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1,3-THIAZINES AS PYRIMIDINE PRECURSORS. IV*
AN UNAMBIGUOUS SYNTHESIS OF N(1)-SUBSTITUTED OROTIC AND 2-THIO-OROTIC ACIDS

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It has been amply demonstrated that of the free pyrimidines, orotic acid occupies a rather unique position in being the sole effective precursor of nucleic acids in certain animal tissues (1,2). Orotic acid itself is now available from several synthetic routes (3). However, despite several different synthetic approaches (4) only a single $\underline{N}_{(1)}$-substituted orotic acid (related to the naturally occuring nucleoside, orotidine) is known. In this case Fox, Yung and Wempen (5) obtained 1-methyl-orotic acid by oxidation of 1,6-dimethyluracil with alkaline potassium ferricyanide. Attempts by Ralph, Shaw and Naylor (4) to extend this reaction to other $\underline{N}$-alkyl derivatives were unsuccessful. More recently Angier and Curran (6,7) described the first chemical synthesis of orotidine, which was obtained, together with the $\underline{N}_{(3)}$-ribosyl isomer, from the condensation of the mercury derivative of n-butyl orotate with 2,3,5-tri-$\underline{O}$-benzoyl-ribofuranosyl chloride. This glycosylation result conflicted strongly with previous predictions (5) and results (4) concerning the alkylation of orotic acid. Although this reaction has yet to be applied to the simple alkyl derivatives it is subject to the orientational restrictions inherent in alkylation reactions.

*for 1,3-Thiazines part III see Tetrahedron Letters, 1966, 3225.
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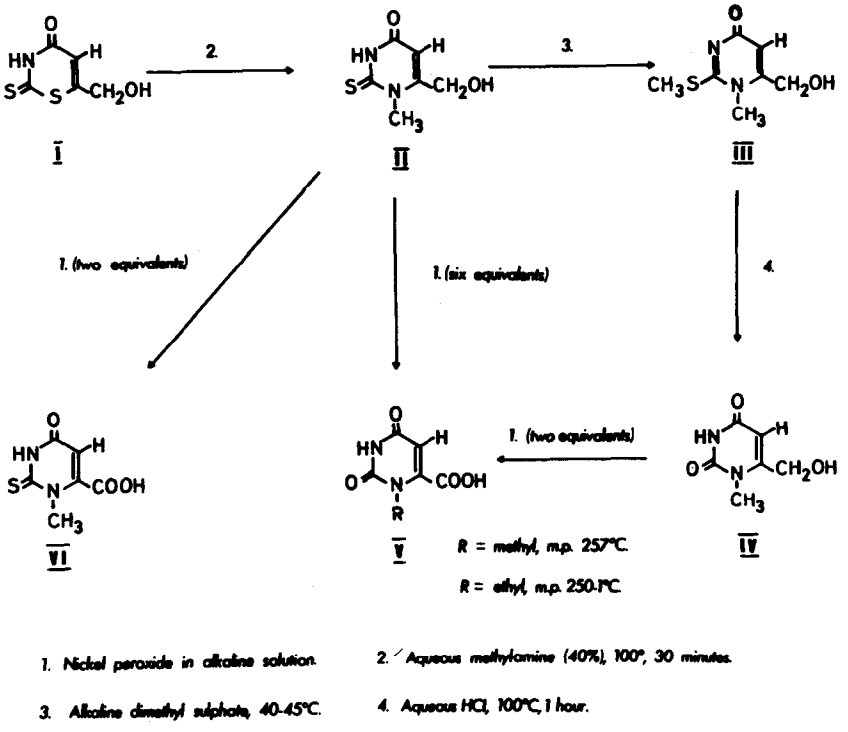
We have chosen to approach the synthesis of the N-alkyl orotic acids via our 1,3-thiazine → pyrimidine interconversion which proved so successful with the simple uracils (8). In this communication we wish to report the application of this method to the synthesis of $N_{(1)}$-alkyl orotic acids, $N_{(1)}$-alkyl-2-thio-orotic acid and to 1-hydroxy-orotic acid.

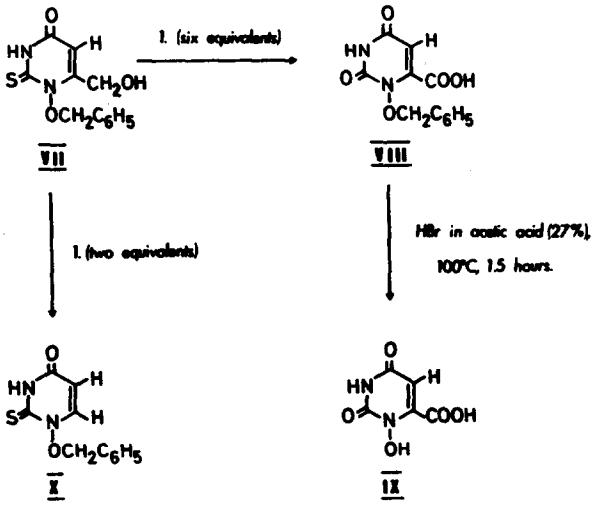
SCHEME I



The required 1,3-thiazine (I), m.p.203°C, was synthesised (8,9) by condensation between dithiocarbamic acid and ethyl γ-hydroxytetrolate. The reason for the choice of this particular 1,3-thiazine and the problems encountered in related condensations will be presented in detail in the full publication. This 1,3-thiazine (I) was converted to 6-hydroxymethyl-1-methyl-2-thiouracil (II), m.p.225°C, by treatment with aqueous methylamine;

