N,N'-Cyclization of Carbodiimides with 2-(Bromomethyl)acrylic Acid.
A Direct Entry to the System 5-Methylene-6H-Pyrimidine-2,4-dione,
A New Class of Thymine Analogues

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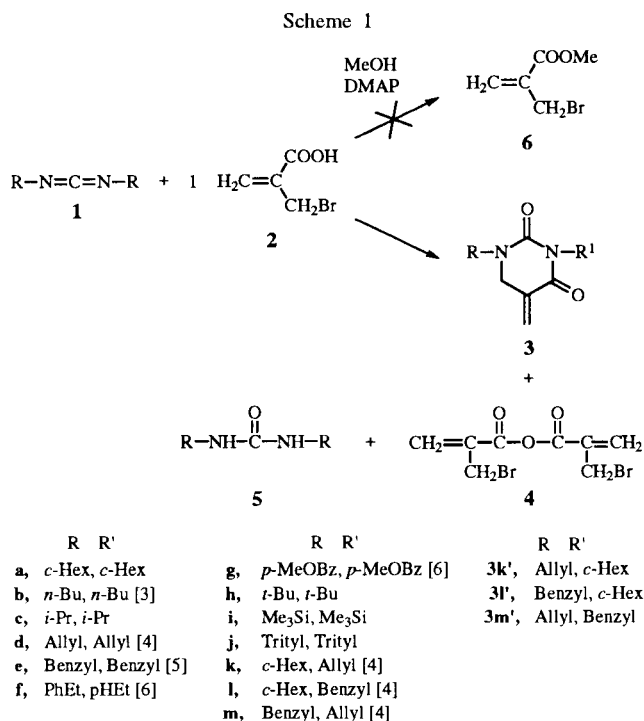Received November 20, 1995

Carbodiimides react under very mild conditions with 2-(bromomethyl)acrylic acid at both N atoms to give 1,3-disubstituted-5-methylene-6H-pyrimidine 2,4-dione derivatives in moderate to good yields. These products behaved as good Michael acceptors towards a variety of nucleophiles such as bromine, hydrochloric acid, hydrides, etc. A plausible mechanism is proposed based on theoretical approaches and experimental results.

N,N'-Disubstituted carbodiimides have become common reagents for formation of the ester and ether linkage. As cumulenes, they also give cycloaddition reactions with different substrates although almost exclusively behaving as a 1,2-dipole. In all of them only half of the basic functionality is integrated in the ring [1].

In an attempt to prepare the methyl ester of 2-(bromomethyl)acrylic acid (**6**) following the protocol put forward by Hassner and Alexanian [2] we were surprised to find that, instead of the expected ester, compound **3** was a reaction product (8%) accompanying the corresponding anhydride **4** (20%) and the N,N'-disubstituted urea **5** (30%) (Scheme 1).

Scheme 1

R	R'		R	R'		R	R'
a,	c-Hex, c-Hex	g,	p-MeOBz, p-MeOBz [6]	3k',	Allyl, c-Hex
b,	n-Bu, n-Bu [3]	h,	t-Bu, t-Bu	3l',	Benzyl, c-Hex
c,	i-Pr, i-Pr	i,	Me₃Si, Me₃Si	3m',	Allyl, Benzyl
d,	Allyl, Allyl [4]	j,	Trityl, Trityl		
e,	Benzyl, Benzyl [5]	k,	c-Hex, Allyl [4]		
f,	PhEt, pHEt [6]	l,	c-Hex, Benzyl [4]		
		m,	Benzyl, Allyl [4]		

Compounds of type **3** represent a new class of nucleotide base derivatives with an exocyclic α,β-conjugated double bond highly promising with regard to potential bioactivity.

Indeed, the cytotoxic activity of a variety of natural products such as helenalin, vernolepin, sarkomicyn and others has been attributed, after structure-activity relationship studies, to the occurrence of an exocyclic methylene group conjugated with the carbonyl of a lactone or cyclopentenone ring, this structural arrangement conferring enough activity to these compounds to act as alkylating agents of biological nucleophiles by conjugate addition [7-11]. This potential interest urged us to study this unprecedented reaction and its scope. The results are presented hereafter.

Structural Features and Scope of the Reaction.

Although the parent compound of this series has been reported [12] it was poorly characterized and we were unable to reproduce the last step of its sequential preparation. Thus, the structure of these compounds had to be established from the spectroscopic data of compound **3a**. The ¹³C nmr and ir spectra accounted for two amide carbonyls (cf values of δ = 153.0 and 165.0 and ν 1705 cm⁻¹ in chloroform solution for **3a** with the reported values of δ 151.5 and 164.8 ppm and ν 1728 cm⁻¹ in potassium bromide for thymine, respectively). The presence of an exocyclic methylene was deduced from the ¹H and ¹³C nmr spectra (values of δ = 6.2, 5.5 and δ = 133.4, 122.9, respectively). The two cyclohexyl methyne protons are strongly deshielded by the nearby carbonyls (δ = 4.2-4.4 ppm) appearing as two triplets of triplets with coupling constants indicating an axial arrangement for both protons as it may be expected to be in the most favored conformation (that placing the heterocycle in an equatorial arrangement). The system for the cyclohexyl methyne at N3 appears slightly downfield since it is affected by two carbonyls. The isomeric oxazinone structure derived from the corresponding O-acylisourea **7**, was discarded since these isoureas present a strong ir absorption band at 1795-1800 cm⁻¹ and that of compound **3a** was centered at 1705 cm⁻¹.

The yield of compound **3a** was optimized by variation of the different parameters involved in its preparation. In particular, suppression of the dimethylaminopyridine proved to be beneficial for this purpose (33 % yield in **3a**
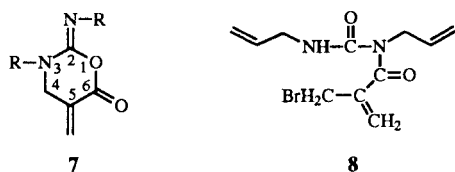
Figure 1

without this catalyst). Change of the solvent (ether) did not cause an improvement in yield and the presence of inorganic bases to neutralize the generated hydrogen bromide which readily adds onto the exocyclic methylene (*vide infra*) turned out to be detrimental (28% and 26% in the presence of calcium carbonate and magnesium oxide, respectively). The best yield (38%) was achieved by using the N,N'-dicyclohexylcarbodiimide as acceptor for the hydrogen bromide produced in the cyclization. The carboxylic acid anhydride was easily separated from heterocyclic compound **3a** by passing the reaction mixture through a chromatography column after no N,N'-dicyclohexylcarbodiimide remained in the crude product. In addition, almost all the urea separates because of its insolubility prior to the chromatography process.

A variety of symmetrically and asymmetrically substituted carbodiimides were reacted, under the optimized conditions, with 2-(bromomethyl)acrylic acid (**2**). The corresponding results are collected on Table I.

Table I

Synthesis of Different 1,3-Disubstituted-5-methylene-6H-pyrimidine-2,4-diones from Carbodiimides

Entry	Carbodiimide	Solvent	Products	Yield (%)
a	**1a**	CH_2Cl_2	**3a**	38
b	**1b**	CH_2Cl_2	**3b**	39
c	**1c**	CH_2Cl_2	**3c**	38
d	**1d**	Et_2O	**3d, 8**	37/7
e	**1e**	CH_2Cl_2	**3e**	37
f	**1f**	THF	**3f**	37
g	**1g**	THF	**3g**	25
h	**1h**	THF	**3h**	31
i	**1i**	CH_2Cl_2	—	—
j	**1j**	CH_2Cl_2	—	—
k	**1k**	CH_2Cl_2	**3k, 3k'**	31 (1:3) [a]
l	**1l**	CH_2Cl_2	**3l, 3l'**	29 (8:1) [a]
m	**1m**	CH_2Cl_2	**3m, 3m'**	32 (1:6) [a]

[a] (N,N'-regioisomeric ratio).

Reasonable yields of the corresponding 5-methylene-6H-pyrimidine-2,4-diones were obtained from all N,N'-disubstituted carbodiimides except from bis trimethylsilyl and bis trityl derivatives that remained unreacted under the general reaction conditions, throughout the experimental process. These results are surprising in view of that obtained from the bis *tert*-butylcarbodiimide that can be considered bearing substituents of similar size.

From the diallyl derivative (entry d) a small amount (7%) of the corresponding N-acylurea **8** was also obtained. This product can be considered a reaction intermediate and in fact further treatment with N,N'-dicyclohexylcarbodiimide led to compound **3d**.

Asymmetrically substituted carbodiimides behaved similarly and the reasonable regioselectivity found for benzylcyclohexyl carbodiimide (**1l**) (entry 1) was not reproduced for the other two asymmetric carbodiimides. The regioisomers could not be separated but their ratio and structural assignments were made from the ^1H nmr data of the corresponding symmetrical derivatives considering the stronger deshielding effect on the imido substituent related to the amido counterpart.

Insight into the Mechanism.

Two different mechanisms have been proposed for the interaction of carbodiimides and carboxylic acids: Khorana assumed an initial ionic protonation of the carbodiimide by the acid, followed by the acylation of the central carbon atom by the anion [13]. The resulting O-acylisourea would evolve either rearranging to the corresponding N-acylurea or, alternatively, rendering the anhydride by further protonation and acylation. While the N-acylurea is stable enough to be isolated, the precursor O-acylisourea has only been trapped in intramolecular reactions [14]. This intermediate is able to proceed in the presence of added alcohols, amines or carboxylic acids to give esters, amides or anhydrides and concurrent formation of the corresponding urea. The alternative mechanism proposed by Kolodziejczyk [15] differs only in the independent generation of the O-acylisourea and the N-acylurea from a four center intermediate by proton or base attack, respectively.

Both mechanisms can explain the formation of the 1,3-diazaridin-2,4-dione derivatives from carbodiimides and 2-(bromomethyl) acrylic acid through a final intramolecular nucleophilic attack in the generated N-acylurea that would lead to the heterocyclic product. While mechanism a) requires initial protonation the alternative one, b), would not require an acidic medium to generate compound **3** and the formation of anhydride **4** and urea **5** would result as a consequence of the formation of hydrobromic acid in the process leading to compound **3**.

To ascertain the extension of these general mechanisms and discriminate one of the two possible ring closure modes (S_N2 or S_N2') a set of different models **9-15** was treated with dicyclohexyl or diisopropyl carbodiimides **1a** and **1c**. The corresponding results are collected in Table II.

