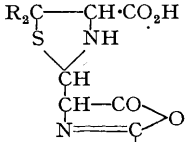
210. *Studies in the Azole Series. Part V. A Synthesis of β-Phenylcysteine.*

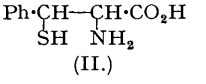
By A. H. Cook, G. Harris, and Sir Ian Heilbron.

Exploratory routes to β-phenylcysteine (which was required in attempts to synthesise a penicillin analogue) by conventional means *via* 2-phenyl-4-benzylideneoxazolone, and α-amino-cinnamic acid derivatives were unsuccessful. 2-Ethylthio-4-benzylidenethiazolone (cf. preceding paper) was, however, converted by three routes into derivatives of 4-carboxy-5-phenyl-2-thiazolidone (XVIII) which were hydrolysed to the required mercaptoamino-acid.

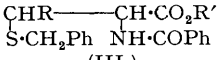
The literature on attempted syntheses of penicillin and its analogues records many attempts to obtain the thiazolidine-oxazolone structure (I), starting both from penicillamine and from



(I.)



(II.)

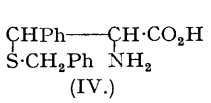


(III.)

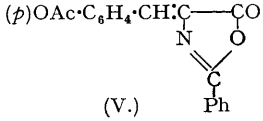
cysteine. Work with numerous derivatives of these mercaptoamino-acids has, however, demonstrated the difficulty of obtaining the combined heterocyclic systems, and the final

products have so far mostly been of the penicilloate or penicillenate type (*Nature*, 1945, **156**, 766; *Science*, 1945, **102**, 622). The present work had for its eventual object the preparation of a thiazolidine-oxazolone and other formulations for the penicillins from β-phenylcysteine (II).

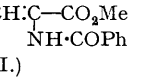
The route by which other mercaptoamino-acids, including penicillamine, are available was first explored. 2-Phenyl-4-benzylideneoxazolone reacted readily with benzylthiol in methanolic sodium methoxide to give the *ester* (III; R = Ph, R′ = Me) in excellent yield. Only one of the two possible stereoisomeric esters was obtained, and this was hydrolysed to β-*phenyl*-S-*benzylcysteine* (IV). On reduction of this with sodium in liquid ammonia, benzylthiol was regenerated, showing that fission of the molecule had taken place on the undesired side of the sulphur atom, and the sole acid product isolated was β-phenylalanine [(IV) may be regarded as a substituted dibenzyl sulphide, fission of which depends upon the particular nature of the substituents]. *p*-Hydroxybenzaldehyde has also been condensed with hippuric acid under acetylating conditions to give 2-phenyl-4-*p*-acetoxybenzylidene-oxazolone (V), previously described by Erlenmeyer and Halsey (*Annalen*, 1899, **307**, 139). Attempts to prepare the cysteine derivative (III; R = *p*-OH·C_6H_4, R′ = Me) by reaction of (V) with benzylthiol in presence of methanolic sodium methoxide were not successful however, the product consisting of the *ester* (VI).



(IV.)



(V.)

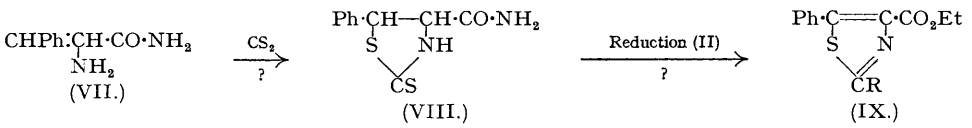


(VI.)

It was clear that a route which evaded the reduction of the *S*-benzyl compound would have to be used, and additions of hydrogen sulphide and thioacetic acid to appropriate amino-acid derivatives were examined. Treatment of 4-benzylidene-2-methyloxazolone with hydrogen sulphide in methanolic sodium methoxide resulted only in the formation of methyl α-acetamidocinnamate, and attempts to add hydrogen sulphide or thioacetic acid to this ester or its corresponding acid under various conditions were also unsuccessful.

An unsuccessful route, which was examined, consisted in reaction of the amide (VII) of α-aminocinnamic acid (Braucke, *Rec. Trav. chim.*, 1896, **15**, 131) with carbon disulphide in the hope of forming (VIII) which might have been reduced; a similar route to penicillamine starting from α-amino-ββ-dimethylacrylic esters has been described in a penicillin report which has now been published (Cook, Heilbron, and Shaw, CPS 311).

