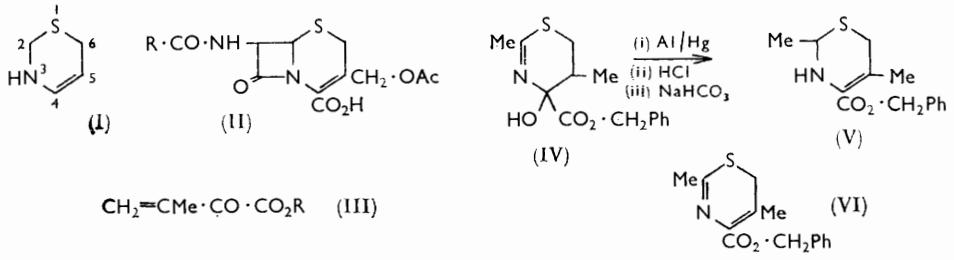
221. *Studies Related to Cephalosporin C. Part III.*[1] *A Synthetical Route to* 6H-1,3-*Thiazines and the Synthesis of a New Fragmentation Product of a Cephalosporanic Acid Derivative.**

By S. H. Eggers, V. V. Kane, and G. Lowe.

Michael addition of α-alkyloxycarbonyl-thioacetamides (VII) to α-oxo-β-methylenebutyric esters (III) takes place by methylene addition under neutral conditions and at room temperature to give the dihydropyranyl-esters (IX), which on treatment with anhydrous hydrogen chloride recyclise and dehydrate to give the Δ^5-dihydropyridine-2-thiones (X). However, addition of thioamides (VII and XIII) to α-oxo-β-methylenebutyric esters under anhydrous acidic conditions leads to the substituted 6*H*-1,3-thiazines (XIV and XVIII). One of these has been shown to be identical with the ester of a new degradation product (XIV; R = H) of 7-phenylacetamidocephalosporanic acid (XXII).

In Part II [1] a convenient synthetical route was established to the Δ^4-dihydro-6*H*-1,3-thiazine system (I), which is found in the naturally occurring antibiotic cephalosporin C{II; R = D-O_2C·$CH(NH_3^+)$·$[CH_2]_3$·}. This was accomplished by the addition of thioacetamide to the vinyl-keto-ester (III; R = Ph·CH_2) under neutral conditions to give the Δ^2-dihydrothiazine (IV), which when reduced with aluminium–amalgam gave the corresponding tetrahydrothiazine. Dehydration with anhydrous hydrogen chloride followed by basification gave the Δ^4-dihydrothiazine (V) (see also ref. 2). Direct dehydration of the Δ^2-dihydrothiazine (IV) to the 6*H*-1,3-thiazine (VI) had proved unsuccessful. We now describe the synthesis of some 6*H*-1,3-thiazines which may prove useful for the preparation of cephalosporanic acid derivatives (II).



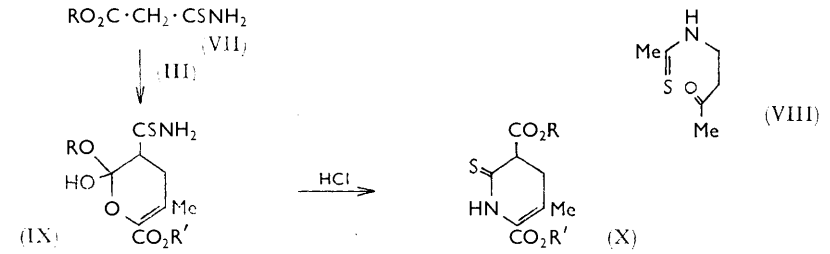
α-Alkyloxycarbonyl-thioacetamides (VII; R = Me, Ph·CH_2, or Me_3C) were prepared by the addition of hydrogen sulphide to the corresponding cyanoacetic ester in the presence

* Some of these results were in a preliminary communication; Eggers, Emerson, Kane, and Lowe, *Proc. Chem. Soc.*, 1963, 248.

[1] Part II, Barrett, Eggers, Emerson, and Lowe, *J.*, 1964, 788.
[2] Green, Long, May, and Turner, *J.*, 1964, 766.

of pyridine and triethylamine. Good yields of the thioamides were obtained in this way (cf. ref. 3) in spite of difficulties having been reported with similar thioamides.[4]

The thioamides (VII; R = Me, Ph·CH_2, and Me_3C) reacted smoothly at room temperature under neutral conditions with the vinyl-keto-esters (III; R = Et or Ph·CH_2), conditions under which thioacetamide gives the Δ^2-dihydrothiazine (IV).[1] From each reaction, crystalline material was obtained but it was clear from the ultraviolet absorption spectra ($\lambda_{max.}$ 2630—2650 Å) that the Δ^2-dihydrothiazines ($\lambda_{max.}$ 2380 Å) had not been formed. The alternatives which seemed most likely were that addition to the vinyl-ketone had taken place through the nitrogen or the reactive methylene group of the thioamide. The addition of thioacetamide to methyl vinyl ketone through nitrogen has already been observed and the product (VIII) has an ultraviolet absorption maximum at 2640 Å.[1] The nuclear magnetic resonance spectra, however, favoured methylene addition. The dibenzyl ester (IX; R = R′ = Ph·CH_2) had in addition to signals which could be assigned to the ester groups, a singlet at τ = 8·20 p.p.m. assigned to the methyl group, multiplets of an ABX system centred near 6·9 and 6·0 p.p.m., and a singlet at 3·25 and a broad singlet at 1·40 p.p.m. both of which were exchanged on addition of deuterium oxide and were assigned to hydroxyl and amino-groups respectively. This evidence together with the lack of colour with ferric chloride solution, favoured the cyclic rather than the acyclic tautomer.* Treatment of these adducts with anhydrous hydrogen chloride in dioxan gave a new series of crystalline esters with ultraviolet absorption maxima at 3270 and 2450 Å. The nuclear magnetic resonance spectra confirmed that they were the expected cyclisation products (X).



In an attempt to circumvent the reactivity of the methylene group, benzyl cyanoacetate was nitrosated with sodium nitrite in acetic acid to give the hydroximino-nitrile (XI) (cf. ref. 5). Treatment of this nitrile, however, with thioacetamide and dimethylformamidinium chloride [6] left the nitrile unchanged, while treatment with hydrogen sulphide in pyridine and triethylamine although giving the thioamide, also reduced the oxime.