The simultaneous presence of a carboxylic acid and an allylic halide proved to be a requirement given the absence of any reaction from either the ester **14** or allyl halide **15**. Besides, from the products obtained from non halogenated acrylic acids **9-11** one can deduce that the former reaction mechanisms may operate in all cases and while for acid **11**

Scheme 2

a)

b)
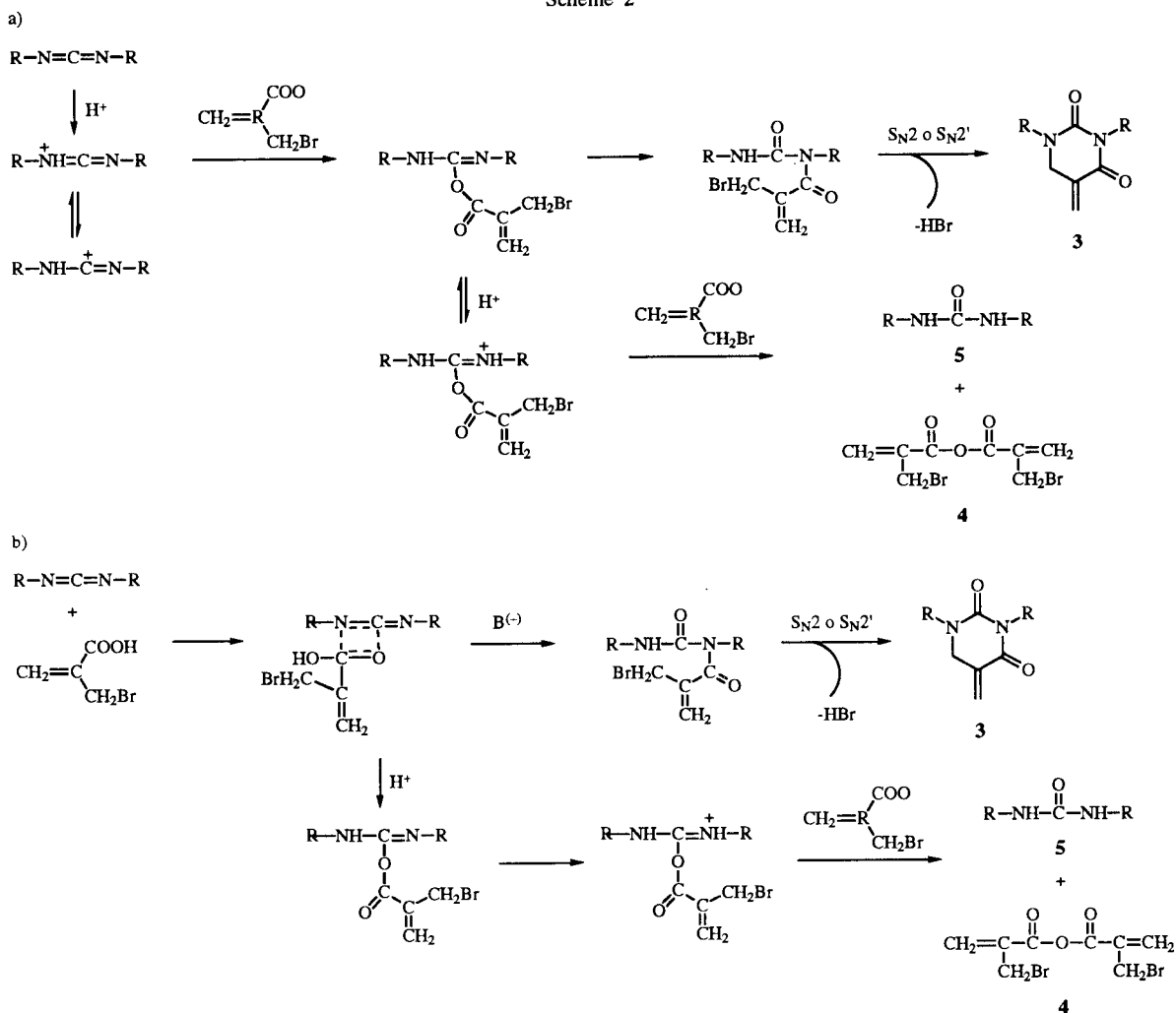
Mechanisms proposed to explain the formation of compound 3: a) after Khorana b) after Kolodziejczyk.

no *O*-acylisourea could be detected, minor amounts of these derivatives were isolated from the reactions of methyl acrylic acids 9 and 10. In all cases, the *N*-acylureas were produced in yields similar to those obtained for 5-methylene-6*H*-pyrimidine-2,4-diones derivatives 3. In the three cases, the *N*-acylurea could have cyclized by a plain Michael addition had this been the operating mechanism for the ring closure, in the general reaction of Scheme 1. Thus, the presence of an activating halogen at allylic position is also a requirement for cyclization.
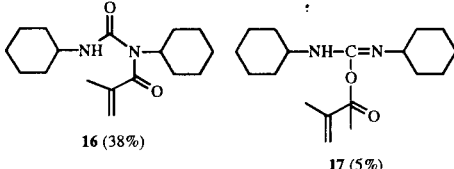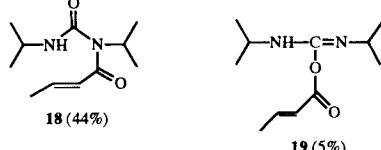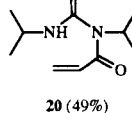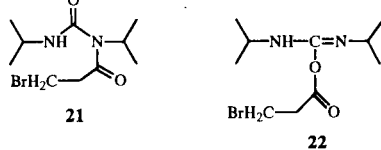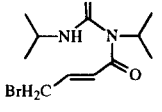
From the model acid 12 little *N*-acylurea was produced and the absence of a simple nucleophilic attack of the distal amido group on a β-halomethyl center leading to the heterocycle pointed out that the three functionalities (a carbonyl conjugated to allyl halide) were required in the final step to produce the ring closure.

Model haloacid 13 gave a moderate yield of the corresponding *N*-acylurea. For this resulting product 23,

Michael addition and a S_N2' process were expected to be antagonist mechanisms and, thus no product from cyclization was found again. From these experiments one would conclude that only the presence of a Michael acceptor in synergy with a good leaving group in allylic position could drive the *N*-acylurea to cyclize. However, these results do not bring about a conclusive decision concerning the type of nucleophilic attack (S_N2 or S_N2').

In order to go deeply into this mechanism, a theoretical study was undertaken for the reaction of the carbodiimide 1h with 2-(bromomethyl)acrylic acid, using the molecular orbital semiempiric method AM1 [16] in gas phase and in solution. The search for stationary points in the reaction hypersurface was carried out using the algorithm proposed by Bofill [17]. The solution model used is the so called surface charge algorithm, implemented in its AM1 version by Luque *et al.* [18].

Table II
Reactions of Different Model Compounds with Carbodiimides

Entry	Reagent	Product (Yield)	
a	1a + H₂C=C(COOH)(CH₃) 9	16 (38%)	17 (5%)
b	1c + (10) COOH	18 (44%)	19 (5%)
c	1c + (11) COOH	20 (49%)	— —
d	1c + BrH₂C–CH₂–COOH 12	21	22 (Global yield: 32%; isomer ratio 1:1)
e	1c + BrH₂C–CH=CH–COOH 12	23 (38%; 12.5 Z:87.5 E)	— —
f	1c + H₂C=C(COOEt)(CH₂Br) 14	— —	— —
g	1a or 1c + BrH₂C–CH=CH₂ 15	— —	— —

In Figure 2 we have represented the free energy profile of the reaction, computed at 298 K, for both, gas phase and solution models (values in parenthesis). The structures of the intermediates of the reaction are schematized in Figure 3.

The starting point in this theoretical study is the O-acylurea intermediate **1ha** which evolve to the corresponding N-acylurea **1hc**. The process could take place through the transition structure **1hb** and the computed free energy barrier is 36.4 kcal/mol in gas phase and 29.2 kcal/mol in solution. Steps **1hc-1hg** correspond to conformational changes in the N-acylurea intermediate.

The S_N2' mechanism occurs from **1he** through **1hi-1hj** structures and the calculated free energy barrier is 39.9 kcal/mol in gas phase and 36.5 kcal/mol in solution. Alternatively, the S_N2 mechanism would take place from **1hg** through **1hk** transition state, involving a free energy barrier as high as 75.3 kcal/mol in gas phase. The solution model produces a relative stabilization of 16.2 kcal/mol in the S_N2 transition state but the computed free energy barrier, of 59.1 kcal/mol, is still 22.6 kcal/mol higher than the S_N2' step.

This result supports the conclusion that the nucleophilic attack is of the S_N2' type, which is the limiting step of the reaction. Comparable results on the preference for S_N2' versus S_N2 mechanism have been recently reported for a similar acrylic acid derivate bearing a leaving group smaller and weaker than bromide [19].

Theoretical studies have also been undertaken in order to bring some insight on the lack of reaction from bis-trimethylsilylcarbodiimide (**1i**). As a first approach, the same kind of semiempirical AM1 calculations reported
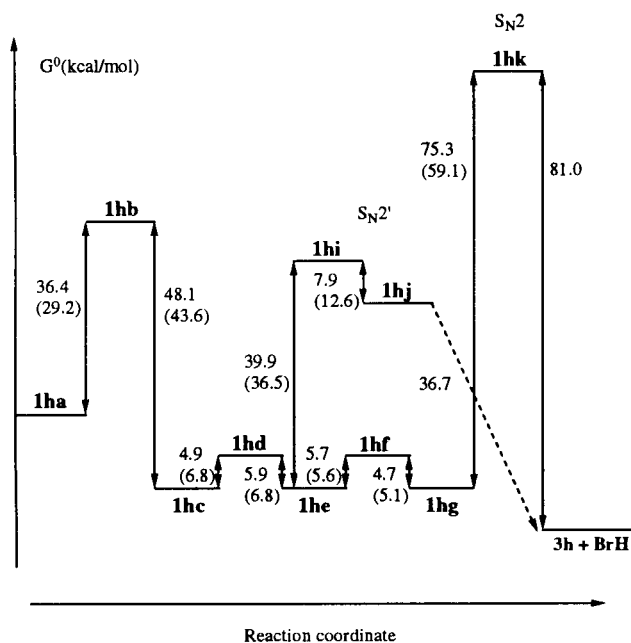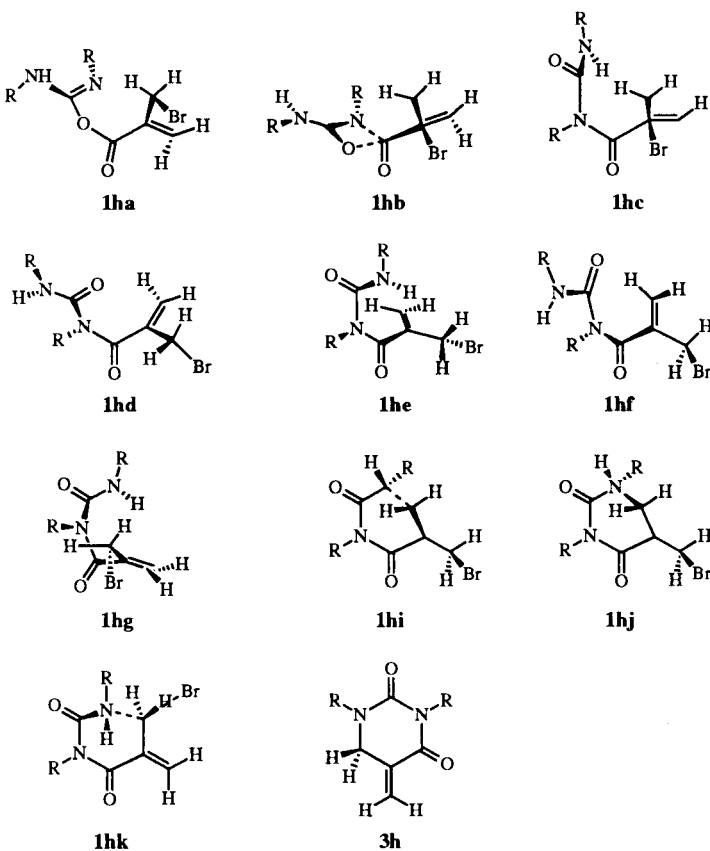
Figure 2.

