N-Acylation of 1,3-Dimethyl-6-aminouracils. A Reversal in the Regiospecificity of an Electrophilic Substitution Induced by an Intramolecular Proton-transfer

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Electrophilic reactions of 1,3-dimethyl-6-aminouracil lead to 5-substituted derivatives. The introduction of a dialkylaminoalkylamino chain in the 6-position of 1,3-dimethyluracil modifies the regiospecificity of the acylation reaction to give N-6 acylated compounds. This reversal in acylation is induced by an intramolecular proton-transfer which introduces a change in the electron density of the enamine system. The cyclic transition state and the spatial conformation of the final products substantiate the proposed mechanism, on the basis of X-ray and ^{1}H nmr data.

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The enamine system may be regarded as a resonance hybrid consisting of canonical forms (a) and (b). Hence, electrophilic reagents may attack the system at either the nitrogen atom to give the ammonium salt or, more frequently, at the carbon β to the nitrogen to yield an iminium salt [3].

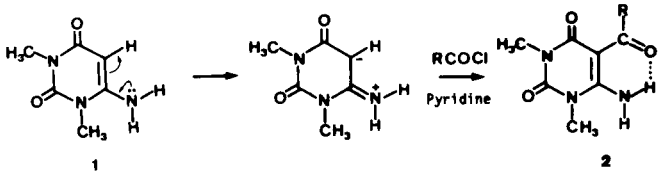
Scheme 1

Pyrimidines, unsubstituted at the 5-position and substituted by an amino group at the 6-position can be considered as cyclic enamines and theoretically react with electrophiles as described above. In fact, electrophiles attack at the 5-position [4] of 6-aminopyrimidines to give 5-substituted derivatives (**4**).

C-Acylation of 1,3-Dimethyl-6-aminouracil.

In the case of the 1,3-dimethyl-6-aminouracil **1**, the regioselective C-5 reactivity towards electrophilic reagents has been widely established [5-9]. This compound can be considered as a vinylogous amide and the reaction at nitrogen is less favorable than for enamines due to the electron withdrawal effect of the carbonyl. The regiospecificity of the C-5 site reactivity is easily explained by a delocalization of the exocyclic nitrogen free doublet, inducing a higher electronic density at the 5-position which becomes a nucleophilic site.

Scheme 2



1 2

The delocalization of the nitrogen electrons lone pair is substantiated by X-ray crystallographic data [10] which shows that all the nitrogens of the molecule **1** are in an sp_2 hybridization (although having three valence bonds). The degree of p-π overlap between the free pair and the double bond can also be evaluated by ^{1}H nmr, observing the chemical shift of the C-5 proton [7,8]. The greater the electron density at the carbon atom, the greater the magnetic shielding of the vinylic proton [3,11,12]. Thus, for **1**, the chemical shift of the olefinic proton is at significantly high field (δ dimethylsulfoxide-d_6, 4.7 ppm, s).

Among electrophilic substitutions, acylation of **1** at the 5-position has been well established [6-8]. Previously we have described conditions which give 5-acyl derivatives **2** in high yields using acyl chlorides in the presence of pyridine, and have found that these 5-acyl-6-aminouracils were stabilized by strong hydrogen bonding [8]. This has been demonstrated by X-ray crystallography [10].

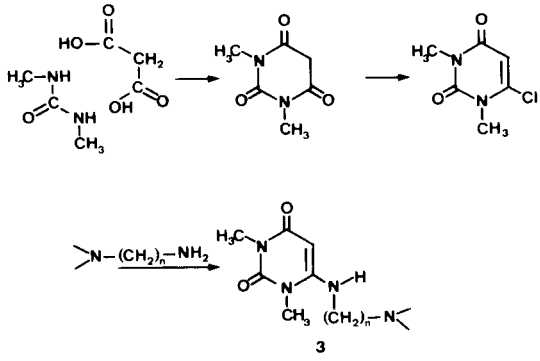
The ^{1}H nmr results are in accordance with X-ray crystallographic data since the two protons of the exocyclic amino group are not equivalent at room temperature when the 5-position is substituted by an acyl group (δ dimethylsulfoxide-d_6 average values for compounds **2**: 11 ppm for the proton engaged in the hydrogen bonding *vs* 8 ppm for the other one). The downfield shift of the former is a reflection of the deshielding effect of the close carbonyl and the different value of the latter indicates a restriction of rotation around the C(6)-N(6) bond. This hydrogen bonding is broken by heating the dimethylsulfoxide solution at 120°; in this case, both protons appear as a single peak at 9.5 ppm.

