

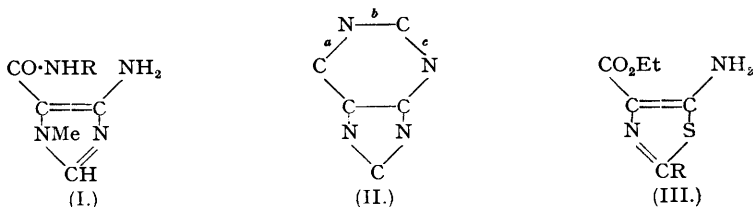
226. Studies in the Azole Series. Part XII. Some Thiazolopyrimidines.

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5-Amino-4-carbomethoxythiazoles (III) are readily converted into the corresponding thioureido-derivatives (V); the latter lose the elements of ethanol in cold dilute sodium hydroxide, passing into thiazolopyrimidines (VI) which are analogues of purines. Attempts to synthesise such compounds by attaching the thiazole to the pyrimidine ring were unsuccessful, one approach leading to the related ring system present in the thiazolopyrimidine (IX).

ONE of the prime objectives of the work described in this series has been, almost from its inception, the provision of simple and flexible methods of synthesising purines. The present memoir describes some experiments culminating in the preparation of thiazolopyrimidines which are skeletally similar to the purines. The following paper (Part XIII) records some further compounds of the thiazolopyrimidine group obtained by a somewhat different route, and a proof of the structures assigned by the conversion of one of the new compounds into a true purine of known structure. Finally, Part XIV generalises the method as one of wide applicability for the facile production of purines.

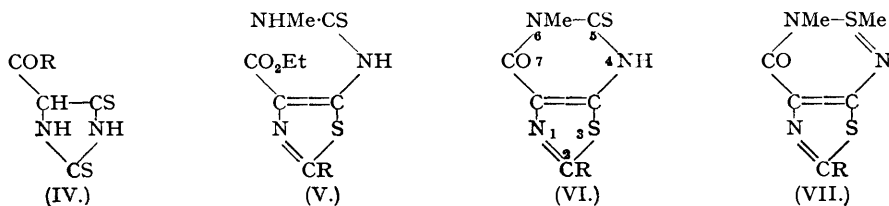
In recent years several syntheses of purines have been described in which the pyrimidine ring is affixed to an already existing iminazole group. Thus Sarasin and Wegmann (*Helv. Chim. Acta*, 1924, 7, 713) used 4-amino-5-carbamyl-1-methylglyoxaline (I; R = H), completing the 6-membered ring by the use of ethyl carbonate, and Mann and Porter (*J.*, 1945, 751) used the related compounds (I; R = Me or Et) with ethyl chloroformate. The related synthesis of



purines by Allsebrook, Gulland, and Story (*J.*, 1942, 232) may be said to consist in effecting the bond *a* in the skeletal structure (II); those of Montequi (*Anal. Soc. Fis. Quim.*, 1927, 25, 182) and of Baxter and Spring (*J.*, 1945, 232) in making the link *b*, and that of Mitter and Chatterjee (*J. Indian Chem. Soc.*, 1934, 11, 867) in closing the bond *c*. None of these reactions appeared, however, to afford the desired flexibility and certain of them at least used intermediates which were the result of a series of tedious and sometimes drastic operations.

It was observed (Cook, Heilbron, and Levy, *J.*, 1947, 1598) that interaction of carbon disulphide and ethyl aminocynoacetate yielded the thiazole (III; R = SH). In the present

work it has been shown that this compound could be easily converted into 4-carbethoxydithiohydantoin (IV; R = OEt), and it was hoped that this by the action of ammonia might afford a 4(5)-amino-5(4)-carbethoxy- or -carbamyl-glyoxaline. The experiment, however, resulted only in the formation of 4-carbamylthiohydantoin (IV; R = NH₂) and it was therefore



