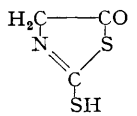
496. *Studies in the Azole Series. Part XXII. The Synthesis of N-Alkylamino-acids.*

By A. H. Cook and S. F. Cox.

The condensation of aldehydes and ketones with 2-thio-3-methylthiazolid-5-one (II), 5-acetamido-2-thio-3-methylthiazoline (VI), and several 3-substituted 2-thio-1-alkylhydantoins (XIV), and the conversion of the products into *N*-alkylamino-acids have been studied. It is concluded that, for steric and other reasons, no single azole satisfies completely the requirements of a general synthesis of *N*-alkylamino-acids although individual acids are obtainable by selecting the appropriate heterocyclic intermediates.

Many of the methods used for the formation of amino-acids involve an intermediate containing potential amino- and carboxy-groups to which a substituent corresponding to the side chain of the amino-acid is attached. For such a synthesis to be of preparative value, the intermediate should be stable, easily prepared, and readily convertible into the substituted product which must be easily separable from any uncondensed material; further, the condensation product should be convertible without difficulty into the corresponding amino-acid. No such general method for the synthesis of *N*-alkylamino-acids has been described in the literature. Various azoles which are potentially useful as intermediates in this connection are considered below.

2-Mercaptothiazol-5-one (I) has been shown (Part XIX, this vol., p. 2323) to be the basis of a convenient synthesis of amino-acids, and the first compound to be investigated in the present work was the related 2-thio-3-methylthiazolid-5-one (II). This condensed with benzaldehyde when heated in acetic acid containing morpholine, with the formation of 2-*thio*-4-*benzylidene*-3-*methylthiazolid*-5-*one* (III) which was converted into β-phenyl-*N*-methyl-α-alanine by boiling hydriodic acid and red phosphorus; treatment with alkali rearranged the compound (III) to 2-*thio*-5-*phenyl*-3-*methylthiazolidine*-4-*carboxylic acid* (IV). Unlike the unmethylated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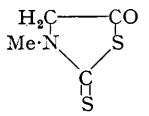
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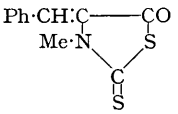
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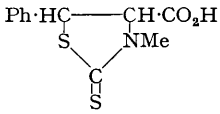
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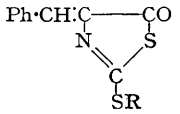
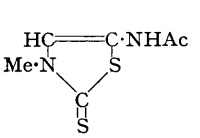

(V.)

compound, however, 2-thio-3-methyl-4-benzylidenethiazolid-5-one did not crystallise from the reaction mixture on cooling, so that its isolation in a pure state was rather tedious, and it was relatively low melting. *n*-Butyraldehyde appeared to undergo condensation with 2-thio-3-methylthiazolid-5-one in acetic acid solution but the product was a dark oil which could not be induced to crystallise, and acetone, under a variety of conditions, yielded only unchanged starting materials. These difficulties made it clear that 2-thio-3-methylthiazolid-5-one did not form the basis of a useful general method for the synthesis of *N*-alkylamino-acids, whilst an attempt to avoid its use as in the methylation of 2-mercapto-4-benzylidenethiazol-5-one (V; R = H) led only to the S-methyl *derivative* (V; R = Me).

5-Amino-2-thio-3-methylthiazoline condenses with aldehydes to form the corresponding Schiff's bases, but it was thought that by using instead its acetyl derivative (VI) a product of type (VII) might be obtained. 5-Acetamido-2-thio-3-methylthiazoline (VI) did not react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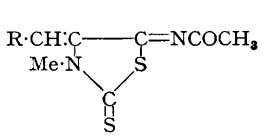
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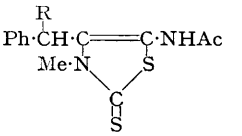
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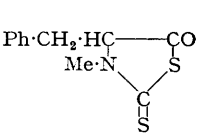
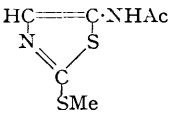

(IX.)

