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SYNTHESIS OF HETEROCYCLES VIA ENAMINES - XIII[1]. STERIC CONTROL ON THE MODE OF REACTIONS OF β-ISOTHIOCYANATOKETONES WITH AMINO-ACIDS.

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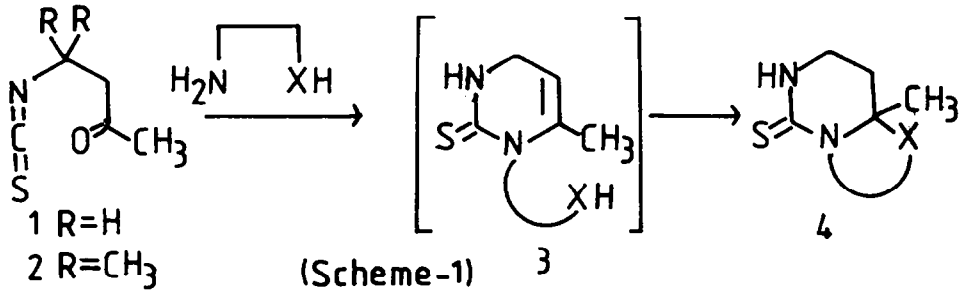
Abstract - Glycine and anthranilic acid with 4-isothiocyanato-butan-2-one (1) gives 3-(3-oxobutyl)-4-oxoimidazolidine-2-thione (11) and 3-(3-oxobutyl)-2-thioxoquinazolin-4-one (15) whereas with 4-isothiocyanato-4-methylpentan-2-one (2), having a gem-dimethyl group at the carbon bearing isothiocyanate group, tetrahydro-7,7,8a-trimethyl-5-thioxo-6H-oxazolo[3,2-c] pyrimidine-2(3H)-one (14) and 2,3,4,4a-tetrahydro-3,3,4a-trimethyl-1-thioxo-1H,6H-pyrimido[1,6a][3,1]-benzoxazin-6-one (17) are formed.

An intramolecular nucleophilic addition of -OH, SH, NH_2 on α-carbon (C-6) of the enamine moiety embedded in 1-β/γ-functionalized (OH, SH, NH_2) alkyl/o-substituted (OH,SH,NH_2) aryl-1,4-dihydropyrimidine-2(3H)-thiones (3), formed by the condensations of 4-isothiocyanatobutan-2-one (1), with correspondingly β/γ-functionalised or o-substituted alkylamines/anilines, provides a one pot biomimetic synthesis of a variety of polynuclear heterocyclic systems (4)[1,2] (Scheme 1). In the 1,4-dihydropyrimidine derivative (5) possessing SH and COOH at β and α positions respectively of the N-1 substituent, formed from 1 and cysteine, of the two necleophiles (SH and COOH), SH adds preferably at C-6 carbon to give hexahydro-3-carboxyl-8a-methyl-6H-thiazolo[3,2-c]pyrimidine-5-thione (6). The isomeric product, 7, expected from the addition of COOH in 5 has not been detected[1]. However, inter[3] as well as intramolecular[2] additions of oxygen nucleophiles (OH) at C-6 carbon of such 1,4-dihydropyrimidine derivatives have been reported. In order to investigate whether OH of carboxylic acid undergoes a similar nucleophilic addition in intermediates, 3(XH = COOH), reactions of amino-acids viz. glycine and anthranilic acid with β-isothiocyanatoketones (1,2) have been performed.

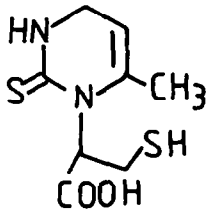


1 R=H
2 R=CH_3

(Scheme-1)

3

4



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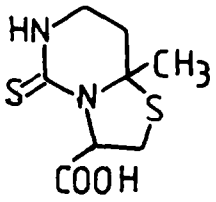

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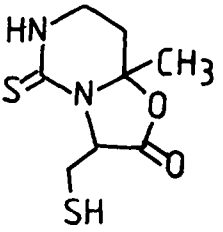
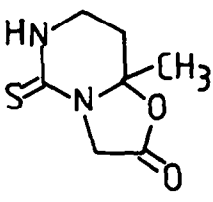


(7)

