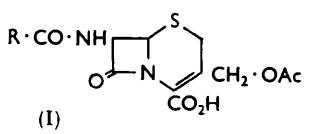
154. *Studies Related to Cephalosporin C. Part II.* A Synthetical Route to 5,6-Dihydro-4H-1,3-thiazines and 3,6-Dihydro-2H-1,3-thiazines.*

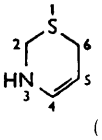
By G. C. Barrett, S. H. Eggers, T. R. Emerson, and G. Lowe.

The addition of thiobenzamide to methyl vinyl ketone has been found to give 5,6-dihydro-4-hydroxy-4-methyl-2-phenyl-4*H*-1,3-thiazine (VIII) under neutral, basic, and acidic conditions. The addition of thioacetamide to the vinyl keto-ester (XIII) gave the dihydrothiazine (XIV). Reduction of the latter with aluminium–amalgam gave the tetrahydrothiazine (XV) which with anhydrous acid at 0° was dehydrated to give, after basification, the 3,6-dihydro-2*H*-1,3-thiazine (XVII). This constitutes the first † synthesis of this heterocyclic system which is found in the antibiotic cephalosporin C.

The structure of cephalosporin C {I; R = D-^-O_2C·CH(NH_3^+)·[CH_2]$_3$·} was shown by chemical [1] and *X*-ray-analytical [2] methods to embody the hitherto unknown heterocyclic system 3,6-dihydro-2*H*-1,3-thiazine (II). A convenient synthetical route to this system is therefore a prerequisite to a total synthesis of cephalosporin C. Since, however, this heterocyclic system contains an enamine rather than a secondary amine, synthesis of the dihydrothiazine-β-lactam system (III) ‡ can be expected (because of the weak nucleophilic character of the enamine) to be difficult, and a desirable feature of the synthetical route would therefore be to introduce the double bond at a late stage of the synthesis. A synthetical route accommodating this feature has now been found.



(I)



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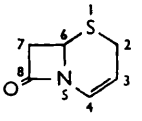
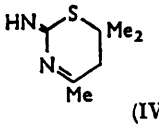
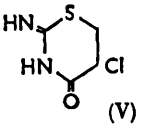


(III)

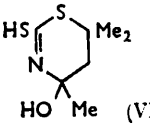
The nucleophilic character of sulphur derivatives is well known and their addition to double bonds which are αβ to an electron-withdrawing group, well established.[3] In spite of this we have been unable to find any description of the addition of a thioamide to an αβ-unsaturated ketone. Thiourea, however, has been shown to add to mesityl oxide [4] and to methyl α-chloroacrylate,[5] both initial products cyclising under the acidic conditions used, to give the heterocyclic compounds (IV) and (V), respectively. The addition



(IV)



(V)



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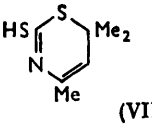


(VII)

of dithiocarbamic acid to mesityl oxide has also been described,[6] and the dihydrothiazine (VI), formed under virtually neutral conditions, was converted with aqueous acid into the thiazine (VII). This was the only product when dithiocarbamic acid and mesityl oxide

* Part I, preceding paper.

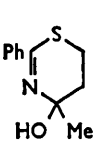
† Green *et al.*, ref. 7, describe a related synthesis. *Note added in Proof.* The conversion of a penicillin sulphoxide and its methyl ester into dihydrothiazine β-lactams has recently been reported by Morin *et al.*, *J. Amer. Chem. Soc.*, 1963, **85**, 1896.

‡ The name Δ^3-cephem has been suggested for this bicyclic system (see Morin *et al.*, *J. Amer. Chem. Soc.*, 1962, **84**, 3400).

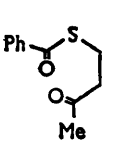
[1] Abraham and Newton, *Biochem. J.*, 1961, **79**, 377.
[2] Hodgkin and Maslen, *Biochem. J.*, 1961, **79**, 393.
[3] Houben-Weyl, "Methoden der Organischen Chemie," 1955, **9**, 120, and references there cited.
[4] Chase and Walker, *J.*, 1955, 4443.
[5] Behringer and Zillikens, *Annalen*, 1951, **574**, 140.
[6] Jansen and Mathes, *J. Amer. Chem. Soc.*, 1955, **77**, 2866.

were allowed to react in an aqueous acidic medium. The addition of thiols to αβ-unsaturated ketones, esters, and nitriles is usually base catalysed.[3]