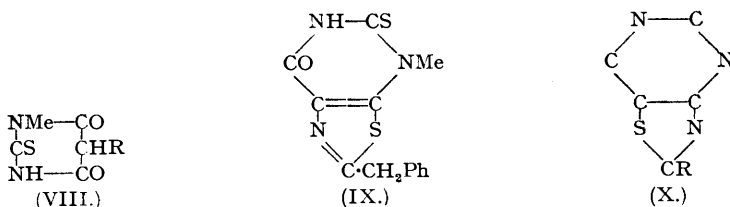
resolved, in view of the similarity between the glyoxaline and thiazole ring systems, to investigate the possibility in the first instance of fusing a pyrimidine ring to the thiazole ring of (III). Repeated attempts to make (III; R = SH) react with sodium cyanate in order to obtain the corresponding ureido-compound (cf. Allsebrook, Gulland, and Story, *loc. cit.*) were unavailing, but the related reaction with methyl isothiocyanate proceeded readily to give 5-(N'-methylthio-ureido)-2-mercapto-4-carbethoxythiazole (V; R = SH); this compound dissolved in cold dilute sodium hydroxide to give a yellow solution, and the product isolated on acidification after 2 hours' standing could on analytical evidence only be the thiazolopyrimidine (VI; R = SH) (the nomenclature and numbering follow "The Ring Index"). Methylation of this compound in alkaline solution with methyl sulphate afforded the thiazolopyrimidine (VII; R = SMe). The presence of the 2-methylthio-grouping was established by methylating (III; R = SH) to give 5-amino-2-methylthio-4-carbethoxythiazole (III; R = SMe) (Cook, Heilbron, and Levy, *J.*, 1947, 1598), which was characterised as its acetyl derivative and as the azo-dye obtained by coupling the diazotised product with β -naphthol. The parent amino-compound with methyl isothiocyanate afforded the thioureido-derivative (V; R = SMe) and thence the thiazolopyrimidine (VI; R = SMe), first isolated as its sodium salt; methylation of this resulted in the formation of (VII; R = SMe), identical with the earlier preparation. Although the closure of the 6-membered ring in these and the following compounds is conveniently effected in cold alkaline solution, yet it also takes place with ease in other circumstances; thus (V; R = SMe) was cyclised to (VI; R = SMe) by heating with aqueous or alcoholic ammonia, or in boiling pyridine. Indeed, by carrying out the formation of (V; R = SMe) and analogous reactions for a prolonged period in hot pyridine, the pyrimidines could be isolated in a single stage.

With similar ease the thiazoles (III; R = H and CH₂Ph) were converted into the corresponding N'-methylthioureido-compounds (V; R = H and CH₂Ph) and thence into the thiazolopyrimidines (VI; R = H and CH₂Ph). These were methylated in alkaline solution to the corresponding methyl derivatives (VII; R = H and CH₂Ph). Earlier, attempts had been made to remove the mercapto-group in (III; R = SH) by means of chloroacetic acid in ethanol (cf. Foerster, *Ber.*, 1888, 21, 1857) but the product was 5-amino-2-carbethoxymethylthio-4-carbethoxythiazole (III; R = S·CH₂·CO₂Et) which was more conveniently prepared from (III; R = SH) by reaction with ethyl chloroacetate. This new thiazole also afforded a N'-methylthioureido-compound (V; R = S·CH₂·CO₂Et) and thence the thiazolopyrimidine (VI; R = S·CH₂·CO₂H), the acid obviously arising by simultaneous hydrolysis.

Although the pyrimidine nature of these products could hardly be doubted, further evidence was desirable. All gave a positive murexide reaction when oxidised by potassium chlorate in hydrochloric acid solution; oxidation products were obtained on treating (VI; R = SMe and H) with acid potassium chlorate and nitric acid, respectively, but their exact nature was not established. In these circumstances experiments were instituted to synthesise the thiazolopyrimidines by building the 5-membered on to a pre-formed 6-membered ring.

Condensation between N-methylthiourea and ethyl malonate afforded 2-thio-1-methylbarbituric acid (VIII; R = H), which was converted by means of nitrous acid into the nitroso-derivative (VIII; R = NO) and thence into 5-amino-2-thio-1-methylbarbituric acid (VIII; R = NH₂). All attempts, however, to make the last compound react with sodium dithioformate, or sodium or methyl dithiophenylacetate as a preliminary to attaching the 5-membered ring proved abortive, and steps were taken to circumvent this lack of reactivity. Ethyl thiophenylacetamidomalonalate has been prepared by Todd and Topham (C.P.S. 93) from ethyl aminomalonalate and methyl dithiophenylacetate. This compound has now been obtained from dithiophenylacetic acid, and a similar use of sodium dithioformate affords ethyl

thioformamidomalonate. Condensation between *N*-methylthiourea and ethyl thiophenylacetamidomalonate gave an *isomeride* of (VI; R = CH₂Ph), which must be (IX) formed by ring



closure of (VIII; R = NH·CS·CH₂Ph) in the undesired of the two possible directions. *N*-Methylation of (IX) and (VI; R = CH₂Ph) should formally lead to a common derivative, but experiments with the latter thiazolopyrimidine afforded only an *S*-methyl derivative (VII; R = CH₂Ph). In view, however, of the developments reported in the succeeding papers, the need for still another proof of the pyrimidine nature of the present compounds disappeared, and this part of the project was abandoned.

