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The synthesis of N^1-substituted 4-pyrimidones is described. These compounds were prepared from their corresponding 4-oxopyrimidinium perchlorates or from a reaction of a primary amine with a *N*-acyl-β-ketoamide.

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Pyrimidines are important heterocycles in biochemistry and medicinal chemistry. They represent 50% of the DNA and RNA bases and occur in a series of therapeutically active agents. We were particularly interested in 4-pyrimidones with N^1-aryl or N^2-alkyl substitution as possible building blocks in drug design and development. Most cyclization pathways, described in literature, afford N^3-substituted analogues [1-8]. An exception is the reaction between *N*-aryl substituted amidines and ethyl acetylenecarboxylate [4]. Alkylation of 4-pyrimidones, in contrast, gives usually N^3-substituted derivatives [10-13]. N^3-Substituted pyrimidones can also be obtained when 4-aminopyrimidines are alkylated and subsequently hydrolyzed [9].

In a research program on the reaction of 4-oxo-1,3-oxazinium perchlorates with amines we found that a 4-oxo-oxazinium salt afforded the corresponding N^1-substituted 4-oxopyrimidinium salts. The latter could be deprotonated to the non-cationic 4-pyrimidone by treatment with sodium bicarbonate solution. We already reported some pharmacological results, obtained with compounds from the reaction between oxazinium cations and aminophenols [14]. In this article we report the general feasibility of this synthetic pathway to 4-pyrimidones. Moreover, we report on an alternative method we have developed during these investigations.

Starting material in our synthetic scheme were phenylacetamides **1a-b**. The compounds are *C,N*-acylated with boron trifluoride in acetic or propionic anhydride into *N*-acetyl- or *N*-propionyl-β-ketoamides **2a-c** [15] (Table 1).

These β-ketoamides undergo cyclisation into 4-oxo-1,3-oxazinium perchlorates **3a-c** (Table 2) when treated with perchloric acid and acetic anhydride in chloroform. This reaction affords 2,6-symmetrically substituted 4-oxo-1,3-oxazinium ions. Oxazinium ion **3d** with different 2,6-substitutions can be obtained from an anhydride

Table 1

N-Acyl-2-aryl-β-ketoamides **2**

Compound	mp (°C)	Yield (%)	ir, (cm^{-1}) [a] NH	ir, (cm^{-1}) [a] C=O	^{1}H nmr, (ppm) [b]
2a	117-119	90	3360	1735 1720 1700	2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 7.2 (s, 5H, phenyl)
2b [c]	164	70	3260	1748 1742	2.0 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.1-7.2 (m, 4H, phenyl)
2c	108-109	78	3295	1745 1725 1700	1.0 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.1 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.5 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.5 (q, J = 7.6 Hz, CH_2CH_3), 2.0 7.3 (s, 5H, phenyl)
2c	108-109	78	3295	1745 1725 1700	1.0 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.1 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.5 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.5 (q, J = 7.6 Hz, CH_2CH_3), 2.0 7.3 (s, 5H, phenyl)
2d [d]	111-113	58	3365	1740 1720 1700	1.1 (t, J = 6.9 Hz, 3H, CH_2CH_3), 2.1 (s, 3H, CH_3), 2.4 (q, J = 6.9 Hz, 2H, CH_2CH_3), 7.3 (s, 5H, phenyl)

[a] Potassium bromide. [b] Deuteriochloroform, tetramethylsilane as the internal standard. [c] ^{13}C nmr (deuteriochloroform): δ 20.6 (e), 24.7 (k), 25.4 (e), 29.1 (k), 65.8 (k), 103.9 (e), 115.9 (e) (d, J_{CCF} = 21.6 Hz), 116.8 (k), 127.6 (e), 127.7 (k), 131.6 (e) (d, J_{CCCF} = 8.2 Hz), 133.4 (k) (d, J_{CCCF} = 8.2 Hz), 162.8 (d, J_{CF} = 249.5 Hz), 162.9 (d, J_{CF} = 249.5 Hz), 169.5, 170.3, 171.7, 172.2, 177.8, 202.6. [d] For the preparation we used the 4-oxooxazinium perchlorate **3e**.

Table 2

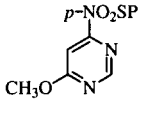
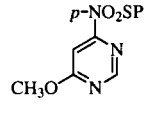
4-Oxo-1,3-oxazinium Perchlorates **3**

Compound	mp (°C)	Yield (%)	ir (cm^{-1}) [a] NH	C=O	C=C	^{1}H nmr, ppm [b]
3a	190	96	3330	1755	1670 1610	2.6 (s, 3H, 6-CH_3), 2.7 (s, 3H, 2-CH_3), 7.3 (s, 5H, phenyl)
3b [c]	203	92	3340	1735	1665 1610	2.4 (s, 3H, 6-CH_3), 3.0 (s, 3H, 2-CH_3), 7.1-7.3 (m, 4H, phenyl)
3c	193	95	3360	1755	1660 1605	1.3 (t, J = 7.4 Hz, 3H, 6-CH_2CH_3), 1.6 (t, J = 6.7 Hz, 3H, 2-CH_2CH_3), 2.7 (q, J = 7.4 Hz, 2H, 6-CH_2CH_3), 3.3 (q, J = 6.7 Hz, 2H, 2-CH_2CH_3), 7.3-7.4 (m, 5H, phenyl)
3d	194	46	3280	1750	1655 1610	1.1 (t, J = 6.7 Hz, 3H, 2-CH_2CH_3), 2.2 (s, 3H, 6-CH_3), 2.9 (q, J = 6.7 Hz, 2H, 2-CH_2CH_3), 7.0 (s, 5H, phenyl)
3e	177	50		1720	1660 1610	2.2 (s, 3H, 6-CH_3), 2.4 (s, 3H, 2-CH_3), 4.0 (s, 3H, OCH_3), 5.1 (s, 1H, C=CH), 7.1-7.3 (m, 4H, phenyl)

[a] Nujol. [b] Trifluoroacetic acid, tetramethylsilane as the internal standard. [c] ^{13}C nmr (trifluoroacetic acid): 19.9 (q, J_{CH} = 132.6 Hz), 22.7 (q, J_{CH} = 135.3), 119.5 (dd, J_{CCF} = 22.5 Hz, J_{CH} = 166.8 Hz), 125.3, 125.6, 134.7 (d, J_{CCCF} = 7.8 Hz), 159.7, 167.4 (d, J_{CF} = 253.2 Hz), 174.2, 183.0.