The hydroximino-nitrile (XI) was therefore reduced with aluminium-amalgam and the resulting amine acylated with phenylacetyl chloride. Treatment of the acylaminonitrile (XII) with hydrogen sulphide in pyridine and triethylamine gave the thioamide (XIII) (cf. ref. 3). Evidence [7] suggested that a methine group in such an environment may be sufficiently sterically hindered so as to prevent Michael addition with the vinyl-keto-ester (III). This proved to be the case, but surprisingly it also prevented reaction

* We are grateful to a Referee for suggesting the cyclic, rather than the acyclic tautomeric structure. The keto-ester, Me·CO·S·CH_2·CHMe·CO·CO_2Et gives a ferric chloride colour.[2] but the enolic tautomer could not be detected in the n.m.r. spectrum.

[3] Houben-Weyl, " Methoden der Organischen Chemie," 1955, **9**, 763; Long and Tulley, *J.*, 1964, 1190.

[4] Fairfull, Lowe, and Peak, *J.*, 1952, 742.

[5] Conrad and Schulze, *Chem. Ber.*, 1909, **42**, 739; cf. Wilson, *J.*, 1948, 1157; Tatsuoken, Kinoshita, and Nakemori, *Chem. Abs.*, 1952, **46**, 1978.

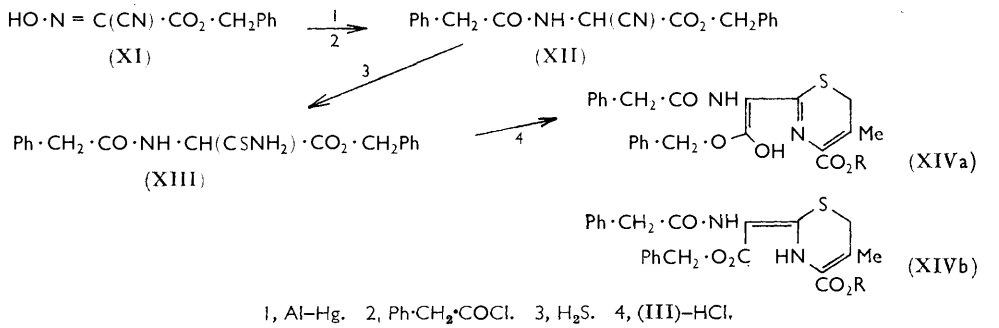
[6] Taylor and Zoltewicz, *J. Amer. Chem. Soc.*, 1960, **82**, 2656; cf. Schmidt and Kubitzek, *Chem. Ber.*, 1960, **93**, 1559.

[7] Connor and Andrews, *J. Amer. Chem. Soc.*, 1934, **56**, 2713, and references there cited.

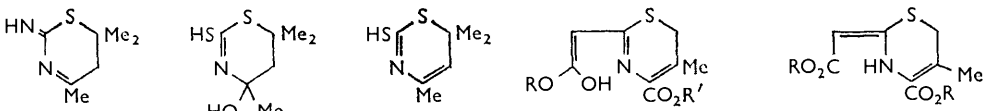
of the thioamide. Indeed no reaction could be observed even when the thioamide (XIII) and the vinyl-keto-ester (III) were refluxed together in ethanol.

Although the addition of thioacetamide to methyl vinyl ketone was unsatisfactory in the presence of aqueous mineral acid or boron trifluoride–ether complex, the addition of thiobenzamide was satisfactory and moreover acid-catalysed.[1] The unsatisfactory nature of the reaction between thioacetamide and methyl vinyl ketone in the presence of aqueous hydrobromic acid was probably due to the Δ^2-dihydrothiazine being hydrolysed readily. Boron trifluoride on the other hand formed an insoluble complex with thioacetamide thus preventing reaction.[1]

The thioamide (XIII) and the vinyl-keto-ester (III; R = Ph·CH_2) were therefore dissolved in dry dioxan and the solution saturated with dry hydrogen chloride. The crystalline product (50% yield) had $\lambda_{max.}$ 3420 and 2850 Å and analytical data indicated that dehydration as well as addition had taken place. The nuclear magnetic resonance spectrum was remarkably simple. The phenylacetyl group and the two benzyl esters could be easily assigned to a set of well resolved sharp singlets. In addition there was a singlet (two protons) at τ = 6·77 p.p.m. which was assigned to a methylene adjacent to sulphur (in cephalosporanic acid derivatives the CH_2·S group is an AB system centred at 6·6 p.p.m.), a singlet (three protons) at 7·74 p.p.m. assigned to the methyl group (cf. refs. 8 and 9) and two broad singlets at 3·55 (one proton) and −1·5 p.p.m. (one proton) assigned to the NH and OH(or NH) groups respectively. This evidence led to the formulation of the product as the thiazine (XIVa; R = Ph·CH_2) or its tautomer (XIVb; R = Ph·CH_2).



The ease with which dehydration occurred is of interest in view of the many unsuccessful attempts to dehydrate the Δ^2-dihydrothiazine (IV).[1,2] This difference is most likely due to the ability of the ester to enolise and thus provide a source of electrons to initiate this transformation. Two analogies from the literature support this view. Thiourea adds to mesityl oxide in aqueous acid to give the dihydrothiazine (XV),[10] and the dihydrothiazine (XVI) formed by the addition of dithiocarbamic acid to mesityl oxide under neutral conditions, is converted by aqueous acid into the thiazine (XVII).[11] In each case an exocyclic hetero-atom provides the source of electrons required to initiate the dehydration.



The alkyloxycarbonyl-thioacetamides (VII; R = Me, Ph·CH_2, and Me_3C) were now made to react similarly with the vinyl-keto-esters (III; R = Et or Ph·CH_2) and in each

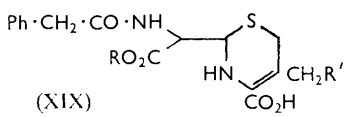
[8] Burrell, Jackman, and Weedon, *Proc. Chem. Soc.*, 1959, 263.
[9] Morin, Jackson, Mueller, Lavagnino, Scanlon, and Andrews, *J. Amer. Chem. Soc.*, 1963, **85**, 1896.
[10] Chase and Walker, *J.*, 1955, 4443.
[11] Jansen and Mathes, *J. Amer. Chem. Soc.*, 1955, **77**, 2866.

case the crystalline product had ultraviolet absorption similar to that of the thiazine (XIV). The nuclear magnetic resonance spectra in addition to the signals due to the ester groups, and the methyl, methylene, and hydroxyl (or amino) groups, now contained a singlet (one proton) near $\tau = 5{\cdot}0$ p.p.m. when measured in dimethyl sulphoxide, which can be assigned to the olefinic proton of the enolised ester. When the spectra were measured in chloroform, no sharp peaks were observed for the olefinic and hydroxlyic (or amino) protons, presumably owing to line broadening arising from the different rate of exchange in this solvent. Support for this conclusion was obtained when it was shown that the olefinic and hydroxylic (or amino) protons exchanged rapidly with deuterium oxide. The products were therefore formulated as the thiazines (XVIIIa) or their tautomers (XVIIIb).

