Benzimidazole Condensed Ring Systems. 1. Syntheses and Biological Investigations of Some Substituted Pyrido[1,2-*a*]benzimidazoles

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The synthesis of some substituted 3-hydroxy-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles and 4-ethyl carboxylates **3** and their *O*- and *N*-dialkyl derivatives **5,6** is described. 3-Ethoxy-5-ethyl-2-phenyl-1*H*,5*H*-pyrido[1,2-*a*]benzimidazol-1-one **7** was obtained during the course of ethylating the parent ester **3t** with triethyl phosphate. Chlorination of **3** with phosphorus oxychloride afforded the corresponding 1,3-dichloropyrido[1,2-*a*]benzimidazoles **8** which were converted to a variety of azido, amino, morpholino and methoxy derivatives of the system. The synthesis of the indolopyridobenzimidazole **15** is also described. Two compounds exhibited *in vitro* antibacterial activity. Many compounds were screened for antileukemic, antimicrobial, herbicidal and plant antifungal potencies but were inactive.

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In a previous publication [1] we have described a novel synthetic route for 1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole ring system. The interesting *in vitro* antibacterial and antifungal potencies associated with some of its substituents prompted the synthesis of a wider range of derivatives of the tricyclic system for chemical and biological investigations. It is worth mentioning that this system, which has received little interest, possesses certain structural features in common with natural and synthetic purines.

Compounds **3a-u** (Table 1), namely, 3-hydroxy-1-oxo-2,7,8-trisubstituted-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles **3a-l** and 4-ethyl carboxylates **3m-u** were prepared in high yields by condensing the selected 1*H*-benzimidazole-2-acetonitriles **1a,b** or ethyl 1*H*-benzimidazole-2-acetates **1c,d** [2] with some bis-2,4,6-trichlorophenyl monosubstituted malonates **2a-f** [3] following our reported conditions [1] (Scheme 1). The benzimidazoles **1b** and **d** have not been described before. The utility of trimethyl and triethyl phosphates **4a,b** as excellent non toxic reagents for the alkylation of *N*-heterocycles [4-6], prompted the use of these esters for the alkylation of **3**. When some of the substituted 3-hydroxy-1-oxo-1*H*,5*H*-pyrido-[1,2-*a*]benzimidazole-4-carbonitriles **3** (X = CN) were refluxed with excess **4a** or **b** in the presence of potassium carbonate, the corresponding *O*-and *N*-dimethyl or diethyl derivatives **5a-h** (Table 2) were obtained in good yields. Analogously, methylation of ethyl 3-hydroxy-1-oxo-2-substituted-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carboxylates **3m,t** (X = $CO_2C_2H_5$) with **4a** yielded the respective *O*- and *N*-dimethyl derivatives **6a,b**. On the other hand, reacting the 4-ethyl carboxylate **3t** with **4b** using the adopted conditions resulted in the 4-deethoxycarbonylated *O*- and *N*-diethylated product **7** (Scheme 1). Chlorinating **3** with phosphorus oxychloride afforded the corresponding 1,3-dichloropyrido[1,2-*a*]benzimidazole-4-carbonitriles **8a-f** or 4-ethyl carboxylates **8g-l** (Table 3). The chloro com-

Scheme 1

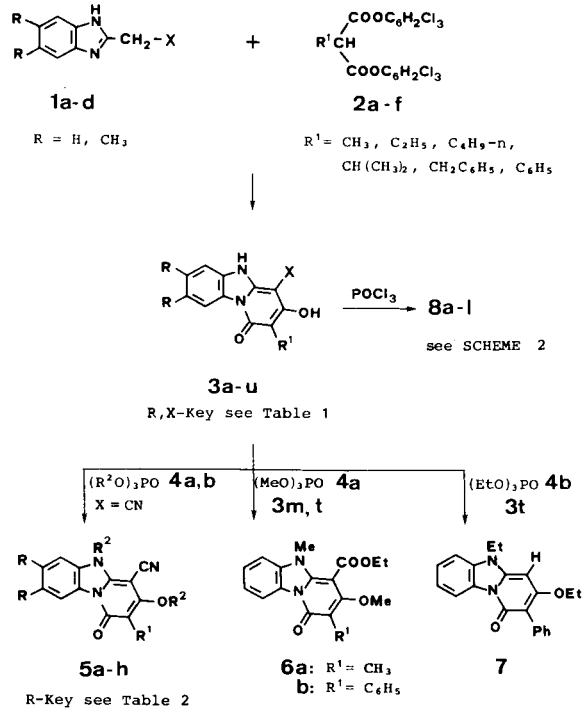


Table 1

3-Hydroxy-1-oxo-2,7,8-trisubstituted-1*H*,5*H*-pyrido[1,2,-*a*]benzimidazole-4-carbonitriles and 4-Ethyl Carboxylates

