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DEAMINATION OF 6-AMINOPENICILLANIC ACID - THE ORIGIN OF A 2,3-DIHYDRO-1,4-THIAZIN-3-ONE

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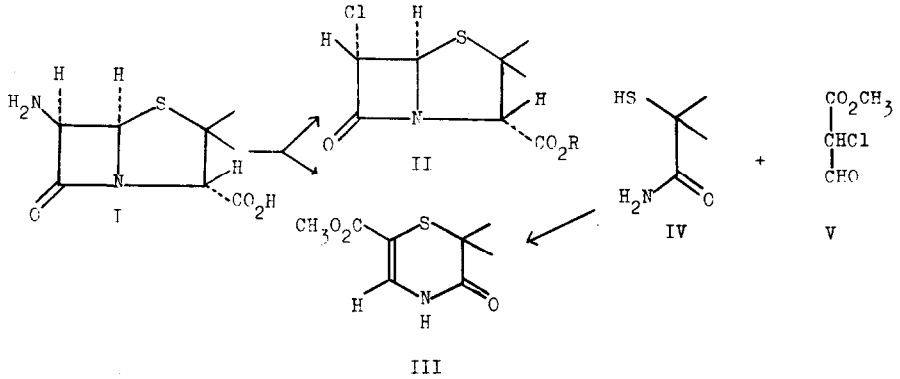
Deamination of 6-aminopenicillanic acid (I) with sodium nitrite in aqueous hydrochloric acid gives 6-chloropenicillanic acid (1). The stereochemistry of this product has been assigned recently (2) and is shown in II (R = H).

When I was treated with sodium nitrite in methanolic hydrochloric acid for four hours a neutral product was obtained which was fractionated by silica gel chromatography to give II (R = CH_3) in about 15% yield; m.p. 77-78°; $[\alpha]_D$ + 198° (0.25% in acetone). In addition a second crystalline material was isolated which was considered to be 6-carbomethoxy-2,2-dimethyl-2,3-dihydro-1,4-thiazin-3-one (III) on the basis of analytical and spectral information. Anal. Calcd. for $C_8H_{11}O_3NS$: C, 47.76; H, 5.47; N, 6.97; S, 15.92; mol. wt., 201.0460. Found: C, 47.71; H, 5.85; N, 6.75; S, 15.63; mol. wt., 201.0467 (mass spectrum, molecular ion). III was obtained in about 8% yield; m.p. 154-156°; ν_{max}^{KBr} 3250, 1705, 1680, 1660 and 1625 cm^{-1}; λ_{max}^{EtOH} 322 mμ (ε , 5,700). The n.m.r. spectrum of III was measured at 60 Mc in deuterochloroform solution with tetramethylsilane as an internal standard; it showed a singlet at τ8.55 p.p.m. for the gem dimethyl group, a singlet at τ6.25 p.p.m. for the ester methyl group, a doublet centred at τ2.65 p.p.m. (J = 6 c.p.s.) for the vinyl proton and a broadened signal for the NH proton at τ1.1 p.p.m. The latter peak disappeared upon addition of deuterium oxide to the solution and the doublet collapsed to a singlet.

In order to substantiate the structure proposed for III we considered a synthesis involving the condensation of 2-mercapto 2-methyl propionamide (IV) with methyl formylchloroacetate (V); a number of workers (3-5) have successfully prepared 2,3-dihydro-1,4-thiazin-3-ones from α-mercapto-amides and α-haloketones.

Although IV does not appear to have been reported, its synthesis was achieved by conventional methods. O-Ethyl S-2-(2-methyl propionamido) xanthate (6) was converted to its mixed anhydride with triethylamine and ethyl chloroformate. The anhydride was treated with ammonia and the product was fractionated by silica gel chromatography to give IV in about 20% yield; m.p. 126-127°; ν_{max}^{KBr} 3400, 3180 and 1665 cm^{-1}. IV gave a transient blue colour with aqueous ferric chloride solution. Anal. Calcd. for C_4H_9ONS: C, 40.34; H, 7.56; N, 11.76; S, 26.89. Found: C, 40.41; H, 7.60; N, 11.90; S, 26.95.

