Synthesis of (Imidazo[1,2-*c*]pyrimidin-2-yl)phenylmethanones and 6-Benzoylpyrrolo[2,3-*d*]pyrimidinones

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4-Pyrimidinamines have been reacted with 3-bromo-1-phenylpropane-1,2-dione to give a series of (imidazo[1,2-*c*]pyrimidin-2-yl)phenylmethanones. The dione also reacted with ethyl amidinoacetate to yield ethyl 2-amino-5-benzoylpyrrole-2-carboxylate which was used to prepare a series of 6-benzoylpyrrolo[2,3-*a*]pyrimidines.

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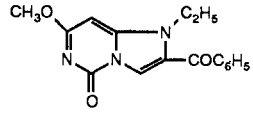
Continuing our search for non-sedative anxiolytics unrelated in structure to benzodiazepines [1], we synthesized a series of (imidazo[1,2-*c*]pyrimidin-2-yl)phenylmethanones [2] by reacting 3-bromo-1-phenylpropane-1,2-dione with 4-pyrimidinamines. The initial reaction in dry tetrahydrofuran or ether precipitated an iminium salt which was then cyclized in hot ethanol to give the methanones **1a-1d**. Under these conditions the salt from 2,6-dimethoxy-4-pyrimidinamine yielded the imidazo[1,2-*c*]pyrimidinone **2a** due to hydrolysis of the methoxyl group adjacent



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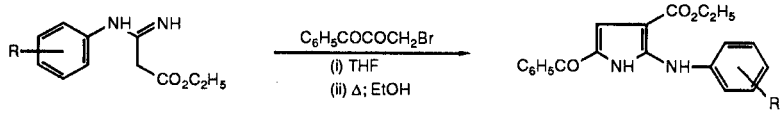
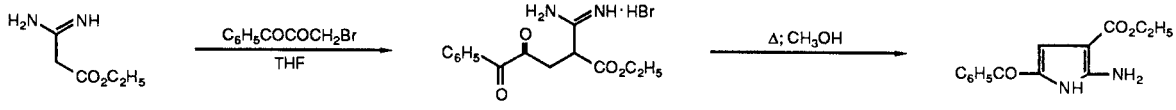


4

a, R = 4-CH_3
b, R = 4-C_2H_5
c, R = 3,4-$(CH_3)_2$
d, R = 4-$COCH_3$
e, R = 4-Cl

5

a, R = 4-CH_3
b, R = 4-C_2H_5
c, R = 3,4-$(CH_3)_2$
d, R = 4-$COCH_3$
e, R = 4-Cl



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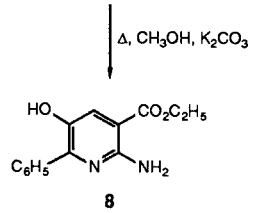
7



