Synthesis of Novel Dihydropyrimidines and Tetrahydropyrimidines

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Condensation of alkyl 2-acetyl-3-aryl-2-propenoate with acetamidine, benzamidine, guanidine, or 1,1-dimethylguanidine followed by dehydration of the resulting compound **2** with *p*-TsOH or Al_2O_3 gave 1,4(3,4)-dihydropyrimidine **3**. Regioselective alkoxycarbonylation, acylation, and alkylation of compound **3** with alkyl chloroformate, acyl halide, or alkyl halide in the presence of NaH afforded the series of novel N-substituted 3,4-dihydropyrimidines **4**, **5**, and **6** in good yield. Stereoselective $NaBH_4$ reduction of the 3,4-dihydropyrimidine hydrochloride **4** provided a single stereoisomer of 1,2,3,4-tetrahydropyrimidine **7** whose stereochemistry was assigned as cis by X-ray crystallographic analysis. Conversely, the same reduction of the HCl salts of **3** or **6** gave a cis–trans mixture of tetrahydropyrimidines **8**.

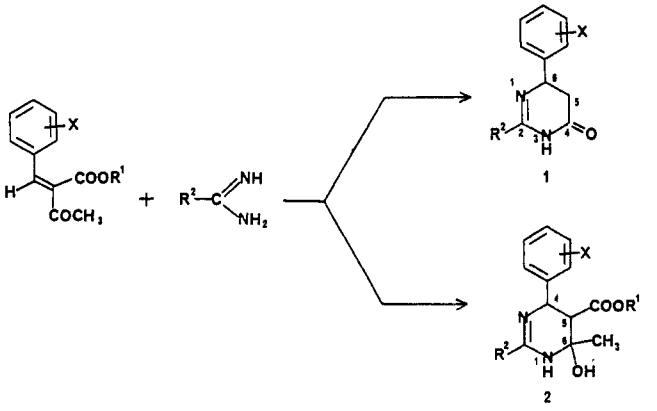
The literature contains only a few papers[1] on the synthesis of dihydropyrimidines. These compounds have only been reported as poorly characterized isomeric mixtures which in some cases are spontaneously oxidized to the pyrimidine by atmospheric oxygen.[2,3]

Since various pyrimidine derivatives have been synthesized from amidines and α,β-unsaturated carbonyl compounds with a good leaving group at the position β to the carbonyl group,[4] we have initiated an investigation of the synthesis of dihydropyrimidine derivatives by cyclization of amidines with α,β-unsaturated carbonyl compounds that do not have a leaving group at the β position.

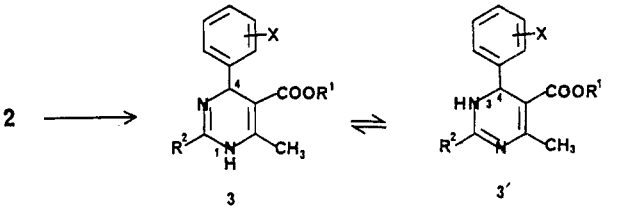
We report here the synthesis (a) of a series of novel 1,4(3,4)-dihydropyrimidines from alkyl 2-acetyl-3-aryl-2-propenoates and four different amidines, (b) of N-substituted 3,4-dihydropyrimidines by the regioselective alkoxycarbonylation, acylation, or alkylation, and (c) of 1,2,3,4-tetrahydropyrimidines by stereoselective $NaBH_4$ reduction.

