Synthesis of Ethyl 2-Aminodihydro-5-pyrimidinecarboxylate Derivatives and 3,7-Diethoxycarbonyl-4,6-dihydro-2,4,6,8-tetraaryl-1*H*-pyrimido[1,2-*a*]pyrimidines

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Reactions of ethyl 3-aryl-2-benzoylpropenoates **1** with guanidine and *N*-alkyl(or benzyl)guanidines have been investigated. Ethyl 2-aminodihydro-5-pyrimidinecarboxylate derivatives **3**, **4** or **5**, and 3,7-diethoxycarbonyl-4,6-dihydro-2,4,6,8-tetraaryl-1*H*-pyrimido[1,2-*a*]pyrimidines **6** have been synthesized.

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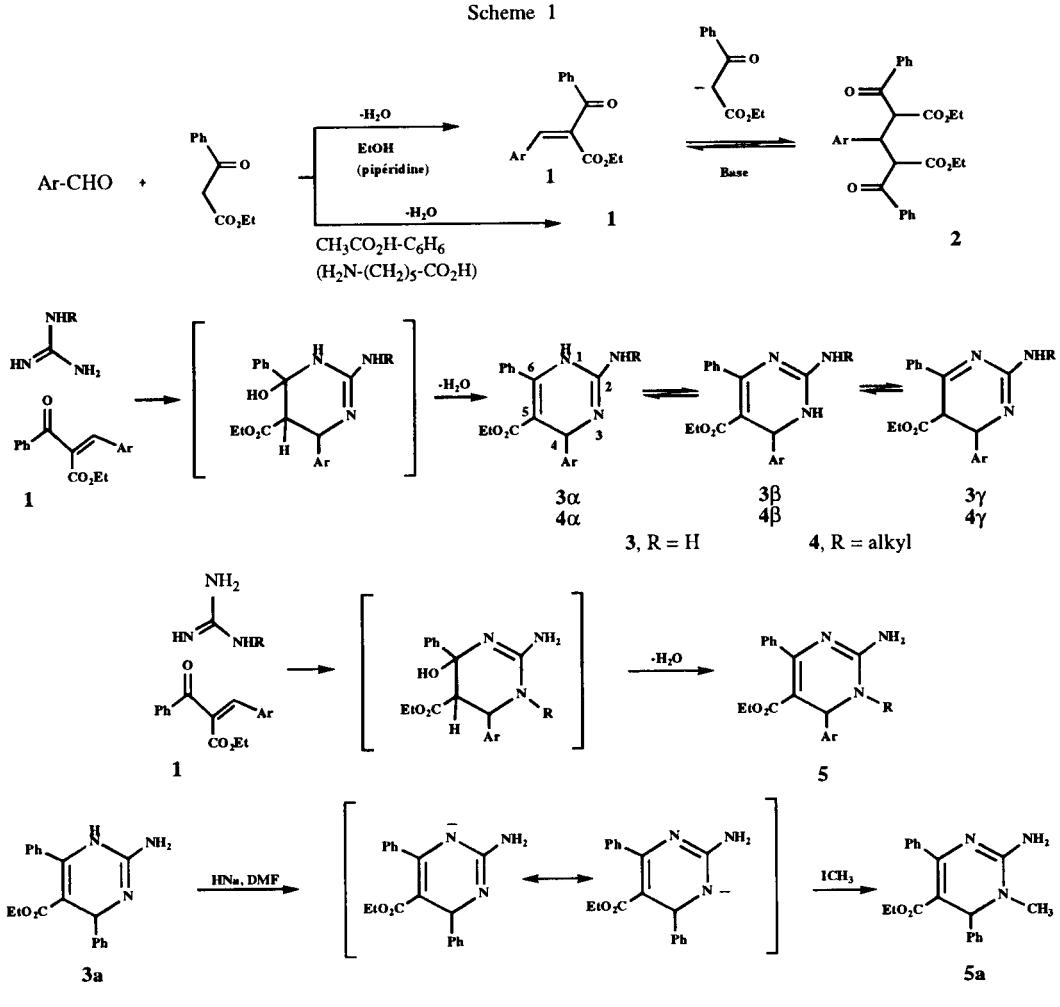
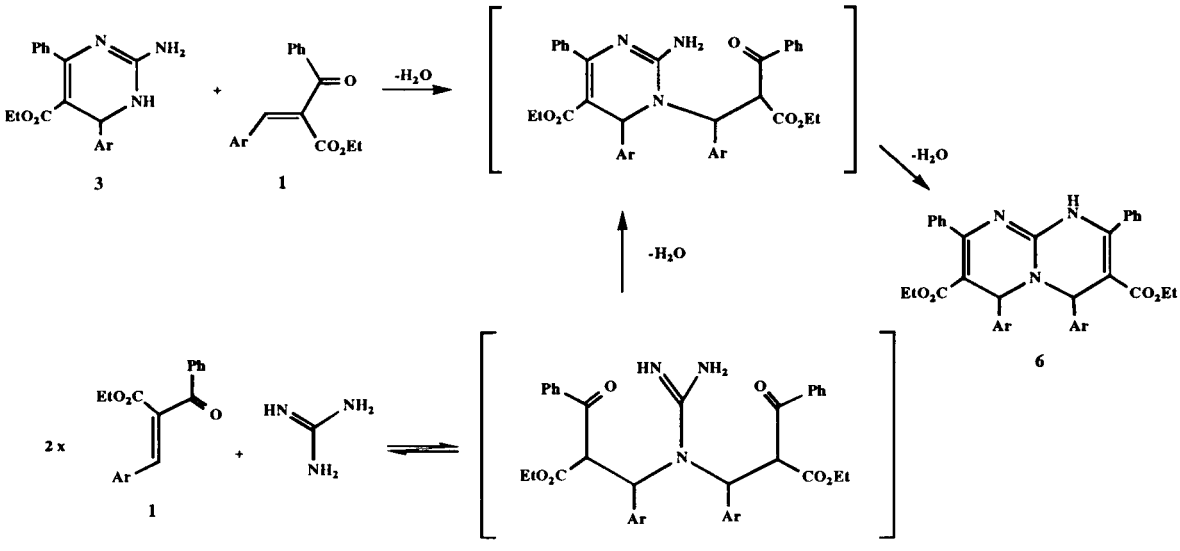
The 1,4-dihydropyrimidines have many biological activities. For example, they represent the largest and most studied class of organic calcium channel blockers widely used in the management of angina pectoris and hypertension as some dihydropyridines (*e.g.*, Nifedipine) [1]. The Crambines, naturally occurring cytotoxic molecules extracted from the *Crambe crambe* sponges [2] are 1,4-dihydropyrimidine derivatives.