8

9

a, R = H
b, R = $CSNHC_2H_5$

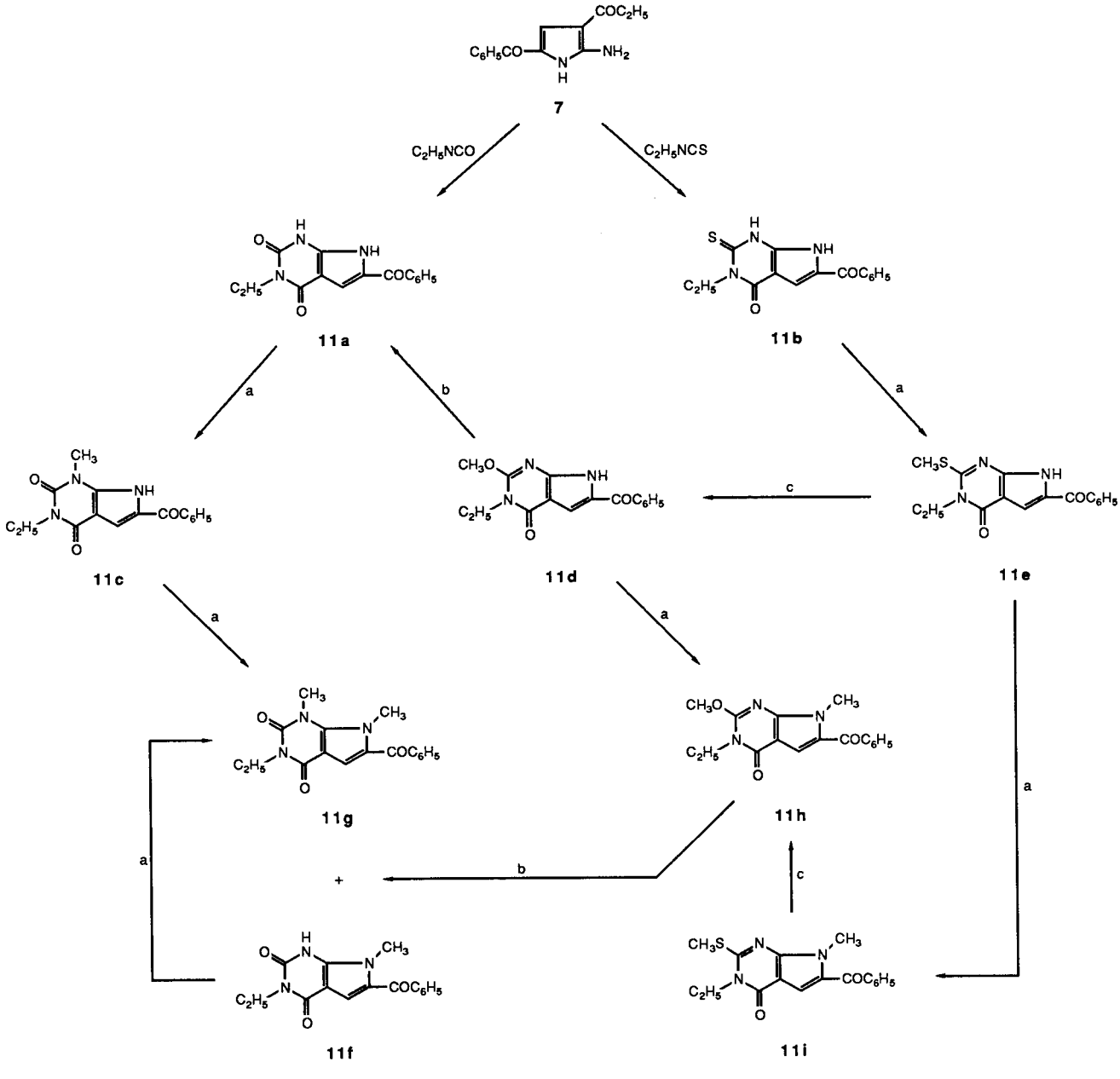
10

a, R = O
b, R = S

to the bridge-head nitrogen. To obtain the dimethoxy derivative **1e** the cyclization was carried out in hot methanol. Formation of the anion of **2a** with sodium hydride in dimethylformamide followed by treatment with alkyl halides yielded the 6-alkyl derivatives **2b-2e**. In the case of **2c** byproducts were separated by chromatography and identified as **1f** and **3** on the basis of their pmr spectra. Compounds **2f-2h** were prepared in the same way from 2-methoxy-6-(methylthio)-4-pyrimidinamine.

Whilst looking for an alternative synthesis of (imidazo[1,2-*a*]quinolin-2-yl)phenylmethanones [3] it was found that 3-bromo-1-phenylpropane-1,2-dione reacted with amidinoacetic esters **4a-4e** to give pyrroles **5a-5e** instead of the desired imidazoles due to initial alkylation of the ester α-carbon atom. This novel route to pyrroles has recently been reported [4]. It was realized that use could be made of the synthesis to prepare pyrrolo[2,3-*d*]pyrimidine analogues of imidazopyrimidinones **2** by reacting the pyrroles with isocyanates [5]. Ethyl amidinoacetate was therefore treated with the bromodiketone to give ethyl 2-amino-5-

Scheme 1



Reagents: a, CH_3I, K_2CO_3, DMF, 1 hour. b, conc HBr; 100°, 4 hours. c, CH_3ONa; CH_3OH, reflux, 24 hours.

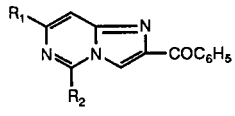
benzoylpyrrole-3-carboxylate **7**. The initial exothermic reaction was carried out in tetrahydrofuran and after removal of solvent the unisolated intermediate, thought to be **6**, cyclized to the pyrrole in refluxing methanol. If potassium carbonate was added to the methanol then cyclization took place onto the aryl ketone instead to give the bright yellow base-soluble nicotinic ester **8** for which there is only one carbonyl absorption (1655 cm^{-1}) in the infra-red spectrum in contrast to the two (1690 and 1630 cm^{-1}) in that of **7**. In their pmr spectra the single aromatic proton is 1.0 ppm lower and the phenyl *ortho* protons 0.4 ppm lower in **8** than they are in **7**.

Hydrolysis of ester **7** gave the corresponding acid which in refluxing pyridine decarboxylated to the 2-pyrrolamine **9a**. Addition of ethyl isothiocyanate to the reaction mixture resulted in the formation of thiourea **9b**, again due to decarboxylation. The ester **7** was therefore treated with ethyl isocyanate or ethyl isothiocyanate and the resulting ureas **10a** and **10b** cyclized to the pyrrolo[2,3-*d*]pyrimidinones **11a** and **11b** by refluxing in dmf or pyridine with sodium hydride. Scheme 1 shows the reactions carried out on these compounds, the most interesting observation being the partial rearrangement of **11h** to **11g** in hot concentrated hydrobromic acid.