with benzaldehyde in hot acetic acid containing sodium acetate, but, when the two compounds were heated under reflux in pyridine containing one equivalent of piperidine, a product crystallised from the reaction mixture which from its analysis must be 5-*acetamido*-2-*thio*-4-α-*piperidinobenzyl*-3-*methylthiazoline* (VIII; R = N<[CH$_2$]$_5$). This compound was stable in alkaline solution but was hydrolysed when warmed with dilute acid; on treatment with alcoholic hydrogen chloride, it formed a hydrochloride from which the parent compound was recovered by ammonia. When heated under reflux with hydriodic acid and red phos-

phorus for 16 hours, (VIII; R = N<[CH_2]$_5$) was converted into β-phenyl-*N*-methylalanine, interruption of the reaction after 5 hours affording the intermediate 2-*thio*-4-*benzyl*-3-*methylthiazolid*-5-*one* (IX). On repetition of the condensation with morpholine instead of piperidine, 5-*acetamido*-2-*thio*-4-α-*morpholinobenzyl*-3-*methylthiazoline* (VIII; R = N<[CH_2·CH_2]$_2$>O) was formed, but with diethylamine only unchanged starting material was recovered. A mixture of benzaldehyde and piperidine in pyridine condensed similarly with 5-acetamido-2-methylthiothiazole (X) to form 5-*acetamido*-2-*methylthio*-4-α-*piperidinobenzylthiazole*. The compound (VI) appeared to condense with *n*-butyraldehyde in presence of piperidine and pyridine, but the product was a dark gum, and likewise no satisfactory condensation could be affected between acetone and (VI) under these conditions, so that the usefulness of this method also was limited.

During one of the condensations of benzaldehyde with (VI) in the presence of piperidine, the reaction mixture was distilled in steam, and a white crystalline material was observed in the distillate. Examination of this compound showed it to be benzylidenebis-1-piperidine (XI; R = N<[CH_2]$_5$), a product obtained by Laun (*Ber.*, 1884, **17**, 678) by heating benzaldehyde with piperidine in a sealed tube, which he described as unstable and rapidly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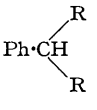
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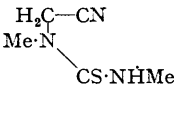
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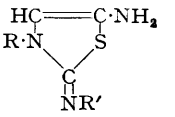
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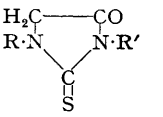
(XIV.)

hydrolysed by water. It was more conveniently obtained by boiling the two components for a few minutes in pyridine and crystallised from the mixture on cooling it in ice. It reacted with (VI) in hot pyridine and may be presumed to be the intermediate in the reactions described above. No product separated on heating a mixture of morpholine and benzaldehyde in pyridine, but fractional distillation gave *benzylidenebis*-4-*morpholine* (XI; R = morpholino). It is significant that diethylamine, which did not induce a reaction between benzaldehyde and (VI), appeared not to react with benzaldehyde in pyridine, fractionation of the reaction mixture yielding only unchanged materials.

Boyd and Robson (*Biochem. J.*, 1935, **29**, 546) obtained condensation products from aromatic aldehydes and acetyl-2-thiohydantoin under basic conditions in excellent yields, and converted the products into amino-acids. The use of the corresponding 2-thio-1-alkylhydantoins was not attempted in this work as these can not be conveniently obtained from *N*-alkylamino-nitriles, but Delépine (*Bull. Soc. chim.*, 1903, **29**, 1198) described a synthesis of 2-thio-1 : 3-dimethylhydantoin (XIV; R = R′ = Me) starting with methylaminoacetonitrile and methyl *iso*thiocyanate although he did not identify the intermediate material. When the two components were mixed in ether, a *product* was obtained which might be formulated as (XII) or (XIII; R = R′ = Me) (cf. Part IX, *J.*, 1948, 2028); the former was considered to be correct as the substance failed to give an acetyl or benzylidene derivative under appropriate conditions. On being heated with aqueous acid, it was converted into 2-thio-1 : 3-dimethylhydantoin, the overall yield being 85%. The thiohydantoin condensed smoothly with benzaldehyde in hot pyridine containing morpholine, to form 2-*thio*-5-*benzylidene*-1 : 3-*dimethylhydantoin*, and with acetone similarly to give 2-*thio*-1 : 3-*dimethyl*-5-iso*propylidenehydantoin*. The use of other carbonyl compounds, however, afforded only gummy products and accordingly it was decided to investigate the use of intermediates derived from phenyl *iso*thiocyanate as these were expected to have higher m. p., and to be less soluble in organic solvents, than those obtained from methyl *iso*thiocyanate.