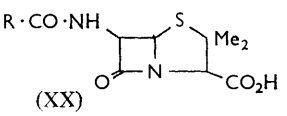
Attempts to remove the ester groups of the thiazine (XVIII; R = R′ = Ph·CH_2) by catalytic hydrogenolysis at atmospheric pressure over 10% palladium on charcoal or palladium black in dioxan or in 10% acetic acid in dioxan were without success. Dry hydrogen bromide in glacial acetic acid at 60° did not yield useful products although some reaction took place. Hydrolysis with aqueous ethanolic sodium carbonate solution, however, gave the sodium salt of the thiazine half-ester (XVIII; R = Ph·CH_2,R′ = Na). The thiazine esters (XIV; R = Et and Ph·CH_2) were both hydrolysed with aqueous ethanolic sodium carbonate solution to the thiazine half-ester (XIV; R = H).

In an attempt to remove selectively the t-butyl ester of the thiazine (XVIII; R = Me_3C, R′ = Et) the compound was treated first at 0° and then at room temperature with dioxan saturated with dry hydrogen chloride, but little or no ester cleavage was observed. When a benzene solution of the thiazine ester saturated with dry hydrogen chloride was refluxed, rearrangement occurred to give the Δ^5-dihydropyrid-2-thione (X; R = Me_3C, R′ = Et) with the t-butyl ester still intact.

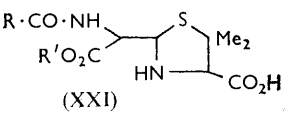
Reduction of the thiazine (XIV), if performed non-stereoselectively would give rise to a mixture of diastereoisomers. It was therefore desirable to know the properties of the required diastereoisomer of the dihydrothiazines (XIX; R′ = OAc or H). The inactivation of the penicillins (XX) by alcohols is known to be due to the cleavage of the β-lactam ring to give the corresponding penicilloic esters (XXI) and it has been shown that metal ions are required for this reaction.[12] Treatment of 7-phenylacetamidocephalosporanic acid [13] (XXII) with alcohols in the presence or absence of metal salts failed to cleave the β-lactam ring.



(XIX)



(XX)



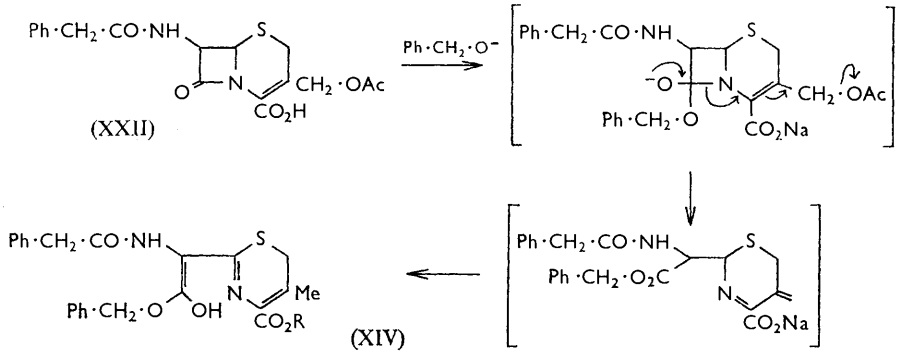
(XXI)

When 7-phenylacetamidocephalosporanic acid (XXII) was treated with two equivalents of sodium benzyloxide in benzyl alcohol, however, it was smoothly transformed into the thiazine half-ester (XIV; R = H) which was isolated in 60% yield. The half-ester (XIV; R = H) and the dibenzyl ester (XIV; R = Ph·CH_2) prepared by treatment of the half-ester with phenyldiazomethane were identical with the synthetic materials. The transformation can be regarded as a fragmentation reaction [14] the product of which undergoes a prototropic rearrangement to the 6*H*-1,3-thiazine system. The facility of the reaction and the high yield of the fragmentation product suggests that the fragmentation may be a concerted reaction. This reaction has furnished a valuable relay compound which should facilitate further synthetic progress.

[12] " The Chemistry of Penicillin," ed. Clarke, Johnson, and Robinson, Oxford Univ. Press, 1949, p. 544.

[13] Chauvette, Flynn, Jackson, Lavagnino, Morin, Meuller, Pioch, Roeske, Ryan, Spencer, and Van Heyningen, *J. Amer. Chem. Soc.*, 1962, **84**, 3401.

[14] Grob in " Theoretical Organic Chemistry," Kekule Symposium, Butterworths, London, 1958, p. 114.



Experimental

Ultraviolet (Carey model 14M double beam recording spectrometer) and infrared (Perkin-Elmer 21 or Perkin-Elmer 237) absorption spectra were recorded in ethanol and chloroform respectively, except where otherwise stated. Nuclear magnetic resonance spectra were measured on an AEI RS2 spectrometer or a Perkin-Elmer n.m.r. spectrometer operating at 60 Mc./sec. with tetramethylsilane as internal standard. M. p.s were determined on a Kofler hot-stage apparatus.

α-Methoxycarbonylthioacetamide (VII; R = Me).—Hydrogen sulphide was passed through a solution of methyl cyanoacetate (35 g.) in pyridine (35 ml.) and triethylamine (24 ml.) for 4·5 hr.[3] The solution was poured into brine, extracted with ether and the extract dried ($MgSO_4$). Removal of the ether and crystallisation from ether–light petroleum (b. p. 40—60°) mixture gave the *thioamide* (30 g.) m. p. 78—79°. Recrystallisation from ether at −20° gave colourless prisms, m. p. 79° (Found: C, 36·7; H, 5·4; N, 10·6; S, 23·8. $C_4H_7NO_2S$ requires C, 36·1; H, 5·3; N, 10·5; S, 24·1%); $\lambda_{max.}$ 2700 Å (ε 11,100); $\nu_{max.}$ 3460, 3370—3300 (NH), 1725 (CO_2Me), 1595 cm.$^{-1}$, τ ($CHCl_3$) 6·20 (singlet, O·CH_3), 6·10 (singlet, CH_2·CO) p.p.m.

