Studies Related to Penicillins. Part II.[1] The Rearrangement of 6-β-Aminopenicillanic Acid to 2,3-Dihydro-6-methoxycarbonyl-2,2-dimethyl-1,4-thiazin-3-one[2]

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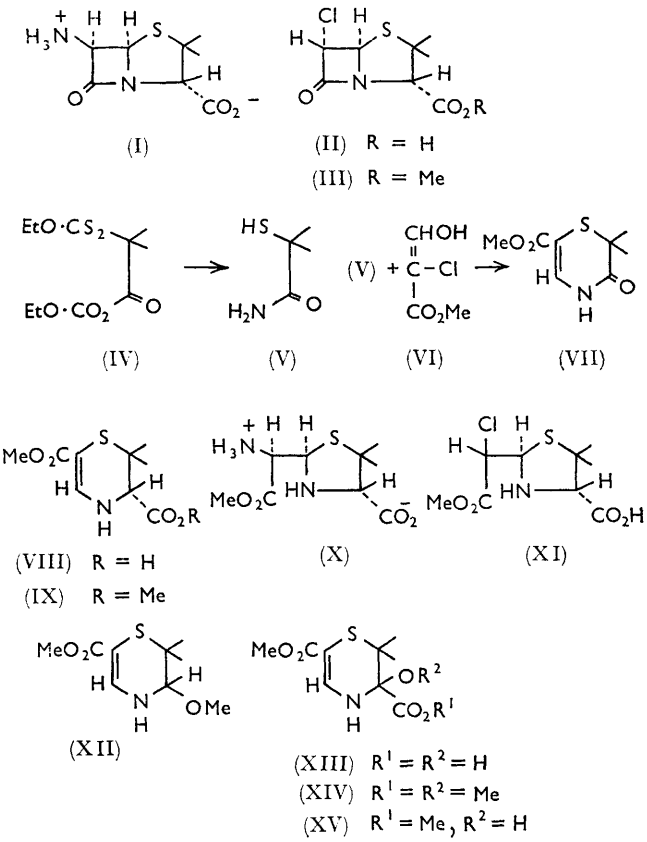
2,3-Dihydro-6-methoxycarbonyl-2,2-dimethyl-1,4-thiazin-3-one has been isolated from the reaction of 6-β-aminopenicillanic acid with sodium nitrite in methanolic hydrogen chloride. The mechanism of this rearrangement has been investigated and a pathway is proposed.

In connection with work aimed at the chemical modification of penicillins at position 6, we have studied the deamination of 6-β-aminopenicillanic acid (I), which is converted into 6-α-chloropenicillanic acid (II) in *ca.* 60% yield by sodium nitrite and dilute hydrochloric acid (*ca.* N).[1] In attempting to improve the yield of the acid (II), we studied the influence of methanol upon the reaction. Thus, with 70% methanolic hydrochloric acid (*ca.* N) the acid (II) was formed in an optimal yield of *ca.* 75%;[1] with 90% methanolic hydrochloric acid (*ca.* N) the yield was reduced to *ca.* 15%,[2] and no acid (II) was detected when freshly prepared methanolic hydrogen chloride (*ca.* N) was used. However, in the last two cases a crystalline, neutral compound, which was considered to be 2,3-dihydro-6-methoxycarbonyl-2,2-dimethyl-1,4-thiazin-3-one (VII) on the basis of analytical and spectral information, was isolated in low yield. The yield was subsequently increased to *ca.* 30% when the reaction was performed in methanolic hydrogen chloride (*ca.* N) containing an excess of sodium nitrite. Because of the unusual and complex nature of this rearrangement we investigated it more closely and now present some evidence for the sequence of reactions involved.

In order to substantiate the proposed structure (VII), a synthesis involving the reaction of methyl 2-chloro-3-oxopropionate (VI)[3] with 2-mercapto-2-methylpropionamide (V) was considered, since a number of workers have successfully prepared 2,3-dihydro-1,4-thiazin-3-ones from α-mercaptoamides and α-halogenoketones.[4] The mercapto-amide (V) was synthesised by ammonolysis of the mixed anhydride (IV) obtained from 2-ethoxythiocarbonylthio-2,2-dimethylacetic acid[5] and ethyl chloroformate. When the amide (V) was heated under reflux in methanol with methyl 2-chloro-3-oxopropionate (VI), a product was obtained in low yield which was indistinguishable from the thiazinone (VII).