Attempts were made to reduce suitable thiazoles to derivatives of (II). Ethyl β-bromo-β-phenylpyruvate (Gault and Wieck, *Bull. Soc. chim.*, 1922, **31**, 881) was easily condensed with thiourea to the *aminothiazole* (IX; R = NH_2) and with thiobenzamide to the *diphenylthiazole* (IX; R = Ph) (cf. Erlenmeyer and Morel, *Helv. Chim. Acta*, 1942, **25**, 1073, where similar reactions with ethyl bromopyruvate are described). These thiazoles were characterised as their *picrates* and by alkaline hydrolysis to the corresponding *acids*. Treatment of (IX; R = NH_2) with sodium amalgam failed to give a reduced product, yielding only an unidentified isomer of the original amino-compound, while similar treatment of (IX; R = Ph) furnished

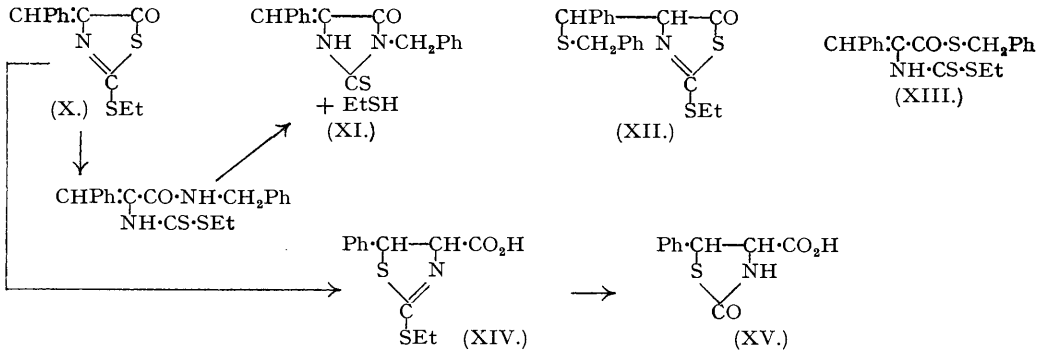


(VII.) (VIII.) (IX.)

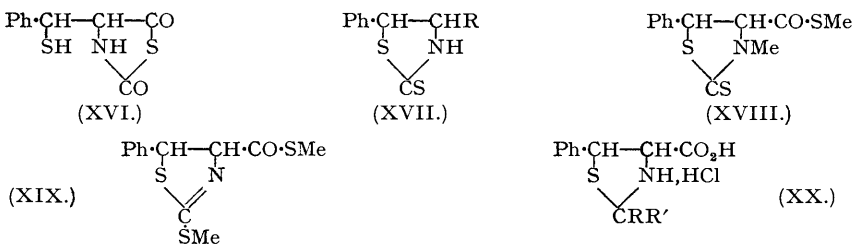
benzaldehyde, presumably as a result of fission of the primary product, and a compound which gave a mercury derivative and the ferric chloride and nitroprusside colour reactions expected of (II); this material was, however, not obtained pure.

2-Ethyl- and 2-benzyl-thio-4-benzylidenethiazol-5-one were described in the preceding paper, and attention was turned to these as possibly affording intermediates which might be more useful. As described in the preceding paper, the ethyl compound (X) exhibited a rather unexpected reactivity; with cold ethereal benzylamine ready reaction ensued with elimination of ethylthiol, the *thiohydantoin* (XI) being formed, perhaps in the manner indicated. On the other hand, the thiazolone (X) reacted with benzylthiol to give a compound first considered to be the thiazolone (XII) but probably correctly formulated as the *thio-ester* (XIII) since, on reaction with benzylamine, it was converted into the thiohydantoin (XI). A similar ring fission was observed on boiling (X) with aqueous ethanolic alkali, whereby it was converted into an acid with simultaneous loss of ethylthiol. The crystalline acid still contained sulphur and was

formulated as 4-*carboxy*-5-*phenylthiazolid*-2-*one* (XV) formed *via* (XIV); (XV) yielded one form of the required β-phenylcysteine on hydrolysis but only in poor overall yield.



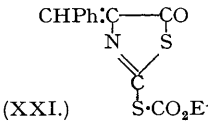
When (X) was treated in methanolic sodium methoxide with hydrogen sulphide reaction was sluggish as inferred from the extremely slow evolution of ethylthiol. A small quantity of a crystalline *substance* was isolated and from its properties may have been (XVI), but in view of its difficult accessibility it did not appear to be very useful.



