Pergamon

Tetrahedron 54 (1998) 7563–7572

TETRAHEDRON

Acid Catalysed Reactions of 5-Formyluracils with Enamines. A Facile Synthesis of 5-Acylvinyluracils.

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Received 2 March 1998; revised 21 April 1998; accepted 23 April 1998

Abstract: 5-Formyl-1,3-dimethyluracil (**1**) reacts with secondary amine derived enamines of ketones and aldehydes to provide 5-(acyvinyl)uracil derivatives. The presence of a CH_3 group at C-6 of **1** induces a competitive annulation reaction. Depending on the bulk of substituents 5-(acylvinyl)-uracils acquire cis -diene and E or Z configurations on the vinyl unit. Enamines derived from 1,3-cyclohexanedione and ethyl acetoacetate react with **1** in 1: 2 stoichiometric manner to provide 5-(9-xanthenyl)uracil and 5-(6-cycohexadienyl)uracil (X-ray) derivatives.

Introduction

In antitumor and anti HSV-1 agents 5-fluorouridine and 5-bromovinyluridine, the presence of highly electronegative F and Br creates the electron deficiencies which facilitate the attack of a thiol group at C-6 or vinyl carbon to form a stable enzyme - uracil complex and this phenomenon affects the enzyme function.[1-3] The presence of stronger electron withdrawing groups at C-5 β-vinyl carbon (fig. 1, **B**), due to enhanced Michael acceptor character, would influence the mode of enzyme attack and consequently, there has been immense interest in the development of synthetic approaches for such 5-(alkenyl)uracils.[4-9]

Recently, we have reported that 5-formyl-1,3-dimethyluracil(1), under acidic conditions, undergoes annulation reactions with enamines possessing NH_2 group (fig.1, R=H).[10,11] We envisaged that similar reactions of enamines possessing tertiary nitrogen (RR=-$(CH_2)_n$-) would get interrupted at the intermediate (**A**) stage and hydrolytic work up would provide 6-acylvinyluracil derivatives (**C**). It has been found that the reactions of secondary amine derived enamines of ketones and aldehydes with **1** provide the respective

0040-4020/98/$19.00
PII: S0040-4020(98)00390-1

5-(acylvinyl)uracils but enaminone / ester derived from 1,3-cyclohexanedione / ethyl acetoacetate provides 2:1 stoichiometric 5-(9-xanthenyl) / 5-(6-cyclohexadienyl)uracils.

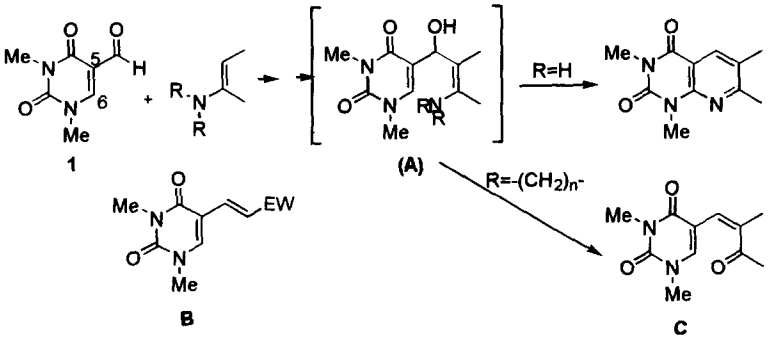

Fig: 1

Synthesis:

5-Formyl-1,3-dimethyluracil **(1)** on reaction with 1-morpholinocyclohexene **(2a)** in CH_3CN-TFA (100:1) gave a product (50%), m.p. 92 °C, M^+(m/z) 248. In its ^{1}Hnmr the presence of one double triplet (J_1 =4.4Hz, J_2 =1.6Hz) at δ 2.65 due to 2H (-CH_2-) and one triplet (J = 1.6 Hz) at δ 7.30 (1H) points towards the olefinic unit possessing H and CH_2 substituents *trans* to each other along with two quartenary carbons (fig. 2, B). Its ^{13}C nmr spectrum shows the absence of a formyl carbon signal and the presence of an olefinic CH at δ 126.54, a quaternary carbon at δ 162.36 along with the remaining uracil and cyclohexanone carbon signals, and