Table 3

4-Oxopyrimidinium Perchlorates **6** [a]

Compound	R^1	R^2	R^3	R^5	R^6	mp (°C)	Yield (%)
6/1	H	CH_3	H	Ph	CH_3	N.D.	72
6/2	H	CH_3	H	*p*-FPh	CH_3	N.D.	45
6/3	CH_3	CH_3	H	Ph	CH_3	N.D.	40
6/4	CH_2Ph	CH_3	H	Ph	CH_3	147	56
6/5	Ph	CH_3	H	Ph	CH_3	260	80
6/6	*p*-CH_3OPh	CH_3	H	Ph	CH_3	185 [b]	61
6/7	*o*-HOPh	CH_3	H	Ph	CH_3	167	94
6/8	*m*-HOPh	CH_3	H	Ph	CH_3	174	96
6/9	*p*-OHPh	CH_3	H	Ph	CH_3	177	100
6/10	*p*-OHPh	CH_3	H	*p*-FPh	CH_3	315 [b]	68
6/11	*o*-HOOCPh	CH_3	H	Ph	CH_3	300 [b]	78
6/12	*m*-HOOCPh	CH_3	H	Ph	CH_3	242 [b]	83
6/13	*p*-HOOCPh	CH_3	H	Ph	CH_3	248 [b]	99
6/14	*o*-CH_3OOCPh	CH_3	H	Ph	CH_3	202	63
6/15	*o*-CH_3OOCPh	C_2H_5	H	Ph	CH_3	220	23
6/16	*o*-CH_3OOCPh	C_2H_5	H	Ph	C_2H_5	275	11
6/17	*m*-H_2NPh	CH_3	H	Ph	CH_3	160	71
6/18	*p*-H_2NPh	CH_3	H	Ph	CH_3	167	40
6/19	*p*-$(CH_3)_2NPh$	CH_3	H	Ph	CH_3	241	46
6/20	*p*-H_2NSO_2Ph	CH_3	H	Ph	CH_3	264	40
6/21		CH_3	H	Ph	CH_3	260	65
6/22	*p*-HOOC(*m*-OH)Ph	C_2H_5	H	Ph	C_2H_5	218	31
6/23	p-CH_3OOCPh	CH_3	H	Ph	CH_3	229	39
6/24	*o*-C_2H_5OOCPh	C_2H_5	H	Ph	CH_3	N.D.	44
6/25	Ph	CH_3	*o*-CH_3O Ph	H	CH_3	213	52
6/26	*p*-HOPh	CH_3	*o*-CH_3OPh	H	CH_3	196	40
6/27		CH_3	*o*-CH_3OPh	H	CH_3	251	35

[a] All compound were crystallized from acetic acid (with a drop of perchloric acid). [b] With decomposition. [c] The product was prepared from **7**.

and β-ketonitrile **4** [16]. N^3-Aryl 4-oxo-1,3-oxazinium perchlorate **3e** can be synthesized from *N*-aryl-β-ketoamides **5** in acetic anhydride. Analytical data of compounds **3** are summarized in Table 2.

The above prepared 4-oxo-1,3-oxazinium perchlorates **3**, dissolved in acetic acid, react with aliphatic and aromatic amines, affording the corresponding N^1-substituted 4-oxopyrimidinium perchlorates **6** (Tables 3 and 4) (Scheme 2).

Table 4

Analytical Data on 4-Oxopyrimidinium Perchlorates **6**

Compound	ir (cm^{-1})			Elemental analysis (%) [a]			
	NH	C=O	C=C	C	H	N	Cl
6/1	3180	1720	1690	47.99	4.00	9.71	-
			1620	(48.09)	(4.04)	(9.35)	
			1565				
6/2 [b]	3180	1720	1690	-	-	-	-
			1623	-	-	-	-
			1565				
6/3	3190	1715	1650	49.62	4.79	8.88	11.45
			1600	(49.61)	(4.80)	(8.90)	(11.22)
			1580				
6/4	3200	1720	1650	58.41	4.79	7.21	9.07
			1610	(58.39)	(4.90)	(7.17)	(9.07)
			1580				
6/5 [c]	3280	1720	1650	-	-	-	9.55
			1600	-	-	-	(9.44)
			1580				
6/6 [h]	3270	1705	1650	56.12	5.01	-	8.90
			1610	(56.10)	(4.71)	-	(8.71)
			1520				
6/7	3190	1712	1652	54.90	4.49	6.93	9.09
			1610	(55.10)	(4.34)	(7.14)	(8.93)
			1580				
6/8	3210	1700	1654	55.30	4.30	7.33	8.95
			1620	(55.10)	(4.34)	(7.14)	(8.93)
			1585				
6/9 [c]	3200	1709	1648	55.13	4.21	7.21	8.98
			1605	(55.10)	(4.34)	(7.14)	(8.93)
			1580				
6/10 [d]	3330	1700	1680	-	-	-	-
			1640	-	-	-	-
			1600				
6/11 [f]	3460	1720	1660	54.26	4.01	-	8.39
		1700	1610	(54.29)	(4.05)		(8.33)
			1580				
6/12	3360	1715	1650	54.30	4.14	-	8.27
		1700	1605	(54.29)	(4.05)	-	(8.33)
			1595				
6/14	3180	1730	1650	55.30	4.47	-	7.99
		1710	1610	(55.29)	(4.37)	-	(8.06)
			1580				
6/15	3200	1725	1650	56.13	4.70	-	7.81
			1610	(56.25)	(4.68)	-	(7.81)
			1600				
6/16	3230	1745	1660	57.12	5.10	6.12	7.71
		1710	1610	(57.14)	(4.97)	(6.06)	(7.57)
			1600				
6/17	3345	1705	1650	55.25	4.63	-	9.0
	3515 (NH_2)		1600	(55.24)	(4.60)	-	(8.95)
			1560				
6/18	3350	1700	1630	55.31	4.59	-	8.97
	3415 (NH_2)		1600	(55.24)	(4.60)	-	(8.95)
6/19	3390	1690	1645	67.58	6.12	13.33	10.01
			1620	(67.60)	(6.19)	(13.16)	(9.85)
6/20 [g]	3300	1720	1650	47.08	3.68	6.79	7.79
			1580	(47.42)	(3.95)	(7.03)	(7.79)
6/21	3070	1715	1645	52.30	4.02	-	8.31
		1690	1610	(52.29)	(3.89)	-	(8.02)
			1595				
6/22	3200	1730	1630	57.61	5.06	6.19	-
			1610				
		1700	1580	(57.14)	(4.97)	(6.06)	-

Table 4 (continued)