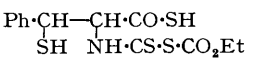
The addition of hydrogen sulphide to (X) in the presence of methanolic triethylamine, however, resulted in rapid elimination of ethylthiol, and the product was an acid, $C_{10}H_9ONS_3$, obtained as its *triethylamine* salt, which must be formulated as the *thiothiazolidone* (XVII; R = CO·SH). On being heated with dilute hydrochloric acid this yielded a stable acid, $C_{10}H_9O_2NS_2$, which is to be represented as 4-*carboxy*-5-*phenyl*-2-*thiothiazolidone* (XVII; R = CO_2H). (XVII; R = CO·SH) was further characterised by reaction with diazomethane and with diazomethane followed by methyl sulphate, being so converted into two *dimethyl* derivatives, (XVIII) and (XIX), which structures are supported by the experimental conditions employed. (XVII; R = CO_2H) is exactly comparable with an intermediate which afforded penicillamine by reduction, and was indeed sought earlier with the intention of submitting it to reduction. Extensive attempts were therefore made to convert it into β-phenylcysteine [reduction with sodium in liquid ammonia, aluminium and acid, sodium amalgam under various conditions, stannous chloride (*e.g.*, in butanol), by electrolytic reduction commonly applicable to thioamides, as well as by fairly mild alkaline or acid hydrolysis] but, to judge by the weak colour reaction of the products with ferric chloride, no more than traces of the required mercaptoamino-acid were formed. After these abortive efforts it was found that the hydrolytic fission of (XVII; R = CO_2H) could be effected surprisingly cleanly by heating for several hours with concentrated hydrochloric acid under pressure (cf. Gabriel and Posner, *Ber.*, 1894, **27**, 3509). The product was a thiol giving the anticipated intense indigo-blue colour with ferric chloride, and also an α-amino-acid hydrochloride giving a red-purple ninhydrin reaction; analysis left no doubt of its formulation as β-*phenylcysteine hydrochloride*, apparently only one of the two possible stereoisomerides being formed. Like other acids of its class, it reacted readily with carbonyl compounds with disappearance of the thiol grouping, and was characterised as its product with acetone, 4-*carboxy*-5-*phenyl*-2 : 2-*dimethylthiazolidine hydrochloride* (XX; R = R′ = Me) and with benzaldehyde, 4-*carboxy*-2 : 5-*diphenylthiazolidine hydrochloride* (XX; R = H, R′ = Ph).

Before this synthesis had been completed, other routes which might have proceeded through more readily hydrolysable intermediates had been projected. For instance, dithiocarbocarbethoxyglycine (preceding paper), with benzaldehyde in presence of acetic anhydride, afforded 2-*carbethoxythio*-4-*benzylidenethiazolone* (XXI); it was expected that treatment of the latter

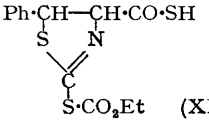
with hydrogen sulphide would lead to either (XXII) or (XXIII). Treatment of the former with alkali, followed by acidification, would have yielded phenylcysteine; or reduction of the



(XXI.)



(XXII.)



(XXIII.)

latter with aluminium amalgam, followed by acid hydrolysis or treatment with mercuric chloride, would have yielded the same product. In fact, however, it was found that treatment with hydrogen sulphide in a basic medium yielded (XVII; R = CO·SH) by loss of carbon dioxide and ethylthiol.

Experimental.