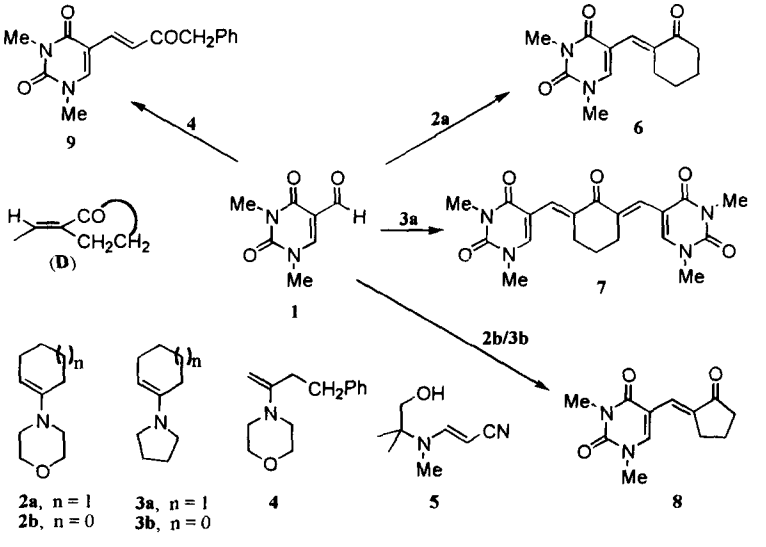

Fig: 2

support the presence of olefinic unit (**D**). All these data and the elemental analysis corroborate the structure **6** for this compound. The reaction of **1** with more reactive 1-pyrrolidinocyclohexene (**3a**) provides **6** (25%) along with a yellow coloured product (22%), m.p. 262°C, M^+(m/z) 398. The latter in its ^{1}Hnmr spectrum shows a quintet (δ 1.81, 2H), a triplet (δ 2.69, 4H) and two downfield 2H singlets at δ 7.32 and 7.57 due to olefinic H alongwith two 2 x N-Me signals. These spectral data show that this compound is a 2:1 condensation product of **1** with enamine **3a** and has been assigned the structure **7**. Evidently, the more reactive enamine derived from an analog of intermediate A (fig. 1) reacts with another molecule of **1** to form **7**.

The reaction of **1** with 1-morpholinocyclopentene (**2b**) or 1-pyrrolidinocyclopentene (**3b**) affords only 5-vinyluracil derivative **8** (65% and 55%), m.p. 166°C, M^+ m/z 234. Similarly, **1** with enamine **4** provides 5-vinyluracil **9** (65%), m.p. 155°C, M^+ m/z 284.

5-Formyl-1,3,6-trimethyluracil (**10**) on reaction with 1-morpholinocyclohexene (**2a**) in CH_3CN-TFA solution gives a product (50%), m.p. 160-162°C, M^+(m/z) 244. In its ^{1}Hnmr spectrum the absence of 6-Me singlet and the presence of two 1H singlets at δ 6.61 and 7.66 along with two multiplets (δ 1.75-1.85, 4H; 2.81-2.89,4H) and N-Me singlets (δ 3.45, 3.53) show that 6-CH_3 unit of uracil has reacted with carbonyl unit to constitute an additional CH unit. These data corroborate the structure **12** (fig. 3) for this compound. The presence of six quaternay carbons, two CH, four CH_2 and two CH_3 carbons in its ^{13}Cnmr further support this assignment. Evidently, in these reactions, the initial attack of enamine at CHO carbon is followed by

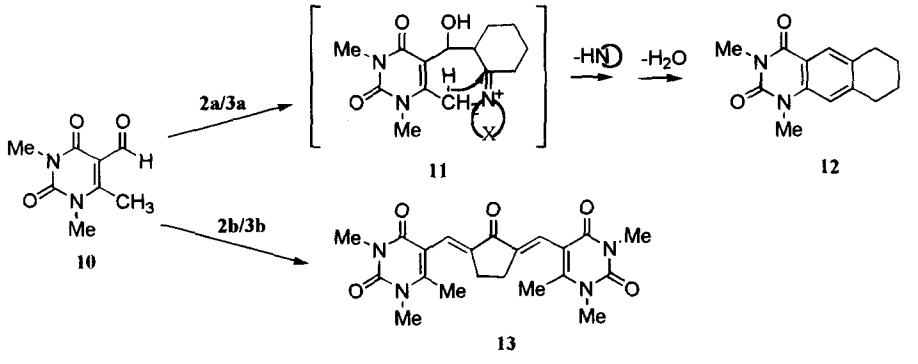

Fig: 3

condensation of C6-CH_3 with the iminium / carbonyl carbon of cyclohexanone unit. 5-Formyl-1,3,6-trimethyluracil (**10**) on reaction with 1-morpholinocyclopentene (**2b**) and 1-pyrrolidinocyclopentene (**3b**) gives only **13** (fig. 3), m.p. 235-240°C in 30% and 50% yields, respectively. In the latter reactions the corresponding 5-vinyluracil derivative is not isolated. Here, due to the difficulty in formation of relatively strained 5,6 membered ring fused system, the formation of the annulation product is also inhibited.