Phenyl *iso*thiocyanate reacted readily with methylaminoacetonitrile, and the fact that the product had cyclised was established by the ease with which it formed an *acetyl* derivative. 5-*Amino*-2-*anilo*-3-*methylthiazoline* (XIII; R = Me, R′ = Ph), obtained in this way, was converted into 2-*thio*-3-*phenyl*-1-*methylhydantoin* (XIV; R = Me, R′ = Ph) on being heated with hydrochloric acid, and the thiohydantoin condensed with benzaldehyde, *n*-butyraldehyde, or acetone to give 2-*thio*-3-*phenyl*-5-*benzylidene*-1-*methylhydantoin*, 2-*thio*-3-*phenyl*-1-*methyl*-5-n-*butylidenehydantoin*, and 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylidenehydantoin*, respectively, in excellent yields. It was hoped to convert these products directly into the corresponding amino-acids by reductive hydrolysis, using hydriodic acid and red phosphorus, but, when the benzylidenehydantoin was heated under reflux with 25% hydriodic acid in acetic acid for 24 hours, 2-*thio*-3-*phenyl*-5-*benzyl*-1-*methylhydantoin* was obtained in good yield. This was

hydrolysed to β-phenyl-*N*-methylalanine under alkaline conditions, and the overall yield in the degradation was 74%. In the same way, 2-thio-3-phenyl-1-methyl-5-*iso*propylidenehydantoin was reduced to 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylhydantoin* and hydrolysed with alkali to *N*-methylvaline.

In order to examine possible further application of this method, *iso*propylaminoacetonitrile was treated with phenyl *iso*thiocyanate in ether, the 5-*amino*-2-*anilo*-3-iso*propylthiazoline* (XIII; R = Pr^i, R′ = Ph) which was formed being hydrolysed with acid to 2-*thio*-3-*phenyl*-1-iso*propylhydantoin* (XIV; R = Pr^i, R′ = Ph). This hydantoin was condensed with benzaldehyde in a mixture of pyridine and morpholine to form 2-*thio*-3-*phenyl*-5-*benzylidene*-1-iso*propylhydantoin*, which was reduced to 2-*thio*-3-*phenyl*-5-*benzyl*-1-iso*propylhydantoin* and hydrolysed with alkali to 2-*phenyl*-N-iso*propylalanine*. In the same way, *n*-butyraldehyde yielded 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylidenehydantoin*, 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylhydantoin*, and N-iso*propylnorleucine*. Acetone, however, could not be condensed with the parent thiohydantoin even when the reaction period was extended from 1 to 24 hours. Similar differences in the ease of condensation of hydantoins and thiohydantoins with aldehydes and ketones have been recorded by a number of workers, but the conditions used have varied to such an extent that it is difficult to judge the exact effect of the factors involved. In the present work, it was found that the use of sodium acetate in acetic acid instead of a medium consisting of morpholine and pyridine did not affect the condensation of 2-thio-3-phenyl-1-methylhydantoin with benzaldehyde but prevented the reaction with acetone. The corresponding hydantoin did not react with either benzaldehyde or acetone in the presence of morpholine in pyridine as the condensing agent. It seems from these results that four factors can be distinguished in this type of condensation: (1) the reactivity of the carbonyl compound; (2) the reactivity of the methylene group which is adversely affected by the replacement of sulphur by oxygen; (3) a steric effect involving the group attached to the nitrogen atom adjacent to the methylene group; and (4) the efficiency of the condensing agent, morpholine in pyridine being more effective than sodium acetate in acetic acid. It must be concluded that this third method for the synthesis of *N*-alkylamino-acids does not have the desired general applicability and suffers from the necessity of converting the condensation product into the amino-acid in two steps; it is useful, however, for preparing a wide range of these amino-acids and good yields are obtained at each stage.