When R is a styryl group, the planar conformation and the size of the extended conjugated system of molecule **2** are characteristic features for an antitumor activity [13] as most of the well established interacalating drugs [14].

N-Acylation of 1,3-Dimethyl-6-(dialkylaminoalkyl)aminouracils.

In the course of a program aimed at providing new anticancerous intercalating drugs [9a,10,15-18], we have investigated a series of 5-cinnamoyl-1,3-dimethyl-6-aminouracil (NSC 290115). In order to induce a better activity we have introduced on **1** a hydrophylic moiety as shown in Scheme 3.

Scheme 3



3

With such a dialkylaminoalkyl side chain, acylation of **3** by cinnamoyl chloride in the presence of pyridine lead to a mixture of C-5 and N-6 substituted derivatives [19]. Starting from **3** as the free base and 0.5 equivalent of acyl chloride, the N-6 substituted derivative **4** is obtained exclusively, while using the hydrochloride of **3** with a stoichiometric amount of acid chloride, only the C-5 substituted derivative is produced. In the first case, *N*-acylation of **3** can be considered as a reversal of the electrophilic reaction regiospecificity.

The ^{1}H nmr data of compounds **3**, **4** and **5** bring interesting information about the three-dimensional structure and the electronic density of the molecules. The deshielding of the C-5 protons of compounds **4** (δ = 5.9 ppm, dimethylsulfoxide-d_6) *vs* C-5 protons of compounds **3** (δ = 4.8 ppm, dimethylsulfoxide-d_6) is the consequence of a lower electronic density on the C-5 site of *N*-acyl substituted derivatives **4**. The downfield shift of the N-6 proton of **5** (δ = 11 ppm) against the N-6 proton of **3** (δ = 7 ppm) indicates that it is involved in a hydrogen bond.

X-Ray crystallographic data of **4a** are in accordance with ^{1}H nmr data. The exocyclic nitrogen is in a sp_2 hybridization, but its lone pair overlap the cinnamoyl group π cloud in a plane perpendicular to the aromatic uracil ring, involving a lower electronic density on the C-5. The computer generated picture of **5b** establishes that the chlorine atom draws back the two exocyclic diamino-chain NH's. This disrupts the planarity of the molecule. The stabilizing hydrogen bonding between the N-6 proton and the C-5 carbonyl does not exist any more and the downfield shift of this proton in the ^{1}H nmr spectrum cannot be attributed to the anisotropic deshielding effect of the C-5 carbonyl. It can be explained however by the establishment of a hydrogen bond with the chlorine atom. It is noteworthy that two electron pairs of this chlorine atom are involved in a hydrogen bonding with two different protons.

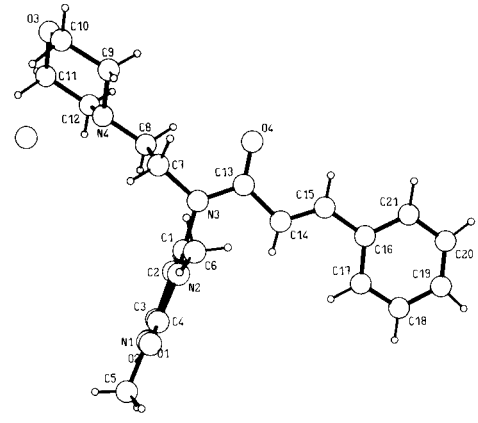


Figure 1. View of **4a** drawn by PLUTO. Crystal data are as follows: mol wt: $C_{21}H_{26}N_4O_4$ 398.46, monoclinic space group $P2_1$, a = 10.833 (7) Å, b = 10.465 (7) Å and c = 11.725 (6) Å, α = 98.02 (5)°, β = 123.54 (4)°, γ = 93.62 (4)°, V = 1081.84 Å^3, Z = 2, D (calcd) = 1.21, D (measd) = 1.17 Mgm^{-3}, (MoKα) = 0.7107 Å, and R = 0.049 for 2155 reflections considered as observed $F > 6\sigma(F)$.

