SYNTHESIS OF IMIDAZO[1,2-a]PYRIDINE AND PYRIDO[1,2-a]PYRIMIDINE DERIVATIVES BY THE ADDITION AND CYCLOCONDENSATION REACTIONS OF KETENAMINALS CONTAINING IMIDAZOLIDINE OR HEXAHYDROPYRIMIDINE RING WITH ESTERS OF α,β-UNSATURATED ACIDS

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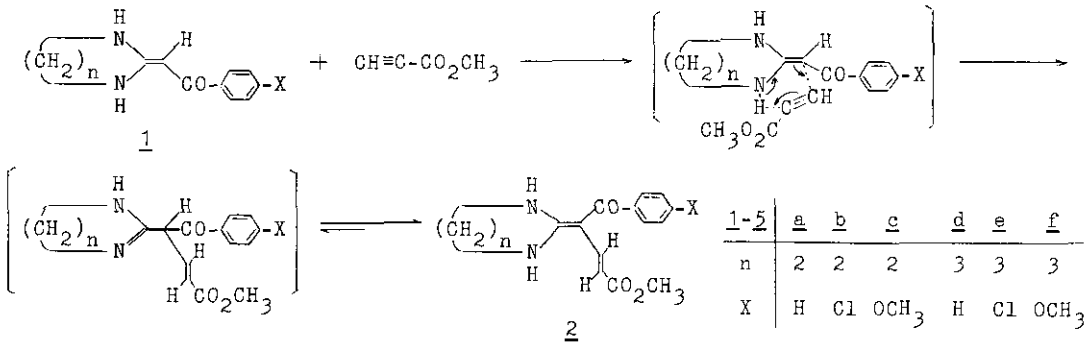
Abstract —— Ketenaminals 1 react with methyl propiolate, methyl acrylate and dimethyl acetylenedicarboxylate to afford the fused imidazo[1,2-a]pyridines and pyrido[1,2-a]pyrimidines 3, 4 and 5, respectively. In some cases, the intermediate addition products 2 and 6b are isolated.

Ketenaminals containing imidazolidine or hexahydropyrimidine ring had been reported in literature only in few cases[1-6]. Because the α-carbon atom of these ketenaminals possesses higher electron density and they may be as nucleophiles to attack the electron deficient compounds, therefore, they are useful precursors in organic synthesis. We have reported some results of the reactions of ketenaminals with esters of α,β-unsaturated acids and synthesis of some fused heterocycles[7-9]. Recently, we reported a convenient method for synthesis of ketenaminals containing imidazolidine or hexahydropyrimidine ring and benzoyl groups by condensation of ethyl benzoylacetimidates with diamines[10]. Here, we will report some reactions of these ketenaminals with esters of α,β-unsaturated acids and synthesis of imidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine derivatives *via* addition and cyclocondensation reactions.

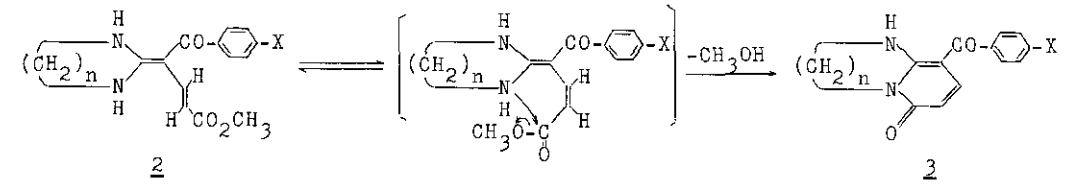
Ketenaminals 1 react smoothly with methyl propiolate in dioxane at ambient temperature. From the MS and elemental analyses data, the products can be considered as 1:1 adduct. The occurrence of two NH signals both in the ^{1}H nmr and ir spectra and two ethylenic proton signals excludes all the other possible constitutions, such as [2+2]-cycloaddition and N-addition product and the tautomeric isomers, and only the α-carbon addition product 2 is the accepted constitution. As the coupling constants of the two olefinic protons range in 16 Hz, these two protons are nuambigously in *trans*-position *via* *syn*-addition. There are two possible mechanisms for this *syn*-addition, the one is the α-carbon atom and its proton add

to triple bond through the four-membered ring transition state, and the other is the α-carbon atom and N-proton add to triple bond through the six-membered ring transition state. We tend to the latter possibility, because in case of no α-carbon proton this reaction takes place smoothly too[7]. Therefore, a reasonable reaction mechanism and constitutional proposal of the adducts formed from 1 and methyl propiolate can be rationalized as follows:

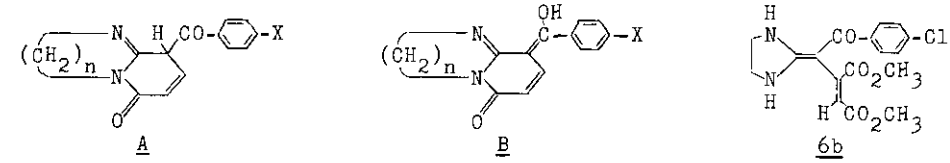


1-5	a	b	c	d	e	f
n	2	2	2	3	3	3
X	H	Cl	OCH_3	H	Cl	OCH_3

When 2 are refluxed in methanol, spectra and elemental analyses data indicate that in fact a cyclocondensation takes place accompanied with loss of one molecule of methanol. It is resulted from that 2 undergoes cis-trans-isomerization in the protic solvent with the aid of acidic or basic catalyst at first, then the cis-intermediate is cyclized to give imidazo[1,2-a]pyridines and pyrido[1,2-a]pyrimidines 3 by elimination of methanol:

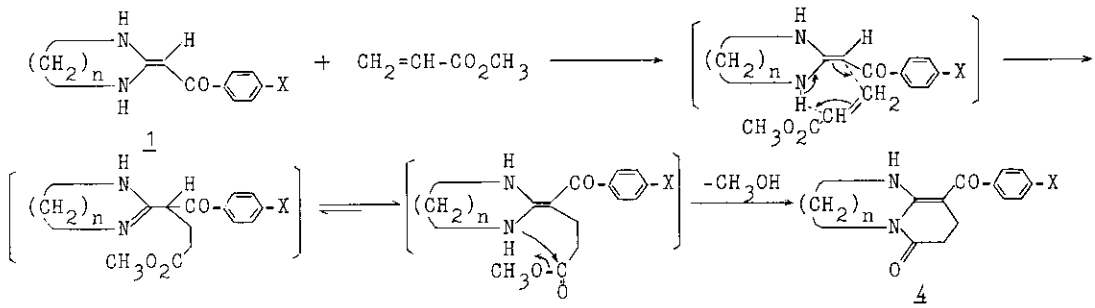


The presence of NH signal both in the ir and ^1H nmr spectra and one ketonic carbonyl carbon signal (ca. 190 ppm) in the ^{13}C nmr spectra excludes its tautomeric constitution A and B.

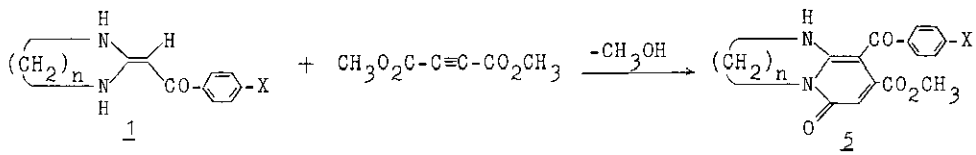


Compound 1 show no reactions with methyl acrylate at room temperature in dioxane, but reaction takes place on refluxing. Spectra and elemental analyses indicate that an addition of methyl acrylate takes place which is accompanied, however, by

a cyclocondensation reaction with the elimination of methanol. The reaction is very similar to that of 1 with methyl propiolate, but because of no cis-trans-isomerization problem, hence the addition product can not be isolated and imidazo-[1,2-a]pyridine and pyrido[1,2-a]pyrimidine 4 are obtained immediately:



Dimethyl acetylenedicarboxylate is a more active electrophilic reagent, therefore, 1 react easily with this reagent at ambient temperature in dioxane. From the spectral and elemental analytical data of the products obtained, only the addition product from 1b can be isolated, and in the other cases one molecule of acetylene ester has been added to 1 but accompanied by subsequent elimination of methanol, and similar to 4 imidazo[1,2-a]pyridine and pyrido[1,2-a]pyrimidine 5 are directly formed by the cyclocondensation reaction:

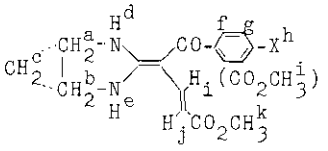


From the comparison of the chemical shift of the olefinic proton of the addition product from 1b with that from the empirical formula[11], the configuration of this addition product may be as 6b. This is undoubtedly resulted from the syn-addition to the acetylene ester, just as this configuration is unfavorable to cyclization, hence the addition intermediate can be isolated. From our experimental facts, the ketenaminals containing hexahydropyrimidine ring is more reactive than that containing imidazolidine ring and electron withdrawing substituent in the para position of the benzoyl group will retard the nucleophilic reaction, therefore, 1b is the least reactive member in all the ketenaminals in this report. It is probable that 1b is favorable to syn-addition to the acetylene ester due to this cause, but it is worth to further investigation.

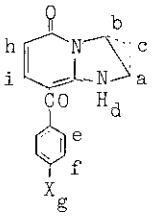
The ^{1}H and ^{13}C nmr data of 2, 3, 4, 5 and 6b are listed in Tables 1 and 2, respectively.

Table 1. The ^1H nmr data of 2, 3, 4, 5 and 6b in $CDCl_3$

TMS as internal standard, δ in ppm, (J in Hz)



2, 6b



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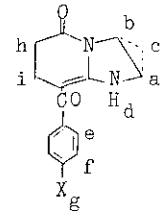

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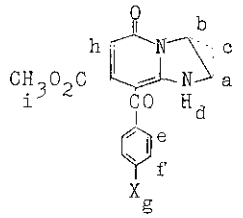

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Compd.	H^a	H^b	H^c	H^d	H^e	H^f	H^g	H^h	H^i	H^j	H^k
2a	3.60s			8.17s	7.76s		7.36s		7.67d(16)	5.36d(16)	3.53s
2b	3.67s			8.00s	7.30s	7.23s			7.50d(16)	5.33d(16)	3.56s
2d	3.33t		1.90quin	8.90s	7.67s		7.26s		7.56d(16)	5.30d(16)	3.53s
2f	3.33t		1.90quin	8.93s	7.33s	7.26d	6.78d	3.73s	7.67d(16)	5.31d(16)	3.54s
3a	3.92t	4.20t		8.67s		7.42-7.46m		5.68d(10)	7.40d(10)		
3b	4.03t	4.10t		8.56s	7.40s			5.67d(10)	7.38d(10)		
3c	3.76t	4.04t		8.90s	6.96-7.62m		3.80s	5.48d(10)	7.97d(10)		
3d	3.70t	4.00t	2.10quin	11.14s		7.38s		5.63d(10)	7.36d(10)		
4a	3.70t	3.80t		8.13s		7.26s		2.57t	2.53t		
4d	3.46t	3.83t	2.00quin	12.60s		7.40s		2.56t	2.50t		
5a	3.97t	4.03t		8.30s		7.37s		5.97s	3.00s		
5d	3.50t		2.07quin	9.86s		7.40s		6.10s	3.00s		
5e	3.53t		2.03quin	9.70s	7.17-7.56m			6.07s	3.03s		
6b	3.63t			8.13s	7.37s	7.20s			3.60s	6.50s	3.40s

EXPERIMENTAL

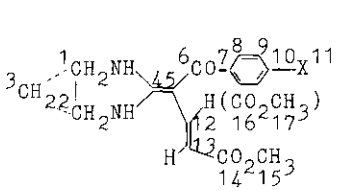
Ir spectra: Shimadzu 430. - ^1H nmr spectra: Varian-360L and CAMECA RMN-250. - ^{13}C nmr spectra: Jeol FX-100. - MS: AEI MS-50. - uv spectra: Hitachi 340. - Melting point: not corrected. - Elemental analyses: Analytical Laboratory of this Institute.

Methyl 4-[Benzoyl(2-imidazolidinylidene)]-(E)-but-2-enoate (2a): A solution of 84 mg (1 mmol) of methyl propiolate in 7 ml of dioxane was dropped slowly into a solution of 188 mg (1 mmol) of 1a in 25 ml of the same solvent, then stirred at ambient temperature for 2 days. After removal of solvent, the product was washed twice with small amount of dry diethyl ether, 2a was obtained in quantitative yield, mp 165-167°C. Ir(KBr): 3400, 3200 (NH), 1685 (ester C=O), 1605 (C=O), 1545 (C=C); uv (ethanol): λ (lg ε) 322 (4.29), 236 (4.16). MS: m/z 272 (M^+). Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C,66.16; H,5.92; N,10.29. Found: C,65.32; H,5.91; N,9.85.

