Synthesis and Reactions of "Biginelli-Compounds". Part I

Christian Oliver Kappe* and Peter Roschger

Institut für Organische Chemie, Universität Graz, Heinrichstr. 28,
A-8010 Graz, Austria

Received July 5, 1988

Dedicated to Prof. Dr. Hans Junek on the occasion of his 60th birthday.

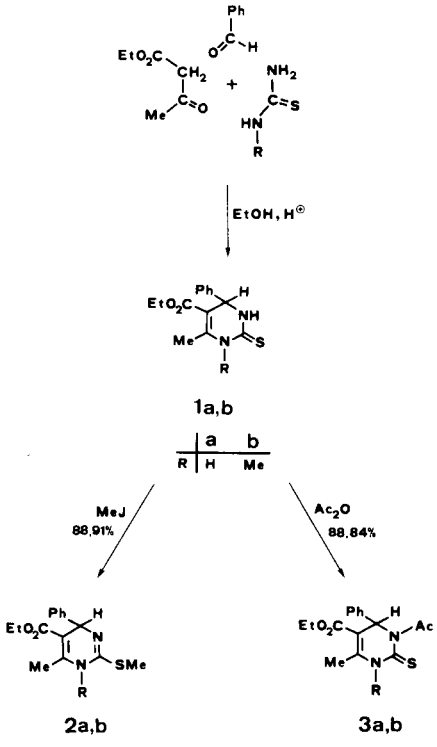
Various reactions of 2-oxo(or thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives (Biginelli-compounds) were investigated. The site of methylation and acylation on 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester **1a** and its 2-oxo derivative **9a** was studied. The synthesis of pyrimido[2,3-*b*]thiazines and thiazolo[3,2-*a*]pyrimidines was accomplished by condensation of **1a** with 1,3-and 1,2-dielectrophiles. A Dimroth-like rearrangement yielding 6*H*-1,3-thiazines can be observed when **1a** was treated with dimethylformamide and phosphorus oxychloride. The formation of indeno[1,2-*d*]pyrimidines can be achieved by intramolecular Friedl-Crafts acylation of **9a** and **13**, respectively. Finally a route for the preparation of 4,6-disubstituted-pyrimidine-5-carbonitriles is presented, starting with Biginelli-compound **25**.

J. Heterocyclic Chem., **26**, 55 (1989).

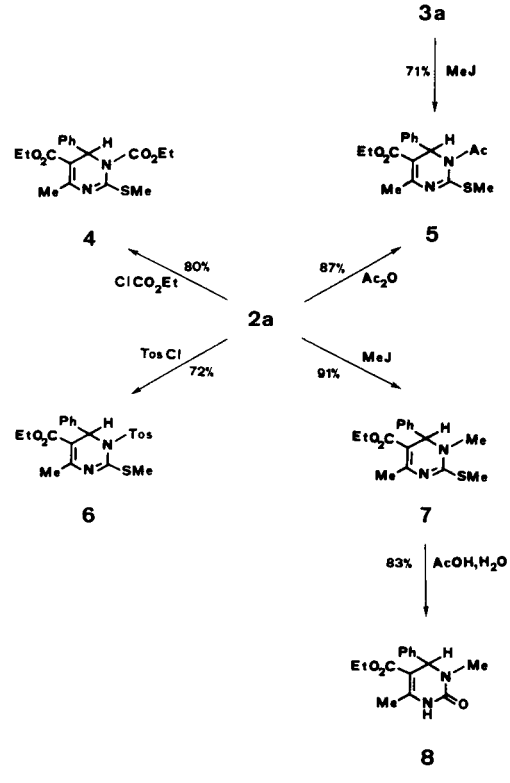
Recently much interest has been focused on the chemistry of 2-oxo(or thioxo)tetrahydropyrimidine-5-carboxylic acids and their derivatives, known as Biginelli-compounds. When properly substituted they can act as cardiovascular agents, which is not surprising since they can be regarded as aza-analogs of nifedipine-related dihydropyridines [1-3]. We now report our results on this subject.

The synthesis of 6-methyl-4-substituted-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters by condensation of an aldehyde, urea and ethyl acetoacetate was first described by Biginelli in 1893 [4,5]. The 2-thioxo derivative **1a** was prepared in a similar way, using thiourea instead of urea [6-8]. With *N*-methylthiourea we obtained 1,6-dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester **1b** (Scheme 1). The position of the *N*-methyl group on the pyrimidine ring follows from ^{1}H-nmr spectroscopic data. Thus the signals for the protons at C(4) and N(3) appear as doublets (δ 5.32

Scheme 1



Scheme 2

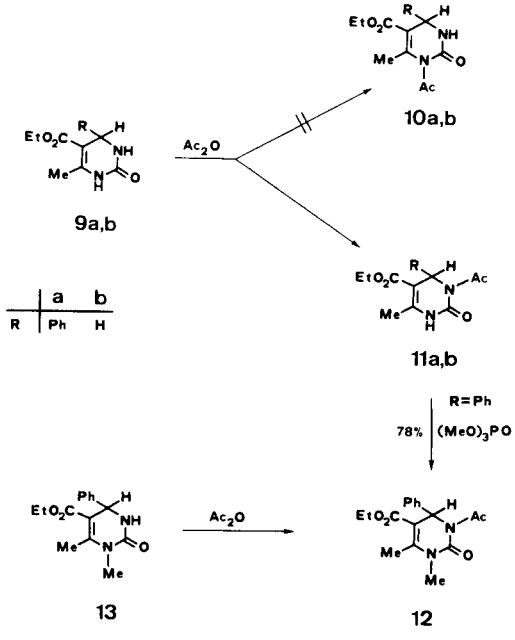


and δ 8.42, J = 4.6 Hz). Therefore, the product was identified as *N*(1)-methyl and not as *N*(3)-methyl derivative.

The reaction of **1a,b** with methyl iodide in refluxing methanol afforded the *S*-methylated compounds **2a,b** in excellent yield [9]. The action of acetic anhydride on **1a** and **1b** led to the corresponding 3-acetyl derivatives **3a,b**. The site of acetylation in **3a** was determined from the ^{1}H-nmr spectrum. The signal for the C(4) proton collapsed from a doublet in **1a** (δ 5.15, J = 4.0 Hz) to a singlet in **3a** (δ 6.70). Due to the anisotropic effect of the carbonyl group at N(3) a downfield shift of the C(4) proton can be observed in **3a**. The same effect was observed with the *N*(1)-methyl derivative **3b**, which can be acetylated in 3-position of the pyrimidine ring only.

The 2-methylthio-1,4-dihydropyrimidine **2a** reacts with various electrophiles under mild conditions (Scheme 2). The electrophile attacks the pyrimidine regiospecifically at the N(3) nitrogen, which was confirmed by ^{1}H-nmr spectroscopic data. Thus, the spectra show the same downfield shift for the C(4) proton as discussed above for **3a,b** (see Experimental). Additional proof for the site of substitution was obtained by alternative synthesis of **5** through methylation of **3a**. The action of an excess of methyl iodide on **2a** at elevated temperature in the presence of potassium carbonate led to the *N*(3)-methylated product **7**. Acid-catalyzed hydrolyses of **7** affords 3,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester **8** [10]. The structure of this compound was assigned by its ^{1}H-nmr spectrum. The most distinct signal is due to the C(4) proton which appeared as a singlet (δ = 5.16); in contrast the isomeric *N*(1)-methyl compound **13** shows doublets for the C(4) and N(3) protons (δ = 5.15 and 7.85, J = 4.0 Hz) [11]. "Biginelli-compounds" alkylated in position 3 (type **8**) can not be obtained by classical Biginelli-condensation (using *N*-alkylureas instead of urea) or alkylation of **9a**. In both cases *N*(1)-alkylated products are formed [12a-b].

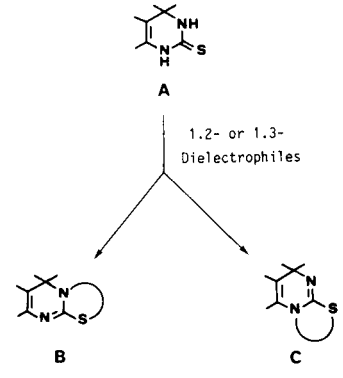
Scheme 3



The action of acetic anhydride on **9a,b** led to the corresponding 3-acetyl derivatives **11a,b** and not to 1-acetyl derivatives as previously assumed [13,14] (Scheme 3). This was confirmed not only by spectroscopic data (singlet for the C(4)-proton, δ 6.52 for **11a**) but also by derivation. Thus, when **11a** was refluxed with trimethylphosphate in the presence of potassium carbonate the 1-methyl-3-acetyl-tetrahydropyrimidine **12** was obtained. This compound was identical with a sample prepared by acetylation of **13** which has been reported earlier [13,15]. From the above acylation reactions it is quite obvious that the *N*(3)-nitrogen in compounds *e.g.* **1a, 2a, 9** is more reactive towards electrophiles than the *N*(1)-nitrogen, which is part of a push-pull system with the ester group in the 5-position of the pyrimidine ring.