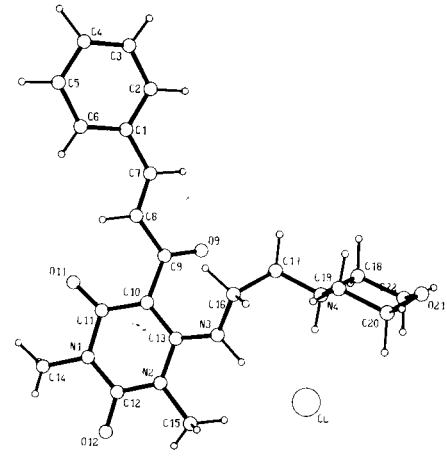


Figure 2. View of **5b** drawn by PLUTO. Crystal data are as follows: mol wt: $C_{21}H_{27}ClN_4O_4$ 434.92, orthorhombic space group Pcba, a = 24.635 (9) Å, b = 14.463 (3) Å, c = 12.147 (6) Å, $\alpha = \beta = \gamma$ = 90.0°, V = 4327.92 Å^3, Z = 8, D (calcd) = 1.32, D (measd) = 1.33 Mgm^{-3}, (CuKα) = 1.5418 Å, and R = 0.049 for 1423 reflections considered as observed $F > 6\sigma(F)$.

Mechanism of the *N*-Acylation.

Three mechanisms can be postulated to explain the reversal in the regiospecificity of this electrophilic substitution.

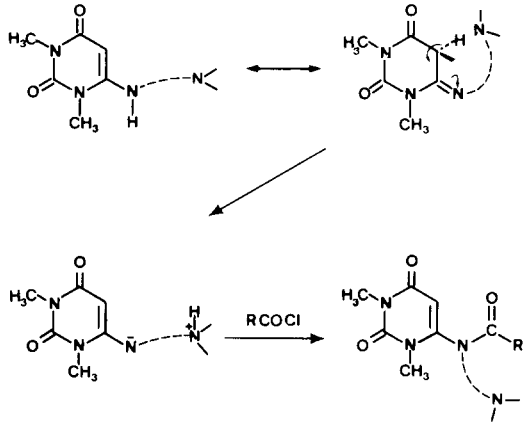
First, the acid chloride could react on the basic (morph-

oline) nitrogen to give a labile intermediate with powerful acylating properties. Then, through an intramolecular trans-acylation process, the *N*-acyl derivative would be formed. Such an acyl transfer has been proposed for the N-6 acylation of N-1 unsubstituted-6-aminouracils [7], but in our case, even if N-6 acylation was slightly favored *vs* C-5 owing to stereochemical considerations, the C-5 position remains the better nucleophilic site considering the electron density of the molecule. Such a mechanism would probably give rise to a mixture of **4** and **5**.

A proton-transfer between the C-5 proton and the basic nitrogen, leading to a higher electronic density on the N-6 atom, can be envisaged. Structural requirements for such an intramolecular proton-transfer have been well established [21,22]. In the initial state, four of the atoms, which are going to be part of the cyclic transition state are coplanar and three of them remain coplanar in the final product. This fact together with the fact that the bond of the proton which is transferred has to lie in a perpendicular plane, and that a linear N-H-C bond must be formed, induce certain steric restrictions on the transition state.

