32. *Purines, Pyrimidines, and Glyoxalines. Part VII.* New Syntheses of 2-Thiouracils and 2-Thiothymines.*

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β-Ethoxyacryloyl and β-methoxy-α-methylacryloyl *iso*thiocyanate have been prepared by reaction of the corresponding acid chlorides with potassium thiocyanate. The *iso*thiocyanates with ammonia and primary amines gave linear acylthioureas which when treated with dilute aqueous alkali afforded 1-substituted 2-thiouracils and 2-thiothymines. Reaction of the acyl *iso*thiocyanates with phenylhydrazine similarly gave acylthiosemicarbazides which with alkali afforded thiotriazoles.

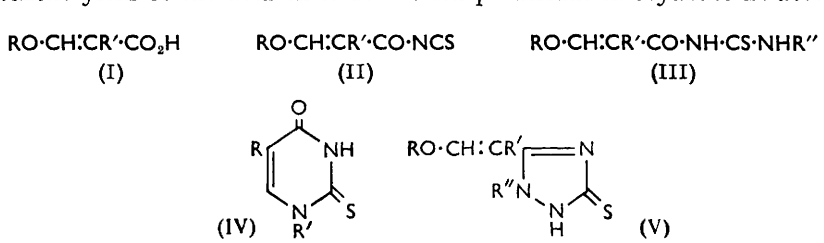
In Part III [1] of this series a new synthesis of 1-substituted 5-cyano-2-thiouracils, by the reaction of a primary amine with a 5-cyanothiazine, was described. As part of our anti-metabolite studies and for other reasons we also wished to prepare 1-substituted 2-thiouracils and 2-thiothymines by routes which would be suitable for the preparation of nucleosides

* Part VI, *J.*, 1957, 3207.

[1] Part III, Atkinson, Shaw, Schaffner, and Warrener, *J.*, 1956, 3847.

from amino-sugars. The only recorded formation of derivatives of this type appears to be due to Johnson and his co-workers who obtained 1-methyl-2-thiothymine [2] and 1-benzyl-2-thiouracil [3] as by-products from the acid hydrolysis of 1 : 5-dimethyl-2-ethylthio- and 1-benzyl-2-benzylthio-4-pyrimidone respectively; the major products in these reactions were the 2-pyrimidones. We now report a simple route to 2-thiopyrimidones.

Ethyl β-ethoxyacrylate, prepared by an improvement of Deno's method,[4] was hydrolysed to the acid (I; R = Et, R′ = H), the dried sodium salt of which with thionyl chloride gave an excellent yield of the acid chloride. With potassium thiocyanate in acetonitrile [5] at



room temperature this gave a good yield of the acyl *iso*thiocyanate (II; R = Et, R′ = H), which with ammonia, methylamine, aniline, and phenylhydrazine gave almost quantitatively the acylthioureas (III; R = Et, R′ = H; R″ = H, Me, Ph) and the thiosemicarbazide (III; R = Et, R′ = H, R″ = NHPh). Treatment of the thioureas with warm dilute sodium hydroxide solution readily gave the 2-thiouracils (IV; R = H, R′ = H, Me, Ph) but the thiosemicarbazide, not unexpectedly, was dehydrated by alkali to the thiotriazole (V; R = Et, R′ = H, R″ = Ph).

Addition of bromine to methyl α-methylacrylate and reaction of the resulting methyl αβ-dibromo-α-methylpropionate with hot methanolic sodium methoxide gave a mixture of methyl ββ-dimethoxy-α-methylpropionate and β-methoxy-α-methylacrylate which when distilled from sodium hydrogen sulphate gave an excellent yield of the last-mentioned ester; [6] alkaline hydrolysis then gave the acid (I; R = R′ = Me).[6] This was smoothly converted *via* the acid chloride into the *iso*thiocyanate (II; R = R′ = Me) which with ammonia, methylamine, aniline, and phenylhydrazine gave linear compounds (III; R = R′ = Me, R″ = H, Me, Ph, NHPh). The reaction of the compounds (III; R = R′ = Me, R″ = Me, Ph, NHPh) with sodium hydroxide solution gave excellent yields of the 2-thiothymines (IV; R = Me, R′ = Me, Ph) and the thiotriazole (V; R = R′ = Me, R″ = Ph). However the thiourea (III; R = R′ = Me, R″ = H) was recovered unchanged from warm dilute sodium hydroxide solution, and was decomposed by more drastic treatment. For the preparation of the 2-thiopyrimidones, isolation of the intermediate thioureas is not necessary. Thus the *iso*thiocyanate (II; R = R′ = Me) with an alkaline solution of glycine gave directly the substituted 2-thiothymine (IV; R = Me, R′ = CH_2·CO_2H).

Experimental

Thionyl chloride was purified before use by distillation from dry quinoline and fractionation of the distillate. Compounds were dried for analysis at 56°/0·1 mm. for 1—2 hr.