Figure 3.

above for the bis *tert*-butylcarbodiimide **1h** were carried out for **1i**, starting from the *O*-acylurea intermediate. Such cal-

culations indicate that the final product **3i** should be reached to the same extent as **3h**, since similar energy barriers were obtained independently on the *tert*-butyl or trimethylsylil substituents. However, experiments show that carbodiimide **1i** is recovered unchanged at the end of the reaction time. Further AM1 calculations showed us that acylation on the central carbon atom is possible from a steric point of view, and all these facts indicate that the lack of reactivity should be found in the first step of the process, that is, before acylation on the central carbon atom by the anion.

A possible alternative to the first step of the reaction is acylation taking place at the silicon atom instead of at the central carbon atom, because of the higher electropositive character of silicon (AM1 calculations on the protonated **1i** carbodiimide give a net positive charge of 0.3 on the central carbon atom and 1.5 on silicon). Thus, a pentacoordinate silicon intermediate would be plausibly formed, which would dissociate back to the starting reagents. This hypothesis would agree with the results found by Bassindale *et al.* [20], who pointed out that no stable five or six coordinate Me_3SiY_n (n = 2 or 3) complexes have been ever isolated or characterized.

In order to give theoretical support to this hypothesis, we have carried out further theoretical studies on a simplified model. In this simplified model calculations, the carbodiimide we have used has Me_3Si and H_3Si as substituents and we have assumed its initial protonation. Moreover, the 2-(bromomethyl)acrylic anion has been replaced by an OH⁻ group. Calculations have been done at the *ab-initio* level of theory including correlation energy in the Moeller Plesset of second order (MP2) approach and we have used the standard 6-31G* basis set [21]. The computations were done with the Gaussian 92 system of programs [22] on the VAX alpha 2100 in CTI of CSIC and on the Fujitsu VP 2400 in CESGA. Here, the main goal was to look for stationary structures where the OH anion is linked to the central carbon atom (**A**) or to the silicon in the Me_3Si group (**B**) (see Figure 4).

Results indicate that structure **A** is more stable energetically than **B** but only by 2.7 kcal/mol. Moreover, the pentacoordinate silicon compound **B** shows a very long SiN bond distance of 3.75 Å and it may be thought that **B** could dissociate into silylcyanamide (**C**) and trimethylsilanol (**D**). Therefore, in order to account for energetic stability, we have also taken into account both **C** and **D** products. The calculations show that these products (**C** + **D**) are less stable energetically than the silicon pentacoordinate compound **B** by 7.8 kcal/mol.

As we have found a stationary structure **B** with the anion linked to silicon and forming a pentacoordinate compound, we may conclude that acylation of 2-(bromomethyl)acrylic acid at silicon in **1i** should not be ruled out. Therefore this could be a plausible alternative to acylation at the central carbon atom for **1i** [23].
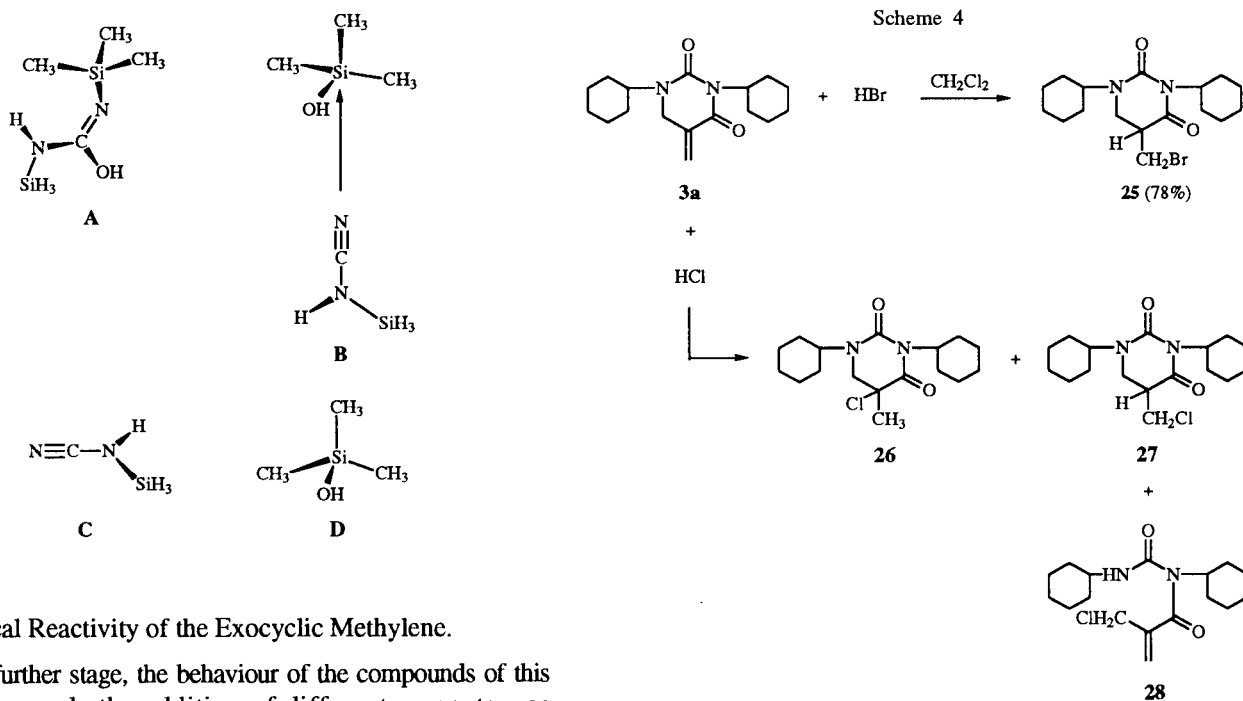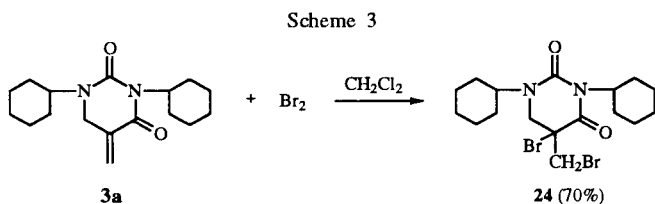
Figure 4.

Scheme 4

Chemical Reactivity of the Exocyclic Methylene.

In a further stage, the behaviour of the compounds of this series towards the addition of different reagents was attempted. Thus, bromine added smoothly onto the double bond giving the corresponding adduct 24 in 70% (Scheme 3).

Scheme 3

Likewise, treatment of compound 3a with hydrogen bromide in solution at room temperature afforded the corresponding anti-Markovnikov product 25 (78%) only in consonance with a conjugate Michael addition while hydrogen chloride proved to be less selective in this reaction giving also products from radical addition 26, 27, together with that from ring opening 28 (Scheme 4).

Although this last product was a minor component of the resulting mixture its formation points out to a potential reversibility of the reaction for formation of the basic methylenepyrimidinedione system. Only the presence of an excess of the starting carbodiimide, as a base, in the preparation of these compounds prevents further addition of the hydrogen bromide and/or the ring opening of the previously formed heterocycle.

As it could be expected, typical Michael nucleophiles added readily to the exocyclic double bond. Thus, sodium ethoxide, cyclohexylamine and piperidine gave the corresponding adducts 29, 30 and 31 in 88, 60 and 58% yield respectively. While sodium methylthiolate was not selective