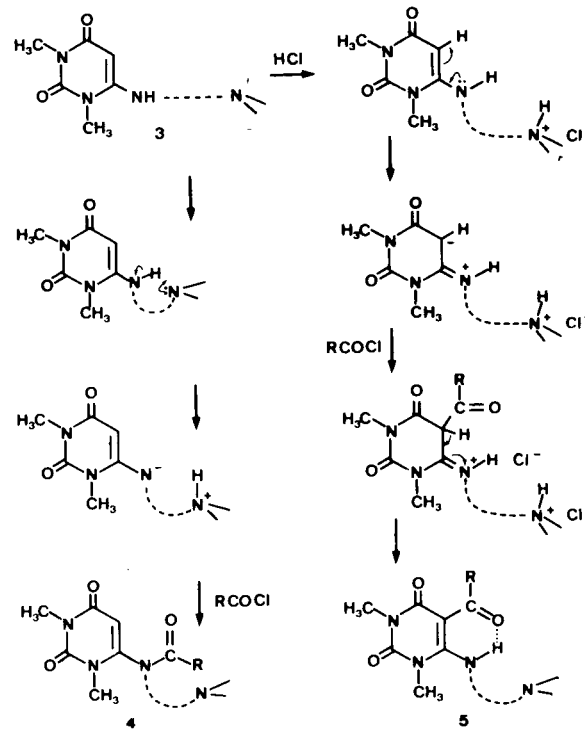
N-Disubstituted-(aminopropyl) or -(aminoethyl)-6-aminouracils are good candidates for a cyclic transition state containing a seven or eight membered ring. Meanwhile, it supposes that the C-5 atom would be tetrahedral. The ketimine form of molecule **3** is not favored since this tautomeric form would disrupt the aromaticity of the uracil ring. Furthermore, this canonical form has never been pointed out by ^{1}H nmr spectroscopy.

Scheme 4



A more probable mechanism is proposed [23,24]. After puckering of the diamino side chain, a proton-transfer between the exocyclic N-6 and the basic side chain nitrogen may occur introducing a higher electronic density on the N-6 which becomes a nucleophilic site (Scheme 5). Starting from the hydrochloride of **3**, such a H-transfer is no more possible and in this case, the classical mechanism leading to a 5-substituted derivative takes place.

Scheme 5



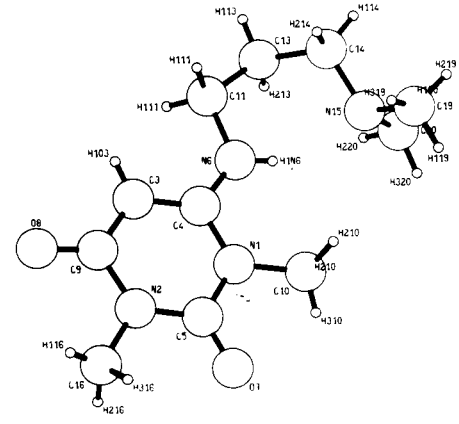


Figure 3. View of **3d**. Crystal data as follows: mol wt: $C_{11}H_{20}N_4O_2$ 240.30, space group $P\bar{1}$, a = 8.813 (3) Å, b = 8.75 (2) Å, c = 8.463 (4) Å, α = 95.60 (5)°, β = 100.63 (2)°, γ = 92.64 (3)°, V = 637.05 Å^3, Z = 2, D (calcd) = 1.25, D (measd) = 1.23 Mgm^{-3}, (MoKα) = 0.7107 Å and R = 0.050 for 2164 reflections considered as observed F > 6σ(F).

The X-ray data of **3d** (Tables I and II) account for this proposal. The steric view (Figure 3) yields information about the conformation of the side chain which appears puckered in such a way that the exocyclic basic nitrogen and the N-6 atom are forced to be rather close (2.70 Å). A

hydrogen bonding cannot be involved (N(6)-H...N(15) = 2.115 Å) but a through space interaction is imposed by the side chain nitrogen lone-pair on the N-6 proton. The exocyclic nitrogen lone-pair orbital is found to be coplanar with the N(6)-H bond with an angle of 148°. All these constraints allow a H-transfer process with a six-membered transition state involving a bent conformation as depicted in Scheme 6.

Scheme 6

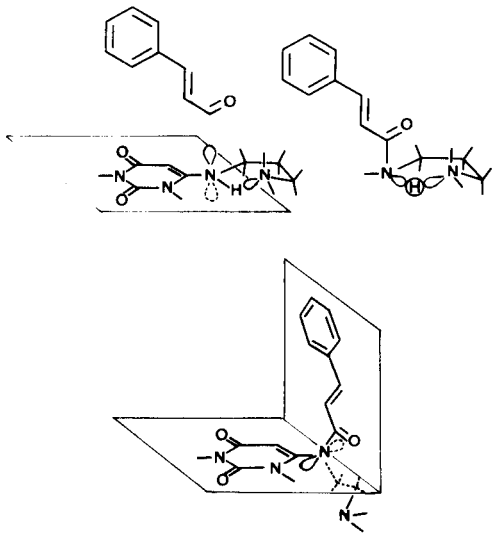


Table I

Interatomic Distances (Å)