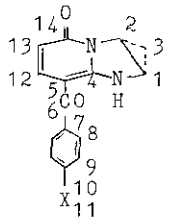
Methyl 4-[(4-Chlorobenzoyl-2-imidazolidinylidene]-(E)-but-2-enoate (2b): Similar to

Table 2. The ^{13}C nmr data of 2, 3, 4, 5 and 6b in $CDCl_3$

TMS as internal standard, δ in ppm



2, 6b



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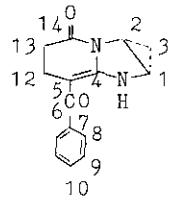

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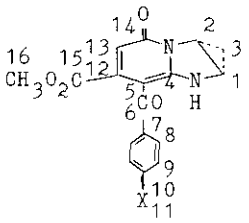

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Compd.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
2a	41.1t			163.4s	92.1s	191.9s	138.8s	125.8d	125.6d	127.6d
2b	41.1t			158.1s	88.6s	189.0s	133.2s	127.2d	126.0d	136.8s
2d	36.2t	36.5t	17.6t	157.3s	90.7s	188.9s	139.9s	125.7d	125.6d	126.7d
2f	36.5t		17.6t	157.2s	90.5s	188.5s	132.5s	127.7d	111.0d	158.1s
3a	42.6t	43.3t		157.2s	97.0s	192.3s	139.0s	128.3d	128.0d	130.7d
3b	42.7t	43.3t		157.1s	96.6s	190.5s	136.6s	129.2d	128.3d	137.0s
3c	42.7t	43.0t		156.5s	92.6s	189.6s	131.7s	130.0d	113.6d	159.5s
3d	38.4t	39.1t	19.1t	154.7s	97.2s	192.9s	139.7s	127.8d	127.6d	129.8d
4a	41.7t	42.6t		156.7s	85.0s	190.4s	140.9s	127.6d	126.5d	128.9d
4d	38.6t	39.0t	20.6t	156.3s	87.1s	188.4s	141.7s	127.7d	126.4d	128.4d
5a	42.5t	43.4t		156.5s	93.9s	192.0s	140.2s	127.9d	127.1d	130.9d
5d	36.9t	39.1t	19.9t	159.7s	90.1s	188.5s	140.6s	127.9d	126.7d	130.1d
5e	36.9t	39.1t	19.9t	159.7s	87.3s	187.2s	134.9s	128.6d	128.0d	136.2s
6b	43.0t	43.3t		164.6s	86.3s	186.6s	134.4s	128.7d	127.5d	140.8s

Compd.	C-11	C-12	C-13	C-14	C-15	C-16	C-17
2a		143.2d	102.6d	166.8s	49.0q		
2b		142.8d	103.1d	167.9s	49.1q		
2d		143.9d	101.0d	166.6s	48.9q		
2f	53.2q	144.2d	100.2d	167.0s	48.9q		
3a		143.0d	106.0d	161.3s			
3b		142.1d	106.1d	161.2s			
3c	55.3q	142.6d	104.3d	160.9s			
3d		143.1d	103.0d	161.4s			
4a		22.1t	32.4t	168.9s			
4d		21.6t	32.7t	170.2s			
5a		145.3s	108.4d	159.7s	166.5s	51.8q	
5d		141.3s	109.5d	166.6s	167.7s	50.7q	
5e		139.9s	109.5d	166.4s	167.7s	50.9q	
6b		142.6s	125.1d	165.7s	51.8q	168.1s	52.4q

2a, a mixture of 222 mg (1 mmol) of 1b and 84 mg of methyl propiolate was stirred at 40-50°C for 6 h. After removal of solvent, the crude product was recrystallized from methylene chloride, 240 mg (78%) of 2b was obtained, mp 157-159°C. Ir(KBr): 3400, 3280 (NH), 1683 (ester C=O), 1570 (C=O), 1540 (C=C); uv (ethanol): λ (lg ε) 325 (4.41), 240 (4.25). MS: m/z 306 (M^+). Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C,58.73; H,4.93; N,9.13. Found: C,58.47; H,5.04; N,9.96.