in its attack giving a profusion of products, propanethiol in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene was able to produce a modest 20% of the conjugate adduct 32 without indiscriminate decomposition of the starting product (Scheme 5).
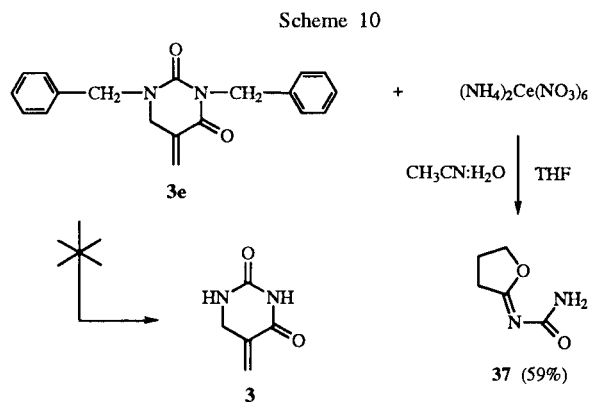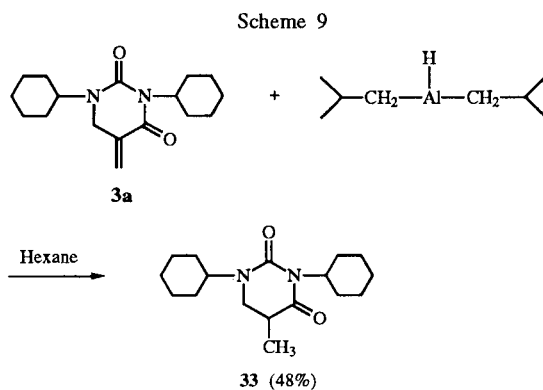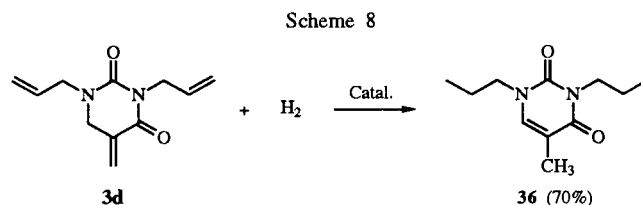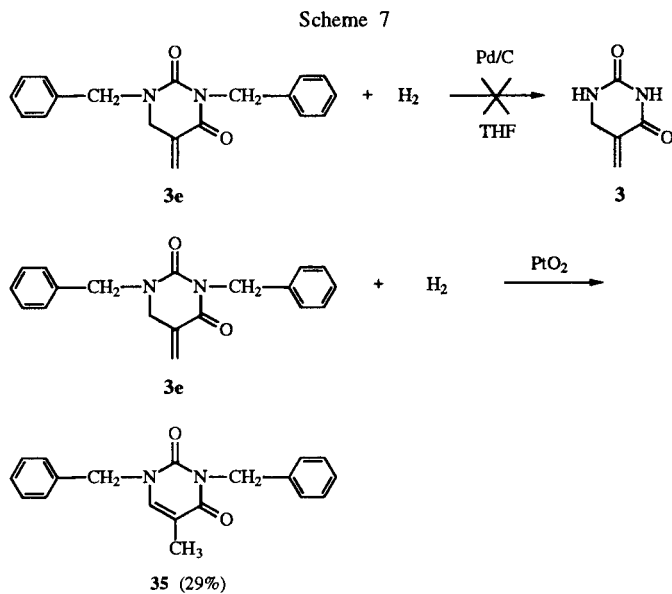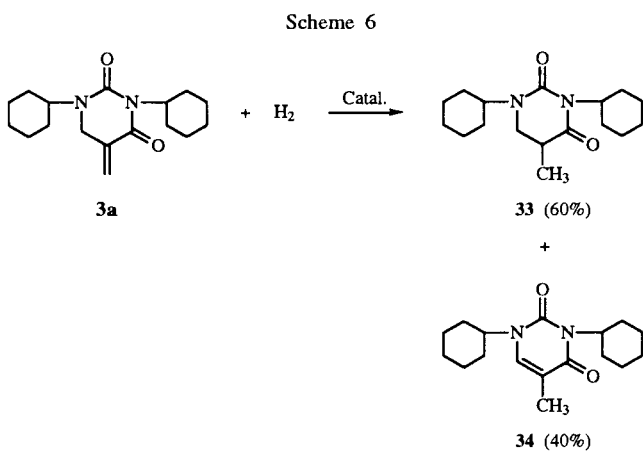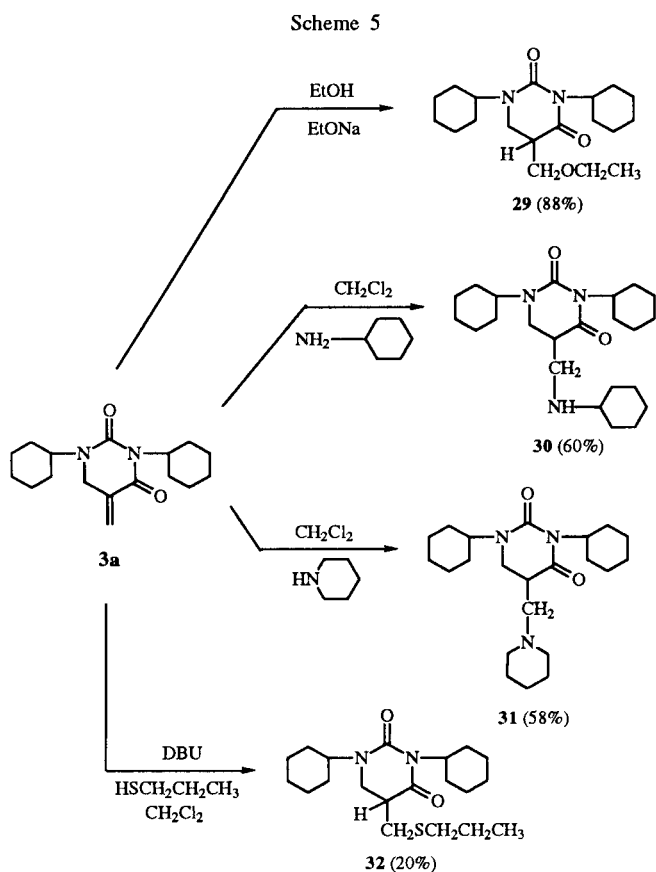
Catalytic hydrogenation of the double bond was attempted with palladium on charcoal; 24 hours were required for the total conversion of the original product 3a into a 6/4 mixture of the hydrogenated heterocycle 33 and the isomerized thymine 34. Change of the catalyst for platinum oxide led to the same products and ratio in only 2 hours. Therefore, this process seems to invariably lead to a mixture derived from a thermodynamic equilibrium.

Surprisingly, despite isomerization seemed a process slower than hydrogenation, the dibenzylderivative 3e gave, under the former hydrogenation conditions the corresponding N,N'-dibenzylthymine 35 without any sign of hydrogenolysis of the N-benzyl substituent (Scheme 7).

Attempted release of both N,N'-substituents also failed from the diallyl derivative 3d. In this case, however, while the conjugated double bond was isomerized those of the allyl substituents were efficiently saturated to give 36 (Scheme 8).

Complete saturation of the exocyclic methylene was achieved, (with no concurrent isomerization), for the dicyclohexyl derivative 3a by treatment with diisobutylaluminum hydride (DIBAL) giving the saturated heterocycle 33 in 48% without any sign of isomerization (Scheme 9) [24].

Oxidation of the dibenzylderivative 3e with cerium ammonium nitrate [25-26] was also attempted with the purpose of obtaining the parent compound (3, R = R' = H)

Scheme 5

Scheme 7

29 (88%)

3e   **3**

30 (60%)

3e

31 (58%)

35 (29%)

3a

Scheme 8

3d   **36** (70%)

32 (20%)

Scheme 9

Scheme 6

3a

3a   **33** (60%)

Hexane

33 (48%)

34 (40%)

Scheme 10

3e

of this series. However, even at room temperature all the starting heterocycle was transformed and the major product **37** turned out to be that of oxidative coupling of the released urea and the solvent (Scheme 10). This fact evidences a particularly easy monoelectron transfer leading to the disruption of the pyrimidindione ring, one of whose fragments (the urea) may be subsequently quenched by the putative α-furanyl cation easily formed under oxidative conditions.

3   **37** (59%)

EXPERIMENTAL

All ir spectra were determined with a Perkin Elmer Model 399 B; the uv spectra were recorded with a Perkin Elmer Model 137-uv and Kontron Uvikon Model 820 spectrophotometer; ^{1}H nmr spectra were taken with a 200 MHz Varian Gemini 200 HC apparatus using tetramethylsilane as internal standard and deuteriochloroform as solvent; proton chemical shifts are given in δ (ppm) and coupling constants in Hz; ^{13}C nmr spectra were recorded with a 50.3 or 75.0 MHz Varian Gemini Model 200 HC or a Varian Unity Model 300 XL instrument respectively in deuteriochloroform solution; mass spectra were obtained with a VG AEI Model 902 S mass spectrometer and high resolution mass spectra (hrms) were performed in a VG-AutoSpec Q mass spectrometer; elemental analysis were taken using a C, H, N Model 1107 Carlo Erba Analyzer.

General Procedure for the Reaction of *N,N'*-Disubstituted Carbodiimides **1a-1m** with 2-(Bromomethyl)acrylic Acid (**2**).

A solution of *N,N'*-dibutylcarbodiimide (**1b**) (1.5 g, 10.0 mmoles) in dry dichloromethane (10 ml) was added dropwise onto another solution of 2-(bromomethyl)acrylic acid (0.83 g, 5.0 mmoles) in the same solvent (15 ml). The mixture was allowed to react at room temperature for 2 hours, the solvent evaporated and the residue purified by column chromatography (silica gel, ethyl acetate/hexane 1/4) to obtain the corresponding cycloadduct, 1,3-dibutyl-5-methylenehexahydropyrimidine-2,4-dione (**3b**) (0.4 g, 39%); ir (chloroform): ν 1710, 1670 (CONR-CONRR') cm^{-1}; uv (ether): max 221.5 nm; ^{1}H nmr: δ 6.3 (bs, 1H, =CH), 5.6 (bs, 1H, =CH), 4.05 (bs, 2H, C(6)H$_2$), 3.8 (t, J = 7.2 Hz, 2H, N3-CH$_2$), 3.4 (t, J = 7.2 Hz, 2H, N1-CH$_2$), 1.6-1.2 (m, 8H,-CH$_2$-), 0.9 (t, J = 7.2 Hz, 6H, CH$_3$); ^{13}C nmr: δ 163.0 (s), 152.7 (s), 132.1 (s), 123.5 (t), 47.9 (t), 47.4 (t), 41.1 (t), 30.5 (t), 29.2 (t), 20.2 (t), 19.9 (t), 13.8 (2 x q); ms: (EI) m/z 238 (M$^+$, 70), 224 (9), 209 (9), 195 (67), 183 (25), 181 (10), 167 (9), 153 (17), 139 (13), 126 (4), 106 (51), 96 (100), 91 (77), 69 (31), 56 (18).

Hrms Calcd. for C$_{13}$H$_{22}$N$_2$O$_2$: 238.1681. Found: 238.1655.

1,3-Dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (**3a**).

This compound had ir (chloroform): ν 1705, 1670 (CONRCONRR') cm^{-1}; uv (ether): max 220.7, 272.1 nm; ^{1}H nmr: δ 6.2 (bs, 1H, =CH), 5.5 (bs, 1H, =CH), 4.3 (tt, J = 8.0 and 2.4 Hz, 1H, N3-CH), 4.2 (tt, J = 7.8 and 2.4 Hz, 1H, N1-CH), 3.85 (bs, 2H, C(6)H$_2$), 2.4 (q, J = 8.0 Hz, 1H, N3-CH-*CH* ax), 2.2 (q, J = 8.0 Hz, 1H, N3-CH-*CH* ax), 1.8-1.1 (m, 18H, CH$_2$); ^{13}C nmr: δ 165.0 (s), 153.0 (s), 133.4 (s), 122.9 (t), 55.1 (d), 54.2 (d), 42.3 (t), 29.9 (t), 29.5 (t), 26.5 (t), 25.6 (t) and 25.5 (t); ms: (EI) m/z 290 (M$^+$, 8), 209 (100), 165 (5), 149 (6), 127 (30), 110 (13), 98 (7), 84 (12), 69 (19), 58 (45).

Hrms Calcd. for C$_{17}$H$_{26}$N$_2$O$_2$: 290.1994. Found: 290.1997.

1,3-Diisopropyl-5-methylenehexahydropyrimidine-2,4-dione (**3c**).

