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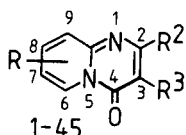
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The characteristic features of ir and uv spectra of 43 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives with electron donor or acceptor groups in position 3, and positions 6, 7, 8, or 9, respectively, have been systematically studied. On the basis of the spectra some conclusions have been drawn for the molecular structure. The negative solvent effect of the lowest-energy  $\pi \rightarrow \pi^*$  transition is investigated by the PPP method.

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The representatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **1** have considerable pharmacological activities [1-19] and show remarkable features in their electronic structures, too. In previous papers it was reported on derivatives with characteristic  $\pi$ -electronic spectra [20-22], and on frequency coupling between carbonyl stretching vibrations of 3-carbonyl-substituted derivatives [23].

The following compounds have been studied:



R = H, Me, COOEt  
 R<sup>2</sup> = H, Me, Cl  
 R<sup>3</sup> = H, Me, Cl, Br, NH<sub>2</sub>,  
 NO<sub>2</sub>, CN, COMe,  
 COOEt, CH<sub>2</sub>COOEt

A survey of the methyl, chloro, nitro, amino, and cyano derivatives shows (Table 1) that the frequency of  $\nu$  C=O

Table 1

The Characteristic IR Bands in cm<sup>-1</sup> of the Derivatives Substituted in Positions 2-, 3- and 6- Respectively, in Potassium Bromide

No.	R <sup>2</sup>	R <sup>3</sup>	R <sup>6</sup>	$\nu$ C=O	$\nu$ C-C
1	H	H	H	1710 vs 1640 s	1580 m 1535 m 1486 vs
2	Me	H	H	1705 vs 1640 s	1585 m 1535 m 1490 vs
3	H	Me	H	1690 vs 1635 s	1590 m 1540 m 1495 vs
4	H	H	Me	1705 vs 1650 m	1590 m 1550 w 1495 vs
5	H	Me	Me	1680 vs 1645 m	1600 m 1500 s —
6	Cl	H	H	1730 vs 1640 m	1575 m 1530 s 1465 vs
7	Me	Cl	Me	1700 vs 1645 m	1575 m 1560 m 1475 s
8	Cl	Cl	Me	1700 s 1645 sh	1580 w 1525 m 1480 vs
9	Cl	Br	Me	1700 vs 1650 m	1575 w 1535 m 1480 s
10	H	NO <sub>2</sub>	Me	1728 vs 1635 m	1585 m 1535 m 1490 vs
11	H	NH <sub>2</sub>	H	1730 vs 1640 m	1585 m 1505 s 1490 s
12	H	CN	Me	1720 vs 1640 m	1590 m 1500 vs —

sh denotes shoulder

## 1. IR Spectra.

From the normal vibrations only those will be considered which are characteristic: the carbonyl stretching vibration ( $\nu$  C=O) and four ring skeletal stretching vibrations ( $\nu$  C-C). Primarily the effect of ring substitution on the above normal vibrations was investigated in order to determine the type of substituent effect. In the case of derivatives with carbonyl-containing group in position 3 coupling between the carbonyl stretching frequencies hinders the evaluation of the substituent effect. For this reason at first derivatives without carbonyl-containing group in 3-position are considered.

(of the carbonyl group in position 4) changes according to the inductive effect of the substituent, *i.e.* it decreases if methyl group is the substituent. The effect of methyl group is the largest in position 3. Halogeno groups in position 2 and 3 cause smaller, 3-nitro, amino, or cyano groups, however, larger shifts than the 6-methyl group, considering the substituent shifts additive.

Among the skeletal vibrations only that of 1535 cm<sup>-1</sup> undergoes characteristic shifts on substitution, it changes in the 1500-1560 cm<sup>-1</sup> interval. The three other vibrations show, with a few exceptions, shifts of only  $\pm 10$  cm<sup>-1</sup>. Similarly to  $\nu$  C=O the position of the 1535 cm<sup>-1</sup> vibration

Table 2

The Characteristic IR Bands of Carbonyl-containing Derivatives, in Potassium Bromide