Experimental.

Reactions with 2-Thio-3-methylthiazolid-5-one.—The thiazolidone (5 g.) was heated under reflux for 2 hours with benzaldehyde (4 g.) in acetic acid (25 c.c.) containing several drops of morpholine. The solvent was removed *in vacuo* leaving a thick dark residue; after several crystallisations from aqueous ethanol, 2-*thio*-4-*benzylidene*-3-*methylthiazolid*-5-*one* was obtained as orange prisms, m. p. 117° (5·5 g., 68%) (Found: C, 56·6; H, 4·0; N, 6·2. $C_{11}H_9ONS_2$ requires C, 56·2; H, 3·8; N, 6·0%). The benzylidene compound (10 g.) was dissolved in acetic acid (30 c.c.) containing 57% hydriodic acid (12 c.c.) and red phosphorus (2 g.) and refluxed for 8 hours. The mixture was cooled, filtered, and evaporated to dryness *in vacuo*. Water (100 c.c.) was added and, after being heated (charcoal) for several minutes on a steam-bath, the mixture was filtered, made alkaline with ammonia, and evaporated to 100 c.c. On cooling, β-phenyl-*N*-methylalanine separated as white plates which were collected and washed with water. The product sublimed without melting (yield, 5·5 g., 72%). A mixture of 2-thio-4-benzylidene-3-methylthiazolid-5-one (2 g.) and potassium hydroxide (0·6 g.) in methanol (10 c.c.) was kept at 20° for 18 hours. It was evaporated *in vacuo*, dissolved in water (10 c.c.), extracted with ethyl acetate (10 c.c.), acidified, and re-extracted with ethyl acetate (10 c.c.). Evaporation gave a gum which crystallised from aqueous ethanol as pale brown prisms of 2-*thio*-5-*phenyl*-3-*methylthiazolidine*-4-*carboxylic acid*, m. p. 177° (1·6 g., 75%) (Found: C, 52·2; H, 4·6; N, 5·5. $C_{11}H_{11}O_2NS_2$ requires C, 52·2; H, 4·3; N, 5·5%).

2-Thio-3-methylthiazolid-5-one (5 g.) and *n*-butyraldehyde (5 c.c.) in acetic acid (25 c.c.) containing two drops of morpholine, were heated on the steam-bath for 2 hours. Evaporation *in vacuo* gave a dark oil which did not crystallise if seeded by the starting material or otherwise treated. 3-Methylthiazolone (5 g.) in acetic acid (20 c.c.) and acetone (10 c.c.) containing 2 drops of morpholine was heated under reflux for 2 hours. On being cooled and diluted with water, the starting material was recovered unchanged. No condensation was effected using sodium acetate in acetic acid or on heating the thiazolone in acetone containing fused zinc chloride.

2-Mercapto-4-benzylidenethiazol-5-one (Part III, *J.*, 1948, 201) was unaffected by prolonged heating with methyl iodide or methyl sulphate in ethanol. The benzylidenethiazolone (5 g.) was dissolved in N-sodium hydroxide (23 c.c., 1 equiv.) and shaken with methyl iodide (5 g.); the oily solid which separated was collected after 30 minutes and crystallised from ethanol. 2-*Methylthio*-4-*benzylidenethiazol*-5-*one* was obtained as golden needles, m. p. 99—100° (5 g., 94%) (Found: C, 56·2; H, 4·1; N, 5·9. $C_{11}H_9ONS_2$ requires C, 56·2; H, 3·8; N, 6·0%).

Reactions with 5-Acetamido-2-thio-3-methylthiazoline.—The acetamidothiazoline (10 g.) in pyridine (20 c.c.) containing benzaldehyde (8 g.) and piperidine (8 g.) was heated under reflux for 1 hour. On cooling, 5-*acetamido*-2-*thio*-4-α-*piperidinobenzyl*-3-*methylthiazoline* (15 g., 81%) crystallised from the