This compound had ir (chloroform): ν 1700, 1664 (CONRCONRR') cm^{-1}; ^{1}H nmr: δ 6.25 (bs, 1H, =CH), 5.5 (bs, 1H, =CH), 5.0-4.5 (m, 2H, N3-CH and N1-CH), 3.85 (bs, 2H, C(6)H$_2$), 1.4 (d, J = 7.4 Hz, 6H, (CH$_3$)$_2$CH-N3), 1.0 (d, J = 7.2 Hz, 6H, (CH$_3$)$_2$CH-N1); ^{13}C nmr: δ 162.8 (s), 152.2 (s), 132.7 (s), 122.3 (t), 45.8 (d), 45.2 (d), 40.5 (t), 19.4 (q) and 18.8 (q); ms: (EI) m/z 210 (M$^+$, 18), 195 (21), 167 (6), 153 (9), 125 (8), 110 (57), 82 (9), 70 (12), 58 (100).

Hrms Calcd. for C$_{11}$H$_{18}$N$_2$O$_2$: 210.1368. Found: 210.1365.

1,3-Diallyl-5-methylenehexahydropyrimidine-2,4-dione (**3d**).

This compound was obtained from **1d** in ether as solvent, according to the general procedure; ir (chloroform): ν 1710, 1670 (CONRCONRR') cm^{-1}; ^{1}H nmr: δ 6.3 (bs, 1H, =CH), 6.15-5.7 (m, 2H, =CH), 5.6 (bs, 1H, =CH), 5.4-5.0 (m, 4H, =CH$_2$), 4.5 (dt, J = 4.8 and 1.2 Hz, 2H, N3-CH$_2$), 4.15 (dt, J = 4.8 and 1.2 Hz, 2H, N1-CH$_2$), 4.0-3.8 (m, 2H, C(6)H$_2$); ^{13}C nmr: δ 163.0 (s), 152.4 (s), 133.9 (t), 131.9 (t), 130.0 (s), 124.2 (t), 118.4 (t), 117.0 (t), 50.2 (t), 46.5 (t) and 43.2 (t); ms: (EI) m/z 206 (M$^+$, 42), 191 (50), 164 (10), 150 (10), 123 (100), 110 (18), 94 (25), 85 (59), 68 (48), 54 (45).

Hrms Calcd. for C$_{11}$H$_{14}$N$_2$O$_2$: 206.1055. Found: 206.1076.

N-(2-Bromomethylacryloyl)-*N,N'*-diallylurea (**8**).

This compound had ir (chloroform): ν 3300 (NH), 1700, 1654 (CONRCONRR'), 1630 (C=CH$_2$) cm^{-1}; ^{1}H nmr: δ 8.9 (bs, 1H, NH), 6.0-5.8 (m, 2H, =CH), 5.6 (s, 1H, =CH), 5.5 (s, 1H, =CH), 5.2-5.1 (m, 4H, =CH$_2$), 4.46 (dt, J = 5.0 and 1.6 Hz, 2H, N-CH$_2$), 4.2 (s, 2H, CH$_2$Br), 3.9 (dt, J = 5.6 and 1.4 Hz, 2H, N-CH$_2$); ^{13}C nmr; δ 172.6 (s), 154.0 (s), 140.1 (s), 134.4 (d), 133.7 (d), 119.2 (t), 116.6 (t), 116.2 (t), 48.8 (t), 43.0 (t), 32.0 (t); ms: (EI) m/z 287 (M$^+$, 38), 207 (60), 149 (58), 124 (54), 82 (41), 68 (37), 56 (100).

1,3-Dibenzyl-5-methylenehexahydropyrimidine-2,4-dione (**3e**).

This compound had ir (chloroform): ν 1710, 1670 (CONRCONRR') cm^{-1}; ^{1}H nmr: δ 7.5-7.2 (m, 10 H, C$_6$H$_5$), 6.3 (bs, 1H, =CH), 5.5 (bs, 1H, =CH), 5.1 (s, 2H, N3-CH$_2$), 4.65 (s, 2H, N1-CH$_2$), 3.9 (bs, 2H, C(6)H$_2$); ^{13}C nmr: δ 163.0 (s), 153.2 (s), 137.8 (s), 135.9 (s), 135.8 (s), 128.8 (d), 128.6 (d), 128.5 (d), 128.0 (d), 127.9 (d), 127.2 (d), 124.4 (t), 51.5 (t), 46.7 (t) and 44.4 (t); ms: (EI) m/z 306 (M$^+$, 39), 215 (13), 172 (21), 132 (16), 110 (14), 91 (100), 65 (16).

These three compounds **3f**, **3g**, and **3h** were obtained from the corresponding carbodiimides using dry tetrahydrofuran as solvent, according to the general procedure:

1,3-Di-benzylmethyl-5-methylenehexahydropyrimidine-2,4-dione (**3f**).

This compound had ir (chloroform): ν 1710, 1670 (CONR-CONRR') cm^{-1}; ^{1}H nmr: δ 7.3-7.1 (m, 10H, C$_6$H$_5$), 6.2 (bs, 1H, =CH), 5.43 (bs, 1H, =CH), 4.1 (t, J = 5.4 Hz, 2H, N3-CH$_2$), 3.78 (bs, 2H, C6), 3.6 (t, J = 5.0 Hz, 2H, N1-CH$_2$), 2.9-2.8 (m, 4H, CH$_2$-C$_6$H$_5$); ^{13}C nmr: δ 163.01 (s), 152.4 (s), 138.8 (s), 138.5 (s), 131.7 (s), 129.0 (d), 128.8 (d), 128.7 (d), 128.6 (d), 126.6 (d), 126.3 (d), 123.8 (t), 50.3 (t), 48.3 (t), 42.4 (t), 34.4 (t), 33.9 (t); ms: (EI) m/z 334 (M$^+$, 8), 243 (46), 230 (7), 146 (18), 104 (100), 96 (89), 91 (76), 83 (94), 77 (32), 69 (63), 65 (36), 47 (50).

Hrms Calcd. for C$_{21}$H$_{22}$N$_2$O$_2$: 334.1681. Found: 334.1699.

1,3-Di-*p*-methoxybenzyl-5-methylenehexahydropyrimidine-2,4-dione (**3g**).

This compound had ir (chloroform): ν 1710, 1670 (CONR-CONRR') cm^{-1}; ^{1}H nmr: δ 7.35 (d, J = 8.6 Hz, 2H, C$_6$H$_4$), 7.12 (d, J = 8.6 Hz, 2H, C$_6$H$_4$), 6.78 (dd, J = 6.8 and 2.1 Hz, 4H, C$_6$H$_4$), 6.25 (bs, 1H, =CH), 5.43 (bs, 1H, =CH), 4.9 (s, 2H, N-CH$_2$), 4.5 (s, 2H, N1-CH$_2$), 3.8 (bs, 2H, C(6)H$_2$), 3.7 (2 x s, 6H, OCH$_3$); ^{13}C nmr: δ 162.9 (s), 159.3 (s), 158.8 (s), 153.1 (s), 131.5 (s), 130.4 (d), 130.0 (d), 129.5 (d), 127.9 (d), 124.3 (t), 114.2 (s), 113.6 (s), 55.3 (q), 55.2 (q), 50.8 (t), 46.4 (t), 43.8 (t);

ms: (EI) m/z 366 (M$^+$, 64), 258 (6), 245 (32), 202 (7), 162 (15), 121 (100), 78 (15).

1,3-Di-*tert*-butyl-5-methylenehexahydropyrimidine-2,4-dione (3h).

This compound had ir (chloroform): ν 1710, 1670 (*CONR-CONRR'*) cm^{-1}; ^{1}H nmr: δ 6.05 (bs, 1H, =CH), 5.4 (bs, 1H, =CH), 3.8 (bs, 2H, C(6)H$_2$), 1.6-1.4 (2 x s, 18H, CH$_3$); ^{13}C nmr: δ 165.2 (s), 153.2 (s), 137.2 (s), 121.3 (t), 58.3 (s), 53.4 (t), 44.2 (s), 28.8 (q); ms: (EI) m/z 238 (M$^+$, 5), 224 (9), 184 (7), 168 (40), 147 (6), 124 (24), 110 (14), 84 (100), 70 (18), 58 (62), 47 (21).

1-Allyl-3-cyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (3k) and 3-Allyl-1-cyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (3k').

This compound had ir (chloroform): ν 1705, 1670 (*CONRCON-R'R''*) cm^{-1}; ^{1}H nmr: δ 6.3 (bs, 2H, =CH), 6.1-5.7 (m, 2H, =CH), 5.5 (bs, 2H, =CH), 5.4-5.1 (m, 4H, =CH$_2$), 4.3 (dt, J = 7.2 and 2.4, 2H, N3-CH$_2$), 4.3-4.1 (bs, 2H, N3-CH and N1-CH), 4.05 (dt, J = 7.2 and 2.4, 2H, N1-CH$_2$), 3.9-3.8 (m, 4H, C(6)H$_2$), 2.4-2.0 (bs, 2H, N3-CH-C*H*), 2.0-0.8 (m, 18H, -CH$_2$-); ^{13}C nmr: δ 163.5 (s), 163.4 (s), 153.1 (s), 153.0 (s), 133.1 (s), 133.0 (s), 132.6 (d), 132.2 (d), 123.5 (t), 123.3 (t), 118.1 (t), 117.0 (t), 54.9 (d), 54.4 (d), 50.3 (t), 46.8 (t), 43.4 (t), 42.1 (t), 29.8 (t), 29.3 (t), 26.4 (t), 25.5 (t) and 25.3 (t); ms: (EI) m/z 248 (M$^+$, 16), 205 (18), 181 (16), 167 (100), 151 (11), 122 (33), 110 (22), 96 (16), 82 (25), 69 (29).

Hrms Calcd. for C$_{14}$H$_{26}$N$_2$O$_2$: 248.1525. Found: 248.1533.

1-Benzyl-3-cyclohexyl-5-methylenehexahydropyrimidin-2,4-dione (31) and 3-Benzyl-1-cyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (31').

This compound had ir (chloroform): ν 1670 (*CONRCO-NR'R'*) cm^{-1}; ^{1}H nmr: δ 7.4-7.0 (m, 10H, C$_6$H$_5$), 6.15 (bs, 2H, =CH), 5.5 (bs, 2H, =CH), 5.3 (s, 2H, N3-C*H$_2$*-C$_6$H$_5$), 4.5 (s, 2H, N1-C*H$_2$*-C$_6$H$_5$), 4.3-4.2 (bs, 1H, N3-CH), 3.6 (bs, 4H, C6), 3.5-3.2 (bs, 1H, N3-CH), 1.9-1.1 (m, 10 H, CH$_2$); ^{13}C nmr: [a] δ 165.2 (s), 144.1 (s), 138.4 (s), 135.4 (s), 128.6 (d), 128.2 (d), 126.8 (d), 128.9 (t), 59.6 (d), 45.9 (t), 33.4 (t), 28.4 (t), 25.7 (t) and 24.3 (t). [a] ^{13}C nmr spectra data reported correspond to the major *N,N'*-regioisomer 31.