Methyl 4-[Benzoyl(2-hexahydropyrimidinylidene)]-(E)-but-2-enoate (2d): Like 2a from 202 mg (1 mmol) of 1d and 84 mg (1 mmol) of methyl propiolate, 2d was obtained in quantitative yield, mp 104-106°C. Ir(KBr): 3350, 3250 (NH), 1680 (ester C=O), 1600 (C=O), 1515 (C=C); uv (ethanol): λ (lg ε) 342 (4.20), 236 (4.11). MS: m/z 286 (M^+). Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C,67.11; H,6.34; N,9.79. Found: C,66.85; H,6.25; N, 9.25.

Methyl 4-[(2-Hexahydropyrimidinylidene)-4-methoxybenzoyl]-(E)-but-2-enoate (2f): Like 2a from 232 mg (1 mmol) of 1f and 84 mg (1 mmol) of methyl propiolate, 2f was obtained in quantitative yield, mp 150-152°C. Ir(KBr): 3400, 3250 (NH), 1645 (ester C=O), 1595 (C=O), 1515 (C=C); uv (ethanol): λ (lg ε) 348 (4.33), 242 (4.06). MS: m/z 284 ($M-CH_3OH)^+$. Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C,64.54; H,6.37; N,8.86. Found: H,6.41; N,9.01.

8-Benzoyl-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one(3a): A solution of 140 mg of 2a in 15 ml of methanol was refluxed for 16 h, and then partial solvent was evaporated. After cooling 105 mg (85%) of crystal of 3a was obtained, mp 195-196°C. Ir(KBr): 3370 (NH), 1670 (amide C=O), 1600 (C=O), 1570 (C=C); uv (ethanol): λ (lg ε) 349 (4.31), 310 (3.93), 237 (4.09). MS: m/z 240 (M^+). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C,69.98; H,5.03; N,11.66. Found: C,69.68; H,4.96; N,11.42.

8-(4-Chlorobenzoyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (3b): Like 3a a solution of 150 mg of 2b in 10 ml of methanol was refluxed for 22 h, 120 mg (91%) of 3b was obtained, mp 229-230°C. Ir(KBr): 3370 (NH), 1670 (amide C=O), 1590 (C=O), 1565 (C=C); uv (ethanol): λ (lg ε) 341 (4.24), 310 (3.95), 244 (4.21). MS: m/z 274 (M^+). Anal. Calcd. for $C_{14}H_{11}ClN_2O_2$: C,61.21; H,4.04; N,10.20. Found: H,4.20; N,9.43.

2,3-Dihydro-8-(4-methoxybenzoyl)imidazo[1,2-a]pyridin-5(1H)-one (3c): Similar to 2a a dioxane solution of 213 mg (1 mmol) of 1c and 84 mg (1 mmol) of methyl propiolate was stirred at room temperature for 2 days. After removal of solvent, the residue was soluble in 15 ml of methanol and refluxed for 20 h, 150 mg (56%) of 3c was obtained, mp 152-153°C. Ir(KBr): 3360 (NH), 1670 (amide C=O), 1600 (C=O), 1570 (C=C); uv (ethanol): λ (lg ε) 341 (4.32), 312 (4.15), 229 (4.17). MS: m/z 270 (M^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C,66.65; H,5.22; N,10.37. Found: C,66.42; H,5.21; N, 10.21.

9-Benzoyl-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidin-6-one (3d): Like 3a from 150 mg of 2d in 15 ml of methanol, 110 mg (84%) of 3d was obtained, mp 167-168°C. Ir(KBr): 3350 (NH), 1670 (amide C=O), 1595 (C=O), 1560 (C=C); uv (ethanol): λ(lg ε) 341 (4.33), 308 (4.03), 239 (4.16). MS: m/z 254 (M^+). Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C,70.85; H,5.55; N,11.02. Found: C,70.36; H,5.52; N,10.92.

8-Benzoyl-2,3,6,7-tetrahydroimidazo[1,2-a]pyridin-5(1H)-one (4a): A solution of 188 mg (1 mmol) of 1a and 86 mg (1 mmol) of methyl acrylate in 10 ml of dioxane was stirred at 50°C for 1 h, and then refluxed for 20 h. After removal of solvent, the product was washed twice with small amount of dry diethyl ether, 4a was obtained in quantitative yield, mp 139-140°C. Ir(KBr): 3320 (NH), 1680 (amide C=O), 1630 (C=O), 1515 (C=C); uv (ethanol): λ(lg ε) 334 (4.23), 236 (4.13). MS: m/z 242 (M^+). Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C,69.40; H,5.82; N,11.57. Found: C,68.85; H,5.81; N, 11.21.