Compound **1a** can be considered as a cyclic thiourea derivative, and therefore can react with various dielectrophiles to yield fused pyrimidines. However, two isomeric

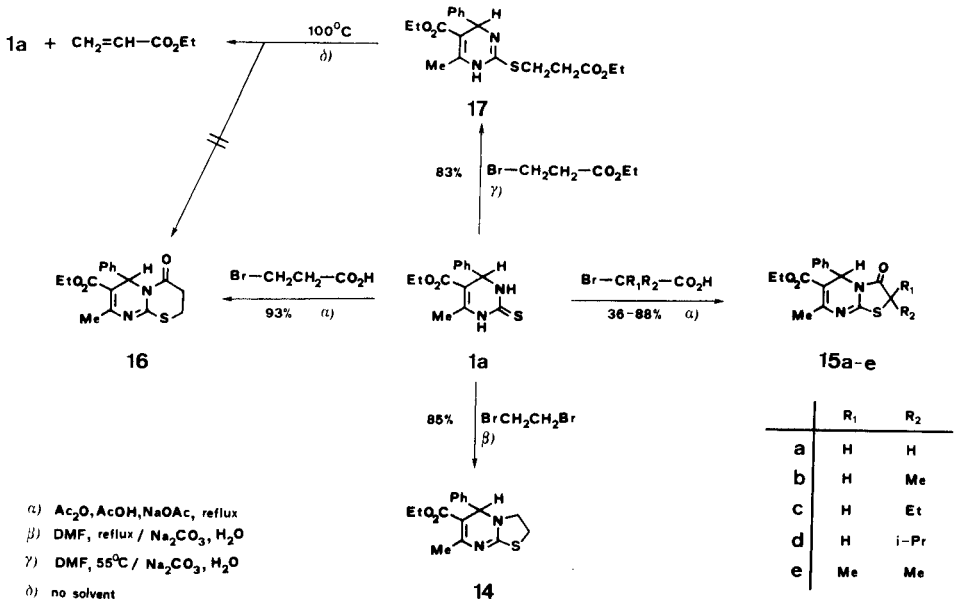
Scheme 4



cyclization products may be expected (Scheme 4). For both pathways examples are known, deriving from other dihydropyrimidines of type **A** [16,17]. Thus, when **1a** was refluxed with 1,2-dibromoethane in dimethylformamide **14** was obtained as a hydrobromide. Treatment with sodium carbonate solution yielded the free base as an oil (Scheme 5). Reaction of **1a** with various 2-bromoalkanoic acids - under the conditions given in Scheme 5 - afforded the corresponding 2,2-substituted-5*H*-thiazolo[3,2-*a*]-pyrimidines **15a-e**, whereas reaction with 3-bromopropionic acid led to 6*H*-pyrimido[2,3-*b*]thiazine **16** [18].

On the other hand, an attempt to substitute ethyl 3-bromopropionate for 3-bromopropionic acid in the reaction above, failed. However, under mild conditions we were able to isolate the *S*-alkylated-1,4-dihydropyrimidine **17** in

Scheme 5



	R_1	R_2
a	H	H
b	H	Me
c	H	Et
d	H	i-Pr
e	Me	Me

high yield. Upon heating, **17** eliminates ethyl acrylate to give the original tetrahydropyrimidine **1a** instead of the expected pyrimidothiazine **16**. This reaction can be considered as *retro*-Michael addition.

On the basis of ^{1}H-nmr and ^{13}C-nmr spectra (Figure 1) the structures of compounds **14-16** can be assigned to a type **B** condensation product (Scheme 4). Thus, the ^{1}H-nmr spectra of **15** and **16** show singlets for the C(4) protons, which are observed at δ 6.05 and δ 6.75 respectively. These values are in good agreement with chemical shifts observed for 3-acylated-tetrahydropyrimidines **3-6, 11a, 12**. It is evident that the effect of the carbonyl group is greater in the six-membered than in the five-membered ring. In addition the structure of **16** was determined by an X-ray crystallographic analysis.

The X-ray data of **16** are summarized in Table 1, and the thermal ellipsoids of the crystal structure along with the atom numbering scheme are shown in Figure 2. As expected, neither the pyrimidine nor the thiazine ring are planar. However, the ring atoms S(1), C(2), N(5), C(7), N(9) and C(10) are coplanar to within 0.020 Å. The other ring atoms are placed below this plane (0.926 Å for C(3), 0.435 Å for C(4) and 0.179 Å for C(8)) except for C(6) which is

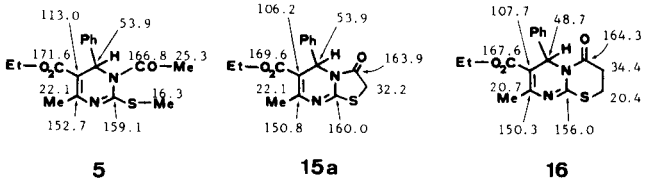


Figure 1. ^{13}C-nmr Assignments of important carbon atoms of compounds **5**, **15a** and **16**.

Table 1

Crystallographic Data for Compound **16**

Formula	$C_{17}H_{18}N_2O_3S$
Molecular Weight	330.41
Space Group	$P2_1/c$
a, Å	10.161(4)
b, Å	8.145(4)
c, Å	20.036(8)
β, deg.	98.36
V, Å^3	1640.4(7)
Z	4
D_{calc}, g cm^{-1}	1.338
D_{obs}, g cm^{-1} [a]	1.324
μ, cm^{-1}	2.03
F(000)	696
T, °K	295
2θ range, deg.	3-45
Reflections measured	3300
Unique reflections with I $\geq 3\sigma$ (I)	1743
R	0.074

[a] Flotation method in CsCl/H_2O.

placed 0.448 Å above the plane. The dihedral angle between the phenyl ring and the least-squares mean plane is 89.88°. Final atomic coordinates for all nonhydrogen atoms are given with estimated standard deviations in Table 2, the bond lengths and bond angles in Table 3.

The Dimroth-like rearrangement of 3,4-dihydropyrimidine-2(1*H*)-thiones to the isomeric 2-amino-6*H*-1,3-thiazine system [19] and *vice versa* [20] has been described previously. However, under the conditions given in the

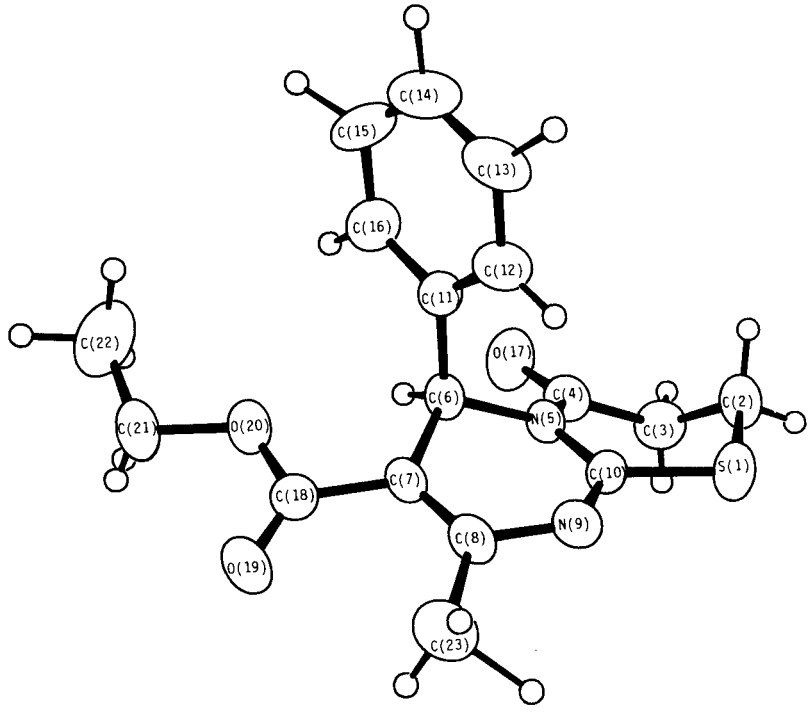


Figure 2. ORTEP drawing for the solid-state structure of **16**.