Compound	ir (cm^{-1})			Elemental analysis (%) [a]			
	NH	C=O	C=C	C	H	N	Cl
6/23	3210	1710	1620	48.05	4.23	-	6.42
			1600	(47.97)	(3.90)	-	(6.29)
6/24	3320	1740	1660	57.19	5.03	-	7.61
		1715	1610	(57.14)	(4.97)	-	(7.57)
			1595				
6/25		1731	1663	56.32	4.74	-	8.89
			1610	(56.10)	(4.71)	-	(8.71)
			1600				
6/26		1727	1650	53.91	4.45	-	7.98
		1615	1580	(54.03)	(4.50)	-	(8.29)
6/27	3200	1750	1630	47.39	3.99	-	5.98
			1600	(47.52)	(4.04)	-	(5.98)

[a] Calculated values in parentheses. [b] ^{1}H nmr (trifluoroacetic acid): δ 2.4 (s, 3H, 6-CH_3), 3.0 (s, 3H, 2-CH_3), 7.2-7.3 (m, 4H, phenyl); ^{13}C nmr (trifluoroacetic acid): δ 19.9 (q, J_{CH} = 132 Hz), 20.8 (q, J_{CH} = 134.5 Hz), 119.2 (dd, J_{CH} = 166.18 Hz, J_{CCF} = 22.1 Hz), 126.9, 128.8, 134.5 (d, J_{CH} = 163.7 Hz), 155.7, 164.7, 165.4, 169.1 [c] ^{1}H nmr (trifluoroacetic acid): δ 1.6 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 7.0 (s, 5H, phenyl), 7.2 (s, 5H, *N*-phenyl). [d] ^{1}H nmr (trifluoroacetic acid): δ 1.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 6.7-7.1 (m, 9H, phenyl). [e] ^{13}C nmr (trifluoroacetic acid): δ 21.67 (q, J_{CH} = 132.6 Hz), 23.4 (q, J_{CH} = 135 Hz), 119.4 (dd, J_{CH} = 166.7 Hz, J_{CCF} = 22.5 Hz), 128.2, 130.4, 131.0 (d, J_{CH} = 163.2 Hz), 132.1, 134.6 (d, J_{CH} = 164.2 Hz), 159.8, 161.0, 167.9, 168.0, 169.1. [f] ^{1}H nmr (trifluoroacetic acid): δ 1.6 (s, 3H, 6-CH_3), 2.3 (s, 3H, 2-CH_3), 6.7-7.1 (s, 9H, phenyl). [g] ^{1}H nmr (trifluoroacetic acid): δ 1.7 (s, 3H, 6-CH_3), 2.3 (s, 3H, 2-CH_3), 7.5-8.1 (m, 9H, phenyl). [h] ^{1}H nmr (trifluoroacetic acid): δ 1.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 3.8 (s, 3H, OCH_3), 6.9-7.2 (m, 9H, phenyl). [i] The other pyrimidinium cations are ^{1}H-nmr characterized as their corresponding 4-oxo-1,4-dihydropyrimidines **8** (see Table 7).

Scheme 1

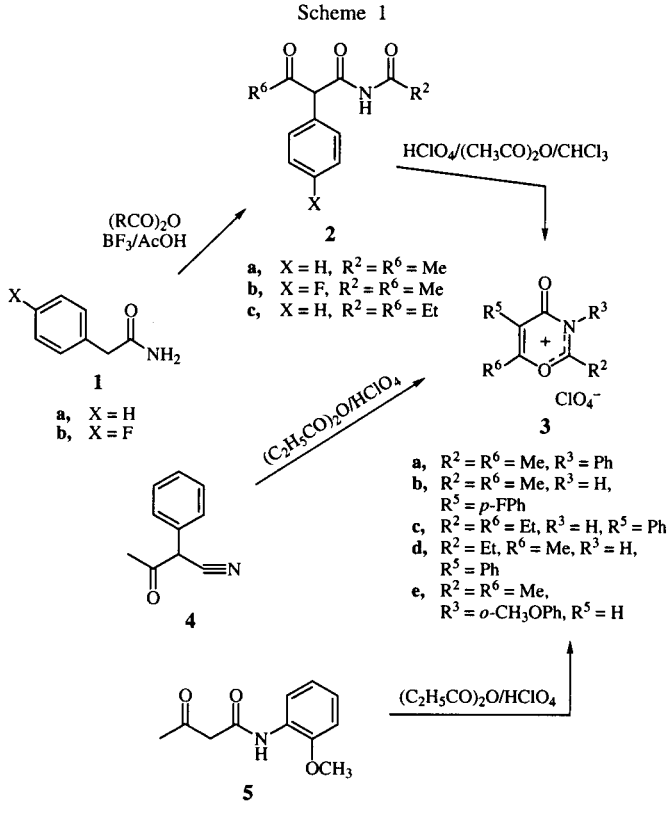
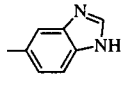
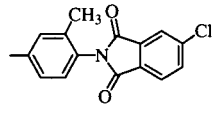
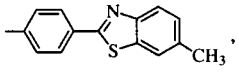
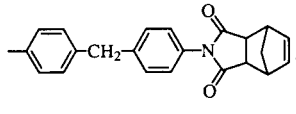


Table 5

4-Oxo-1,4-dihydropyrimidines **8**

Compound	R^1	R^2	R^5	R^6	mp (°C)	Solvent	Yield % B	Yield % A
8/1	H	CH_3	Ph	CH_3	224	EtOH	70	-
8/2	H	CH_3	*p*-FPh	CH_3	276	C_6H_6	58	-
8/3	CH_3	CH_3	Ph	CH_3	205	$CHCl_3$	35	-
8/4	Bn	CH_3	Ph	CH_3	211	AcOEt	62	-
8/4A	Bn	CH_3	*p*-FPh	CH_3	196	AcOEt	77	76
8/5	Ph	CH_3	Ph	CH_3	170	C_6H_6	-	99
8/6	*o*-OCH_3Ph	CH_3	Ph	CH_3	216	AcOEt	63	-
8/7	*o*-HOPh	CH_3	Ph	CH_3	312 [a]	EtOH	93	94
8/8	*m*-HOPh	CH_3	Ph	CH_3	299 [a]	EtOH	95	60
8/9	*p*-HOPh	CH_3	Ph	CH_3	302 [a]	AcOEt	84	97
8/10	*p*-HOPh	CH_3	*p*-FPh	CH_3	>260	*i*-PrOH	50	-
8/11	*o*-HOOCPh	CH_3	Ph	CH_3	279	EtOH	16	78
8/12	*m*-HOOCPh	CH_3	Ph	CH_3	254	CH_3CN	53	39
8/13	*p*-HOOCPh	CH_3	Ph	CH_3	314	EtOH	-	100
8/14	*o*-CH_3OOCPh	CH_3	Ph	CH_3	150	C_6H_6	18	54
8/15	*o*-CH_3OOCPh	C_2H_5	Ph	C_2H_5	158	EtOH	-	40
8/16	*m*-H_2NPh	CH_3	Ph	CH_3	200	$CHCl_3$/hexane	-	30
8/17	*p*-H_2NPh	CH_3	Ph	CH_3	177	$CHCl_3$/hexane	37	50
8/19	*p*-$(H_3C)_2NPh$	CH_3	Ph	CH_3	226	AcOEt	-	90
8/20	*p*-CH_3OOCPh	C_2H_5	Ph	C_2H_5	218	C_6H_6	40	40
8/28	*o*-CF_3Ph	CH_3	*p*-FPh	CH_3	195	C_6H_6/hexane	75	-
8/29	*m*-CH_3OOCPh	CH_3	Ph	CH_3	N.D.	C_6H_6	70	63
8/30	*p*-CH_3OOCPh	CH_3	Ph	CH_3	237	C_6H_6	64	75
8/31	*p*-C_2H_5OOCPh	CH_3	*p*-FPh	CH_3	173	AcOEt	55	
8/32	*o*-C_2H_5OOCPh	CH_3	Ph	CH_3	N.D.	C_6H_6	68	
8/33 [b]	cyclohexyl	CH_3	*p*-FPh	CH_3	179	EtOH		30
8/34	CH_2COOEt	CH_3	Ph	CH_3	202	EtOH		35
8/35	[c]	CH_3	*p*-FPh	CH_3	302	EtOH		62
8/36	[d]	CH_3	*p*-FPh	CH_3	179	CH_2Cl_2		85
8/37	[e]	CH_3	*p*-FPh	CH_3	215	EtOH		65
8/38	[f]	CH_3	*p*-FPh	CH_3	181	EtOH		58