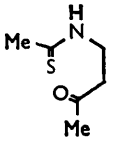
The addition of thiobenzamide to methyl vinyl ketone under neutral, basic (cf. ref. 7), aqueous acidic, and non-aqueous acidic conditions at 20° gave the dihydrothiazine (VIII) in each case. The structure was confirmed by acidic hydrolysis to the thiol-ester (IX). The reaction appears to be catalysed by acid since under these conditions reaction times are shorter and yields higher; base has little or no effect. Attempts to dehydrate the dihydrothiazine (VIII) under a variety of conditions were unsuccessful. The reaction of thioacetamide with methyl vinyl ketone under neutral, basic, or acidic conditions did not lead to a dihydrothiazine derivative. With constant-boiling hydrobromic acid, 4-mercaptobutan-2-one and an unidentified nitrogen-free product were obtained, suggesting that addition had taken place but that hydrolysis had subsequently occurred. Under basic conditions a small yield of a crystalline product was obtained which showed NH (3310 cm.$^{-1}$) and C=O (1705 cm.$^{-1}$) absorption bands. The nuclear magnetic resonance spectrum had signals at τ 7·80 (singlet, 3 protons) 7·47 (singlet, 3 protons), 7·13 (triplet, 2 protons), and 6·11 (quartet, 2 protons). The quartet centred at 6·11 became a triplet centred at 6·10 when deuterium oxide was added to the solution. This clearly indicated (cf. ref. 8) that the adduct was the *N*-substituted thioamide (X). When the reaction was performed in the absence of catalyst or with boron trifluoride etherate, only starting material was recovered.



(VIII)

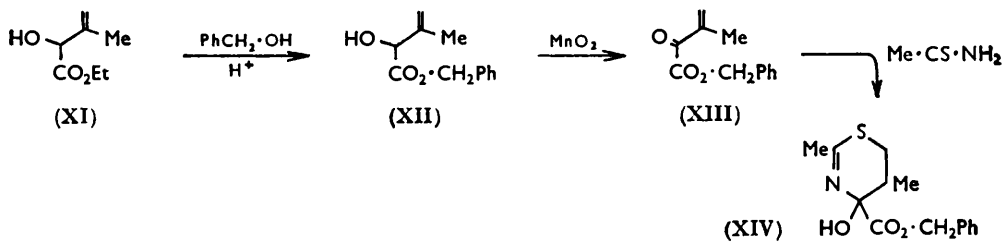


(IX)



(X)

Ethyl α-hydroxy-β-methylenebutyrate (XI), prepared by Vogel and Schinz's method,[9] gave the benzyl ester (XII) on transesterification with benzyl alcohol in the presence of toluene-*p*-sulphonic acid. Oxidation of the allylic alcohol with manganese dioxide gave the vinyl ketone (XIII) in good yield. Addition of thioacetamide to this material under neutral conditions gave a crystalline product in high yield which was assigned, on the basis of analytical and spectroscopic evidence, the dihydrothiazine structure (XIV), and was a single diastereoisomer.

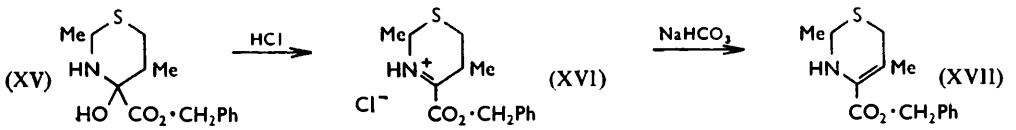


(XI) (XII) (XIII) (XIV)

Reduction of the dihydrothiazine (XIV) with aluminium–amalgam gave the tetrahydrothiazine (XV) as a reasonably stable crystalline compound. It was readily dehydrated in ether saturated with hydrogen chloride to the dihydrothiazine hydrochloride (XVI). Treatment of this salt with sodium hydrogen carbonate solution gave the free base as an unstable oil which was shown by its infrared spectrum to be essentially the enamine (XVII). The ultraviolet absorption spectrum had a single maximum at 2850 Å.

[7] Green, Long, May, and Turner, *J.*, 1964, 766.
[8] Dudek and Holm, *J. Amer. Chem. Soc.*, 1962, **84**, 2691.
[9] Vogel and Schinz, *Helv. Chim. Acta*, 1950, **33**, 116.

A discussion of the significance of this result in connection with the absorption spectrum of cephalosporin C is given in the preceding paper.



