747. *Purines, Pyrimidines, and Glyoxalines. Part III.* A New Synthesis of 2-Thiouracils.*

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5-Cyano-2-ethylthio-4-oxo-1 : 3-thiazine (V) results from the reaction of ethyl *N*-cyanoacetyldithiocarbamate (I), ethyl orthoformate, and acetic anhydride. Treatment of the thiazine with primary amines and subsequent treatment of the products with sodium hydroxide solution gave derivatives of 2-thiouracil.

2-Thiouracil and its derivatives have assumed some importance in recent years in the treatment of hyperthyroidism and as metabolite antagonists.[1] The literature records two general synthetical routes to the thiouracils, namely, the condensation of thiourea with a β-oxo-ester [2] or derivative, and the substitution of oxygen in a preformed oxygenated pyrimidine by sulphur.[3–5] Earlier papers in this series [6] have described a general synthesis of 5-cyanouracils by reaction of primary amines with α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide, particularly convenient for the preparation of 1-substituted uracils. For tests of similar 2-thiouracils as potential antimetabolites, and for other reasons, this reaction has now been extended to derivatives of dithiocarbamic acid.

Cyanoacetic acid and ethyl dithiocarbamate in acetic anhydride at 25° give a readily separable mixture of ethyl *N*-cyanoacetyl- (I) and *N*-acetyl-dithiocarbamate (II), but at higher temperatures afford also the diacyl compound (III). An attempt to convert the cyanoacetyldithiocarbamate (I) into the ethoxymethylene derivative (IV) by reaction with ethyl orthoformate and acetic anhydride gave 5-cyano-2-ethylthio-4-oxo-1 : 3-thiazine (V) instead, by cyclisation.

$CN\cdot CH_2\cdot CO\cdot NH\cdot CS_2Et$ (I)

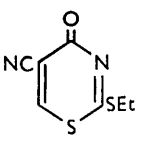
$Me\cdot CO\cdot NH\cdot CS_2Et$ (II)

$CN\cdot CH_2\cdot CO\cdot NAc\cdot CS_2Et$ (III)

$CN\cdot C(:CH\cdot OEt)\cdot CO\cdot NH\cdot CS_2Et$ (IV)

$CN\cdot C(:CH\cdot NHR)\cdot CO\cdot NH\cdot CS_2Et$ (VI)

$CN\cdot CH_2\cdot CO\cdot NH\cdot CO\cdot SEt$ (VIII)



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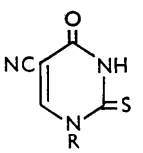

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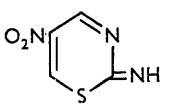

(IX)

The thiazine structure (V), assigned on the basis of analysis and chemical reactions, is confirmed by the infrared weak absorption band (Nujol mull) at 2250 cm.$^{-1}$ (CN) and the strong double band at 1650—1622 cm.$^{-1}$ (CO). A somewhat similar reaction, between thiourea and nitromalondialdehyde, has been reported to give the thiazine (IX).[7] The thiazine (V) reacted very readily at room temperature with ammonia, methylamine, and

* Part II, *J.*, 1956, 1877.

[1] Roblin, *Chem. Rev.*, 1946, **38**, 255; Wright, *Vitamins and Hormones*, 1951, **9**, 131; Woolley, A Study of Antimetabolites," Wiley, New York, 1952; Albert, " Selective Toxicity with Special Reference to Chemotherapy," Methuen, London, 1951.

[2] Wheeler and Bristol, *Amer. Chem. J.*, 1905, **33**, 458; Wheeler and Liddle, *ibid.*, 1908, **40**, 550; de Bollemont, *Bull. Soc. chim. France*, 1901, **25**, 20; Anderson, Halverstadt, Miller, and Roblin, *J. Amer. Chem. Soc.*, 1945, **67**, 2197.

[3] Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2138; Russell, Elion, Falco, and Hitchings, *ibid.*, 1949, **71**, 2279; Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

[4] Wheeler and Liddle, ref. 2; Wheeler and McFarland, *Amer. Chem. J.*, 1910, **43**, 19.

[5] McOmie and Boarland, *Chem. and Ind.*, 1950, 602; *J.*, 1951, 1218; 1952, 3722.

[6] Parts I and II, *J.*, 1955, 1834; 1956, 1877.

[7] Hale and Brill, *J. Amer. Chem. Soc.*, 1912, **34**, 295.

aniline, to give the linear aminomethylene derivatives (VI; R = H, Me, and Ph) in excellent yields, the last two of which with aqueous sodium hydroxide gave the corresponding 2-thiouracils (VII; R = Me and Ph). Similarly, the thiazine and an alkaline solution of glycine gave directly the thiouracil (VII; R = $CH_2 \cdot CO_2H$). The linear compound (VI; R = H) was unexpectedly recovered unchanged from solutions in aqueous sodium hydroxide and ethanolic sodium ethoxide; it was eventually converted, in low yield, into 5-cyano-2-thiouracil (VII; R = H) when warmed for several hours with dilute sodium hydroxide solution. An increased yield of 5-cyano-2-thiouracil was obtained by the reaction of the thiazine with ammonia in acetonitrile, and in the presence of triethylamine.