[a] With decomposition. [b] Purified on a silica column with ethyl acetate: methanol (5/1). [c] R^1 =  , [d]] R^1 =  ,

[e] R^1 =  , [f] R^1 =  .

This reaction succeeds under slightly different reaction conditions (ethanol as the solvent) with N^3-aryl-4-oxo-1,3-oxazinium cation **3e** and affords N^3-aryl substituted 4-oxopyrimidinium perchlorates **6/25-6/27**.

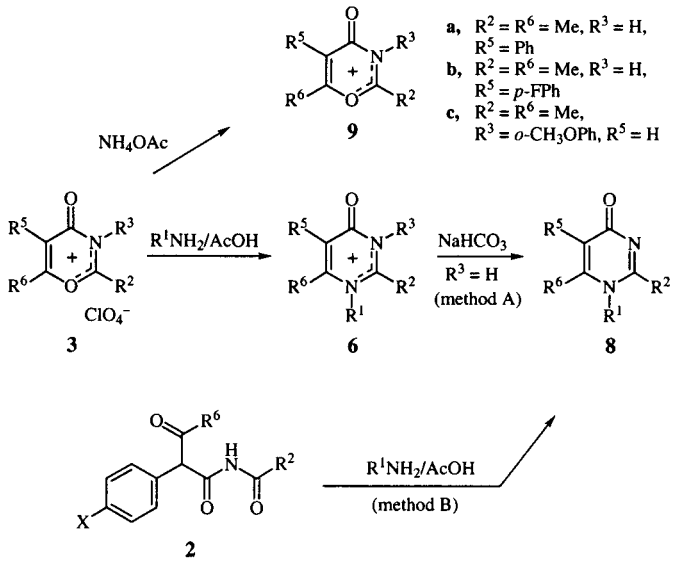
We tried to obtain 4-oxopyrimidinium salts **6** in a one step cyclization between *N*-acyl-β–ketoamides **2** and an amine in perchloric acid-acetic acid. This reaction however did not succeed. In a stepwise reaction scheme using the *N*-arylenamine derivative **7** of the β-ketoamide as an intermediate, we could however obtain the desired 4-oxopyrimidinium perchlorates (Scheme 3). The yields were however very poor and this method can hardly been considered as a general method. Compound **7** was obtained from β-ketonitrile **4** by treatment with an aromatic amine and borontrifluoride-acetic acid and subsequent acylation with acetic anhydride.

Our target N^1-substituted 4-pyrimidones **8** (Table 5-7) were prepared by treatment of the parent pyrimidinium perchlorates **6** with an aqueous solution of sodium bicarbonate.

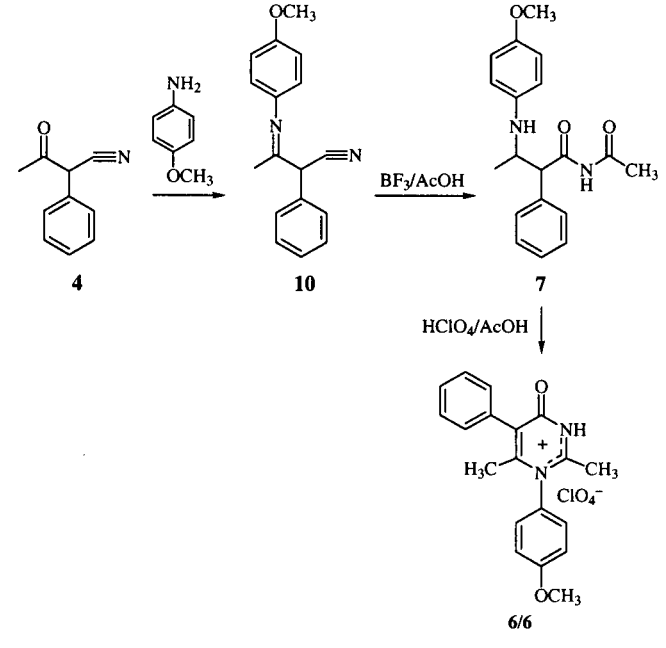
Although, as mentioned earlier, the concerted cyclization between *N*-acyl-β-ketoamide **2** and an amide in perchloric acid-acetic acid did not afford 4-oxopyrimidinium cations, we found rather unexpectedly that omitting perchloric acid in this reactions afforded the target 4-pyrimidones **8** in moderate to high yield. This direct cyclization also can be considered as an excellent synthetic method for **8**, in case $R^2 = R^6$ (Scheme 2). Treatment of N^3-aryl 4-oxo-1,3-oxazinium perchlorate with ammonium acetate solution afforded (3*H*)4-pyrimidone **9**.

We observed that when *o*-aminobenzoic acid or its methyl ester was used as the amine, 4-pyrimidone **8** was obtained in poor yield. We isolated from the reaction mixture the corresponding *N*-aryl-β-ketoamide **11** (Scheme 4). This reaction can be explained by an initial attack of the amine on the amide carbonyl at the β-ketoamide site and subsequent elimination of the *N*-acylamide group. This is probably due to steric reasons.

