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STEREOSPECIFIC SYNTHESIS AND OXIDATIVE TRANSFORMATION OF A SYNTHETIC 1,4-THIAZEPINE FROM D-PENICILLAMINE

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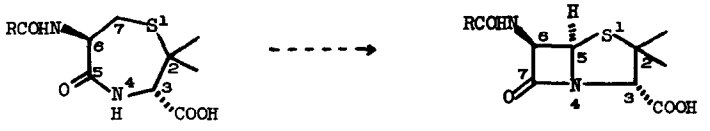
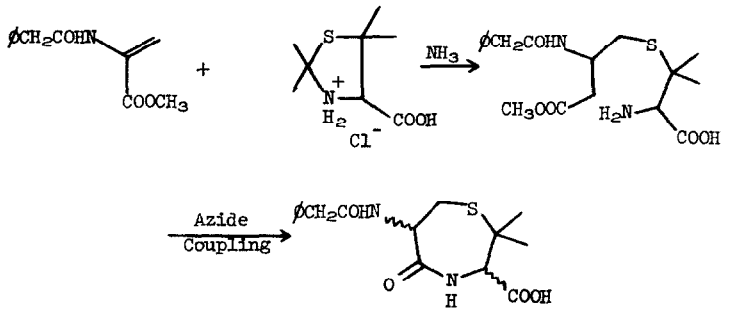
An advanced stage has been reached in the elucidation of the intermediates involved in the pathway of penicillin biosynthesis (1,2), but the place in the sequence where oxidative condensation between the β-position of the cyst(e)ine moiety and the peptide nitrogen atom occurs has not been determined. We consider that the earlier suggestions of the transannular formation of the C-N bond across a substituted 1,4-thiazepine derivative (I → II) (3-5) have not as yet received a definitive test.



I II

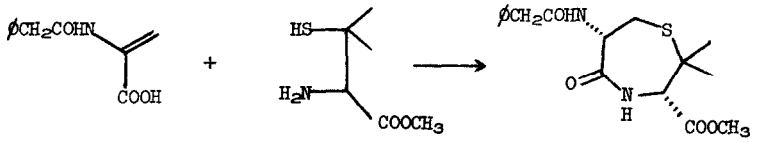
The requirement that the configurations at C-6 and C-3 of II be fixed before creation of the bicyclic ring system is implicit in the findings of Arnstein and his co-workers (1,6). Therefore, 3D-carboxy-2,2-dimethyl-5-oxo-6L-phenylacetamidoperhydro-1,4-thiazepine (I, R = $C_6H_5CH_2$) would be a desired stereomer to test for biosynthetic conversion to benzylpenicillin. By the steps shown below Arnstein and Clubb (5) synthesized 3-carboxy-2,2-dimethyl-5-oxo-6-phenylacetamidoperhydro-1,4-thiazepine (III) from DL-

penicillamine. This material, presumed by the authors to be a mixture of all four isomers, gave no indication of utilization for penicillin biosynthesis in P. chrysogenum.



III

We have found that syntheses of the 1,4-thiazepine VI from D-penicillamine methyl ester (IV) and α-phenylacetamidoacrylic acid (V) are stereospecific. In acetonitrile solution at ambient temperature, with N,N'-dicyclohexylcarbodiimide to form the peptide bond and triethylamine to



V IV VI

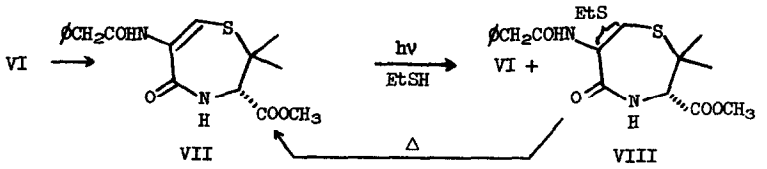
catalyze the addition of the thiol to the double bond, 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (VI) was obtained in 71% yield, m.p. 174-176°(reported for DL (7,8), 167°); $[\alpha]_D^{25}$ -36.5° (2% in $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3380 (N-H), 1742 (ester C=O) and 1660 $cm.^{-1}$ (amide C=O); λ_{max}^{EtOH} 252 (ε 215), 258 (ε 218), 264 (ε 167) and 268 mμ (ε 102). Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 7.99; mol. wt.,

350.43. Found: C, 58.03; H, 6.43; N, 7.98; mol. wt., 350 (mass spectrum, molecular ion), 357 (osmometric in benzene). The n.m.r. spectrum showed singlets at τ 6.20, 8.64 and 8.72 p.p.m. for the three methyl groups, and multiplets at τ 5.05 and 7.14 p.p.m. assignable to the C-6 and C-7 protons respectively. The amide protons exchanged in D_2O, whereupon the doublet at τ 5.37 p.p.m. (J = 8 c.p.s.) for the C-3 proton collapsed to a singlet. Aromatic and benzylic signals were found at τ 2.66 and 6.40 p.p.m.