α-Benzyloxycarbonylthioacetamide (VII; R = Ph·CH_2).—Hydrogen sulphide was passed through a solution of benzyl cyanoacetate [15] (10 g.) in pyridine (10 ml.) and triethylamine (7 ml.) for 6 hr. The mixture was poured into water and the aqueous layer discarded. The oil was dissolved in ether, washed several times with brine, dried ($MgSO_4$), and the solvent evaporated. The residual solid was recrystallised from benzene–light petroleum (b. p. 40—60°) to give the *thioamide* as colourless needles (9·6 g.) m. p. 70—71° (Found: C, 57·5; H, 5·4; N, 6·6; S, 15·3. $C_{10}H_{11}NO_2S$ requires C, 57·4; H, 5·3; N, 6·7; S, 15·3%); $\lambda_{max.}$ 2690 Å (ε 13,200); $\nu_{max.}$ 3350 and 3130 (NH), 1725 (CO_2R), 1648 cm.$^{-1}$, τ ($CDCl_3$) 6·18 (singlet, CH_2·CO), 4·80 (singlet, O·CH_2), 2·63 (singlet, Ph) p.p.m.

α-t-Butoxycarbonylthioacetamide (VII; R = Me_3C).—Hydrogen sulphide was passed through a solution of t-butyl cyanoacetate [16] (3·0 g.) in pyridine (5 ml.) containing triethylamine (2·2 g.) for 3·5 hr. The mixture was poured into brine, extracted with ether, and the extracts washed with brine, dried ($MgSO_4$) and the solvent removed to leave the *thioamide* (2·86 g.) m. p. 90—92° which crystallised from di-isopropyl ether–light petroleum (b. p. 40—60°) as needles, m. p. 94—95° (Found: C, 47·8; H, 7·5; N, 7·7. $C_7H_{13}NO_2S$ requires C, 48·0; H, 7·5; N, 8·0%); $\lambda_{max.}$ 2690 Å (ε 11,600); $\nu_{max.}$ 3310 and 3280 (NH), 1725 (CO_2R) and 1630 cm.$^{-1}$, τ ($CDCl_3$) 8·51 (singlet, CMe_3) 6·24 (singlet, CH_2) p.p.m.

Benzyl α-Hydroxyiminocyanoacetate (XI).—A solution of sodium nitrite (8·3 g.) in water (43 ml.) was added to benzyl cyanoacetate (17·5 g.) and the mixture cooled to 16° (cf. ref. 5). Glacial acetic acid (8 ml.) was added during 15 min. with stirring, the temperature being kept close to 20°. The precipitate which separated when addition was complete, was treated after 2 days with concentrated hydrochloric acid (10 ml.) and the solution extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$), and the solvent removed. The residual *ester* (19 g.) crystallised from di-isopropyl ether–light petroleum (b. p. 40—60°) as colourless needles, m. p. 116—118° (Found: C, 58·9; H, 3·9; N, 13·5. $C_{10}H_8N_2O_3$ requires C, 58·8; H, 3·9; N, 13·7%); $\lambda_{max.}$ 2370 Å (ε 10,500); $\nu_{max.}$ 3460 (OH), 1730 (CO_2R) cm.$^{-1}$.

[15] McElvain and Olson, *J. Amer. Chem. Soc.*, 1951, **73**, 4824.
[16] Ireland and Chaykovsky, *Org. Synth.*, 1961, **41**, 5.

Benzyl α-Phenylacetamidocyanoacetate (XII).—Benzyl α-hydroxyiminocyanoacetate (6·0 g.) was added to a mixture of aluminium-amalgam (12 g.) in wet ether (300 ml.).[17] After 5 hr. (when the ultraviolet absorption spectrum of the hydroxyimino-compound had disappeared) the mixture was filtered, the filtrate dried ($MgSO_4$), the solvent removed, and the residual oil (4·8 g.) had $\nu_{max.}$ 3400, 1750 cm.$^{-1}$.

Phenylacetyl chloride (7·0 g.) was added with stirring to the oil (4·8 g.) suspended in water (50 ml.) containing sodium hydrogen carbonate (5 g.). The suspended *amido-ester* (4·6 g.), m. p. 164—168°, was recrystallised from ethanol as colourless needles, m. p. 171—172° (Found: C, 69·8; H, 5·2; N, 9·2. $C_{18}H_{16}N_2O_2$ requires C, 70·1; H, 5·2; N, 9·1%); $\nu_{max.}$ (Nujol) 3219 (NH), 1725 (CO_2R), 1652 (CONH) cm.$^{-1}$, τ (Me_2SO), 6·40 (singlet, CH_2·Ph), 4·80 (singlet, CH_2O), 4·42 (doublet, J = 7 c./sec., CH·NH) 2·73, 2·61 (singlets, 2Ph), 0·55 (doublet, J = 7 c./sec., CH·NH) p.p.m.

α-Benzyloxycarbonyl-α-phenylacetamidothioacetamide (XIII).—Hydrogen sulphide was passed through a solution of benzyl α-phenylacetamidocyanoacetate (1·0 g.) in pyridine (4 ml.) and triethylamine (0·6 ml.) for 3·5 hr. The dark solution was poured into water and the *thioamide* (0·9 g.), m. p. 127—130°, filtered and recrystallised from benzene as pale yellow needles, m. p. 135—136° (Found: C, 63·3; H, 5·4; N, 8·4; S, 9·6. $C_{18}H_{18}N_2O_3S$ requires C, 63·2; H, 5·3; N, 8·2; S, 9·4%); $\lambda_{max.}$ 2720 Å (ε 11,000); $\nu_{max.}$ 3300, 3220, 3100 (NH), 1740 (CO_2R), 1657 (CONH) cm.$^{-1}$; τ (Me_2SO) 6·35 (singlet, CH_2·Ph), 4·80 (singlet, CH_2·O), 4·49 (doublet, J = 8 c./sec., CH·NH), 2·69, 2·78 (singlets, 2Ph) p.p.m.