Scheme 2



Scheme 3



Scheme 4

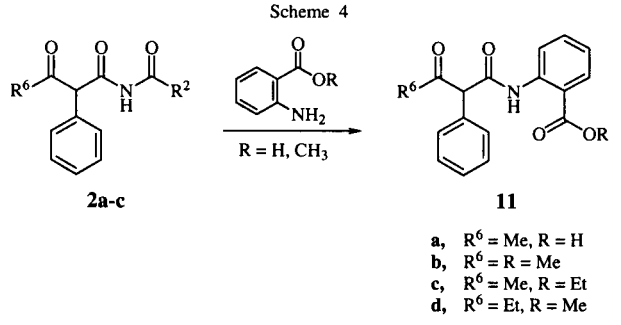


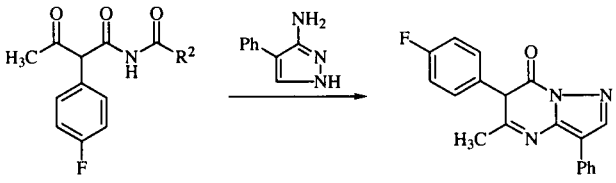
Table 6

4-Oxo-1,4-dihydropyrimidines **8**, IR and Analytical Data

Compound	ir (cm^{-1})		Elemental Analysis (%)		
	C=O	C=C, C=N	C	H	N
8/1	1680	1650	72.00	5.98	14.12
			(71.98)	(6.04)	(13.99)
8/2	1655	1615	-	-	-
		1600			
		1565			
8/3	1625	1605	72.58	5.99	13.10
		1580	(72.87)	(6.59)	(13.07)
8/4	1620	1607	80.22	4.19	10.01
		1590	(80.27)	(4.25)	(9.85)
8/4A	1623	1600	71.49	5.43	8.58
		1590	(74.01)	(5.56)	(9.08)
8/5	1640	1605	78.25	5.86	10.19
		1595	(78.24)	(5.84)	(10.14)
8/6	1630	1615	74.18	6.10	9.10
	1615	1600	(74.49)	(5.92)	(9.14)
		1545			
8/7	1647	1610	73.74	5.61	9.60
		1575	(73.98)	(5.48)	(9.59)
8/8	1649	1605	74.14	5.25	9.55
		1580	(73.98)	(5.48)	(9.59)
8/9	1631	1603	73.70	5.39	9.42
		1580	(73.98)	(5.48)	(9.59)
8/10	1625	1580	68.77	4.92	8.77
			(69.67)	(4.87)	(9.03)
8/11	1705	1605	71.17	4.89	8.73
	1645	1580	(71.25)	(5.00)	(8.75)
8/12	1710	1605	71.22	5.01	8.68
	1640	1595	(71.25)	(5.00)	(8.75)
8/13	1710	1590	71.22	4.89	8.73
	1630		(71.25)	(5.00)	(8.75)
8/14	1720	1600	71.96	5.47	8.39
	1630	1580	(71.84)	(5.43)	(8.38)
8/16	1690	1610	72.89	6.11	7.81
	1625	1580	(72.92)	(6.07)	(7.73)
8/17	1630	1600	74.25	5.90	-
			(74.22)	(5.84)	-
8/18	1635	1600	74.19	5.85	-
			(74.22)	(5.84)	-
8/19	1630	1600	75.24	6.60	11.60
			(75.23)	(6.58)	(11.80)
8/22	1730	1600	73.00	6.12	-
	1630	1580	(72.92)	(6.07)	-
8/28	1630	1595	62.34	3.84	7.58
			(62.98)	(3.89)	(7.73)
8/29	1720	1600	71.88	5.29	8.29
	1630	1590	(71.84)	(5.43)	(8.38)
8/30	1720	1590	71.89	5.36	8.39
	1635		(71.84)	(5.43)	(8.38)
8/31	1720	1600	68.90	5.25	7.39
		1640	(68.84)	(5.23)	(7.65)
8/32	1720	1600			
	1625	1590			
8/33	1628	1615	70.85	6.93	9.21
		1525	(71.97)	(7.05)	(9.33)
8/34	1740	1575			
	1615	1540			
8/35	1630	1595	67.99	4.47	16.59
		1535	(68.25)	(4.52)	(16.76)
8/36	1630	1600	65.03	3.92	8.31
		1535	(66.47)	(3.93)	(8.61)
8/37	1720	1600	68.06	4.84	9.11
	1630	1545	(67.96)	(4.83)	(9.14)
8/38	1710	1595	72.48	5.11	7.40
	1635	1540	(74.85)	(5.17)	(7.70)

Using 3-amino-4-phenylpyrazole as the amine, 4-pyrimidone formation was not observed. As expected [17], the heterocyclic nitrogen was involved in the cyclization and a 4-oxo-3,4-dihydropyrazolo[1,5-*a*]pyrimidine **12** was formed (Scheme 5). To the best of our knowledge the formation of this heterocycle has never been reported using a β-ketoamide as the starting material.

Scheme 5



2b **12**

EXPERIMENTAL

The ^{1}H nmr spectra were recorded at room temperature on a "Tesla BS-487C 80 MHz", "Bruker AM 360 MHz spectrometer" or a "Varian EM360 A 60 MHz spectrometer" with tetramethylsilane