5-(Substitutedvinyl)uracils, due to extended conjugation with C5-C6 double bond, can exist as *trans* and *cis* diene geometrical isomers and each of these isomers depending on substituents on vinyl unit can exist as (*E*)- or (*Z*)- isomers around the vinyl bond (fig. 4) constituting four geometrical isomers.

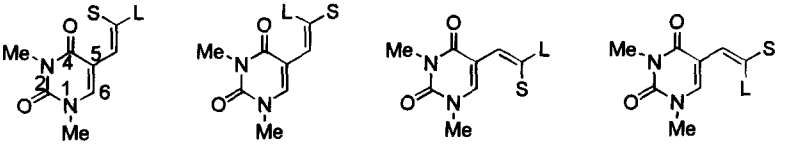

Fig: 4

In the NOESY spectrum of compound **6**, the U-6 olefin H shows two cross peaks at δ 3.5 and 2.5 corresponding to N-Me and CH_2 (dt) of cyclohexane unit but there is no cross peak between NMe and CH_2 protons. These data point to the *cis-(E)* configuration for compound **6**. Similarly, the NOESY spectrum of **8** shows the interaction of U_6-H with CH_2(dt) and NMe signals and should also have *cis-(E)* structure.

The force field energy minimizations[12] on different geometrical isomers of 5-vinyluracils **6** and **8** show that *trans*-diene derivatives have higher energy and on minimization process are converted to *cis*-diene isomers. During energy minimization, compound **6** shows that *cis-(E)* and *cis-(Z)* configurations do not undergo isomerisation and the two isomers have small difference in their energies (27 KJ/ mol). Similarly, energy minimization on compound **8** shows that it can exist in two *cis- (E)* (-137.84 KJ/mole) and *cis-(Z)* (-101.09 KJ/mole) configurations. In both these cases *cis-(E)* configurations are more stable than *cis-(Z)*. The energy minimizations on compound **9** lead to only *cis-(E)* isomer and unlike **6** and **8**, *cis-(Z)* isomer is not stabilised. Thus, in case of 5-vinyluracils **6**, **8** and **9**, the *cis-(E)* isomers are the most stable ones.

The reaction of **1** with ethyl 3-morpholinobuten-2-oate (**14**) provides a yellow compound (25%), mp. 165-68°C, M^+ m/z 461. Its ^1H nmr spectrum shows the presence of one uracil (NMe - δ 3.32, 3.37, 6-H - 6.64), two ethoxy (δ 1.20, 1.24 (t), 4.04, 4.18 (q), one morpholine (NCH_2 - 3.00-3.18(m); OCH_2 -3.65 - 3.71(m)) and one methyl (2.34) unit. Its proton decoupled off resonance ^{13}C nmr spectrum shows five quartets, four triplets, four doublets and eight singlets. These data show this compound to be a 1:2 stoichiometric condensation product of **1** and **14** and in the process one morpholine unit is lost and one CH_3 of enaminone is converted to CH. Also, 6-H of uracil, which in X-ray structure (fig. 6) faces the π cloud of cyclohexadiene, is shifted upfield (δ 6.64) from its normal position (δ7.0). The ^1H -^{13}C COSY spectrum (table - 1) shows the presence of two sp^2 CH [δ101.34 (4.89), 140.35 (6.64)] and two sp^3 CH [δ44.40(3.65), 35.36 (4.76)] units. These spectral data corroborate structures **15** and **16** for this compound, but the ^1H nmr does not show the coupling between 5'H and 6' H of the cyclohexadiene unit.