When Woodward's Reagent K (9) was substituted for dicyclohexylcarbodiimide or N-phenylacetyl-2-bromovaline (10) was used in place of V, the same product was obtained but in lower yield. In no instance, however, could any of the 3D-6L diastereomer (I, methyl ester, with R = ϕCH_2) be isolated. Models show that VI (3D-6D) can assume both boat- and chair-like conformations in which both the amide and the ester groups occupy pseudo-equatorial positions. Thus, it probably possesses a significantly lower ground state energy than the 3D-6L diastereomer, and if reversibility of the Michael-type addition may be assumed, the stereochemical outcome matches prediction. The dependency upon peptide bond formation for the final step as followed in the Arnstein procedure (5), does not evade the likelihood of ring closure occurring readily only in the stereochemically-favored case (i.e., to give VI, as the acid) even though a mixture of isomers may be present at the penultimate stage.

The complete stereochemistry of our product was readily established as that shown in VI. Raney nickel desulfurization afforded methyl N-(N'-phenylacetyl-D-alanyl)-D-valinate, m.p. 117.5-118°, $[\alpha]_D^{25}$ 77.8° (3% in EtOH), in 97% yield, identical with a sample prepared from phenylacetyl-D-alanine and D-valine by azide coupling and diazomethane esterification. Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.72; H, 7.55; N, 8.75. Found: C, 63.43; H, 7.43; N, 8.56.

Reversal of the stereochemistry at C-6 is being attempted to achieve the correct configuration. To this end, chlorination (11) of VI at -60° in methylene chloride-carbon tetrachloride solution followed by dehydrochlorination of the metastable chlorosulfonium salt intermediate at 60° afforded 3D-carbomethoxy-2,2-dimethyl-5-oxo-6-phenylacetamido-2,3,4,5-tetrahydro-1,4-thiazepine (VII), m.p. 142.8-143° (12) (reported for DL (7), 185°); ν_{max}^{KBr} 1745 (ester C=0) and 1660 cm.$^{-1}$ (amide C=0); λ_{max}^{EtOH} 235 (ε 9650), 305 mμ (ε 5250); $[\alpha]_D^{25}$ 135° (3.5% in $CHCl_3$). Anal. Calcd. for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; mol. wt., 348.41. Found: C, 58.66; H, 5.89; N, 7.88; mol. wt., 348 (mass spectrum, molecular ion). The n.m.r. spectrum of VII showed singlets at τ 6.21, 8.48 and 8.72 p.p.m. for the three methyl groups, singlets for aromatic and benzylic protons at τ 2.72 and 6.37 p.p.m., and a doublet for the tertiary proton, J = 7 c.p.s., which collapsed upon addition of D_2O to the deuteriochloroform solution, τ 5.82 p.p.m. The sharp singlet, non-exchangeable with D_2O, at τ 2.34 p.p.m., was indicative of the C-7 proton.



Catalytic hydrogenation of VII has been unsuccessful to date under a variety of conditions, but it was a photoreduction of VII in ethyl mercaptan solution at 55° which regenerated 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamidoperhydro-1,4-thiazepine (VI) in 68% yield, thereby adding chemical proof to the spectroscopic assignment of structure VII and providing another example of stereospecificity in the generation of an optically active center at C-6. The 3D-6L- diastereomer (I, methyl ester, with

R = ϕCH_2) could not be isolated from the photoreaction, but a photoadduct VIII (20% yield) was obtained as a by-product, from which VII was regenerated quantitatively at 210°.

At this stage, we have presented a case encouraging experimental reinvestigation of the hypothesis that a transannular route is operative in the biosynthesis of penicillin. In this laboratory we are aiming at the synthesis of the 6L-3D isomer and a study of its oxidative transformations.

ACKNOWLEDGMENT

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