No.	Substituents	$\nu$ C=O		$\nu$ C-C			
		sym	antisym				
13	3-COOEt	1750 vs	1684 m [a]	1640 m	1582 m	1515 m	1500 vs
14	6-COOEt	1736 vs	1695 s	1646 m	1586 w	1530 m	1486 m
15	7-COOEt	1720 vs	1700 s	1643 m	1569 w	1542 m	1500 m
16	8-COOEt	1726 s	1680 s	1642 s	1569 m	1522 m	1492 s
17	9-COOEt	1728 s	1688 s	1633 s	1578 m	1525 sh	1492 s
18	3-COOEt, 6-Me	1738 s	1670 w	1630 m	1580 m	1525 m	1482 s
19	3-COOEt, 7-Me	1730 s	1702 s	1645 m	1580 m	1530 m	1495 s
20	3-COOEt, 8-Me	1712 s		1655 m	1580 m	1522 m	1495 m
21	3-COOEt, 9-Me	1745 s	1680 m	1632 m	1575 m	1530 m	1488 m
22	3-Me, 6-COOEt	1725 vs	1685 vs	1642 m	1590 w	1548 w	1498 s
23	3-Me, 7-COOEt	1721 vs	1685 vs	1643 m	1587 m	1543 w	1505 s
24	3-Me, 8-COOEt	1724 vs	1683 vs	1639 m	1583 m	1525 sh	1506 m
25	3-Me, 9-COOEt	1730 s	1682 vs	1636 m	1590 w	1544 w	1496 vs
26	3,6-diCOOEt	1735 vs 1752 vs	1685 m	1640 m	1580 m	1540 m	1490 vs
27	3,7-diCOOEt	1720 vs	1690 m	1635 m	1575 w	1530 m	1495 vs
28	3,8-diCOOEt	1720 vs	1695 m	1642 m	1575 m		1510 s
29	3,9-diCOOEt	1740 vs	1690 m	1622 m	1580 m	1535 w	1485 vs
30	3-COOH, 6-Me	1710 m [b]	1650 vs	1605 vs	1595 vs	1495 m	1470 vs
31	3-CH <sub>2</sub> -COOEt	1746 vs	1682 vs	1648 s	1590 m	1540 m	1515 vs

[a] Frequency coupling. [b] Intramolecular hydrogen bonding.

Table 3

The Shift Caused by the Polar Solvent and the Transition Moments of the Electron Transitions of Lowest Energy

No.	Substituents	$\nu$ max, cm <sup>-1</sup>	$\Delta\nu$ , cm <sup>-1</sup>	$\Delta\nu$ , cm <sup>-1</sup>	Q
		Carbon tetrachloride	Chloroform	Ethanol	
3	3-Me	27 780	392	578	
22	3-Me, 6-COOEt planar	29 240	0	172	0.7517
22	3-Me, 6-COOEt 60°	29 240	0	172	0.7536
23	3-Me, 7-COOEt	28 410	0	162	0.5977
24	3-Me, 8-COOEt	25 840	476	1938	1.0017
25	3-Me, 9-COOEt	28 330	80	243	
13	3-COOEt	26 460	572	1000	
18	3-COOEt, 6-Me <i>cis</i>	25 000	253	707	1.1562
18	3-COOEt, 6-Me <i>trans</i>	25 000	253	707	1.2920
19	3-COOEt, 7-Me <i>cis</i>	25 840	407	1114	1.2455
20	3-COOEt, 8-Me <i>cis</i>	26 600	286	879	1.2437
20	3-COOEt, 8-Me <i>trans</i>	26 600	286	879	1.3859
21	3-COOEt, 9-Me	26 250	279	780	
32	3-Ph	26 250	486	1075	
33	3-Ph, 6-COOEt	26 880	145	516	
34	3-Ph, 7-COOEt	26 320	351	1007	
35	3-Ph, 8-COOEt	24 390	926	1517	
36	3-Ph, 9-COOEt	27 470	76	305	
37	3-CN	27 170	223	604	
38	3-CN, 6-COOEt	25 130	515	1260	1.0800
39	3-CN, 7-COOEt	25 770	268	823	1.4336
40	3-CN, 8-COOEt	25 450	395	870	1.4711
41	3-CN, 9-COOEt	26 390	140	353	
26	3-COOEt, 6-COOEt	26 740	289	289	
27	3-COOEt, 7-COOEt	25 910	409	760	
28	3-COOEt, 8-COOEt	25 380	393	935	
29	3-COOEt, 9-COOEt	27 030	446	751	

changes according to the inductive effect of the substituent, the direction of shifts is, however, opposite of that of the carbonyl band. This suggests that in the 1535 cm<sup>-1</sup> vibration changes of internal coordinates near the positive charge centre are dominating.