1-Allyl-3-benzyl-5-methylenehexahydropyrimidine-2,4-dione (3m) and 3-Allyl-1-benzyl-5-methylenehexahydropyrimidine-2,4-dione (3m').

This compound had ir (chloroform): ν 1670 (*CONRCONR'R'*) cm^{-1}; ^{1}H nmr: δ 7.4-7.2 (m, 10 H, C$_6$H$_5$), 6.2 (bs, 2H, =CH), 6.1-5.7 (m, 2H, =CH), 5.6 (bs, 2H, =CH), 5.4 (s, 2H, N3-C*H$_2$*-C$_6$H$_5$), 5.3-5.0 (m, 4H, =CH$_2$), 4.8 (dt, J = 4.8 and 1.2 Hz, 2H, N3-C*H$_2$*-CH=), 4.4 (s, 2H, N1-C*H$_2$*-C$_6$H$_5$), 4.0 (dt, J = 4.8 and 1.2 Hz, 2H, N1-C*H$_2$*-CH=), 3.65 (bs, 4H, C(6)H$_2$); ^{13}C nmr: δ 165.5 (s), 165.1 (s), 148.2 (s), 148.1 (s), 139.7 (s), 138.1 (s), 135.3 (s), 135.0 (s), 134.8 (d), 133.2 (d), 131.1 (d), 128.3 (d), 128.2 (d), 127.3 (d), 126.9 (d), 126.7 (d), 123.6 (t), 123.5 (t), 117.2 (t), 115.2 (t), 54.4 (t), 53.2 (t), 46.1 (t), 45.9 (t), 28.7 (t) and 28.5 (t).

N-(2-Methylacryloyl)-*N,N'*-dicyclohexylurea (16) and O-2-Methylacryloyl)-*N,N'*-dicyclohexylisourea (17).

To a solution of 3.5 g (0.017 mole) of *N,N'*-dicyclohexylcarbodiimide (1a) in 15 ml of dry dichloromethane under a nitrogen atmosphere 0.75 ml (0.009 mole) of methacrylic acid (9) previously dissolved in 10 ml of dry dichloromethane was dropwise

added and the reaction mixture was stirred at room temperature for 3 hours. Evaporation of the solvent gave a residue which was purified by column chromatography (silica gel; ethyl acetate/-hexane 1/4) to afford 0.48 g (38%) of 16 and 0.06 g (5%) of 17.

N-2-Methylacryloyl)-*N,N'*-dicyclohexylurea (16).

This compound had ir (chloroform): ν 1700 (CO), 1630 (C=CH$_2$) cm^{-1}; ^{1}H nmr: δ 7.4-7.3 (bs, 1H, N'-CH), 5.2 (s, 1H, C3), 5.1 (s, 1H, C3), 3.9 (tt, J = 7.2 and 3.6 Hz, 1H, N-CH), 3.6-3.5 (bs, 1H, N'-CH), 2.2-0.9 (m, 23H, CH$_3$ and CH$_2$); ^{13}C nmr: δ 174.0 (s), 154.0 (s), 141.9 (s), 115.6 (t), 58.3 (d), 49.5 (d), 32.5 (t), 30.6 (t), 26.3 (t), 25.4 (t), 24.5 (t) and 19.8 (q); ms: (EI) m/z 292 (M$^+$, 8), 277 (3), 211 (18), 167 (27), 152 (7), 124 (22), 98 (25), 86 (85), 69 (100).

Anal. Calcd. for C$_{17}$H$_{28}$N$_2$O$_2$: C, 69.83; H, 9.65; N, 9.57. Found: C, 69.82; H, 9.62; N, 9.52.

O-(2-Methylacryloyl)-*N,N'*-dicyclohexylisourea (17).

This compound had ir (chloroform): ν 3500 (NH), 1790 (CO), 1630 (C=CH$_2$), 1300-1050 (C-O) cm^{-1}; ^{1}H nmr: δ 6.1-6.0 (m, 1H, C(3)H), 5.76-5.74 (m, 1H, C(3)H), 3.1 (tt, J = 9.9 and 3.9 Hz, 2H, N-CH and N'-CH), 1.9-1.1 (m, 23H, CH$_3$ and CH$_2$); ^{13}C nmr: δ 162.9 (s), 139.6 (s), 135.7 (s), 128.8 (t), 55.6 (s), 55.5 (s), 34.8 (t), 25.4 (t), 24.6 (t) and 17.8 (q); ms: (EI) m/z 292 (M$^+$, 5), 227 (6), 211 (11), 177 (10), 163 (28), 124 (35), 110 (11), 98 (25), 83 (72), 69 (100).

N-Crotonyl-*N,N'*-diisopropylurea (18) and O-Crotonyl-*N,N'*-diisopropylisourea (19).

To a solution of 2.63 ml (0.017 mole) of *N,N'*-diisopropylcarbodiimide (1c) in 15 ml of dry dichloromethane under nitrogen atmosphere, 0.75 g (0.009 mole) of *trans*-crotonic acid (10) previously dissolved in 10 ml of dry dichloromethane was added. In this way, following the general procedure, 0.40 g (44%) of compound 18 and 0.04 g (5%) of a yellow oil which was identified as the compound 19 were obtained.

N-Crotonyl-*N,N'*-Diisopropylurea (18).

This compound had ir (chloroform): ν 1700 (CO), 1640 (C=CH$_2$) cm^{-1}; ^{1}H nmr: δ 7.7-7.6 (bs, 1H, NH), 6.8 (dq, J = 14.8 and 6.9 Hz, 1H, C(3)H), 6.10 (dq, J = 14.8 and 1.8 Hz, 1H, C(2)H), 4.4-4.3 (bs, 1H, N-CH), 4.0-3.9 (bs, 1H, N'-CH), 1.8 (dd, J = 6.9 and 1.8 Hz, 3H, C(4)H$_3$), 1.3 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CH-N), 1.1 (d, J = 6.3 Hz, 6H, (CH$_3$)$_2$CH-N'); ^{13}C nmr: δ 167.7 (s), 153.9 (s), 143.1 (d), 124.2 (d), 48.2 (d), 42.6 (d), 22.5 (q), 20.8 (q) and 18.2 (q); ms: EM m/e (%) 212 (M$^+$, 5), 197 (5), 155 (3), 127 (11), 112 (36), 69 (100).

Anal. Calcd. for C$_{11}$H$_{20}$N$_2$O$_2$: C, 62.24; H, 9.49; N, 13.19. Found: C, 62.02; H, 9.37; N, 13.12.

O-Crotonyl-*N,N'*-diisopropylisourea (19).

This compound had ir (chloroform): ν 3400 (NH), 1790 (CO), 1650 (C=C), 1300-1050 (C-O) cm^{-1}; ^{1}H nmr: δ 7.8-7.5 (bs, 1H, NH), 6.8 (dq, J = 15 and 6.9 Hz, 1H, C(3)H), 6.2 (dq, J = 15 and 1.8 Hz, 1H, C(2)H), 4.6-4.3 (bs, 1H, N-CH), 4.1-3.8 (bs, 1H, N'-CH), 1.8 (dd, J = 6.9 and 1.8 Hz, 3H, C(4)H$_3$), 1.4 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CH-N), 1.2 (d, J = 6.3 Hz, 6H, (CH$_3$)$_2$CH-N'); ^{13}C nmr: δ 158.1 (s), 139.0 (s), 143.2 (d), 121.9 (d), 48.6 (d), 42.6 (d), 22.6 (q), 20.9 (q) and 18.2 (q).

N-Acryloyl-*N,N'*-diisopropylurea (20).

To a solution of 2.63 ml (0.017 mole) of *N,N'*-diisopropylcarbodiimide (1c) in 15 ml of dry dichloromethane under nitrogen

atmosphere, 0.617 ml (0.009 mole) of acrylic acid (11) previously dissolved in 10 ml of dry dichloromethane was added. In this way, and following the general procedure, 0.30 g (49%) of compound 20 was obtained.

This compound had ir (chloroform): ν 3300 (NH), 1700-1750 (CO), 1650 (C=CH$_2$) cm^{-1}; ^{1}H nmr: δ 7.6-7.4 (bs, 1H, NH), 6.49 (dd, J = 16.6 and 10.0 Hz, 1H, C(3) =CH$_Z$), 6.37 (dd, J = 16.6 and 2.2 Hz, 1H, C(3) =CH$_E$), 5.7 (dd, J = 10.0 and 2.2 Hz, 1H, C(2)H), 4.4-4.3 (m, 1H, N-CH), 4.0-3.9 (m, 1H, N'-CH), 1.4 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CH-N), 1.2 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CH-N'); ^{13}C nmr: δ 167.3 (s), 153.7 (s), 130.0 (d), 128.5 (t), 48.3 (d), 42.8 (d), 22.3 (q), 20.8 (q); ms: (EI) m/z 198 (M$^+$, 8), 184 (15), 113 (28), 98 (99), 84 (71), 70 (66), 58 (44), 55 (100).

Anal. Calcd. for C$_{10}$H$_{18}$N$_2$O$_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.55; H, 9.13; N, 14.11.

N-(3-Bromopropionyl)-*N,N'*-diisopropylurea (21) and *O*-(3-Bromopropionyl)-*N,N'*-diisopropylisourea (22).

To a solution of 2.63 ml (0.017 mole) of *N,N'*-diisopropylcarbodiimide (1c) in 15 ml of dry dichloromethane under nitrogen atmosphere, 0.93 ml (0.009 mole) of 3-bromopropionic acid (12) previously dissolved in 10 ml of dry dichloromethane was added. Following the general procedure, 0.40 g (32%) of a mixture of compounds 21 and 22 was obtained; ir (chloroform): ν 3310 (NH), 1710 (CO), 1660 (C=N) cm^{-1}; ^{1}H nmr: δ 7.5-7.4 (bs, 1H, NH), 7.0-6.9 (bs, 1H, NH), 4.37-4.30 (m, 2H, N-CH), 4.0-3.8 (m, 2H, N'-CH), 3.6 (t, J = 6.9 Hz, 2H, C(3)H$_2$), 3.5 (t, J = 6.8 Hz, 2H, C(3)H$_2$), 3.0 (t, J = 6.9 Hz 2H, C(2)H$_2$), 2.9 (t, J = 6.8 Hz, 2H, C(2)H$_2$), 1.41 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CH-N), 1.37 (d, J = 6.9 Hz, 6H, (CH$_3$)$_2$CH-N), 1.21 (d, J = 6.6 Hz, 6H, (CH$_3$)$_2$CH-N'), 1.19 (d, J = 6.6 Hz, 6H, (CH$_3$)$_2$CH-N'); ^{13}C nmr: δ 174.2 (s), 170.7 (s), 153.3 (s), 138.1 (s), 47.7 (d), 43.0 (d), 38.6 (t), 37.4 (t), 27.1 (t), 25.4 (t), 22.4 (q), 22.3 (q), 20.8 (q) and 20.7 (q); ms: (EI) m/z (^{79}Br) 279.3 (M$^+$, 16), 263 (17), 178 (58), 114 (69), 70 (64), 58 (100).