Experiments with Oxazolones.—2-Phenyl-4-benzylideneoxazolone (Erlenmeyer *et al.*, *Annalen*, 1893, **275**, 3; 1904, **337**, 266) (50 g.) in dry methanol (500 c.c.) containing sodium methoxide (11 g.) was slowly treated with benzylthiol (25 g.); much solid had separated after 2 hours' stirring but the suspension was kept overnight, filtered, and the product washed well with methanol. The crude *methyl* ester of N-*benzoyl*-β-*phenyl*-S-*benzylcysteine* (yield 76 g., 98%) was practically insoluble in methanol but separated in needles, m. p. 164°, from dioxan–water or chloroform–light petroleum (Found: C, 71·0; H, 5·6; N, 3·75. $C_{24}H_{23}O_3NS$ requires C, 71·1; H, 5·7; N, 3·5%). This ester (165 g.) was refluxed for 2½ hours with water (375 c.c.) and 50% hydrogen bromide in acetic acid (750 c.c.) and acetic acid (375 c.c.). The solution was evaporated to small bulk and the residue stirred with ether. The filtered aqueous solution was diluted to 3 l. and further extracted with ether to remove benzoic acid after adding concentrated hydrochloric acid (100 c.c.). Adjustment of the aqueous solution to pH 7 with ammonia gave β-*phenyl*-S-*benzylcysteine* (69 g., 55%); it was insoluble in common organic solvents except warm acetic acid, but separated in needles, m. p. 181—185° (sintering at 175°), from acetic acid in ether (Found: N, 5·1, 5·1. $C_{16}H_{17}O_2NS$ requires N, 4·9%). The foregoing *S*-benzyl compound (10 g.) in liquid ammonia (500 c.c.) was reduced in the normal manner with sodium (2·5 g., 3 equivs.); ammonium chloride (7 g.) was added, and ammonia removed, the dry residue being stirred with ethereal hydrogen chloride and then with cold ethanol (100 c.c.). Removal of solvent from the alcoholic filtrate gave an amino-acid hydrochloride (ninhydrin reaction) which, however, contained no sulphur (yield, 5·4 g.). It crystallised from concentrated hydrochloric acid or ethanol–ether in rectangular plates, m. p. 230° (decomp.), and was evidently β-phenylalanine hydrochloride (Found: C, 53·4; H, 5·7; N, 6·6. Calc. for $C_9H_{12}O_2NCl$: C, 53·6; H, 6·0; N, 6·9%); it afforded free phenylalanine identical with this material obtained by literature methods.

p-Hydroxybenzaldehyde (34 g.), anhydrous sodium acetate (23 g.), acetic anhydride (120 g.), and hippuric acid (50 g.) were warmed on the steam-bath for 1 hour though the reaction mixture set to a solid mass within 5 mins. The product was filtered off, washed with acetic acid, and crystallised from the same solvent. 2-Phenyl-4-*p*-acetoxybenzylideneoxazolone separated in pale yellow needles, m. p. 179°, from acetic acid or chloroform (Found: C, 70·0; H, 4·3; N, 4·6. Calc. for $C_{18}H_{13}O_4N$: C, 70·3; H, 4·3; N, 4·6%) (yield 63 g., 73%). The azlactone (20 g.) in methanol (250 c.c.) containing sodium methoxide (3·5 g.) was kept for 3—4 days with benzylthiol (8·5 g.). Acidification (Congo-red), evaporation in a vacuum, and rubbing the residue with water gave a crystalline solid (16·1 g.). This was a mixture eventually separated by crystallisation from acetone–light petroleum. The less soluble component was identified as dibenzyl disulphide; it separated from acetone–water or ethanol in prismatic needles, m. p. 69—73° (Found: C, 67·9; H, 5·7. Calc. for $C_{14}H_{14}S_2$: C, 68·3; H, 5·7%). The more soluble *ester* (V) crystallised from acetone–light petroleum in hexagonal prisms, m. p. 184—185° (Found: C, 68·6; H, 5·2; N, 5·0. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·1; N, 4·7%).

Experiments with Derivatives of α-Aminocinnamic Acid.—4-Benzylidene-2-methyloxazolone (Raiford and Burman, *J. Org. Chem.*, 1943, **8**, 469) (40 g.) in dry methanol (450 c.c.) containing sodium methoxide (6 g.) was treated overnight with hydrogen sulphide at 0°. The solution was neutralised and evaporated in a vacuum, and the residues stirred with water. The crystalline product was washed well with ether (yield 28 g.) and crystallised from chloroform–light petroleum to give *methyl α-acetamidocinnamate* in laths, m. p. 125° (softening at 122°) (Found: C, 65·4; H, 6·1; N, 6·2. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 6·0; N, 6·4%). Attempts to add thioacetic acid or hydrogen sulphide as such or as sodium sulphide to this ester at 105—120° for 15—20 hours led either to no change or to formation of α-acetamidocinnamic acid.

Ethyl αβ-dibromo-β-phenylpropionate (90 g.) was shaken for 3 days at 45—60° with ammonia (500 c.c., *d* 0·880). On cooling and standing, the crude α-*amino*-β-*phenylacrylamide* separated and was fractionally crystallised from acetone–light petroleum. The less soluble crops comprised the known amide, m. p. 170—176° (Braucke, *loc. cit.*, gives m. p. 172°); the more soluble crops provided an *isomeride*, which separated from chloroform–light petroleum in rhombic plates, m. p. 122—124° (Found: C, 66·3; H, 6·3; N, 17·1. $C_9H_{10}ON_2$ requires C, 66·6; H, 6·2; N, 17·3%); the total yield was 21·9 g. (51%).