With 3-carbonyl derivatives again the 1535 cm<sup>-1</sup> skeletal vibration is sensitive to substituent changes and therefore only this will be considered further (Table 2). It varies in the interval 1510-1550 cm<sup>-1</sup>. The frequency is decreased by a 3-ethoxycarbonyl group, additional methyl substituent in any position X (X = 6, 7, 8 or 9) causes an increment but the latter shift is smaller, the frequencies remain below 1535 cm<sup>-1</sup>. Additional ethoxycarbonyl groups in the pyridine ring generally produces somewhat larger frequencies than the corresponding methyl group. The 3-methyl group causes larger shift than the ethoxycarbonyl group substituted in the pyridine ring. The direction of the shift corresponds to an inductive effect on a positive charge centre as stated with derivatives shown in Table 1. It can be stated that the effect of substituent of the pyridine ring on the 1535 cm<sup>-1</sup> vibration is only secondary. The frequencies do not follow a unique trend as a function of position X. The dominating role of position 3 is demonstrated by the large shift caused by the carboxy group. A CH<sub>2</sub>-COOC<sub>2</sub>H<sub>5</sub> group has the same effect as a methyl group.

Spectra were recorded between 400 and 4000 cm<sup>-1</sup> by a Zeiss UR 20 spectrometer in potassium bromide pellets or in carbon tetrachloride and chloroform solutions using sodium chloride cells.

## 2. UV Spectra.

The spectra show 2-4 high-intensity bands in the region 200-400 nm belonging to  $\pi \rightarrow \pi^*$  transitions [21]. The disubstituted derivatives can be arranged in three groups according to the electron donor (*D*) or acceptor (*A*) ability

of the substituents: 1. 3-*D*-*X*-*A*, 2. 3-*A*-*X*-*D*, and 3. 3-*A*-*X*-*A*. The band positions of the isomers substituted in position 6, 7, 8, or 9 show considerable differences (Table 3 and 4).

Concerning these differences general relationships can be given only for the lowest-energy bands, the data refer to the spectra of 3-monosubstituted derivatives measured in ethanolic and carbon tetrachloride solutions.

For group 1 the red shift is largest when substitution is in position 8 (blue shift in position 6), for group 2 in position 6 (blue shift in position 8). For group 3 the largest red shift is in position 8.

The first two absorption bands in groups 2 and 3 consist of 2-3 vibrational bands with the exception of the 8-derivatives in group 2. The non-substituted parent compound also shows vibrational structure though its first absorption bands are superimposed. The solution spectra were also recorded with higher resolution ( $\Delta\lambda/\lambda = 2.5 \times 10^{-4}$ ,  $\lambda = 400$  nm) and at liquid air temperature, but the absorption bands could not be resolved into more components. The difference between the first two vibrational maxima is 1200 cm<sup>-1</sup>, probably corresponding to a skeletal vibration of the excited state.

Considering the molecular-structural conditions of the appearance of vibronic bands it is remarkable that compounds of group 1 have diffuse absorption bands. This suggests that the condition for the appearance of vibronic bands is a 3-substituent being coplanar by conjugation with the ring system thus producing a rigid molecular framework.

Molecules of group 1 contain a methyl group in position 3 having low-frequency torsional vibration. The 3-CH<sub>2</sub>-COOC<sub>2</sub>H<sub>5</sub> and 3-NH<sub>2</sub> derivatives have no vibronic bands too, the 3-chloro- and 3-bromo-derivatives, on the other hand, possess vibrational structure. The conjugative interaction (deduced from the red shifts) is less pronounced