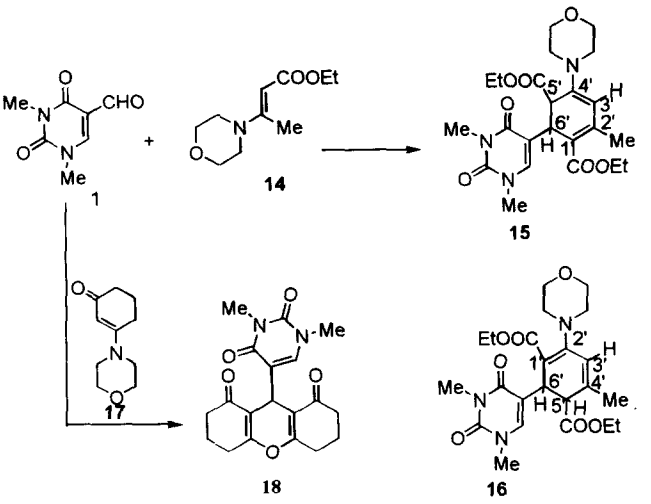

Fig. 5

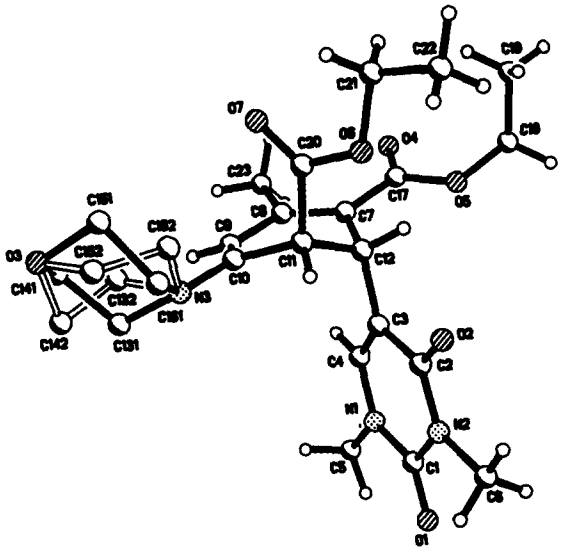

Fig. 6: SCHAKAL View of Compound 16. The hydrogens of morpholine unit have been eliminated for the sake of clarity.

The single crystal X-ray structure analysis confirms the structure **15** (fig. 6) for this compound. Table 2 lists the selected bond distances and angles of the molecule. The uracil ring is almost planar (r.m.s. deviation 0.02Å), the cyclohexadiene ring possesses half chair conformation and the morpholine ring shows disorder between two alternate chair conformations. The uracil ring is perpendicular to the cyclohexadiene ring (dihedral angle 88°) whereas the morpholine ring makes a dihedral angle of 51° with the cyclohexadiene ring. The uracil and ester units on the cyclohexadiene ring remain *trans* to each other and 6-H of uracil faces the π-cloud of diene unit being placed at 2.26Å.

However, **1** reacts with 1-morpholinocyclohex-2-enone (**17**) to give 1:2 stoichiometric product **18** (60%), m.p. 279°C, M^+ m/z 356. Here the α-CH_2 of the cyclic enamine cannot participate in cyclisation and two morpholine units are lost probably during work-up and subsequent cyclisation leads to **18**.

Table-1: ^1H -^{13}C correlations in **15** as determined from ^1H-^{13}C HETCOR NMR spectrum

Signal	OCH_2 $\underline{CH_3}$	CH_3	NCH_2	NMe	CH	CH_2	$O\underline{CH_2}$ CH_3	CH	CH	CH
^1H nmr	1.20, 1.24	2.34	3.00-3.18	3.32, 3.37	3.65-3.71	3.65-3.71	4.04, 4.18	4.76	4.89	6.64
^{13}C nmr	14.09, 14.36	21.78	46.37	27.86, 37.16	4.40	65.98	59.41, 61.24	35.36	101.34	140.35

Table 2. Selective Bond lengths and angles of compound 15.