The aim of this work was to synthesize new ethyl 2-aminodihydro-5-pyrimidinecarboxylate derivatives in

Scheme 1



Scheme 2



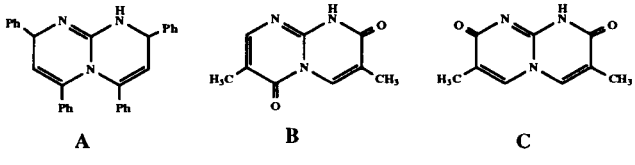


Figure 1

order to study their biological activity. In this series, some derivatives have been synthesized. They were substituted at positions 4 and 6 by one alkyl group and one aryl group [3-5]. We report here the synthesis of unknown derivatives disubstituted by two aryl groups at these positions. These compounds were prepared by reaction of ethyl 3-aryl-2-benzoylpropenoates **1** with guanidine, for compounds **3**, or with *N*-alkyl(or benzyl)guanidines for compounds **4** and **5** (Scheme 1). As reported in the literature [6-8], compounds **1**, besides diethyl 2,4-dibenzoylglutarate derivatives **2**, were the result of the reaction of ethyl benzoylacetate with various aromatic aldehydes in ethanol in the presence of piperidine. Compound **1** was predominated when benzaldehyde or 4-hydroxybenzaldehyde was used. But with 4-methoxybenzaldehyde, 4-methylbenzaldehyde, or 4-nitrobenzaldehyde, the corresponding compound **2** was obtained in a very high yield. As reported in the literature, the separation of **1** from **2** was often very difficult. However, compounds **1** were prepared without side products in good yields by using 6-aminohexanoic acid as a catalyst, in the presence of acetic acid, according to the method of Prout for the synthesis of alkylidenecyanoacetates [9].

Compounds **1** were treated with guanidine, or its alkyl(or benzyl) derivatives at 60-80° in dimethylformamide for 8 to 48 hours. When guanidine was used, two compounds were isolated, a dihydropyrimidine **3** and a 3,7-diethoxycarbonyl-4,6-dihydro-2,4,6,8-tetraaryl-1*H*-pyrimido[1,2-*a*]pyrimidine **6** (Scheme 2). With alkyl(or benzyl)guanidines, the dihydropyrimidines **4** were obtained in the presence of a very small quantity of their isomers **5** but without any formation of bicyclic compounds **6**. Only **5a** has been isolated. As reported by Cho *et al.* [4] for compounds of the same series, the N-3 nitrogen should bear a greater electron density than N-1 and therefore be more nucleophilic in the mesomeric anion formed by the action of sodium hydride on **3a**. Addition of methyl iodide to this anion gave a compound which was **5a**. This result confirmed its proposed structure.

No example of the fused heterocyclic system of **6** was reported in the literature. However, some compounds structurally close to **6** are known. The 1,8-dihydro-2,4,6,-8-tetraphenyl-1*H*-pyrimido[1,2-*a*]pyrimidine (**A**) was the result of the reaction of 1,3-diphenyl-2-propen-1-one with guanidine [10]. As by-products of a guanidine based thymine synthesis, 3,7-dimethyl-1*H*-pyrimido[1,2-*a*]-pyrimidine-2,6-dione **B** or the corresponding 2,8-dione **C** were isolated [11].

