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1-THIAPYRIMIDINES
SULPHUR ANALOGUES OF NUCLEIC ACID BASES*

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Analogues of nucleic acid bases have been shown to be incorporated[1] into the R.N.A. or D.N.A. of certain viruses, micro organisms and mammalian cells. This results in the formation of "deformed" nucleic acids, which may subsequently interfere with growth and reproductive processes. These analogues are of value as antiviral and antitumour agents.[1]

Replacement of the $\underline{N}_{(1)}$ of a pyrimidine base by a sulphur atom yields a new series of nucleic acid base analogues. 1-Thiauracil (II) and 1-thiathymine (VIII) are the first such derivatives which have a substitution pattern similar to that of the naturally occurring nucleic acid pyrimidine bases.

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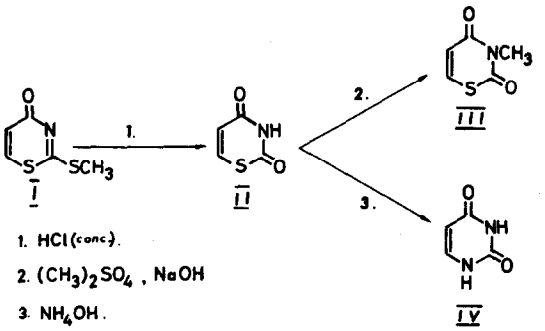
* 1,3-Thiazines Part III. For Part II, see Chem. and Ind., 1966, 289.

** General Motors-Holden's Scholar 1964-1966.

1-Thiauracil (II) was readily obtained by acid hydrolysis of 2-methylmercapto-4-oxo-4H-1,3-thiazine (I)*,[2]. The structure of 1-thiauracil (m.p. 197-198°C) was based on elemental analysis[3], spectral properties ($\lambda_{max.}$ (EtOH) 223, 270 mu, ϵ = 7850, 6250; N.M.R. (see Table 1); I.R. ($CHCl_3$) ν_{co} 1685 cm^{-1} broad), and conversion into the N-methyl derivative (III), (m.p. 84-85°C: I.R. ($CHCl_3$) ν_{co} 1655, 1690 cm^{-1}) with alkaline dimethyl sulphate, and into uracil (IV), (m.p. and mixed m.p. 336°C; infrared spectrum identical with that from authentic material) on heating with concentrated ammonium hydroxide solution.



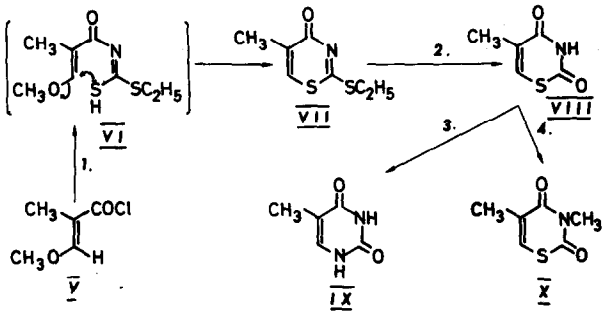
I II III IV

In order to extend this method to the synthesis of 1-thiathymine, the corresponding 2-ethylmercapto-4-keto-5-methyl-1,3-4H- thiazine (VII) was required. In the course of our studies directed towards the synthesis of this thiazine, we have developed a convenient general route for the synthesis

*This thiazine (I) was better synthesised by alkylation of the parent 2-thio-4-oxo-3,4-dihydro-1,3-2H-thiazine[2] with alkaline dimethyl sulphate at 45°C, than with diazomethane as previously reported[2].

of 1,3-thiazines, which allows the introduction of a variety of substituents into either the 5- or 6*-positions. This method utilises the intramolecular nucleophilic attack of an acyldithiourethane sulphur atom onto a carbonyl group or its enol ether.

Thus, treatment of the acid chloride (V)[4] with dithiourethane in refluxing benzene afforded the unstable acyldithiourethane (VI) which, when set aside, slowly deposited 2-ethylmercapto-4-keto-5-methyl-1,3-4H-thiazine (VII)** (m.p. 111-112°C; $\lambda_{max.}$ (EtOH) 255, 286 (infl.) mu). Acid hydrolysis of this



thiazine gave 1-thiathymine (VIII), (m.p. 222-223°C; $\lambda_{max.}$ (EtOH) 224, 272 mu, ϵ = 7300, 6290; I.R. ($CHCl_3$) ν_{co} 1690 cm^{-1} broad). Methylation of (VIII) with diazomethane or alkaline dimethyl sulphate afforded the N-methyl derivative (X), (m.p. 99°C; I.R. ($CHCl_3$) ν_{co} 1645, 1685 cm^{-1}). Concentrated ammonia converted 1-thiathymine into thymine (IX), (m.p. and mixed m.p. 315-320°C; infrared spectrum identical with that of an authentic sample).