Experiments on Selected Thiazoles.—Ethyl β-bromo-β-phenylpyruvate (Gault and Wieck, *loc. cit.*) (10 g.) was added to thiourea (5 g.) in hot ethanol (70 c.c.), and reaction completed by heating for 5 mins. on the steam-bath. The thiazole was precipitated by pouring into 25% aqueous ammonia (200 c.c.), and recrystallised from dilute ethanol (yield, 10·5 g.). 2-*Amino*-4-*carbethoxy*-5-*phenylthiazole* (IX; R = NH_2) separated in colourless plates, m. p. 182° (Found: C, 57·8; H, 4·9; N, 11·4. $C_{12}H_{12}O_2N_2S$ requires C, 58·1; H, 4·9; N, 11·3%); its *picrate* separated from methanol in needles, m. p. 201° (Found: N, 14·7. $C_{18}H_{15}O_9N_5S$ requires N, 14·7%). The thiazole ester (0·5 g.) in water (20 c.c.) containing

ethanol (2 c.c.) was treated with 3% sodium amalgam (17 g.). On completion of the reaction the aqueous solution was allowed to stand and the *isomeride* of (IX; R = NH_2) (400 mg.) collected; it separated from methanol–water in thin colourless needles, m. p. 202°, which depressed the m. p. of the initial compound (Found: C, 57·9; H, 4·9; N, 11·3%); its *picrate* separated from ethanol in needles, m. p. 194°, which depressed the m. p. of the picrate described above (Found: N, 14·8%). The amine (IX; R = NH_2) was hydrolysed with hot aqueous-ethanolic potassium hydroxide during 20 mins. Acidification with acetic acid yielded an acid. Recrystallised from ethanol, *2-amino-4-carboxy-5-phenylthiazole* separated as colourless needles, m. p. 225—226° (decomp.) (Found: C, 54·6; H, 3·8; N, 12·9. $C_{10}H_8O_2N_2S$ requires C, 54·5; H, 3·7; N, 12·7%).

Ethyl β-bromo-β-phenylpyruvate (1 g.) and thiobenzamide (0·5 g.) were heated in refluxing ethanol (10 c.c.) for 30 mins., and on cooling, the thiazole (0·8 g.) separated. *4-Carbethoxy-2 : 5-diphenylthiazole* (IX; R = Ph) crystallised from ethanol in colourless needles, m. p. 110—111° (Found: C, 69·9; H, 5·3; N, 4·5. $C_{18}H_{15}O_2NS$ requires C, 69·9; H, 4·9; N, 4·5%). *4-Carboxy-2 : 5-diphenylthiazole,* obtained from this as for the above thiazole acid, crystallised from aqueous ethanol as colourless needles, m. p. 140—141° (Found: C, 67·9; H, 4·0; N, 5·3. $C_{16}H_{11}O_2NS$ requires C, 68·3; H, 4·0; N, 5·0%).

Experiments with 2-Ethylthio-4-benzylidenethiazol-5-one (CPS 440).—The thiazolone (5 g.) in methanol (100 c.c.) containing sodium methoxide (1·0 g.) was saturated with hydrogen sulphide at 0° for *ca.* 16 hours, and the solution then evaporated at a low temperature. Extraction of the residue with chloroform and concentration of the extract gave crystals which, recrystallised from toluene, separated as platelets, m. p. 145—148° (decomp.); this product was not acidic and was probably the slightly impure *thiazolidione* (XVI) (Found: C, 49·3; H, 4·1; N, 5·6. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·8%). It could not be hydrolysed to the required mercaptoamino-acid. The mother-liquors from the preceding compound reacted with benzylamine to give 1-benzyl-4-benzylidenethiohydantoin, which separated from chloroform–light petroleum in rhombic plates, m. p. 226—227°. This compound had been previously obtained from the original thiazolone. 2-Ethylthio-4-benzylidenethiazol-5-one (0·2 g.) was treated in ether with excess of benzylamine, ethylthiol being evolved. After 1 hour, removal of ether and addition of water gave a yellow solid. On repeated crystallisation from chloroform–light petroleum *1-benzyl-4-benzylidene-2-thiohydantoin* (XIV) was obtained in long rhombic plates, m. p. 226—227° (Found: C, 69·2: H, 4·7; N, 9·1. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·7; N, 9·5%).