Formation of **6** in the reaction between esters **1** and guanidine could be the result of a Michael type addition of the cyclic secondary amino group of the dihydropyrimidine **3** formed in a first step, with a second molecule of ester **1**, followed by ring closure and dehydration to give **6**. If this proposed mechanism is correct, **6** could be formed through treatment of dihydropyrimidines **3** with esters **1** in alkaline media. Experimental assays under various conditions failed to establish this point. An alternative mechanism could first be a formation of an acyclic intermediate from the reaction of two molecules

Table 1

Ethyl 2-Aminodihydro-5-pyrimidinecarboxylate Derivatives **3** and **4**

No.	Ar	R	Yield % [a]	Mp °C	Mp °C [b]	Formula (mol.wt.)	Analyses, % Calcd./Found C H N	IR, ν cm^{-1}	^{1}H NMR [c] δ ppm
3a	Ph	H	39	295 dec [d]	210	$C_{19}H_{19}N_3O_2$ (321.36)	71.01 5.96 13.08 71.01 5.93 13.17	3390, 3330, 1650, 1630, 1565	0.75 (t, 3H), 3.7 (q, 2H), 5.3 (s, 1H), 6.35 (bs, 2H), 7.1-7.4 (m, 10H), 7.5 (bs, 1H)
3b	4-MePh	H	30	284 [d]	200	$C_{20}H_{21}N_3O_2$ (335.39)	71.62 6.31 12.53 71.48 6.25 12.67	3400, 3300, 1650, 1615, 1580	0.75 (t, 3H), 2.3 (s, 3H), 3.7 (q, 2H), 5.3 (s, 1H), 6.25 (bs, 2H), 7.1-7.5 (m, 10H)
3c	4-MeOPh	H	34	272-275 [e]	245	$C_{20}H_{21}N_3O_3$ (351.39)	68.36 6.02 11.96 68.54 6.01 11.92	3400, 3300, 1650, 1610 (b), 1580	0.75 (t, 3H), 3.65 (q, 2H), 3.75 (s, 3H), 5.25 (s, 1H), 6.25 (bs, 2H), 6.9 (d, 2H), 7.2-7.3 (m, 7H), 7.4 (bs, 1H)
3d	4-ClPh	H	42	285 [d]	220	$C_{19}H_{18}ClN_3O_2$ (355.81)	64.13 5.10 11.81 64.27 5.13 11.89	3400, 3300, 1650, 1615, 1570 (b)	0.75 (t, 3H), 3.7 (q, 2H), 5.35 (s, 1H), 6.4 (bs, 2H), 7.1-7.5 (m, 10H)
3e	4-NO_2Ph	H	36	262 [e]	264	$C_{19}H_{18}N_4O_4$ (366.36)	62.29 4.95 15.29 62.07 4.91 15.41	3430, 3380, 3300, 1650, 1630, 1570	0.75 (t, 3H), 3.7 (q, 2H), 5.5 (s, 1H), 6.5 (bs, 2H), 7.3 (bs, 6H), 7.7 and 8.3 (2d, 4H)
4a	Ph	Me	45	247 [d]	172	$C_{20}H_{21}N_3O_2$ (335.39)	71.62 6.31 12.53 71.20 6.39 12.64	3300, 3200, 3110, 1630, 1600 (b)	0.75 (t, 3H), 2.7 (s, 3H), 3.7 (q, 2H), 5.3 (s, 1H), 6.55 and 7.55 (2bs, 2H), 7.15-7.4 (m, 10H)
4b	4-MePh	Me	47	207 [e]	176	$C_{21}H_{23}N_3O_2$ (349.42)	72.18 6.64 12.03 72.04 6.66 12.13	3310, 3200, 3110, 1630, 1590 (b)	0.75 (t, 3H), 2.3 (s, 3H), 2.65 (s, 3H), 3.75 (q, 2H), 5.35 (s, 1H), 6.9 (bs, 1H), 7.1-7.5 (m, 10H)
4c	4-ClPh	Me	50	232 [e]	130 dec	$C_{20}H_{20}ClN_3O_2$ (369.83)	64.95 5.45 11.36 65.12 5.43 11.40	3300, 3210, 3110, 1630, 1590 (b)	0.75 (t, 3H), 2.7 (s, 3H), 3.75 (q, 2H), 5.35 (s, 1H), 6.6 and 7.6 (2bs, 2H), 7.1-7.5 (m, 9H)
4d	Ph	Et	47	148 dec [f,g]	140	$C_{21}H_{23}N_3O_2$ (349.42)	72.18 6.64 12.03 72.10 6.71 12.10	3300, 3200, 3110, 1630, 1580 (b)	0.75 and 1 (2t, 6H), 3.2 (m, 2H), 3.7 (q, 2H), 5.3 (s, 1H), 6.6 and 7.5 (2bs, 2H), 7.15-7.4 (m, 10H)
4e	Ph	nPr	51	136 dec [f,g]	[h]	$C_{22}H_{25}N_3O_2$ (363.44)	72.70 6.93 11.56 73.00 7.07 11.62	3310, 3210, 3120, 1650, 1580 (b)	0.75 and 0.85 (2t, 6H), 1.35-1.55 (m, 2H), 3.1 (m, 2H), 3.7 (q, 2H), 5.3 (s, 1H), 6.6 (bs, 1H), 7.15-7.5 (m, 11H)
4f	Ph	nBu	63	135 dec [f,g]	130	$C_{23}H_{27}N_3O_2$ (377.47)	73.18 7.21 11.13 73.48 7.25 11.77	3310, 3210, 3100, 1630, 1580 (b)	0.75 and 0.85 (2t, 6H), 1.15-1.5 (m, 4H), 3.15 (m, 2H), 3.7 (q, 2H), 5.3 (s, 1H), 6.65 (bs, 1H), 7.1-7.5 (m, 11H)
4g	Ph	$PhCH_2$	72	164 [f,g]	183	$C_{26}H_{25}N_3O_2$ (411.48)	75.89 6.12 10.21 75.81 6.14 10.10	3300, 3200, 3100, 1630, 1585	0.8 (t, 3H), 3.75 (t, 2H), 4.35 and 4.5 (2d, 2H), 5.35 (s, 1H), 7.1 and 7.55 (2bs, 2H), 7.15-7.45 (m, 15H)

