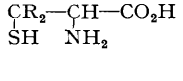
633. *Studies in the Azole Series. Part XXIV. The Interaction of Carbonyl Compounds and 2-Thio-5-thiazolidone.*

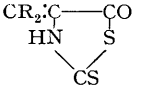
By A. H. Cook and J. R. A. Pollock.

The condensation of 2-thio-5-thiazolidone (III) with aldehydes or ketones leads to products such as (II; $R_2 = <[CH_2]_4$ which may be converted into *e.g.*, (V; R = OH) and related compounds. More complex transformations of the condensation product with isatin are also discussed.

The isolation of penicillamine (I; R = Me) and of 1-amino-2-(1-mercapto-1-*cyclo*hexyl)acetic acid (I; $R_2 = <[CH_2]_5$), respectively, in two steps from 2-thio-4-*iso*propylidene- (II; R = Me) and 2-thio-4-*cyclo*hexylidene-5-thiazolidone (II; $R_2 = <[CH_2]_5$) (Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337; Billimoria, Cook, and Heilbron, this vol., p. 1437) led us to investigate the condensation of 2-thio-5-thiazolidone (III), the precursor of (II), with other ketones.



(I.)



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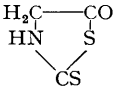
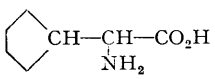


(III.)

The condensation of (III) with *cyclo*pentanone, effected by dry hydrogen chloride, or, better, anhydrous zinc chloride, gave 2-*thio*-4-cyclo*pentylidene*-5-*thiazolidone* (II; $R = <[CH_2]_4$), which was characterised by its reductive degradation to α-*amino*cyclo*pentylacetic acid* (α-cyclo-

pentylglycine) (IV). Reaction of (II; R = <[CH_2]$_4$) with ethanolic sodium ethoxide gave *ethyl 2-mercapto-5 : 5-tetramethylene-*Δ^2*-thiazoline-4-carboxylate* (V; R = OEt), and methanolic sodium methoxide afforded the corresponding *methyl* ester (V; R = OMe), which on alkaline hydrolysis afforded the *acid* (V; R = OH). The acid resulted also, together with the methyl ester, from a similar rearrangement in methanolic sodium hydroxide.

The methyl ester (V; R = OMe) was heated in concentrated hydrochloric acid at 100—130° for several hours in an attempt to effect fission to the amino-mercapto-acid (*cf.* Billimoria, Cook, and Heilbron, *loc. cit.*; Cook, Harris, and Heilbron, *J.*, 1948, 1060; Gabriel and Posner, *Ber.*, 1894, **21**, 3509), but, although some of the desired compound was undoubtedly present in the reaction mixture, as shown by the deep purple colour given with ferric chloride, and the isolation, in small yield, of 2 : 2-*dimethyl-5 : 5-tetramethylenethiazolidine-4-carboxylic acid hydrochloride* (VI) on treating the crude product with acetone, the main product had an empirical formula $C_9H_{15}NS_2Cl_2$ and was not identified. Decomposition of the thiazolidine (VI) in hot



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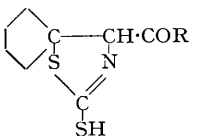

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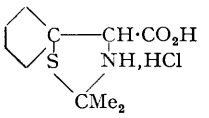
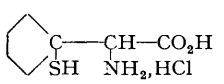


(VI.)

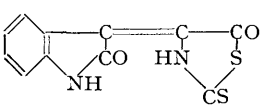
dilute acid was shown qualitatively to yield the amino-mercapto-acid, but, as the preparation of the thiazolidine was erratic this did not provide a satisfactory route. 2-Mercapto-5 : 5-dimethyl-Δ^2-thiazoline-4-carboxylic acid, which was comparable with (V; R = OH) and had been shown to be remarkably stable to acid, was readily degraded with aluminium and hydrochloric acid to penicillamine (Cook, Heilbron, and Shaw, *CPS* 311; "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 458), and a similar reductive fission in the present case seemed feasible. Tin and hydrochloric acid appeared to be a more promising reducing agent, however, as the removal of the metal as the sulphide presented no difficulties, whereas the removal of the aluminium was associated with losses by adsorption, and by this means *α-amino-α-(1-mercapto-*cyclo*pentyl)acetic acid hydrochloride* (VII) was obtained. On reaction with acetone, (VII) yielded the thiazolidine (VI) identical with the previous sample.