The conversion of 6-β-aminopenicillanic acid (I) into the thiazinone (VII) must involve a large number of steps. However, there is some precedent for the formation of the 2,3-dihydro-1,4-thiazine ring system from the penicillin nucleus: 6-α-chloropenicillanic acid (II) is readily rearranged to (3*S*)-2,2-dihydro-6-methoxycarbonyl-2,2-dimethyl-1,4-thiazine-3-carboxylic acid (VIII) in the presence of sodium methoxide (2 equiv.).[1] Consequently, the acid (VIII) was treated with sodium nitrite in methanolic hydrogen chloride and the thiazinone (VII) was formed (*ca.* 40%). This result, which provides strong support for the intermediacy of the acid (VIII) in the rearrangement, allows the problem to be



restated in terms of two simpler questions. How is 6-β-aminopenicillanic acid (I) transformed into the thiazinecarboxylic acid (VIII), and how is the acid (VIII) converted into the thiazinone (VII)?

The transformation of 6-β-aminopenicillanic acid (I) into the thiazinecarboxylic acid (VIII) must involve a deamination, a methanolysis of the β-lactam, and a ring enlargement. However, since 6-α-chloropenicillanic

[1] Part I, I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.

[2] Part of this work has been previously published in preliminary form R. J. Stoodley, *Tetrahedron Letters*, 1967, 941.

[3] M. Erne, F. Ramirez, and A. Burger, *Helv. Chem. Acta*, 1951, **34**, 143; H. D. Pathak and D. R. Gupta, *Agra Univ. J. Research*, 1961, **10**, 147 (*Chem. Abs.*, 1962, **57**, 5797).

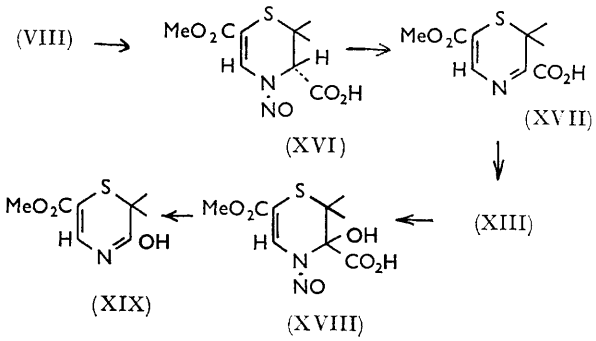
[4] H. Sokol and J. J. Ritter, *J. Amer. Chem. Soc.*, 1948, **70**, 3517; G. De Stevens, A. Halamadaris, and L. Dorfman, *ibid.*, 1958, **80**, 5198; G. S. Skinner, J. S. Elmslie, and J. D. Gabbert, *ibid.*, 1959, **81**, 3756.

[5] E. Biilmann, *Annalen*, 1906, **348**, 120.

acid (II) was not converted into the thiazinone (VII) under the reaction conditions, it was not an intermediate in the rearrangement. This result suggests that the methanolysis of 6-β-aminopenicillanic acid (I) precedes its deamination. Accordingly, (2*R*, 4*S*)-2-(*R*)-(methoxycarbonyl)aminomethyl-5,5-dimethylthiazolidine-4-carboxylic acid (X),† prepared from 6-β-aminopenicillanic acid (I) and methanolic sodium methoxide, was treated with sodium nitrite in methanolic hydrogen chloride, to give the thiazinone (VII) (*ca.* 30%). Furthermore, (2*R*,4*S*)-2-chloro(methoxycarbonyl)methyl-5,5-dimethylthiazolidine-4-carboxylic acid (XI) was not an intermediate, since under the reaction conditions it was not converted into the thiazinone (VII). Therefore, the rearrangement of 6-β-aminopenicillanic acid (I) to the thiazinecarboxylic acid (VIII) probably involves the initial formation of the amino-acid (X), which undergoes a deaminative ring expansion to give the acid (VIII). The dependence of the outcome of the reaction upon the methanol concentration may now be appreciated. Presumably in methanolic hydrogen chloride and sodium nitrite 6-β-aminopenicillanic acid (I) undergoes methanolysis faster than deamination, whereas the reverse is true in 70% methanolic hydrochloric acid.