[a] Non optimized yields. [b] Picrate derivative; recrystallization solvent for **3a**, **4c**,**g**: methanol and others ethanol. [c] In DMSO-d_6. [d] 1-Butanol. [e] Ethanol. [f] Ethyl acetate. [g] Petroleum ether 40-60. [h] This compound was obtained as a resinous product.

Table 2

3,7-Diethoxycarbonyl-4,6-dihydro-2,4,6,8-tetraaryl-1*H*-pyrimido[1,2-*a*]pyrimidines **6**

6	Ar	Yield % [a]	Mp °C	Mp °C [b]	Formula (mol.wt.)	Analysis, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [c] δ ppm
a	Ph	24	253 [d,e]	230 [f]	$C_{37}H_{33}N_3O_4$ (583.66)	76.14 75.66	5.70 5.68	7.20 7.14	3400 (b), 1660, 1590	0.75 (t, 2 x 3H), 3.7 (m, 4H), 5.35 (s, 2 x 1H), 6.9-7.5 (m, 21H)
b	4-MePh	39	278-280 [f]	236 [g]	$C_{39}H_{37}N_3O_4$ (611.71)	76.57 76.42	6.10 6.12	6.87 6.96	3400 (b), 1660, 1590	0.75 (t, 2 x 3H), 2.4 (s, 2 x 3H), 3.7 (m, 4H), 5.25 (s, 2 x 1H), 6.95 (d, 4H), 7.1-7.4 (m, 15H)
c	4-MeOPh	14	315 [d,h]	246 [g]	$C_{39}H_{37}N_3O_6$ (643.71)	72.76 72.75	5.79 5.83	6.53 6.51	3400 (b), 1660, 1590	0.75 (t, 2 x 3H), 3.7 (m, 4H), 3.85 (s, 2 x 3H), 5.25 (s, 2 x 1H), 6.9-7.4 (m, 19H)
d	4-ClPh	35	290 [f]	263 [f]	$C_{37}H_{31}Cl_2N_3O_4$ (652.55)	68.10 68.24	4.79 4.69	6.44 6.51	3400 (b), 1660, 1590	0.75 (t, 2 x 3H), 3.7 (m, 4H), 5.25 (s, 2 x 1H), 6.9 (d, 4H), 7.05-7.45 (m, 15H)
e	4-NO_2Ph	25	298 [f]	282 [f]	$C_{37}H_{31}N_5O_8$ (673.65)	65.96 65.94	4.64 4.48	10.40 10.45	3400 (b), 1660, 1590	0.75 (t, 2 x 3H), 3.75 (q, 4H), 5.4 (s, 2 x 1H), 6.95 (d, 4H), 7-7.6 (m, 11H), 8.35 (d, 4H)
f	4-HOPh	55	274 [i,j]	185 [i]	$C_{37}H_{33}N_3O_6 \cdot H_2O$ (633.67) [k]	70.12 70.33	5.57 5.64	6.63 6.69	3400 (b), 3200 (b), 1650, 1630, 1595	0.75 (t, 2 x 3H), 3.6 (q, 4H), 5.2 (s, 2 x 1H), 6.85 (d, 4H), 7-7.35 (m, 15H), 9.9 (bs, 2H)

[a] Non optimized yields. [b] Picrate derivative. [c] **6a-e** in deuteriochloroform and **6f** in DMSO-d_6. [d] Ethyl acetate. [e] Petroleum ether 40-60. [f] 1-Butanol. [g] Ethanol. [h] Chloroform. [i] Methanol. [j] Water. [k] Calculated with 1 mole of water.

Table 3

Experimental Data for the Crystallographic Analysis of **6b**

Formula	$C_{39}H_{37}O_4N_3$ (611,71)
a (Å)	14.839(5)
b (Å)	15.482(5)
c (Å)	15.628(3)
α (°)	88.29(2)
β (°)	71.22(2)
γ (°)	78.93(3)
V (Å^3)	3334(30)
Z	4
Crystal system	triclinic
Space group	P -1
Linear absorption coefficient μ (cm^{-1})	0.74
Density ρ (g.cm^{-3})	1.22
Diffractometer	CAD4 - Enraf-Nonius
Radiation	MoKα (λ = 0.71069 Å)
Scan type	ω /2θ
Scan range (°)	0.8 + 0.345 tgθ
θ Limits (°)	1 - 22
Temperature of measurement	room temperature
Octants collected	h: -14, 15; k: -18, 16; l: 0, 16
Nb of data collected	8774
Nb of unique data collected	8202
Nb of unique data used for refinement	4308 $(Fo)^2 > 3\sigma(Fo)^2$
R (int)	0.021
$R = \Sigma \mid\mid Fo \mid - \mid Fc \mid\mid / \Sigma \mid Fo \mid$	0.054
$Rw = \Sigma w(\mid Fo \mid - \mid Fc \mid)^2 / \Sigma wFo^2$	0.053, w = 1.0
Extinction parameter (x 10^6)	216
Goodness of fit *s*	2.5
Nb of variables	832
Δρmin (e.Å^{-3})	-0.22
Δρmax (e.Å^{-3})	0.32

of ester **1** with one molecule of guanidine, through two consecutive Michaël type additions. Then, two successive cyclizations with elimination of two molecules of water could afford the bicyclic system of **6**.