Table 4

UV Maxima of Disubstituted Derivatives in Carbon Tetrachloride

No.	Substituents	$\lambda$ max nm (log $\epsilon$ )
22	3-Me-6-COOEt	342 (3.96)
23	3-Me-7-COOEt	352 (4.01)
24	3-Me-8-COOEt	410 sh - 387 (3.92) 370 (3.83) 351 (3.00)
25	3-Me-9-COOEt	353 (4.08)
18	3-COOEt-6-Me	400 (4.12) 384 (4.24) 330 (3.68) 317 (3.70)
19	3-COOEt-7-Me	387 (4.10) 369 (4.23) 324 (3.66) 313 sh -
20	3-COOEt-8-Me	376 (4.28)
21	3-COOEt-9-Me	381 (4.15) 366 (4.24) 323 (3.68) 309 sh -
38	3-CN-6-COOEt	397 (3.98) 376 (3.90)
39	3-CN-7-COOEt	389 (4.20) 379 (4.12) 370 (4.17)
40	3-CN-8-COOEt	413 (4.09) 393 (4.13) 376 (4.09) 337 (3.58) 323 (3.50)
41	3-CN-9-COOEt	379 (4.11)
		268 (4.02) 260 (4.08)
		285 (3.76) 276 (3.82)
		263 (3.38)
		273 (3.89) 264 (3.82)
		263 (3.96)

sh denotes shoulder.

Table 5  
Spectral Data of 3-Methyl Derivatives

Compound	Calculated		Experimental		Carbon Tetrachloride $\Delta E$
	$\Delta E$ [a]	f [a]	$\Delta E$ [a]	f	
3-Me	3.516	0.254	3.563	0.457	3.444
	4.073	0.278			
	5.095	0.089	5.166	0.501	
	5.437	0.499			
3-Me-6-C plane	3.355	0.221	3.647	0.204	3.594
	3.938	0.245			
	4.877	0.197	5.040	0.282	
	4.978	0.223			
3-Me-6-C 60°	3.472	0.229	3.647	0.204	3.594
	4.013	0.280			
	4.999	0.093	5.040	0.282	
	5.261	0.363			
3-Me-7-C	3.542	0.185	3.542	0.245	3.522
	3.709	0.375			
	4.950	0.150			
	5.251	0.402	5.276	0.389	
3-Me-8-C	3.246	0.285	3.444	0.162	3.187
	4.036	0.252			
	4.919	0.137	4.805	0.257	
	5.260	0.433			

[a]  $\Delta E$  denotes the transition energy in eV, f means the oscillator strength, the experimental value of which is calculated by the formula  $f = \epsilon/41700^{35}$  from the molar absorption coefficients given in  $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$ .

in group 3 than in group 2 as can be seen from a comparison of the 3-COOC<sub>2</sub>H<sub>5</sub> derivatives substituted by donor and acceptor groups, respectively. Accordingly, vibronic bands are more frequently appearing in group 2. The absence of vibronic bands in the spectrum of the 8-substituted derivative in group 2 can also be explained in this way: conjugation is relatively the smallest, blue is observed (*cf.* results of PPP calculations).

### 2.1. Solvent Effect.

In all three groups the first bands show blue shifts in polar solvents (*e.g.* ethanol) with respect to carbon tetrachloride (Table 3). The shifts are calculated from the maxima of the largest-wave-length vibronic bands.

The three groups of compounds can be arranged in two groups on the basis of their solvent shifts: 1. Group 1 and 3 characterized by largest solvent blue shift in position 8 (with exception of the 3-CN-8-COOC<sub>2</sub>H<sub>5</sub> derivative), 2. Compounds of group 2 where the solvent shift is nearly the same for all isomers.

The spectra were recorded on a Unicam SP 8-100 spectrophotometer in 96% ethanol, carbon tetrachloride and chloroform solvents.

### Calculations.

The molecules studied contain characteristic  $\pi$ -electron system, thus the PPP method seems appropriate to the

quantum-chemical calculation of their electronic spectra. The following substituents were considered as representatives of the three groups: 1. 3-Methyl-X-ethoxy carbonyl, 2. 3-Ethoxycarbonyl-X-methyl, 3. 3-Cyano-X-ethoxycarbonyl. The calculations were performed for these derivatives.

The PPP method was used in the same form as in previous works [20]. For groups 1 and 3 there are no experimental geometries available, therefore the X-ray diffraction geometry [24] of group 2 was used for the ring systems in each calculation. Standard data were used for the substituents [20] Carboxy group was taken instead of the ethyl ester.

According to the X-ray diffraction measurement the molecules of group 2 exist in crystalline state in *O,O-cis* forms, in solution the *O,O-trans* form is present according to ir measurements [23] The calculations were performed for both forms but no significant difference was detected. The molecules of group 1 are presumably planar, too. The heavy atoms of the substituents may be in the plane of the ring system with the exception of the 6-COOC<sub>2</sub>H<sub>5</sub> derivative where non-planar ester group was also considered in the calculation (the interplanar angle was varied by 15° steps). In the calculation of group 3 only the *O,O-trans* form was taken.