Table 2

Atomic Coordinates and Equivalent Isotropic Thermal Parameters (x 10^4, U-values in $Å^2$) for Nonhydrogen Atoms of Compound **16**

atom [a]	x	y	z	Ueq [b]
S(1)	5398(2)	3194(2)	2164(1)	521(6)
O(17)	8325(4)	2815(6)	801(2)	588(17)
O(19)	4924(5)	-3003(6)	-4(3)	615(16)
O(20)	7036(4)	-2270(6)	64(2)	547(16)
N(5)	6700(4)	1603(5)	1267(2)	315(14)
N(9)	4729(5)	532(6)	1558(2)	389(16)
C(2)	6778(7)	4495(9)	2088(4)	498(24)
C(3)	7022(8)	4583(8)	1370(4)	492(25)
C(4)	7424(6)	2972(8)	1119(3)	441(20)
C(6)	7064(5)	13(7)	995(3)	332(17)
C(7)	5810(5)	-947(7)	780(3)	327(17)
C(8)	4736(6)	-668(7)	1074(3)	384(19)
C(10)	5622(5)	1630(7)	1607(3)	343(18)
C(11)	8063(6)	-884(7)	1489(3)	381(19)
C(12)	7814(7)	-1210(8)	2127(3)	515(23)
C(13)	8708(7)	-2108(9)	2587(4)	619(25)
C(14)	9853(8)	-2670(10)	2385(5)	744(32)
C(15)	10110(7)	-2347(10)	1746(5)	751(33)
C(16)	9223(7)	-1427(9)	1297(4)	579(25)
C(18)	5832(6)	-2174(7)	244(3)	435(20)
C(21)	7207(10)	-3556(12)	-422(4)	772(34)
C(22)	8617(12)	-3729(20)	-438(6)	1145(59)
C(23)	3432(8)	-1557(12)	932(6)	605(30)

[a] Atoms are labelled in agreement with Figure 2. [b] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

Table 3

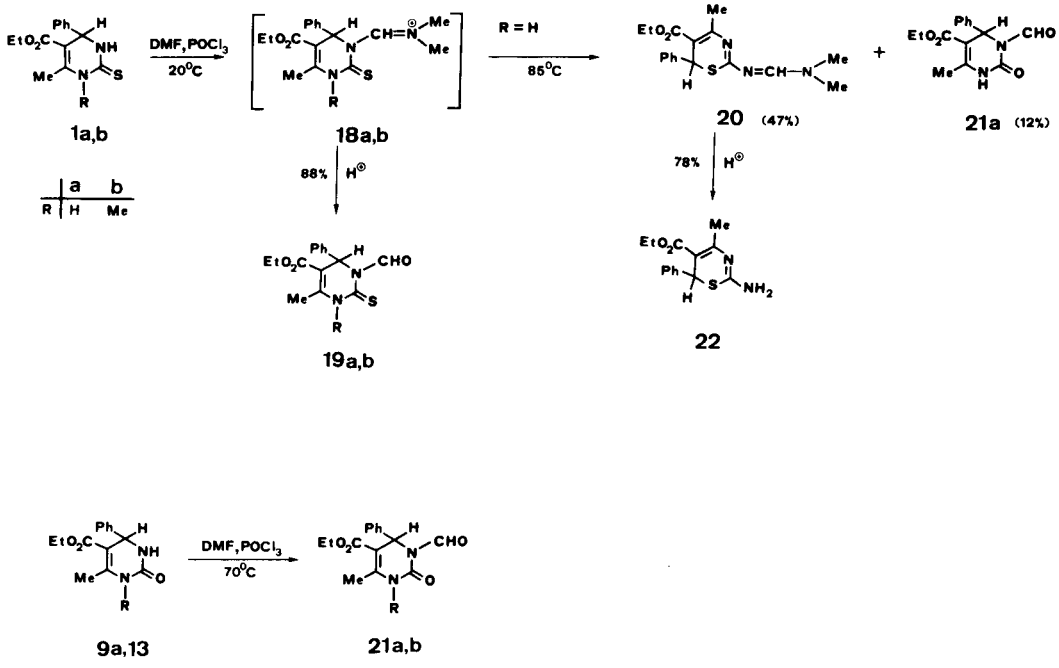
Bond Lengths (Å) and Bond Angles (°) Involving Nonhydrogen Atoms of Compound **16** [a]

S(1) -C(2)	1.781(8)	S(1) -C(10)	1.731(6)
O(17)-C(4)	1.196(7)	O(19)-C(18)	1.193(8)
O(20)-C(18)	1.327(8)	O(20)-C(21)	1.456(10)
N(5) -C(4)	1.391(8)	N(5) -C(10)	1.371(7)
N(5) -C(6)	1.474(7)	N(9) -C(8)	1.376(7)
N(9) -C(10)	1.268(7)	C(2) -C(3)	1.470(11)
C(3) -C(4)	1.484(9)	C(6) -C(7)	1.503(8)
C(6) -C(11)	1.500(8)	C(7) -C(8)	1.333(8)
C(7) -C(18)	1.471(8)	C(8) -C(23)	1.501(11)
C(11)-C(12)	1.364(9)	C(11)-C(16)	1.365(9)
C(12)-C(13)	1.403(10)	C(13)-C(14)	1.365(11)
C(14)-C(15)	1.369(14)	C(15)-C(16)	1.400(12)
C(21)-C(22)	1.445(16)		

C(2) -S(1) -C(10)	101.8(3)	C(12)-C(13)-C(14)	118.5(7)
C(4) -N(5) -C(10)	125.4(5)	C(14)-C(15)-C(16)	120.8(7)
C(4) -N(5) -C(6)	117.2(4)	C(11)-C(16)-C(15)	119.7(7)
C(8) -N(9) -C(10)	118.6(5)	C(7) -C(18)-O(20)	110.6(5)
S(1) -C(2) -C(3)	110.7(5)	O(19)-C(18)-O(20)	122.8(6)
C(3) -C(4) -O(17)	123.0(6)	C(18)-O(20)-C(21)	115.4(6)
C(3) -C(4) -N(5)	117.2(5)	C(10)-N(5) -C(6)	117.3(4)
N(5) -C(6) -C(7)	108.3(4)	C(2) -C(3) -C(4)	112.1(6)
N(5) -C(6) -C(11)	111.5(5)	O(17)-C(4) -N(5)	119.8(6)
C(6) -C(7) -C(8)	120.1(5)	C(7) -C(6) -C(11)	113.6(5)
C(6) -C(7) -C(18)	117.4(5)	C(8) -C(7) -C(18)	122.6(5)
C(7) -C(8) -N(9)	121.3(5)	N(9) -C(8) -C(23)	112.4(6)
C(7) -C(8) -C(23)	126.3(6)	N(5) -C(10)-N(9)	124.4(5)
S(1) -C(10)-N(5)	121.4(4)	C(12)-C(11)-C(16)	119.2(6)
S(1) -C(10)-N(9)	114.2(4)	C(13)-C(14)-C(15)	120.0(8)
C(6) -C(11)-C(12)	120.8(6)	C(7) -C(18)-O(19)	126.6(6)
C(6) -C(11)-C(16)	120.0(6)	O(20)-C(21)-C(22)	107.5(9)
C(11)-C(12)-C(13)	121.8(7)		

[a] Atoms are labelled in agreement with Figure 2.