The condensation of alkyl 2-acetyl-3-aryl-2-propenoates and amidines under basic conditions was investigated by treating ethyl 2-acetyl-3-(*o*-nitrophenyl)-2-propenoate with 1.0 equiv of acetamidine hydrochloride in the presence of 2.0 equiv of NaOEt in EtOH under reflux for 1.5 h. Only the unexpected 5,6-dihydropyrimidin-4(3*H*)-one (**1**)[5,6] was obtained in 10% yield. This may have been produced by successive reactions of Michael addition, deacetylation, and cyclization. However, reaction under milder conditions afforded the desired tetrahydropyrimidine **2** in good yield (see Scheme I and Table I). Specifically, the reaction of ethyl 2-acetyl-3-aryl-2-propenoate with 1.1 equiv of acetamidine hydrochloride in the presence of 1.0 equiv of NaOEt at room temperature for 1 h gave quantitatively the 4-aryl-5-(ethoxycarbonyl)-6-hydroxy-2,6-dimethyl-

Scheme I



Scheme II



1,4,5,6-tetrahydropyrimidines (**2**). Normally, the crude product was used for the subsequent dehydration reaction, but in a few representative cases the initial cyclization product was purified and characterized. The formation of the tetrahydropyrimidine skeleton in this reaction was clearly demonstrated by the fact that the 6-carbon of **2b** appeared at 77.0 ppm in the ^{13}C NMR spectrum. Using the above-mentioned cyclization conditions with esters where R^1 was larger than ethyl resulted in transesterification. Hence, in these cases the reaction was carried out in *t*-BuOH (room temperature, 1 h) in the presence of *t*-BuOK. Dehydration of compounds **2** was performed with 2.0 equiv of *p*-TsOH in refluxing benzene for 1.5 h or with Al_2O_3 powder at 120 °C for 30 min to provide the expected 5-(alkoxycarbonyl)-4-aryl-2,6-dimethyl-1,4(3,4)-dihydropyrimidines (**3a–h**) (see Scheme II).

The generality of this reaction is illustrated by the fact that other amidines besides acetamidine were effective. Specifically, when ethyl 2-acetyl-3-(*o*-nitrophenyl)-2-propenoate was reacted with 1.1 equiv of guanidine, 1,1-dimethylguanidine, or benzamidine hydrochloride in NaOEt–EtOH and the crude tetrahydropyrimidine was dehydrated with *p*-TsOH or Al_2O_3, the dihydropyrimidines

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(6) All new compounds described here gave satisfactory IR, NMR, and MS spectra and elemental analyses.

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Table I. Synthesis of Dihydropyrimidines 3 via Tetrahydropyrimidines 2

compd	X	R^1	R^2	method[a]	yield, %	mp, °C (solv)
2a	*m*-NO_2	Et	Me		99	oil
2b	*o*-NO_2	Et	Me		99	oil
2c	*m*-Cl	*t*-Bu	Me		99	122–126 (C_6H_6)
3a	*m*-NO_2	Et	Me	A	54	223–226[b] (MeOH–Et_2O)
3b	*o*-NO_2	Et	Me	A	42	239–241[b] (EtOH–Et_2O)
3c	*m*-Cl	*t*-Bu	Me	B	32	oil
3d	H	Et	Me	A	68	156–157 (Et_2O–C_6H_{14})
3e	*o*-Cl	Et	Me	A	35	195–197 (AcOEt)
3f	*p*-SMe	Et	Me	A	63	227–228[b] (MeOH–Et_2O)
3g	*o*-NO_2	Et	C_6H_5	A	47	77–79 ($CHCl_3$–C_6H_{14})
3h	*o*-NO_2	Et	NH_2	B	20	196–198 ($CHCl_3$–Et_2O)
3i	*o*-NO_2	Et	NMe_2	B	14	140–142 ($CHCl_3$–C_6H_{14})
3j	*o*-Br	*n*-C_5H_{11}	Me	C	72	oil
3k	*m*-NO_2	CH_2-*c*-C_3H_5	Me	C	70	oil
3l	*o*-NO_2	$(CH_2)_2N(Me)Bzl$	Me	B	80	oil

[a] Method: (1) cyclization conditions, (A) NaOEt–EtOH; (B) KO-*t*-Bu–*t*-BuOH; (C) KO-*t*-Bu–DMF or NaOEt–EtOH; (2) dehydration conditions, (A) *p*-TsOH–C_6H_6, (B) Al_2O_3 powder, (C) *p*-TsOH–DMF. [b] Of the HCl salt.