Compound No.	R^1	R	X	Yield (%)	MP (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, %: Calcd./Found C	H	N
3a	CH_3	H	CN	70	>300	DMF/H_2O	$C_{13}H_9N_3O_2$ 239.24	65.27 64.99	3.79 3.77	17.57 17.47
b	CH_3	CH_3	CN	75	>300	DMF/H_2O	$C_{15}H_{13}N_3O_2 \cdot H_2O$ 285.28	63.15 63.23	5.30 5.02	14.79 14.73
c	C_2H_5	H	CN	90	>300	EtOH/H_2O	$C_{14}H_{11}N_3O_2$ [a]			
d	C_2H_5	CH_3	CN	61	>300	DMF/H_2O	$C_{16}H_{15}N_3O_2$ 281.32	68.31 68.10	5.37 5.35	14.94 14.98
e	n-C_4H_9	H	CN	68	255-257	EtOH/H_2O	$C_{16}H_{15}N_3O_2$ [a]			
f	n-C_4H_9	CH_3	CN	63	290-291	EtOH/H_2O	$C_{18}H_{19}N_3O_2$ 309.36	69.88 69.58	6.19 6.46	13.58 13.48
g	$CH(CH_3)_2$	H	CN	74	282-284	EtOH/H_2O	$C_{15}H_{13}N_3O_2$ 267.28			15.72 15.41
h	$CH(CH_3)_2$	CH_3	CN	64	>300	AcOH	$C_{17}H_{16}N_2O_2$ 314.33	64.95 64.70	5.77 5.75	8.91 8.82
i	$CH_2C_6H_5$	H	CN	79	275-276	EtOH/H_2O	$C_{19}H_{13}N_3O_2$ [a]			
j	$CH_2C_6H_5$	CH_3	CN	70	>300	EtOH/H_2O	$C_{21}H_{17}N_3O_2$ 343.37	73.54 73.63	5.00 5.14	12.24 12.13
k	C_6H_5	H	CN	53	236	AcOH	$C_{18}H_{20}N_2O_4$ [a]			
l	C_6H_5	CH_3	CN	61	>300	DMF/H_2O	$C_{20}H_{15}N_3O_2 \cdot$ ½C_3H_7NO 365.89	70.57 70.80	5.10 5.19	13.40 13.34
m	CH_3	H	$COOC_2H_5$	68	180	AcOH	$C_{15}H_{14}N_2O_4 \cdot$ ½CH_3COOH 316.30	60.75 60.75	5.10 5.11	8.90 9.06
n	CH_3	CH_3	$COOC_2H_5$	100	260-262	AcOH	$C_{17}H_{18}N_2O_4 \cdot$ CH_3COOH 374.40	60.95 61.04	5.92 5.85	7.48 7.64
o	C_2H_5	H	$COOC_2H_5$	100	173	AcOH	$C_{16}H_{16}N_2O_4$ [a]			
p	$CH(CH_3)_2$	H	$COOC_2H_5$	64	>300	AcOH	$C_{17}H_{18}N_2O_4$ 314.35	64.96 64.70	5.77 5.75	8.91 8.82
q	$CH(CH_3)_2$	CH_3	$COOC_2H_5$	100	260-263	AcOH	$C_{19}H_{22}N_2O_4 \cdot$ CH_3COOH 402.43	62.67 62.37	6.51 6.53	6.96 6.88
r	$CH_2C_6H_5$	H	$COOC_2H_5$	100	232	AcOH	$C_{21}H_{18}N_2O_4$ [a]			
s	$CH_2C_6H_5$	CH_3	$COOC_2H_5$	81	268-270	AcOH	$C_{23}H_{22}N_2O_4 \cdot$ CH_3COOH 450.47	66.65 66.71	5.82 5.83	6.22 6.30
t	C_6H_5	H	$COOC_2H_5$	79	272	AcOH	$C_{20}H_{16}N_2O_4$ [a]			
u	C_6H_5	CH_3	$COOC_2H_5$	64	>300	DMF	$C_{22}H_{20}N_2O_4$ 376.40	70.20 70.44	5.36 5.40	7.44 7.39

[a] Previously reported [1].

pounds **8** were utilized as starting materials for the synthesis of a variety of compounds (Scheme 2 and 3).

Thus, reacting 1,3-dichloro-2-phenylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **8e** (X = CN) with two equivalents of sodium azide at room temperature yielded the 1,3-diazido derivative **9** in good yield. In contrast, similar treatment of ethyl 1,3-dichloro-2-substituted-pyrido[1,2-*a*]-benzimidazoloe-4-carboxylates **8g,k** (X = $CO_2C_2H_5$) resulted in their respective 1-azido-3-chloro derivatives **10a,b**. The azido compounds **9** and **10** were converted to 1,3-di(triphenylphosphoranylideneamino)-4-carbonitrile **11** and 3-chloro-1-(triphenylphosphoranylideneamino)-4-ethyl carboxylates **12**, respectively, upon treatment with triphenylphosphine. Acid hydrolysis of **11** and **12** yielded

Table 2

3-Methoxy and 3-Ethoxy-1-oxo-2,5,7,8-tetrasubstituted-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles

Compound No.	R^1	R^2	R	Yield (%)	MP (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, %: Calcd./Found C	H	N
5a	CH_3	CH_3	H	60	224-226	DMF/H_2O	$C_{15}H_{13}N_3O_2$ 267.29	67.40 67.63	4.90 4.89	15.72 15.76
b	C_2H_5	CH_3	CH_3	64	227-229	DMF	$C_{18}H_{19}N_3O_2$ 309.37	69.88 69.90	6.19 6.24	13.58 13.46
c	n-C_4H_9	C_2H_5	H	96	100-102	EtOH/H_2O	$C_{20}H_{23}N_3O_2$ 337.50	71.19 71.46	6.87 7.01	12.45 12.32
d	$CH(CH_3)_2$	CH_3	CH_3	91	222-225	EtOH	$C_{19}H_{21}N_3O_2$ 323.40	70.57 70.56	6.55 6.68	12.99 12.93
e	$CH_2C_6H_5$	C_2H_5	H	93	227-229	DMF/H_2O	$C_{23}H_{21}N_3O_2$ 371.45	74.37 74.62	5.70 5.79	11.31 11.23
f	C_6H_5	C_2H_5	H	94	212-214	EtOH	$C_{22}H_{19}N_3O_2$ 357.42	73.93 73.97	5.36 5.36	11.76 11.68
g	C_6H_5	CH_3	CH_3	100	>300	DMF	$C_{22}H_{19}N_3O_2$ 357.42	73.93 74.22	5.36 5.43	11.76 11.70
h	C_6H_5	C_2H_5	CH_3	87	240-242	DMF	$C_{24}H_{23}N_3O_2$ 385.47	74.78 75.05	6.01 6.08	10.90 10.80