9-Benzoyl-1,2,3,4,7,8-hexahydropyrido[1,2-a]pyrimidin-6-one (4d): Like 4a from 101 mg (0.5 mmol) of 1d and 43 mg (o.5 mmol) of methyl acrylate, 4d was obtained in quantitative yield, mp 146-147°C. Ir(KBr): 3425 (NH), 1690 (amide C=O), 1615 (C=O), 1535 (C=C); uv (ethanol): λ(lg ε) 340 (4.17), 230 (4.08). MS: m/z 256 (M^+). Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C,70.29; H,6.29; N,10.93. Found: C,70.09; H,6.17; N,10.87.

Methyl 8-Benzoyl-1,2,3,5-tetrahydro-5-oxoimidazo[1,2-a]pyridine-7-carboxylate (5a): A solution of 142 mg (1 mmol) of dimethyl acetylenedicarboxylate in 6 ml of dioxane was dropped slowly into a solution of 188 mg (1 mmol) of 1a in 10 ml of the same solvent, and then stirred at ambient temperature for 2 days. After removal of solvent, the product was washed twice with small amount of dry diethyl ether, 5a was obtained in quantitative yield, mp 180-181°C. Ir(KBr): 3350 (NH), 1728 (ester C=O), 1660 (amide C=O), 1595 (C=O), 1555 (C=C); uv (ethanol): λ(lg ε) 362 (4.05), 238 (4.16). MS: m/z 298 (M^+). Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C,64.42; H,4.73; N,9.39. Found: C,64.21; H,4.71; N,9.31.

Methyl 9-Benzoyl-1,2,3,4-tetrahydro-6-oxo-6H-pyrido[1,2-a]pyrimidine-8-carboxylate (5d): Like 5a from 101 mg (0.5 mmol) of 1d and 71 mg (0.5 mmol) of dimethyl acetylenedicarboxylate, the crude product was recrystallized from methylene chloride-diethyl ether, 125 mg (83%) of 5d was obtained, mp 193-194°C. Ir(KBr): 3430 (NH), 1730 (ester C=O), 1655 (amide C=O), 1605 (C=O); uv (ethanol): λ(lg ε) 359 (3.92), 236 (4.22). MS: m/z 312 (M^+). Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C,65.37; H,5.16; N,8.97.

Found: C,65.42; H,5.22; N,8.98.

Methyl 9-(4-Chlorobenzoyl)-1,2,3,4-tetrahydro-6-oxo-6H-pyrido[1,2-a]pyrimidine-8-carboxylate (5e): Like 5a from 118 mg (0.5 mmol) of 1e and 71 mg (0.5 mmol) of dimethyl acetylenedicarboxylate, the crude product was recrystallized from methylene chloride, 140 mg (81%) of 5e was obtained, mp 187- 188°C. Ir(KBr): 3425 (NH), 1737 (ester C=O), 1655 (amide C=O), 1605 (C=O); uv (ethanol): λ(lg ε) 360 (3.86), 242 (4.20). MS: m/z 314 $(M-CH_3OH)^+$. Anal. Calcd. for $C_{17}H_{15}ClN_2O_4$: C,58.88; H,4.36; N,8.08. Found: C,58.21; H,4.37; N,8.17.

Dimethyl 2-[(4-Chlorobenzoyl)-2-imidazolidinylidene]methylmaleate (6b): Like 5a from 145 mg (0.65 mmol) of 1b and 92 mg (0.65 mmol) of dimethyl acetylenedicarboxylate, the crude product was recrystallized from diethyl ether, 135 mg of 6b was obtained, mp 98-100°C. Ir (KBr): 3400, 3260 (NH), 1725, 1710 (ester C=O), 1585 (C=O), 1525 (C=C); uv (ethanol): λ(lg ε) 364 (4.11), 248 (4.23). MS: m/z 364 (M^+). Anal. Calcd. for $C_{17}H_{17}ClN_2O_5$: C,55.97; H,4.70; N,7.68. Found: C,55.60; H,4.78; N,7.34.

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