Table 7

4-Oxo-1,4-dihydropyrimidines **8**, ^{1}H-NMR Data

Compound	^{1}H-nmr, δ
8/1 [a]	2.1 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 7.3 (s, 5H, phenyl)
8/2 [b,f]	2.1 (s, 3H, 6-CH_3), 2.3 (s, 3H, 2-CH_3), 7.0-7.2 (m, 4H, phenyl)
8/3 [c]	2.1 (s, 3H, 6-CH_3), 2.3 (s, 3H, 2-CH_3), 3.1 (s, 3H, *N*-CH_3), 7.2 (s, 5H, phenyl)
8/4 [a]	2.0 (s, 3H, 6-CH_3), 2.4 (s, 3H, 2-CH_3), 5.2 (s, 2H, CH_2Ph), 7.0-7.4 (m, 10H, phenyl)
8/4^A [a,f]	2.1 (s, 3H, 6-CH_3), 2.5 (s, 3H, 2-CH_3), 5.2 (s, 2H, CH_2Ph), 7.1-7.5 (m, 9H, phenyl)
8/5 [c]	1.6 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 7.0 (s, 5H, phenyl), 7.3 (s, 5H, *N*-phenyl)
8/6 [a]	1.9 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 3.9 (s, 3H, OCH_3), 6.8-7.3 (m, 9H, phenyl)
8/7 [d]	1.7 (s, 3H, 6-CH_3), 2.0 (s, 3H, 2-CH_3), 3.9 (s, 1H, OH), 6.9-7.3 (m, 9H, phenyl)
8/8 [d]	1.8 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 4.3 (s, 1H, OH, 6.9-7.3 (m, 9H, phenyl)
8/9 [d]	1.8 (s, 3H, 6-CH_3), 2.0 (s, 3H, 2-CH_3), 4.0 (s, 1H, OH), 6.9-7.4 (m, 9H, phenyl)
8/10 [b,f]	1.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 7.1 (AA'XX', J = 8.9 Hz, 4H), 7.2 (t, J = 8.5 Hz, 2H, FCCH), 7.3 (dd, J = 5.2 Hz, J = 8.5 Hz, 3H, FCC*H*CH)
8/11 [d]	1.6 (s, 3H, 6-CH_3), 2.0 (s, 3H, 2-CH_3), 6.8-7.4 (m, 9H, pheyl)
8/12 [d]	1.6 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 6.8-7.5 (m, 9H, phenyl)
8/13 [d]	1.7 (s, 3H, 6-CH_3), 2.0 (s, 3H, 2-CH_3), 6.9-7.6 (m, 9H, phenyl)
8/14 [c]	1.5 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 3.6 (s, 3H, CH_3OOC), 6.9-7.6 (m, 9H, phenyl)
8/16 [a]	0.6 (t, J = 6.5 Hz, 3H, 6-CH_2CH_3), 0.9 (t, J = 6.2 Hz, 3H, 2-CH_2CH_3), 2.1 (q, J = 6.5 Hz, 2H, 6-CH_2CH_3), 2.5 (q, J = 6.2 Hz, 2H, 2-CH_2CH_3), 3.5 (s, 3H, CH_3OOC), 6.9-7.9 (m, 9H, phenyl)
8/19 [a]	1.8 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 3.0 (s, 6H, N-$(CH_3)_2$), 6.6-7.1 (AA'XX', J = 8 Hz, 4H), 7.3 (s, 5H, phenyl), 7.4-7.6 (m, 4H, phenyl)
8/22 [a]	0.5 (t, J = 6.5 Hz, 3H, 6-CH_2CH_3), 0.9 (t, J = 6.O Hz, 3H, 2-CH_2CH_3), 2.0 (q, J = 6.5 Hz, 2H, 6-CH_2CH_3), 2.4 (q, J = 6.0 Hz, 2H, 2-CH_2CH_3), 3.7 (s, 3H, CH_3OOC), 6.9-7.2 (m, 5H, phenyl), 7.7 (AA'XX', J = 8 Hz, 4H)
8/28 [a,f]	1.7 (s, 3H, 6-CH_3), 2.1 (s, 3H, 2-CH_3), 7.1 (t, J = 8.55 Hz, 2H, FCCH), 7.3 (dd, J = 5.2 Hz, J = 8.5 Hz, 2H, FCC*H*CH), 7.5 (d, 1H, 3'-H), 7.8 (t, 1H, 4'-H), 7.9 (t, 1H, 5'-H), 80 (d, 1H, 6'-H)
8/29 [c]	1.6 (s, 3H, 6-CH_3), 2.0 (s, 3H, 2-CH_3), 3.7 (s, 3H, OCH_3), 6.9-7.6 (m, 9H, phenyl)
8/30 [b]	1.66 (s, 3H, 6-CH_3), 2.0 (s, 3H, 2-CH_3), 4.0 (s, 3H, $COOCH_3$), 7.3 (s, 5H, phenyl), 7.9 (AA'XX', J = 8 Hz, 4H, phenyl)
8/31 [c,f]	1.5 (t, J = 5.9 Hz, 3H, CH_3CH_2O), 1.8 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 4.4 (q, J = 5.9 Hz, 2H, CH_3CH_2O), 7.1 (t, J = 8.5 Hz, 2H, FCCH), 7.3 (dd, J = 5.2 Hz, J = 8.5 Hz, 2H, FCCHC*H*), 7.9 (AA'XX', J = 8.7 Hz, 4H, phenyl)
8/32 [c]	1.0 (t, J = 7 Hz, 3H, CH_3CH_2O), 1.5 (s, 3H, 6-CH_3), 2.2 (s, 3H, 2-CH_3), 4.1 (q, J = 7 Hz, 2H, CH_3CH_2O), 6.9-7.6 (m, 4H, phenyl)
8/33 [a]	1.18-2.18 (m, 10H, C-H cyclohehyl, J_{aa} = 9.94 Hz, J_{ae} = 2.38 Hz), 2.25 (s, 3H, 6-CH_3), 2.67 (s, 3H, 2-CH_3), 7.09 (t, J = 7.96 Hz, 2H, FCCH), 7.19 (dd, J = 5.17 Hz, J = 8.55 Hz, 2H, FCCHC*H*)
8/34 [a]	1.2 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.9 (s, 3H, 6-CH_3), 2.3 (s, 3H, 2-CH_3), 4.2 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 7.2 (s, 5H, phenyl)
8/35 [b]	1.69 (s, 3H, 6-CH_3), 2.05 (s, 3H, 2-CH_3), 3.38 (s, 1H, NH), 7.24 (t, J = 8.53 Hz, 2H, FCCH), 7.32 (dd, J = 5.17 Hz, J = 8.55 Hz, 2H, FCCHC*H*), 7.50 (dd, J = 2.38 Hz, J = 7.95 Hz, 6'*H*), 7.75 (d, J = 7.95 Hz, 1H, 7'-*H*), 8.23 (s, 1H, 2'-*H*)
8/36 [e,g]	1.85 (s, 3H, CH_3), 2.24 (s, 3H, 6-CH_3), 2.31 (s, 3H, 2-CH_3), 7.11 (t, J = 8.55 Hz, 2H, FCCH), 7.29 (dd, J = 5.17 Hz, J = 8.55 Hz, 2H, FCCHC*H*), 7.31 (d, J = 0.59 Hz, 1H, 4-*H*), 7.35 (d, J = 2.78 Hz, 1H), 7.45 (d, J = 8.35 Hz, 1H, 7-*H*), 7.82 (dd, J = 0.59 Hz, J = 8.35 Hz, 1H, 6-*H*), 7.93-7.99 (m, 4H, phenyl)
8/37 [h]	1.84 (s, 3H, 6"-CH_3), 2.23 (s, 3H, 6-CH_3), 2.55 (s, 3H, 2-CH_3); 7.15 (t, J = 8.53 Hz, 3H, FCCH), 7.29 (dd, J = 5.17 Hz, J = 8.55 Hz, 2H, FCCHC*H*, AA'XX', J = 7.95 Hz), 7.37 (dd, J = 1.98 Hz, 1H, 5"-*H*), 7.76 (s, 1H, 7"-*H*), 7.99 (d, J = 8.35, 1H, 4"-*H*)
8/38 [a]	1.76 (s, 3H, 6'-CH_3), 2.15 (s, 3H, 2'-CH_3), 3.5 (s, 2H, 4-*H* and 7-*H*), 4.07 (s, 2H, CH_2-Ph), 6.26 (t, 2H, -C(5)*H*=C(6)*H*), 6.95-7.40 (m, 12H, phenyl).