mixture; this was collected and washed with ethyl acetate. A sample recrystallised from pyridine as pale yellow cubes, m. p. 208° (Found: C, 59·8; H, 6·5; N, 11·4. $C_{18}H_{23}ON_3S_2$ requires C, 59·9; H, 6·4; N, 11·6%). The crude product (15 g.) was dissolved in acetic acid (60 c.c.) containing 57% hydriodic acid (20 c.c.) and red phosphorus (4 g.) and heated under reflux for 20 hours. The mixture was cooled, filtered, and evaporated to dryness *in vacuo*; water (100 c.c.) and charcoal (0·5 g.) were added and the solution was heated on the steam-bath for 5 minutes, filtered, and made alkaline with ammonia. On partial evaporation (to 100 c.c.) and cooling, β-phenyl-*N*-methylalanine crystallised as white plates (6 g., 77%); these were washed with water; they sublimed without melting. This experiment was repeated, the product being examined after 5 hours' heating. The phosphorus was removed from the hot solution, and on cooling *2-thio-4-benzyl-3-methylthiazolid-5-one* (3·5 g.) was obtained. This recrystallised from methanol as pale yellow prisms, m. p. 113° (Found: C, 55·7; H, 4·9; N, 5·8. $C_{11}H_{11}ONS_2$ requires C, 55·7; H, 4·6; N, 5·9%).

The acetamidothiazoline (10 g.) in pyridine (20 c.c.) containing benzaldehyde (8 g.) and morpholine (8 g.) was boiled under reflux for 1 hour. On cooling, *5-acetamido-2-thio-4-α-morpholinobenzyl-3-methylthiazoline* (14·5 g., 78%) was obtained; a portion was recrystallised from pyridine as pink cubes, m. p. 225° (Found: C, 56·1; H, 5·8; N, 11·6. $C_{17}H_{21}O_2N_3S_2$ requires C, 56·0; H, 5·8; N, 11·6%). 5-Acetamido-2-methylthiothiazole (5 g.) in pyridine (10 c.c.) containing benzaldehyde (4 g.) and piperidine (4 g.) was heated under reflux for 1 hour. The solution remained clear on cooling, but on evaporation *in vacuo* and crystallisation of the product from methanol *5-acetamido-2-methylthio-4-α-piperidinobenzylthiazole* was obtained as colourless cubes, m. p. 141° (6 g., 65%) (Found: C, 60·3; H, 6·4; N, 11·4. $C_{18}H_{23}ON_3S_2$ requires C, 59·9; H, 6·4; N, 11·6%).

The acetamidothiazoline (10 g.) in pyridine (20 c.c.) containing *n*-butyraldehyde (8 g.) and piperidine (8 g.) was heated under reflux for 1 hour. No product was obtained on cooling, and evaporation *in vacuo* gave a dark gum which could not be crystallised from a variety of solvents. Acetone, under the same conditions, yielded the unchanged starting material even when the period of reflux was extended to 24 hours.

A mixture of benzaldehyde (7 g.) and piperidine (10 g.) in pyridine (20 c.c.) was boiled under reflux for 15 minutes and then cooled in ice; benzylidenebis-1-piperidine (11 g., 72%) separated and recrystallised from light petroleum as colourless laths, m. p. 81° (Laun, *loc. cit.*, gives m. p. 80°) (Found: C, 79·3; H, 9·9; N, 11·1. Calc. for $C_{17}H_{26}N_2$: C, 79·1; H, 10·1; N, 10·9%). The compound had an odour of benzaldehyde but could be distilled in steam without appreciable decomposition; it was hydrolysed rapidly on warming it with dilute acid. 5-Acetamido-2-thio-3-methylthiazoline (5 g.) was heated with benzylidenebis-1-piperidine (7 g.) in pyridine (15 c.c.) for 1 hour; on cooling, 5-acetamido-2-thio-4-α-piperidinobenzyl-3-methylthiazoline (7 g.) was obtained.

Benzaldehyde (7 g.) and morpholine (10 g.) in pyridine (20 c.c.) were boiled under reflux for 15 minutes; the reaction mixture remained clear on cooling, but after distillation *in vacuo* a fraction, b. p. 100—120°/20 mm., solidified on being shaken with water. On recrystallisation from light petroleum, *benzylidenebis-4-morpholine* was obtained as colourless prisms, m. p. 105° (5 g., 33%) (Found: C, 69·0; H, 8·4; N, 11·0. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·4; N, 10·7%). When the same procedure was used with benzaldehyde and diethylamine, only starting materials were recovered.