The product obtained from the reaction of the acid (VII) with 2-benzyl-4-ethoxymethylene-5-oxazolone in the presence of pyridine and pyridine hydrochloride (*cf.* Carpenter, Stacey, Genghof, Livermore, and du Vigneaud, *J. Biol. Chem.*, 1948, **176**, 917) had antibiotic activity which, assayed against *Staph. aureus* by the cup-plate method, was equivalent to that of 0·6 penicillin unit per mg. of (VII) and is probably due to a product of the type of a natural penicillin.

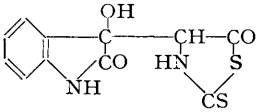
The reaction of 2-thio-5-thiazolidone with isatin under dehydrating conditions gave a deeply coloured condensation product, *2-thio-4-3′-oxindolylidene-5-thiazolidone* (VIII); reaction in glacial acetic acid gave an addition compound, formulated as *2-thio-4-(3′-hydroxy-3′-oxindolyl)-5-thiazolidone* (IX) in view of its dehydration to (VIII) by anhydrous zinc chloride.



(VII.)



(VIII.)

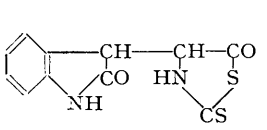


(IX.)

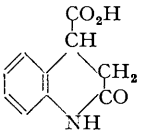
Zinc dust in glacial acetic acid (cf. Billimoria and Cook, *loc. cit.*) reduced (VIII) to the expected dihydro-compound, *2-thio-4-3′-oxindolyl-5-thiazolidone* (X), whilst degradative reduction with hydriodic acid–red phosphorus produced 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid (XI) which persisted as a monohydrate when dried at 40°/14 mm. for 1 hour. This compound (m. p. 217—218°) is evidently identical with the material (m. p. 218°) obtained from similar degradations of oxindolylidene-hydantoin and -diketopiperazine (Hill, Schultz, and Lindwall, *J. Amer. Chem. Soc.*, 1930, **52**, 769; Henze and Blair, *ibid.*, 1933, **55**, 4621; see also Aeschlimann, *J.*, 1926, 2902); the last author observed the difficulty with which the molecule of water was removed, and suggested that although the hydrate behaves as a mono-basic acid it is, in fact, *o*-aminophenylsuccinic acid (XI*a*).

The reactions of the oxindolylidenethiazolone (VIII) with alkalis were in some respects complex. Thus the compound dissolved in cold aqueous sodium hydroxide and was recovered

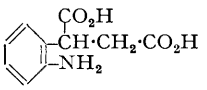
almost completely on acidification, whereas heating such a solution caused transformation to an orange, non-crystalline solid material, from which there could be extracted a small amount of a



(X.)



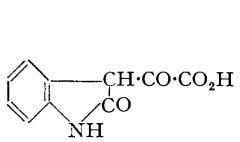
(XI.)



(XI*a*.)

golden-yellow product, which, on the basis of rather poor analytical results and the absence of sulphur, was formulated as *oxindole-3-glyoxylic acid* (XII). Again, with ethanolic sodium ethoxide (VIII) gave an orange mass, from which there was isolated, in poor yield, a sulphur-containing compound which was apparently the expected rearrangement product, *ethyl oxindole-3-spiro-5-(2-mercapto-*Δ^2*-thiazoline-4-carboxylate*) (XIII).

These difficulties led us to attempt rearrangement of (VIII) with ammonia. In aqueous solution, reaction was rapid, the colour of the solution, initially deep-red, being soon discharged, with precipitation of a highly crystalline yellow material. This product was sparingly soluble in hot water (from which it recrystallised unchanged), contained no sulphur, and had an empirical formula $C_{10}H_9O_2N_3$. A basic group was present, but a solution in acid could not be diazotised and was indeed unstable, depositing another crystalline yellow solid which had the empirical formula $C_{10}H_8O_3N_2$, its formation corresponding to the hydrolytic loss of an amino-group.