Thiazolopyrimidines have hitherto been almost unknown. Fischer and Ach (*Annalen*, 1895, 288, 167) prepared one having the same skeleton as the present compounds by boiling 4-thiouramil with acetic anhydride, and Weidel and Niemilowicz (*Monatsh.*, 1895, 16, 723) obtained the same by a modified procedure. More recently Erlenmeyer and Furger (*Helv. Chim. Acta*, 1943, 26, 366; 1947, 30, 585) have obtained thiazolopyrimidines with the related skeletal structure of (X) by the action of thioamides on 5-bromobarbituric acid.

EXPERIMENTAL.

5-Carboethoxy-2 : 4-dithiohydantoin (IV; R = OEt).—5-Amino-2-mercapto-4-carboethoxythiazole (8 g.), anhydrous sodium carbonate (8 g.), and absolute alcohol (40 c.c.) were heated together (sealed tube) at 100° for 18 hours. The solid was then filtered off and washed with ethanol, dissolved in water (150 c.c.) containing acetic acid (9 c.c.), and filtered (charcoal). From the solution the *dithiohydantoin* was precipitated by acidification with concentrated hydrochloric acid (20 c.c.); it was filtered off, washed with water (yield 6.4 g.), and crystallised from hot water as long yellow needles, m. p. 193° (Found : C, 35.6; H, 4.2; N, 13.2; S, 31.0. C₆H₈O₂N₂S₂ requires C, 35.3; H, 3.9; N, 13.7; S, 31.4%). This gave with acetic anhydride a *diacetyl* derivative crystallising from a mixture of ethyl acetate and petroleum as colourless needles, m. p. 113° (Found : C, 42.0; H, 4.1; S, 22.1. C₁₀H₁₂O₄N₂S₂ requires C, 41.7; H, 4.2; S, 22.2%). Desulphurisation of the compound with Raney nickel yielded 4-carboethoxyglyoxaline, identical with a sample prepared by the literature method.

5-Carbamyl-2 : 4-dithiohydantoin (IV; R = NH₂).—The above carboethoxydithiohydantoin (0.5 g.) was heated (sealed tube) with concentrated aqueous ammonia (3 c.c.) at 100° for 6 hours. The solution was evaporated to dryness in a vacuum, the gummy solid dissolved in hot water (5 c.c.), and the solution filtered (charcoal). Acidification with concentrated hydrochloric acid precipitated a yellow compound (0.4 g.), which crystallised slowly from hot water as plates, m. p. 242° (decomp.) (Found : C, 27.1; H, 3.1. C₄H₆ON₂S₂ requires C, 27.4; H, 2.9%).

5-Amino-2-methylthio-4-carboethoxythiazole (III; R = SMe).—5-Amino-2-mercapto-4-carboethoxythiazole (10.2 g.) was dissolved in 5% sodium hydroxide solution (150 c.c.). Methyl sulphate (8 c.c.) was added to the clear solution, and the mixture shaken for a few minutes. The solution warmed considerably and the curdy white solid (9.5 g.) which separated in a short time was filtered off and washed thoroughly with water. This crystallised from 50% ethanol as long flat needles, m. p. 108.5°, which gave with acetic anhydride in presence of a small amount of concentrated sulphuric acid an *acetyl* derivative, crystallising from 50% ethanol as colourless prisms, m. p. 82° (Found : C, 41.5; H, 4.65; N, 10.9. C₉H₁₂O₃N₂S₂ requires C, 41.5; H, 4.50; N, 10.8%). The parent amine (1 g.) was suspended in 5% hydrochloric acid (15 c.c.) and treated with sodium nitrite (0.5 g.) dissolved in a small amount of water. The clear red solution resulting in 15 minutes was dropped into an excess of a solution of β-naphthol in alkali maintained at 0°. The dark red precipitate was filtered off and washed with hot water. **2-Methylthio-4-carboethoxythiazole-5-azo-β-naphthol** crystallised from glacial acetic acid as glistening dark red needles, m. p. 167° (Found : C, 55.2; H, 4.2; N, 11.1. C₁₇H₁₅O₃N₃S₂ requires C, 54.7; H, 4.0; N, 11.3%).