The conversion of the thiazinecarboxylic acid (VIII) into the thiazinone (VII) formally involves a decarboxylation and a four-electron transfer. In order to obtain information about the timing of these processes, the sodium salt of the acid (VIII) [1] was oxidised to methyl 2,3-dihydro-3-methoxy-2,2-dimethyl-1,4-thiazine-6-carboxylate (XII) with methanolic mercuric acetate. However, no thiazinone (VII) could be detected from the reaction of the thiazine (XII) with nitrous acid. Consequently, the transformation does not involve an oxidative decarboxylation followed by an oxidation.

To test if the reaction involved an oxidation followed by an oxidative decarboxylation, 2,3-dihydro-3-hydroxy-6-methoxycarbonyl-2,2-dimethyl-1,4-thiazine-3-carboxylic acid (XIII) was required. Dimethyl 2,3-dihydro-3-methoxy-2,2-dimethyl-1,4-thiazine-3,6-dicarboxylate (XIV) was obtained in moderate yield from the reaction of the ester (IX) with sodium nitrite in methanolic hydrogen chloride, a transformation which incidentally demonstrated that a free 3-carboxy-group was necessary for thiazinone (VII) formation. In the presence of dioxan and dilute hydrochloric acid, the thiazine (XIV) readily exchanged its 3-methoxy-group to give dimethyl 2,3-dihydro-3-hydroxy-2,2-dimethyl-1,4-thiazine-3,6-dicarboxylate (XV), which gave the sodium salt of the desired acid (XIII) upon saponification. The acid (XIII) was converted (*ca.* 60%) into the thiazinone (VII) with sodium nitrite and methanolic hydrogen chloride. Consequently, the transformation of the thiazinecarboxylic acid (VIII) into the thiazinone (VII) occurs by an initial two-electron transfer to give the oxidised acid (XIII) which is converted into the thiazinone (VII) by an oxidative decarboxylation.



SCHEME 1

The precise mechanism of the above transformation is not established. However, the reaction may be accommodated by the route suggested in Scheme 1. Initially, the acid (VIII) is converted into its nitroso-derivative (XVI), which loses the elements of hyponitrous acid to give the imino-acid (XVII). The hydroxy-acid (XIII), formed by hydration of the imino-acid (XVII), is nitrosated to the derivative (XVIII), which undergoes an oxidative decarboxylation to yield the tautomeric form (XIX) of the thiazinone (VII).

The nitrous acid oxidation of the acid (VIII) to its hydroxy-derivative (XIII) has a number of analogies. Smith and Loeppky have shown that tertiary amines may be cleaved oxidatively with nitrous acid.[7] Similarly, Chow and Lee have observed that *N*-nitroso-amides undergo an acid-catalysed cleavage upon photochemical excitation.[8] However, no cleavage is observed in the present example (XIII), presumably because the α-hydroxy-amine grouping is ring-stabilised.

EXPERIMENTAL

For general experimental details see Part I.[1]

Reaction of 6-β-*Aminopenicillanic Acid* (I) *with Nitrous Acid.*—6-β-Aminopenicillanic acid (I) (2·16 g., 0·01 mole) and sodium nitrite (2·76 g., 0·04 mole) were added to ~N-methanolic hydrogen chloride (100 ml.) at 0°. The solution was stirred for 1 hr. at room temperature, diluted with chloroform, and shaken with water. The organic layer was then washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated to leave a crystalline residue (0·917 g.). No methyl 6-α-chloropenicillanate (III) was detected by n.m.r. spectroscopy; the major component was 2,3-*dihydro*-6-*methoxycarbonyl*-2,2-*dimethyl*-1,4-*thiazin*-3-*one* (VII) (*ca.* 30% by integration of n.m.r. spectrum). Ether was added to the crystalline residue, and the insoluble crude thiazinone was collected (0·391 g., 19%); m.p. 154—156° (from ether–chloroform); $\nu_{max.}$ (KBr) 3250 (NH), 1705, 1680, 1660, and 1625 $cm.^{-1}$, $\lambda_{max.}$ 322 mμ (ε 5700) [Found: C, 47·7; H, 5·85; N, 6·75; S, 15·65%; *M*, 201·0467 (mass spectrum). $C_8H_{11}NO_3S$ requires C, 47·75; H, 5·45; N, 6·95; S, 15·9%; *M*,

† The absolute stereochemistry of this compound was confirmed by converting it into ' dimethyl D-α-benzylpenicilloate.' [6]

[6] H. T. Clarke, J. R. Johnson, and R. Robinson, ' The Chemistry of Penicillin,' Princeton University Press, 1949, p. 612.