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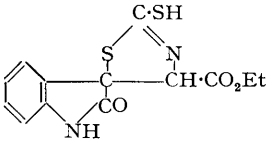
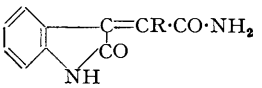
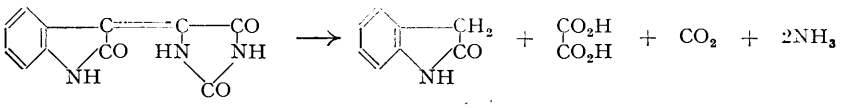


(XIII.)



(XIV.)

The formula $C_{10}H_9O_2N_3$ corresponds to the loss of carbon disulphide from, and addition of ammonia to, (VIII), and *α-amino-α-3-oxindolylideneacetamide* (XIV; R = NH_2) thus appeared to be a possible structure. The deamination product was then regarded as the corresponding *glyoxylamide* (XIV; R = OH). These structures were confirmed when it was shown that a mixture of hot acetic and hydrochloric acid degraded the deamination product to oxindole. The literature revealed that this reaction was not so surprising as it first seemed, for certain azlactones react similarly with warm alkali, substituted 2-phenyl-4-*o*-nitrobenzylidene-5-oxazolones, for example, giving nitrotoluenes (Burton, *J.*, 1935, 1265; Oliverio, *Gazzetta*, 1935, **65**, 143), presumably by way of the nitrophenylpyruvic acids (Burton and Stoves, *J.*, 1937, 402). A still closer analogy is the formation of oxindole on alkaline hydrolysis of 4-3′-oxindolylidenehydantoin (XV) (Henze and Blair, *loc. cit.*).

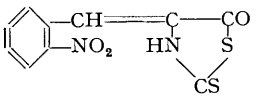
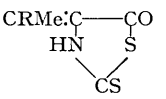


(XV.)

It was interesting to follow the reaction of (VIII) with other amines. Methylamine reacted smoothly in aqueous solution to give a compound similar to that obtained with ammonia, but analysis showed that it contained one methyl group more than was expected. The location of this methyl group on the labile amino-nitrogen atom followed from the elimination of methylamine on reaction with hydrochloric acid, so that the initial product was α-methylamino-*α-3-oxindolylideneacetomethylamide* (cf. XIV), and the substance obtained from it by acid was *α-hydroxy-α-3-oxindolylideneacetomethylamide*. The methylamino-compound was evidently formed by an exchange mechanism, which was further evidence for the aminomethylene type of structure (XIV; R = NH_2). The methylamino-amide gave a *diacetyl* derivative, which was orange, in contrast to the colourless *monoacetyl* derivative of the unmethylated compound (XIV). Perhaps this is a result of the fixation of the oxindole portion of the molecule in the lactim form by acetylation which thus brings the double bonds of the molecule into conjugation.

o-Nitrobenzaldehyde condensed with 2-thio-5-thiazolidone, to give *2-thio-4-o-nitrobenzylidene-5-thiazolidone* (XVI) in good yield, but the product obtained from (XVI) by alkali proved

intractable and its further investigation was abandoned. In the presence of anhydrous zinc chloride mesityl oxide and 2-thio-5-thiazolidone gave 2-*thio*-4-(4-*methylpent*-3-*en*-2-*ylidene*)-5-*thiazolidone* (XVII; R = $-CH{:}CMe_2$). A similar condensation with ethyl acetoacetate gave

(XVI.)   (XVII.)

2-*thio*-4-(1′-*carbethoxy*-2′-*propylidene*)-5-*thiazolidone* (XVII; R = $CH_2{\cdot}CO_2Et$); dissolution in cold alkali, followed by immediate acidification, gave an *isomeride*, so that these compounds are perhaps to be regarded as *cis*- and *trans*-forms respectively.

Experimental.