5-(*N'*-Methylthioureido)-2-methylthio-4-carboethoxythiazole (V; R = SMe).—5-Amino-2-methylthio-4-carboethoxythiazole (11.0 g.) was dissolved in warm pyridine (30 c.c.), and an excess of methyl isothiocyanate (6.0 g.) added. After being heated under reflux for 2 hours, the solution was poured on crushed ice (400 g.) and kept for 1 hour with occasional stirring. The yellowish-white solid (9.1 g.) which separated crystallised from aqueous ethanol as glistening needles, m. p. 157° (Found : C, 37.0; H, 4.7; N, 14.8. C₉H₁₂O₃N₃S₃ requires C, 37.1; H, 4.5; N, 14.4%).

7-Keto-5-thio-2-methylthio-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo[5 : 4-d]pyrimidine (VI; R = SMe).—(a) *Sodium salt*. The above thioureido-compound (9 g.) suspended in ethanol (10 c.c.) was dissolved in warm 2% sodium hydroxide solution (200 c.c.). The yellow solution was filtered and kept overnight. White needles (5.4 g.) separated which, recrystallised from 90% ethanol, had m. p. 347° (decomp.).

(b) *Ammonium salt*. The thioureido-compound (2 g.) was suspended in concentrated aqueous

ammonia (30 c.c.) and heated in a sealed tube at 95° for 4 hours, whereupon most of the solid went into solution. On standing for 12 hours, glistening pale yellow needles (2 g.) had separated which recrystallised from very dilute aqueous ammonia as colourless needles, m. p. 270° (decomp.) (Found: C, 32.4; H, 4.1; N, 20.9. $C_7H_{10}ON_4S_3$ requires C, 32.1; H, 3.8; N, 21.4%). This salt was soluble in boiling water but tended to lose ammonia on continued boiling of the solution.

(c) *Free acid.* The mother-liquor after separation of the sodium salt in (a) was acidified with hydrochloric acid, whereby a greyish-white solid (2.2 g.) was obtained. A further quantity of the same compound was obtained by acidification of the mother-liquor after the precursor thioureido-compound had been filtered off. The free acid crystallised from glacial acetic acid, in which it was only very sparingly soluble, as colourless needles, or from nitrobenzene, as greyish micro-needles which had m. p. 265–266° (decomp.) (Found: N, 17.6; S, 39.6. $C_7H_7ON_3S_3$ requires N, 17.1; S, 39.2%). This was insoluble in water or ethanol and gave the murexide test when the oxidation was carried out with potassium chlorate and hydrochloric acid.

7-Keto-2 : 5-dimethylthio-6-methyl-6 : 7-dihydrothiazolo[5 : 4-d]pyrimidine (VII; R = SMe).—The above compound (1.0 g.) was dissolved in 2% sodium hydroxide solution (50 c.c.), and the solution shaken for a few minutes with methyl sulphate (1 c.c.). The white *pyrimidine* (1.0 g.) which soon separated crystallised from boiling ethanol as glistening felted needles, m. p. 218° (Found: C, 37.4; H, 3.8; N, 15.8; S, 36.9. $C_8H_9ON_3S_2$ requires C, 37.1; H, 3.7; N, 16.2; S, 37.1%).

5-(N'-Methylthioureido)-2-mercapto-4-carbomethoxythiazole (V; R = SH).—5-Amino-2-thio-4-carbomethoxythiazole (3.0 g.) was dissolved in warm pyridine (6 c.c.), and an excess of methyl isothiocyanate (1.5 g.) added. The solution was heated under reflux in an atmosphere of nitrogen for 1 hour and poured on crushed ice (100 g.). The oil which separated solidified on standing, and the *thiol* (2.9 g.) was purified by dissolving it in acetic acid and precipitating it by addition of small amounts of water as micro-plates, m. p. 204° (Found: C, 35.2; H, 3.9; N, 15.0. $C_8H_{11}O_2N_3S_2$ requires C, 34.7; H, 4.0; N, 15.2%).