Bond lengths Å		Bond angles	
N(1)-C(4)	1.361(6)	C(4)-N(1)-C(1)	122.2(4)
N(1)-C(1)	1.374(6)	C(1)-N(2)-C(2)	125.0(4)
N(2)-C(1)	1.383(6)	O(1)-C(1)-N(1)	122.5(4)
N(2)-C(2)	1.395(6)	O(1)-C(1)-N(2)	122.3(4)
N(3)-C(10)	1.394(8)	N(1)-C(1)-N(2)	115.1(4)
O(1)-C(1)	1.220(6)	O(2)-C(2)-N(2)	120.5(4)
O(2)-C(2)	1.226(6)	O(2)-C(2)-C(3)	123.5(4)
C(2)-C(3)	1.450(6)	N(2)-C(2)-C(3)	116.0(4)
C(3)-C(4)	1.337(6)	C(4)-C(3)-C(2)	117.9(4)
C(3)-C(12)	1.516(6)	C(4)-C(3)-C(12)	124.8(4)
C(7)-C(8)	1.374(7)	C(2)-C(3)-C(12)	117.3(4)
C(7)-C(12)	1.510(7)	C(3)-C(4)-N(1)	123.5(4)
C(8)-C(9)	1.425(8)	C(8)-C(7)-C(12)	117.1(6)
C(9)-C(10)	1.364(8)	C(17)-C(7)-C(12)	120.0(4)
C(10)-C(11)	1.514(7)	C(7)-C(8)-C(9)	120.5(5)
C(11)-C(12)	1.555(7)	C(7)-C(8)-C(23)	123.6(6)
		C(9)-C(8)-C(23)	115.9(5)
		C(10)-C(9)-C(8)	123.6(5)
		C(9)-C(10)-N(3)	125.4(5)
		C(9)-C(10)-C(11)	116.3(7)
		N(3)-C(10)-C(11)	118.3(5)
		C(10)-C(11)-C(20)	111.5(4)
		C(10)-C(11)-C(12)	111.4(4)
		C(20)-C(11)-C(12)	110.0(4)
		C(7)-C(12)-C(3)	113.3(4)
		C(7)-C(12)-C(11)	110.3(4)
		C(3)-C(12)-C(11)	111.3(4)

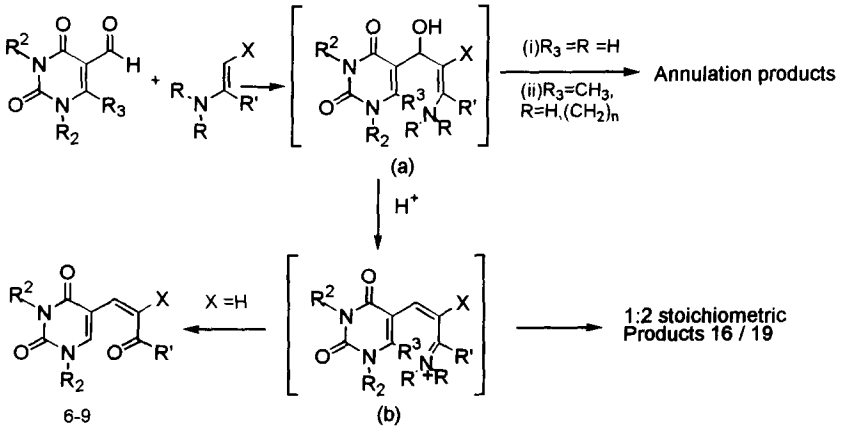

Fig: 7

From the modes of these reactions, it is evident that enamines initially add to the 5-formyl carbon of 5-formyl-1,3-dimethyluracil to form intermediate hydroxy-alkyl derivatives (a) (fig.7), which in the case of X, R_3, R=H and X=H, R_3 =CH_3, R=$(CH_2)_n$ undergo intramolecular cyclization. In the case of X, R_3=H, R =

$(CH_2)_n$, through acid catalysed dehydration to (b) followed by hydrolytic work up 5-(2'-acylvinyl)uracil derivatives are formed. However, when in (b), X = CO or COOEt, another enamine molecule adds and subsequent reactions lead to alternate cyclisation products.

Experimental:

Melting points were determined in capillaries and are uncorrected. ^{1}Hnmr and ^{13}Cnmr spectra were recorded on Bruker 200 MHz instrument in $CDCl_3$, using TMS as internal standard. Infrared and mass spectra were recorded on Pye Unicam SP-300 and Shimadzu GC-MS QP2000 (at 70eV) instruments respectively. Reagent grade CH_3CN was freshly distilled over P_2O_5. Thin layer chromatography (TLC) was performed on precoated silica plates. Molecular modelling was performed using DTMM 2.0.