[7] P. A. S. Smith and R. N. Loeppky, *J. Amer. Chem. Soc.*, 1967, **89**, 1147.

[8] Y. L. Chow and A. C. H. Lee, *Canad. J. Chem.*, 1967, **45** 311.

201·0460], τ ($CDCl_3$) 8·55 (6H, s, *gem*-dimethyl), 6·25 (3H, s, CO_2Me), 2·65 (1H, d, *J* 7 Hz, vinylic proton), and 1·1br (1H, s, NH); addition of deuterium oxide to the solution caused the peak at τ 1·1 to disappear and the doublet to collapse to a singlet.

The sodium hydrogen carbonate extract was acidified and shaken with chloroform and the organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a syrupy residue (0·584 g.). N.m.r. spectroscopy and t.l.c. revealed that this product was a complex mixture containing little or no 6-α-chloropenicillanic acid (I). It was not further investigated.

2-Mercapto-2-methylpropionamide (V).—2-Ethoxythiocarbonylthio-2,2-dimethylacetic acid [5] (3·92 g., 0·02 mole) and triethylamine (2·02 g., 0·02 mole) were dissolved in methylene chloride (50 ml.). The solution was cooled to −5° and ethyl chloroformate (2·17 g., 0·02 mole) in methylene chloride (10 ml.) was added over 5 min. After 1 hr. the solution was washed with sodium hydrogen carbonate solution followed by water, dried ($MgSO_4$), and evaporated to leave a mobile syrup (4·2 g.). Concentrated ammonia (35%; 10 ml.) was added to the mixed anhydride (IV) and, after removal of solvent, the residue was chromatographed on silica gel. The derived *2-mercapto-2-methylpropionamide* (V) (0·50 g., 21%) had m.p. 126—127° (from ether), $\nu_{max.}$ (KBr) 3400 (NH) and 1665 (amide) $cm.^{-1}$ (Found: C, 40·4; H, 7·6; N, 11·9; S, 26·95. C_4H_9NOS requires C, 40·35; H, 7·55; N, 11·75, S, 26·9%). The material gave a transient purple coloration with ferric chloride solution, indicative of a free thiol group.

Reaction of 2-Mercapto-2-methylpropionamide (V) *with 2-Chloro-3-oxopropionate* (VI).—2-Mercapto-2-methylpropionamide (V) (0·476 g., 0·004 mole) and 2-chloro-3-oxopropionate (VI) [3] (0·544 g., 0·004 mole) were heated under reflux in 50% methanol (20 ml.) for 40 hr. The solution was extracted with chloroform and the extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent left a semi-crystalline residue recrystallised from ether (0·02 g., 2·5%), m.p. 155—157°, not depressed on admixture with the thiazinone (VII) obtained from the rearrangement.

Reaction of (3S)-*2,3-Dihydro-6-methoxycarbonyl-2,2-dimethyl-1,4-thiazine-3-carboxylic Acid* (VIII) *with Nitrous Acid*.—The thiazine-carboxylic acid (VI) [1] (2·31 g., (0·01 mole) and sodium nitrite (2·07 g., 0·03 mole) were added to ~N-methanolic hydrogen chloride at 0°, and the solution was stirred for 1 hr. at room temperature. It was then diluted with chloroform and shaken with water. The organic layer was washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation of the solvent left a crystalline residue (1·247 g.), mainly the thiazinone (VII) on the basis of n.m.r. spectroscopy (*ca.* 40% by integration). Ether was added to the crystalline material and the crude thiazinone (0·703 g., 35%) was filtered off; m.p. 154—156° (from ether–chloroform).