2-*Thio*-4-cyclo*pentylidene*-5-*thiazolidone* (II; $R_2 = <[CH_2]_4$).—(*a*) 2-Thio-5-thiazolidone (10 g.) was dissolved in dry *cyclo*pentanone (50 c.c.), and a rapid stream of dry hydrogen chloride was passed in for 7 hours. The liquor was cooled to 0° for 1 hour, whereupon 2-*thio*-4-cyclo*pentylidene*-5-*thiazolidone* (3 g.), m. p. 244—245° (decomp.), separated. This recrystallised from glacial acetic acid as short yellow needles, m. p. 245° (decomp.) (Found : C, 48·4; H, 4·5; N, 7·3. $C_8H_9ONS_2$ requires C, 48·2; H, 4·5; N, 7·3%). (*b*) 2-Thio-5-thiazolidone (25 g.) and *cyclo*pentanone (50 c.c.) were dissolved in ethyl acetate (250 c.c.). Anhydrous zinc chloride (25 g.) was added, and the mixture was heated under reflux for 5 hours. The bright-green liquor was decanted hot from a gummy residue and kept at 0° while the product separated as yellowish-green needles. Washing with glacial acetic acid and water, digestion with warm 2N-hydrochloric acid for 20 minutes, washing with water, and drying gave pure (II; R = $<[CH_2]_4$) (10·5 g., 28%, based on 2-thio-5-thiazolidone), m. p. 244—245° (decomp.).

1-*Amino*cyclo*pentylacetic Acid* (IV).—A mixture of the foregoing product (1 g.), red phosphorus (1 g.), hydriodic acid (5 c.c.), and glacial acetic acid (10 c.c.) was heated under reflux for 4 hours. After cooling, excess of phosphorus was filtered off, and the residue was evaporated to a gum. This was taken up in water (5 c.c.), and the solution treated with pyridine, whereupon the *amino-acid* (0·4 g.) separated. It had no m. p., darkening somewhat at 265° and volatilising above that temperature. Recrystallised from water, it formed colourless hexagonal tablets which sublimed slowly above 250° (Found : C, 59·0; H, 9·2; N, 9·6. $C_7H_{13}O_2N$ requires C, 58·8; H, 9·2; N, 9·8%). The compound gave a purple colour with ninhydrin reagent.

Rearrangement of (II; R = $<[CH_2]_4$) *with Sodium Ethoxide and Sodium Methoxide.*—The thio*cyclo*pentylidenethiazolidone (5 g.) was dissolved in a hot solution of sodium (1·5 g.) in ethanol (25 c.c.). After 1 hour, the solution was poured into ice-cold dilute hydrochloric acid and stirred until the precipitated oil solidified. Recrystallisation from aqueous acetone gave *ethyl* 2-*mercapto*-5 : 5-*tetramethylene*-Δ^2-*thiazoline*-4-*carboxylate* (V; R = OEt) as pale yellow needles having m. p. 90° (3·5 g., 60%). Further recrystallisation in the same way gave colourless needles, m. p. 92° (Found : C, 48·5; H, 6·0; N, 5·8. $C_{10}H_{15}O_2NS_2$ requires C, 48·9; H, 6·2; N, 5·7%). The thio*cyclo*pentylidenethiazolidone (15 g.), dissolved in a hot solution of sodium (3·5 g.) in methanol (30 c.c.) and worked up in the same way, gave the *methyl* ester (14 g., 80%) as colourless needles, m. p. 133° (Found : C, 46·8; H, 5·8; N, 6·2. $C_9H_{13}O_2NS_2$ requires C, 46·8; H, 5·7; N, 6·1%).

The foregoing ethyl ester (1 g.) was dissolved in 10% aqueous sodium hydroxide (5 c.c.), and the solution heated under reflux for 1 hour. Acidification of the cooled solution with hydrochloric acid gave a white solid, which recrystallised from water as large tabular crystals which crumbled at 105° and melted at 160—163°. Dried at 50° (14 mm.), the hydrate effloresced, and 2-*mercapto*-5 : 5-*tetramethylene*-Δ^2-*thiazoline*-4-*carboxylic acid* (V; R = OH) had m. p. 168° (Found : C, 43·9; H, 5·2; N, 6·3. $C_8H_{11}O_2NS_2$ requires C, 44·3; H, 5·1; N, 6·5%).