Reactions with Methyl iso*Thiocyanate*.—Methylaminoacetonitrile (5 g.) in ether (10 c.c.) was added with cooling and stirring under nitrogen to methyl *iso*thiocyanate (5 g.) in ether (10 c.c.). The white solid (9 g., 90%) which slowly separated was collected after 1 hour and washed with a little ether. A sample was recrystallised from ethanol and *NN'-dimethylthioureidoacetonitrile* was obtained as needles, m. p. 112° (Found: C, 42·3; H, 6·4; N, 29·6. $C_5H_9N_3S$ requires C, 42·0; H, 6·3; N, 29·4%). The crystallisation was accompanied by considerable coloration of the solution, and the solid material decomposed when stored at room temperature. The thiourea (9 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (100 c.c.), cooled, filtered, and washed well with water; in this way, 2-thio-1 : 3-dimethylhydantoin was obtained as colourless needles, m. p. 93° (Delépine, *loc. cit.*, gives m. p. 94·5°) (yield, 8·5 g., 94%).

The thiohydantoin (5 g.) in pyridine (10 c.c.) containing morpholine (4 g.) and benzaldehyde (3·5 g.) was heated under reflux for 1 hour; the solvent was partly removed and the mixture poured into 2N-hydrochloric acid (100 c.c.). On shaking, a granular solid was obtained which was collected and washed well with water, followed by a little methanol (yield, 7 g., 87%). *2-Thio-5-benzylidene-1 : 3-dimethylhydantoin* crystallised from acetone–ethanol as orange-red rhombs, m. p. 144° (Found: C, 62·5; H, 5·3; N, 12·1. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·1%). 2-Thio-1 : 3-dimethylhydantoin (5 g.) in pyridine (10 c.c.) containing morpholine (4 g.) and acetone (10 c.c.) was heated under reflux for 1 hour. *2-Thio-1 : 3-dimethyl-5-*iso*propylidenehydantoin* (4·5 g., 72%) was isolated by the procedure described above and crystallised from methanol as orange needles, m. p. 118° (Found: C, 52·1; H, 6·5; N, 15·1. $C_8H_{12}ON_2S$ requires C, 52·2; H, 6·5; N, 15·2%). *n*-Butyraldehyde apparently condensed with the thiohydantoin under similar conditions, but the product was a gum which resisted crystallisation.

Reactions with Phenyl iso*Thiocyanate*.—Methylaminoacetonitrile (5 g.) in ether (10 c.c.) was added with cooling and stirring under nitrogen to phenyl *iso*thiocyanate (10 g.) in ether (15 c.c.). The gum which formed crystallised on scratching, and *5-amino-2-anilo-3-methylthiazole* (13 g., 89%) was obtained; it recrystallised from ethanol as orange needles, m. p. 140° (Found: C, 58·8; H, 5·7; N, 20·3. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·4; N, 13·6%). When the condensation was repeated in ethyl acetate, the solution remained clear and addition of acetic anhydride (6 g.) yielded *5-acetamido-2-anilo-3-methylthiazole* (15 g., 85%). This recrystallised from ethanol as orange needles, m. p. 215° (Found: C, 58·4; H, 5·6. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3%). The aminothiazole (10 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (100 c.c.), and the product collected and washed well with water. *2-Thio-3-phenyl-1-methylhydantoin* (9·5 g., 95%) recrystallised from ethanol as straw-coloured needles, m. p. 163° (Found: C, 58·5; H, 4·9; N, 13·8. $C_{10}H_{10}ON_2S$ requires C, 58·3; H, 4·9; N, 13·6%).