2-Mercapto-7-keto-5-thio-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo[5 : 4-d]pyrimidine (VI; R = SH).—A solution of the above thioureido-compound (1.0 g.) in 2% sodium hydroxide (25 c.c.) was kept for 2 hours and acidified, a grey solid (0.3 g.) being obtained. This could not be crystallised from the usual solvents, though it was slightly soluble in hot water, alcohol, and acetic acid. It was purified by dissolution in alkali and precipitation by hydrochloric acid, and obtained as a grey powder which did not melt below 350° (Found: N, 17.8. $C_8H_9ON_3S_2$ requires N, 18.1%). This *thiol* on methylation with methyl sulphate in alkali solution gave (VII; R = SMe), identical with that prepared from (III; R = SMe).

5-(N'-Methylthioureido)-4-carbomethoxythiazole (V; R = H).—5-Amino-4-carbomethoxythiazole (4.5 g.) in warm pyridine (12 c.c.) was heated under reflux with methyl isothiocyanate (2 g.) for 2 hours, and the solution poured on crushed ice (200 g.). The pale yellow *thiazole* (3.2 g.) crystallised from 50% alcohol as plates, m. p. 180° (Found: C, 39.4; H, 4.9; N, 17.2; S, 26.4. $C_8H_{11}O_2N_3S_2$ requires C, 39.2; H, 4.5; N, 17.1; S, 26.1%).

7-Keto-5-thio-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo[5 : 4-d]pyrimidine (VI; R = H).—A solution of the above ureido-compound (2.7 g.) in 2% sodium hydroxide (50 c.c.) was kept for 2 hours and acidified without removal of the small amount of sodium salt which had separated as glistening white needles. The white compound (1.8 g.) so obtained crystallised from acetic acid in colourless needles, m. p. 295–300° (decomp.) (Found: N, 20.9; S, 32.7. $C_8H_9ON_3S_2$ requires N, 21.1; S, 32.2%).

7-Keto-5-methylthio-6-methyl-6 : 7-dihydrothiazolo[5 : 4-d]pyrimidine (VII; R = H). The preceding compound (1.0 g.) in 3% sodium hydroxide (40 c.c.) was methylated with methyl sulphate (1 c.c.). The white *methyl* derivative (0.9 g.) which separated crystallised from ethanol as needles, m. p. 207° (Found: C, 39.7; H, 3.5; N, 19.4; S, 29.9. $C_7H_9ON_3S_2$ requires C, 39.4; H, 3.3; N, 19.7; S, 30.0%).

7-Keto-5-thio-2-benzyl-6-methyl-4 : 5 : 6 : 7-tetrahydrothiazolo[5 : 4-d]pyrimidine (VI; R = CH_2Ph).—(a) *Sodium salt.* 5-Amino-4-carbomethoxy-2-benzylthiazole (8.7 g.) was heated under reflux in pyridine (25 c.c.) with methyl isothiocyanate (4 g.) and the solution was poured on crushed ice (400 g.). The solid was taken up in warm 2% sodium hydroxide (350 c.c.) and kept for 12 hours; long needles (2.9 g.) of the *sodium* salt had then separated. These crystallised from ethanol as white leaflets melting indefinitely above 300° (Found: N, 13.3; S, 20.6. $C_{13}H_{10}ON_3S_2Na$ requires N, 13.5; S, 20.6%).

(b) *Free acid.* The mother-liquor after separation of the sodium salt was acidified, whereupon a greyish-yellow solid (3.5 g.) separated. This acid crystallised from glacial acetic acid, in which it was very sparingly soluble, or from nitrobenzene as colourless plates, m. p. 285° (decomp.) (Found: C, 54.0; H, 3.4; N, 14.7. $C_{13}H_{11}ON_3S_2$ requires C, 54.0; H, 3.8; N, 14.5%).

7-Keto-5-methylthio-2-benzyl-6-methyl-6 : 7-dihydrothiazolo[5 : 4-d]pyrimidine (VII; R = CH_2Ph).—(a) The above compound (1.0 g.) was powdered and suspended in 5% sodium hydroxide (20 c.c.) and shaken with methyl sulphate (1 c.c.). The curdy white precipitate of the *methyl* compound (0.9 g.) was filtered off and crystallised from ethanol as greyish leaflets, m. p. 155° (Found: N, 13.6. $C_{14}H_{13}ON_3S_2$ requires N, 13.9%).