2-Ethylthio-4-benzylidenethiazol-5-one (1 g.) was boiled with 1N-sodium hydroxide (4·2 c.c.) and a little ethanol until dissolved (2 hours), ethylthiol being evolved. Ethanol was removed in a vacuum, unchanged thiazolone extracted with ether, and the aqueous solution acidified and extracted with chloroform. On removal of solvent, and rubbing the residue with ether–light petroleum it solidified. *4-Carboxy-5-phenyl-2-thiazolidone* separated, after repeated crystallisation from chloroform–light petroleum, in platelets, m. p. 157—158° (Found: C, 51·6; H, 4·1; N, 5·7. $C_{10}H_9O_3NS,\frac{1}{2}H_2O$ requires C, 51·7; H, 4·3; N, 6·0%). It yielded β-phenylcysteine on hydrolysis with concentrated hydrochloric acid (sealed tube).

2-Ethylthio-4-benzylidenethiazol-5-one (5 g.) was stirred with methanol (80 c.c.) containing sodium methoxide (50 mg.) and benzylthiol (2·5 g.) for 2 hours, a clear solution being obtained. The sodium methoxide was neutralised with hydrochloric acid, and the solution evaporated to dryness in a vacuum. The residual oil was distilled repeatedly in a high vacuum at 100—110° (bath temp.) as a pale yellow, mobile oil, regarded as the *thio*-ester (XIII) (Found: C, 60·9; H, 5·4; N, 4·2. $C_{19}H_{19}ONS_3$ requires C, 61·1; H, 5·1; N, 3·8%). Vigorous reaction occurred on treating the ester with excess of ethereal benzylamine. The product, recrystallised from ethyl acetate, separated as pale yellow prisms, m. p. 227°, undepressed by 1-benzyl-4-benzylidene-2-thiohydantoin prepared as above. The original ethylthiothiazolone (5 g.) in methanol (100 c.c.) containing triethylamine (2 g.) was saturated with hydrogen sulphide at 0° for 20 hours, and the solution just neutralised with dilute hydrochloric acid. On scratching and cooling, white crystals (3·9 g.) of an acid separated; it was soluble in ethanol, acetone, or dioxan, and crystallised from chloroform containing a little methanol, but was better purified by solution in aqueous sodium hydrogen carbonate and precipitation with acid, or by precipitation from ethyl acetate with light petroleum. *4-Thiocarboxy-5-phenyl-2-thiothiazolidone* (XVII; R = CO·SH) had m. p. 157—158°, resolidifying and melting again at 180—190° (Found: C, 47·2; H, 3·8; S, 37·6. $C_{10}H_9ONS_3$ requires C, 47·1; H, 3·5; S, 37·6%). The *triethylamine* salt, which provided the best means of isolating the acid in the above preparation (yield, 78%), crystallised from chloroform–light petroleum in rhomboidal prisms, m. p. 132—133° (decomp.) (Found: C, 53·9; H, 7·1; N, 7·7. $C_{16}H_{24}ON_2S_3$ requires C, 53·9; H, 6·8; N, 7·9%). The preceding thiol-acid (2 g.) in acetone was treated with excess of diazomethane in ether. After the reaction, solvents were removed, and the oil deposited crystals on dissolution in acetone and addition of light petroleum. The crystals were no longer acid, and crystallised from chloroform–light petroleum in long laths, m. p. 134—136°, consisting of the *dimethyl* derivative (XVIII) (Found: C, 50·6; H, 4·7; N, 5·0. $C_{12}H_{13}ONS_3$ requires C, 50·9; H, 4·6; N, 5·0%). The oil obtained by removal of solvents from the filtrate was treated with 1 mol. of sodium hydroxided an methyl sulphate in ether. Removal of ether gave an oil, which was distilled in a high vacuum. Upon standing, the distillate crystallised. Recrystallisation from ethanol and water yielded the *compound* (XIX) as octahedra, m. p. 74° (Found: C, 51·0; H, 4·8; N, 4·9. $C_{12}H_{13}ONS_3$ requires C, 50·9; H, 4·6; N, 5·0%).