Table 3

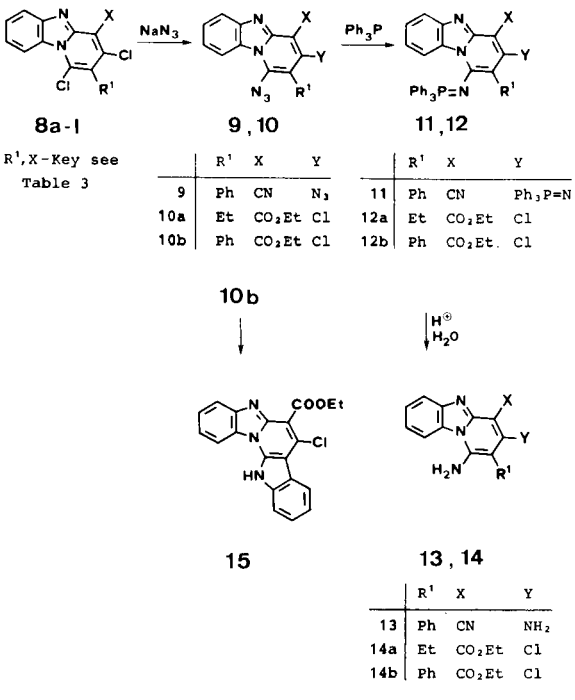
1,3-Dichloro-2,7,8-trisubstituted-pyrido[1,2-*a*]benzimidazole-4-carbonitriles and 4-Ethyl Carboxylates

Compound No.	R^1	R	X	Yield (%)	MP (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, %: Calcd./Found C	H	N	
8a	CH_3	H	CN	72	257-260	DMF/H_2O	$C_{13}H_7Cl_2N_3$ 276.13	56.55 56.76	2.56 2.42	25.68 25.84	15.22 15.32
b	CH_3	CH_3	CN	89	292-294	DMF	$C_{15}H_{11}Cl_2N_3$ 304.18	59.23 59.04	3.65 3.48	23.31 23.38	13.82 13.77
c	C_2H_5	H	CN	77	198-200	EtOH	$C_{14}H_9Cl_2N_3$ 290.16	57.95 58.20	3.13 3.19	24.44 24.13	14.48 14.50
d	$CH_2C_6H_5$	H	CN	45	230	EtOH	$C_{19}H_{11}Cl_2N_3$ 352.23	64.79 64.58	3.15 2.96		11.93 11.84
e	C_6H_5	H	CN	74	257-260	EtOH	$C_{18}H_9Cl_2N_3$ 338.20	63.93 64.08	2.68 2.67	20.97 21.23	12.42 12.37
f	C_6H_5	CH_2	CN	98	>300	DMF	$C_{20}H_{13}Cl_2N_3$ 366.25	65.59 65.83	3.58 3.60		11.47 11.32
g	C_2H_5	H	$COOC_2H_5$	90	123-125	EtOH/H_2O	$C_{16}H_{14}Cl_2N_2O_2$ 337.22	56.99 57.36	4.18 4.26	21.03 21.13	8.13 8.13
h	$CH_2C_2H_6$	H	$COOC_2H_5$	88	117-119	EtOH/H_2O	$C_{21}H_{16}Cl_2N_2O_2$ 390.27	63.17 62.94	4.04 4.29		7.02 6.74
k	C_6H_5	H	$COOC_2H_5$	100	199-201	EtOH	$C_{20}H_{14}Cl_2N_2O_2$ 385.26	62.35 62.77	3.66 3.63	18.41 18.14	7.27 7.28
l	C_6H_5	CH_3	$COOC_2H_5$	90	225-227	DMF	$C_{22}H_{18}Cl_2N_2O_2$ 413.31	63.93 63.87	4.39 4.58		6.78 6.74

the aminopyridobenzimidazoles **13** and **14**, respectively. Thermally induced intramolecular cyclization of ethyl 1-azido-3-chloro-2-phenylpyrido[1,2-*a*]benzimidazole-4-carboxylate **10b** in bromobenzene yielded the indolopyridobenzimidazole **15** with loss of nitrogen (Scheme 2).

The action of excess morpholine on 1,3-dichloro-2-ethylpyrido[1,2-*a*]benzimidazole-4-carbonitrile **8c** (X = CN) in dimethylformamide at 60° resulted in the 3-chloro-1-morpholino derivative **16**. However, substitution of both chloro atoms in the carbonitriles **8c-e** (X = CN) with mor-