The Dihydropyranyl Ester (IX; R = Me, R′ = Et).—A solution of α-methoxycarbonylthioacetamide (4·3 g.) in dry dimethyl sulphoxide (18 ml.) was mixed with a solution of ethyl α-oxo-β-methylenebutyrate [2] (5·3 g., *ca.* 80% pure) in dimethyl sulphoxide (17 ml.). After 4 days at 15° the solution was poured into water, extracted with chloroform, and the extracts washed with aqueous potassium hydrogen carbonate solution, dried ($MgSO_4$), and the solvent removed to give a yellow oil (7·8 g.) which was washed with ether and crystallised from ethanol as colourless needles (1·7 g.) m. p. 125—130°. Recrystallisation from the same solvent gave the *dihydropyranyl ester*, m. p. 134—138° (Found: C, 48·1; H, 6·45; N, 5·25. $C_{11}H_{17}NO_5S$ requires C, 48·0; H, 6·2; N, 5·1%); $\lambda_{max.}$ 2640 Å (ε 25,700); $\nu_{max.}$ (Nujol) 3445, 3375, 3180 (NH_2 and OH), 1730 (CO_2R), 1690 (C=C) cm.$^{-1}$; τ [$(CD_3)_2CO$] 8·71 (triplet, J = 6·6 c./sec., CH_2·CH_3), 8·17 (singlet, =C·CH_3), ABX system, A at 7·02, B at 6·75, and X at 6·03 (JAB = 12 c./sec., JAX = 6·6 c./sec., JBX = 8 c./sec., CH·CH_2·CMe=), 6·38 (singlet, OMe), 5·78 (quartet, J = 6·6 c./sec., CH_2·CH_3), 3·33 (singlet, OH), 1·3 (broad singlet, NH_2) p.p.m. Addition of D_2O caused the disappearance of the signals at τ 1·3 and 3·33 p.p.m.

3-Methoxycarbonyl-5-methyl-6-ethoxycarbonyl-3,4-dihydropyridine-2-thione (X; R = Me, R′ = Et).—A solution of the ester (IX; R = Me, R′ = Et, 0·50 g.) in dioxan (10 ml.) was saturated with dry hydrogen chloride at 16°. After being kept at this temperature for 16 hr. the solvent was removed and the residue crystallised from ether–light petroleum (b. p. 60—80°) to give the *dihydropyridine-2-thione* (0·20 g.) as yellow needles, m. p. 72—74° (Found C, 51·8; H, 6·3; N, 5·6; S, 12·6. $C_{11}H_{15}NO_4S$ requires C, 51·4; H, 5·9; N, 5·4; S, 12·45%); $\lambda_{max.}$ 3270 (ε 16,000) and 2410 Å (ε 6000); $\nu_{max.}$ 3360 (NH), 1740 (CO_2R), 1710 (αβ-unsat. CO_2R); τ ($CDCl_3$) 8·60 (triplet, J = 6·6 c./sec., CH_2·CH_3), 7·71 (singlet, =C·CH_3), 7·25 (doublet, J = 6·6 c./sec., =C·CH_2·CH), 6·20 (singlet, O·CH_3), 6·10 (triplet, J = 6·6 c./sec., CS·CH·CH_2), 5·62 (quartet, J = 6·6 c./sec., CH_2·CH_3), 0·5 (broad singlet, NH) p.p.m. Addition of D_2O caused the disappearance of the signal at 0·5 p.p.m.

The Dihydropyranyl Ester (IX; R = R′ = Ph·CH_2) (with T. R. Emerson).—A solution of α-benzyloxycarbonylthioacetamide (1·3 g.) and benzyl α-oxo-β-methylenebutyrate [1] (*ca.* 70% pure, 2·4 g.) in t-butyl alcohol (5 ml.) was kept at 25° for 24 hr. The solid (0·84 g.) which separated was recrystallised from ethanol to give the *dihydropyranyl ester* as colourless needles, m. p. 142° (Found: C, 63·8; H, 5·6; N, 3·5; S, 7·6. $C_{22}H_{23}NO_5S$ requires C, 63·9; H, 5·6; N, 3·5; S, 7·8%); $\lambda_{max.}$ 2630 (ε 11,400) and 2070 Å (ε 20,200); $\nu_{max.}$ (Nujol) 3440, 3380 (OH and NH), 1720 (CO_2R), 1680 (C=C), 1620 cm.$^{-1}$; τ [$(CD_3)_2CO$] 8·20 (singlet, =C·CH_3), ABX system, A at 7·02, B at 6·75, and X at 6·03 (JAB = 12 c./sec., JAX = 6·6 c./sec., JBX = 8 c./sec., CH·CH_2·CMe=), 4·98 and 4·80 (singlets, 2Ph·CH_2O), 3·25 (singlet OH), 2·70 (singlet, 2Ph) and 1·40 (broad singlet, NH_2) p.p.m. Addition of D_2O caused the disappearance of the signals at 3·25 and 1·40 p.p.m.

[17] *Org. Synth.*, Vol. II, p. 233; Cook, Heilbron, and Levy, *J.*, 1947, 1594.

3,6-Dibenzyloxycarbonyl-5-methyl-Δ⁵-dihydropyridine-2-thione (X; R = R′ = Ph·CH_2).—A solution of the thioamide (IX; R = R′ = Ph·CH_2; 0·35 g.) in dioxan (100 ml.) was saturated with dry hydrogen chloride and kept at 20° for 24 hr. The solvent was removed under reduced pressure to give an oil which solidified on trituration with ether. Recrystallisation from ethyl acetate gave the *dihydropyridine-2-thione* (0·21 g.) as needles, m. p. 142—143° (Found: C, 66·8; H, 5·4; N, 3·3; S, 8·4. $C_{22}H_{21}NO_4S$ requires C, 66·9; H, 5·3; N, 3·5; S, 8·1%); $\lambda_{max.}$ 3270 (ε 11,850) and 2450 Å (ε 5600); $\nu_{max.}$ (Nujol) 3300 (NH), 1735 (CO_2R), 1700 (αβ-unsat. CO_2R) cm.$^{-1}$; τ ($CDCl_3$) 7·85 (singlet, =C·CH_3), 7·35 (doublet, J = 7 c./sec., CH·CH_2·CMe=) 6·15 (triplet, J = 7 c./sec., CH·CH_2·C=), 4·85 and 4·75 (singlets, 2Ph·CH_2·O), 2·71 and 2·68 (singlets, 2Ph) 0·5 (broad singlet, NH) p.p.m. Addition of D_2O caused the disappearance of the signal at 0·5 p.p.m.

The Dihydropyranyl Ester (IX; R = Me_3C, R′ = Ph·CH_2).—A solution of α-t-butoxycarbonylthioacetamide (0·35 g.) and benzyl α-oxo-β-methylenebutyrate [1] (*ca.* 80% pure, 0·41 g.) in t-butyl alcohol (4 ml.) was kept at 25° for 24 hr. The solid (0·3 g.) which separated was recrystallised from ethanol to give the *dihydropyranyl ester* as needles, m. p. 158—160° (Found: C, 60·3; H, 6·3; N, 3·5; S, 8·4. $C_{19}H_{25}NO_5S$ requires C, 60·1; H, 6·6; N, 3·7; S, 8·4%); $\lambda_{max.}$ 2650 Å (ε 11,800); $\nu_{max.}$ (Nujol) 3440, 3380 (OH and NH), 1730 (CO_2R), 1688 (C=C) cm.$^{-1}$.