Table II. Regioselective Synthesis of 3,4-Dihydropyrimidines 4, 5, or 6 from 3

compd	X	R^1	R^2	R^3	yield, %	mp, °C (solv)
4a	*m*-NO_2	Et	Me	Et	92	69 (Et_2O)
4b	*o*-NO_2	Et	Me	Et	95	130–132 (CH_3COCH_3–C_6H_{14})
4g	*o*-NO_2	Et	C_6H_5	Me	82	184 ($CHCl_3$–C_6H_{14})
4h	*o*-NO_2	Et	NHCOOEt	Et	40	128–131
4i	*o*-NO_2	Et	NMe_2	Et	55	132 (Et_2O–C_6H_{14})
4l	*o*-NO_2	$(CH_2)_2N(Me)Bzl$	Me	Me	40	oil
4m	*o*-NO_2	CH_2-*c*-C_3H_5	Me	$(CH_2)_2OMe$	78	oil
5a	*m*-NO_2	Et	Me	Me	99	105–107 (Et_2O)
5b	*o*-NO_2	Et	Me	*c*-C_3H_5	57	138–139 (Et_2O)
6b	*o*-NO_2	Et	Me	*n*-C_7H_{15}	45	oil
6j	*o*-Br	*n*-C_5H_{11}	Me	Me	47	oil

3g–i were obtained in moderate to good yields.

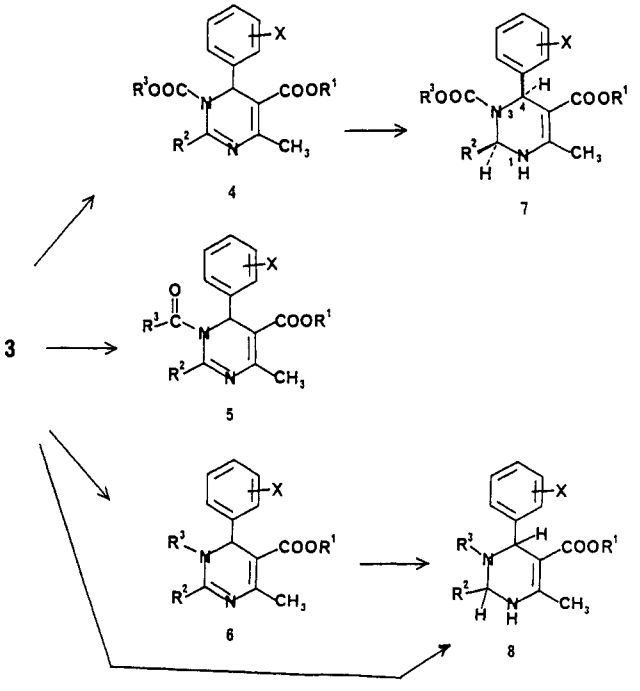
In many cases the dihydropyrimidine could be prepared more conveniently under other conditions without isolation of the tetrahydropyrimidine. For example, the dihydropyrimidine **3k** was synthesized in good yield from the cyclization in 1.0 equiv of *t*-BuOK–DMF (0 °C, 10 min), followed by dehydration in situ by adding 2.0 equiv of *p*-TsOH and heating to 100–110 °C.

Since the ^1H NMR spectra of these dihydropyrimidines **3** exhibited the signal of C-4 methine proton as a broad singlet at δ 5.5–6.0, the possibility of 4,5-dihydropyrimidine was ruled out. In the crystalline state, **3e** exists in the 1,4-dihydro form according to X-ray crystallographic analysis.[7] In solution, however, the NMR of these compounds is more consistent with a mixture of the 1,4-dihydro and 3,4-dihydro forms. This corresponds with the results of Weis et al.[3c] from work on a simpler dihydropyrimidine.