When IV and V were refluxed together in aqueous methanol a crystalline material was isolated in small yield; it was indistinguishable from III by i.r. and u.v. spectroscopy; m.p. 155-157° (undepressed when mixed with III).



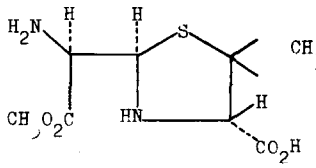
The origin of III from I is intriguing and involves a rearrangement and an oxidative decarboxylation. There is some precedent for the formation of the 2,3-dihydro-1,4-thiazine ring system from the penicillin nucleus; we have shown that II (R = CH_3) is readily rearranged to 3D-carbomethoxy-6-carbomethoxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine (VI, R = CH_3) in the presence of sodium methoxide (2). Consequently, 6-carbomethoxy-3D-carboxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine (VI, R = H) was prepared (2); m.p. 176-178° (decomp.); $[\alpha]_D$ -106 (0.4% in MeOH); ν_{max}^{KBr} 3330, 1750, 1710, 1660 and 1610 cm^{-1}; λ_{max}^{EtOH} 275 mμ (shoulder, ε, 5,500) and 313 mμ (ε, 10,000). Anal. Calcd. for $C_9H_{13}O_4NS$: C, 46.75; H, 5.63; N, 6.06. Found: C, 46.49; H, 5.71; N, 5.99.

When VI (R = H) was treated with sodium nitrite in methanolic hydrochloric acid for one hour, III was isolated in 30% yield, providing strong support for the intermediate participation of VI (R = H) in the formation of III from I.

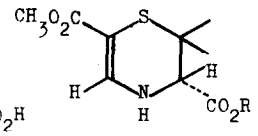
When VI (R = CH_3) was treated with nitrous acid under similar conditions III was not produced, indicating the necessity of the free carboxyl group for the formation of III. The neutral material which was obtained from this reaction was fractionated by silica gel chromatography to give 6-carbomethoxy-3-carbomethoxy-3-methoxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine (VII, R,R' = CH_3) in about 40% yield; m.p. 124-125°; ν_{max}^{KBr} 3330, 1740, 1690 and 1605 cm^{-1}; λ_{max}^{EtOH} 308 mμ (ε, 10,300). The n.m.r. spectrum showed the gem dimethyl group at τ 8.92 and 8.44 p.p.m., a methoxy methyl group at τ 6.80 p.p.m., two ester methyl groups at τ 6.26 and 6.10 p.p.m., a broadened signal at τ 3.8 p.p.m. for the NH proton and a doublet centred at τ 2.45 p.p.m. for the vinyl proton (J = 6 c.p.s.). Addition of deuterium oxide to the deuterochloroform solution caused the signal at τ 3.8 to disappear and the doublet to collapse to a singlet. Anal. Calcd. for $C_{11}H_{17}O_5NS$: C, 48.00; H, 6.18; N, 5.09. Found: C, 48.00; H, 6.23; N, 5.07.

The origin of VI (R = H) from I clearly involves methanolysis of the β-lactam and a deaminative rearrangement. 6-Chloropenicillanic acid (II, R = H) was excluded as an intermediate in this reaction since it failed to yield III in the presence of sodium nitrite and methanolic hydrochloric acid. The neutral product which was isolated in about 35% yield was predominantly methyl 6-chloropenicillanate (II, R = CH_3).