Experimental

Ultraviolet (Carey model 14M double beam recording spectrometer) and infrared (Perkin-Elmer 21) absorption spectra were recorded in ethanol and chloroform, respectively, except where otherwise stated. Nuclear magnetic resonance spectra were measured on an A.E.I. RS2 spectrometer operating at 60 Mc./sec. in carbon tetrachloride with tetramethylsilane as an internal reference. M. p.s (corrected) were determined on a Kofler block. Alumina for chromatography was Woelm " neutral " grade IV.

5,6-Dihydro-4-hydroxy-4-methyl-2-phenyl-4H-1,3-thiazine (VIII).—(*a*) Hydrobromic acid (47%; 20 ml.) was slowly added with cooling to a mixture of thiobenzamide (8·1 g.) and methyl vinyl ketone (4·2 g.), and the mixture then kept at 20° for 24 hr. Neutralisation with sodium hydroxide solution precipitated the *dihydrothiazine* (11·7 g.) which crystallised from ethanol as pale yellow prisms, m. p. 134° (Found: C, 63·8; H, 6·3; N, 6·4; S, 15·4. $C_{11}H_{13}NOS$ requires C, 63·8; H, 6·3; N, 6·8; S, 15·5%); $\lambda_{max.}$ 2380 Å (ε 14,600); $\nu_{max.}$ 3650 (OH), 1690 (C=N), 1560, and 1120 cm.$^{-1}$ (cf. ref. 10).

(*b*) (With V. V. Kane). Boron trifluoride etherate (0·5 ml.) was added to a solution of thiobenzamide (1·37 g.) and methyl vinyl ketone (0·89 g.) in ether (25 ml.). The solid was separated after 15 min. and had m. p. 153—157°, $\lambda_{max.}$ 2590 Å. This material was dissolved in chloroform (50 ml.), and the solution washed with saturated sodium hydrogen carbonate solution and water, and dried (Na_2SO_4), and the solvent distilled. The residual solid (1·57 g.) had $\lambda_{max.}$ 2380 Å (ε 15,200), m. p. and mixed m. p. 131—133° with material obtained by method (*a*).

(*c*) (with V. V. Kane). A solution of thiobenzamide (0·62 g.), methyl vinyl ketone (0·41 g.), triethylamine (0·09 g.), and t-butyl alcohol (2·5 ml.) was kept at 20° for 4 days. The pale yellow crystals (0·72 g.), m. p. 135—136°, which had separated were shown to be identical with material formed by method (*a*).

(*d*) (with V. V. Kane). A solution of thiobenzamide (0·62 g.), methyl vinyl ketone (0·42 g.), and t-butyl alcohol (2·5 ml.) was kept at 20° for 4 days. The pale yellow crystalline solid (0·68 g.), m. p. 135—136°, was shown to be identical with material formed by method (*a*).

S-Benzoyl-4-mercaptobutan-2-one (IX).—5,6-Dihydro-4-hydroxy-4-methyl-2-phenyl-4*H*-1,3-thiazine (0·5 g.) was boiled with 2N-hydrochloric acid for 10 min. *S-Benzoyl-4-mercaptobutan-2-one* (0·30 g.), which separated as a yellow oil from the cooled aqueous solution, was extracted with ether and distilled; it had b. p. 133—134°/0·25 mm. (Found: C, 63·8; H, 6·0; S, 15·1. $C_{11}H_{12}O_2S$ requires C, 63·4; H, 5·8; S, 15·4%); $\lambda_{max.}$ 2370 (ε 21,000), 2650 Å (ε 15,800); $\nu_{max.}$ (liq. film) 1700 (ketone), 1650 (thiol-ester) cm.$^{-1}$; τ (p.p.m.) 7·85 (singlet, Me); A_2B_2 symmetrical multiplet with τ *ca.* 7·3 and 6·7 (·CH_2·CH_2·); multiplets centred at 2·6 and 2·0 (C_6H_5).

The Reaction between Thioacetamide and Methyl Vinyl Ketone.—(*a*) Hydrobromic acid (47%; 20 ml.) was added to a cooled mixture of thioacetamide (15·0 g.) and methyl vinyl ketone (15·0 g.). The solution was kept at 20° for 18 hr., neutralised with sodium hydroxide solution, extracted with ether, and dried ($MgSO_4$), and the solvent removed. The residual oil (15·8 g.) was fractionally distilled to yield 4-mercaptobutan-2-one (2·1 g.), b. p. 63—65°/15 mm. (lit.,[11] b. p. 63—65°/15 mm.) (Found: C, 46·4; H, 8·4. Calc. for C_4H_8OS: C, 46·1; H, 7·7%), and a second fraction (13·0 g.), b. p. 110—120°/15 mm., which did not contain nitrogen.