Bond	Length	Bond	Length
C_4—N_1	1.384(4)	C_{10}—H	1.08(3)
C_5—N_1	1.386(4)	—H	0.85(3)
C_{10}—N_1	1.463(4)	—H	1.01(3)
C_5—O_7	1.213(4)	C_{16}—H	0.78(4)
C_5—N_2	1.371(4)	—H	0.97(3)
N_2—C_{16}	1.463(5)	—H	1.05(3)
N_2—C_9	1.409(4)	C_3—H	0.83(3)
C_9—O_8	1.229(4)	C_{11}—H	1.02(3)
C_9—C_3	1.405(5)	—H	1.07(3)
C_3—C_4	1.366(4)	C_{13}—H	0.89(3)
C_4—N_6	1.335(4)	—H	1.07(3)
N_6—C_{11}	1.456(4)	C_{14}—H	0.95(3)
C_{11}—C_{13}	1.519(5)	—H	0.95(3)
C_{13}—C_{14}	1.515(4)	C_{19}—H	0.96(3)
C_{14}—N_{15}	1.466(4)	—H	0.92(3)
N_{15}—C_{19}	1.449(4)	—H	0.87(3)
N_{15}—C_{20}	1.461(5)	C_{20}—H	0.92(4)
		—H	1.04(3)
		—H	0.94(4)
		N_6—H	0.74(4)

Such a mechanism, in which a nonlinear H-transfer occurs at an angle of 148° would be in accordance with the calculations of Kwart *et al.* [25] who estimated for a (1,5) sigmatropic hydrogen-transfer the angle to be of approximately 145° [26].

The above proposed H-transfer would arise from the presence of an electrophilic agent such as cinnamoyl chloride. The acyl agent attacks on the N-6 electrons lone pair concomitantly with a hydrogen migration. Due to the position of the acceptor N-6 lone pair molecular orbital and of the released one, the substitution occurs according to obvious constraints. In the ultimate state, the cinnamoyl group would be in a plane perpendicular to the uracil ring and its orbitals may be envisioned to overlap with the N-6 lone pair molecular orbital.

This is substantiated by the X-ray structure of **4a** where the geometry of the molecule and the sp_2 state of the N-6 atom are clearly shown. The C-5 proton deshielding on the ^1H nmr spectrum of all final compounds **4** indicates that the N-6 electrons lone pair orbital no longer overlaps with the uracil ring orbitals, which is in accordance with the proposed mechanism.

In conclusion, a proton-transfer due to a neighboring group participation has been pointed out. The steric requirements of this process have been well defined from gathering ^1H nmr and X-ray data. A cyclic transition state is involved leading to an important change in the electronic density of the enamine system. Electrophilic substitutions such as acylation reactions are modified and N-6-substituted uracils have been obtained instead of the usual C-5-derivatives.

Table II

Bond Angles (°)

Bonds	Angle
C_5—N_1—C_4	122.1(.2)
C_{10}—N_1—C_4	120.2(.2)
C_{10}—N_1—C_5	117.7(.2)
N_1—C_5—N_2	116.2(.3)
N_1—C_5—O_7	121.6(.3)
O_7—C_5—N_2	116.2(.3)
C_5—N_2—C_9	125.0(.3)
C_5—N_2—C_{16}	116.4(.3)
C_{16}—N_2—C_9	118.6(.3)
N_2—C_9—O_8	118.5(.3)
N_2—C_9—C_3	115.1(.3)
O_8—C_9—C_3	126.4(.3)
C_9—C_3—C_4	121.9(.3)
C_3—C_4—N_1	119.6(.3)
C_3—C_4—N_6	124.2(.3)
N_1—C_4—N_6	116.1(.3)
C_4—N_6—C_{11}	123.7(.3)
N_6—C_{11}—C_{13}	109.3(.3)
C_{11}—C_{13}—C_{14}	113.5(.3)
C_{13}—C_{14}—N_{15}	112.4(.3)
C_{14}—N_{15}—C_{19}	118.8(.2)
C_{14}—N_{15}—C_{20}	112.3(.3)
C_{19}—N_{15}—C_{20}	109.7(.3)

EXPERIMENTAL

The ^1H nmr spectra were recorded on a Perkin-Elmer 90 MHz spectrometer using dimethylsulfoxide-d_6 as solvent and TMS as an internal reference. Melting points were taken on a Tottoli melting-point apparatus and are uncorrected. Infrared-spectra were recorded with a Perkin-Elmer 177 infrared-spectrometer using potassium bromide pellets.