[a] deuteriochloroform. [b] dimethylsulfoxide. [c] trifluoroacetic acid. [d] dimethylformamide. [e] deuteriomethanol. [f] ^{13}C nmr (deuteriochloroform): δ 17.3 (6-CH_3), 23.3 (2-CH_3), 51.7 (CH_2), 115.3 (d, J_{CCF} = 21.5 Hz), 123.0, 123.9, 128.3, 129.6, 130.7, 132.1 (d, J_{CCCF} = 7.99 Hz), 134.5, 148.3, 160.6, 162.2 (d, J_{CF} = 246.7 Hz), 168.8. [g] ^{13}C nmr (deuteriochloroform): δ 11.0, 11.5 (6-CH_3), 17.0 (2-CH_3), 107.9 (d, J_{CCF} = 21.49 Hz), 114.2, 116.8, 118.0, 118.8, 122.4, 122.7, 122.9, 123.6, 124.7 (d, J_{CCCF} = 7.99 Hz), 124.9, 126.0, 127.5, 132.4, 134.1, 140.5, 152.2, 154.8 (d, J_{CF} = 246.7 Hz), 158.0, 158.3, 161.5. [h] ^{13}C nmr (deuteriochloroform): δ 18.7, 21. 28.0, 115.4 (d, J_{CCF} = 21.49 Hz), 121.5, 121.7, 123.1, 128.4, 128.6, 129.4, 130.0, 132.1 (d, J_{CCCF} = 8.0 Hz), 135.4, 135.6, 136.3, 140.4, 147.8, 152.2, 159.5, 162.3 (d, J_{CF} = 246.9 Hz), 164.3, 169.6. [i] The spectra were recorded on a "Bruker AM 360 MHz spectrometer".

as an internal standard. Spectral data are reported in parts per millions (δ) relative to tetramethylsilane. The ir spectra were recorded in suspension with Nujol or in potassium bromide tablets on a "Specord 71 IR spectrometer" or an "Acculab 4 spectrometer" respectively. Spectral data are reported in cm^{-1}(ν). Melting points were determined with an "Electrothermal digital apparatus" or a capillary melting point apparatus.

2,6-Dimethyl-4-oxo-5-phenyl-1,3-oxazinium Perchlorate (**3a**).

To a stirred and cooled solution of *N*-acetyl-α-phenylacetoacetamide (**2a**) (3.29 g, 15 mmoles) in dry chloroform (30 ml) and acetic anhydride (13 ml, 13.7 mmoles), was added dropwise a perchloric acid (70% solution) (1.5 ml, 17.5 mmoles). After being warmed to room temperature gradually, the mixture was stirred for 2 hours. The precipitate was filtered, washed with dry ether and dried. The perchlorates **3c** and **3b** are prepared in the same way using propionic anhydride for **3c** and *N*-acetyl-α-(*p*-fluorophenyl)acetoacetamide for **3b**.

2-Ethyl-6-methyl-4-oxo-5-phenyl-1,3-oxazinium Perchlorate (**3d**).

To a stirred solution of 3-oxo-2-phenylbutyronitrile (7.95 g, 0.05 mole) in propionic anhydride (29.6 ml, 0.3 mole) was added perchloric acid (70%) (3 ml). The reaction mixture was stirred at room temperature overnight. The precipitate was filtered, washed with ether and recrystallized as above.

3-(*o*-Methoxyphenyl)-2,6-dimethyl-4-oxo-1,3-oxazinium Perchlorate (**3e**).

To a stirred solution of *N*-(*o*-methoxyphenyl)acetoacetamide (2.07 g, 0.01 mole) in acetic anhydride (6 ml) was added perchloric acid (70%) (1 ml) dropwise. The reaction mixture was heated at 70° for 10 minutes. After cooling, the crystals obtained were collected and washed with acetic acid and ether.

N-Acetyl-β-phenylacetoacetamide (**2a**).

To a stirred solution of 2-phenylacetamide (13.5 g, 0.1 mole) in acetic anhydride (37.5 ml, 0.4 mole) was added dropwise boron trifluoride acetate (4 ml, 0.27 mole) and the mixture was stirred for 48 hours. The reaction mixture was neutralized with a solution of sodium acetate trihydrate (80 g) in water (240 ml) and was heated for 20 minutes in a water bath. After cooling the precipitate was filtered and crystallized from ethanol.

The acetamides **2b** and **2c** were prepared in the same way.

4-Oxo-pyrimidinium Perchlorates **6**.

General Procedure.

To a stirred solution of the corresponding 4-oxo-1,3-oxazinium perchlorate (10 mmoles) in acetic acid (10 ml) the requisite amine was added at room temperature. If no spontaneous reaction occurs, the mixture is heated for 10 minutes in a boiling water bath. After complete reaction, the mixture was cooled and ether (20 ml) was added. The target compound precipitates (scratching with a glass rod is often necessary), was collected and washed with ether.

3-(*o*-Methoxyphenyl)-2,6-dimethyl-4-oxo-1-phenylpyrimidinium Perchlorate

A solution of aniline (0.66 g, 7.1 mmoles) in anhydrous ethanol (10 ml) was slowly added to oxazinium perchlorate **3e** (2.36 g, 7.1 mmoles). The mixture was stirred for 48 hours at room temperature. Evaporation of the ethanol give a homogeneous residue, which was crystallized from acetic acid/ether.

Perchlorates **6-29** and **6-30** were prepared in the same way.

3-[*N*-(4-Methoxyphenyl)imino]-2-phenylbutyronitrile (**10**).

To a suspension of 3-oxo-2-phenylbutyronitrile (**4**) (1.58 g, 0.01 mole) in acetic acid (10 ml) was added methoxyaniline (1.23 g, 0.01 mole). The mixture was heated under reflux for 30 minutes. After cooling, water was added and the solution was neutralized (*p*H 7) with sodium bicarbonate. The precipitate was filtered and recrystallized from ethanol to yield 1.72 g (65%), mp 119°; ir (Nujol): ν 3305 (NH), 2180 (C/N), 1605, 1570, 1520 (C=N and C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.0 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 6.7-7.7 (m, 9H, phenyl).

N-Acetyl-[3(*p*-methoxyphenylamino)-3-methyl-2-phenyl]-propenamide (**7**).