When the reaction was carried out at a 6:1 guanidine/-ester **1** molar ratio, dihydropyrimidines **3** were almost exclusively obtained. On the other hand, at a 1:5 molar ratio, compounds **6** were obtained in addition to **3** with better yields. These results favor the second proposed mechanism.

To the resulting compounds **3** and **4** must correspond an equilibrium between several tautomers: 1,4 or 3,4 or 4,5-dihydropyrimidines *i.e.* structures **3**α and **4**α, or **3**β and **4**β, or **3**γ and **4**γ, respectively. However, the possibility of 4,5-dihydropyrimidines **3**γ or **4**γ was ruled out since the ^{1}H nmr spectra exhibited the signal of the C-4 methine proton as a singlet at 5.25-5.5 ppm. The broad singlet of the amino group was present in all the spectra of **3** as a singlet at 6.25-6.5 ppm. The spectra of compounds **4** showed two signals of the NH groups as two singlets at 6.5-7.1 and 7.5-7.6 ppm. The ^{13}C nmr spectra of **3** and **4** confirmed the proposed structural features (Figure 2).

The ^{1}H and ^{13}C nmr spectra of **6** showed a symmetry consistent with the assigned structure and which was confirmed by a X-ray crystallographic study of **6b** (Figure 3).

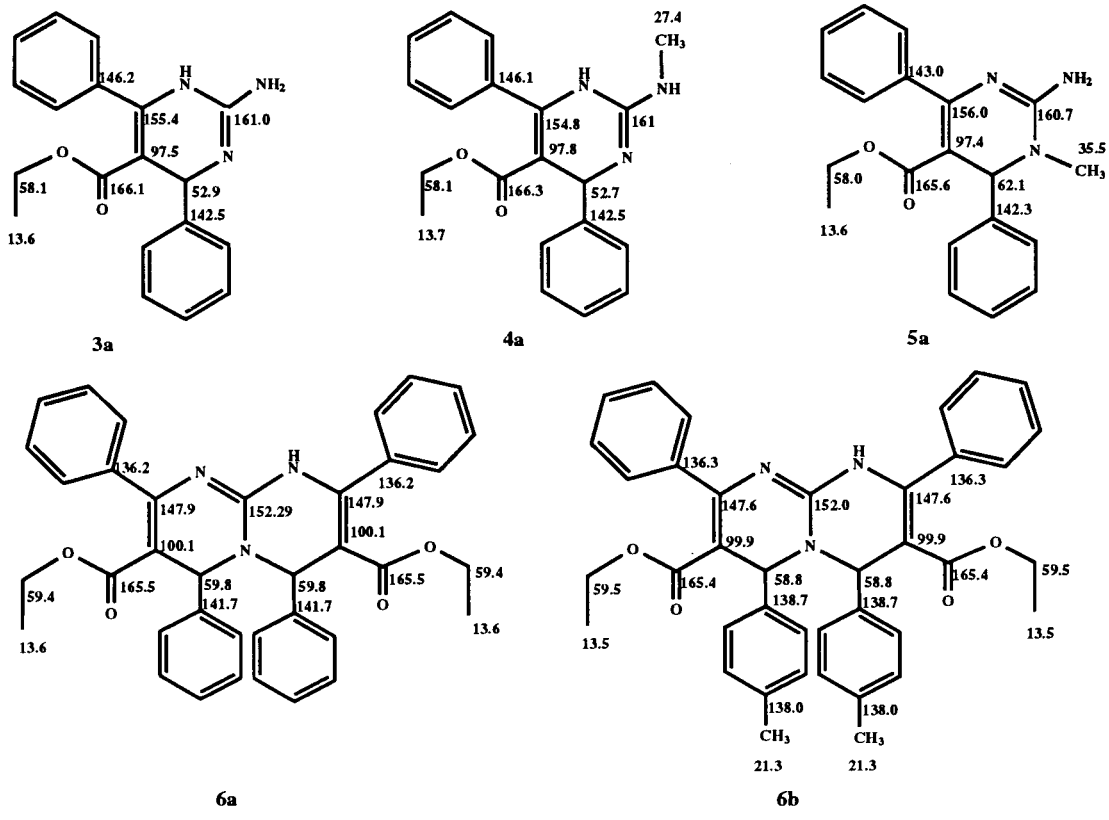


Figure 2. ^{13}C nmr spectral data.