other primary amines reacted similarly (10). Stepwise conversion to the orotic acid was achieved as outlined in scheme I (II → V). However, direct oxidation of the 2-thiouracil (II) with excess nickel peroxide (six equivalents) in a alkaline solution was more effective and formed 1-methyl-orotic acid (V) in 67% yield (17). The key step in this conversion was the use of nickel peroxide (11,12) in the oxidation of CH_2OH to COOH. This was achieved in high yield. In contrast with more conventional oxidising agents this reagent did not degrade the pyrimidine ring.

In the synthesis of the 2-thio-orotic acid advantage was taken of the oxidative selectivity of the nickel peroxide reagent. Thus when a limited amount of nickel peroxide (two equivalents) was used the 2-thione function was not oxidised and 1-methyl-2-thio-orotic acid (VI) was obtained from (II) in 71% yield m.p. 231°C, u.v. spectrum, pH=1 λ_{max} = 229 mμ (ε=24,000), 270 mμ (ε=17,000), 292 mμ inflection (ε=8,950); pH = 13 λ_{max} = 240 mμ (ε=15,000), 270 mμ (ε=17,300). This is the first reported example of a 1-substituted 2-thio-orotic acid.



Interest in N-hydroxy derivatives, a number of which have been recently reported (13,14,15) has prompted us to apply our procedure to the synthesis of 1-hydroxy-orotic acid. Reaction between the 1,3-thiazine (I) and O-benzylhydroxylamine gave the 2-thiouracil (VII) (16). Oxidation of (VII) with excess nickel peroxide formed (VIII), debenzylation of which (with hydrogen bromide in glacial acetic acid) afforded 1-hydroxy-orotic acid (IX), m.p. 260-1°C with effervescence, u.v. spectrum, pH=0 λ_{max} 280mμ (ε=4,600) and pH=14 λ_{max} 307mμ (ε=4,600). The compound gave an intense deep violet colour with ferric chloride ethanol.

A limited amount of the nickel peroxide reagent converted (VII) into 1-benzyloxy-2-thiourcil (X), with concomitant removal of the 6-substituent. We have established that CO_2 is generated during the reaction, but whether this arises by nickel peroxide oxidation of liberated formaldehyde or is formed directly by decarboxylation of the initially-formed 2-thio-orotic acid awaits further experimentation.

Initial attempts to adapt this method to the synthesis of orotidine were unsuccessful.

REFERENCES

1. J.M.Buchanan and S.C.Hartmen, Advances in Enzymology,21,199 (1959).
2. P. Reichard, Advances in Enzymology,21, 263 (1959).
3. G.D. Daves, F.Baiocchi, R.K. Robins and C.C.Cheng, J.Org.Chem., 26, 2755 (1961), and references therein.
4. R.K. Ralph, G.Shaw and R.N.Naylor, J.Chem.Soc., 1169 (1959).
5. J.J. Fox, N.Yung and I.Wempen, Biochim.biophys.Acta, 23, 295 (1957).
6. W.V. Curran and R.B.Angier, Tetrahedron Letters, 533 (1963).
7. W.V. Curran and R.B.Angier, J.Org.Chem., 31, 201 (1966).
8. R.N. Warrener and E.N.Cain, Chem. & Ind.(Rev.,) 1989 (1964. This reaction has now been extended to include products derived from aromatic amines. R.N.Warrener, E.N.Cain and J.F.B.Mercer, unpublished results.

9. J.L. Garraway, J.Chem.Soc., 4077 (1962).

10. R.N. Warrener and E.N. Cain, unpublished results.

11. K. Nakagawa, R. Konaka and T. Nakata, J.Org.Chem., 27, 1597 (1962).

12. W.F. Pickering, Rev.pure Appl.Chem., 16, 185 (1966)

13. W. Kloetzer, Monatsch.Chem., 95, 1729 (1964).

14. W. Kloetzer, Monatsch.Chem., 96, 169 (1965).

15. R.N. Warrener and E.N. Cain, Angew.Chem.,Int.Ed., 5, 511 (1966).

16. This and related compounds readily eliminate benzaldehyde or the related carbonyl compound on thermolysis or under electron impact. R.F.C. Brown, E.N. Cain, G.V. Meehan and R.N. Warrener, unpublished results.

17. Satisfactory elemental analyses were obtained for all new compounds. Spectral measurements were in accord with the assigned structures.