To a stirred solution of **10** (0.52 g, 2.0 mmoles) in acetic anhydride (4 ml) was added perchloric acid (70%) (0.2 ml, 2 mmoles) dropwise. After 3 minutes, ether was added and washed with a saturated sodium bicarbonate solution. The ether was evaporated to give a red oil which was purified on a silica and column. Elution of the column with chloroform gave a homogeneous residue, which was crystallized from benzene to yield 0.09 g (15%); (**7** was very unstable and was immediately used); ir (Nujol): 3225, 1720, 1665, 1645, 1620, 1595, 1425 cm^{-1}.

4-Oxo-1,4-dihydropyrimidines (**8**).

General Procedure A.

A solution of *N*-acetylphenylacetamide (**2a**) (10 mmoles) and the amine (10 mmoles) in aceic acid (10 ml) was heated at reflux. After 1 hour, the mixture was cooled and neutralized with a saturated solution of sodium bicarbonate in water until a basic *p*H was reached. The precipitate was filtered, washed with water until the filtrate was neutral and dried.

4-Oxo-1,4-dihydropyrimidines (**8**).

General Procedure B.

4-Oxopyrimidinium perchlorate (**6**) (10 mmoles) was stirred with a saturated solution of sodium bicarbonate in water for 1 hour at room temperature. The precipitate was filtered, washed with water until the filtrate was neutral and dried.

3-(*o*-Methoxyphenyl)-2,6-dimethyl-4-oxo-3,4-dihydropyrimidine (**9**).

A suspension of 3-(*o*-methoxyphenyl)-2,6-dimethyl-4-oxo-oxazinium perchlorate (**3e**) (3.01 g, 0.01 mole) and ammonium acetate (0.01 mole) in acetic acid (15 ml) was heated at reflux for 20 minutes. After cooling the mixture was diluted with water and extracted with ether (3 x 20 ml). The etheric solution was dried on sodium sulphate. Evaporation of ether gave a white residue which was crystallized from petroleum ether to yield 1.5 g (64%) of 3-(*o*-methoxyphenyl)-2,6-dimethyl-4-oxo-3,4-dihydropyrimidine, mp 133°; ir: ν 1680, 1648 cm^{-1}; ^{1}H nmr (deuteriomethanol): δ 2.2 (s, 6H, 2- and 6-CH_3), 3.5 (s, 3H, OCH_3), 6.3 (s, 1H, 5-H), 6.6-7.5 (m, 4H, phenyl).

N-(β-Oxo-β–phenylbutyryl)anthranilic Acid Methyl Ester (**11b**).

A solution of *N*-acetylphenylacetoacetamide (**2a**) (2.19 g, 0.01 mole) and anthranilic acid methyl ester (1.51 g, 0.01 mole) in acetic acid (10 ml) was heated at reflux for 1 hour. Neutralizetion of the mixture with a saturated solution of sodium bicarbonate in water

until *p*H 5 was reached gave an oil which was washed with water, crystallized from ethyl acetate and recrystallized from 2-propanol to yield 4-oxo-1,4-dihydropyrimidine (**8-17**) 0.59 g (18%).

The filtrate was dried and the compound was recrystallized from benzene to yield 0.49 g (16%). It can be further purified by preparative chromatography (alumina chloroform), mp 108°; ir (Nujol): ν 3215 (OH), 1700 (C=O), 1620, 1585, 1530 cm-1; ^{1}H nmr (deuteriochloroform): δ 1.7 (s, 3H, CH_3), 3.5 (s, 3H, OCH_3), 6.9 (t, J = 7.6 Hz, 3H, 5-H), 7.2-7.5 (m, 6H, phenyl and 4-H), 7.8 (dd, J = 7.6 Hz, J = 1 Hz, 1H, 6-H), 8.5 (d, J = 8.2 Hz, 1H, 3-H); ms: m/z 311 (M^+); 151; 119.

Anal. calcd. for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.46; N, 4.5. Found: C, 69.07; H, 5.95; N, 4.29.

N-(β-Oxo-α-phenylbutyryl)anthranilic Acid (**11a**).

The yield was 16%, mp 183-184° (benzene); ir (Nujol): ν 3275 (OH), 1690 (C=O), 1630, 1590 cm^{-1}; ^{1}H nmr (trifluoroacetic acid): δ 1.9 (s, 3H, CH_3), 4.9 (s, 1H, CH), 6.8-7.9 (m, 9H, phenyl).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 69.86; H, 5.13. Found: C, 69.27; H, 5.17.

N-(β-Oxo-α-phenylbutyryl)anthranilic Acid Ethyl Ester (**11c**).

The yield was 43%; ir (Nujol): ν 3320 (OH), 1700 (C=O), 1630, 1595, 1540 cm^{-1}; ^{1}H nmr (trifluoroacetic acid): δ 1.0 (t, J = 7 Hz, 3H, OCH_2CH_3), 2.1 (s, 3H, CH_3), 4.1 (q, J = 7 Hz, 2H, OCH_2CH_3), 7.0-7.8 (m, 9H, phenyl).

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.15; H, 5.84. Found: C, 70.11; H, 5.69.

N-(β-Oxo-α-phenylpentanoyl)anthranilic Acid Ethyl Ester (**11d**).

The yield was 33%; ir (Nujol): ν 3370, 1700 (C=O), 1620, 1595, 1525 cm^{-1}; ^{1}H nmr (deuteriochloroform):δ 1.0 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.5 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.5 (s, 3H, OCH_3), 6.8 (dt, J = 8 Hz, J = 2 Hz), 7.0-7.4 (m, 6H, phenyl), 7.8 (t, J = 7.2 Hz, 1H), 8.5 (d, J = 8 Hz, 1H), 9.1 (s, 1H, NH).

6-(*p*-Fluorophenyl)-5-methyl-7-oxo(4H)-2-phenylpyrazolo-[1,5-*a*]pyrimidine (**12**).

Compound **12** was prepared from *N*-acetyl-1-phenylacetoacetamide (**2a**) by General Procedure A, mp 330° dec; ir (potassium bromide): ν 1659 (C=O); 1632, 1610, 1568 (C=C and C=N), 1520 cm^{-1}, ^{1}H nmr (deuteriochloroform): δ 2.17 (s, 2H, 5-CH_3), 6.64 (s, 1H, 3-H), 7.27 (t, J = 8.55 Hz, 2H, FCCH), 7.37 (dd, J = 5.17 Hz, J = 8.55 Hz, 2H, FCCHC*H*), 7.42-8.2 (m, 5H, phenyl); ms: m/z 319 (M^+), 290, 184, 133, 103, 77.

Anal. Calcd. for $C_{21}H_{17}FN_4O$: C, 71.46; H, 4.42; N, 13.16; F 5.95. Found: C, 71.65; H, 4.40; N, 13.14.

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