General procedure:

The enamines were prepared by refluxing morpholine or pyrrolidine (1eq.) with respective ketones (1eq.) in benzene by azeotropic removal of water using Dean and Stark's apparatus. After complete removal of water, benzene was distilled off under vacuum. To the enamine residue taken in acetonitrile -TFA mixture (100:1) (20ml) was added 1,3-dimethyl-5-formyluracil derivatives (1eq) and the reaction mixture was refluxed for 5-6h. Acetonitrile was distilled off and the residue was column chromatographed on silica gel using hexane-ethyl acetate mixtures as eluents. The data for the compounds thus obtained are given below:

Compound 6: (50%), m.p. 92^{0}C (EtOH), M^+(m/z) 248, ^{1}H nmr ($CDCl_3$): δ 1.72-1.83 (m, 2H, CH_2), 1.87-1.95 (m, 2H, CH_2), 2.50 (t, J=4Hz, 2H, CH_2), 2.65 (dt, J_2 = 1.6Hz, J_1 = 4.4Hz, 2H= -CH_2), 3.37 (s, 3H, NCH_3), 3.48 (s, 3H, NCH_3), 7.30 (t, J=1.6Hz, C=CH), 7.32 (s,1H,6-H); ^{13}Cnmr ($CDCl_3$) : δ 23.50 (t, CH_2), 23.83 (t, CH_2), 28.24 (q, NCH_3), 29.63 (t, CH_2),37.54 (q, NCH_3), 40.28 (t, CH_2), 109.56 (s, C-5), 126.54 (d, C-5-CH), 136.98 (s, qc), 142.65 (d, C-6), 151.40 (s, C=O), 162.36 (s, qc), 182.80 (s, C=O); IR(KBr)ν_{max}:1698 (C=O), 1680 (C=O), 1658 (C=O) cm^{-1}; λmax (CH_3CN): 318 (ε 1.57x10^4) (Found C 62.5, H 6.6%. $C_{13}H_{16}N_2O_3$ requires C 62.90, H 6.45%).

Compound 7 : (22%), m.p.262^{0}C (EtOH), M^+(m/z) 398, ^{1}Hnmr ($CDCl_3$): δ 1.81 (quintet, J=6Hz, 2H, CH_2), 2.69 (t, J=4Hz, 4H, 2xCH_2), 3.39 (s, 6H, 2xNCH_3), 3.48 (s, 6H, 2xNCH_3), 7.32 (s, 2H, 2xC=CH), 7.57(s, 2H, 2xU_6-H); ^{13}Cnmr($CDCl_3$): δ 22.61 (t, CH_2), 28.69 (q, CH_3), 29.44 (t, CH_2),109. 06 (qc, s), 127.91 (d, CH), 135.43 (qc, s), 143.45 (d, CH),150.79 (C=O, s), 162.20 (C=O, s), 183.58 (C=O, s). IR(KBR) ν_{max}: 1700 (C=O), 1670 (C=O), 1660 (C=O) cm^{-1}. (Found C 60.6, H 5.7, N 13.8% C_{20} H_{22} N_4O_5 requires C 60.30, H 5.53, N 14.07%).

Compound 8: (30%, 65%), m.p.166^{0}C (EtOH), M^+(m/z) 234, ^{1}Hnmr ($CDCl_3$): δ 2.02 (quintet, J = 7.6Hz, 2H, CH_2), 2.3 (t, J=4Hz, 2H, CH_2) 2.76 (dt, J_1=7.6Hz, J_2=2.6Hz, 2H, CH_2), 3.39 (s, 3H, NCH_3), 3.49 (s, 3H, CH_3), 7.41 (t, J = 2.6 Hz, 1H, =CH), 7.45 (s, 1H, U_6-H)., ^{13}Cnmr ($CDCl_3$): δ 20.03 (t, CH_2), 28.24 (q, CH_3), 29.79 (t, CH_2), 37.53 (t, CH_2), 37.66 (q, CH_3),110.04 (s, 5-H), 123.21 (d, CH), 1.35.15 (s, C), 142.74 (d, CH), 150.87 (s, C =O), 162.05 (s, C=O), 206.40 (s, C=O). IR(KBr)ν_{max}:1714 (C=O, ketone), 696 (C=O),

1660 (C=O). λmax (CH_3CN) : 327 (ε 1.64x10^4). (Found C 61.6, H 6.0, N 12.0% $C_{12}H_{14}N_2O_3$ requires C 61.54, H 5.98, N 11.97%).