Methyl 4-Ethoxycarbonyl-5-methyl-6H-1,3-thiazin-2-yl Acetate (XVIII; R = Me, R′ = Et).—A solution of α-methoxycarbonylthioacetamide (5·0 g.) and ethyl α-oxo-β-methylenebutyrate [2] (*ca.* 80% pure, 6·6 g.) in dioxan (20 ml.) was saturated with dry hydrogen chloride at 0° and kept for one day at 15°. The solvent was removed and the residue dissolved in ether, washed with water, and dried ($MgSO_4$). Chromatography on alumina (80 g.) with ether as eluent gave the *thiazine* which crystallised from light petroleum (b. p. 60—80°) in large colourless plates (5·8 g., 60%), m. p. 92° (Found: C, 51·9; H, 5·5; N, 5·4; S, 12·6. $C_{11}H_{15}NO_4S$ requires C, 51·4; H, 5·9; N, 5·4; S, 12·4%); $\lambda_{max.}$ 3370 (ε 13,500), 2800 (ε 4700), and $\lambda_{infl.}$ 2220 Å (ε 8000); $\nu_{max.}$ (CCl_4) 3200, 1735, 1720, 1665 cm.$^{-1}$; τ ($CHCl_3$) 8·59 (triplet, J = 6·9 c./sec., O·CH_2·CH_3), 7·67 (singlet, C=C·Me) 6·70 (singlet, S·CH_2) 6·31 (singlet, O·Me), 5·65 (quartet, J = 6·9 c./sec., O·CH_2·CH_3); τ (Me_2SO) 8·65 (triplet, J = 7·2 c./sec., O·CH_2·CH_3), 6·79 (singlet, S·CH_2), 6·35 (singlet, OMe), 5·62 (quartet, J = 7·2 c./sec., O·CH_2CH_3), 5·08 (singlet, C=CH), −1·10 (singlet, OH or NH) p.p.m. The signal from the methyl group would be obscured by the dimethyl sulphoxide signal.

Benzyl 4-Benzyloxycarbonyl-5-methyl-6H-1,3-thiazin-2-yl Acetate (XVIII; R = R′ = Ph·CH_2). A solution of α-benzyloxycarbonylthioacetamide (5·0 g.) and benzyl α-oxo-β-methylenebutyrate [1] (*ca.* 80% pure, 11 g.) in dioxan (70 ml.) was saturated with dry hydrogen chloride at 0° and kept for 2 days at 15° when the reaction was shown spectroscopically to be complete. The solvent was removed (below 40°) and the crystalline residue recrystallised from ethanol to give the *thiazine* as pale yellow plates (4·6 g., 49%), m. p. 107—108° (Found: C, 66·8; H, 5·4; N, 3·6; S, 8·2. $C_{22}H_{21}NO_4S$ requires C, 66·8; H, 5·3; N, 3·5; S, 8·1%); $\lambda_{max.}$ 3380 (ε 14,000) 2820 (ε 6600) and $\lambda_{infl.}$ 2250 Å (ε 10,400); $\nu_{max.}$ 1735, 1710, 1655 cm.$^{-1}$; τ ($CDCl_3$) 7·73 (singlet, C=C·CH_3), 6·80 (singlet, S·CH_2), 4·82 and 4·67 (singlets, 2PhCH_2·O), 2·62 and 2·59 (singlets, 2Ph), τ (Me_2SO) 6·6 (singlet, S·CH_2), 5·08 (singlet, C=CH), 4·88 and 4·66 (singlets, PhCH_2·O) 2·63 and 2·58 (singlets, 2Ph), −1·19 (singlet, OH or NH) p.p.m. After treatment of the compound in $CHCl_3$ with D_2O, the signals at 5·08 and −1·19 p.p.m. were absent.

t-Butyl 4-Ethoxycarbonyl-5-methyl-6H-1,3-thiazin-2-yl Acetate (XVIII; R = Me_3C, R′ = Et).—A solution of α-t-butoxycarbonylthioacetamide (2·24 g.) and ethyl α-oxo-β-methylenebutyrate [2] (*ca.* 80% pure, 2·27 g.) in dioxan (15 ml.) was saturated with dry hydrogen chloride at 0° and kept for 2 days at 15° when the reaction was shown spectroscopically to be complete. The residue obtained by removal of the solvent was dissolved in chloroform and washed with aqueous sodium hydrogen carbonate solution. The residue (3·48 g.) after removal of the solvent, partially crystallised. Trituration with ether–light petroleum (1 : 1) gave colourless crystals (0·37 g.), m. p. 123—126° (Found: C, 54·6; H, 7·1; N, 4·55; S, 10·4%); $\lambda_{max.}$ 2450 Å (E_1^1, 180); $\nu_{max.}$ (CCl_4) 3220, 1730, 1690 cm.$^{-1}$. The n.m.r. spectrum indicated that the material was a two-component mixture. The mother-liquor from the trituration was chromatographed on alumina. Elution with ether–light petroleum (b. p. 60—80°) (1 : 7) gave pure *thiazine* (0·91 g., 24%) which crystallised from light petroleum (b. p. 60—80°) as colourless plates, m. p. 80° (Found: C, 56·5; H, 7·2; N, 4·8; S, 10·7. $C_{14}H_{21}NO_4S$ requires C, 56·2; H, 7·1; N, 4·7; S, 10·7%); $\lambda_{max.}$ 3380 (ε 12,200), 2820 (ε 5200), and $\lambda_{infl.}$ 2240 Å (ε 7500); $\nu_{max.}$ (CCl_4), 3150, 1730, 1710, 1650 cm.$^{-1}$; τ ($CHCl_3$) 8·62 (triplet, J = 7·2 c./sec., O·CH_2·CH_3), 8·50 (singlet,

O·CMe$_3$), 7·70 (singlet, C:C·Me), 6·73 (singlet, S·CH$_2$) 5·66 (quartet, J = 7·2 c./sec., O·C*H*$_2$·CH$_3$), τ (Me$_2$SO) 8·65 (triplet, J = 7·2 c./sec., O·CH$_2$·C*H*$_3$), 8·54 (singlet, O·CMe$_3$) 6·82 (singlet, S·CH$_2$), 5·69 (quartet, J = 7·2 c./sec., O·C*H*$_2$·CH$_3$), 5·34 (singlet, C=CH), −1·12 (singlet, OH or NH) p.p.m. The signal from the methyl group would be obscured by the dimethyl sulphoxide signal.