### Results and Discussion.

The experimental and calculated spectral data for group 1 are given in Table 5. The calculated values are in overall agreement with the experimental data, though the calculations do not reproduce the experimental order of the shifts caused by substituent X. For the 6-COOC<sub>2</sub>H<sub>5</sub> derivative best result was obtained by the geometry with interplanar angle of 60°.

The results for group 2 are collected in Table 6. The calculated transition energies both for the *trans* and the *cis* forms agree well with the experimental values. Also in this case the order of shifts by substituent X does not follow the experiment.

The calculated and experimental results for group 3 can be found in Table 7. In this case no significant difference was obtained between the planar and non-planar forms of the 6-substituted derivative. It can be seen that good accordance is achieved between calculated and experimental data, and the calculation well reproduces the order of substituent shifts.

On the basis of PPP calculations the following explanation is suggested for the blue shift of the lowest-energy

bands in polar solvents: the calculations confirm that this band belongs to  $\pi \rightarrow \pi^*$  transition having negative solvent effect which is presumably caused by the strongly polar ground state of the molecule. The two groups of compounds can be well characterized by the calculated transition moment (*Q*) of the first band. The shift by polar solvent ( $\Delta\nu$ ) is proportional to the square of the transition moment [25]. Table 3 shows the *Q* values as well as  $\Delta\nu$  values for ethanol and chloroform solutions related to carbon tetrachloride. In group 1 the highest *Q* value is obtained for the 8-COOC<sub>2</sub>H<sub>5</sub> derivative both in the 3-methyl and in the 3-cyano series. In group 2 the three isomers have very similar *Q* values in accordance with their similar blue shifts. It can be stated that the calculations are in accordance with experiment, thus the different solvent effects of the two groups can be explained by their transition-moment differences.

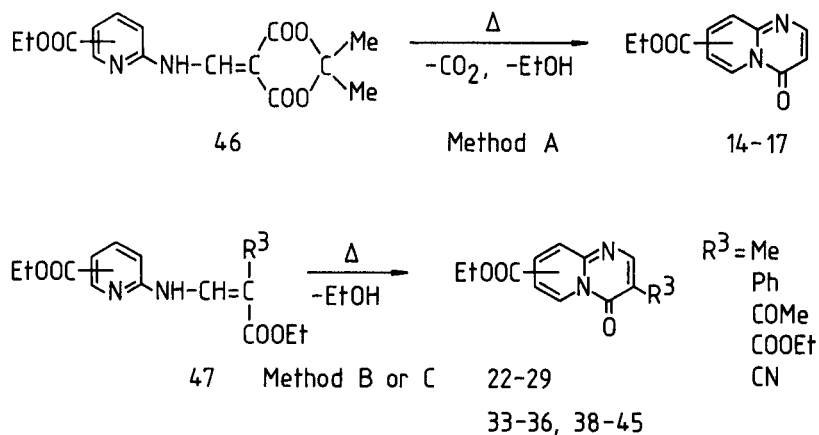
### Synthesis

The pyridopyrimidines **14-17**, **22-29**, **33-36** and **38-45** containing an ester group in the pyridine ring were prepared by thermal ring closure of isopropylidene malonates

Table 6  
Spectral Data of 3-Carboxy Derivatives

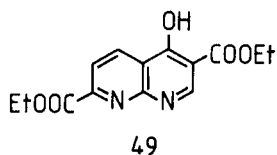
Compound	Calculated		Experimental		
	$\Delta E$ [a]	f [a]	Ethanol $\Delta E$ [a]	f	Carbon Tetrachloride $\Delta E$
3-C O,O- <i>trans</i>	3.454	0.397	3.425	0.363	3.155
	4.088	0.238	3.948	0.100	3.237
	4.990	0.189	4.078	0.096	
	5.307	0.133	4.920	0.200	
3-C-6-Me O,O- <i>trans</i>	3.387	0.383	3.187	0.417	3.107
	4.023	0.236	3.297	0.407	3.237
	4.907	0.190	3.923	0.115	3.757
			4.052	0.129	3.923
3-C-6-Me O,O- <i>cis</i>	3.282	0.332	3.187	0.417	3.107
	3.978	0.253	3.297	0.407	3.237
	4.872	0.155	3.923	0.115	3.757
			4.052	0.129	3.923
3-C-7-Me O,O- <i>cis</i>	3.306	0.360	3.342	0.407	3.220
	3.989	0.241	3.406	0.389	3.360
	4.891	0.136	3.999	0.098	3.827
			4.105	0.098	3.999
3-C-8-Me O,O- <i>cis</i>	3.273	0.356	3.406	0.457	3.315
	4.012	0.236	3.974	0.105	
	4.884	0.154	4.920	0.182	
			5.060	0.191	