*Selected 6-substituted-2-thio-1,3-thiazines are available from the reaction of substituted propiolic acids and dithiocarbamic acids. R.N. Warrener and E.N. Cain, unpublished results.

**The structure of the thiazine (VII) was confirmed by an alternative synthesis from β-methoxy-methacryl isothiocyanate[4] and ethyl mercaptan.

TABLE 1

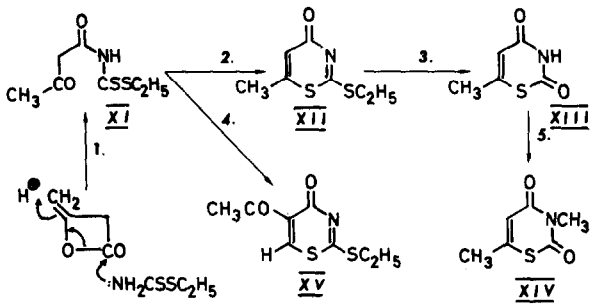
NMR τ Values of 1,3-Thiazines[5]

Compound	Substituent on $C_{(5)}$	Substituent on $C_{(6)}$	Coupling constant
II[b]	H, 3.50	H, 2.07	10.50 c.p.s.
III[a,d]	H, 3.50	H, 2.63	10.20
VII[a,c]	CH_3, 7.84	H, 2.75	-
VIII[b]	CH_3, 8.03	H, 2.40	1.40
X[a,d]	CH_3, 7.89	H, 2.96	1.39
XII[a,c]	H, 3.58	CH_3, 7.72	1.39
XIII[a]	H, 3.68	CH_3, 7.72	1.20
XIV[a,d]	H, 3.66	CH_3, 7.75	1.19
XV[a,c]	$COCH_3$, 7.35	H, 1.64	-

a) in $CDCl_3$; b) in d_6-dimethylsulphoxide.
c) all $-S-CH_2-CH_3$ had methylene at 6.68 and methyl at 8.63 with J = 7.0-7.5 c.p.s.
d) all $-N-CH_3$ at 6.00-6.20.

The versatility of the above thiazine synthesis is demonstrated by the reactions of N-acetoacetyldithiourethane (XI)* (m.p. 89°C; $\lambda_{max.}$ (EtOH) 261, 309 mu, ϵ = 12550, 14950). Cyclodehydration of (XI) with concentrated sulphuric acid gave 2-ethylmercapto-4-keto-6-methyl-1,3-4H-thiazine (XII), (m.p. 37-39°C; $\lambda_{max.}$ (EtOH) 254, 284 (infl.) mu, ϵ = 22100, 10800). The 6-methyl-1-thiauracil (XIII), (m.p. 182°C; $\lambda_{max.}$ (EtOH) 222, 268 mu, ϵ = 6850, 6440) was formed by acid hydrolysis of (XII). The N-methyl derivative (XIV), (m.p. 125-126°C) was obtained by alkylation of (XIII) with diazomethane.

*Formed by the addition of dithiourethane to diketene in glacial acetic acid.



1. CH_3COOH 2. H_2SO_4(conc) 3. $H_3O^{\oplus}$ 4. $CH(OC_2H_5)_3$, Ac_2O

5. CH_2N_2

Condensation of N-acetoacetyldithiourethane with triethylorthoformate in hot acetic anhydride gave 2-ethylmercapto-4-keto-5-acetyl-1,3-4H-thiazine (XV), (m.p. 94°C; $\lambda_{max.}$ (EtOH) 258, 278 (infl.) mu, ϵ = 23500, 17300). N-(α-acetyl-β-ethoxyacrylyl)-dithiourethane is presumed to be an intermediate.

Detailed conversion of the above thiazines to substituted uracils and thiouracils will be discussed in a forthcoming communication.

References

1. A.M. Michelson, The Chemistry of Nucleosides and Nucleotides, Chapter 9, Academic Press, London and New York (1963).
2. R.N. Warrener and E.N. Cain, Chem. and Ind., 1989, 1964.
3. Satisfactory analyses were obtained for all new compounds reported in this communication.
4. G. Shaw and R.N. Warrener, J. Chem. Soc., 153, 1958.
5. N.M.R. Spectra were recorded on a Perkin-Elmer R10 Spectrometer (60 Mc.p.s.), using T.M.S. as internal reference.