Scheme 2

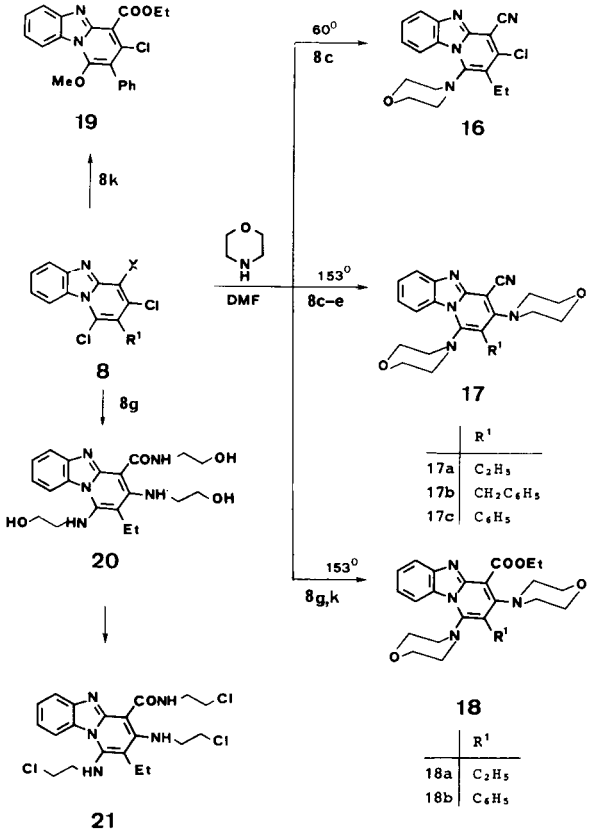


	R¹	X	Y
9	Ph	CN	N_3
10a	Et	CO_2Et	Cl
10b	Ph	CO_2Et	Cl

	R¹	X	Y
11	Ph	CN	$Ph_3P{=}N$
12a	Et	CO_2Et	Cl
12b	Ph	CO_2Et	Cl

	R¹	X	Y
13	Ph	CN	NH_2
14a	Et	CO_2Et	Cl
14b	Ph	CO_2Et	Cl

Scheme 3



	R¹
17a	C_2H_5
17b	$CH_2C_6H_5$
17c	C_6H_5

	R¹
18a	C_2H_5
18b	C_6H_5

pholine to obtain the corresponding 1,3-dimorpholino compounds **17a-c** we acheived in refluxing dimethylformamide. On the other hand, ethyl 3-chloro-1-morpholino-2-substituted-pyrido[1,2-*a*]benzimidazole-4-carboxylates **18a,b** could only be obtained by refluxing their parent 1,3-dichloro-pyrido-benzimidazole esters **8g,k** (X = $CO_2C_2H_5$) with excess morpholine in dimethylformamide. As expected from the foregoing substitution reactions of the dichloro esters, ethyl 1,3-dichloro-2-phenylpyrido-[1,2-*a*]benzimidazole-4-carboxylate **8k** afforded the 3-chloro-1-methoxy ester **19** upon treatment with sodium methoxide. Unexpectedly, refluxing ethyl 1,3-dichloro-2-ethylpyrido[1,2-*a*]benzimidazole-4-carboxylate **8g** with excess ethanoleamine gave **20** which was converted to **21** with thionyl chloride (Scheme 3).

The ^{1}H nmr data of representative compounds of the **3**, **5** and **8** series are recorded in Table 4.

Table 4

^{1}H NMR Data of some Compounds of the **3**, **5**, and **8** Series

Compound No.	δ (ppm)
3a	1.95 (s, CH_3), 7.1-7.7 (m, 3 ArH), 8.55 (d, H at C-9)
d	1.0 (t, J = 7 Hz, CH_3-ethyl), 2.3 (s, 2 CH_3, 3.45 (q, CH_2-ethyl), 7.1 (s, H at C-6)
h	1.5 (d, J = 7 Hz, 2 CH_3-isopropyl), 2.5 (s, 2 CH_3), 3.4 (m, CH-isopropyl), 7.4 (s, H at C-6), 8.2 (s, H at C-9) [a]
n	1.65 (t, J = 7 Hz, CH_3-ethyl), 2.4 (s, CH_3 at C-2), 2.5 (s, 2 CH_3), 4.75 (q, J = 7 Hz, CH_2-ethyl), 7.45 (s, H at C-6), 8.2 (s, H at C-9)
5a	2.0 (s, CH_3 at C-2), 3.9 (s, NCH_3), 4.0 (s, OCH_3), 7.2-7.7 (m, 3 ArH), 8.6 (d, H at C-9)
h	1.3 (t, J = 7 Hz, CH_3-ethyl at N-5), 1.7 (t, J = 7 Hz, CH_3-ethoxy), 1.5 (s), 1.6 (s), (2 CH_3 at C-7 and 8), 4.2 (q, CH_2-ethyl at N-5), 4.9 (q, CH_2-ethoxy), 7.5 (s, 5 ArH + H at C-6), 8.35 (s, H at C-9) [a]
8b	2.55 (s, 2 CH_3 at C-7 and 8), 2.75 (s, CH_3 at C-2), 7.65 (s, H at C-6), 8.6 (s, H at C-9) [a]
g	1.2 (t, J = 7 Hz, CH_3-ethyl at C-2), 1.4 (t, J = 7 Hz, CH_3-ethyl ester), 2.95 (q, CH_2-ethyl at C-2), 4.5 (q, CH_2-ethyl ester), 7.2-7.9 (m, 3 ArH), 8.55 (d, H at C-9)

[a] Trifluoroacetic acid was used as solvent.

Compounds **3b,d,h**, **5a,g**, **6b**, **7**, **8d,h**, **20** and **21** were screened against P388 lymphocytic leukemia in mice according to a standard protocol [7] and were inactive. Compounds **3f,l,m,n**, **5a**, **8d**, and **17a** were screened for *in vitro* activities against three *Staphylococcus aureus* strains (S14, S17, S18) as Gram-positive bacteria, two *Escherichia coli* (E21, E41) as Gram-negative bacteria, and one *candida albicans* (M1). The disc method was adopted to determine the inhibition zones and compounds which showed inhibition zones ≥ 8 mm in diameter were evaluated for their minimal inhibitory concentrations (MIC) against the

most sensitive organisms. Out of the compounds screened, only **3f** and **1** showed activities against *S. aureus* (S14, 17, 18), with MIC (μg/ml) 30 for **3f** and >250 μg for 31 [8]. Additionally, compounds **3h,j,m,s**, **8g,h,k**, **10a** and **10b** were screened for herbicidal and plant fungicidal activity according to standard protocols [9]. All the compounds were inactive. However compound **3m** showed a weak fungicidal activity against Fusarium oxysporon.