N-(4-Bromocrotonyl)-*N,N'*-diisopropylurea (23).

To a solution of 2.63 ml (0.017 mole) of *N,N'*-diisopropylcarbodiimide (1c) in 15 ml of dry dichloromethane under nitrogen atmosphere, 1.48 g (0.009 mole) of 4-bromocrotonic acid (13) previously dissolved in 10 ml of dry dichloromethane was added. Following the general procedure, 0.49 g (38%, isomeric mixture *E* (87.5%) and *Z* (12.5%) detected by ^{1}H nmr) of compound 23 was obtained; ir (chloroform): ν 3300 (NH), 1700 (CO), 1640 (C=CH$_2$) cm^{-1}; ^{1}H nmr: δ 7.3 (d, J = 7.2 Hz, 1H, NH), 6.95 (dt, J = 15.2 and 7.4 Hz, 1H, C(3) =CH$_Z$), 6.85 (dt, J = 14.8 and 7.4 Hz, 1H, C(3) =CH$_E$), 6.3 (d, J = 14.8 Hz, 1H, C(2) =CH$_E$), 5.95 (d, J = 15.2 Hz, 1H, C(2) =CH$_Z$), 4.4-4.3 (m, 1H, N-CH), 3.98 (dd, J = 7.4 and 1.0 Hz, 2H, C(4)H$_2$), 4.0-3.9 (m, 1H, N'-CH), 1.27 (d, J = 6.8 Hz, 6H, (CH$_3$)$_2$CH-N), 1.11 (d, J = 6.6 Hz, 6H, (CH$_3$)$_2$CH-N'); ^{13}C nmr: δ 165.8 (s), 153.5 (s), 143.03 (d), 140.1 (d), 126.02 (d), 124.38 (d), 48.0 (d), 43.07 (d), 29.7 (t), 28.9 (t), 22.4 (q) and 20.8 (q); ms: (EI) m/z (^{79}Br) 291 (M$^+$, 24), 211 (100), 207 (34), 190 (28), 169 (70), 147 (46), 126 (43), 85 (23), 68 (58).

Anal. Calcd. for C$_{11}$H$_{19}$N$_2$O$_2$Br: C, 45.37; H, 6.58; N, 9.62; Br, 27.44. Found: C, 45.36; H, 6.55; N, 9.61; Br, 27.44.

1,3-Dicyclohexyl-5-bromo-5-bromomethyl-hexahydropyrimidine-2,4-dione (24).

A solution of 0.200 g (0.68 mmole) of 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (3a) in 3 ml of dry dichloromethane was added dropwise to 0.52 ml of a recently prepared solution of 1.1 g (6.8 mmoles) of bromine in 5.0 ml of dry dichloromethane. The mixture was allowed to react at room temperature with vigorous stirring for 2 hours, and then extracted with chloroform:water (3 x 10 ml), dried (sodium sulfate), filtered and evaporated. The residue was purified by column chromatography (silica gel; ethyl acetate/hexane 1/4) to afford 0.21 g (70%) of compound 24; ir (chloroform): ν 1710, 1670 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 4.5 (tt, J= 12.0 and 3.6 Hz, 1H, N3-CH), 4.3-4.2 (m, 1H, N1-CH), 4.27 (d, J = 11.0 Hz, 1H, C(6)H$_2$), 3.84 (d, J = 11.0 Hz, 1H, C(6)H$_2$), 3.77 (d, J = 14.8 Hz, 1H, CHBr), 3.42 (d, J = 14.8 Hz, 1H, CHBr), 2.3-2.1 (m, 2H, N3-CH-CH ax), 1.9-1.0 (m, 18H, CH$_2$); ^{13}C nmr: δ 164.8 (s), 151.7 (s), 55.6 (d), 55.4 (s), 54.3 (d), 47.1 (t), 33.7 (t), 30.2 (t), 30.1 (t), 29.3 (t), 28.3 (t), 26.4 (t), 26.2 (t), 25.6 (t), 25.5 (t) and 25.3 (t); ms: (EI) m/z 450 (M$^+$, 10), 369 (34), 287 (9), 209 (100), 165 (7), 127 (37), 122 (9), 110 (19), 98 (12), 82 (22).

Anal. Calcd. for C$_{17}$H$_{26}$N$_2$O$_2$Br$_2$: C, 45.35; H, 5.82; N, 6.22; Br, 35.50. Found: C, 45.33; H, 5.81; N, 6.22; Br, 35.49.

1,3-Dicyclohexyl-5-bromomethylhexahydropyrimidine-2,4-dione (25).

To a solution of 0.250 g (0.9 mmole) of 1,3-dicyclohexyl-5-methylen-hexahydropyrimidine-2,4-dione (3a) in 3 ml of dry dichloromethane 0.4 ml (3.7 mmoles) of a solution of hydrogen bromide (45%) was added dropwise. After addition, this mixture was heated at 40° and stirred for 2 hours. The resulting solution was extracted with chloroform:water (3 x 10 ml), dried (sodium sulfate), filtered and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1/4) to afford 0.26 g (78%) of compound 25; ir (chloroform): ν 1760, 1710 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 4.4 (tt, J = 12.0 and 3.6 Hz, 1H, N3-CH), 4.3-4.2 (m, 1H, N1-CH), 3.76 (dd, J = 10.4 and 3.6 Hz, 1H, CHBr), 3.49 (dd, J = 12.8 and 5.2 Hz, 1H, C(6)H$_2$), 3.44 (dd, J = 10.4 and 10.0 Hz, 1H, CHBr), 3.24 (dd, J = 12.8 and 9.2 Hz, 1H, C(5)H), 2.8-2.7 (m, 1H, C(5)H), 2.2-2.1 (m, 2H, N3-CH-CH ax), 1.8-0.8 (m, 18H, CH$_2$); ^{13}C nmr: δ 168.8 (s), 152.9 (s), 54.8 (d), 54.0 (d), 43.9 (d), 39.4 (t), 30.2 (t), 30.1 (t), 29.6 (t), 29.3 (t), 28.9 (t), 26.4 (t), 26.3 (t), 25.5 (t) and 25.3 (t); ms: (EI) m/z 370 (M$^+$, 12), 327 (30), 289 (100), 263 (7), 209 (36), 127 (15), 98 (15), 83 (31), 67 (15).

Anal. Calcd. for C$_{17}$H$_{27}$N$_2$O$_2$Br: C, 54.99; H, 7.33; N, 7.54; Br, 21.52. Found: C, 54.97; H, 7.30; N, 7.54; Br, 21.51.

1,3-Dicyclohexyl-5-ethoxymethylhexahydropyrimidine-2,4-dione (29).

To a solution of sodium ethoxide, prepared from 0.004 g (0.17 g-atom) of finely divided sodium and 1 ml of absolute ethanol, a solution of 0.050 g (0.17 mmole) of 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (3a) previously dissolved in 1 ml of the same solvent was added dropwise. After addition, this mixture was stirred at room temperature for 2 hours, the solvent evaporated and the residue purified by column chromatography (silica gel, ethyl acetate/hexane 1/4) to afford 0.051 g (88%) of compound 29; ir (chloroform): ν 1710, 1660 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 4.3 (tt, J = 11.6 and 3.6 Hz, 1H, N3-CH), 4.2 (tt, J = 12.2 and 3.8 Hz, 1H, N1-CH), 3.7 (dd, J = 9.4 and 4.4 Hz, 1H, C(6)H), 3.5 (d, J = 9.4 Hz, 1H, C(6)H), 3.51-3.4 (m, 2H, O-CH$_2$-CH$_3$), 3.3-3.1 (part of a ABX system, J$_{ab}$ = 12.4 Hz, J$_{ax}$ =8.2 Hz, J$_{bx}$ = 5.2 Hz, 2H, CH$_2$-O), 2.7-2.6 (m, 1H, C(5)H), 2.2 (2 x q, J = 11.6 Hz, 2H, N3-CH-CH ax), 1.7-1.0 (m, 18H, cyclic CH$_2$), 1.2 (t, J = 7.0 Hz, 3H, CH$_3$); ^{13}C nmr: δ 170.1 (s), 153.1

(s), 66.9 (t), 66.6 (t), 54.4 (d), 53.8 (d), 42.4 (d), 38.2 (t), 30.1 (t), 29.8 (t), 29.6 (t), 29.4 (t), 26.4 (t), 25.6 (t), 25.3 (t), 25.4 (t) and 15.0 (q); ms: (EI) m/z 336 (M$^+$, 20), 308 (12), 278 (11), 256 (59), 209 (26), 195 (12), 173 (19), 127 (28), 84 (100), 67 (28).

Anal. Calcd. for $C_{19}H_{32}N_2O_3$: C, 67.82; H, 9.59; N, 8.32. Found: C, 67.81; H, 9.58; N, 8.32

1,3-Dicyclohexyl-5-cyclohexylaminomethylhexahydropyrimidine-2,4-dione (**30**).

To a solution of 0.20 g (0.7 mmole) of 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (**3a**) in 3 ml of dry dichloromethane 0.38 ml (0.68 mmole of cyclohexylamine) of a previously prepared solution from 1.0 ml (0.867 g, 0.0087 mole) of cyclohexylamine and 4.0 ml of dry dichloromethane was added dropwise. Then, this mixture was stirred at 60° for 24 hours, the solvent evaporated and the residue purified by column chromatography (silica gel; ethyl acetate/hexane 1/3) to afford 0.15 g (60%) of compound **30**; ir (chloroform): ν 1704, 1664 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 4.3 (tt, J = 12.0 and 4.2 Hz, 1H, N3-CH), 4.2-4.1 (m, 1H, N1-CH), 3.3-3.1 (part of a ABX system, J_{ab} =12.4 Hz, J_{ax} = 8.6 Hz, J_{bx} = 6.0 Hz, 2H, CH$_2$-N), 2.9 (dd, J = 11.8 and 6.0 Hz, 1H, C(6)H), 2.7 (dd, J = 11.8 and 6.7 Hz, 1H, C(6)H), 2.6-2.5 (m, 1H, NH-C*H*), 2.4-2.3 (m, 1H, C(5)H), 2.3 (2 x q, J = 12.2 Hz, 2H, N3-CH-C*H* ax), 2.0-0.9 (m, 29H, CH$_2$ and N*H*); ^{13}C nmr: δ 171.8 (s), 153.1 (s), 56.8 (d), 54.3 (d), 53.9 (d), 45.2 (t), 42.6 (d), 39.0 (t), 33.7 (t), 33.4 (t), 30.2 (t), 29.9 (t), 29.7 (t), 29.4 (t), 26.5 (t), 26.0 (t), 25.6 (t), 25.4 (t) and 25.0 (t); ms: (EI) m/z 389.5 (M$^+$, 17), 346 (15), 277 (26), 209 (10), 195 (40), 113 (100), 98 (75), 83 (22), 70 (45), 55 (55).