Next, the alkoxycarbonylation, acylation, and alkylation reactions of the nitrogen atom of the dihydropyrimidines were examined. Successive treatments of **3** with NaH and alkyl chloroformate (ClCOOMe, ClCOOEt, ClCOOBzl, $ClCOOC_7H_{15}$, $ClCOOCHMe_2$, $ClCOOCH_2CH_2OMe$, etc.) or acyl chloride (MeCOCl, EtCOCl, cyclopropanecarbonyl chloride) in THF or dioxane at 0 °C for 15–30 min yielded the single product, **4** or **5**. Similarly, the sodium salts of **3** in THF were heated at reflux for 2 h with 10 equiv of alkyl halide (MeI, EtBr, $C_7H_{15}I$) and 1.0 equiv of HMPA to give the single product **6** (see Scheme III).

The proposed structures **4**, **5**, and **6** were supported by the ^1H NMR and ^{13}C NMR spectra. In compound **4a**, the long-range coupling of the C-4 methine proton [δ 6.26 (1 H, br s)] with the C-6 methyl group [δ 2.45 (3 H, br s)] was observed but not with the C-2 methyl group [δ 2.40 (3 H, s)]. Furthermore, the nondecoupled signal of the carbamate carbon appeared at 152.91 ppm as double triplet, and by long-range selective proton decoupling (LSPD) the irradiation of the C-4 methine proton showed three-bond coupling (J = 2.9 Hz) with the carbamate carbon and also three-bond coupling (J = 3.7 Hz) was observed between the C-5 ester carbon and the methine proton. The similar result of the LSPD experiment was also obtained in the case of **6**. Therefore, it was demonstrated that these reactions occurred regioselectively at the 3-position to pro-

Scheme III



(7) Crystallographic results will be described in a separate forthcoming paper.

Table III. Stereoselective Synthesis of 1,2,3,4-Tetrahydropyrimidines 7 from 4 and Synthesis of 8 from 3 or 6[a]

compd	X	R^1	R^2	R^3	yield, %	cis:trans	mp, °C (solv)
7b	o-NO_2	Et	Me	Et	98	cis only	121–123 (AcOEt–C_6H_{14})
7g	o-NO_2	Et	C_6H_5	Me	98	cis only	oil
8b	o-NO_2	Et	Me	n-C_7H_{15}	99	4:1	oil
8j	o-Br	n-C_5H_{11}	Me	Me	99	4:1	oil
8a	m-NO_2	Et	Me	H	98	1:1	151–152 ($CHCl_3$–C_6H_{14})
8k	m-NO_2	CH_2-c-C_3H_5	Me	H	98	1:1	oil

[a] Reaction time; 30 min for most of compounds, 15 h for compound **7g** in THF–EtOH.

vide N-substituted 3,4-dihydropyrimidines **4**, **5**, or **6** in good yield (see Table II).

This interesting finding can be rationalized in two ways. First, the nitrogen atom at the N-3 position may be less sterically hindered since the dihydropyrimidine ring can assume almost perpendicular relationship to the phenyl ring. Secondly, if one draws the possible resonance structures of the anion that would result from the removal of a proton from the nitrogen of **3**, it is clear that N-3 should bear a greater electron density than N-1 and therefore be more nucleophilic.

Finally, the sodium borohydride reduction (2 mol equiv, room temperature, 30 min) of the dihydropyrimidine salts, prepared with anhydrous HCl/ether in MeOH, was investigated. In the cases with an acyl substituent at N-3 (compounds **5**), reduction gave a complex mixture in part because of the occurrence of reductive deacylation at N-3. In the cases where N-3 was alkyl substituted (compounds **6**) or unsubstituted (compounds **3**), $NaBH_4$ reduction gave diastereomeric mixtures of tetrahydropyrimidines. Thus, reduction of the unsubstituted compounds **3a** or **3k** gave a 1:1 mixture of the stereoisomeric tetrahydropyrimidines **8a** or **8k**, respectively. Reduction of the alkyl-substituted **6b** or **6j** gave a 4:1 mixture of two stereoisomeric tetrahydropyrimidines **8b** or **8j** in each case. As for the major stereoisomer of **8j** (the more polar spot on TLC plate; ether:*n*-hexane = 3:1), an NOE of 4.6% was observed at the C-4 methine proton (δ 5.04) on irradiation of the C-2 methine proton (δ 3.54) (10% acetone-d_6 in benzene-d_6). Therefore, the major isomer **8j** was assigned as a cis stereoisomer. Significantly, the reduction of 3,4-dihydropyrimidine **4** which had alkoxycarbonyl substitution at N-3 afforded stereoselectively sole stereoisomer **7**. Since the NOE experiment of **7b** gave an unclear result on the stereostructure, **7b** was determined as a cis stereoisomer by X-ray crystallographic analysis.[7]