EXPERIMENTAL

Melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. The nmr spectra were recorded in hexadeuteriodimethylsulfoxide (unless otherwise indicated) and with TMS as an internal standard; the instruments used were the Varian EM-360 at 60 MHz and the XL-200 at 200 MHz.

5,6-Dimethyl-1*H*-benzimidazole-2-acetonitrile (**1b**).

This was prepared by the published method [2] by fusing 4,5-dimethyl-*o*-phenylenediamine (5.44 g, 40 mmoles) with ethyl cyanoacetate (6.42 ml, 60 mmoles), yield 6.6 g (89%), mp 230-232°, dec (xylene); ir: 3300 w, 3100-2500 bm, 1640 w, 1510 s cm^{-1}; ^1H nmr: δ 2.3 (s, 2 CH_3), 4.3 (s, CH_2), 7.3 (s, 2 Ar H).

Anal. Calcd. for $C_{11}H_{11}N_3$: N, 22.69. Found: N, 22.31.

Ethyl 5,6-Dimethyl-1*H*-benzimidazole-2-acetate (**1d**).

Under absolute anhydrous conditions, acetyl chloride (10 ml) was added dropwise to a cold stirred solution of **1b** (5.93 g, 32 mmoles) in absolute ethanol (80 ml). After the addition, the reaction mixture was refluxed for 2 hours and the solvent removed under vacuum. The hydrochloride salt was dissolved in water, the solution neutralized with sodium hydrogen carbonate and the precipitated product was filtered, yield 6.6 g (89%), mp 175-178° (aqueous ethanol); ir: 3200-2400 bm, 1735 s (CO), 1590 w, 1550 m cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.4 (t, J = 7 Hz, CH_3-ethyl), 2.4 (s, 2 CH_3), 4.4 (q, J = 7 Hz, CH_2-ethyl), 4.45 (s, CH_2), 7.5 (s, 2 ArH).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.51; H, 6.71; N, 11.80.

3-Hydroxy-1-oxo-2,7,8-trisubstituted-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carbonitriles and 4-Ethyl Carboxylates **3** (Table 1).

These were prepared from **1** and **2** as previously described [1]; ir of the nitriles **3a-l**: 3600-2400 bm, 2220 s (CN), 1670-1650 s (CO), 1620-1550 s-m cm^{-1}; ir of the esters **3m-u**: 3500-2500 bm, 1720 s (CO-ester), 1660 s (C_1=O), 1620-1350 w-m cm^{-1}.

3-Methoxy and 3-Ethoxy-1-oxo-2,5,7,8-tetrasubstituted-1*H*,5*H*-pyrido-[1,2-*a*]benzimidazole-4-carbonitriles **5** (Table 2).

The appropriate **3** (X = CN) (10 mmoles) was refluxed with **4a** or **b** (25 ml) for 1½ hours in the prescence of potassium carbonate (0.5 g). The product was partly deposited on cooling. Addition of water precipitated all the product which was filtered, washed with water, dried and recrystallized; ir: 3000-2900 w, 2210 s (CN), 1670-1650 s (CO), 1610-1550 m, 1210 s, 1050 s (C-O-C) cm^{-1}.

Ethyl 2,5-Dimethyl-3-methoxy-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carboxylate (**6a**).

This was prepared from **3m** (2.86 g, 10 mmoles) and **4a** (25 ml) as described for **5**, yield 2.86 g (91%), mp 164-166° (dimethylformamide): ir: 3100-2800 bm, 1720 s (CO-ester), 1660 s (C_1=O), 1620 m cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.55 (t, J = 7 Hz, CH_3-ethyl ester), 3.9 (s, NCH_3), 4.1 (s, OCH_3), 4.65 (q, CH_2-ethyl ester), 7.3-7.8 (m, 3 ArH), 8.6 (d, H at C-9).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.64; H, 5.94; N, 8.82.

Ethyl 5-Methyl-3-methoxy-2-phenyl-1-oxo-1*H*,5*H*-pyrido[1,2-*a*]benzimidazole-4-carboxylate (**6b**).

This was prepared from **3t** (3.48 g, 10 mmoles) and **4a** (25 ml) as described for **5**, yield 3.24 g (86%), mp 165-166° (ethanol); ir: 3000 w, 1720 s (CO-ester), 1650 s (C_1=O), 1610 w cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.55 (t, J = 7 Hz, CH_3-ethyl ester), 3.6 (s, NCH_3), 4.0 (s, OCH_3), 4.7 (q, CH_2-ethyl ester), 7.55 (s, 5 ArH), 7.75 (s, 3 ArH), 8.55 (d, H at C-9).

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.26; H, 5.43; N, 7.50.

3-Ethoxy-5-ethyl-2-phenyl-1*H*,5*H*-pyrido[1,2-*a*]benzimidazol-1-one (**7**).