(*b*) Thioacetamide (1·35 g.), methyl vinyl ketone (2·55 g.), and triethylamine (0·5 ml.) were warmed in t-butyl alcohol (3 ml.) to effect solution and then kept at 20° for 4 days. The

[10] Meyers, *J. Org. Chem.*, 1961, **26**, 218.
[11] Murata and Arai, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, 1956, **59**, 129 (*Chem. Abs.*, 1957, **51**, 1039).

solution was evaporated under reduced pressure, taken up in ether, and washed thoroughly with water. The dried ($MgSO_4$) solution was evaporated to give an oil (1·5 g.) from which crystals (0·2 g.), m. p. 61—63°, separated. Recrystallisation from ether gave *4-thioacetamidobutan-2-one* (X) as prisms, m. p. 61—62·5° (Found: C, 49·7; H, 7·5; N, 9·6; S, 21·7. $C_6H_{11}NOS$ requires C, 49·6; H, 7·6; N, 9·6; S, 22·0%); $\lambda_{max.}$ 2640 Å (ε 13,700); $\nu_{max.}$ (CCl_4) 3310 (NH), 1705 (C=O) cm.$^{-1}$; τ (p.p.m.) 7·80 (singlet, Me), 7·47 (singlet, Me). 7·13 (triplet, J = 6·0 c/sec., $CH_2{\cdot}CH_2{\cdot}CO$) and 6·11 (quartet, J = 6·0 c/sec., $NH{\cdot}CH_2{\cdot}CH_2$); when D_2O was added, τ (p.p.m.) 7·79 (singlet, Me), 7·47 (singlet, Me), 7·12 (triplet, J = 6·0 c/sec., $CH_2{\cdot}CH_2{\cdot}CO$), 6·10 (triplet, J = 6·0, c/sec., $ND{\cdot}CH_2{\cdot}CH_2{\cdot}$) and 5·27 (singlet, H_2O).

Benzyl α-Hydroxy-β-methylenebutyrate (XII).—Ethyl α-hydroxy-β-methylenebutyrate [9] (65 g.), benzyl alcohol (195 ml.), toluene (260 ml.), and toluene-*p*-sulphonic acid (3·5 g.) were refluxed and slowly distilled under nitrogen for 5 hr. through a 7 in. column filled with glass helices. The distillate (*ca.* 150 ml.) was discarded and the residue washed with sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and fractionally distilled. The fraction (94 g.), b. p. 127—128°/1 mm., contained the benzyl ester but was shown by g.l.c. to contain two components in approximately equal amounts; the second component was identified as dibenzyl ether. Chromatography of a portion (40 g.) of this fraction on alumina (700 g.) effected a clean separation of the two components, the dibenzyl ether (14 g.) being eluted with light petroleum (b. p. 40—60°) and *benzyl α-hydroxy-β-methylenebutyrate* (21 g.) with light petroleum (b. p. 40—60°) containing 10% of ether. The benzyl ester, n_D^{20} 1·5204 (Found: C, 70·6; H, 7·3. $C_{12}H_{14}O_3$ requires C, 70·0; H, 6·8%), gave a single peak g.l.c. and had $\nu_{max.}$ (CCl_4) 3570 (OH), 1740 (ester), 1650 (C=C), and 910 (C=CH_2) cm.$^{-1}$; τ (p.p.m.), 2·75 (singlet, Ph), 4·84 (singlet, $PhCH_2$), 4·94 and 5·06 (CH_2=C, coupling not well resolved), 5·45 (singlet, $CH{\cdot}OH$), 6·86 (singlet, OH), and 8·29 (doublet, J = 1·0 c/sec., Me).

Benzyl α-Oxo-β-methylenebutyrate (XIII).—Benzyl α-hydroxy-β-methylenebutyrate (8·0 g.) in methylene chloride (160 ml.) was shaken with active manganese dioxide [12] (40 g.) for 2 hr. A further portion of manganese dioxide (5 g.) was then added and the mixture was shaken for a further 1 hr., and filtered, and the spent manganese dioxide kept with methylene chloride overnight. The combined filtered solutions were evaporated under reduced pressure and the residual oil (5·3 g.) had $\lambda_{max.}$ 2280 Å (ε 5300); this material was used for subsequent synthetic work. Chromatography of a portion (1·6 g.) of this oil on alumina gave in the light petroleum (b. p. 40—60°) eluate the pure *benzyl α-oxo-β-methylenebutyrate*, n_D^{20} 1·5324 (Found: C, 70·7; H, 6·4. $C_{12}H_{12}O_3$ requires C, 70·7; H, 5·9%); $\lambda_{max.}$ 2290 Å (ε 6400); $\nu_{max.}$ (CCl_4) 1750 (ester), 1680 (unsaturated ketone), 1240, 1060, 945 (C=CH_2) cm.$^{-1}$; τ (p.p.m.), 2·73 (singlet, Ph), 3·98 (quartet, J = 1·1 c/sec.) and 4·80 (coupling unresolved) (CH_2=C), 4·75 (singlet, OCH_2Ph), 8·16 (doublet, J = 1·0 c/sec., Me).