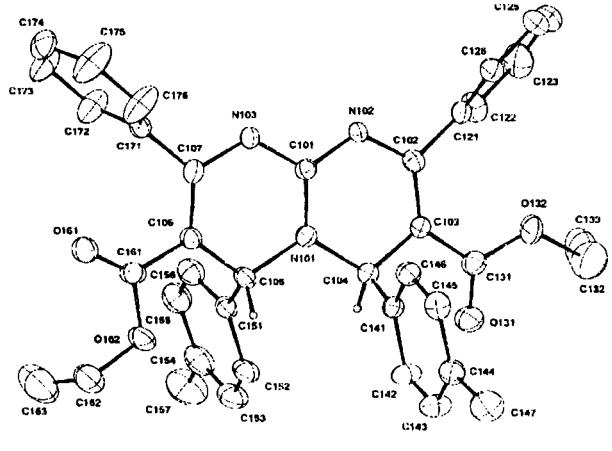


Figure 3. A CAMERON view of the molecule $\mathbf{6b_2}$ with 20% probability ellipsoids.

Selected pertinent crystallographic data are tabulated in Tables 3-5 for **6b**.

The ethyl 2-amino-4-aryl-6-phenyldihydropyrimidinecarboxylates **3** and the ethyl 2-alkyl(or benzyl)amino-4-aryl-6-phenyl-1,4-dihydropyrimidinecarboxylates **4** are presented in Table 1 and the 3,7-diethoxycarbonyl-4,6-dihydro-2,4,6,8-tetraaryl-1*H*-pyrimido[1,2-*a*]pyrimidines **6** are presented in Table 2.

The new dihydropyrimidines **3** and **4** were stable to air oxidation.

Compounds **3**, **4** and **6** gave picrates which were obtained as greasy compounds. Their recrystallization was very difficult or impossible in some cases (Tables 1 and 2). Hydrochlorides of **3**, **4** and **6** were also formed but they were not stable.

EXPERIMENTAL

Melting points (uncorrected) were determined by using a Buchi 510 capillary melting point apparatus. The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer as potassium bromide disks. The ^1H and ^{13}C nmr spectra were recorded on a Bruker 200 MHz spectrometer using tetramethylsilane as the internal standard. Analytical data were determined for new compounds.

Table 4

Selected Interatomic Distances (Å) of **6b$_1$** and **6b$_2$**

C(1) - N(1)	1.340(6)	C(1) - N(2)	1.332(6)
C(1) - N(3)	1.354(6)	N(1) - C(4)	1.470(6)
N(1) - C(5)	1.474(6)	C(2) - N(2)	1.384(6)
C(2) - C(3)	1.367(7)	C(2) - C(21)	1.473(7)
C(3) - C(4)	1.501(7)	C(3) - C(31)	1.461(7)
N(3) - C(7)	1.404(6)	C(4) - C(41)	1.510(7)
C(5) - C(6)	1.515(7)	C(5) - C(51)	1.513(7)
C(6) - C(7)	1.355(7)	C(6) - C(61)	1.475(8)
C(7) - C(71)	1.478(7)	O(31) - C(31)	1.207(6)
C(31) - O(32)	1.325(7)	O(32) - C(32)	1.458(9)
C(32) - C(33)	1.46(1)	O(61) - C(61)	1.204(7)
C(61) - O(62)	1.314(7)	O(62) - C(62)	1.514(9)
C(62) - C(63)	1.37(1)		
C(101) - N(101)	1.343(6)	C(101) - N(102)	1.329(6)
C(101) - N(103)	1.349(6)	N(101) - C(104)	1.479(6)
N(101) - C(105)	1.499(6)	C(102) - N(102)	1.390(6)
C(102) - C(103)	1.348(7)	C(102) - C(121)	1.493(7)
C(103) - C(104)	1.517(7)	C(103) - C(131)	1.453(7)
N(103) - C(107)	1.396(6)	C(104) - C(141)	1.510(8)
C(105) - C(106)	1.493(7)	C(105) - C(151)	1.510(8)
C(106) - C(107)	1.348(7)	C(106) - C(161)	1.467(8)
C(107) - C(171)	1.486(7)	O(131) - C(131)	1.206(7)
C(131) - O(132)	1.337(7)	O(132) - C(132)	1.458(9)
C(132) - C(133)	1.39(2)	O(161) - C(161)	1.192(7)
C(161) - O(162)	1.340(7)	O(162) - C(162)	1.473(9)
C(162) - C(163)	1.40(1)		