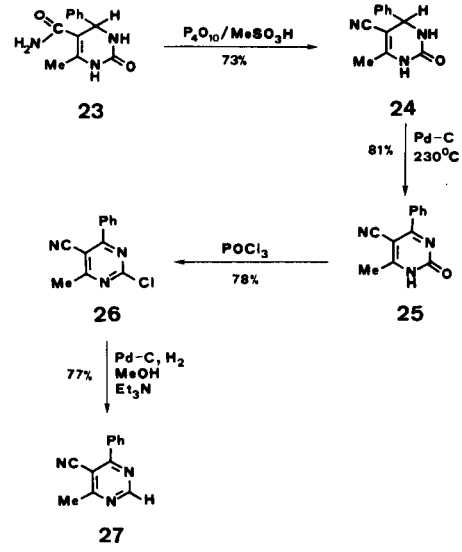
Scheme 6



literature for similar dihydropyrimidines (11 molar hydrochloric acid, 100-110° [19]) no reaction occurred when **1a** was used as the starting material. If the reaction was carried out in dimethylformamide solution we were able to obtain the expected 2-amino-6*H*-1,3-thiazine **22** in a multistep reaction (Scheme 6). Thus, when **1a,b** was treated with phosphorus oxychloride in dimethylformamide at room temperature, intermediates **18a,b** were readily formed *via* Vilsmeier formylation, which can be shown by the formation of the 3-formyl-2-thioxo-derivative **19a,b** upon hydrolysis. If **1a** was used as the entry, rearrangement of **18a** at elevated temperature took place to form thiazinyl-2-formamidine **20** in 47% yield. As a side product **21a** was obtained in 12% yield. This 3-formyl-2-oxopyrimidine derivative as well as its 1-methyl derivative **21b** can be prepared alternatively in high yield by Vilsmeier formylation of the corresponding 2-oxopyrimidines **9a** and **13**, respectively. Finally **20** was hydrolyzed under strongly acidic conditions to give the 2-aminothiazine **22** in 78% yield. Rearrangement of **1b** at even higher temperature could not be observed. The C(4) protons of formylated products **19a,b** and **21a,b** showed the typical downfield shift due to the adjacent carbonyl group at the *N*(3)-nitrogen. Therefore the rearranged products **20** and **22** were identified at 6*H*-1,3-thiazines and not as 4*H*-1,3-thiazines.

The synthesis of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **24** can not be achieved by direct Biginelli condensation, due to the instability of the required cyanoacetone. Therefore, we considered the corresponding pyrimidine-5-carboxamide **23** as suitable entry for the preparation of pyrimidine-5-carbonitriles. Hence, when **23** is dehydrated with phosphorus pentoxide, using methanesulfonic acid as solvent **24** is obtained in 73% yield (Scheme 7). Dehydrogenation of **24** in almost boiling

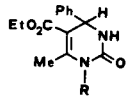
Scheme 7



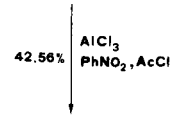
diphenyl ether in the presence of palladium on charcoal afforded compound **25**, which can easily be converted with phosphorus oxychloride to the 2-chloropyrimidine **26**. Catalytic reduction of **26** gives 4-methyl-6-phenylpyrimidine-5-carbonitrile **27**.

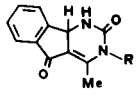
Finally, we made an attempt to synthesize 1,2,3,9b-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidines **28a,b** by an hitherto unknown intramolecular Friedl-Crafts acylation on Biginelli-compounds **9a,13** (Scheme 8). When the usual conditions were employed the yields were unsatisfactory.

Scheme 8

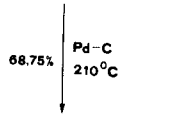


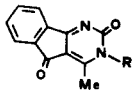
9a,13





28a,b





29a,b

In our studies we observed that the presence of an excess of acetyl chloride increases the yield considerably. However, the role of acetyl chloride in this reaction is yet unknown, and small amounts of an unidentified by-product had to be accepted. The structure of this compound **28a** was determined from its ^{1}H-nmr spectrum, which exhibits singlets at δ 5.37 and δ 9.45 for the C(9b) and N(1) protons respectively, indicating that $J_{1,9b} \cong 0$ Hz. The dihedral angle for these protons must therefore approach 90°. Treatment of **28a,b** with palladium on charcoal in diphenyl ether affords the dehydrogenated products **29a,b** in acceptable yields.

EXPERIMENTAL

The melting points were determined with a Gallenkamp Melting Point Apparatus Mod. MFB-595 and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 298 spectrophotometer using samples in potassium bromide disks. The ^{1}H-nmr spectra were obtained on a Varian EM 360 at 60 MHz or XL-200 at 200 MHz in the solvents indicated. Chemical shifts (δ) are expressed in ppm downfield from TMS used as internal standard. The letters b, s, d, t, q and m are used to indicate broad, singlet, doublet, triplet, quadruplet and multiplet, respectively. The ^{13}C nmr spectra were recorded on a Varian XL-200 in hexadeuteriodimethylsulfoxide using TMS as internal standard. Mass spectra were obtained on a Finnigan mass spectrometer 4500 at 70eV (EI) using a direct inlet system. Microanalyses were performed on a C,H,N-automat Carlo Erba 1106.

The X-ray structure determination was performed on a modified Stoe 4-circle diffractometer, using graphite monochromatized Mo-Kα radiation (λ = 0.71069 Å). Cell constants were determined by a least-squares fit to the diffractometer setting angles of 18 reflections with $9 \leq 2\theta \leq 14°$. Three periodically monitored reflections showed no significant intensity changes. The measured intensities were corrected for Lorentz and polarization effects but not for absorption. The structure was solved with the SHELXS 86 program using direct methods. All non-hydrogen atoms were refined anisotropically; the atomic coordinates for all hydrogen atoms were revealed by a difference Fourier synthesis, and were refined isotropically leading to a final R factor of 0.074.

Compounds **1a**, **9a**, and **13** were prepared according to the method described by Folkers [7,21].

1,6-Dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester **1b**.

A mixture of *N*-methylthiourea (9.0 g, 0.10 mole), benzaldehyde (10.6 g, 10.1 ml, 0.10 mole), ethyl acetoacetate (19.5 g, 18.9 ml, 0.15 mole) and 50 ml of ethanol containing 10 drops of concentrated hydrochloric acid was refluxed for 3 hours. The solution was allowed to stand at -20° for several hours to yield 13.9 g (48%) of product, mp 146-147° (ethanol); ir: 3210, 2990, 1710, 1640, 1540, 1500 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.16 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.46 (s, C6-CH_3), 3.51 (s, 3H, NCH_3), 4.08 (q, J = 7.0 Hz, 2H, OCH_2), 5.32 (d, J = 4.6 Hz, 1H, methine CH), 7.12 (s, 5H, Ph), 8.42 (d, J = 4.6 Hz, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.01; H, 6.25; N, 9.65. Found: C, 61.76; H, 6.36; N, 9.51.

6-Methyl-2-methylthio-4-phenyl-1,4-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (**2a**).

To a suspension of 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (2.76 g, 0.01 mole) **1a** [7] in 20 ml of methanol methyl iodide (1.56 g, 0.7 ml, 0.011 mole) was added. The mixture was then refluxed for 2 hours, and after addition of pyridine (2.93 g, 3.0 ml, 0.037 mole) the solution was refluxed for another 5 minutes, then was allowed to cool to room temperature and poured into 200 ml of ice-water to yield 2.55 g (88%) of **2a**, mp 171-172° (ethanol) (lit [9] 169-171°); ir: 3320, 1655, 1470 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.10 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.27 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.98 (q, J = 7.0 Hz, 2H, OCH_2), 5.44 (s, 1H, methine CH), 7.22 (s, 5H, Ph), 9.45 (b, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65; S, 11.04. Found: C, 62.20; H, 6.25; N, 9.60; S, 10.96.

1,6-Dimethyl-2-methylthio-4-phenyl-1,4-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (**2b**).

This compound was prepared according to the procedure described above for **2a**, starting with 1,6-dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (2.90 g, 0.01 mole) (**1b**). The yield of **2b** was 2.76 g (91%), mp 60-61° (cyclohexane); ir: 2965, 1695, 1640, 1580, 1490, 1450 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.23 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.17 (s, 3H, NCH_3), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 5.85 (s, 1H, methine CH), 7.24 (s, 5H, Ph).

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.12; H, 6.64; N, 9.20. Found: C, 62.94; H, 6.47; N, 9.23.

3-Acetyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**3a**).

A solution of **1a** (2.76 g, 0.01 mole) in 15 ml of acetic anhydride was heated under reflux for one hour. The solution was then poured into 150 ml of ice-water and stirred for several hours until crystallization was complete. The precipitate was filtered and washed with water to yield 2.88 g (88%) of **3a**, mp 144-145° (benzene/petroleum ether); ir: 3245, 2990, 1705, 1660, 1510 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.23 (t, J = 7.0 Hz, 3H ethyl CH_3), 2.35 (s, 3H, C6-CH_3), 2.77 (s, 3H, acetyl CH_3), 4.22 (q, J = 7.0 Hz, 2H, OCH_2), 6.70 (s, 1H, methine CH), 7.32 (s, 5H, Ph), 8.72 (s,

1H, NH).

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.57; H, 5.60; N, 8.78.

3-Acetyl-1,6-dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**3b**).