Experimental Section

General Methods. Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. ^1H NMR spectra were recorded with a JEOL GX-270 (270 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane (Me_4Si) as an internal standard, unless otherwise noted. ^{13}C NMR (LSPD) spectra were obtained on a JEOL FX-100 (25 MHz) in $CDCl_3$ solution at 25 °C. IR spectra were taken on a Hitachi 260-10 infrared spectrometer in $CHCl_3$ and UV spectra on a Beckman DU-8 spectrophotometer. High-resolution mass spectra were obtained with a JEOL JMS-01SG-2 spectrometer at an ionizing voltage of 70 eV. TLC was carried out on Merck silica gel plates 60F-254. Column chromatography was performed on Merck silica gel (70–230 mesh).

Typical Procedure for the Preparation of Dihydropyrimidine and Tetrahydropyrimidine. 5-(Ethoxycarbonyl)-6-hydroxy-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4,5,6-tetrahydropyrimidine (2a). To a stirred suspension of 680 mg of sodium ethoxide in 50 mL of anhydrous ethanol was added 945 mg of acetamidine hydrochloride at room temperature. After 5 min, a solution of 2.63 g of ethyl 2-acetyl-3-(*m*-nitrophenyl)-2-propenoate in 100 mL of ethanol was added. The mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give 3.20 g of compound **2a**: IR 3440, 1710, 1660 cm^{-1}; ^1H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.50 (3 H, s), 2.03 (3 H, s), 2.52 (1 H, d, J = 12 Hz), 3.94 (2 H, q, J = 7 Hz), 4.87 (1 H, d, J = 12 Hz), 7.45–8.19 (4 H, m). Anal. Calcd for $C_{15}H_{20}ClN_3O_5$ as HCl salts of **2a**: C, 50.35; H, 5.63; N, 11.75. Found: C, 50.23; H, 5.53; N, 11.61.

5-(Ethoxycarbonyl)-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-(3,4)-dihydropyrimidine (3a). To a solution of 2.84 g of compound **2a** in 150 mL of benzene was added 1.85 g of *p*-toluenesulfonic acid monohydrate, and the mixture was refluxed for 1.5 h with Dean–Stark apparatus. The reaction mixture was washed with saturated aqueous K_2CO_3 and brine and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Purification of the residue on SiO_2 column chromatography (solvent, 5–10% MeOH in $CHCl_3$) gave 1.43 g (54%) of compound **3a**: mp 223–226 °C (MeOH–Et_2O) as HCl salts; IR 3440, 1690 cm^{-1}; UV λ_{max}^{MeOH} 302 nm (ϵ 4100), 260 (7900) as HCl salts; ^1H NMR δ 1.18 (3 H, t, J = 7 Hz), 2.05 (3 H, s), 2.37 (3 H, s), 4.09 (2 H, q, J = 7 Hz), 5.67 (1 H, s), 7.40–8.20 (4 H, m). Anal. Calcd for $C_{15}H_{18}ClN_3O_4$: C, 53.02; H, 5.34; N, 12.37. Found: C, 53.12; H, 5.28; N, 12.24.

