Specific Action of Methoxide Ion on Thio-derivatives of Dihydropyrimidines

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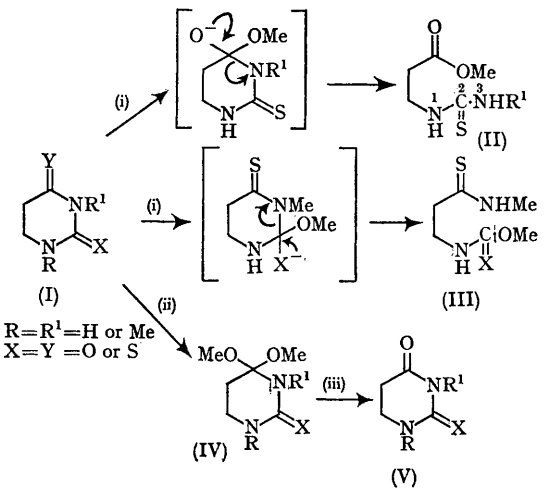
HERE we report some new transformations of thio-analogues of 5,6-dihydrouracil and its methyl derivatives (I).[1] An increased interest in these compounds is being shown since the discovery of 5,6-dihydro-[2] and 4-thio-uridylic acid[3] in soluble ribonucleic acids.

The sulphur-substituted dihydropyrimidines[4] of possible importance as antitumour agents and bacterial growth antagonists show interesting behaviour towards nucleophiles. These reactions depend on the position of the functional groups in 5,6-dihydro-thiouracil and its methyl derivatives (I). These reactions are conveniently studied in methanol solutions, containing the methoxide ion.

Thus, ring opening takes place at the 3,4-position on attack by the methoxide ion at carbonyl C(4) of 5,6-dihydro-2-thiouracil† (I; R, R^1= H, X = S, Y = O) and its 3-methyl derivative (I; R = H, R^1= Me, X = S, Y = O).



Reagents: (i) $Na^+{}^-OMe$, MeOH; (ii) $Na^+{}^-OMe(-H_2S)$, MeOH; (iii) H^+, MeOH.

In the course of this reaction *N*-methoxycarbonylethylthiourea (II; R^1= H), m.p. 95—96°, and its 3-methyl derivative (II; R^1= Me), b.p. 145°/10^{-2} mm., are formed in 70—75% yield. It should be emphasized that such reaction does not take place with 5,6-dihydro-1-methyl-2-thiouracil (I; R = Me, R^1= H, X = S, Y = O).

In contrast to the former cleavage the ring rupture of 4-thio-analogues, with a methyl group in position 3, takes place at the 2,3-bond. Thus, 5,6-dihydro-3-methyl-4-thiouracil (I; R = H, R^1 = Me, X = O, Y = S) and 5,6-dihydro-3-methyl-2,4-dithiouracil (I; R = H; R^1= Me, X = Y = S) yield *N*-(methylthiocarbamoylethyl)carbamate (III; X = O) m.p. 62—63°, in 31% yield, and oily *N*-(methylthiocarbamoylethyl)thiocarbamate (III; X = S) in 58% yield.

It seems that the presence of the methyl group at the position 3 is a prerequisite for the ring opening in the 4-thio-compounds. All the other 4-thioanalogues of 5,6-dihydrouracil examined, unsubstituted at position 3, preserve their cyclic structures under the conditions described. For instance, reactions of 5,6-dihydro-4-thiouracil (I; R = R^1= H, X = O, Y = S), 5,6-dihydro-2,4-dithiouracil (I; R = R^1= H, X = Y = S) and its 1-methyl derivative (I; R = Me, R^1= H, X = Y = S) result in the corresponding 5,6-dihydro-4,4-dimethoxypyrimidine (IV; R = R^1= H, X = O), m.p. 145° in 66% yield, 5,6-dihydro-4,4-dimethoxy-2-thiopyrimidine (IV; R = R^1= H, X = S), m.p. 148—149° in 63% yield, and its methyl derivative (IV; R = Me, R^1 = H, X = S), m.p. 132—134° in 44% yield.

4,4-Dimethoxypyrimidines (IV) are easily hydrolysed by mineral acid into the corresponding 4-oxo-compounds (V),[4] thus providing a very simple route for the replacement of sulphur by oxygen at position 4 in these compounds.

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† The substituted hydropyrimidines are named without regard to *keto–enol* tautomerism.

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