Table 5

Selected Bond Angles (°) of **6b$_1$** and **6b$_2$**

N(1) - C(1) - N(2)	123.7(5)	N(1) - C(1) - N(3)	120.1(5)
N(2) - C(1) - N(3)	116.2(5)	C(1) - N(1) - C(4)	119.8(4)
C(1) - N(1) - C(5)	122.5(4)	C(4) - N(1) - C(5)	117.6(4)
N(2) - C(2) - C(3)	120.7(5)	N(2) - C(2) - C(21)	113.8(5)
C(3) - C(2) - C(21)	125.5(5)	C(1) - N(2) - C(2)	117.7(5)
C(2) - C(3) - C(4)	118.8(5)	C(2) - C(3) - C(31)	126.2(6)
C(4) - C(3) - C(31)	114.7(5)	C(1) - N(3) - C(7)	120.5(5)
N(1) - C(4) - C(3)	108.9(4)	N(1) - C(4) - C(41)	111.1(4)
C(3) - C(4) - C(41)	112.2(4)	N(1) - C(5) - C(6)	109.2(4)
N(1) - C(5) - C(51)	110.2(4)	C(6) - C(5) - C(51)	115.6(4)
C(5) - C(6) - C(7)	120.5(5)	C(5) - C(6) - C(61)	111.5(5)
C(7) - C(6) - C(61)	128.0(5)	N(3) - C(7) - C(6)	119.5(5)
N(3) - C(7) - C(71)	111.3(5)	C(6) - C(7) - C(71)	129.1(5)
C(3) - C(31) - O(31)	124.0(6)	C(3) - C(31) - O(32)	114.0(6)
O(31) - C(31) - O(32)	121.9(6)	C(31) - O(32) - C(32)	118.9(5)
O(32) - C(32) - C(33)	108.3(6)	C(6) - C(61) - O(61)	122.6(6)
C(6) - C(61) - O(62)	115.1(6)	O(61) - C(61) - O(62)	122.3(6)
C(61) - O(62) - C(62)	116.8(6)	O(62) - C(62) - C(63)	107.0(9)
N(101) - C(101) - N(102)	124.3(5)	N(101) - C(101) - N(103)	120.4(5)
N(102) - C(101) - N(103)	115.2(5)	C(101) - N(101) - C(104)	121.6(4)
C(101) - N(101) - C(105)	123.3(4)	C(104) - N(101) - C(105)	115.1(4)
N(102) - C(102) - C(103)	122.4(5)	N(102) - C(102) - C(121)	112.1(5)
C(103) - C(102) - C(121)	125.5(5)	C(101) - N(102) - C(102)	117.7(4)
C(102) - C(103) - C(104)	120.9(5)	C(102) - C(103) - C(131)	127.0(5)
C(104) - C(103) - C(131)	112.2(5)	C(101) - N(103) - C(107)	121.0(5)
N(101) - C(104) - C(103)	109.9(4)	N(101) - C(104) - C(141)	111.2(4)
C(103) - C(104) - C(141)	110.7(5)	N(101) - C(105) - C(106)	109.9(4)
N(101) - C(105) - C(151)	110.4(4)	C(106) - C(105) - C(151)	114.0(5)
C(105) - C(106) - C(107)	121.8(5)	C(105) - C(106) - C(161)	118.6(5)
C(107) - C(106) - C(161)	119.6(5)	N(103) - C(107) - C(106)	120.8(5)
N(103) - C(107) - C(171)	112.0(5)	C(106) - C(107) - C(171)	127.2(5)
C(103) - C(131) - O(131)	123.9(6)	C(103) - C(131) - O(132)	113.8(5)
O(131) - C(131) - O(132)	122.2(6)	C(131) - O(132) - C(132)	119.2(6)
O(132) - C(132) - C(133)	105.2(9)	C(106) - C(161) - O(161)	127.7(6)
C(106) - C(161) - O(162)	110.1(5)	O(161) - C(161) - O(162)	122.2(6)
C(161) - O(162) - C(162)	115.2(5)	O(162) - C(162) - C(163)	107.2(10)

Ethyl 3-Aryl-2-benzoylpropenoates **1**.

Compounds **1a** (Ar = Ph) and **1f** (Ar = 4-HO-Ph) were prepared by action of the corresponding aromatic aldehydes (0.11 mole) with ethyl benzoylacetate (19.2 g, 0.1 mole) in ethanol (20 ml), with stirring in the presence of piperidine (0.5 g) at room temperature for 24 hours, according to the method of Ruhemann [6]. This method failed for the preparation of the other compounds **1** because under these conditions the diethyl glutarates **2** were formed preponderantly and it was very difficult to separate **1** from **2**. Compounds **1b** (Ar = 4-MePh), **1c** (Ar = 4-MeOPh), **1d** (Ar = 4-ClPh) and **1e** (Ar = 4-NO_2Ph) were prepared following a procedure described by Prout to synthesize alkylidenecyanoacetates [9]. By this method, compounds **2** were not detected.

A mixture of aromatic aldehyde (0.11 mole), ethyl benzoylacetate (19.2 g, 0.1 mole), acetic acid (15 ml), 6-aminohexanoic acid (0.5 g) and benzene (40 ml) was heated under reflux using a Dean Stark apparatus for azeotropic distillation of water. After 8 hours, benzene and acetic acid were removed by distillation *in vacuo* and a greasy yellow residue was obtained. By addition of cold propanol (50 ml), **1c** or **1e** slowly crystallized. They were filtered and recrystallized from a suitable solvent. For oily compounds **1b** or **1d**, the residue was distillated *in vacuo*.

Ethyl (*Z*)-3-Phenyl-2-benzoylpropenoates (**1a**).

This compound had mp 95° (from cyclohexane-benzene), lit [12] mp 95-96°.

Ethyl (*Z*)-3-(4-Methylphenyl)-2-benzoylpropenoates (**1b**).

This compound had bp 220°/15mm Hg, lit [13] bp 175°/3 mm Hg.

Ethyl (*Z*)-3-(4-Methoxyphenyl)-2-benzoylpropenoates (**1c**).

This compound had mp 94° (from propanol), lit [13] mp 94-95°.

Ethyl (*Z*)-3-(4-Chlorophenyl)-2-benzoylpropenoates (**1d**).

This compound had bp 215-218°/16mm Hg, lit [13] bp 200°/2mm Hg.