Rearrangement of the Thiazine Ester (XVIII; R = Me$_3$C, R′ = Et) *to the* Δ^5*-Dihydropyridine-2-thione* (X; R = Me$_3$C, R′ = Et).—A solution of t-butyl 4-ethoxycarbonyl-5-methyl-6*H*-1,3-thiazin-2-yl acetate (1·0 g.) in dry benzene (50 ml.) was saturated with dry hydrogen chloride and the solution kept at 50—60° for 18 hr., and finally refluxed for 30 min. Removal of solvent *in vacuo* and chromatography of the residue on alumina gave unchanged thiazine (0·15 g.) and the *dihydropyridine-2-thione* (0·39 g.) which crystallised from ether–light petroleum (b. p. 40—60°) as pale yellow needles, m. p. 112—114° (Found: C, 56·4; H, 7·1; N, 4·6; S, 10·5. C$_{14}$H$_{21}$NO$_4$S requires C, 56·2; H, 7·1; N, 4·7; S, 10·7%), λ$_{max.}$ 3270 (ε 15,700) and 2410 Å (ε 6000), ν$_{max.}$ 3360 (NH), 1735 (CO$_2$R), 1710 (αβ-unsat. CO$_2$R), 1690 (weak, C=C) cm.$^{-1}$, τ (CDCl$_3$) 8·67 (triplet, J = 6·6 c./sec., CH$_2$·C*H*$_3$), 8·58 (singlet, CMe$_3$), 7·78 (singlet, =C·CH$_3$), 7·35 (doublet, J = 7 c./sec., CH·C*H*$_2$·CMe=), 6·27 (triplet, J = 7 c./sec., C*H*·CH$_2$·CMe=), 5·67 (quartet, J = 6·6 c./sec., C*H*$_2$·CH$_3$), 0·52 (broad singlet, NH) p.p.m. Addition of D$_2$O caused the disappearance of the signal at 0·52 p.p.m.

Benzyl 4-*Carboxy-5-methyl*-6H-1,3-*thiazin-2-yl Acetate* (XVIII; R = Ph·CH$_2$, R = H).—Benzyl 4-benzyloxycarbonyl-5-methyl-6*H*-1,3-thiazin-2-yl acetate (0·50 g.) in 50% aqueous ethanol (100 ml.) containing sodium carbonate (0·15 g.) was refluxed for 30 min. Removal of most of the solvent and dilution with brine (100 ml.) gave crystals (0·09 g.) of the *sodium salt*, m. p. 220—223° (decomp.) (Found: N, 4·7; S, 9·7. C$_{15}$H$_{14}$NNaO$_4$S requires N, 4·3; S, 9·8%); λ$_{max.}$ 3500 (ε 12,500), 2820 (ε 2300) and λ$_{infl.}$ 2250 Å (ε 3800); ν$_{max.}$ (Nujol) 3450—3100 (bonded OH), 1660, 1610 (CO$_2$Na), 1530 cm.$^{-1}$; τ (Me$_2$SO) 6·70 (singlet, S·CH$_2$), 5·33 (singlet, C=CH), 4·93 (singlet, O·C*H*$_2$·Ph), 2·64 (singlet, Ph) p.p.m. The solvent would obscure the signal from the methyl group.

Acidification of the aqueous solution and extraction with chloroform gave the *thiazine-carboxylic acid* which after trituration with methanol and recrystallisation from chloroform–light petroleum (b. p. 60—80°) gave colourless needles, m. p. 181—183° (decomp.) (Found: C, 58·6; H, 5·1; N, 4·65. C$_{15}$H$_{15}$NO$_4$S requires C, 59·0; H, 4·9; N, 4·6%); λ$_{max.}$ 3380 (ε 25,000), 2800 (ε 7700) and λ$_{infl.}$ 2250 Å (ε 3400); λ$_{max.}$ [in presence of Zn(OAc)$_2$] 3680 and λ$_{infl.}$ 2950 Å; ν$_{max.}$ (Nujol) 3100 (bonded OH), 1730 (CO$_2$H) cm.$^{-1}$; τ (Me$_2$SO) 6·78 (singlet, S·CH$_2$), 5·10 (singlet, C=CH), 4·87 (singlet, O·C*H*$_2$·Ph), 2·61 (singlet, Ph) p.p.m.

Benzyl 4-*Benzyloxycarbonyl-5-methyl*-6H-1,3-*thiazin-2-yl* α-*Phenylacetamidoacetate* (XIV; R = Ph·CH$_2$).—A solution of α-benzyloxycarbonyl-α-phenylacetamidothioacetamide (1·03 g.) and benzyl α-oxo-β-methylenebutyrate (0·61 g.) in dioxan (10 ml.) was saturated with dry hydrogen chloride at 15° and the course of the reaction followed spectroscopically. When reaction was complete (2 days) the solvent was removed and the residue crystallised from ethanol to give the *thiazine* (0·80 g.). Slow recrystallisation from ethanol gave pale yellow needles, m. p. 156—158°, rapid recrystallisation gave cubes, m. p. 167—169° (Found: C, 67·6; H, 5·1; N, 5·6; S, 6·1. C$_{30}$H$_{28}$N$_2$O$_5$S requires C, 68·2; H, 5·3; N, 5·3; S, 6·05%); λ$_{max.}$ 3420 (ε 15,000), 2850 (ε 6400), and λ$_{infl.}$ 2250 Å (ε 12,700); ν$_{max.}$ 3280 (NH), 1710 (CO$_2$R), 1660 (CONH), cm.$^{-1}$; τ (CDCl$_3$) 7·74 (singlet, CH$_3$), 6·77 (singlet, S·CH$_2$), 6·35 (singlet, Ph·C*H*$_2$·CO), 4·85 and 4·70 (singlets, Ph·C*H*$_2$·O) 3·55 (not sharp, NH), 2·70, 2·60, and 2·55 (aromatic protons), −1·5 (not sharp, OH or NH), τ (Me$_2$SO) 6·67 (singlet, S·CH$_2$), 6·44 (singlet, Ph·C*H*$_2$·CO), 4·88, and 4·69 (singlets Ph·C*H*$_2$·O), 2·73, 2·64, and 2·57 (aromatic protons) p.p.m. The signal from the CH$_3$ group would be obscured by the solvent signal.