Glycine and 4-isothiocyanatobutan-2-one (1) form a product which in its mass spectrum shows the parent ion at m/z 186 and ions at m/e 43 ($CH_3\overset{+}{C}O$) and m/e 143(M^+-CH_3CO) expected for the structure, tetrahydro-8a-methyl-5-thioxo-6H-oxazolo[3,2-c]pyrimidine-2(3H)-one (8). But (i) the presence of two carbonyl absorption bands (1730, 1710 cm^{-1}) in the i.r. spectrum, (ii) the absence of a signal at δ80-100 expected for C-8a in 8 in ^{13}C nmr spectrum[2], (iii) the appearance of two well-defined 2H triplets as against multiplets for $-CH_2-CH_2-$ in ^1H nmr spectra of analogs of 8, do not confirm to the structure 8 for this product. Since i.r., ^1H and ^{13}C nmr data could be explained equally well by isomeric structures, 1-acetoxy-2-thio-5,6-dihydrouracil (9), 3-acetonyl-2-thio-5,6-dihydrouracil (10) and 3-(3-oxobutyl)-4-oxoimidazolidine-2-thione (11) for this product, a single crystal X-ray analysis[5] was undertaken and structure 11 was assigned to this product. Thus glycine and 1 have not reacted in the manner depicted in scheme 1. But glycine and 4-isothiocyanato-4-methylpentan-2-one (2) are reported[4] to form 14 through a similar sequence of reactions. In view of this anomaly the reaction of 2 with glycine has been repeated and the product has been found to have structure 14 from its spectral data.



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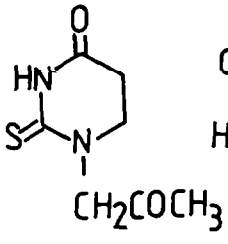

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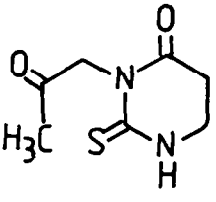

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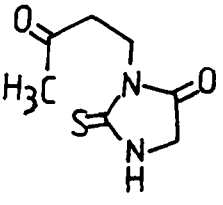
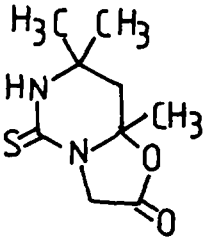


(11)

a R=H



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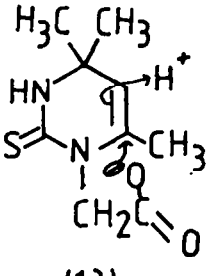
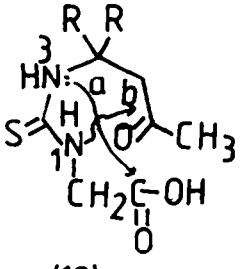


(13)

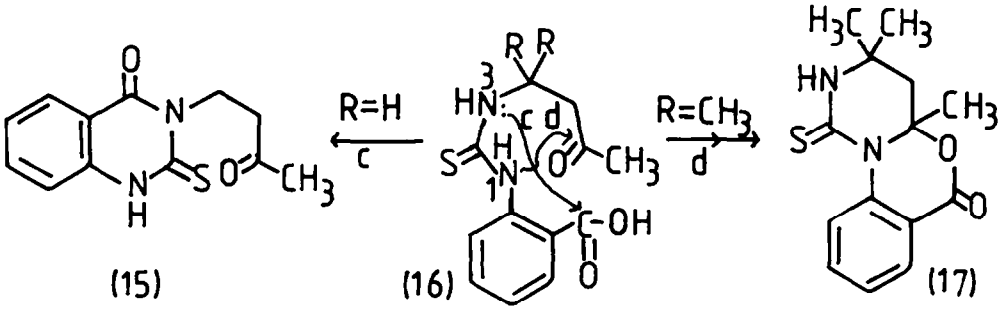
R=CH_3 b



(12)

The formation of products of different categories i.e. 11 and 14, in the reactions of glycine with β-isothiocyanatoketones 1 and 2 be rationalised through different modes of cyclodehydration in the initially formed thiourea adducts (12). In the case of 12 (R = H), cyclisation between N-3 and COOH group (mode a) to form five membered ring (11) is preferred[6] over that of the interaction of N-1 and C-O to form the six-membered ring via mode b. But in the case of 12 (R = CH_3), the interaction of N-1 and $COCH_3$ (mode b) is preferred because of the steric hindrance of gem-dimethyl group at carbon adjacent to N-3 for its reaction with COOH (mode a) and 13 is formed. Subsequently, 13 undergoes intramolecular nucleophilic addition to give 14.

4-Isothiocyanatobutan-2-one (1) with anthranilic acid gives 3-(3-oxobutyl)-2-thioxoquinzolin-4-one (15), which undergoes an acid as well as base catalysed β-elimination to form 2-thio-4-quinazolone. Again, 4-isothiocyanato-4-methylpentan-2-one (2) with anthranilic acid has been reported to give 2,3,4,4a-tetrahydro-3,3,4a-trimethyl-1-thioxo-1H,6H-pyrimido[1,6-a][3,1]benzoxazi n-6-one (17)[7]. The difference in the behaviours of 1 and 2 in their condensations with anthranilic acid can also be rationalised through steric control of the cyclodehydration reaction of the initially formed thiourea derivative (16, R = H, CH_3). But, in the thiourea adduct (16, R = H) formed from 1 and anthranilic acid, of the two possibilities of cyclodehydration (modes c and d) giving six-membered rings, mode c is preferred because N-3 is more reactive than arylamino N-1.



Thus, the mode of reactions of β-isothiocyanatoketones and amino-acids depends upon a combination of factors such as substitution pattern of β-isothiocyanatoketone (steric hindrance), basicity of N-1 and N-3 of thiourea adduct and ring size of the product.