The thiol-acid (XVII; R = CO·SH) (20 g.) was heated with 2N-hydrochloric acid at 90° for 30 minutes, *i.e.*, until evolution of hydrogen sulphide ceased. The cold solution was decanted from the heavy orange oil, which was then stirred with ether. On evaporation of the ether and treatment of the gum with a little chloroform, the material crystallised but retained gum which was only removed on triturating with solvents. The solid was soluble in chloroform or ethyl acetate, sparingly soluble in ether or light petroleum; it was further purified by solution in aqueous sodium hydrogen carbonate and precipitation with acid, and recrystallisation from ethanol–light petroleum. *4-Carboxy-5-phenyl-2-thiothiazolidone* (XVII; R = CO_2H) separated in very small laths, m. p. 173—175° (Found: C, 50·6; H, 3·9; N, 5·8. $C_{10}H_9O_2NS_2$ requires C, 50·2; H, 3·8; N, 5·9%); a further quantity was eventually obtained from the original acid hydrolysate by standing at 0° (total yield, 10·1 g.).

β-Phenylcysteine.—The preceding acid (5·9 g.) was heated for 13 hours with concentrated hydrochloric

acid (50 c.c.) at 100° (sealed tube). Much hydrogen sulphide was generated and, on cooling, a solid hydrochloride separated (3·7 g.). This was dried over phosphoric oxide to remove water of crystallisation and recrystallised from *iso*propanol containing a little light petroleum. *β-Phenylcysteine hydrochloride* separated in platelets, m. p. 202—203° (decomp.) (Found : C, 46·6; H, 5·4; N, 5·8. $C_9H_{12}O_2NClS$ requires C, 46·4; H, 5·2; N, 6·0%). The hydrochloride was slightly soluble in *iso*propanol, cold water, hot or cold acetone, chloroform, or *tert.*-butanol, but was easily soluble in ethanol. Like penicillamine, it gave an intense blue colour with ferric chloride and a red-purple ninhydrin reaction. The hydrochloride (0·5 g.) in hot ethanol (11 c.c.) was refluxed with acetone (20 c.c.) for 20 minutes, test portions then no longer giving thiol colour reactions. The solution was evaporated in a vacuum, and the residue repeatedly treated with ethereal hydrogen chloride. It was recrystallised several times from chloroform containing a little methanol by addition of ether, with rejection of a little gummy material which separated first, and *4-carboxy-5-phenyl-2 : 2-dimethylthiazolidine hydrochloride* separated in clusters of prisms, m. p. 195° (decomp.) (Found : C, 50·2; H, 6·4; N, 4·7. $C_{12}H_{16}O_2NClS$,MeOH requires C, 50·2; H, 6·5; N, 4·6%); it was soluble in water and very soluble in methanol but sparingly soluble in chloroform. It regenerated β-phenylcysteine by boiling in 2N-hydrochloric acid for a few minutes.

β-Phenylcysteine hydrochloride (0·5 g.), benzaldehyde (0·3 g.), and a few drops of methanol were heated on the steam-bath for 3 mins., after which the resin was broken down to a white powder on rubbing with dry ether. *4-Carboxy-2 : 5-diphenylthiazolidine hydrochloride* was soluble in methanol, sparingly soluble in *iso*propanol, and insoluble in ether, chloroform, or acetone. It separated from methanol–ether in rosettes of microscopic needles, m. p. 174—175° (decomp.) (Found : C, 59·3; H, 5·2; N, 4·2. $C_{16}H_{16}O_2NClS$ requires C, 59·7; H, 5·0; N, 4·4%).

Dithiocarbocarbethoxyglycine (5·0 g.) was heated with benzaldehyde (2·5 g.) and acetic anhydride (10 c.c.) for 3—4 mins. on the steam-bath. Removal of solvents in a vacuum and treatment of the residue with cold methanol yielded a solid. Recrystallised from acetone–water and methanol, *2-carbethoxythio-4-benzylidenethiazol-5-one* (XXI) separated as yellow needles, m. p. 121—123° (yield 16%) (Found : C, 53·5; H, 3·9; N, 4·7. $C_{13}H_{11}O_3NS_2$ requires C, 53·2; H, 3·8; N, 4·8%). Reaction of the thiazolone with hydrogen sulphide in methanolic triethylamine yielded (XVII; R = CO·SH).

We thank the Therapeutic Research Corporation of Great Britain, Ltd., for assistance.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W. 7.

[*Received, August 2nd,* 1947.]