Anal. Calcd. for $C_{23}H_{39}N_3O_2$: C, 70.91; H, 10.09; N, 10.78. Found: C, 70.90; H, 10.0; N, 10.66.

1,3-Dicyclohexyl-5-pyperidinomethylhexahydropyrimidine-2,4-dione (**31**).

This compound was obtained in 58% yield from 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (**3a**) and pyperidine following the same procedure as indicated; ir (chloroform): ν 1700, 1660 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 4.3 (tt, J = 12.0 and 3.6 Hz, 1H, N3-CH), 4.2-4.1 (m, 1H, N1-CH), 3.2 (dd, J = 2.6 and 1.6 Hz, 2H, CH$_2$-N), 3.1 (dd, J = 6.0 and 5.6 Hz, 2H, CH$_2$-N), 2.7-2.6 (m, 1H, C5), 2.5-2.4 (m, 4H, N-C*H*$_2$-CH$_2$), 2.2-2.1 (m, 2H, N3-CH-C*H* ax), 1.9-1.1 (m, 24H, CH$_2$); ^{13}C nmr: δ 171.7 (s), 153.1 (s), 56.0 (t), 54.4 (t), 54.1 (d), 53.8 (d), 44.5 (t), 39.7 (d), 38.3 (t), 29.9 (t), 29.5 (t), 29.4 (t), 26.4 (t), 25.9 (t), 25.6 (t) and 25.5 (t); ms: (EI) m/z 375 (M$^+$, 10), 278 (13), 234 (9), 209 (55), 195 (53), 167 (25), 152 (29), 138 (28), 124 (52), 113 (72), 98 (100), 84 (22).

Anal. Calcd. for $C_{22}H_{37}N_3O_2$: C, 70.36; H, 9.93; N, 11.19. Found: C, 70.30; H, 9.91; N, 11.13.

1,3-Dicyclohexyl-5-propanthiomethylhexahydropyrimidine-2,4-dione (**32**).

To a solution of 0.14 g (0.49 mmole) of 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (**3a**) in 5 ml of dry dichloromethane at room temperature, 0.04 ml (0.49 mmole) of propanothiol containing a drop of 1,8-diazabicyclo[5.4.0]undec-7-ene was dropwise added. After addition, this mixture was stirred for 12 hours. The resulting solution was evaporated. The residue was purified by column chromatography (silica gel; ethyl acetate/hexane 1/4) to afford 0.04 g (20%) of compound **32**; ir (chloroform): ν 1700, 1650 (*CONRCONRR'*) cm^{-1};

^{1}H nmr: δ 4.3 (tt, J = 12.2 and 3.6 Hz, 1H, N3-CH), 4.2-4.1 (m, 1H, N1-CH), 3.6-3.4 (m, 1H, CH C(6)H), 3.3-3.1 (m, 1H, CH C(6)H), 3.0-2.7 (m, 2H, S-C*H*$_2$), 2.6-2.4 (m, 3H, CH$_2$-S, C(5)H), 2.3-2.0 (m, 2H, N3-CH-C*H* ax), 1.9-1.1 (m, 20H, CH$_2$), 0.9 (t, J = 7.2 Hz, 3H, CH$_3$); ^{13}C nmr: δ 170.9 (s), 153.0 (s), 54.5 (d), 53.9 (d), 41.8 (d), 39.0 (t), 34.5 (t), 30.1 (t), 29.5 (t), 29.4 (t), 29.4 (t), 26.4 (t), 25.9 (t), 25.3 (t), 22.7 (t) and 13.3 (q).

Anal. Calcd. for $C_{20}H_{34}N_2O_2S$: C, 65.53; H, 9.35; N, 7.64; S, 8.75. Found: C, 65.52; H, 9.33; N, 7.62; S, 8.74.

1,3-Dicyclohexylhexahydrothymine (**33**).

To a stirred and cooled at 0° solution of 0.050 g (0.17 mmole) of 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (**3a**) in 2 ml of hexane under a nitrogen atmosphere, 0.17 ml (0.17 mmole) of a 0.1 *M* solution of diisobutylaluminum hydride (DIBAL) in hexane was added. After addition, the mixture was allowed to stand at room temperature, under stirring until tlc elution of an aliquot (ethyl acetate/hexane 1/4) indicated complete reaction after 18 hours. The resulting solution was evaporated, the residue extracted with hexane:water (3 x 10 ml), dried (sodium sulfate), filtered and evaporated. The solid was purified by column chromatography (silica gel; ethyl acetate/hexane 1/4) to afford 0.03 g (48%) of compound **33**; ir (chloroform): ν 1710, 1665 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 4.4 (tt, J = 12.0 and 3.6 Hz, 1H, N3-CH), 4.3-4.2 (m, 1H, N1-CH), 3.3 (dd, J = 12.5 and 5.4 Hz, 1H, C(6)H), 2.9 (dd, J = 12.5 and 9.6 Hz, 1H, C(6)H), 2.6-2.4 (m, 1H, C(5)H), 2.3 (2 x q, J = 12.0 Hz, 2H, N3-CH-C*H* ax), 1.8-1.3 (m, 18H, CH$_2$), 1.2 (d, J = 7.0 Hz, 3H, CH$_3$); ^{13}C nmr: δ 172.7 (s), 153.3 (s), 54.3 (d), 53.7 (d), 42.2 (t), 36.5 (d), 30.3 (t), 30.0 (t), 29.8 (t), 29.3 (t), 26.5 (t), 26.4 (t), 25.6 (t), 25.4 (t) and 13.4 (q); ms: (EI) m/z 293 (M$^+$,30), 250 (28), 212 (100), 167 (9), 129 (27), 112 (8), 98 (8), 83 (10), 69 (7).

Anal. Calcd. for $C_{17}H_{23}N_2O_2$: C, 69.83; H, 9.65; N, 9.58. Found: C, 69.80; H, 9.59; N, 9.56.

1,3-Dicyclohexylthymine (**34**).

A solution of 0.050 g (0.17 mmole) of 1,3-dicyclohexyl-5-methylenehexahydropyrimidine-2,4-dione (**3a**) in 3 ml of absolute ethanol was hydrogenated, at room temperature and under atmospheric pressure, using a 10% (4 mg) of platinum oxide as catalyst. After 2 hours the mixture was filtered and evaporated. The residue was identified as a mixture of compounds **33** and **34** in a ratio 3:2 respectively from its ^{1}H nmr.

The spectral data for 1,3-dicylohexylthymine (**34**) were obtained by excluding the signals of product **33**, independently prepared, from those of the inseparable mixture of **33** and **34**.

This compound had ir (chloroform): ν 1690, 1660 (*CO* α,β-conj), 1650 (C=C) cm^{-1} ; ^{1}H nmr: δ 6.9 (s, 1H, C(6)H), 4.7-4.6 (m, 1H, N3-CH), 4.3-4.2 (m, 1H, N1-CH), 2.3-2.2 (m, 2H, N3-CH-C*H*), 1.9 (s, 3H, CH$_3$), 1.8-1.0 (m, 18H, CH$_2$); ^{13}C nmr: δ 163.8 (s), 151.4 (s), 134.4 (d), 109.6 (s), 54.2 (d), 53.1 (d), 30.3 (t), 30.0 (t), 29.8 (t), 29.3 (t), 26.5 (t), 26.4 (t), 25.6 (t), 25.4 (t) and 13.4 (q).

1,3-Dipropylthymine (**36**).

A solution of 1,3-diallyl-5-methylenehexahydropyrimidine-2,4-dione (**3d**) 0.1 g (0.48 mmole) in 3 ml of absolute ethanol was hydrogenated on 10% platinum oxide (10 mg) as catalyst, at room temperature under atmospheric pressure. After 2 hours the mixture was filtered and evaporated to yield 0.07 g (70%) of the compound **36**; ir (chloroform): ν 1693, 1666 (*CO* α,β-unsaturat), 1650 (C=C), 1463 (CH$_3$) cm^{-1}; ^{1}H nmr: δ 6.9 (s, 1H,

C(6)H), 3.9 (t, J = 7.4 Hz, 2H, N-CH$_2$), 3.6 (t, J = 7.4 Hz, 2H, N-CH$_2$), 1.9 (s, 3H, CH$_3$), 1.7-1.5 (m, 4H, CH$_2$), 0.9-0.8 (2xt, J = 7.5 and 7.5 Hz, 6H, CH$_3$); ^{13}C nmr: δ 163.8 (s), 151.4 (s), 138.3 (d), 109.6 (s), 50.9 (t), 42.9 (t), 22.3 (t), 20.8 (t), 13.1 (q), 11.3 (q) and 10.9 (q); ms: (EI) m/z 210 (M$^+$, 28), 195 (7), 181 (7), 168 (52), 153 (12), 140 (20), 126 (100), 110 (17), 96 (80), 84 (47), 70 (11), 49 (88).

Anal. Calcd. for C$_{11}$H$_{18}$N$_2$O$_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.80; H, 8.61; N, 13.21.

2-Ureylidene-2,3,4,5-tetrahydrofuran (**37**).

A solution of 0.17 g (0.56 mmole) of 1,3-dibenzyl-5-methyl-enehexahydropyrimidine-2,4-dione (**3e**) in 3 ml of THF was added, at room temperature and stirring, to 1.24 g (2.26 mmoles) of ammonium cerium(IV) nitrate dissolved in 4 ml of a solution of acetonitrile-water (100:1). After the mixture was allowed to react for 2 hours, the resulting solution was filtered, evaporated and the residue obtained was purified by column chromatography (silica gel; ethyl acetate/hexane 1/3) to afford 0.04 g (59%) of compound **37**; ir (chloroform): ν 3438 (NH), 1772, 1718, 1670 (*CONRCONRR'*) cm^{-1}; ^{1}H nmr: δ 10.0 (bs, 1H, NH), 8.1 (bs, 1H, NH), 4.3 (t, J = 7.0 Hz, 2H, O-CH$_2$), 2.5-2.4 (m, 2H, CH$_2$), 2.3-2.1 (m, 2H, CH$_2$); ^{13}C nmr: δ 177.7 (s), 160.6 (s), 68.5 (t), 27.8 (t) and 27.2 (t); ms: (EI) m/z 128 (M$^+$, 10), 86 (80), 71 (100).

Anal. Calcd. for C$_5$H$_8$N$_2$O$_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.87; H, 6.29; N, 21.85.

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