4-Benzyloxycarbonyl-5,6-dihydro-4-hydroxy-2,5-dimethyl-4H-1,3-thiazine (XIV).—Benzyl α-oxo-β-methylenebutyrate (*ca.* 80% pure; 5·3 g.) was added to a solution of thioacetamide (1·95 g.) in t-butyl alcohol (26 ml.) and kept at 20° for 4 days. The crystals (4·0 g.) which had formed were crystallised from a mixture of ether and light petroleum (b. p. 40—60°) to give the *dihydrothiazine* as prisms, m. p. 96—97° (Found: C, 59·8; H, 5·7; N, 4·6; S, 10·8. $C_{14}H_{17}NO_3S$ requires C, 60·0; H, 6·1; N, 5·0; S, 11·4%); $\lambda_{max.}$ 2380 Å (ε 5000); $\nu_{max.}$ (CCl_4) 3580 (OH), 1740 (ester), and 1620 (C=N) cm.$^{-1}$.

4-Benzyloxycarbonyl-tetrahydro-4-hydroxy-2,5-dimethyl-1,3-thiazine (XV).—The dihydro-4*H*-1,3-thiazine (XIV; 2·0 g.), in aqueous dioxan (3%; 150 ml.), was stirred with aluminium–amalgam [13] (prepared from thin aluminium strips, 6 g.). The reaction was followed by the disappearance of the absorption band at 2380 Å. After the mixture had been stirred at 20° for 4 hr., water (2 ml.) was added and after a further 1 hr., the mixture was filtered, the solvent removed, and the residue crystallised from ether–light petroleum to give the *perhydrothiazine* (1·05 g.) as needles, m. p. 114—119° (decomp.) (Found: C, 59·6; H, 6·8; N, 4·7. $C_{14}H_{19}NO_3S$ requires C, 59·8; H, 6·8; N, 5·0%).

4-Benzyloxycarbonyl-5,6-dihydro-2,5-dimethyl-2H-1,3-thiazine Hydrochloride (XVI).—The perhydrothiazine (XV; 1·0 g.) in dry ether (250 ml.) was kept at 0° whilst a fast stream of dry hydrogen chloride was passed through the solution for 1 hr. After being kept at 0° for 4 hr. the precipitated *dihydrothiazine hydrochloride* (0·85 g.) was collected and washed with ether; it had

[12] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[13] *Org. Synth.*, Vol. II, 233.

m. p. 114—116° (Found: Cl, 11·9; N, 4·7; S, 10·7. $C_{14}H_{18}ClNO_2S$ requires Cl, 11·7; N, 4·8; S, 10·7%); $\nu_{max.}$ (Nujol) 2600—2300 ($\overset{+}{N}H$), 1745 (ester), and 1715 ($C=\overset{+}{N}H$) cm.$^{-1}$ (cf. ref. 14).

4-Benzyloxycarbonyl-3,6-dihydro-2,5-dimethyl-2H-1,3-thiazine (XVII).—The dihydrothiazine hydrochloride (XVI; 2·0 g.) was dissolved with water and basified with sodium hydrogen carbonate solution, and the free base extracted *via* ether. The product was purified by extraction with a mixture of benzene–light petroleum to give the *dihydrothiazine* (1·46 g.) (Found: N, 5·1; S, 12·6. $C_{14}H_{17}NO_2S$ requires N, 5·3; S, 12·15%); $\lambda_{max.}$ 2850 Å (ε 3300); $\nu_{max.}$ (Nujol), 3400 (NH), 1735 (ester), 1710sh., 1640 (C=C) cm.$^{-1}$.

The authors thank Glaxo Group Ltd. for research fellowships (to G. C. B. and T. R. E.) and for many valuable discussions. They also express their thanks for a Commonwealth Scholarship (to S. H. E.) and to Professor Sir Ewart Jones, F.R.S., for continued interest and advice.

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[14] Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781.