This was prepared from **3t** (1.4 g, 4 mmoles) and **4b** (15 ml) as described for **5**, yield 0.98 g (74%), mp 210-212° (ethanol-light petroleum 60-80°); ir: 3000 bm, 1650 s (CO), 1620 m, 1580 s, 1220 s, 1040 s (C-O-C) cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.5 (t, J = 7 Hz, CH_3-ethyl at N-5), 1.7 (t, J = 7 Hz, CH_3-ethoxy), 4.3 (q, CH_2-ethyl at N-5), 4.6 (q, CH_2-ethoxy), 6.7 (s, H at C-4), 7.3 (s, 5 ArH), 7.6 (s, 3 ArH), 8.5 (d, H at C-9).

Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.24; H, 6.09; N, 8.35.

1,3-Dichloro-2,7,8-trisubstituted-pyrido[1,2-*a*]benzimidazole-4-carbonitriles and 4-Ethyl Carboxylates **8** (Table 3).

The appropriate **3** (15 mmoles) and phosphorus oxychloride (30 ml) were refluxed for 30-40 minutes. Subsequently, the excess phosphorus oxychloride was distilled under vacuum and the semi-solid residue stirred with ice-water. After neutralization with saturated sodium hydrogen carbonate solution, the precipitate was filtered, washed with cold water, dried and recrystallized; ir of the nitriles **8a-f**: 3100-2900 w, 2210 s (CN), 1620-1540 w-m cm^{-1}; ir of the ester **8g-l**: 3000-2900 w, 1740-1735 s (CO), 1620-1540 w-s cm^{-1}.

1,3-Diazido-2-phenylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**9**).

Sodium azide (1.3 g, 20 mmoles) was added to a stirred solution of **8e** (3.38 g, 10 mmoles) in dimethylformamide (25 ml) at room temperature. After stirring for 30 minutes, water was added to precipitate the yellow product, yield 3.4 g (97%), mp 175°, dec (dimethylformamide-water); ir: 3250 w, 2210 s, (CN), 2110 s (N_3), 1620 w cm^{-1}. Because of the poor stability of this compound, satisfactory elemental analysis could not be obtained and was used without delay in the next reaction.

Ethyl 1-Azido-3-chloro-2-ethylpyrido[1,2-*a*]benzimidazole-4-carboxylate (**10a**).

This was prepared from **8g** (3.37 g, 10 mmoles) and sodium azide (1.3 g, 20 mmoles) as described for **9**, yield 2.26 g (66%), mp 113-115°, dec (aqueous ethanol); ir: 2920 w, 2110 s (N_3), 1740 s (CO), 1630 m cm^{-1}; ^1H nmr: δ 1.3 (t, J = 7 Hz, CH_3-ethyl at C-2), 1.45 (t, J = 7 Hz, CH_3-ethyl ester), 4.3 (q, CH_2-ethyl at C-2), 4.6 (q, CH_2-ethyl ester), 7.2-7.9 (m, 3 ArH), 8.5 (d, H at C-9).

Anal. Calcd. for $C_{16}H_{14}ClN_5O_2$: C, 55.90; H, 4.10; Cl, 10.31; N, 20.37. Found: C, 55.81; H, 4.08; Cl, 10.09; N, 20.67.

Ethyl 1-Azido-3-chloro-2-phenylpyrido[1,2-*a*]benzimidazole-4-carboxylate (**10b**).

This was prepared in an almost quantitative yield from **8k** (3.85 g, 10 mmoles) and sodium azide (1.3 g, 20 mmoles) as described for **9**, mp 148-150°, dec (aqueous ethanol); ir: 3000 w, 2120 s (N_3), 1750 s (CO), 1620 w, 1600 m cm^{-1}; ^1H nmr: δ 1.55 (t, J = 7 Hz, CH_3), 4.65 (q, CH_2), 7.2-7.9 (m, 8 ArH), 8.7 (d, H at C-9).

Anal. Calcd. for $C_{20}H_{14}ClN_5O_2$: C, 61.31; H, 3.60; Cl, 9.05; N, 17.88. Found: C, 61.54; H, 3.66; Cl, 8.79; N, 18.07.

1,3-Di(triphenylphosphoranylideneamino)-2-phenylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**11**).

To a stirred suspension of **9** (3.5 g, 10 mmoles) in benzene (25 ml), a solution of triphenylphosphine (2.62 g, 20 mmoles) in benzene (20 ml) was added at room temperature. An immediate orange-red clear solution was formed with evolution of nitrogen. Stirring was maintained for 45 minutes during which the yellowish product was separated out. It was filtered, washed with benzene and dried, yield 7.7 g (94%), mp 301-305° (dimethylformamide); ir: 3100 w, 2230 s (CN), 1620 w, 1590 s cm^{-1}.

Anal. Calcd. for $C_{54}H_{39}N_5P_2 \cdot C_3H_7NO$: C, 76.67; H, 5.19; N, 9.41. Found: C, 76.80; H, 5.18; N, 9.28.

Ethyl 3-Chloro-2-ethyl-1-(triphenylphosphoranylideneamino)pyrido-[1,2-*a*]benzimidazole-4-carboxylate (**12a**).

This was prepared in an almost quantitative yield by treating **10a** (1.36 g, 4 mmoles) in benzene (20 ml) with triphenylphosphine (1.3 g, 5 mmoles) in benzene (20 ml) as described above. After being stirred for 30 minutes, cyclohexane was added to precipitate the yellow **12a**, mp 267-268° (methanol); ir: 3000 w, 1740 s (CO), 1620 w, 1580 m cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.15 (t, J = 7 Hz, CH_3-ethyl at C-2), 1.6 (t, J = 7 Hz, CH_3-ethyl ester), 2.8 (q, CH_2-ethyl at C-2), 4.65 (q, CH_2-ethyl ester), 7.3-8.2 (m, 19 ArH).