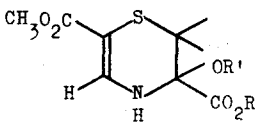
Methyl 4D-carboxy-5,5-dimethyl-α-amino-2-thiazolidineacetate (VIII) was prepared from I and sodium methoxide; m.p. 135-136°; ν_{max}^{KBr} 3350 (broad), 1745 and 1590 cm^{-1}. Anal. Calcd. for $C_9H_{16}O_4N_2S$: C, 43.55; H, 6.45; N, 11.29. Found: C, 43.59; H, 6.34; N, 11.12. When VIII was treated with nitrous acid III was obtained in about 10% yield, suggesting that I undergoes a preliminary methanolysis to VIII, which then undergoes deamination and ring expansion to VI (R = H).



VIII



VI

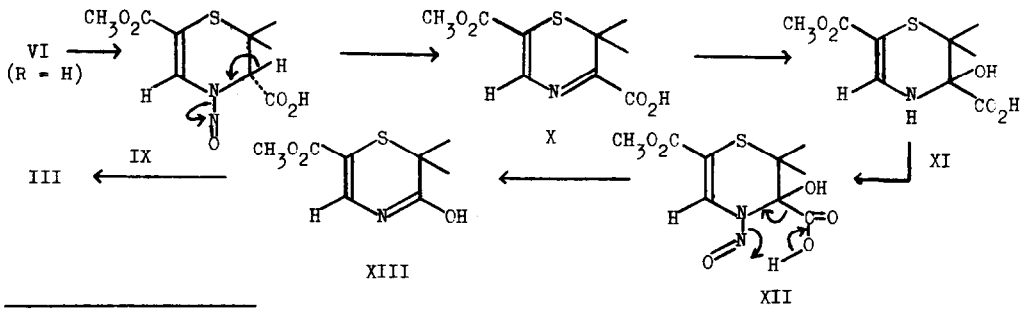


VII

Formally, the conversion of VI (R = H) to III involves a decarboxylation and a 4-electron transfer. In order to gain some information about the timing of these processes 6-carbomethoxy-3-carboxy-3-hydroxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine (VII, R, R' = H) was prepared. VII (R, R' = CH_3) was dissolved in dioxan-dilute hydrochloric acid to give VII (R = CH_3, R' = H)[a]; m.p. 116-118°; ν_{max}^{KBr} 3340, 3470, 1735, 1685 and 1605 cm^{-1}; λ_{max}^{EtOH} 307 mμ (ε, 10,600). The n.m.r. spectrum showed peaks at τ 8.87 and 8.56 p.p.m. for the gem dimethyl group, a broadened signal at τ 6.8 p.p.m. for the OH proton, two signals at τ 6.27 and 6.11 p.p.m. for the ester methyl groups, a broadened signal at τ 3.7 p.p.m. for the NH proton and a doublet centred at τ 2.43 p.p.m. (J = 6 c.p.s.) for the vinyl proton. The signals at τ 6.8 and 3.7 p.p.m. disappeared after the addition of deuterium oxide to the deuterochloroform solution and the doublet collapsed to a single line. Anal. Calcd. for $C_{10}H_{15}O_5NS$: C, 46.00; H, 5.75; N, 5.36; S, 12.27; mol. wt., 261.0666. Found: C, 46.07; H, 5.78; N, 5.46; S, 12.68; mol. wt. 261.0664 (mass spectrum, molecular ion).

Alkaline hydrolysis of VII (R = CH_3, R' = H) led to VII (R, R' = H)[b], which was converted to III in 57% yield when treated with sodium nitrite in methanolic hydrochloric acid.

The available evidence therefore indicates that the preliminary step in the conversion of VI (R = H) to III is a two-electron transfer which is followed by an oxidative decarboxylation. The reaction can be rationalised by assuming that VI (R = H) is nitrosated by the nitrous acid to give IX, which undergoes electron reorganization to yield X and hyponitrous acid. Hydration of X will yield XI which may be further nitrosated to XII. XII may then undergo an oxidative decarboxylation to give XIII which is the tautomeric form of III.



[a] This compound was first prepared in these laboratories by Mr. I. McMillan in an independent investigation.

[b] The structure of this acid was established by reconverting it to VII (R = CH_3, R' = H) with diazomethane.

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