Reaction of 6-α-Chloropenicillanic Acid (II) *with Nitrous Acid*.—6-α-Chloropenicillanic acid (II) [1] (2·35 g., 0·01 mole) and sodium nitrite (2·07 g., 0·03 mole) were added to ~N-methanolic hydrogen chloride (100 ml.) at 0°, and the solution was stirred for 1 hr. at room temperature. It was then diluted with chloroform and the organic layer was washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation of the solvent left a syrup (0·985 g.), which contained two components (*ca.* 3 : 1 by n.m.r. spectroscopy). The major compound was methyl 6-α-chloropenicillanate (III) and the minor appeared to be 2-chloro(methoxycarbonyl)methyl-5,5-dimethyl-3-nitrosothiazolidine-4-carboxylic acid. Some of the signals attributable to the latter overlapped with those of the ester (III), although the CHCl and 2-protons gave rise to doublets with centres at τ 4·90 and 3·66 (*J* 7 Hz). No thiazinone (VII) was detected.

The sodium hydrogen carbonate extract was acidified and shaken with chloroform and the organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a syrup (1·06 g.). This material (n.m.r. spectroscopy) contained 6-α-chloropenicillanic acid (II) and probably 2-chloro(methoxycarbonyl)methyl-5,5-dimethyl-3-nitrosothiazolidine-4-carboxylic acid (*ca.* 1 : 3). Although there was overlap of some of the signals of each component the CHCl and 2-protons of the thiazolidine gave rise to doublets with centres at τ 4·95 and 3·73 (*J* 7 Hz), and the tertiary 4-proton gave a singlet at τ 5·36.

(2R,4S)*2-(R)-(Methoxycarbonyl)aminomethyl-5,5-dimethylthiazolidine-4-carboxylic Acid* (X).—1·3N-Sodium methoxide (40 ml., 0·05 mole) was added to a stirred suspension of 6-β-aminopenicillanic acid (I) (10·80 g., 0·05 mole) in methanol (200 ml.). After 5 min. the insoluble sodium 6-β-aminopenicillanate (3·575 g., 30%) was filtered off; $\nu_{max.}$ (KBr) 3390 (NH), 1750 (azetidinone), and 1615 (CO_2^-) $cm.^{-1}$. The filtrate was evaporated and the residue was dissolved in water (25 ml.). Concentrated hydrochloric acid was added dropwise, till crystallisation was initiated, and the suspension was cooled in a refrigerator. The crystalline *thiazolidinecarboxylic acid* (X) was collected, washed with a little ice-cold water and dried (5·952 g., 48%); m.p. 135—136° (from methanol), $\nu_{max.}$ (KBr) 3350 (NH), 1745 (CO_2Me), and 1590 (CO_2^-) $cm.^{-1}$ (Found: C, 43·6; H, 6·35; N, 11·1. $C_9H_{16}N_2O_4S$ requires C, 43·55; H, 6·45; N, 11·3%).

Reaction of the Thiazolidinecarboxylic Acid (X) *with Nitrous Acid*.—The acid (X) (2·48 g., 0·01 mole) and sodium nitrite (2·76 g., 0·04 mole) were added to ~N-methanolic hydrogen chloride (100 ml.) at 0°, and the solution was stirred for 1 hr. at room temperature. It was then diluted with chloroform and the organic layer was washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation of the solvent left a crystalline residue (0·915 g.), mainly the thiazinone (VII) (n.m.r. spectroscopy) (integration suggested *ca.* 30% yield). Ether was added to the residue and the thiazinone (VII) was filtered off (0·421 g., 21%); m.p. 155—156° (from ether–chloroform).

(2R,4S)*-2-Chloro(methoxycarbonyl)methyl-5,5-dimethylthiazolidine-4-carboxylic Acid* (XI). *Hydrochloride*.—The acidic material (1·06 g.), isolated from the reaction of 6-α-chloropenicillanic acid (II) with nitrous acid, was dissolved in ether (15 ml.), and an excess of ethereal hydrogen chloride was added. The crystalline *hydrochloride* which formed slowly, was collected after 12 hr. (0·355 g.); it was recrystallised from ether containing a little methanol; m.p. 149° (decomp.), $\nu_{max.}$ (KBr) 1725 $cm.^{-1}$ (CO_2Me and CO_2H) (Found: C, 35·55; H, 4·85; Cl, 23·4; N, 4·45. $C_9H_{15}Cl_2NO_4S$ requires C, 35·55; H, 4·95; Cl, 23·35; N, 4·6%), τ (pyridine) 8·46 and 8·16 (each 3H, s, *gem*-dimethyl), 6·36 (3H, s, CO_2Me), 5·78 (1H, s, 4-H), and 5·24 and 4·36 (each 1H, d, *J* 10 Hz, CHCl and 2-H respectively). The chemical shift of the 4-proton established the *S*-configuration at position 2.[9]