Electron impact mass spectra were obtained with a quadrupole mass spectrometer (Ribermag R10-10, combined with Riber 400 data system) at 70 ev by using direct insertion. X-Ray diffraction data were collected on a Philips PW 1100 diffractometer.

1,3-Dimethyl-5-acyl-6-aminouracil (**2**).

To a solution of 1,3-dimethyl-6-aminouracil **1** [5] (15.5 g, 0.1 mole) in pyridine (100 ml), was added 0.1 mole of acid chloride. This mixture was stirred and heated under reflux for 2 hours. The solvent was then evaporated *in vacuo*. The residue was washed by water to give **2** as a crude powder which was filtered and dried.

1,3-Dimethyl-5-cinnamoyl-6-aminouracil (**2a**).

This compound was obtained as light yellow crystals (88%), mp 245°; ir: 3360, 1730 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.30, 3.46 (s, 2 × 3H N-CH_3), 8.50 (d, 1H, J = 16 Hz), 7.65 (d, 1H, J = 16 Hz, ethylenic CH), 7.60 (m, 5H, arom CH), 11.52 (s, 1H, NH bonded), 8.35 (s, 1H, second NH proton, 20°), or after heating, 9.75 (s, 2H, NH_2, 130°); ms: m/e 285 (M^+).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.17; H, 5.28; N, 14.67.

By the above general procedure compound **3a** was prepared (81%), mp 138°; ir: 3250, 3100, 2950, 2840, 1700 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.1, 3.3 (s, 2 × 3H, N-CH_3), 4.8 (s, 1H, CH), 7.0 (t, 1H, J = 6.6 Hz, NH), 3.1-4.2 (m, 12H, morpholinoethyl CH_2); ms: m/e 268 (M^+).

Anal. Calcd. for $C_{12}H_{20}N_4O_3$: C, 53.72; H, 7.51; N, 20.88. Found: C, 53.77; H, 7.56; N, 20.93.

1,3-Dimethyl-6-(2-morpholinopropyl)aminouracil (**3b**).

Compound **3b** was obtained in a manner similar to compound **3a** (77%), mp 124°; ir: 3240, 3100, 2980, 2840, 1700 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.1, 3.3 (s, 2 × 3H, N-CH_3), 4.6 (s, 1H, CH), 6.6 (t, 1H, J = 5.25 Hz, NH), 1.8-4.1 (m, 14H, morpholinopropyl CH_2); ms: m/e 282 (M^+).

Anal. Calcd. for $C_{13}H_{22}N_4O_3$: C, 55.30; H, 7.85; N, 19.34. Found: C, 55.34; H, 7.84; N, 19.81.

1,3-Dimethyl-6-(2-dimethylaminoethyl)aminouracil (**3c**).

Compound **3c** was obtained in a manner similar to compound **3a** (87%), mp 101°; ir: 3500, 3250, 2990, 2850, 2800, 1710 cm^{-1}; nmr (deuteriochloroform): δ 3.25, 3.35 (s, 2 × 3H, N-CH_3), 2.25 (s, 6H, $N(CH_3)_2$), 4.8 (s, 1H, CH), 5.55 (d, 1H, NH), 3.10 (dt, 2H, NH-CH_2), 2.55 (t, 2H, CH_2-CH_2); ms: m/e 226 (M^+).

Anal. Calcd. for $C_{10}H_{18}N_4O_2$: C, 53.08; H, 8.01; N, 24.76. Found: C, 53.12; H, 8.10; N, 24.85.

1,3-Dimethyl-6-(dimethylaminopropyl)aminouracil (**3d**).