The thio*cyclo*pentylidenethiazolidone (3 g.) was dissolved in a hot solution of sodium hydroxide (1·1 g.) in methanol (20 c.c.). After 1 hour, the solution was stirred into dilute hydrochloric acid, and, when the gummy precipitate had separated, the aqueous layer was decanted. The residue was extracted with aqueous sodium hydrogen carbonate. The insoluble residue, on recrystallisation from aqueous acetone, afforded the methyl ester (V; R = OMe) (0·5 g.), m. p. 90—92°. Acidification of the sodium hydrogen carbonate extract yielded the acid (V; R = OH) which, recrystallised from water and dried *in vacuo*, had m. p. and mixed m. p. 168°.

Acid Hydrolysis of the Methyl Ester (V; R = OMe).—The ester (2 g.) was sealed in a glass tube with concentrated hydrochloric acid (10 c.c.) and heated at 130° for 24 hours. The evil-smelling liquor was evaporated to give a brown gum, which was dissolved in methanol (3 c.c.). This solution, which with aqueous sodium hydrogen carbonate and ferric chloride gave a purple colour, was diluted with ether, decanted from the gum which separated, and kept at 0° for 3 hours. The supernatant liquid (which still gave a purple colour with ferric chloride) was decanted from a sticky semicrystalline residue and evaporated to give a small quantity of gum which did not crystallise. Fractionation of the residue above from methanol–ether gave a *compound* (0·2 g.) as rosettes of colourless needles, m. p. 154—155° (decomp.) (Found : C, 40·5; H, 5·5; N, 5·2; S, 23·4; Cl, 27·0. $C_9H_{15}NS_2Cl_2$ requires C, 39·7; H, 5·6; N, 5·2; S, 23·5; Cl, 26·1%). In other experiments on the same scale the liquor from the reaction was evaporated to a brown gum which was heated in boiling acetone (10 c.c.) and methanolic hydrogen chloride (2 c.c.) for 0·5 hour. The colourless crystals of 2 : 2-*dimethyl*-5 : 5-*tetramethylenethiazolidine*-4-*carboxylic acid hydrochloride* (VI) (0·06 g.) which separated were recrystallised from glacial acetic acid–light petroleum (b. p. 40—60°) as plates, m. p. 204° (decomp.) (Found : C, 47·5; H, 6·8; N, 5·2. $C_{10}H_{17}O_2NS,HCl$ requires C, 48·2; H, 7·2; N, 5·6%). The compound gave no colour with ferric chloride until after boiling for a few minutes with dilute hydrochloric acid, which regenerated the amino-mercapto-acid.

α-Amino-α-(1-mercapto-1-cyclopentyl)acetic Acid Hydrochloride (VII).—The methyl ester (V; R = OMe) (1·5 g.) was suspended in concentrated hydrochloric acid (6 c.c.). Granulated tin (1·5 g.) was added and, when the reaction had moderated, the reaction mixture was boiled under reflux for 4 hours. The clear solution was diluted to 100 c.c. with water. A resulting curdy white precipitate was well stirred, and the liquid saturated with hydrogen sulphide. Stannous sulphide was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The pale yellow solid remaining was dissolved in methanol, whereafter addition of ether precipitated the *amino-mercapto-acid hydrochloride* (VII) (0·5 g., 40%) as pointed plates, m. p. 199—200° (frothing) (Found : N, 6·7; S, 14·7; Cl, 16·4. $C_7H_{13}O_2NS$,HCl requires N, 6·7; S, 15·1; Cl, 16·8%). The compound gave an intense purple colour with ferric chloride in neutral solution, and a rose one with ninhydrin reagent. With acetone it yielded the thiazolidine (VI), m. p. and mixed m. p. 204°.