The thiohydantoin (5 g.) in pyridine (10 c.c.) containing morpholine (3 g.) and benzaldehyde (3 g.) was boiled under reflux for 1 hour, and the solution partly evaporated and shaken with 2N-hydrochloric acid (100 c.c.). The solid (6·5 g., 92%) obtained was washed with water, followed by a little methanol, and on recrystallisation from acetone–ethanol *2-thio-3-phenyl-5-benzylidene-1-methylhydantoin* was

obtained as pale yellow sheaves, m. p. 196° (Found : C, 69·8; H, 4·9; N, 9·5. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·8; N, 9·5%). The benzylidene compound (5 g.) was dissolved in acetic acid (10 c.c.) containing red phosphorus (3 g.) and heated under reflux for 24 hours. After cooling, filtration, and evaporation of the mixture to dryness *in vacuo*, addition of water (50 c.c.) gavea gum which was separated and crystallised from methanol. 2-*Thio*-3-*phenyl*-5-*benzyl*-1-*methylhydantoin* was obtained as colourless cubes, m. p. 133° (4 g., 80%) (Found : C, 69·2; H, 5·6; N, 9·2. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4; N, 9·5%). With a reflux period of 5 hours, a yield of 90% was obtained; use of dilute aqueous ammonia instead of water at the appropriate stage of the isolation removed most of the colour from the crude product. The benzylhydantoin (5 g.) in water (10 c.c.) and ethanol (10 c.c.) containing sodium hydroxide (4 g.) was heated under reflux for 24 hours; sulphuric acid (4·9 g., 1 equiv.) in water (10 c.c.) was added and the mixture evaporated to dryness. Extraction with hot methanol (4 × 100 c.c.) and evaporation of the solution gave a solid which, after washing with acetone and a little water, was pure β-phenyl-*N*-methylalanine (yield, 2·5 g., 82%).

In the same way, acetone (8 g.) was condensed with 2-thio-3-phenyl-1-methylhydantoin (5 g.) to give 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylidenehydantoin* (4·5 g., 75%) which crystallised from methanol as orange rhombs, m. p. 152° (Found : C, 63·5; H, 5·8; N, 11·5. $C_{13}H_{14}ON_2S$ requires C, 63·4; H, 5·7; N, 11·4%). This was reduced with hydriodic acid and red phosphorus in acetic acid to 2-*thio*-3-*phenyl*-1-*methyl*-5-iso*propylhydantoin* (yield, 85%) which was obtained from methanol as colourless needles, m. p. 118—119° (Found : C, 63·0; H, 6·5; N, 11·3. $C_{13}H_{16}ON_2S$ requires C, 62·9; H, 6·5; N, 11·3%). Hydrolysis with aqueous alcoholic sodium hydroxide gave *N*-methylvaline (yield, 85%) which was isolated by the procedure described above. 2-Thio-3-phenyl-1-methylhydantoin (5 g.) and *n*-butyraldehyde (3 g.) in pyridine (10 c.c.) and morpholine (3 c.c.) were boiled under reflux for 1 hour. The solution was partly evaporated and shaken with 2N-hydrochloric acid (100 c.c.), whereupon a solid separated; this was washed with water and a little methanol. 2-*Thio*-3-*phenyl*-1-*methyl*-5-n-*butylidene*-*hydantoin* (yield, 4·5 g., 71%) was crystallised from methanol as pale yellow prisms, m. p. 123° (Found : C, 64·9; H, 6·4. $C_{14}H_{16}ON_2S$ requires C, 64·6; H, 6·2%).

*iso*Propylaminoacetonitrile (5 g.) in ether (10 c.c.) was added with cooling and stirring under nitrogen to phenyl *iso*thiocyanate (7 g.) in ether (15 c.c.). The solid (10 g., 85%) which crystallised from the solution was collected after 1 hour and washed with ether; 5-*amino*-2-*anilo*-3-iso*propylthiazole* recrystallised from ethanol as orange-red needles, m. p. 133° (Found : C, 61·8; H, 6·6; N, 18·4. $C_{12}H_{15}N_3S$ requires C, 61·8; H, 6·4; N, 18·0%). The aminothiazole (10 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (100 c.c.), and the product (9·5 g., 95%) collected and washed well with water, followed by a little ethanol. 2-*Thio*-3-*phenyl*-1-iso*propylhydantoin* recrystallised from ethanol as pale yellow needles, m. p. 198° (Found : C, 61·4; H, 6·2; N, 12·4. $C_{12}H_{14}ON_2S$ requires C, 61·6; H, 6·0; N, 12·0%).