Ethyl (*Z*)-3-(4-Nitrophenyl)-2-benzoylpropenoates (**1e**).

This compound had mp 116° (from methanol or hexane-benzene), lit [12] mp 116°.

Ethyl (*Z*)-3-(4-Hydroxyphenyl)-2-benzoylpropenoates (**1f**).

This compound had mp 181° (from propanol), lit [14] mp 180°.

Reactions of Guanidine and its Alkyl or Benzyl Derivatives with Esters **1**.

N-Alkyl(or benzyl)guanidinium sulfates were prepared by the procedure of Weiss and Krommer [15]. A mixture of **1** (30 mmoles), guanidine hydrochloride (4.3 g, 45 mmoles) for **3** or alkyl(or benzyl)guanidinium sulfate (22.5 mmoles) for **4**, and sodium bicarbonate (5 g, 60 mmoles) in anhydrous dimethylformamide (40 ml) was stirred at 60° for 8 to 48 hours when **1** disappeared. Then, the reaction mixture was poured into ice-water (300 ml) under strong stirring. A precipitate was formed. It was collected by filtration and dried *in vacuo* to give a yellow or red crude solid.

For the reaction of guanidine with **1c** or **1e**, the crude solid was treated with boiling ethanol or methanol (150 ml) and the resulting mixture was hot filtered. The bicyclic compound **6c** or **6e** which was insoluble in hot alcohol was recovered. Evaporation of the alcoholic filtrate gave **3c** or **3e**. For the same reaction with the other compounds **1**, the crude solid was treated with cold chloroform (200 ml) with stirring for 1 hour. The resulting suspension was allowed to stand at 4° for 24 hours, then filtered. The resulting white solid was the corresponding compound **3**. Evaporation of the chloroform filtrate afforded the corresponding compound **6**. In the preparation of dihydropyrimidines **4**, the crude solid contained no bicyclic compound **6** but a small quantity of the isomer **5** which was not isolated, except for **5a**. Compounds **3**, **4** and **6** were recrystallized from a suitable solvent (Tables 1 and 2).

Ethyl 2-Amino-3,4-dihydro-3-methyl-5-pyrimidinecarboxylate (**5a**).

Method A.

Compound **5a** was obtained in addition to **4a** by the general procedure described above. Treatment of the crude solid with cold chloroform (100 ml) and filtration gave **4a** as a solid. After evaporation of the filtrate *in vacuo*, the resulting greasy residue **5a** was recrystallized from ethyl acetate-petroleum ether giving 0.5 g (5%), mp 232°; ir: 3480, 3280, 1700, 1660 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.75 (t, 3H), 2.89 (s, 3H), 3.65 (q, 2H), 5.2 (s, 1H), 6.7 (s, 2H), 7.15-7.45 (m, 10H).

Anal. Calcd. for $C_{20}H_{21}N_3O_2$ (335.39): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.80; H, 6.22; N, 12.45.

Method B.

To a suspension of sodium hydride (0.1 g, 4.2 mmoles) in anhydrous dimethylformamide (5 ml) was added slowly at 0° with stirring a solution of **3a** (1.3 g, 4 mmoles) in the same solvent (15 ml). When hydrogen gas evolution has ceased, the reaction mixture was warmed to 60° for 30 minutes. After cooling at 0°, a solution of methyl iodide (0.6 g, 4.2 mmoles) in dimethylformamide (5 ml) was added. After standing at room temperature for 1.5 hours, the mixture was poured into ice-water (100 ml). Compound **5a** precipitated. It was collected by filtration, dried *in vacuo* and recrystallized from ethyl acetate-petroleum ether giving 0.65 g (49%), mp 232°. The ir and ^{1}H nmr spectral data of this compound were identical to that of **5a** obtained by Method A above.

Picrates of **3**, **4** and **6**.

Each compound **3**, **4** or **6** was added to a concentrated alcoholic solution of picric acid which was refluxed for certain periods of time. After cooling in the freezer, crystals of the picrates were obtained, sometimes with difficulty. They were recrystallized from a suitable alcohol.

X-ray Crystal Structure Determination of **6b**.

Suitable crystals of **6b** were obtained by slow crystallization in cyclohexane. Accurate cell dimensions and orientation matrices were obtained by least-squares refinements of 25 accurately centered reflections. No significant variations were observed in the intensities of two checked reflections during data collections. Complete crystallographic data and collection parameters are listed in Table 3. The data were corrected for Lorentz and polarization effects. Computations were performed by using the PC version of CRYSTALS [16]. Scattering factors and corrections

for anomalous dispersion were taken from a reference [17]. The structures were solved by using SHELXS [18] and refined by full-matrix least-squares with anisotropic thermal parameters. Hydrogen atoms were introduced in calculated positions in the last refinement, and only an overall isotropic thermal parameter was refined. The asymmetric unit is made of two independent molecules **6b$_1$** and **6b$_2$**. The molecule **6b$_2$** is shown in Figure 3. The molecule **6b$_1$** which is similarly the same is not shown. For both molecules **6b$_1$** and **6b$_2$**, selected bond lengths and bond angles are given in Tables 4 and 5. Tables of atomic coordinates, thermal parameters, complete bond lengths and bond angles are available on request from the authors as well as a complete set of crystallographic data for compound **6a** which are not described in this paper but gave an analogous result.

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