Condensation of the Amino-mercapto-acid with 2-Benzyl-4-ethoxymethylene-5-oxazolone.—The amino-mercapto-acid hydrochloride (10·6 mg.), the oxazolone (21·2 mg.), and pyridine (2·5 c.c.) were heated on the steam-bath for 0·5 hour. Pyridine hydrochloride (0·6 mg.) was added, and the solution was heated in a tightly stoppered flask for 15 minutes at 110—115° (bath temperature). After chilling in ice-water, the contents were evaporated *in vacuo* at room temperature, to leave a brown gum which was dissolved in acetone (2 c.c.). 5% Phosphate buffer at pH 7 (5 c.c.) was added, and the solution was made up to 11 c.c. with distilled water and submitted to microbiological assay against *Staph. aureus* for penicillin-type activity (cf. p. 3008). Blank solutions prepared from the reactants and solvents were devoid of activity.

Reactions between Isatin and 2-Thio-5-thiazolidone.—(*a*) Isatin (7 g.), 2-thio-5-thiazolidone (6 g.), and anhydrous zinc chloride (10 g.) were heated under reflux with ethyl acetate (200 c.c.) for 0·5 hour. The liquor was cooled for 2 hours, and the purple solid was filtered off, washed with glacial acetic acid and water, digested for 15 minutes with warm 2N-hydrochloric acid (200 c.c.), washed with water, and dried (9 g., 75%). The product had m. p. 300°; for analysis *2-thio-4-3′-oxindolylidene-5-thiazolidone* (VIII) was recrystallised as purplish-red needles, m. p. 307° (decomp.) (Found : C, 50·5; H, 2·4; N, 10·2. $C_{11}H_6O_2N_2S_2$ requires C, 50·4; H, 2·3; N, 10·7%). (*b*) Isatin (7 g.) and 2-thio-5-thiazolidone (6 g.) were dissolved in warm glacial acetic acid (30 c.c.), and the solution was brought to the boil and set aside for 4 hours, the separation of long discoloured needles of the *compound* (IX) being then complete. The product was obtained, after repeated recrystallisation from glacial acetic acid, as nearly colourless needles, decomp. >60° (Found : C, 47·3; H, 3·0; N, 9·6. $C_{11}H_8O_3N_2S_2$ requires C, 47·1; H, 2·9; N, 10·0%). The compound (1 g.), in refluxing ethyl acetate (15 c.c.), was treated with anhydrous zinc chloride (1 g.) (the colour of the solution deepened), and after 1 hour the solution was decanted from undissolved zinc salt and cooled, whereupon (VIII; 0·4 g.), m. p. and mixed m. p. 305—307° (decomp.), separated.

2-Thio-4-3′-oxindolyl-5-thiazolidone (X).—The oxindolylidenethiazolidone (2 g.) was heated under reflux with glacial acetic acid (75 c.c.) containing zinc dust (2 g.) for 10 minutes. Excess of zinc was removed. The filtrate deposited colourless needles, m. p. 242° (decomp.). The product could not be recrystallised, but a sample of *2-thio-4-3′-oxindolyl-5-thiazolidone* which crystallised from the reaction mixture was washed with glacial acetic acid, concentrated hydrochloric acid, and glacial acetic acid, and then had m. p. 242° (decomp.) (Found : C, 49·9; H, 3·4. $C_{11}H_8O_2N_2S_2$ requires C, 50·0; H, 3·1%).

Reductive Degradation of the Oxindolylidenethiazolidone.—The oxindolylidenethiazolidone (3 g.), hydriodic acid (20 c.c.), glacial acetic acid (10 c.c.), and red phosphorus (2 g.) were heated under reflux for 2 hours. Excess of phosphorus was removed and the filtrate evaporated to a black residue. Recrystallisation from water (charcoal) gave glistening long colourless needles (0·5 g.), of 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid monohydrate (XI), m. p. 216° (Found : C, 57·5; H, 5·3. Calc. for $C_{10}H_9O_3N,H_2O$: C, 57·4; H, 5·3%). Hill, Schultz, and Lindwall (*J. Amer. Chem. Soc.*, 1930, **52**, 769) give m. p. 216°.