β-Ethoxyacryloyl Chloride (cf. ref. 4).—Ethyl bromoacetate (334 g.), ethyl orthoformate (400 ml.), and zinc shavings (1 kg.) gave ethyl β-ethoxyacrylate (104 g.), b. p. 189—191°; Deno [4] records b. p. 189—193°. The ester (48 g.) was stirred on a water-bath with 2N-sodium hydroxide (180 ml.) for 2 hr., cooled, and acidified, to precipitate β-ethoxyacrylic acid (35 g.), m. p. 109°; Tschitschibabin [4] gives m. p. 110·5°.

Dry sodium β-ethoxyacrylate (prepared from the acid by neutralisation with sodium

[2] Johnson and Clapp, *J. Biol. Chem.*, 1908, **5**, 56.
[3] Johnson and Joyce, *J. Amer. Chem. Soc.*, 1916, **38**, 1390.
[4] Deno, *J. Amer. Chem. Soc.*, 1947, **69**, 2233; Tschitschibabin, *J. prakt. Chem.*, 1906, **73**, 335.
[5] Cf. Elmore, Ogle, Fletcher, and Toseland, *J.*, 1956, 4458.
[6] Bieber, *Compt. rend.*, 1951, **233**, 655.

hydroxide solution and evaporation *in vacuo*) (15 g.) was refluxed with thionyl chloride (10 ml.) in ether (200 ml.) for 4 hr., kept overnight, and filtered through asbestos. Distillation of the filtrate *in vacuo* gave β-*ethoxyacryloyl chloride* (11·5 g.), b. p. 104°/35 mm. (Found: C, 44·45; H, 5·35. $C_5H_7O_2Cl$ requires C, 44·65; H, 5·25%).

β-*Ethoxyacryloyl* iso*Thiocyanate*.—The foregoing acid chloride (9·33 g.) in dry acetonitrile (50 ml.) was shaken with freshly dried potassium thiocyanate (6·8 g.) for 3 hr., then filtered from potassium chloride, and the orange filtrate distilled *in vacuo*, to give pale yellow β-*ethoxyacryloyl* iso*thiocyanate* (6·2 g.), b. p. 90°/1·5 mm. (Found: C, 46·45; H, 4·7; N, 8·85. $C_6H_7O_2NS$ requires C, 45·85; H, 4·5; N, 8 9%).

2-*Thiouracil*.—The foregoing *iso*thiocyanate (1·35 g.) reacted vigorously with 3·34N-methanolic ammonia (3 ml.). N-β-*Ethoxyacryloylthiourea* separated; it recrystallised from ethanol as prisms (0·74 g.), m. p. 165° (Found: C, 41·6; H, 5·85; N, 15·85. $C_6H_{10}O_2N_2S$ requires C, 41·4; H, 5·8; N, 16·1%). The thiourea (0·5 g.) was heated on a water-bath for 45 min. with 2N-sodium hydroxide (5 ml.), cooled, and acidified with hydrochloric acid, to precipitate a gummy solid. This, when triturated with a little ethanol, gave 2-thiouracil (0·05 g.) which separated from water as needles, m. p. 304° (decomp.) (Found: C, 37·45; H, 3·45; N, 21·5. Calc. for $C_4H_4ON_2S$: C, 37·5; H, 3·15; N, 21·85%).

1-*Methyl*-2-*thiouracil*.—The *iso*thiocyanate (0·84 g.) in ether (15 ml.) was treated with 33% methanolic methylamine (0·5 ml.). The solution was evaporated to dryness and the residue crystallised from ethanol, to give N-β-*ethoxyacryloyl*-N′-*methylthiourea* (0·45 g.) as needles, m. p. 124° (Found: C, 45·1; H, 6·35; N, 14·7. $C_7H_{12}O_2N_2S$ requires C, 44·7; H, 6·45; N, 14·9%). The thiourea (0·35 g.) was warmed for 10 min. with 2N-sodium hydroxide (4 ml.). The cooled solution when acidified gave a precipitate of 1-*methyl*-2-*thiouracil* (0·23 g.) which recrystallised from ethanol as needles, which changed to plates, m. p. 228° (Found: C, 42·55; H, 3·95; N, 19·6. $C_5H_6ON_2S$ requires C, 42·25; H, 4·25; N, 19·7%).