[a] For notation see footnote to Table 5.

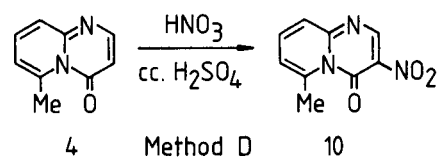


Scheme 1

**46** [26] (Method A) and acrylates **47** [26] (Method B and C) (Scheme 1). The ring closure of diethyl-(6-ethoxycarbonyl-2-pyridylamino)methylenemalonate produced besides diethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3,6-dicarboxylate (**26**) also 1,8-naphthyridine (**49**).



The 6-methyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from 6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with nitric acid in concentrated sulfuric acid (Method D). The 3-halogeno derivatives **7-9** were prepared from the



corresponding 3-unsubstituted pyridopyrimidines [27] by halogenating agents phosphorus pentachloride, bromine

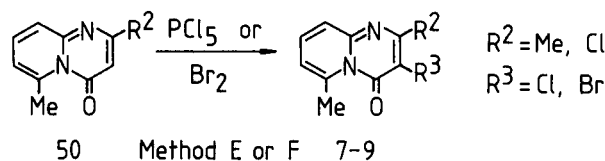


Table 7

Spectral Data of 3-Carbonitrile Derivatives

Compound	Calculated		Experimental		
	$\Delta E$ [a]	f [a]	$\Delta E$ [a]	Ethanol f	Carbon Tetrachloride $\Delta E$
3-CN-6-C	3.274	0.309	3.271	0.182	3.115
	3.862	0.262	3.522	0.186	3.297
	4.775	0.258	4.558	0.200	4.350
	4.907	0.256			
3-CN-7-C	3.419	0.429	3.297	0.380	3.187
					3.271
	3.679	0.254	3.406	0.355	3.351
	4.852	0.153	4.769	0.102	
3-CN-8-C	5.191	0.415			
	3.155	0.406	3.263	0.363	3.009
					3.155
					3.289
	3.967	0.240	3.803	0.069	3.679
		3.999	0.072	3.850	
	4.808	0.211			4.541
	5.208	0.377			4.696

[a] For notation see footnote to Table 5.