This compound was prepared as described above, using **1b** (2.90 g, 0.01 mole) as the starting compound to yield 2.79 g (84%) of **3b**, mp 118-120° (cyclohexane); ir: 2990, 1710, 1690, 1640, 1500 cm^{-1}; ^1H-nmr (deuteriochloroform): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.49 (s, 3H, C6-CH_3), 2.62 (s, 3H, acetyl CH_3), 3.37 (s, 3H, NCH_3), 4.18 (q, J = 7.0 Hz, 2H, OCH_2), 6.70 (s, 1H, methine CH), 7.18 (s, 5H, Ph).

Anal. Calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.41; H, 6.08; N, 8.43. Found: C, 61.40; H, 5.97; N, 8.39.

4-Methyl-2-methylthio-4-phenyl-1,6-dihydropyrimidine-1,5-dicarboxylic Acid Diethyl Ester (**4**).

A solution of **2a** (2.90 g, 0.01 mole) in 50 ml of dry tetrahydrofuran was treated with ethyl chloroformate (2.17 g, 1.90 ml, 0.02 mole) and pyridine (1.76 g, 1.80 ml, 0.022 mole) with stirring, and kept at room temperature for an additional 30 minutes. The reaction mixture was poured into 400 ml of ice-water and the precipitate was immediately filtered off to yield 1.90 g (80%) of **4**, mp 86-87° (methanol); ir: 2980, 2920, 1730, 1705, 1620, 1515 cm^{-1}; ^1H-nmr (DMSO-d_6) δ = 1.18, 1.29 (2t, J = 7.0 Hz, 6H, 2 ethyl CH_3), 2.35 (s, 6H, C4-CH_3, SCH_3), 4.10, 4.25 (2q, J = 7.0 Hz, 4H, 2 OCH_2), 6.14 (s, 1H, methine CH), 7.20 (s, 5H, Ph).

Anal. Calcd. for $C_{18}H_{22}N_2O_4S$: C, 59.64; H, 6.13; N, 7.73. Found: C, 59.73; H, 6.02; N, 7.83.

3-Acetyl-6-methyl-2-methylthio-4-phenyl-3,4-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (**5**).

Method A.

A solution of **2a** (2.90 g, 0.01 mole) in 15 ml of acetic anhydride was refluxed for 30 minutes. After standing overnight at 0° the precipitate was removed by filtration and dried over potassium hydroxide *in vacuo* to give 2.90 g (87% of **5**, mp 122-123° (ethanol).

Method B.

A mixture of **3a** (1.59 g, 0.005 mole), anhydrous potassium carbonate (1.38 g, 0.01 mole), methyl iodide (1.42 g, 0.62 ml, 0.01 mole) and 25 ml of dry dimethylformamide was stirred at room temperature for 2 hours and then poured into 300 ml of ice-water. After the addition of petroleum ether (30 ml) the mixture was stirred until crystallization of the product. The precipitate was filtered to yield 1.18 g (71%) of product, mp 122-123° (ethanol); ir: 2980, 1710, 1685, 1610, 1520 cm^{-1}; ^1H-nmr (deuteriochloroform): δ = 1.25 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.47 (s, 9H, 3 CH_3), 4.22 (q, J = 7.0 Hz, 2H, OCH_2), 6.47 (s, 1H, methine CH), 7.28 (s, 5H, Ph).

Anal. Calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.41; H, 6.08; N, 8.43. Found Method A: C, 61.66; H, 5.79; N, 8.45. Method B: C, 61.56; H, 6.01; N, 8.43.

The products obtained by Methods A and B are identical in their ir and ^1H-nmr spectra and melting points.

6-Methyl-2-methylthio-4-phenyl-3-tosyl-3,4-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (**6**).

A mixture of **2a** (1.45 g, 0.005 mole), tosyl chloride (1.05 g, 0.0055 mole) and 10 ml of dry pyridine was stirred overnight at room temperature. The reaction mixture was poured into 150 ml of ice-water; after complete crystallization the product was removed by filtration and washed with water to yield 1.60 g (72%) of product, mp 89-90° (methanol); ir: 2975, 1680, 1605, 1595, 1510 cm^{-1}; ^1H-nmr (deuteriochloroform): δ = 1.23 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.13 (s, 3H, tolyl CH_3), 2.31 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 6.37 (s, 1H, methine CH), 7.21 (d, J = 8.4 Hz, 2H, Ar), 7.25 (s, 5H, Ph), 7.68 (d, J = 8.4 Hz, 2H, Ar).

Anal. Calcd. for $C_{22}H_{24}N_2O_4S_2$: C, 59.43; H, 5.45; N, 6.30. Found: C, 59.48; H, 5.51; N, 6.41.

3,6-Dimethyl-2-methylthio-4-phenyl-3,4-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (**7**).

A mixture of **2a** (5.80 g, 0.02 mole), methyl iodide (5.68 g, 2.50 ml, 0.04 mole), potassium carbonate (5.0 g, 0.036 mole) and dimethylformamide (30 ml) was heated under stirring in a sealed tube for 4 hours at 60° bath temperature. The suspension was poured into ice-water (300 ml), and the product was filtered after complete crystallization to give 5.53 g (91%) of **7**, mp 112-114° (methanol); ir: 2970, 1660, 1590, 1500 cm^{-1}; ^1H-nmr (deuteriochloroform): δ = 1.23 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.40 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 4.10 (q, J = 7.0 Hz, 2H, OCH_2), 5.23 (s, 1H, methine CH), 7.32 (s, 5H, Ph).

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.08; H, 6.40; N, 9.06.

3,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**8**).

Compound **7** (3.04 g, 0.01 mole) was heated under reflux in 20 ml of methanol, containing acetic acid (5 ml) and water (5 ml). After 24 hours methanol was distilled off and the remaining solution was treated portion wise with water until the precipitation of product was completed. After standing for several hours at 4° the product was removed by filtration to yield 2.28 g (83%) of **8**, mp 183-184° (ethanol), ([10], mp 159-160°); ir: 3210, 3090, 2960, 1700, 1680, 1640, 1480, 1450 cm^{-1}; ^1H-nmr (DMSO-d_6): δ = 1.12 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.25 (s, 3H, C6-CH_3), 2.71 (s, 3H, NCH_3), 3.97 (q, J = 7.0 Hz, 2H, OCH_2), 5.16 (s, 1H, methine CH), 7.31 (s, 5H, Ph), 9.36 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.76; H, 6.42; N, 10.23.

3-Acetyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**11a**).

This compound was prepared by acetylation of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**9a**) as described earlier [13,14] (no spectral data given). The yield of **11a** was 81%, mp 175-176°; (85.5%, 175.5-177° [13]; 68.3%, 176-177° [14]); ir: 3240, 3140, 2980, 1705, 1650, 1495 cm^{-1}; ^1H-nmr (DMSO-d_6): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.35 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 6.52 (s, 1H, methine CH), 7.30 (s, 5H, Ph), 10.10 (s, 1H, NH).

3-Acetyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**11b**).

This compound was prepared by acetylation of 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**9b**) [21] as described in the literature [14] (no spectral data given). The yield of **11b** was 58%, mp 150-151° (61.9%, 149.5-150.5° [14]); ir: 3300, 2980, 1730, 1685, 1655 cm^{-1}; ^1H-nmr (DMSO-d_6): δ = 1.23 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.23 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 4.37 (s, 2H, NCH_2), 9.85 (s, 1H, NH).

3-Acetyl-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**12**).

A mixture of **11a** (1.52 g, 0.005 mole), anhydrous potassium carbonate (1.38 g, 0.01 mole) and 20 ml of trimethyl phosphate was refluxed for 30 minutes, then poured into 200 ml of ice-water and the resulting precipitate was collected by filtration to give 1.23 g (78%) of **12**, mp 109-110° (methanol); ir: 2980, 1710, 1695, 1630 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.51 (s, 6H, 2 CH_3), 3.14 (s, 3H, NCH_3), 4.18 (q, J = 7.0 Hz, 2H, OCH_2), 6.67 (s, 1H, methine CH), 7.22 (s, 5H, Ph).

This compound is identical in melting point, ir and ^1H-nmr spectra with a sample obtained by acetylation of 1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**13**), which has been reported earlier [13,15].

7-Methyl-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic Acid Ethyl Ester (**14**).

To a boiling solution of **1a** (2.76 g, 0.01 mole) in 10 ml of dimethylformamide, dibromoethane (2.07 g, 0.95 ml, 0.011 mole) was added and the mixture refluxed for 25 minutes. After standing overnight at room temperature the precipitate was filtered by suction. To increase the yield the filtrate may be evaporated. The total yield of the hydrobromide was 3.55 g (85%), mp 215-216° (ethanol). The free base was obtained as an oil by treating the aqueous solution of the hydrobromide with an excess of 5% sodium carbonate solution. The hydrobromide had ir: 3600, 2980, 2720, 1695, 1660, 1610, 1530 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.59 (s, 3H, C7-CH_3), 3.50-3.90 (m, 4H, thiazole CH_2), 4.24 (q, J = 7.0 Hz, 2H, OCH_2), 5.78 (s, 1H, methine CH), 7.50 (s, 5H, Ph); ms: m/e (relative intensity) 302 (M+ -HBr, 11), 273 (21), 257 (7), 225 (100), 197 (41), 179 (7), 151 (8), 115 (7).