Reaction of (VIII) *with Sodium Hydroxide.*—The oxindolylidenethiazolidone (3 g.) was dissolved in 2N-sodium hydroxide (20 c.c.) and heated on the steam-bath for 15 minutes. The solution was stirred slowly into iced 2N-hydrochloric acid (50 c.c.), and the orange solid, m. p. 130—150°, was filtered off. The material was extracted with aqueous sodium hydrogen carbonate, and a small quantity of insoluble residue filtered off. The extract was acidified with hydrochloric acid, and the yellow precipitate (1·5 g.), m. p. 130—160°, was collected, washed with water, dried, and extracted with boiling glacial acetic acid (7·5 c.c.) to yield a yellow solution, which on cooling, deposited magnificent golden plates of *oxindole-3-glyoxylic acid* (XII), m. p. 260—263° (decomp.) (Found : C, 57·6; H, 3·5; N, 6·2. $C_{10}H_7O_4N$ requires C, 58·5; H, 3·4; N, 6·75%). The material gave an olive-green colour with ferric chloride.

Reaction of (VIII) *with Sodium Ethoxide.*—The oxindolylidenethiazolidone (5 g.) was dissolved in a hot solution of sodium (0·5 g.) in ethanol (25 c.c.), and the solution heated under reflux for 1 hour. It was cooled and poured rapidly into cold 1 : 1 aqueous hydrochloric acid (25 c.c.). The recovered starting material (3 g.) was immediately filtered off, and the orange filtrate, on dilution with water, gave a yellow precipitate, which was filtered off after being kept for 24 hours at 0°. One recrystallisation from aqueous acetone yielded yellow crystals (1·1 g.), m. p. 200—208° (decomp.), and further recrystallisation gave colourless plates of *ethyl oxindole-3-spiro-5-(2-mercapto-Δ²-thiazoline-4-carboxylate)* (XIII), which became deep red at 208° and had m. p. 217° (decomp.) (Found : C, 50·4; H, 3·9. $C_{13}H_{12}O_3N_2S_2$ requires C, 50·7; H, 3·8%).

Reaction of (VIII) *with Ammonia.*—The oxindolylidenethiazolidone (2 g.) was dissolved in concentrated aqueous ammonia (*d* 0·880; 10 c.c.), and the red solution was warmed for 10 minutes, whereupon the colour became yellow and *α-amino-α-3-oxindolylideneacetamide* (XIV; R = NH_2) (1·3 g.), m. p. 242—245°, separated. It recrystallised from much water as sparkling yellow plates, m. p. 245° (Found : C, 59·0; H, 4·1; N, 20·4. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·5; N, 20·7%), giving an olive-green colour with ferric chloride. Acetylation in the usual manner gave the *monoacetyl* derivative which separated from a little methanol in colourless needles, m. p. 128° (decomp.) (Found : C, 58·8; H, 5·0. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·9%).

Deamination of (XIV; R = NH_2).—The amine (2 g.) was dissolved in warm concentrated hydrochloric acid (10 c.c.), and the solution diluted with water (20 c.c.) and heated on the steam-bath for 0·5 hour. The yellow product (1·8 g.), m. p. 250°, recrystallised from glacial acetic acid as microscopic yellow plates,

m. p. 245° (decomp.) (Found: C, 58·5; H, 3·9; N, 14·0. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 4·1; N, 13·7%), which gave an olive-gree colour with ferric chloride.

Degradation of (XIV).—The amine (2 g.) was dissolved in a hot mixture of acetic acid (20 c.c.) and concentrated hydrochloric acid (20 c.c.). After a few minutes, the deamination product separated. The mixture was heated under reflux for 18 hours and evaporated to dryness *in vacuo*. Extraction with water left oxindole as a crystalline red solid, which recrystallised from benzene–light petroleum (b. p. 60—80°) as colourless needles (0·5 g.), m. p. 128° (Found: C, 72·4; H, 5·4. Calc. for C_8H_7ON: C, 72·2; H, 5·4%). Henze and Blair (*J. Amer. Chem. Soc.*, 1935, **55**, 4621) give m. p. 128°.