Compound **3d** was prepared in a manner similar to compound **3a** (83%), mp 102°; ir: 3500, 3150, 2990, 2850, 2800, 1700 cm^{-1}; nmr (deuteriochloroform): δ 3.30, 3.35 (s, 2 × 3H, N-CH_3), 2.25 (s, 6H, $N(CH_3)_2$), 3.20 (dt, 2H, NH-CH_2), 1.80 (m, 2H, CH_2-CH_2-CH_2), 2.55 (m, 2H, CH_2-$N(CH_3)_2$), 8.40 (d, 1H, NH); ms: m/e 240 (M^+).

Anal. Calcd. for $C_{11}H_{20}N_4O_2$: C, 54.98; H, 8.39; N, 23.32. Found: C, 54.84; H, 8.45; N, 23.30.

1,3-Dimethyl-5-(3',4',5'-trimethoxycinnamoyl)-6-aminouracil (**2b**).

Compound **6b** was prepared in a manner similar to the preparation of compound **2a** as yellow crystals (83%), mp 240°; ir: 3320, 1705 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.25, 3.40 (s, 2 × 3H, N-CH_3), 3.95 (s, 9H, O-CH_3), 8.45 (d, 2H, J = 16 Hz), 7.60 (d, 2H, J = 16 Hz, ethylenic protons), 7.10 (s, 2H arom protons), 11.80 (s, 1H, NH bonded), 8.37 (s, 1H, other NH proton, 20°), or 9.90 (s, 2H, NH_2, 130°); ms: m/e 375 (M^+).

Anal. Calcd. for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.62; H, 5.58; N, 11.18.

1,3-Dimethyl-5-(4'-methoxycinnamoyl)-6-aminouracil (**2c**).

Compound **2c** was prepared in a manner similar to the preparation of compound **2a** as yellow crystals (79%), mp 178°; ir: 3340, 1710 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.16, 3.32 (s, 2 × 3H, NCH_3), 2.80 (t, 2H, J = 3 Hz), 2.70 (t, 2H, J = 3 Hz, CH_2), 7.36 (s, 5H, H arom), 11.50 (s, 1H, NH bonded), 8.38 (s, 1H, other NH 20°) or 9.68 (s, 2H, NH_2, 135°); ms: m/e 287 (M^+).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96; N, 14.62. Found: C, 62.75; H, 4.06; N, 14.60.

1,3-Dimethyl-6-(dialkylaminoalkyl)aminouracil (**3**).

1,3-Dimethyl-6-chlorouracil (**6a**) (17.6 g, 0.1 mole) was treated by an equimolar amount of *N*-aminoalkylmorpholine (0.1 mole) in the presence of sodium carbonate (28.6 g, 0.1 mole). The mixture was stirred and heated under reflux for 24 hours. After elimination of the precipitate of sodium chloride, the filtrate was concentrated *in vacuo* to dryness. The residual solid was taken up with acetone and recrystallized twice from this solvent to give white crystals.

1,3-Dimethyl-6-*N*-cinnamoyl-*N'*-dialkylaminoalkyl)aminouracil (**4**).

1,3-Dimethyl-6-*N*-(dialkylaminoalkyl)aminouracil **3** (0.2 mole) was heated under reflux with cinnamoyl chloride (16.6 g, 0.1 mole) in dry acetone for 6 hours. After cooling, a precipitate of hydrochloride **3** was separated by filtration. The filtrate was evaporated *in vacuo*. The residue was triturated with ether to give **4** as a crude powder which can be recrystallized from ethanol.

1,3-Dimethyl-6-*N*-cinnamoyl-(2-morpholinoethyl)aminouracil (**4a**).

By the above general procedure compound **4a** was prepared (75%), mp 131°; ir: 3580, 3120, 2980, 2880, 2830, 1730 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.2, 3.25 (s, 2 * 3H, N-CH_3), 5.85 (s, 1H, CH), 2.5-4.0 (m, 12H, morpholinoethyl CH_2), 7.25-7.75 (m, 7H, ethylenic and arom protons); ms: m/e 398 (M^+).

Anal. Calcd. for $C_{21}H_{25}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.42; H, 6.63; N, 13.89.

1,3-Dimethyl-6-*N*-cinnamoyl-(2-morpholinopropyl)aminouracil (**4b**).

Compound **4b** was obtained in a manner similar to compound **4a** (53%), mp 158°; ir: 3600, 3140, 2960, 2870, 2820, 1720 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.18, 3.22 (s, 2 × 3H, N-CH_3), 5.8 (s, 1H, CH), 1.6-4.0 (m, 14H, morpholinopropyl CH_2), 7.2-7.8 (m, 7H, ethylenic and arom CH); ms: m/e 412 (M^+).