Anal. Calcd. for $C_{16}H_{19}BrN_2O_2S$: C, 50.14; H, 5.00; N, 7.31. Found: C, 50.16; H, 4.91; N, 7.92.

The free base had ^{1}H-nmr (DMSO-d_6): δ = 1.07 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.26 (s, 3H, C7-CH_3), 3.11-3.38 (m, 4H, thiazole CH_2), 3.96 (q, J = 7.0 Hz, 2H, OCH_2), 5.44 (s, 1H, methine CH), 7.33 (s, 5H, Ph).

7-Methyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic Acid Ethyl Ester (**15a**).

A mixture of **1a** (2.76 g, 0.01 mole), bromoacetic acid (1.53 g, 0.011 mole), anhydrous sodium acetate (1.64 g, 0.02 mole), acetic anhydride (12 ml) and acetic acid (20 ml) was heated under reflux for 30 minutes. Then the mixture was taken to dryness *in vacuo*. The residue was treated with water (100 ml) and after crystallization occurred the precipitate was filtered to yield 2.78 g (88%) of **15a**, mp 110-112° (ethanol); ir: 2990, 1750, 1740, 1710, 1700, 1620, 1545 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.15 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.47 (s, 3H, C7-CH_3), 3.75 (s, 2H, thiazole CH_2), 4.08 (q, J = 7.0 Hz, 2H, OCH_2), 6.05 (s, 1H, methine CH), 7.32 (s, 5H, Ph); ms: m/e (relative intensity) 316 (M+, 70), 287 (21), 271 (14), 259 (10), 239 (100), 211 (53), 165 (18), 123 (20), 115 (14).

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.80; H, 5.08; N, 8.83.

2,2-R1,R2-Substituted-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidine-5-carboxylic Acid Esters **15b-e**.

These compounds were prepared in the way described above for **15a** using a 3 molar excess of R1,R2-substituted bromoacetic acids and extending the reaction time to 4 hours.

Compound **15b** was obtained from *dl*-2-bromopropionic acid in a yield of 46%, mp 137-140° (ethanol); ir 2980, 1740, 1700, 1610, 1540 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.21 (t, J = 7.0 Hz, 3H, ethyl CH_3), 1.46 (d, J = 7.0 Hz, 3H, C2-CH_3), 2.50 (s, 3H, C7-CH_3), 4.15 (2q, J = 7.0 Hz, 3H, OCH_2, thiazole CH), 6.09 (s, 1H, methine CH), 7.39 (s, 5H, Ph).

Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 62.06; H, 5.39; N, 8.49.

Compound **15c** was obtained from *dl*-2-bromobutyric acid in a yield of 79%, mp 133-135° (ethanol); ir: 2970, 2920, 1730, 1690, 1610, 1530 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 0.64 (t, J = 7.0 Hz, 3H, ethyl CH_3), 1.18 (t, J = 7.0 Hz, 3H, ethyl CH_3), 1.81 (dq, J = 6.5 and 7.0 Hz, 2H, ethyl CH_2), 2.47 (s, 3H, C7-CH_3), 4.10 (q, J = 7.0 Hz, 2H, OCH_2), 4.13 (t, J = 6.5 Hz, 1H, thiazole CH), 6.05 (s, 1H, methine CH), 7.33 (s, 5H, Ph).

Anal. Calcd. for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.77; H, 5.75; N, 8.07.

Compound **15d** was obtained from *dl*-2-bromo-3-methylbutyric acid in a yield of 39%, mp, 122-126° (ethanol); ir: 2970, 1730, 1705, 1615, 1540 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 0.33, 0.83 (2d, J = 7.0 Hz, 6H, isopropyl CH_3), 1.15 (t, J = 7.0 Hz, 3H, ethyl CH_3), 1.00-1.25 (m, 1H, isopropyl CH), 2.50 (s, 3H, C7-CH_3), 4.10 (q, J = 7.0 Hz, 2H, OCH_2), 4.13 (s, 1H, thiazole CH), 6.05 (s, 1H, methine CH), 7.30 (s, 5H, Ph).

Anal. Calcd. for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.90; H, 6.14; N, 7.78.

Compound **15e** was obtained from 2-bromo-2-methylpropionic acid in a yield of 36%, mp 143-144° (ethanol); ir: 2980, 1735, 1700, 1615, 1540 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 1.42, 1.70 (2s, 6H, 2 CH_3), 2.50 (s, 3H, C7-CH_3), 4.12 (q, J = 7.0 Hz, 2H, OCH_2), 6.08 (s, 1H, methine CH), 7.38 (s, 5H, Ph).

Anal. Calcd. for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.90; H, 5.63; N, 8.16.

8-Methyl-4-oxo-6-phenyl-2,3-dihydro-6*H*-pyrimido[2,3-*b*]thiazine-7-carboxylic Acid Ethyl Ester (**16**).

A mixture of **1a** (2.76 g, 0.01 mole), 3-bromopropionic acid (1.68 g, 0.011 mole), anhydrous sodium acetate (1.64 g, 0.02 mole), acetic anhydride (12 ml) and acetic acid (20 ml) was heated under reflux for 2 hours. Then the mixture was taken to dryness *in vacuo*. The remaining residue was treated with water (100 ml) and after crystallization the precipitate was filtered to give 3.07 g (93%) of **16**, mp 141-142° (ethanol); ir: 2980, 1700, 1610, 1500 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.43 (s, 3H, C8-CH_3), 2.60-3.10 (m, 4H, thiazine CH_2), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 6.75 (s, 1H, methine CH), 7.33 (s, 5H, Ph).

Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 62.04; H, 5.44; N, 8.46.

2-(2-Ethoxycarbonylethyl)thio-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylic Acid Ethyl Ester (**17**).

A solution of **1a** (2.76 g, 0.01 mole) and ethyl-3-bromopropionate (2.17 g, 0.012 mole) in 20 ml of dimethylformamide was stirred for 60 hours at 55° and then was allowed to stand at room temperature for another 6 hours. The mixture was poured into ice-water (200 ml), and unchanged starting material was removed by filtration (100-200 mg). The solution was made distinctly alkaline by addition of 2*N* sodium carbonate solution. The resulting oily precipitate was allowed to stand for at least 48 hours at 4° to yield 3.12 g (83%) of **17**, mp 84-86° dec (chloroform/petroleum ether); ir: 3340, 2980, 1720, 1700, 1650, 1480 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.21, 1.28 (2t, J = 7.0 Hz, 6H, 2 ethyl CH_3), 2.34 (s, 3H, C6-CH_3), 2.68, 3.25 (2t, J = 6.7 Hz, 4H, ethylene CH_2), 4.10, 4.19 (2q, J = 7.0 Hz, 4H, 2 OCH_2), 5.60 (s, 1H, methine CH), 7.25 (s, 5H, Ph); ms: m/e (relative intensity) 377 (M+, 65), 347 (29), 331 (30), 299 (100), 275 (72), 253 (28), 247 (60), 199 (64), 171 (28), 55 (70).

Anal. Calcd. for $C_{19}H_{24}N_2O_4S$: C, 60.62; H, 6.43; N, 7.44. Found: C, 60.84; H, 6.25; N, 7.46.

If compound **17** was heated in an oil bath at 100° until the liberation of ethyl acrylate was completed, **2a** was formed quantitatively. This compound was shown to be identical in all respects with an authentic sample prepared by the Biginelli reaction [7].

3-Formyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**19a**).

To a solution of **1a** (5.52 g, 0.02 mole) in 30 ml of dry dimethylformamide, phosphorus oxychloride (4.68 g, 2.80 ml, 0.03 mole) was added under stirring in an ice-bath. Stirring was continued at room temperature for another 15 minutes and then the solution was poured into 400 ml of ice-water to give 5.36 g (88%) of **19a**, mp 165-166° (ethanol); ir 3200, 3150, 3000, 1710, 1660, 1520 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.43 (s, 3H, C6-CH_3), 4.14 (q, J = 7.0 Hz, 2H, OCH_2), 6.27 (s, 1H, methine CH), 7.28 (s, 5H, Ph), 9.74 (s, 1H, formyl CH), 11.65 (b, 1H, NH).