Table 8  
Chemical Characteristics of the Compounds Investigated

Compound No.	R <sup>3</sup>	Position of COOEt	Method	Yield %	Mp °C Recrystn solvent	HCl salt		Mol weight	Analysis		Calcd/Found	
						M.p. °C	Formula		C %	H %	N %	Cl %
14	H	6	A	64	oil	217-219 EtOH	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> .HCl	254.675	51.88 51.81	4.35 4.40	11.00 11.19	13.92 13.70
15	H	7	A	91	125-127 EtOAc		C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	218.213	60.55 60.27	4.62 4.30	12.84 12.59	
16	H	8	A	72	121-123 EtOAc		C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	218.213	60.55 60.58	4.62 4.63	12.84 12.78	
17	H	9	A	85	oil	218 EtOH	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> .HCl	254.675	51.88 51.99	4.35 4.28	11.00 11.02	13.92 14.04
22	Me	6	B	98	117-119 EtOH		C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	232.249	62.00 62.10	5.00 5.02	12.00 12.06	
23	Me	7	B	79.7	109-110 EtOH		C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	232.249	62.00 61.81	5.00 5.10	12.00 11.95	
24	Me	8	B	75.4	113-114 EtOH		C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	232.249	62.00 62.11	5.00 4.85	12.00 12.02	
25	Me	9	B	69.5	87-89 EtOH		C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	232.249	62.00 61.91	5.00 5.03	12.00 12.07	
33	Ph	6	B	78.2	103-105 EtOH		C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	294.311	69.38 69.50	4.80 4.82	9.52 9.45	
34	Ph	7	B	97	122-123 EtOH		C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	294.311	69.38 69.28	4.80 4.78	9.52 9.59	
35	Ph	8	B	92.5	180-181 EtOH		C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	294.311	69.38 69.20	4.80 4.89	9.52 9.71	
36	Ph	9	B	92	122-124 EtOH		C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	294.311	69.38 69.49	4.80 4.88	9.52 9.60	
42	COMe	6	B	28.8	131-133 EtOH		C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	260.252	60.00 59.98	4.65 4.67	10.76 10.78	
43	COMe	7	B	88.5	109-110 EtOH		C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	260.252	60.00 59.75	4.65 4.64	10.76 10.76	
44	COMe	8	B	73.1	179-180 EtOH		C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	260.252	60.00 59.97	4.65 4.63	10.76 10.67	
45	COMe	9	B	80.7	124-126 EtOH		C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	260.252	60.00 59.88	4.65 4.67	10.76 10.63	
26	COOEt	6	B	48.2	108-109 EtOH		C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub>	290.277	57.93 57.96	4.86 4.78	9.66 9.51	
27	COOEt	7	B	82.8	110-111 EtOH		C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub>	290.277	57.93 57.95	4.86 4.86	9.66 9.54	
28	COOEt	8	B	85.2	134-135 EtOH		C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub>	290.277	57.93 57.85	4.86 4.89	9.66 9.65	
29	COOEt	9	B	98	74-76 EtOH		C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub>	290.277	57.93 57.95	4.86 4.83	9.77 9.77	
38	CN	6	C	8	215-217 EtOH		C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>	243.224	59.26 58.98	3.72 3.49	17.28 17.03	
39	CN	7	C	8.2	150-151 EtOH		C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>	243.224	59.26 59.18	3.72 3.67	17.28 17.31	
40	CN	8	C	24.5	180-181 EtOH		C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>	243.224	59.26 59.13	3.72 3.84	17.28 17.31	
41	CN	9	C	57.6	165-167 EtOH		C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>	243.224	59.26 59.25	3.72 3.73	17.28 17.26	

(Method E and F), while the 3-amino derivative **11** was obtained by the acidic hydrolysis of the 3-benzylamino derivative **51** [28] (Method G). The other pyridopyrimidine derivatives were prepared by methods given in the literature [29-33].

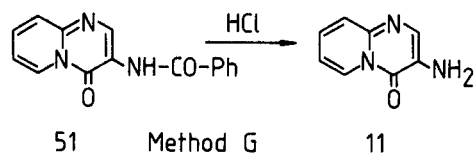


Table 9

## Chemical Characteristics of the Compounds Investigated

Compound No.	R <sup>6</sup>	R <sup>2</sup>	R <sup>3</sup>	Method	Yield %	Mp °C	Recrystn solvent	Formula	Mol weight	Analysis		Calcd/Found	
										C %	H %	N %	Cl/Br %
7	Me	Me	Cl	E	80	197	<i>i</i> -PrOH	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O	208.648	57.56	4.35	16.99	13.43
8	Me	Cl	Cl	E	94	210-211	<i>i</i> -PrOH	C <sub>9</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>2</sub> O	229.066	57.55	4.41	17.23	13.32
										47.19	2.64	12.23	30.45
9	Me	Cl	Br	F	88	227	EtOH	C <sub>9</sub> H <sub>6</sub> BrClN <sub>2</sub> O	273.522	47.24	2.40	12.18	30.57
										39.52	2.21	10.24	42.18
10	Me	H	NO <sub>2</sub>	D	83	181	MeCN	C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub>	205.174	39.60	2.19	10.13	42.00
										52.68	3.44	20.48	
11	Me	H	NH <sub>2</sub>	G	28	180-182	EtOH	C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> O	161.164	52.74	3.31	20.31	
										59.62	4.38	26.07	
										59.43	4.29	25.98	

## EXPERIMENTAL

Analytical results on the new compounds agreed with calculated data.