Benzyl 4-*ethoxycarbonyl-5-methyl*-6H-1,3-*thiazin-2-yl* α-*Phenylacetamidoacetate* (XIV; R = Et).—A solution of α-benzyloxycarbonyl-α-phenylacetamidothioacetamide (4·84 g.) and ethyl α-oxo-β-methylene butyrate [2] (2·84 g.) in dioxan (50 ml.) was saturated with dry hydrogen chloride at 15° and the course of the reaction followed spectroscopically. When reaction was complete (2 days) the solvent was removed and the residual solid crystallised from ethanol to give the *thiazine* as needles (1·6 g.), m. p. 138° (Found: C, 64·5; H, 5·7; N, 6·2; S, 7·0. C$_{25}$H$_{28}$N$_2$O$_5$S requires C, 64·4; H, 5·8; N, 6·0; S, 6·9%); λ$_{max.}$ 3420 (ε 18,600), 2850 (ε 6300), and λ$_{infl.}$ 2250 Å (ε 16,000); ν$_{max.}$ 3330, 3140 (NH and bond OH or NH), 1735 (CO$_2$R), 1665 (CONH) cm.$^{-1}$; τ (CDCl$_3$) 8·68 triplet, J = 7 c./sec., CH$_2$·C*H*$_3$), 7·75 (singlet, C=C·CH$_3$), 6·80 (singlet, S·CH$_2$), 6·36 (singlet, Ph·C*H*$_2$·CO), 4·72 (singlet, Ph·C*H*$_2$·O), 5·70 (quartet, J = 7 c./sec., C*H*$_2$·CH$_3$), 3·48 (singlet NH), 2·79 and 2·69 (singlets, 2Ph) p.p.m.

Benzyl 4-carboxy-5-methyl-6H-1,3-thiazin-2-yl α-Phenylacetamidoacetate (XIV; R = H).—(*a*) The thiazine ester (XIV; R = Et, 0·47 g.) in 50% aqueous ethanol (50 ml.) containing sodium carbonate (0·12 g.) was refluxed for 10 min. The solvent was removed and the residue acidified and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and the solvent removed to give the *thiazinecarboxylic acid* (0·16 g.) which was twice crystallised from ethyl acetate to give colourless needles (0·14 g.), m. p. 213—214° (Found: C, 62·7; H, 5·1; N, 6·3; S, 7·4. $C_{23}H_{22}N_2O_5S$ requires C, 63·0; H, 5·0; N, 6·4; S, 7·3%), $\lambda_{max.}$ 3390 (ε 14,000), 2850 (ε 5800), and $\lambda_{infl.}$ 2240 Å (ε 12,000), $\nu_{max.}$ (Nujol) 3240, 3180 (NH and bonded OH or NH), 2700—2300 (CO_2H), 1725 (CO_2H), 1660 (CONH), 1650, 1610 cm.$^{-1}$, τ (Me_2SO) 7·80 (singlet, C=C·CH_3), 6·60 (singlet, S·CH_2), 6·50 (singlet, Ph·CH_2·CO), 4·84 (singlet, Ph·CH_2·O), 2·76, and 2·60 (singlets, 2Ph), 0·96 (singlet, NH), and −1·20 (singlet, OH or NH) p.p.m.

(*b*) The thiazine ester (XIV; R = Ph·CH_2, 1·0 g.) in 50% aqueous ethanol (200 ml.) containing sodium carbonate (0·24 g.) was refluxed for 10 min. and worked up as in (*a*). The thiazine carboxylic acid (0·25 g.) was twice recrystallised from ethyl acetate to give colourless needles, m. p. and mixed m. p. 213—214° with material from (*a*).

Benzyl 4-benzyloxycarbonyl-5-methyl-6H-1,3-thiazin-2-yl α-Phenylacetamidoacetate (XIV; R = Ph·CH_2) *from 7-Phenylacetamidocephalosporanic Acid* (XXII).—A solution of sodium benzyl oxide (from 0·05 g. of sodium) in benzyl alcohol (20 ml.) was added with stirring to a solution of 7-phenylacetamidocephalosporanic acid [13] (0·39 g.) in benzyl alcohol (10 ml.) at 15°. The ultraviolet absorption spectrum of the product appeared after a few minutes but the reaction mixture was kept at 15° for 20 hr. The sodium salt of the product was precipitated by addition of the reaction mixture to ether–light petroleum (b. p. 40—60°) (1 : 1), collected by centrifugation, and washed with ether–light petroleum (1 : 1). The salt was suspended in dioxan (20 ml.), acidified with acetic acid, treated with an excess of phenyldiazomethane for 4 hr. after which the excess was destroyed with 2N-hydrochloric acid, the solvents removed, and the residual oil chromatographed on alumina. The thiazine (XIV; R = Ph·CH_2) was eluted with light petroleum (b. p. 60—80°) containing 7% ether to give a solid which recrystallised from ethanol as prisms (0·32 g.), m. p. and mixed m. p. with synthetic material 167—169° (Found: C, 67·8; H, 5·51; N, 5·6; S, 6·4%); $\lambda_{max.}$ 3410 (ε 15,000), 2860 (ε 6400), and $\lambda_{infl.}$ 2280 Å (ε 12,700); the infrared and n.m.r. spectra were identical with those of the synthetic material.

Benzyl 4-carboxy-5-methyl-6H-1,3-thiazin-2-yl α-Phenylacetamidoacetate (XIV; R = H) *from 7-Phenylacetamidocephalosporanic Acid* (XXII).—A solution of sodium benzyl oxide (from 0·60 g. of sodium) in benzyl alcohol (20 ml.) was added to a stirred solution of 7-phenylacetamidocephelosporanic acid [13] (5·0 g.) in benzyl alcohol (40 ml.). After 2 hr. the sodium salt was isolated as above, suspended in dioxan (130 ml.), acidified with acetic acid and the solution warmed until dissolution was complete. Addition of water now caused the thiazinecarboxylic acid to crystallise as needles, m. p. 207—209° (3·0 g.). Recrystallisation from the same solvent gave needles, m. p. and mixed m. p. with synthetic material 211—213° (Found: C, 62·7; H, 5·5; N, 6·2; S, 7·1%); $\lambda_{max.}$ 3390 (ε 15,700), 2830 (ε 5400), and $\lambda_{infl.}$ 2250 Å (ε 10,800). The infrared and n.m.r. spectra were identical with those of the synthetic material.

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