(b) The compound (1.0 g.) was treated with an ethereal solution (20 c.c.) of diazomethane (ca. 0.6 g.) (cf. Erlenmeyer and Furger, *Helv. Chim. Acta*, 1947, **30**, 585). There was immediate effervescence and a gummy solid separated. The reaction was completed by 4 hours' standing and removal of the solvent. The residue (0.75 g.) crystallised from aqueous ethanol as pale yellowish-grey needles, m. p. 155°, identical with those obtained by methylation with methyl sulphate.

(c) The compound (1.0 g.) was heated under reflux in ethanol (15 c.c.) with methyl iodide (0.5 c.c.) in presence of silver oxide (1.0 g.) for 3 hours. The dark solution was filtered and diluted with water, whereupon a turbidity appeared. Extraction with ether and evaporation of the ethereal extract gave a greyish-yellow solid (0.5 g.). This on repeated crystallisation from aqueous ethanol was found to be identical with the methylated product obtained by the preceding two methods.

5-Amino-2-carbomethoxymethylthio-4-carbomethoxythiazole (III; R = $S \cdot CH_2 \cdot CO_2Et$).—5-Amino-2-mercapto-4-carbomethoxythiazole (7 g.) and ethyl chloroacetate (5 g.) in ethanol (40 c.c.) were heated under reflux for 6 hours. The solution was diluted with warm water (100 c.c.) and cooled slowly. The solid *thiazole* (7.2 g.) recrystallised from light petroleum as colourless leaflets, m. p. 72° (Found: C, 41.4; H, 5.3;

N, 9.3; S, 21.6. $C_{10}H_{14}O_4N_2S_2$ requires C, 41.4; H, 4.8; N, 9.6; S, 22.1%). It was easily soluble in ethanol, ethyl acetate, or acetic acid. It gave an *acetyl* derivative on treatment with acetic anhydride, which crystallised from 30% ethanol in needles, m. p. 91° (Found: C, 43.7; H, 4.8. $C_{12}H_{16}O_5N_2S_2$ requires C, 43.7; H, 4.8%). The base could be diazotised in dilute hydrochloric acid and the diazonium salt coupled with β -naphthol to give a deep purple alkali-soluble dye.

The above compound (8.7 g.) in pyridine (15 c.c.) was refluxed with methyl isothiocyanate (5 g.), the solution was added to crushed ice (300 g.), and the resulting solid crystallised from 50% ethanol (charcoal). 5-(*N*-Methylthioureido)-2-carbethoxymethylthio-4-carbethoxythiazole (V; R = $S\cdot CH_2\cdot CO_2Et$) was obtained as slightly brown glistening needles (2 g.), m. p. 137° (Found: C, 39.8; H, 4.7; N, 11.5; S, 26.4%). $C_{12}H_{17}O_4N_2S_3$ requires C, 39.8; H, 4.7; N, 11.5; S, 26.4%.

7-Keto-5-thio-2-carboxymethylthio-6-methyl-4:5:6:7-tetrahydrothiazolo[5:4-d]pyrimidine (VI; R = $S\cdot CH_2\cdot CO_2H$).—The above thioureido-compound (1.5 g.) was dissolved in 5% sodium hydroxide (20 c.c.) and after 2 hours the solution was acidified, a yellowish-white solid (1.0 g.) being obtained. This compound crystallised from alcohol as glistening plates, m. p. 248° (decomp.) (Found: C, 33.9; H, 2.6; N, 14.0; S, 32.6. $C_8H_7O_3N_3S_3$ requires C, 33.8; H, 2.4; N, 14.5; S, 33.2%). It was sparingly soluble in hot ethanol but more readily soluble in hot acetic acid.

Oxidation of (VI; R = SMe) (cf. Fischer, *Ber.*, 1881, 14, 1912; *Annalen*, 1882, 215, 258).—To a solution of the compound (1.0 g.) in 15% hydrochloric acid (30 c.c.) was added in small amounts potassium chlorate (0.6 g.), the temperature being kept at 50–60°. After a further hour at 50° the solid compound (0.3 g.) was filtered off and crystallised from alcohol in glistening plates, m. p. 200°, sparingly soluble in hot water and soluble in alcoholic alkali (Found: N, 14.7. $C_5H_6O_4N_2S$ requires N, 14.7%).

Action of Nitric Acid on (VI; R = H).—To a suspension of (VI; R = H) (0.2 g.) in 35% nitric acid (4 c.c.) was added concentrated nitric acid (1 c.c.). In a few minutes a dark red solution was obtained and immediately a very pale yellow precipitate was formed. After dilution with water and separation, this solid (0.15 g.) crystallised with difficulty from glacial acetic acid–nitrobenzene as micro-needles, m. p. 243°.