## Method A.

Isopropylidene (ethoxycarbonyl-2-pyridylamino)methylenemalonate (**46**) (10 mmoles, 3.2 g) was added to Dowtherm A (60 ml) at 250-255° and the reaction mixture was stirred for 5 minutes. After cooling to ambient temperature the reaction mixture was diluted with ligroine (60 ml) and was extracted with 20% hydrochloric acid (3 × 30 ml). The pH of the combined aqueous phase was adjusted to 7 with 20% sodium carbonate solution. The aqueous phase was extracted with chloroform (3 × 30 ml). The dried (sodium sulfate) organic phase was evaporated *in vacuo*. The residue was crystallized. If the residue was an oil, it was dissolved in ethanol and the hydrochloric salt was prepared with hydrogen chloride gas. (See Table 8)

## Method B.

Ethyl 2-(ethoxycarbonyl-2-pyridylamino)acrylate (**47**) (10 mmoles) was added to Dowtherm A (60 ml) at 250-255° and the reaction mixture was stirred for 0.5 hours. The reaction mixture was cooled to ambient temperature and was diluted with ligroine (60 ml). The organic phase was extracted with 20% hydrochloric acid (3 × 30 ml). The combined aqueous phase was neutralized with 20% sodium carbonate solution. Then it was extracted with chloroform (3 × 30 ml). The dried (sodium sulfate) organic phase was evaporated *in vacuo*. The residue was crystallized. (See Table 8)

When Dowtherm A was diluted with ligroine, at the preparation of the ethyl 3-acetyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-6-carboxylate (**42**) the unreacted starting material (1.35 g) precipitated which was filtered off.

When Dowtherm A was diluted with ligroine, at the preparation of the diethyl 4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3,6-dicarboxylate (**26**), diethyl 4-hydroxy-1,8-naphthyridine-3,7-dicarboxylate (**49**) (0.2 g, 6.8%) precipitated, which was filtered off, mp 255-256° (DMF).

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>: C, 57.93; H, 4.86; N, 9.66. Found: C, 58.12; H, 4.69; N, 9.55.

## Method C.

Ethyl (ethoxycarbonyl-2-pyridylamino) methylene cyanoacetate [26] (**47**, R = CN) (10 mmoles, 2.9 g) was added to liquid paraffin (300 ml) at 300° and the reaction mixture was stirred for 5 minutes. After cooling to ambient temperature the reaction mixture was diluted with ligroine (300 ml). The diluted organic phase was left to stand in a refrigerator for 24 hours. The precipitated cyano derivatives **38-41** were filtered off and crystallized (See Table 8).

## Method D

To a cooled solution of 6-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (**4**)

[34] (10 mmoles) in 98% sulfuric acid (5.0 ml) was added, dropwise, aqueous nitric acid (d = 1.4; 2.5 ml) at 20-25°. The mixture was stirred at 25° during 2 hours, and then was poured onto crushed ice (50.0 g) and the pH of the aqueous phase was adjusted to 7 with 10% aqueous sodium hydroxide. The precipitated nitro compound **10** was filtered off and was recrystallized from acetonitrile (yields and mp given in Table 9).

## Method E.

A mixture of pyridopyrimidine (**50**) [27] (30 mmoles), phosphorus pentachloride (30 mmoles) and phosphorus oxychloride (10 ml) was heated during 1.5 hours at 105-110°. After the mixture had cooled it was poured onto crushed ice (200 g) and the pH of the aqueous phase was adjusted to 7 with 10% aqueous sodium hydroxide, the precipitated 3-chloro derivative **7, 8** was filtered off and was recrystallized from 2-propanol.

## Method F.

To a stirred solution of 2-chloro-6-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one [27] (10 mmoles) in chloroform (20 ml) was added dropwise of bromine (11 mmoles) in chloroform (5 ml) and the mixture was stirred at 25° for 2 hours. The precipitated 3-bromo derivative **9** was filtered off and recrystallized from ethanol.

## Method G.

The 3-benzamido-4H-pyrido[1,2-*a*]pyrimidin-4-one (**51**) [28] (20 mmoles) was dissolved in concentrated hydrochloric acid (30 ml) and was stirred at 65-70° for 8 hours. After cooling the precipitated benzoic acid was filtered off. The filtrate was neutralized with potassium carbonate and extracted with chloroform (3 × 20 ml). The combined extracts were dried (sodium sulfate) and evaporated to dryness. The residue (0.9 g, 28%) was crystallized from ethanol to give 3-amino derivative **11**

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