Anal. Calcd. for $C_{34}H_{29}ClN_3O_2P$: C, 70.64; H, 5.06; N, 7.27. Found: C, 70.73; H, 4.96; N, 7.36.

Ethyl 3-Chloro-2-phenyl-1-(triphenylphosphoranylideneamino)pyrido-[1,2-*a*]benzimidazole-4-carboxylate (**12b**).

This was prepared from **10b** (1.56 g, 4 mmoles) and triphenylphosphine as described for **12a**, yield 2.0 g (80%), mp 277-279° (dioxane); ir: 3080 w, 3000 w, 1740 s (CO), 1625 w cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.55 (t, J = 7 Hz, CH_3), 4.7 (q, CH_2), 6.7-8.2 (m, 24 ArH).

Anal. Calcd. for $C_{36}H_{29}ClN_3P$: C, 72.90; H, 4.67; N, 6.71. Found: C, 72.94; H, 4.73; N, 6.60.

1,3-Diamino-2-phenylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**13**).

Compound **11** (1.64 g, 2 mmoles) was refluxed with a mixture of hydrochloric acid (2*N*) (40 ml) and methanol (20 ml) for 2 hours. The reaction mixture was concentrated to remove the excess methanol and then neutralized with ammonia to precipitate the product. A few mls of acetone were added to keep the triphenylphosphine oxide in solution. The yellowish diamino product was filtered, washed with water and dried, yield 0.5 g (85%), mp 180-183° (aqueous ethanol); ir: 3500-2900 bm, 2200 s (CN), 1640 m, 1600 m cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 72.03; H, 4.50; N, 23.35.

Ethyl 1-Amino-3-chloro-2-ethylpyrido[1,2-*a*]benzimidazole-4-carboxylate (**14a**).

Following the method described for **13**, the title compound was obtained from **12a** (1.16 g, 2 mmoles), yield 0.58 g (91%), mp 209-211° (methanol); ir: 3300 m (NH_2), 2900 w, 1710 s (CO), 1630 m, 1590 m cm^{-1}; ^1H nmr: δ 1.15 (t, J = 7 Hz, CH_3-ethyl at C-2), 1.4 (t, J = 7 Hz, CH_3-ethyl ester), 2.9 (q, CH_2-ethyl at C-2), 4.5 (q, CH_2-ethyl ester), 7.15 (s, NH_2), 7.3-7.9 (m, 3 ArH), 8.5 (d, H at C-9).

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: C, 60.50; H, 5.08; N, 13.22. Found: C, 60.18; H, 5.29; N, 13.07.

Ethyl 1-Amino-3-chloro-2-phenylpyrido[1,2-*a*]benzimidazole-4-carboxylate (**14b**).

This was obtained by hydrolysis of **12b** (1.26 g, 2 mmoles) as described for **13**, yield 0.68 g (93%), mp 154-156° (ethanol); ir: 3600-3000 bm (NH_2), 1740 s (CO), 1630 s, 1590 s cm^{-1}; ^1H nmr: δ 1.5 (t, J = 7 Hz, CH_3-ethyl), 4.6 (q, J = 7 Hz, CH_2), 6.7 (s, NH_2), 7.3-8.0 (m, 8 ArH), 8.5 (d, H at C-9).

Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: N, 11.49; Cl, 9.69. Found: N, 11.28; Cl, 9.87.

Ethyl 13-Chloro-5*H*-indolo[2′,3′:1,2]pyrido[1,2-*a*]benzimidazole-12-carboxylate (**15**).

This was obtained by refluxing **10b** (1.2 g, 3 mmoles) in bromobenzene (15 ml) for 30 minutes. After cooling, the yellowish product was filtered, washed with benzene and dried, yield 0.7 g (64%), mp 266-267° (dioxane); ir: 3300-2600 bm, 1685 s (CO), 1630 m, 1590 m cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.6 (t, J = 7 Hz, CH_3), 4.7 (q, CH_2), 7.0-8.5 (m, 8 ArH).

Anal. Calcd. for $C_{20}H_{14}ClN_3O$: C, 66.03; H, 3.88; N, 11.55. Found: C, 66.12; H, 3.83; N, 11.49.

3-Chloro-2-ethyl-1-(1-morpholino)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**16**).

A solution of **8c** (1.16 g, 4 mmoles) in dimethylformamide (10 ml) was warmed with morpholine (1.4 ml, 16 mmoles) at 60° for 15 minutes during which a yellowish product was separated out. It was then filtered and dried, yield 0.9 g (77%), mp >300° (dimethylformamide); ir: 2900 bm, 2220 s (CN), 1630 w, 1590 s cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.5 (t, J = 7 Hz, CH_3), 3.3 (q, CH_2), 3.7 (m, CH_2-N-CH_2 in morpholino), 4.4 (m, CH_2-O-CH_2 in morpholino), 7.9 (s, 3 ArH), 9.1 (d, H at C-9).

Anal. Calcd. for $C_{18}H_{17}ClN_4O$: C, 63.42; H, 5.03; N, 16.44. Found: C, 63.23; H, 5.04; N, 16.43.

1,3-Di(1-morpholino)-2-ethylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**17a**).

A solution of **8c** (1.16 g, 4 mmoles) in dimethylfomamide (10 ml) was refluxed with morpholine (1.4 ml, 16 mmoles) for 1 hour. Water was then added and the yellowish product was filtered, washed with water and dried, yield 1.01 g (75%), mp 245-248° (dimethylformamide-water); ir: 290 m, 2210 s (CN), 1620 s, 1590 s cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (t, J = 7 Hz, CH_3), 2.9 (q, CH_2), 3.35 (t, J = 7 Hz, CH_2-N-CH_2 in morpholino at C-3), 3.5 (t, J = 7 Hz, CH_2-N-CH_2 in morpholino at C-1), 3.9 (t, CH_2-O-CH_2 in morpholino at C-3), 4.15 (t, CH_2-O-CH_2 in morpholino at C-1), 7.3-7.7 (m, 3 ArH), 8.7 (d, H at C-9).