2-Thio-1-methylbarbituric acid (VIII; R = H) (cf. Miller, Munch, Crossley, and Hartung, *J. Amer. Chem. Soc.*, 1936, 58, 1090).—Sodium (9 g.) was dissolved in anhydrous ethanol (250 c.c.) and *N*-methylthiourea (17 g.) was added to the solution with stirring. Ethyl malonate (21 g.) was then quickly introduced, and the mixture heated under reflux for 7 hours. A very pale yellow solid separated, and after being kept for 12 hours at room temperature, the mixture was concentrated to a small volume (150 c.c.) and diluted with water (75 c.c.), a clear solution being obtained. This was made strongly acid with hydrochloric acid and cooled in ice. The acid (VIII; R = H) was obtained as a pale yellow solid (15.8 g.) which crystallised from boiling water as rods, m. p. 197° (Found: N, 17.5; S, 19.7. $C_6H_8O_2N_2S$ requires N, 17.7; S, 20.3%).

5-Amino-4:6-diketo-2-thio-1-methylhexahydropyrimidine (VIII; R = NH_2).—The above acid (15 g.), dissolved in 3% sodium hydroxide (200 c.c.), was treated with sodium nitrite (7 g.), and acetic acid (20 c.c.) added. After standing for 12 hours the dark liquid deposited a dark red precipitate; this was made into a paste with water (80 c.c.) and a solution of 16% ammonium sulphide (50 c.c.) was added. Heat was evolved and after standing for 1 hour the red solution was acidified and the precipitate filtered off. This was extracted with 10% sodium carbonate solution (3×20 c.c.) and the alkaline extract again acidified. The solid obtained (7 g.) was insoluble in all common solvents, turned pink on exposure to air and on boiling with solvents, and was purified by dissolution in alkali and reprecipitation by acid, then having m. p. 266° (decomp.) (Found: N, 23.8; S, 18.0. $C_8H_{10}O_2N_3S$ requires N, 24.3; S, 18.5%). All attempts to make this *amine* react with either sodium dithioformate or dithiophenylacetic acid proved unsuccessful.

Ethyl Thiophenylacetamidomalonate (cf. C.P.S. 93).—To ethyl aminomalonate (15 g.) was added an ethereal solution (150 c.c.) of dithiophenylacetic acid (15 g.), and the mixture kept at 5° for 24 hours. Hydrogen sulphide was evolved, and a white solid separated. After slow evaporation of the solvent, the residue was crystallised twice from light petroleum, white needles (12 g.), m. p. 74.5°, being obtained (C.P.S. 93 does not give a m. p. for this compound) (Found: C, 58.2; H, 6.5; N, 4.6; S, 10.7. Calc. for $C_{15}H_{19}O_4NS$: C, 58.3; H, 6.2; N, 4.5; S, 10.4%).

Ethyl Thioformamidomalonate.—To a solution of ethyl aminomalonate (10 g.) in ether (25 c.c.) was added a solution of sodium dithioformate (7.5 g.) in water (75 c.c.). The mixture was shaken for 3 hours and kept at 5° for 12 hours, a pale yellow crystalline solid separating. This *ester* recrystallised from light petroleum in long white needles (5 g.), m. p. 82° (Found: N, 6.1. $C_8H_{13}O_4NS$ requires N, 6.4%), easily soluble in alcohol, benzene, and ethyl acetate.

7-Keto-5-thio-2-benzyl-4-methyl-4:5:6:7-tetrahydrothiazolo[5:4-d]pyrimidine (IX).—Sodium (7.4 g.) was dissolved in ethanol (120 c.c.) and *N*-methylthiourea (14.5 g.) was added. After addition of ethyl thiophenylacetamidomalonate (16 g.) the mixture was heated under reflux for 9 hours, a yellowish-white solid separating. This was brought into solution by addition of water (100 c.c.), and the solution acidified. On standing for 12 hours, a grey crystalline solid (4 g.) was obtained which recrystallised from acetic acid in plates, m. p. 214° (Found: N, 14.6. $C_{13}H_{11}ON_3S_2$ requires N, 14.5%). This *pyrimidine* was very sparingly soluble in ethanol and more soluble in boiling acetic acid.

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