A SINGLE STEP BIOMIMETIC SYNTHESIS OF BICYCLIC OXAZOLO-, IMIDAZOLO AND THIAZOLOPYRIMIDINES

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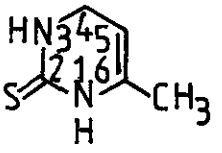
Abstract - 4-Isothiocyanatobutan-2-one with ethanolamine, ethylene diamine and 2-mercaptoethylamine give title systems through intramolecular nucleophilic addition on enamine double bond of pyrimidine derivative first formed.

Since for providing a rational to the catalytic role of thymidylate synthetase in the C_5 electrophilic substitution of uracil derivatives, an initial reaction of nucleophile (enzyme)[1] at the enamine alpha-carbon (C_6)[2] has been proposed, a variety of reactions of nucleophiles with biological pyrimidines and related compounds have been investigated.[3] In uracil derivatives most of the inter- and intramolecular additions of nucleophiles are reversible[1,5] which character is due to the stability and ease of formation of enolate anion (3) from the adduct. Methanol undergoes base-catalysed addition on 6-methyl-2-thio-4-deoxyuracil (1), a cyclic enamine, to form a stable adduct, 6-methyl-6-methoxy-2-thio-4-deoxy-5,6-dihydrouracil (2)[4]. Since anions from adduct like 2, are not stabilised, the chances of reversible elimination of nucleophile are less. Using this postulate, title systems have been synthesised through intramolecular cycloaddition of nucleophiles at enamine carbon-carbon double bond.

4-Isothiocyanatobutan-2-one (4) with excess of 2-aminoethanol in ethanol solution (pH 8.5-9.5) gave a product, mp 140°C (60%), M^+ m/e 172, which could be 1-beta-hydroxyethyl-6-methyl-2-thio-4-deoxyuracil (5, X = O) or hexahydro-8a-methyl-5H-oxazolo [3,2-c] pyrimidine-5-thione (6, X = O). Its ^{1}H nmr ($CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.65 - 2.37 (m, 2H, CH_2), 3.12 - 3.40 (m, 2H), 3.82 - 4.38 (m, 4H), 7.02 - 7.45 (b, NH, exchangeable with D_2O); in comparison with that of 2, exhibits an upfield shift of C_6-CH_3 (δ 1.77) and the absence of CH=(δ 4.6) and favours structure 6 (X=O). The ^{13}C nmr ($CDCl_3$): δ 23.4 (q, CH_3), 31.2 (t, CH_2), 38.4 (t, CH_2), 48.0 (t, CH_2),

62.4 (t,CH_2), 90.0 (s, $\rangle C\langle$) and 175.2 (s, $\rangle C{=}S$) shows only one sp^2 carbon as against three sp^2 carbons expected for 5 and the absence of signal for $=C_5H$ of 5. In the mass spectrum, the fragmentation of parent ion (m/e 172), which constitutes the base peak, starts with the loss of CH_3 (m/e 157) and prominent loss of acetyl radical from the parent ion to form fragment ion m/e 129 is significant as it could arise only from 6 (X=O) and not from 5 (X=O). As the reaction progresses, an absorption band at 275 nm (5) appears (15 min). Its intensity increases till (30 min) a band at 245 nm (6) appears. The intensity of the latter increases at the cost of former band which disappears after 6h. Thus as envisaged, 5 formed initially undergoes intramolecular addition of OH at enamine double bond to form 6 (X=O) which is stable towards alkali and dil. acids.



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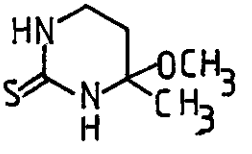

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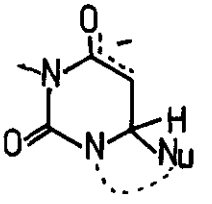

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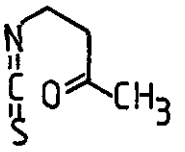

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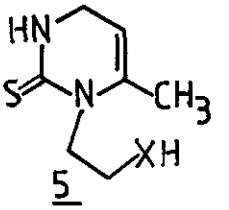

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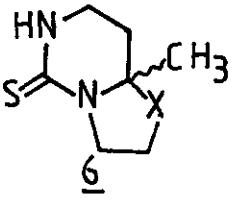

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For investigating the intramolecular cycloaddition of nitrogen nucleophile, the reaction of 4 with ethylene diamine has been found to give hexahydro-8a-methyl-imidazo [1,2-c] pyrimidine-5(1H)-thione (6, X=NH), mp 184°C (20%)[6]. Mass : m/e 171, 156 (M^+-CH_3) and 129 ($M^+-CH_3-C{=}NH$). ^1H nmr (DMSO) : δ 1.2 (s,3H,CH_3), 2.66 - 3.48 (m,8H,4xCH_2), 7.65 - 7.92 (b,2H,exchangeable with D_2O). ^{13}C nmr (DMSO) : δ27.2 (q,CH_3), 30.4 (t,CH_2), 37.6 (t,CH_2), 41.7 (t,CH_2), 50.2 (t,CH_2), 75.4 (s,$\rangle C\langle$) and 173.3 (s, $\rangle C{=}S$).

Since nucleophilic intramolecular addition of thiols would be a more relevant case in relation to the catalytic role of thymidylate synthetase, the reaction of 2-mercaptoethylamine with 4 has been investigated and hexahydro-8a-methyl-5H-thiazolo [3,2-c] pyrimidine-5-thione (6, X=S)[6], mp 166-167°C (25%) is formed[6].

Mass : m/e 188 (M^+), 173 (M^+-CH_3), 129 ($M^+-CH_3-C=S$). ^1H nmr ($CDCl_3$) : δ 1.65 (s,3H,CH_3), 2.05 - 2.30 (m,2H,CH_2), 2.97 - 3.52 (m,4H,N-CH_2-CH_2-S), 3.87 - 4.30 (m,1H), 4.55 - 4.97 (m,1H) (NH-$\underline{CH_2}$), 7.20 - 7.47 (b,1H,NH, exchangeable with D_2O). ^{13}C nmr ($CDCl_3$) : δ 26.8 (t,CH_2), 28.0 (q,CH_3), 32.6 (t,CH_2), 37.4 (t,CH_2), 54.1 (t,CH_2), 67.1 (s, $\geq C<$) and 174.1 (s, $\geq C=S$).

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6 6 (X=O, S, NH) show λ_{max} 235 (5.42×10^3), 235 (4.94×10^3) and 235 (5.10×10^3) respectively as against λ_{max} 255 (55.2×10^3) for compounds like 5.

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