5-(2-Phenylacetylvinyl)-1,3-dimethyluracil (9): (65%), m.p.155^{0}C (EtOH), M^+(m/z) 284, ^{1}Hnmr ($CDCl_3$): δ 3.36 (s, 3H, NCH_3), 3.45 (s, 3H, NCH_3), 3.85 (s, 2H, CH_2), 7.19-7.36 (m, 7H, C=CH, ArH), 7.45 (s, 1H, U6-H).^{13}C nmr : δ 28.17 (q, NCH_3), 37.51 (q, NCH_3), 49.33 (t, CH_2), 108.31 (s, C-5), 125.30 (d, CH), 126.95 (d, CH), 128.72 (d, CH), 129.58 (d, CH), 134.46 (s), 135.09 (d, =CH), 145.86 (d, CH),150.66 (s, C=O), 161.43 (s, C=O), 197.75 (s, C=O). IR (KBr)ν_{max}: 1710 (C=O), 1665 (C=O) ,1650 (C=O) cm^{-1}. λmax: 317 (ε 2.38x10^4). (Found C 67.3, H 5.5, N 9.9%. $C_{16}H_{16}N_2O_3$ requires C 67.61, H 5.63, N 9.86%).

1,3-Dimethyl-6,7,8,9-tetrahydronaphtho[2,3-e]pyrimidine-2,4(1H,3H)dione (12): (50%), m.p. 160-162^{0}C (EtOH), M^+(m/z) 244, ^{1}Hnmr ($CDCl_3$): δ 1.75-1.85 (m, 4H, 2xCH_2), 2.81-2.89 (m, 4H, 2xCH_2), 3.45 (s, 3H, NCH_3), 3.53 (s, 3H, NCH_3), 6.61 (s, 1H, =CH), 7.66 (s, 1H, =CH); ^{13}Cnmr ($CDCl_3$): δ 22.72 (-ve, CH_2), 22.94 (-ve, CH_2), 26.33 (+ve, NCH_3), 30.33 (+ve, NCH_3), 113.24 (+ve, CH), 128.79 (+ve, CH), 132.35 (absent), 138.0 (absent), 145.32 (absent), 151.17 (absent), 161.83 (absent)171.82; IR (KBr) ν_{max} : 1650 (C=O), 1701 (C=O) cm^{-1}. (Found C 68.7, H 6.5, N 11.1%, $C_{14}H_{16}N_2O_2$ requires C 68.85, H 6.56, N 11.48%).

Compound 13: (30%), m.p.235-240^{0}C (EtOH), M^+(m/z) 412, ^{1}Hnmr ($CDCl_3$): δ 2.29 (s, 6H, 2xCH_3), 2.55 (s, 4H, 2xCH_2), 3.46 (s, 6H, 2xNH_3), 3.50 (s, 6H, 2xNCH_3), 7.26 (s, 2H, =CH), ^{13}Cnmr ($CDCl_3$)(Normal / DEPT-135): δ 17.95 (+ve, CH_3), 26.45 (-ve, CH_2), 26.93 (+ve, NCH_3), 32.42 (+ve, NCH_3), 126.00 (+ve, CH), 140.1 (absent), 142.47 (absent), 143.65 (absent), 150.62 (absent), 151.65 (absent), 160.05 (absent); IR (KBr) ν_{max} : 1650 (C=O), 1710 (C=O) cm^{-1}. (Found C 61.0, H 6.1, N 13.8%. $C_{21}H_{24}N_4O_5$ requires C 61.17, H 5.82, N 13.59%)

Compound 15: (25%), m.p. 165-68°C, M^+ m/z 461; ^{1}H nmr($CDCl_3$): δ 1.20 (t, J 7Hz, 3H, CH_3), 1.24(t, J 7Hz, 3H, CH_3), 2.34(s, 3H, CH_3), 3.00-3.18(m, 4H, z 2 x NCH_2), 3.32(s, 3H, NCH_3), 3.37(s, 3H, CH_3), 3.65-3.71(m, 5H, 1H+ 2 x OCH_2), 4.04 (q, J 7Hz, 2H, OCH_2), 4.18 (q, J 7Hz, 2H, OCH_2), 4.76(s, 1H, CH), 4.89(s, 1H, CH), 6.64(s, 1H, CH); ^{13}C nmr (normal / proton decoupled off resonance): δ 14.09(+ve, CH_3), 14.36(q, CH_3), 21.78(q, CH_3), 27.86(q, CH_3), 35.36(d, CH), 37.16(q, CH_3), 44.40(d, CH), 46.37 (t, CH_2), 59.41(t, CH_2), 61.24(t, CH_2), 65.98(t, CH_2), 101.34(d, CH), 108.42(s, C), 109.62(s, C), 140.35 (d, CH), 149.19 (s, C), 150.86(s, C), 151.60(s, C), 163.32(s, C), 166.73(s, C), 170.41(s, C). (Found C 60.1, H 6.9, N 8.9%. $C_{23}H_{31}N_3O_7$ requires C 59.87, H 6.72, N 9.11%).