In a parallel experiment, ethyl *N*-cyanoacetylthiocarbamate (VIII) was obtained in low yield from cyanoacetic acid and *O*-ethyl thiocarbamate at 80—100° in acetic anhydride. When it was heated with ethyl orthoformate and acetic anhydride, however, extensive decomposition occurred.

Experimental

Ethyl N-*Cyanoacetyldithiocarbamate*.—Cyanoacetic acid (8·5 g.) and ethyl dithiocarbamate (12·1 g.) were shaken with acetic anhydride (11 ml.) at 25° for 60 hr. The resulting precipitate was filtered off, washed with a little ether (2 × 30 ml.), and extracted (Soxhlet) with ether (150 ml.) for 18 hr.; *ethyl* N-*cyanoacetyldithiocarbamate* (5·7 g.) crystallised from the extract as yellow needles, m. p. 140—142° and, recrystallised from methanol, had m. p. 142° (Found: C, 38·1; H, 4·1; N, 14·6. $C_6H_8ON_2S_2$ requires C, 38·3; H, 4·3; N, 14·9%). Evaporation of the original filtrate *in vacuo* gave ethyl *N*-acetyldithiocarbamate (5·7 g.) which separated from water as yellow needles, m. p. and mixed m. p. 124°.

Ethyl N-*Acetyl*-N-*cyanoacetyldithiocarbamate*.—A solution of cyanoacetic acid (51 g.) and ethyl dithiocarbamate (73 g.) in acetic anhydride (220 ml.) was kept at 80—100° for 0·5 hr. On cooling crystallisation occurred; the solid (42 g.) was filtered off, washed with ether (2 × 50 ml.), and recrystallised from methanol, to give a mixture of pale yellow and bright yellow needles. The latter were removed by washing with hot ether (5 × 10 ml.), to leave *ethyl* N-*acetyl*-N-*cyanoacetyldithiocarbamate* (3·3 g.) which separated from acetic acid as pale yellow needles; the m. p. was 194—196° (decomp.) when the compound was placed on a metal block at 180° and heated rapidly, otherwise the substance decomposed below 200° without melting (Found: C, 41·95; H, 4·6; N, 12·45. $C_8H_{10}O_2N_2S_2$ requires C, 41·7; H, 4·4; N, 12·2%). The residue obtained by evaporation of the ether and alcohol filtrates was crystallised from water, to give ethyl *N*-acetyldithiocarbamate (26 g.), m. p. and mixed m. p. 124°.

5-*Cyano*-2-*ethylthio*-4-*oxo*-1 : 3-*thiazine*.—Ethyl *N*-cyanoacetyldithiocarbamate (20 g.), ethyl orthoformate (28 g.), and acetic anhydride (40 ml.) were boiled under reflux for 1 hr. The red solution, when cooled, gave crystals which were filtered off and washed with a little ice-cold ethyl acetate; 5-*cyano*-2-*ethylthio*-4-*oxo*-1 : 3-*thiazine* (8·5 g.) separated from benzene–carbon tetrachloride as orange-yellow leaflets, m. p. 140° (Found: C, 42·8; H, 2·9; N, 14·1. $C_7H_6ON_2S_2$ requires C, 42·4; H, 3·05; N, 14·1%). The filtrate was evaporated and the residue boiled under reflux for 1 hr.; when the solution was cooled a further quantity of the thiazine (4 g.) separated. The crude thiazine obtained in these experiments is pure enough for most purposes.

5-*Cyano*-1-*phenyl*-2-*thiouracil*.—To a solution of the thiazine (1 g.) in warm benzene (10 ml.) was added aniline (0·5 g.); the solution was cooled; after several minutes, crystals appeared (crystallisation may be induced with a seed crystal a few seconds after mixing); *ethyl* N-(β-*anilino*-α-*cyanoacryloyl*)*dithiocarbamate* (1·1 g.) separated from ethanol as yellow laths, m. p. 149° (decomp., resolidified, and then had m. p. 267°) (Found: C, 53·9; H, 4·4; N, 14·3. $C_{13}H_{13}ON_3S_2$ requires C, 53·6; H, 4·5; N, 14·45%). The anilino-compound (0·35 g.) rapidly dissolved when heated at 80° for 10 min. with aqueous 0·5N-sodium hydroxide (10 ml.), and ethanethiol was evolved. The solution was acidified with 2N-sulphuric acid (3 ml.), yielding pale yellow 5-*cyano*-1-*phenyl*-2-*thiouracil* (0·24 g.) which crystallised from acetic acid as pale yellow plates, m. p. 267° (Found: C, 57·6; H, 3·3; N, 18·0. $C_{11}H_7ON_3S$ requires C, 57·65; H, 3·1; N, 18·3%).