5-(*tert*-Butoxycarbonyl)-4-(*m*-chlorophenyl)-2,6-dimethyl-1,4(3,4)-dihydropyrimidine (3c). To a solution of 1.0 g of 5-(*tert*-butoxycarbonyl)-4-(*m*-chlorophenyl)-6-hydroxy-2,6-dimethyl-1,4,5,6-tetrahydropyrimidine in 5 mL of $CHCl_3$ was added 10 g of activated alumina powder (Wako k.k., 300 mesh). After careful removal of the solvent, the dry alumina powder was heated at 120 °C for 30 min. After cooling, elution with $CHCl_3$ yielded 310 mg (32%) of compound **3c** as an oil: IR 3420, 1690 cm^{-1}; ^1H NMR δ 1.27 (9 H, s), 1.78 (3 H, s), 2.16 (3 H, s), 5.32 (1 H, s), 7.08–7.20 (4 H, m); HRMS, calcd for $C_{17}H_{21}ClN_2O_2$ m/z 320.1289, found m/z 320.1279.

5-[(Cyclopropylmethoxy)carbonyl]-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4(3,4)-dihydropyrimidine (3k). To a stirred solution of 1.80 g of acetamidine hydrochloride in 10 mL of *N*,*N*-dimethylformamide (DMF) were added a solution of 1.60 g of potassium *tert*-butoxide in 10 mL of DMF and a solution of 3.80 g of cyclopropylmethyl 2-acetyl-3-(*m*-nitrophenyl)-2-propenoate in 5 mL of DMF at 0 °C. After the mixture was stirred for 10 min at 0 °C, 5.0 g of *p*-toluenesulfonic acid monohydrate was added. The mixture was heated at 100–110 °C for 1.5 h. After cooling, the reaction mixture was quenched with aqueous NaOH solution and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to leave an oily residue, which was chromatographed on SiO_2 to afford 3.06 g (70%) of compound (**3k**) as an oil: IR 3430, 1700 cm^{-1}; ^1H NMR δ 0.13–0.50 (4 H, m), 0.98–1.10 (1 H, m), 2.04 (3 H, s), 2.36 (3 H, s), 3.80–3.90 (2 H, m), 5.69 (1 H, s), 7.43–8.16 (4 H, m); HRMS, calcd for $C_{17}H_{19}N_3O_4$ (molecular ion) m/z 329.1373, found m/z 329.1368.

2-Amino-5-(ethoxycarbonyl)-6-methyl-4-(*o*-nitrophenyl)-1,4(3,4)-dihydropyrimidine (3h). To a stirred suspension of 260 mg of potassium *tert*-butoxide in 5 mL of anhydrous *tert*-butyl alcohol was added 280 mg of guanidine hydrochloride at room temperature. After 5 min, a solution of 500 mg of ethyl 2-acetyl-3-(*o*-nitrophenyl)-2-propenoate in 15 mL of *tert*-butyl alcohol was added. The mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure to leave the residue, which was thoroughly washed with $CHCl_3$. The filtrate was concentrated to 3 mL of the solution, to which was added 5 g of activated alumina powder. After careful removal of the solvent, the dry alumina powder was heated at 120 °C for 30 min, and elution with $CHCl_3$ gave 125 mg (20%) of pale yellow crystals of **3h**: mp 196–198 °C ($CHCl_3$–Et_2O); IR 3400, 1690 cm^{-1}; UV λ_{max}^{MeOH} 316 nm (ϵ 8200), 250 (9800); ^1H

NMR (CD_3OD) δ 0.95 (3 H, t, J = 7 Hz), 2.40 (3 H, s), 3.88 (2 H, q, J = 7 Hz), 5.72 (1 H, s), 7.30–7.90 (4 H, m); HRMS, calcd for $C_{14}H_{16}N_4O_4$ m/z 304.1171, found m/z 304.1170.