[9] I. McMillan and R. J. Stoodley, *Chem. Comm.*, 1968, 11.

Reaction of the Thiazolidinecarboxylic Acid (XI) *with Nitrous Acid.*—The hydrochloride of the thiazolidinecarboxylic acid (XI) (0·304 g., 0·001 mole) and sodium nitrite (0·207 g., 0·003 mole) were added to ~N-methanolic hydrogen chloride (10 ml.) at 0°, and the solution was stirred for 1 hr. at room temperature. It was then diluted with chloroform and the organic layer was washed with sodium hydrogen carbonate solution and water. Evaporation of the solvent left a residue (0·012 g.) which contained no thiazinone (VII) (t.l.c.).

Methyl 2,3-*Dihydro*-3-*methoxy*-2,2-*dimethyl*-1,4-*thiazine*-6-*carboxylate* (XII).—The sodium salt of the thiazinecarboxylic acid (VIII) [1] (1·215 g., 0·005 mole) was dissolved in methanol (50 ml.) and added to a solution of mercuric acetate (6·374 g., 0·02 mole) in methanol (50 ml.). An orange colour developed when the solutions were mixed, and the mercurous acetate which precipitated was collected (2·58 g., 100%) after 1 hr. The filtrate was saturated with hydrogen sulphide, filtered, evaporated to a small volume, diluted with chloroform, and washed with sodium hydrogen carbonate solution followed by water. The organic layer was dried ($MgSO_4$) and evaporated to leave a syrup (0·898 g., 83%), which crystallised upon addition of ether. The *thiazine* (XII) was recrystallised from ether containing a little chloroform; m.p. 128°, $\nu_{max.}$ (KBr) 3310 (NH), 1655 (unsaturated CO), and 1605 (C=C), cm.$^{-1}$, $\lambda_{max.}$ 305 mμ (ε 9400) [Found: C, 49·7; H, 7·0; N, 6·35%; *M*, 217·0771 (mass spectrum). $C_9H_{15}NO_3S$ requires C, 49·75; H, 6·9; N, 6·45%; *M*, 217·0773], τ ($CDCl_3$) 8·81 and 8·63 (each 3H, s, *gem*-dimethyl), 6·56 (3H, s, OMe), 6·26 (3H, s, CO_2Me), 5·91 (1H, d, *J* 5 Hz), 3·9br (1H, s, NH), and 2·40 (1H, d, *J* 7 Hz, vinylic 5-proton); addition of D_2O caused the peak at τ 3·9 to disappear and the doublets to collapse to singlets.

Reaction of the Thiazine (XII) *with Nitrous Acid.*—The thiazine (XII) (0·217 g., 0·001 mole) and sodium nitrite (0·138 g., 0·002 mole) were added to ~N-methanolic hydrogen chloride (10 ml.) at 0°, and the solution was stirred for 1 hr. It was then diluted with chloroform, washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation of the chloroform left a syrup (0·282 g.), which contained no thiazinone (VII) (n.m.r. spectroscopy).