5-*Cyano*-1-*methyl*-2-*thiouracil*.—To a solution of the thiazine (1 g.) in warm methanol (20 ml.) was added ethanolic methylamine (33%) until the smell of the base persisted. The solution was kept at room temperature for 5 min., then treated with an excess of N-sulphuric acid to precipitate cream-coloured *ethyl* N-(α-*cyano*-β-*methylaminoacryloyl*)*dithiocarbamate* (0·9 g.)

which separated from ethanol as pale yellow laths, m. p. 138° (Found: C, 42·05; H, 4·7; N, 18·3. $C_8H_{11}ON_3S_2$ requires C, 41·9; H, 4·85; N, 18·35%). This derivative (0·5 g.) was heated with N-sodium hydroxide (5 ml.) at 80—100° for 10 min., the solution cooled and acidified, and the precipitated *5-cyano-1-methyl-2-thiouracil* (0·27 g.) obtained from water as very pale yellow prisms, m. p. 295° (decomp.) (Found: C, 42·95; H, 2·85; N, 25·05. $C_6H_5ON_3S$ requires C, 43·1; H, 3·0; N, 25·15%).

5-Cyano-2-thiouracil.—(*a*) To a solution of the thiazine (1 g.) in benzene (50 ml.) was added ethereal ammonia until the smell of ammonia persisted; a small precipitate was obtained. The solution was evaporated to dryness *in vacuo* and the residue dissolved in N-sodium carbonate (20 ml.); the solution was acidified, to precipitate an oil which soon crystallised; *ethyl* N-(β-*amino-α-cyanoacryloyl*)*dithiocarbamate* (0·6 g.) separated from ethanol as yellow laths, m. p. 135° (Found: C, 39·0; H, 4·15; N, 19·3. $C_7H_9ON_3S_2$ requires C, 39·05; H, 4·2; N, 19·55%); it was recovered from an ethanolic solution containing sodium ethoxide after 24 hr. at room temperature. The amine (0·5 g.) was heated on a water-bath with 0·1N-sodium hydroxide (50 ml.) for 5 hr.; ethanethiol was evolved and a pale yellow solution was obtained; this was neutralised with hydrochloric acid and evaporated to dryness *in vacuo*; the residue, crystallised from water, gave 5-cyano-2-thiouracil (0·05 g.) as pale yellow prisms, m. p. 285° (decomp.) (Found: C, 38·9; H, 1·65; N, 27·4. Calc. for $C_5H_3ON_3S$: C, 39·2; H, 1·95; N, 27·45%); Anderson *et al.*[2] give m. p. 282—283° (decomp.).

(*b*) A solution of the thiazine (1·3 g.) in warm acetonitrile (12 ml.) was added to a mixture of 15N-ammonia (3 ml.) and triethylamine (1 ml.). The solution was heated at 60—80° for 10 min., treated with 15N-ammonia (3 ml.), and evaporated to dryness *in vacuo*. The residue was dissolved in water (20 ml.), and the solution adjusted to pH 12 with sodium hydroxide solution, then heated on a water-bath for 5 min., cooled, and brought to pH 4 with hydrochloric acid; 5-cyano-2-thiouracil (0·5 g.) separated and, recrystallised from water or butan-1-ol, had m. p. and mixed m. p. 283° (decomp.).

1-Carboxymethyl-5-cyano-2-thiouracil.—The preceding thiazine (1 g.) and glycine (0·4 g.) in 2N-sodium hydroxide (6 ml.) were heated at 80° for 10 min. Ethanethiol was liberated, and a clear pale yellow solution was obtained; this was cooled and acidified with 10N-hydrochloric acid (1·5 ml.); the precipitated *1-carboxymethyl-5-cyano-2-thiouracil* (0·65 g.) separated from water as orange-yellow plates, m. p. 340° (Found: C, 40·0; H, 2·8; N, 19·5. $C_7H_5O_3N_3S$ requires C, 39·8; H, 2·4; N, 19·9%).

O-Ethyl N-Cyanoacetyl(thiocarbamate).—Cyanoacetic acid (14·2 g.), *O*-ethyl thiocarbamate (16 g.), and acetic anhydride (20 ml.) were heated together at 85° for 0·5 hr.; much decomposition and darkening occurred but the cooled solution gave a crystalline precipitate; *O-ethyl N-cyanoacetyl(thiocarbamate)* (2·5 g.) separated from methanol as colourless needles, m. p. 198° (Found: C, 41·6; H, 4·8; N, 16·3. $C_6H_8O_2N_2S$ requires C, 41·85; H, 4·7; N, 16·3%). An attempt to obtain this compound by keeping the reactants at 25° for several days was unsuccessful.

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