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.18; H, 5.31; N, 9.21. Found: C, 59.46; H, 5.43; N, 9.27.

1,6-Dimethyl-3-formyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**19b**).

The product was prepared as described above for **19a** starting from **1b** (5.80 g, 0.02 mole) to yield 5.60 g (88%) of **19b**, mp 91-93° (methanol); ir: 3070, 3000, 2980, 2940, 1710, 1635, 1500 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.19 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.55 (s, 3H, C6-CH_3), 3.50 (s, 3H, NCH_3), 4.13 (q, J = 7.0 Hz, 2H, OCH_2), 6.38 (s, 1H, methine CH), 7.20 (s, 5H, Ph), 9.70 (s, 1H, formyl CH).

Anal. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.35; H, 5.71; N, 8.80. Found: C, 60.26; H, 5.59; N, 8.77.

N,N-Dimethyl-*N'*-(5-ethoxycarbonyl-4-methyl-6-phenyl-6*H*-1,3-thiazin-2-yl)formamidine (**20**).

To a suspension of **1a** (2.76 g, 0.01 mole) in 15 ml of dry dimethylformamide, phosphorus oxychloride (1.65 g, 1.0 ml, 0.011 mole) was added dropwise with stirring in an ice-bath. After all starting material had dissolved, the reaction mixture was heated in an oil bath to 85°. After one hour the solution was allowed to cool and poured into 100 ml of ice-water, the precipitated side product **21a** (12%) was removed by filtration and the filtrate was made distinctly alkaline with 2*N* sodium hydroxide solution at 4°. After the precipitated oil had become crystalline it was filtered by suction and recrystallized from ethanol to yield 1.56 g of yellow crystals of **20** (47%), mp 140°; ir: 2990, 2930, 1690, 1615, 1580, 1485 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.13 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.42 (s, 3H, C4-CH_3), 2.91, 3.10 (2s, 6H, 2 NCH_3), 4.05 (q, J = 7.0 Hz, 2H, OCH_2), 5.24 (s, 1H, methine CH), 7.20 (s, 5H, Ph), 8.39 (s, 1H, formamidine CH).

Anal. Calcd. for $C_{17}H_{21}N_3O_3S$: C, 61.61; H, 6.39; N, 12.68. Found: C, 61.57; H, 6.22; N, 12.59.

2-Amino-4-methyl-6-phenyl-6*H*-1,3-thiazine-5-carboxylic Acid Ethyl Ester (**22**).

A solution of **20** (3.31 g, 0.01 mole) in 20 ml of concentrated hydrochloric acid and 10 ml of water was kept at 80° for 10 minutes. The precipitated product was filtered by suction to give 2.65 g (85%) of the hydrochloride, mp 191° dec (chloroform/petroleum ether).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_2S$: C, 53.75; H, 5.48; N, 8.95. Found: C, 53.53; H, 5.56; N, 8.80.

The free amine was prepared by treating the ice-cold solution of the hydrochloride (2.6 g, 0.0083 mole) in ethanol with 2*N* sodium hydroxide solution (5 ml), and precipitating the amine with ice-water. The yield of **22** was 2.1 g (91%), mp 120-122° (chloroform/petroleum ether); total yield calculated on **20** 78%; ir: 3390, 3290, 3130, 2980, 1680, 1630, 1600, 1525 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.42 (s, 3H, C4-CH_3), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 5.32 (s, 1H, methine CH), 5.68 (s, 2H, NH_2), 7.24 (s, 5H, Ph).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.13. Found: C, 60.88; H, 5.72; N, 10.01.

3-Formyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**21a**).

To a suspension of **9a** (5.20 g, 0.02 mole) [21] in 20 ml of dry dimethylformamide, phosphorus oxychloride (3.07 g, 1.90 ml, 0.02 mole) was added in an ice-bath. The resulting solution was heated at 70° and kept there for 40 minutes, and then was poured into 150 ml of ice-water to yield 4.70 g (80%) of **21a**, mp 216° (ethanol); ir: 3240, 3140, 2970, 1730, 1720, 1700, 1650, 1490 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.20 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.39 (s, 3H, C6-CH_3), 4.10 (q, J = 7.0 Hz, 2H, OCH_2), 6.23 (s, 1H, methine CH), 7.38 (s, 5H, Ph), 9.30 (s, 1H, formyl CH), 10.26 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.70; H, 5.51; N, 9.67.

Compound **21a** is identical in melting point, ir and ^{1}H-nmr spectra and microanalysis with the side product formed during the synthesis of **20**.

1,6-Dimethyl-3-formyl-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Ethyl Ester (**21b**).

This compound was prepared in the way shown above for **21a**, using **13** (5.48 g, 0.02 mole) [7] as starting compound. The yield of **21b** was 78%, mp 96-97° (ethanol); ir: 2980, 1725, 1705, 1630, 1500 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 1.18 (t, J = 7.0 Hz, 3H, ethyl CH_3), 2.59 (s, 3H, C6-CH_3), 3.25 (s, 3H, NCH_3), 4.11 (q, J = 7.0 Hz, 2H, OCH_2), 6.30 (s, 1H, methine CH), 7.30 (s, 5H, Ph), 9.16 (s, 1H, formyl CH).

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.90; H, 6.01; N, 9.14.

6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**24**).

A solution of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (69.3 g, 0.30 mole) (**23**) [22,23] in 150 ml of methanesulfonic acid containing 30 g of phosphorus pentoxide was heated in an oil bath at 140°, and kept there for 30 minutes. The hot reaction mixture was allowed to cool off to about 40°, before it was poured into 1200 ml of water to give 47 g (73%) of **24**, mp 238-242° (acetic acid/ethanol); ir: 3390, 3280, 3100, 2930, 2205, 1715, 1700, 1655 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 2.00 (s, 3H, C6-CH_3), 5.05 (d, J = 2.0 Hz, 1H, methine CH), 7.36 (s, 5H, Ph), 7.79 (d, J = 2.0 Hz, 1H, NH), 9.50 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.60; H, 5.20; N, 19.71. Found: C, 67.48; H, 5.27; N, 19.58.

6-Methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carbonitrile (**25**).

To a solution of **24** (2.13 g, 0.01 mole) in 20 ml of diphenyl ether, 1 g of palladium on charcoal (10%) was added at 230° bath temperature. After one hour an additional amount of 1 g of catalyst was added and the reaction mixture was kept for another hour at 230°. The hot mixture was then diluted with 50 ml of acetic acid, the catalyst filtered from the hot solution and the solvent was removed *in vacuo*. The residue was digested with petroleum ether to yield 1.71 g (81%) of **25**, mp 240° (acetic acid); ir: 3100-2500, 2220, 1660, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 2.50 (s, 3H, C6-CH_3), 3.35 (b, 1H, NH), 7.35-7.90 (m, 5H, Ph).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.20; N, 19.89. Found: C, 68.27; H, 4.51; N, 19.66.

2-Chloro-4-methyl-6-phenylpyrimidine-5-carbonitrile (**26**).

This compound was prepared by refluxing a mixture of **25** (2.11 g, 0.01 mole) with 10 ml or phosphorus oxychloride for 30 minutes. The resulting solution was poured into ice-water (100 ml) to give 1.79 g (78%) of **26**, mp 123-124° (ethanol); ir: 2220, 1600, 1530, 1490 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 2.89 (s, 3H, CH_3), 7.40-8.25 (m, 5H, Ph).

Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 63.06; H, 3.75; N, 18.05.

4-Methyl-6-phenylpyrimidine-5-carbonitrile (**27**).

A solution of **26** (2.30 g, 0.01 mole) in 50 ml of methanol containing triethylamine (2.0 g, 0.02 mole) was hydrogenated at room temperature under atmospheric pressure for 2 hours in the presence of 0.3 g of palladium on charcoal (10%). The warmed solution was filtered from the catalyst and evaporated *in vacuo*; the residue obtained was digested with ice-cold methanol to yield 1.50 g (77%) of **27**, mp 104-105° (ethanol); ir: 2220, 1600, 1540 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 2.72 (s, 3H, CH_3), 7.50-8.15 (m, 5H, Ph), 9.33 (s, 1H, C2-H).

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.56; H, 4.45; N, 21.46.

4-Methyl-1,2,3,9b-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-2,5-dione (**28a**).