Dimethyl 2,3-*Dihydro*-3-*methoxy*-2,2-*dimethyl*-1,4-*thiazine*-3,6-*dicarboxylate* (XIV).—The ester (IX) (2·45 g., 0·01 mole) and sodium nitrite were added to ~N-methanolic hydrogen chloride at 0°, and the solution was stirred at room temperature for 1 hr. It was then diluted with chloroform, washed with water, and dried ($MgSO_4$). Removal of the solvent left a syrup (2·04 g.), which was mainly the *ester* (XIV) (n.m.r. spectroscopy). Addition of ether to the syrup initiated crystallisation; the crystals (1·22 g., 44%) were collected and recrystallised from ether; m.p. 124—125°, $\nu_{max.}$ (KBr) 3330 (NH), 1740 (CO_2Me) 1690 (unsaturated CO), and 1605 (C=C) cm.$^{-1}$, $\lambda_{max.}$ 308 mμ (ε 10,300) (Found: C, 48·0; H, 6·25; N, 5·05. $C_{11}H_{17}NO_5S$ requires C, 48·0; H, 6·2; N, 5·1%), τ ($CDCl_3$) 8·92 and 8·44 (each 3H, s, *gem*-dimethyl), 6·80 (3H, s, OMe), 6·26 and 6·10 (each 3H, s, CO_2Me), 3·8br (1H, s, NH), and 2·45 (1H, d, *J* 7 Hz, vinylic 5-proton); addition of D_2O caused the signal at τ 3·8 to disappear and the doublet to collapse to a singlet.

Dimethyl 2,3-*Dihydro*-3-*hydroxy*-2,2-*dimethyl*-1,4-*thiazine*-3,6-*dicarboxylate* (XV).—The ester (XIV) (0·825 g., 0·003 mole) was dissolved in dioxan (30 ml.) and ~N-hydrochloric acid (30 ml.) was added. After 5 min. the solution was extracted with chloroform and the extract was washed with water and dried ($MgSO_4$). Removal of the solvent left the *thiazine* (XV) (0·45 g., 57%), m.p. 116—118° (from ether); $\nu_{max.}$ (KBr) 3340 (NH), 3470 (OH), 1735 (CO_2Me), 1685 (unsaturated CO), and 1605 (C=C) cm.$^{-1}$ $\lambda_{max.}$ 307 mμ (ε 10,600) [Found: C, 46·05; H, 5·8; N, 5·45; S, 12·7%; *M*, 261·0664 (mass spectrum). $C_{10}H_{15}NO_5S$ requires C, 46·0; H, 5·75; N, 5·35; S, 12·25%; *M*, 261·0666], τ ($CDCl_3$) 8·87 and 8·56 (each 3H, s, *gem*-dimethyl), 6·8br (1H, s, OH), 6·27 and 6·11 (each 3H, s, CO_2Me), 3·7br (1H, s, NH), and 2·43 (1H, d, *J* 7 Hz, vinylic 5-proton). The signals at τ 6·8 and 3·7 disappeared after addition of D_2O and the doublet collapsed to a singlet.

2,3-*Dihydro*-3-*hydroxy*-6-*methoxycarbonyl*-2,2-*dimethyl*-1,4-*thiazine*-3-*carboxylic Acid* (XIII).—The ester (XV) (0·261 g., 0·001 mole) was suspended in water and N-sodium hydroxide solution (1 ml., 0·001 mole) was added. The solid dissolved and after ~1 hr. the solution was evaporated to leave a glass, $\nu_{max.}$ 3400 (NH and OH), 1640br (unsaturated CO), and 1600 (CO_2^- and C=C) cm.$^{-1}$, τ (D_2O with sodium 3-trimethylsilylpropane-1-sulphonate as internal standard) 8·83 and 8·62 (each 3H, s, *gem*-dimethyl), 6·30 (3H, s, *gem*-dimethyl), and 2·38 (1H, s, vinylic 5-proton). The salt was dissolved in water and sodium ions were removed with IR 120 (H^+) resin. The syrup which remained after evaporation of the water was treated with an excess of diazomethane; t.l.c. and n.m.r. spectroscopy then indicated that it contained *ca.* equal amounts of the esters (XIV) and (XV).

Reaction of Sodium 2,3-*Dihydro*-3-*hydroxy*-6-*methoxycarbonyl*-1,4-*thiazine*-3-*carboxylate with Nitrous Acid.*—The salt (0·283 g., 0·001 mole) and sodium nitrite (0·138 g., 0·002 mole) were added to ~N-methanolic hydrogen chloride (10 ml.) at 0°, and the solution was stirred for 1 hr. at room temperature. It was then diluted with chloroform, washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Removal of the solvent left a crystalline residue (0·129 g., 60%), which was the thiazinone (VII) (n.m.r. spectroscopy), m.p. 154—156° (from ether-chloroform).

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