3,5-Bis(ethoxycarbonyl)-2,6-dimethyl-4-(*m*-nitrophenyl)-3,4-dihydropyrimidine (4a). To a stirred slurry of 18 mg of 50% NaH–mineral oil in 4 mL of THF was added a solution of 107 mg of **3a** in 3 mL of THF at 0 °C. After 5 min, 40 μL of ethyl chloroformate was added at 0 °C. Stirring was continued at room temperature for 30 min. The reaction mixture was quenched with brine and extracted with $CHCl_3$. The organic layer was dried and evaporated to leave 121 mg (92%) of compound **4a**: mp 69 °C (Et_2O); IR 1725, 1710 cm^{-1}; UV λ_{max}^{MeOH} 313 nm (ϵ 5900), 261 (9500); ^1H NMR δ 1.25 (3 H, t, J = 7 Hz), 1.40 (3 H, t, J = 7 Hz), 2.40 (3 H, s), 2.45 (3 H, s), 4.19 (2 H, m), 4.35 (2 H, q, J = 7 Hz), 6.26 (1 H, s), 7.47 (1 H, t, J = 8 Hz), 7.60 (1 H, d, J = 7 Hz), 8.14 (1 H, d, J = 8 Hz), 8.15 (1 H, s); ^{13}C NMR δ 165.40 (s, C-5=O), 154.87 (s, C-2), 152.91 (2 s, each C-6 and C-3=O), 148.34 (s, CNO_2), 141.82 (s, Ar C), 133.02 (d, Ar C), 129.62 (d, Ar C), 123.16 (d, Ar C), 122.25 (d, Ar C), 111.17 (s, C-5), 63.81 and 60.74 (2 t, OCH_2CH_3), 53.13 (d, C-4), 25.08 (q, 2-CH_3), 21.07 (q, 6-CH_3), 14.20 and 14.14 (2 q, OCH_2CH_3); HRMS, calcd for $C_{18}H_{21}N_3O_6$ m/z 375.1430, found m/z 375.1430.

5-(Ethoxycarbonyl)-3-*n*-heptyl-2,6-dimethyl-4-(*o*-nitrophenyl)-3,4-dihydropyrimidine (6b). To a stirred slurry of 29 mg of 50% NaH–mineral oil in 1 mL of THF was added a solution of 150 mg of 5-(ethoxycarbonyl)-2,6-dimethyl-4-(*o*-nitrophenyl)-1,4(3,4)-dihydropyrimidine in 2 mL of THF at 0 °C. To the suspension were added successively 87 μL of HMPA and 82 μL of *n*-heptyl iodide at 0 °C. The mixture was refluxed for 4.5 h, quenched with ice–water, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to leave the residue, which was purified on preparative SiO_2 TLC (development, $CHCl_3$:acetone = 1:1) to yield 90 mg (45%) of compound **6b** as an oil: IR 1695, 1670, 1610 cm^{-1}; UV λ_{max}^{MeOH} 330 nm (ϵ 3700), 250 (5900); ^1H NMR δ 0.88 (3 H, m), 1.10 (3 H, t, J = 7 Hz), 1.20–1.85 (10 H, m), 2.23 (3 H, s), 2.34 (3 H, s), 3.35 (2 H, m), 4.00 (2 H, t, J = 7 Hz), 6.10 (1 H, s), 7.38 (1 H, br t, J = 7 Hz), 7.56 (1 H, br t, J = 7 Hz), 7.72 (1 H, br d, J = 7 Hz), 7.83 (1 H, br d, J = 7 Hz); HRMS, calcd for $C_{22}H_{31}N_3O_4$ m/z 401.2312, found m/z 401.2307.

3,5-Bis(ethoxycarbonyl)-2,6-dimethyl-4-(*o*-nitrophenyl)-1,2,3,4-tetrahydropyrimidine (7b). To a stirred solution of 0.49 g of 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-4-(*o*-nitrophenyl)-3,4-dihydropyrimidine in 5 mL of MeOH was added anhydrous HCl/ether solution. After immediate evaporation, the residue was dissolved in 25 mL of MeOH and 0.1 g of $NaBH_4$ in small portions at room temperature. After the mixture was stirred for 30 min, the solvent was removed under reduced pressure. The residue was mixed with brine and extracted with $CHCl_3$. The organic layer was separated, dried over $MgSO_4$, and evaporated to give 0.48 g (98%) of compound **7b**: mp 121–123 °C (AcOEt–C_6H_{14}); IR 3440, 1690, 1605 cm^{-1}; UV λ_{max}^{MeOH} 279 nm (ϵ 20 000); ^1H NMR δ 0.77 (3 H, d, J = 7 Hz), 1.12 (3 H, t, J = 7 Hz), 1.34 (3 H, t, J = 7 Hz), 2.42 (3 H, s), 4.10 (2 H, m), 4.21 (2 H, q, J = 7 Hz), 5.61 (1 H, m), 6.91 (1 H, s), 7.30–7.65 (4 H, m); HRMS, calcd for $C_{18}H_{23}N_3O_6$ m/z 377.1588, found m/z 377.1593.