1-*Phenyl*-2-*thiouracil*.—The *iso*thiocyanate (1·15 g.) and aniline (0·7 g.) were mixed in ether (25 ml.). Precipitated N-β-*ethoxyacryloyl*-N′-*phenylthiourea* (1·25 g.) crystallised from ethanol as plates, m. p. 152° (Found: C, 57·7; H, 5·4; N, 11·0. $C_{12}H_{14}O_2N_2S$ requires C, 57·6; H, 5·65; N, 11·2%). This (0·85 g.) was heated on a water-bath with 2N-sodium hydroxide (5 ml.) for 15 min., a clear solution being obtained; this was acidified and the solid filtered off. 1-*Phenyl*-2-*thiouracil* (0·68 g.) crystallised from ethanol as laths, m. p. 236° (Found: C, 58·85; H, 3·85; N, 13·6. $C_{10}H_8ON_2S$ requires C, 58·8; H, 3·95; N, 13·7%).

5-β-*Ethoxyvinyl*-2 : 3-*dihydro*-1-*phenyl*-3-*thio*-1 : 2 : 4-*triazole*.—The *iso*thiocyanate (0·87 g.), phenylhydrazine (0·6 g.), and ethanol (5 ml.) gave a precipitate of N^1-β-*ethoxyacryloyl*-N^3-*phenylthiosemicarbazide* (0·87 g.), plates (from ethanol), m. p. 161° (Found: C, 54·05; H, 5·8; N, 15·6. $C_{12}H_{15}O_2N_3S$ requires C, 54·35; H, 5·7; N, 15·85%). The thiosemicarbazide (0·4 g.) was heated with 2N-sodium hydroxide (5 ml.) for 5 min. and the cooled solution acidified; the precipitated 5-β-*ethoxyvinyl*-2 : 3-*dihydro*-1-*phenyl*-3-*thio*-1 : 2 : 4-*triazole* (0·37 g.) separated from ethanol as prisms, m. p. 161° (Found: C, 58·3; H, 5·1; N, 16·8. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3; N, 17·0%).

β-*Methoxy*-α-*methylacrylic Acid*.—The following method has been found to be suitable for the preparation of this acid, which was described without experimental directions by Bieber.[6]

Methyl αβ-dibromo-α-methylpropionate [6] (467 g.) in methanol (500 ml.) was added to a hot solution from sodium (82·6 g.) and methanol (1 l.) at a rate sufficient to keep the mixture boiling. Next morning the mixture was filtered from sodium bromide which was washed with methanol. The filtrate and washings were evaporated to about half volume and sodium bromide was again removed. Most of the solvent was removed, the semi-gelatinous residue treated with water (250 ml.), and the precipitated oil extracted into ether. The dried solution was evaporated and the residue heated with freshly fused sodium hydrogen sulphate (1·5 g.) at 170° under a small fractionating column until evolution of ethanol was complete. The residue, distilled *in vacuo*, gave methyl β-methoxy-α-methylacrylate (159 g., 68%), b. p. 66—67°/10 mm., n_D^{23} 1·455; Bieber gives n_D^{18} 1·460. The ester (39 g.) was heated on a water-bath with 2N-sodium hydroxide (255 ml.) with stirring until a clear solution was obtained (3 hr.); this was cooled and acidified with 2N-hydrochloric acid (225 ml.), to precipitate β-methoxy-α-methylacrylic acid (35·5 g.) which separated from light petroleum (b. p. 60—80°) as plates, m. p. 106° (Found: C, 51·85; H, 7·0. Calc. for $C_5H_8O_3$: C, 51·7; H, 6·95%).

β-*Methoxy*-α-*methylacryloyl Chloride*.—Sodium β-methoxy-α-methylacrylate was prepared by neutralising (to phenolphthalein) a suspension of the acid in water with 2N-sodium hydroxide.

The solution was evaporated to dryness *in vacuo* and the residual salt dried at 100°/0·5 mm. for 4·5 hr. before use; almost exactly 1 mol. of water was lost during the drying. To a suspension of this salt (25·72 g.) in ether (100 ml.) was added thionyl chloride (16 ml.) in ether (100 ml.). When the initial vigorous reaction had subsided, the mixture was boiled under reflux for 3 hr., filtered, and evaporated to an oil which was distilled *in vacuo*, giving β-*methoxy*-α-*methylacryloyl chloride* (20·0 g.), b. p. 102°/35 mm. (Found: C, 45·2; H, 5·2. $C_5H_7O_2Cl$ requires C, 44·6; H, 5·25%). The acid chloride with a little water gave the acid, m. p. and mixed m. p. 105°.

β-*Methoxy*-α-*methylacryloyl* iso*Thiocyanate*.—To a solution of the foregoing acid chloride (8·6 g.) in dry acetonitrile (50 ml.) was added dry potassium thiocyanate (6·2 g.) giving, as in the analogous case, β-*methoxy*-α-*methylacryloyl* iso*thiocyanate* (7·2 g.), b. p. 102°/2 mm. (Found: C, 45·85; H, 4·2; N, 8·75. $C_6H_7O_2NS$ requires C, 45·85; H, 4·5; N, 8·9%). The *iso*thiocyanate crystallised at room temperature as large plates which melted a little above room temperature. The compound should be kept in the refrigerator, otherwise it slowly darkens and deposits some sludge.