Reaction of (VIII) *with Methylamine*.—The oxindolylidenethiazolidone (2 g.) was warmed with 40% aqueous methylamine (10 c.c.) for 1 hour, the colour rapidly fading. After 1 hour at room temperature, the product (1·4 g.), m. p. 250—255° (decomp.), was filtered off and recrystallised from water; *α-methylamino-α-3-oxindolylideneacetomethylamide* separated as very pale yellow rhombohedra, m. p. 258—260° (decomp.) (Found: C, 62·3; H, 5·9; N, 18·7. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·7; N, 18·2%). Acetylation in the usual way gave the *diacetyl* derivative, which recrystallised from a little methanol as long orange needles, m. p. 169—170° (decomp.) (Found: C, 61·0; H, 5·7; N, 13·2. $C_{16}H_{17}O_4N_3$ requires C, 61·0; H, 5·4; N, 13·3%). The free amine (2 g.) was dissolved in warm concentrated hydrochloric acid (10 c.c.), and the solution diluted to 30 c.c. with water and warmed for 0·5 hour, after which the product (1·7 g.), m. p. 260—262° (decomp.), was filtered off. *α-Hydroxy-α-3-oxindolylideneacetomethylamide* recrystallised from glacial acetic acid in glistening yellow plates, m. p. 263° (decomp.) (Found: C, 60·4; H, 4·7; N, 12·4. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 5·0; N, 12·8%).

2-Thio-4-o-nitrobenzylidene-5-thiazolidone.—*o*-Nitrobenzaldehyde (4 g.) and 2-thio-5-thiazolidone (3·2 g.) were dissolved in boiling glacial acetic acid (75 c.c.), and morpholine (7 drops) was added. After 2 hours the product was filtered off, washed with water, and dried (5 g., 75%). Recrystallised from glacial acetic acid as orange small needles, *2-thio-4-o-nitrobenzylidene-5-thiazolidone* had m. p. 213° (decomp.) (Found: C, 45·6; H, 1·9; N, 10·2; S, 24·2. $C_{10}H_6O_3N_2S_2$ requires C, 45·1; H, 2·3; N, 10·5; S, 24·1%). The compound dissolved in alkali to give a brilliant red solution. Acidification gave an orange amorphous material, m. p. 150—230°, which could not be purified.

Condensation of Mesityl Oxide with 2-Thio-5-thiazolidone.—Mesityl oxide (5 g.), 2-thio-5-thiazolidone (6·6 g.), and anhydrous zinc chloride (7 g.) were heated in refluxing ethyl acetate (25 c.c.) for 3 hours. The solution was decanted from gummy material, and the solvent was removed *in vacuo*, leaving a dark green oil. It was dissolved in acetone (10 c.c.) and diluted with an equal volume of water, whereupon dark plates, m. p. 110°, separated. Recrystallisation several times from acetone–water gave bright-yellow rhombic plates (1 g.) of *2-thio-4-(4′-methylpent-3′-en-2′-ylidene)-5-thiazolidone monohydrate*, m. p. 133° (Found: C, 46·6; H, 5·9; N, 6·1. $C_9H_{11}O_2NS_2,H_2O$ requires C, 46·7; H, 5·7; N, 6·1%).

Condensation of Ethyl Acetoacetate with 2-Thio-5-thiazolidone.—Ethyl acetoacetate (4 g.), 2-thio-5-thiazolidone (4 g.), and anhydrous zinc chloride (5 g.) were heated under reflux with ethyl acetate for 2 hours. Removal of solvent left a black oil, one-half of which was stirred with cold 10% aqueous sodium hydroxide (10 c.c.), and the red solution was filtered into dilute hydrochloric acid. The yellowish-brown *product* (XVII; R = $CH_2{\cdot}CO_2Et$) (0·8 g.), m. p. 100—102°, was filtered off and recrystallised from much hot water as small yellowish-pink needles, m. p. 114° (Found: C, 43·7; H, 4·8. $C_9H_{11}O_3NS_2$ requires C, 44·0; H, 4·5%). The remainder of the black oil was dissolved in hot glacial acetic acid, filtered, and diluted with water. Pale yellow crystals (0·5 g.) separated. This *isomeride* recrystallised from hot water as yellow plates, m. p. 98° (Found: C, 43·6; H, 4·7%). Mixtures of these materials melted between 96° and 104°.

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

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