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Registry No. **2a**, 98064-08-5; **2b**, 98050-61-4; **2c**, 98050-62-5; **2d**, 98050-63-6; **2e**, 98050-64-7; **2f**, 98050-65-8; **2g**, 98050-66-9; **2h**, 98050-67-0; **2i**, 98050-68-1; **2j**, 98050-69-2; **2k**, 98050-70-5; **2l**, 98050-71-6; **3a**, 98050-72-7; **3a**·HCl, 98050-99-8; **3b**·HCl, 98050-73-8; **3c**, 98050-74-9; **3d**, 98050-75-0; **3e**, 98050-76-1; **3f**·HCl, 98050-77-2; **3g**, 90961-15-2; **3h**, 98050-78-3; **3i**, 98050-79-4; **3j**, 98050-80-7; **3k**, 98050-81-8; **3k**·HCl, 98051-00-4; **3l**, 98050-82-9; **3m**, 98050-83-0; **4a**, 98050-84-1; **4b**, 98050-85-2; **4b**·HCl, 98050-95-4; **4g**, 98050-86-3; **4g**·HCl, 98050-96-5; **4h**, 98050-87-4; **4i**, 98050-88-5; **4l**, 98050-89-6; **4m**, 98050-90-9; **5a**, 98050-91-0; **5b**, 98050-92-1; **6b**, 98050-93-2; **6b**·HCl, 98050-97-6; **6j**, 98050-94-3; **6j**·HCl, 98050-98-7; *cis*-**7b**, 98051-01-5; *cis*-**7g**, 98051-02-6; *cis*-**8a**, 98051-07-1; *trans*-**8a**, 98051-08-2; *cis*-**8b**, 98051-03-7; *trans*-**8b**, 98051-04-8; *cis*-**8j**, 98051-05-9; *trans*-**8j**, 98051-06-0; *cis*-**8k**, 98051-09-3; *trans*-**8k**, 98051-10-6; *m*-$NO_2C_6H_4CH$=$C(COCH_3)COOEt$, 39562-16-8; *o*-$NO_2C_6H_4CH$=$C(COCH_3)COOEt$, 67593-37-7; *m*-ClC_6H_4CH=$C(COCH_3)COOBu$-*t*, 98050-57-8; C_6H_5CH=$C(COCH_3)COOEt$, 620-80-4; *o*-ClC_6H_4CH=$C(COCH_3)COOEt$, 15725-22-1; *p*-$MeSC_6H_4CH$=$C(COCH_3)COOOEt$, 50626-73-8; *o*-BrC_6H_4CH=$C(COCH_3)COOC_5HN$-*n*, 98050-58-9; *m*-$NO_2C_6H_4CH$=$C(COCH_3)COOCH_2$-c-C_3H_5, 98050-59-0; *o*-$NO_2C_6H_4CH$=$C(COCH_3)COOCH_2N(Me)Bzl$, 98050-60-3; HN=$C(NH_2)Me$·HCl, 124-42-5; HN=$C(NH_2)C_6H_5$·HCl, 1670-14-0; HN=$C(NH_2)_2$·HCl, 50-01-1; HN=$C(NH_2)NMe_2$·HCl, 22583-29-5; ClCOOEt, 541-41-3; ClCOOMe, 79-22-1; $ClCOO(CH_2)_2OMe$, 628-12-6; *c*-C_3H_5COCl, 4023-34-1; *n*-$C_7H_{15}I$, 4282-40-0.