EXPERIMENTAL

M.P.s were determined in capillaries and are uncorrected. I.R. and ^1H nmr spectra were recorded with PYE UNICAM SP3-300 and Perkin Elmer R-32, 90MHz instruments respectively. ^{13}C nmr spectra were recorded on JNM-FX 90Q FT NMR spectrometer. Elemental analysis were performed at RSIC, Punjab University, Chandigarh, India. For tlc, plates were coated with silica gel G, spots were developed with iodine.

3-(3-Oxobutyl)-4-oxoimidazolidine-2-thione (11)

A solution of 4-isothiocyanatobutan-2-one (1) (1.29 g, 0.01 mol) and glycine (0.79 g, 0.01 mol) in ethanol was refluxed on a water-bath. After completion of the reaction (t.l.c., 6-7 hours), the solvent was distilled off and the residue was purified by column chromatography on silica gel by using benzene and benzene-ethyl acetate mixture as eluents to isolate 11, m.p. 114°C (from EtOH) (940 m.g., 50%), MS m/z: 186 (M^+). IR, ν_{max}($CHCl_3$): 1730 (C=O), 1710 (C=O) cm^{-1}, ^1H nmr($CDCl_3$): δ2.20 (3H, s, CH_3), 2.88 (2H, t, CH_2), 4.00 (2H, t, CH_2),

4.10 (2H, s, N-CH_2), 8.05 (1H, b, NH, exchangeable with D_2O). ^{13}C-NMR[8] ($CDCl_3$): δ30.0 (q, CH_3), 36.0 (t,CH_2), 41.0 (t,CH_2), 48.0 (t,CH_2), 171.60 (s,C-S), 185.0 (s, C-O), [Found: C, 45.04; H, 5.21; N, 14.86. $C_7H_{10}N_2O_2S$ requires C, 45.16; H, 5.37; N, 15.05%].

Tetrahydro-7,7,8a-trimethyl-5-thioxo-6H-oxazolo[3,2-c]pyrimidin-2(3H)-one(14):
A solution of 4-isothiocyanato-4-methylpentan-2-one (2) (1.57 g, 0.01 mol) and glycine (0.79 g, 0.01 mol) in ethanol was reluxed on a waterbath. The reaction mixture was cooled to yield white solid product 14, m.p. 185°C (Lit.,[4] m.p. 189-192°C). ^{1}H nmr[$(CD_3)_2SO$]: δ1.39 (9H, s, $3CH_3$), 1.60-2.00 (2H, m, CH_2), 4.25-5.23 (AB quartet, J_{AB} = 18 Hz, 2H, N-CH_2) and 8.95-9.15 (1H, b, NH). ^{13}C-nmr[$(CD_3)_2SO$]: δ29.20 (q, CH_3), 32.00 (q, CH_3), 38.81 (q, CH_3), 41.66 (t, CH_2), 42.18 (t, CH_2), 50.83 (s, >C-N), 94.28 (s, >C-N), 170.04 (s, C-S), 175.03 (s, C-O).

3-(3-Oxobutyl)-2-thioxoquinazolin-4-one (15):
A solution of 1 (1.29 g, 0.01 mol) and anthranilic acid (1.37 g, 0.01 mol) in ethanol was refluxed on a water bath for 6-7 hours. The reaction mixture was cooled and product separated was collected to yield 15 (1.70 g, 70%). On concentrating the mother liquor, another crop (250 m.g.) of 15 was separated. m.p. 204-205°C (from EtOH), yield (1.90 g, 78%). MS m/z 248 (M^+), 205 (248-CH_3CO). ^{1}H-nmr[$(CD_3)_2SO$]: δ2.18 (3H, s, CH_3), 2.90 (2H, t, CH_2), 3.30 (1H, s, NH, exchangeable with D_2O), 3.90 (2H, t, CH_2), 7.15-8.05 (4H, m, ArH). ^{13}C-nmr[$(CD_3)_2$]SO]: δ29.49 (q, CH_3), 39.92 (t, CH_2), 40.98 (t, CH_2), 115.26, 115.30 (s, ArC), 123.97, 126.85, 134.89, 138.74 (d, ArCH), 158.86, 174.7 (s, C-O, C-S), IR, ν_{max}(KBr): 1690(C-O) cm^{-1} [Found: C, 58.25; H, 4.63; N, 11.66. $C_{12}H_{12}N_2O_2S$ requires C, 58.06; H, 4.84; N, 11.29%].

Conversion of 15 to 2-thio-4-quinzolone
A solution of 15 (500 mg, 0.002 mol) in ethanol containing HCl (or NaOH in another experiment) was reluxed on a water-bath. After completion of the reaction (3-4 hours), ethanol was evaporated and reaction mixture was neutralised. The compound separated was filtered to yield 2-thio-4-quinazolone, m.p. 306°C. (Lit.[9], m.p. 315-316°C).

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