The thiohydantoin (5 g.) was condensed with benzaldehyde (2·5 g.) in pyridine containing morpholine, and the product isolated in the usual way. 2-*Thio*-3-*phenyl*-5-*benzylidene*-1-iso*propylhydantoin* (6 g., 87%) was recrystallised from acetone–methanol as yellow needles, m. p. 174° (Found : C, 70·8; H, 5·9; N, 8·5. $C_{19}H_{16}ON_2S$ requires C, 70·8; H, 5·6; N, 8·7%). On reduction with hydriodic acid and red phosphorus in acetic acid, 2-*thio*-3-*phenyl*-5-*benzyl*-1-iso*propylhydantoin* (yield, 92%) was obtained, and this crystallised from methanol as colourless cubes, m. p. 133° (Found : C, 70·4; H, 6·4; N, 8·3. $C_{19}H_{20}ON_2S$ requires C, 70·4; H, 6·2; N, 8·6%). The benzylhydantoin (5 g.) was hydrolysed by boiling it under reflux for 24 hours with sodium hydroxide (4 g.) in water (10 c.c.) and ethanol (10 c.c.); neutralisation with sulphuric acid (1 equivalent) and evaporation to dryness, followed by extraction with hot methanol (5 × 100 c.c.), gave crude β-*phenyl*-N-iso*propylalanine* which was purified by washing it with acetone, followed by water (yield, 2·7 g., 83%). The amino-acid sublimed without melting and was only sparingly soluble in methanol or water; it recrystallised from a large volume of the latter as colourless plates (Found : N, 6·8. $C_{12}H_{17}O_2N$ requires N, 6·8%).

2-Thio-3-phenyl-1-*iso*propylhydantoin (5 g.) was condensed with *n*-butyraldehyde (2·5 g). in pyridine and morpholine, and the mixture shaken with 2N-hydrochloric acid (100 c.c.). The product was obtained as an oil but it crystallised from methanol as pale yellow needles, m. p. 124° (4·5 g., 70%), of 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylidenehydantoin* (Found : C, 66·6; H, 7·2; N, 9·7. $C_{16}H_{20}ON_2S$ requires C, 66·7; H, 6·9; N, 9·7%). This was reduced with hydriodic acid and red phosphorus in acetic acid to 2-*thio*-3-*phenyl*-1-iso*propyl*-5-n-*butylhydantoin* (yield, 89%) which crystallised from light petroleum as colourless needles, m. p. 63° (Found : C, 66·4; H, 7·8; N, 9·6. $C_{16}H_{22}ON_2S$ requires C, 66·2; H, 7·6; N, 9·7%). Alkaline hydrolysis and isolation as above gave N-iso*propylnorleucine* (90%) which sublimed without melting and was crystallised from aqueous methanol as colourless prisms (Found : N, 8·0. $C_9H_{19}O_2N$ requires N, 8·1%). 2-Thio-3-phenyl-1-*iso*propylhydantoin (5 g.) was heated under reflux for 24 hours with acetone (10 c.c.) in pyridine (10 c.c.) containing morpholine (3 g.). On isolation of the product, it was found to contain only starting material. 2-Thio-3-phenyl-1-methylhydantoin (5 g.) was heated under reflux for 24 hours with acetone (10 c.c.) in acetic acid (10 c.c.) containing fused sodium acetate (5 g.); the starting material was isolated unchanged. 2-Thio-3-phenyl-1-methylhydantoin (5 g.) was heated under reflux for 2 hours with benzaldehyde (3 g.) in acetic acid (10 c.c.) containing fused sodium acetate (5 g.); on pouring the mixture into water (100 c.c.) and washing of the product with ethanol, 2-thio-3-phenyl-5-benzylidene-1-methylhydantoin (6 g.) was obtained.

3-Phenyl-1-methylhydantoin (Delepine, *loc. cit.*) (5 g.) and benzaldehyde (3 g.) in pyridine (10 c.c.) and morpholine (3 g.) were heated under reflux for 10 hours, and the product was distilled in steam until the distillate was free from solvent or benzaldehyde; the residue contained only unchanged hydantoin. Acetone failed to condense with the hydantoin under similar conditions.

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