Anal. Calcd. for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.87; H, 6.95; N, 13.70.

1,3-Dimethyl-6-*N*-cinnamoyl-*N'*-dialkylaminoalkyl)aminouracil (**4c**).

Compound **4c** was prepared in a manner similar to compound **4a** (61%), mp 142°; ir: 3460, 3050, 2960, 2700, 1710, 1660 cm^{-1}; nmr (deuteriochloroform): δ 3.30, 3.35 (s, 2 × 3H, N-CH_3), 2.30 (s, 6H, $N(CH_3)_2$), 5.85 (s, 1H, CH), 3.45 (t, 2H, N-CH_2), 2.75 (t, 2H, CH_2-$N(CH_3)_2$), 7.20-7.60 (m, 7H, ethylenic and arom protons); ms: m/e 356 (M^+).

Anal. Calcd. for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72. Found: C, 64.22; H, 6.87; N, 15.57.

1,3-Dimethyl-6-*N*-cinnamoyl-(2-diethylaminopropyl)aminouracil (**4d**).

Compound **4d** was prepared in a manner similar to compound **4a** (57%), mp 148°; ir: 3450, 3060, 2960, 2700, 1720, 1670 cm^{-1}; nmr (deuteriochloroform): δ 3.30, 3.35 (s, 2 × 3H, N-CH_3), 2.90 (s, 6H, $N(CH_3)_2$), 2.00, 3.50 (m, 6H, propyl CH_2), 6.00 (s, 1H, CH), 7.20, 7.80 (m, 7H, ethylenic and arom protons); ms: m/e 370 (M^+).

Anal. Calcd. for $C_{20}H_{26}N_4O_3$: C, 64.84; H, 7.07; N, 15.12. Found: C, 64.72; H, 7.21; N, 15.13.

1,3-Dimethyl-5-cinnamoyl-6-(morpholinoethyl)aminouracil (**5**).

To a suspension of 1,3-dimethyl-6-(morpholinoalkyl)aminouracil hydrochloride **3** (0.10 mole) in pyridine (100 ml), was added cinnamoyl chloride

(16.6 g, 0.10 mole). The mixture was heated at 115° for 3 hours. After cooling the resulting precipitate was filtered and washed with water to give **5** as a crude yellow powder.

1,3-Dimethyl-5-cinnamoyl-6-(morpholinoethyl)aminouracil (**5a**).

By the above general procedure, compound **5a** was prepared (83%), mp 202°; ir: 3230, 3100, 3080, 3030, 2980, 2900, 2440, 1720 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.25, 3.45 (s, 2 × 3H, N-CH_3), 9.75 (t, 1H, J = 3.5 Hz, NH), 7.50 (d, 1H, J = 15 Hz) and 8.25 (d, 1H, J = 15 Hz, ethylenic CH), 7.50 (m, 5H, arom CH), 2.8, 4.0 (m, 12H, morpholinoethyl CH_2); ms: m/e 398 (M^+).

Anal. Calcd. for $C_{21}H_{26}N_4O_4$·HCl: C, 57.99; H, 6.26; N, 12.88. Found: 57.92; H, 6.18; N, 12.96.

1,3-Dimethyl-5-cinnamoyl-6-(morpholinopropyl)aminouracil (**5b**).

Compound **5b** was obtained in a manner similar to compound **5a** (76%), mp 164°; ir: 3280, 3140, 3060, 3020, 2980, 2880, 2460, 1740 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 3.20, 3.45 (s, 2 × 3H, N-CH_3), 11.45 (t, 1H, J = 3 Hz, NH), 8.20 (d, 2H, J = 15 Hz) and 7.50 (d, 2H, J = 15 Hz, ethylenic CH), 7.45 (m, 5H, arom protons), 1.8, 4.2 (m, 14 H, morpholinopropyl CH_2); ms: m/e 412 (M^+).

Anal. Calcd. for $C_{22}H_{28}N_4O_4$·HCl: C, 58.86; H, 6.51; N, 12.48. Found: C, 58.72; H, 6.60; N, 12.45.

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