1-*Methyl*-2-*thiothymine*.—25% Ethanolic methylamine (0·6 ml.) was added to a solution of this *iso*thiocyanate (0·86 g.) in methanol (5 ml.); a vigorous reaction occurred and a crystalline precipitate separated immediately; N-(β-*methoxy*-α-*methylacryloyl*)-N′-*methylthiourea* (0·55 g.) recrystallised from ethanol as thick needles, m. p. 140° (Found: C, 44·45; H, 6·15; N, 14·8. $C_7H_{12}O_2N_2S$ requires C, 44·7; H, 6·45; N, 14·9%). The thiourea (0·28 g.) was gently warmed with 2N-sodium hydroxide (2 ml.) until a clear solution was obtained. This was cooled and acidified to precipitate 1-methyl-2-thiothymine (0·19 g.) which separated from ethanol as needles, m. p. 226—227° (Johnson and Clapp [2] give m. p. 229—230°) (Found: C, 45·85; H, 4·9; N, 17·85. Calc. for $C_6H_8ON_2S$: C, 46·15; H, 5·15; N, 17·95%).

1-*Phenyl*-2-*thiothymine*.—The *iso*thiocyanate (0·5 g.) with aniline (0·5 g.) in ethanol (5 ml.) gave N-(β-*methoxy*-α-*methylacryloyl*)-N′-*phenylthiourea* (0·6 g.), needles (from ethanol), m. p. 110—112° (Found: C, 57·8; H, 5·4; N, 11·1. $C_{12}H_{14}O_2N_2S$ requires C, 57·6; H, 5·65; N, 11·2%). The thiourea (0·2 g.) dissolved after a few min. in 2N-sodium hydroxide; acidification of the cooled solution gave 1-*phenyl*-2-*thiothymine* (0·15 g.), needles (from ethanol), m. p. 202—203° (Found: C, 60·4; H, 4·75; N, 12·4. $C_{11}H_{10}ON_2S$ requires C, 60·55; H, 4·6; N, 12·85%).

1-*Carboxymethyl*-2-*thiothymine*.—The *iso*thiocyanate (1·12 g.) was shaken with glycine (0·54 g.) in 1·94N-sodium hydroxide (7·4 ml.) until a clear solution was obtained (10 min.) and then for a further 10—15 min., cooled, acidified, and kept at 0° overnight. A solid precipitate separated. This was dissolved in aqueous sodium hydrogen carbonate, the solution filtered, and the filtrate acidified to give 1-*carboxymethyl*-2-*thiothymine* (0·7 g.) which crystallised from water as needles, m. p. 246—247° (decomp.) (Found: C, 41·9; H, 3·8; N, 13·8. $C_7H_8O_3N_2S$ requires C, 42·0; H, 4·05; N, 14·0%).

2 : 3-*Dihydro*-5-(β-*methoxy*-α-*methylvinyl*)-1-*phenyl*-3-*thio*-1 : 2 : 4-*triazole*.—Phenylhydrazine (0·5 g.) in ethanol (5 ml.) was added to the *iso*thiocyanate (0·68 g.); the cooled solution afforded N^1-(β-*methoxy*-α-*methylacryloyl*)-N^3-*phenylthiosemicarbazide* (0·75 g.), plates (from ethanol), m. p. 180—181° (decomp.) (Found: C, 54·6; H, 5·6; N, 15·6. $C_{12}H_{15}O_2N_3S$ requires C, 54·35; H, 5·7; N, 15·85%). The thiosemicarbazide (0·31 g.) was warmed with 2N-sodium hydroxide until the solution was clear. Acidification of this precipitated 2 : 3-*dihydro*-5-(β-*methoxy*-α-*methylvinyl*)-1-*phenyl*-3-*thio*-1 : 2 : 4-*triazole* (0·28 g.) which crystallised from ethanol as needles, m. p. 195—196° (Found: C, 58·45; H, 5·45; N, 16·9. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3; N, 17·0%).

N-β-*Methoxy*-α-*methylacryloylthiourea*.—The *iso*thiocyanate (0·935 g.) in a little ethanol was added to saturated methanolic ammonia (1·5 ml.), to precipitate N-β-*methoxy*-α-*methylacryloylthiourea* (0·85 g.) which crystallised from ethanol as prisms, m. p. 163° (Found: C, 41·15; H, 5·7; N, 16·0. $C_6H_{10}O_2N_2S$ requires C, 41·4; H, 5·8; N, 16·1%). The thiourea was recovered unchanged from its solution in 2N-sodium hydroxide; longer heating gave hydrogen sulphide and no evidence of pyrimidine formation.

We thank the N.S.W. State Cancer Council for a research grant and Dr. E. Challen for the microanalyses.

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[*Received, May 27th,* 1957.]