**) → (**7**)[4]], and Raney-nickel desulphurisation. In addition, two otherwise inexplicable observations can be understood in terms of β-elimination mechanisms, *viz.*, the ready C-7 epimerization of cephalosporin sulphoxides,[13] and the (*R*) → (*S*) epimerization of penicillin sulphoxides.[14] Although the barrier to stereomutation of sulphoxides by pyramidal inversion is

35—43 kcal mol^{-1},[15] the (*R*) → (*S*) epimerization of penicillin sulphoxides proceeds in refluxing benzene.

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