Anal. Calcd. for $C_{22}H_{25}N_5O_2$: C, 67.50; H, 6.44; N, 17.89. Found: C, 67.62; H, 6.43; N, 17.91.

2-Benzyl-1,3-di(1-morpholino)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**17b**).

Prepared from **8d** (1.41 g, 4 mmoles) and morpholine (1.4 ml, 16 mmoles) as described for **17a**, yield 0.86 g (67%), mp 262-265° (dimethylformamide-water); ir: 2980 m, 2890 s, 2220 s (CN), 1630 m, 1600 m cm^{-1}.

Anal. Calcd. for $C_{27}H_{27}N_5O_2$: C, 71.50; H, 6.00; N, 15.44. Found: C, 71.75; H, 6.04; N, 15.52.

1,3-Di(1-morpholino)-2-phenylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**17c**).

This was prepared in an almost quantitative yield from **8e** (1.36 g, 4 mmoles) and morpholine (1.4 ml, 16 mmoles) as described for **17a**, mp >300° (dimethylformamide-water); ir: 2900 m, 2210 s, (CN), 1620 s, 1590 s cm^{-1}.

Anal. Calcd. for $C_{26}H_{25}N_5O_2$: C, 71.10; H, 5.73; N, 15.94. Found: C, 71.52; H, 5.78; N, 16.11.

Ethyl 3-Chloro-2-ethyl-1-(1-morpholino)pyrido[1,2-*a*]benzimidazole-4-carboxylate (**18a**).

This was prepared from **8g** (1.36 g, 4 mmoles) and morpholine (1.4 ml, 16 mmoles) as described for **17a**, yield 0.71 g (62%), mp 180-182° (aqueous ethanol); ir: 2900 bm, 1730 s (CO), 1620 w, 1590 w cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.5 (t, J = 7 Hz, CH_3-ethyl at C-2), 1.65 (t, J = 7 Hz, CH_3-ethyl ester), 3.2 (q, CH_2-ethyl at C-2), 3.7 (t, -CH_2-N-CH_2), 4.2 (t, -CH_2-O-CH_2-), 4.7 (q, CH_2-ethyl ester), 7.6-8.0 (m, 8 ArH), 8.9 (d, H at C-9).

Anal. Calcd. for $C_{20}H_{22}ClN_3O$: Cl, 9.14; N,, 10.83. Found: Cl, 8.86; N, 10.81.

Ethyl 3-Chloro-1-(1-morpholino)-2-phenylpyrido[1,2-*a*]benzimidazole-4-carboxylate (**18b**).

It was prepared from **8k** (1.54 g, 4 mmoles) and morpholine (1.4 ml, 16 mmoles) as described for **17a**, yield 0.5 g (44%), mp 213-215° (aqueous ethanol); ir: 2900 bm, 1730 s (CO), 1620 m, 1540 w cm^{-1}.

Anal. Calcd. for $C_{24}H_{22}ClN_3O$: C, 66.13, H, 5.09; Cl, 8.13; N, 9.64.

Found: C, 66.15; H, 5.09; Cl, 8.41; N, 9.59.

Ethyl 3-Chloro-1-methoxy-2-phenylpyrido[1,2-*a*]benzimidazole-4-carboxylate (**19**).

Compound **8k** (0.77 g, 2 mmoles) was refluxed with sodium methoxide solution (5 mmoles) in methanol (20 ml) for 3 hours. The solution was then concentrated and the yellowish product which deposited upon addition of water was filtered, washed with water, and dried, yield 0.2 g (26%), mp 180-182° (aqueous-ethanol); ir: 2900 m, 1720 s (CO), 1620 m, 1250 s, 1050 s (C-O-C) cm^{-1}.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.49; N, 7.36. Found: C, 65.87; H, 4.28; N, 7.43.

1,3-Di(2-hydroxyethylamino)-2-ethyl-4-(2-hydroxyethylcarbamoyl)-pyrido[1,2-**a**]benzimidazole (**20**).

Compound **8g** (1.69 g, 5 mmoles) was refluxed with ethanol-amine (20 ml) for 2 hours and then poured with stirring onto cold water. The precipitated product was filtered, washed with water and dried, yield 1.21 g (60%), mp 168-170° (aqueous ethanol); ir: 3500-2800 bm, 1650 s (CO), 1620 w, 1590 w cm^{-1}.

Anal. Calcd. for $C_{20}H_{27}N_5O$: N, 17.45. Found: N, 17.59.

4-(2-Chloroethylcarbamoyl)-1,3-di(2-chloroethylamino)-2-ethylpyrido-[1,2-*a*]benzimidazole (**21**).

Compound **20** (1.37 g, 3 mmoles) in dry benzene (30 ml) was refluxed with thionyl chloride (10 ml) for 30 minutes. The excess thionyl chloride was then distilled under vacuum and the residue was mixed with benzene. The deposited yellow product was filtered, yield 1.25 g (80%), mp >300° (aqueous-ethanol); ir: 3000-2800 bm, 1650 s (CO), 1610 w, 1560 m cm^{-1}.

Anal. Calcd. for $C_{20}H_{24}Cl_3N_5O$: C, 52.58; H, 5.30; N, 15.33. Found: C, 52.99; H, 5.40; N, 15.53.

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