1,8-Dioxo-(1,3-dimethyluracil-5yl)-1,2,3,4,5,6,7,8-octahydroxanthene (18): (60%), m.p. 279^{0}C (EtOH), M^+(m/z) 356; ^{1}Hnmr ($CDCl_3$): δ 1.93-2.07 (m, 2H, CH_2), 2.23-2.78 (m,8H, 4xCH_2), 3.22 (s, 3H, NCH_3), 3.39 (s, 3H, NCH_3), 4.44 (s, 1H, 9-H), 7.49 (s, 1H, U-6H); ^{13}C nmr ($CDCl_3$): δ 20.16 (t, CH_2). 27.74 (t, CH_2), 27.33 (q, CH_3), 27.30 (d, CH), 36.80 (t, q, CH_2, CH_3), 110.83 (s, C), 112.10 (s, C), 143.05 (d, =CH), 151.39 (s, C=O), 162.01 (s, C=O), 166.37 (s, qc), 197.41 (s, C=O). IR(KBr)ν_{max}: 1720 (C=O), 1670(C=O) cm^{-1};

λmax: 284 (ε 1.14x104), 230 ($2.13x10^4$) (Found C 64.3, H 5.9, N 7.9% $C_{19}H_{20}N_2O_5$ requires C 64.04, H 5.62, N 7.86%).

Crystal stucture determination:[13] Needle shaped yellow crystals of 0.3 x 0.2 x 0.1 mm, Siemens P4 diffractometer, cell constants from least square fit of setting angles of 25 reflections with 2θ range 15-25°, w - 2 θ scan, 2 θ(max) 45°, graphite monochromatized Mo Kα radiation, index range $0 \leq h \leq 10$, $0 \leq k \leq 8$, $-22 \leq l \leq 21$, 2661 reflections collected, 2514 independent reflections ($R_{int.}$ = 0.0244), 2304 considered observed [$I \geq 2s$ (I)]. Three standard reflections measured every 100 reflections. Corrections for Lorentz - polarization effects but none for absorption. The structure was solved by direct methods. Anisotropic refinement based on F^2 revealed two very short C13-C14 and C15-C16 distances (1.212 and 1.217 Å) with nearly eclipsed torsion angles in the morpholine ring and very large U components of the temperature factor for four C and one O atoms in morpholine ring, indicating disorder in the two C-C bonds and O3 atom.

During subsequent refinement the bond lengths involving these C atoms, which were assigned isotropic, U values were restrained to realistic values (C-C 1.520(5), C-O 1.440(5) and C-N 1.470(5) Å) and the site occupation factor (s.o.f.'s) of the C atoms were fixed at 0.70. After refinement, the difference Fourier maps yielded one satellite peak near each of the four disordered C atoms. Because of the satisfactory geometry, these peaks were refined with the same restraints as above. The occupation factors of the C atoms of the disordered C-C bonds converged to 0.64 for C131-C141 and C151-C161. A similar treatment with O3 did not show any satellite peak although the thermal parameter for this atom was also high and O3 was not treated as a disordered atom, only C-O bond lengths were restrained as stated above. In the final stages of refinement, these four C atoms were also made anisotropic by means of applying rigid bond restraints, which restrained the differences in the components of the displacement parameters of the two atoms to zero along 1,2- and 1,3-vector directions introducing four extra restraints. All the hydrogen atoms were fixed geometrically including those attached to the disordered C atoms and they were made to ride on their respective C atoms. All the bond distances and angles were obtained within a satisfactory range except for C21-C22 which was on a shorter side (1.340 Å). As these terminal atoms show relatively large thermal parameters, this bond was also restrained to a realistic value of C-C = 1.520(5) Å. The final full matrix least squares anisotropic refinement of all the 39 non-hydrogen atoms with 17 restraints and 334 parameters converged to R1 = 0.07, R_w = 0.19 for the observed data and R1 = 0.09, R_w = 0.23 for all the data, with w = 1, GOOF = 1.069, Max. and min. electron densities 0.489 and -0.324 e $Å^{-3}$ in the final difference Fourier map. $w = 1\ [s^2 (F_o)^2 + (0.1416p)^2 + 1.5124p]$ where $p = (F_o^2 + 2F_c^2)/3$.

Acknowledgements: The financial assistance from UGC (India) is greatfully acknowledged.

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