A mixture of **9a** (2.60 g, 0.01 mole), anhydrous aluminum chloride (8.00 g, 0.06 mole), acetyl chloride (4.30 g, 3.90 ml, 0.055 mole) and 20 ml of nitrobenzene was heated under stirring for 4 hours at 90°. The solution was then poured into 200 ml of ice-water containing 20 ml concentrated hydrochloric acid, and was treated with 100 ml of ligroin, and stirred for 3 hours. The precipitated product was filtered by suction and was recrystallized twice from acetic acid to yield 0.9 g (42%) mp 279° dec; ir: 3270, 3110, 2960, 1700, 1685, 1630 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 5.37 (s, 1H, methine CH), 7.40-7.88 (m, 4H, Ar), 8.18 (s, 1H, N1-H), 9.45 (s, 1H, N3-H).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.27; H, 4.71; N, 13.08. Found: C, 66.94; H, 4.68; N, 12.87.

3,4-Dimethyl-1,2,3,9b-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-2,5-dione (**28b**).

This compound was prepared according to the method described above using **13** (2.74 g, 0.01 mole) as the starting material. The reaction was completed after 2.5 hours at 70° and treated as above to give 1.28 g (56%) of **28b**, mp 250° dec; ir: 3210, 3090, 2910, 1695, 1680, 1635, 1600 cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 2.73 (s, 3H, CH_3), 3.41 (s, 3H, NCH_3), 5.51 (s, 1H, methine CH), 7.45-8.15 (m, 4H, Ar).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.31; N, 12.27. Found: C, 68.48; H, 5.40; N, 12.15.

4-Methyl-2,3-dihydro-5*H*-indeno[1,2-*d*]pyrimidine-2,5-dione (**29a**).

To a suspension of **28a** (2.14 g, 0.01 mole) in 50 ml of diphenyl ether, 1

g palladium on charcoal (10%) was added at 210°. After 30 minutes an additional amount of 0.5 g of catalyst was added and the reaction mixture was kept for another 30 minutes at 210°. The hot mixture was then diluted with 100 ml of acetic acid, the catalyst filtered from the hot solution and the solvent was removed *in vacuo*. The residue was treated with petroleum ether to yield 1.44 g (68%) of **29a**, mp 300° dec (acetic acid); ir: 2850, 1705, 1660, 1625, 1580 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 7.21 (s, 1H, NH), 7.50-8.00 (m, 4H, Ar).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.71; H, 3.80; N, 12.98.

3,4-Dimethyl-2,3-dihydro-5H-indeno[1,2-*d*]pyrimidine-2,5-dione (**29b**).

This compound was prepared in the same way described above starting with **28b** (2.28 g, 0.01 mole) to yield 1.70 g (75%) of **29b**, mp 280° dec (acetic acid); ir: 1720, 1665, 1625, 1600, 1590, 1565 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ = 2.75 (s, 3H, CH_3), 3.46 (s, 3H, NCH_3), 7.60-8.05 (m, 4H, Ar).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.76; H, 4.46; N, 12.13.

Acknowledgements.

The authors thank Doz. Christoph Kratky for the possibility to obtain X-ray crystallographic data of compound **16**. We are also grateful to Prof. Heinz Sterk for recording the ^{13}C-nmr spectra and to Erhard Hohenester for measuring the mass spectra.

REFERENCES AND NOTES

[1] K. S. Atwal (E. R. Squibb and Sons, Inc.), European Patent Application EP 202,654 (1986); *Chem. Abstr.*, **106**, 84631z (1987); K. S. Atwal, G. C. Rovnyak, and S. D. Kimball (E. R. Squibb and Sons, Inc.), European Patent Application EP 204,317 (1986); *Chem. Abstr.*, **107**, 39847j (1987); K. S. Atwal (E. R. Squibb and Sons, Inc.), U. S. Patent 4,684,655 (1987); *Chem. Abstr.*, **107**, 176066t (1987); K. S. Atwal (E. R. Squibb and Sons, Inc.), U. S. Patent 4,684,656 (1987); *Chem. Abstr.*, **107**, 198355p (1987).

[2] J. J. Baldwin, D. A. Claremon, and D. E. McClure (Merck and Co., Inc.), U. S. Patent 4,609,494 (1986); *Chem. Abstr.*, **106**, 18636d (1987).

[3] V. V. Kastron, R. O. Vitolin, E. L. Khanina, G. Ya. Duburs, A. A. Kimenis, *Khim. Farm. Zh.*, **21**, 948 (1987).

[4] P. Biginelli, *Gazz. Chim. Ital.*, **23**, 360 (1893).

[5] See also D. J. Brown, in "The Chemistry of Heterocyclic Compounds", Vol **16**, A. Weissberger and E. C. Taylor, eds, John Wiley and Sons, Inc., New York, NY, 1962, p 440; *ibid.*, Supplement I, 1970, p 326; *ibid.*, Supplement II, 1985, p 422.

[6] L. E. Hinkel and D. H. Hey, *Rec. Trav. Chim.*, **48**, 1280 (1929).

[7] K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.*, **55**, 2886 (1933).

[8] Recently an alternative route to 4-substituted-1,2,3,4-tetrahydro-6-methyl-2-oxo(or thioxo)pyrimidine-5-carboxylic acid esters has been reported using 2-methylene-3-oxobutanoic acid esters and *O*-methylisourea hydrogensulfate (or 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride) as precursors: B. C. O'Reilly and K. S. Atwal, *Heterocycles*, **26**, 1185 (1987); K. S. Atwal, B. C. O'Reilly, J. Z. Gougoutas, and M. F. Malley, *Heterocycles*, **26**, 1189 (1987).

[9] The 2-methylthiopyrimidine **2a** has previously been synthesized in poor yield by addition of phenylmagnesium bromide to 4-methyl-2-methylthiopyrimidine-5-carboxylic acid ethyl ester: Z. Budesinsky, J. Vavrina, L. Langsadl, and J. Holubek, *Collect. Czech. Chem. Commun.*, **45**, 539 (1980).

[10] It has been stated earlier that **8** was formed upon reaction of **9a** with phosphorus oxychloride, following treatment with sodium methoxide solution [7]. However, the two products have not the same melting point (see Experimental).

[11] Spectrum recorded in DMSO-d_6; for synthesis of **13** see: lit [7] and F. Sweet, J. D. Fissekis, *J. Am. Chem. Soc.*, **95**, 8741 (1973).

[12a] T. George, R. Tahilramani, and D. V. Mehta, *Synthesis*, 405 (1975); [b] E. L. Khanina, M. B. Andaburskaya, G. Duburs, and R. M. Zolotoyabko, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 197 (1978); *Chem. Abstr.*, **89**, 43319r (1978).

[13] K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.*, **56**, 1374 (1934).

[14] N. V. Khromov-Borisov and A. M. Savchenko, *J. Obshch. Chim.*, **22**, 1680 (1952).

[15] E. L. Khanina, G. Duburs, *Khim. Geterosikl. Soedin.*, 535 (1982).

[16] Type B: synthesis and antihypertensive activity: K.-C. Liu, L.-W. Chern, M.-H. Yen, and Y.-O. Lin, *Arch. Pharm.*, **316**, 379 (1983); *ibid*, **316**, 569 (1983).

[17] Type C: N. Gill, N. K. Ralhan, H. S. Sachdev, and K. S. Narang, *J. Org. Chem.*, **26**, 968 (1961); H. K. Gakhar, K. K. Narula, and N. K. Ralhan, *Indian J. Chem.*, **7**, 967 (1969); A.-E. G. Hammam and M. I. Ali, *J. Chem. Eng. Data*, **26**, 99 (1981).

[18] In the absence of anhydrous sodium acetate the hydrobromides of **15a** (mp 210° dec, acetic acid) and **16** (mp 230° dec, acetic acid) were obtained.

[19] H. Singh, P. Singh, *J. Chem. Soc., Perkin Trans. 1*, 1013 (1980) and literature cited therein.

[20] G. Zigeuner, T. Strallhofer, F. Wede, and W. B. Lintschinger, *Monatsh. Chem.*, **106**, 1469 (1975).

[21] K. Folkers, H. J. Harwood, T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 3751 (1932).

[22] G. Duburs, E. L. Khanina, *Khim. Geterosikl. Soedin.*, 220 (1976).

[23] T. Kato, T. Chiba, M. Sasaki, *Yakugaku Zasshi*, **101**, 182 (1981).

Note Added in Proof (Nov. 22, 1988).

Compound **1b** has recently been described by E. L. Khanina, D. K. H. Muceniece, V. P. Kadysh, and G. Ya. Duburs, *Khim. Geterosikl. Soedin.*, 1223 (1986); *Chem. Abstr.*, **107**, 39737 (1987).