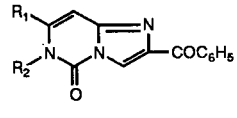
In contrast with the imidazo[1,2-*c*]pyrimidinones **2** and other fused imidazoles which demonstrated affinity for the benzodiazepine receptor with IC_{50}s of 2 μM or less, [1,2] the IC_{50}s of the pyrrolo[2,3-*d*]pyrimidinones, **11a-11i**, were all greater than 10 μM. Since compound **3** was also inactive it appears that an sp^2 nitrogen atom adjacent to the

Table 1

Imidazo[1,2-*c*]pyrimidines



1a-1f



2a-2h

Compound	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%): Calcd./Found C	H	N
1a	CH_3O	CH_3	67	165-167	$C_{15}H_{13}N_3O_2$	67.4 67.2	4.9 5.0	15.7 15.65
1b	CH_3O	C_2H_5	45	152-153	$C_{16}H_{15}N_3O_2$	68.3 68.2	5.4 5.4	14.9 14.9
1c	CH_3O	CH_3S	29	149-150	$C_{15}H_{13}N_3O_2S$	60.2 60.2	4.4 4.4	14.0 14.1
1d	CH_3S	CH_3S	25	154-155	$C_{15}H_{13}N_3OS_2$	57.1 57.3	4.15 4.2	13.3 13.4
1e	CH_3O	CH_3O	71	141-143	$C_{15}H_{13}N_3O_3$	63.6 63.7	4.6 4.6	14.8 14.9
1f	CH_3O	C_2H_5O	—	116-118	$C_{16}H_{15}N_3O_3$	64.6 64.5	5.1 5.1	14.1 14.1
2a	CH_3O	H	82	209-211	$C_{14}H_{11}N_3O_3$	62.45 62.2	4.1 4.15	15.6 15.4
2b	CH_3O	CH_3	40	191-192	$C_{15}H_{13}N_3O_3$	63.6 63.5	4.6 4.7	14.8 14.9
2c	CH_3O	C_2H_5	44	159-160	$C_{16}H_{15}N_3O_3$	64.6 64.5	5.1 5.2	14.1 14.0
2d	CH_3O	C_3H_7	18	106-107	$C_{17}H_{17}N_3O_3$	65.6 65.6	5.5 5.8	13.5 13.4
2e	CH_3O	$CH_2=CHCH_2$	26	139-141	$C_{17}H_{15}N_3O_3$	66.0 65.8	4.9 5.0	13.6 13.6
2f	CH_3S	H	79	234-237	$C_{14}H_{11}N_3O_2S$	58.9 58.8	3.9 3.9	14.7 14.7
2g	CH_3S	C_2H_5	47	153-154	$C_{16}H_{15}N_3O_2S$	61.3 61.7	4.8 4.9	13.4 13.4
2h	CH_3S	$CH_2=CHCH_2$	52	161	$C_{17}H_{15}N_3O_2S$	62.75 62.8	4.65 4.7	12.9 12.9

benzoyl group is essential for receptor binding. This observation further emphasises the strict steric and electronic requirements for activity in this type of molecule.

EXPERIMENTAL

Melting points were determined either with a Townson and Mercer capillary melting point apparatus or with a Reichert Kofler hot stage. Infra-Red spectra were determined for potassium bromide discs with a Pye-Unicam SP1000 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Perkin-Elmer R12A spectrometer at 60 MHz and tetramethylsilane as internal standard.

3-Bromo-1-phenylpropane-1,2-dione (**6**).

Propiophenone (6.0 kg) and anhydrous aluminium chloride (92 g) were added to ether (6.0 ℓ) followed by bromine (17.2 kg) at a rate to maintain gentle reflux. When addition was complete (approximately 6 hours) the mixture was heated to reflux overnight and the solvent was then removed under reduced pressure to leave a dark orange-red oil (lachrymatory). The oil was added slowly to a solution of sodium (2.81 kg) in methanol (45 ℓ) while keeping the temperature below 20°. When addition was complete concentrated hydrochloric acid (12.5 ℓ) was added and the mixture was stirred at room temperature for 1 hour. The precipitate was filtered off and the filtrate was reduced in volume to 25 ℓ by distillation of methanol. The residue was partitioned between chloroform (10 ℓ) and water (10 ℓ). The organic phase was separated and the aqueous phase was extracted with chloroform (2 × 5 ℓ). The combined chloroform solutions were dried (sodium sulphate) and solvent was removed under reduced pressure. The residue was fractionally distilled under vacuum through a 30 cm fenske column to give 1-phenylpropane-1,2-dione (5.7 kg, 86%), bp 77-85° (1-2 mm).

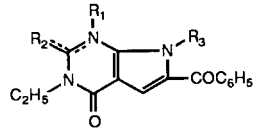
1-Phenylpropane-1,2-dione (5.32 kg) was dissolved in chloroform (36 ℓ) and heated to 50°. A solution of bromine (5.66 kg) in chloroform (8 ℓ) was added slowly to maintain gentle reflux and immediate decolourisation of the bromine (approximately 6 hours). The solution was cooled to room temperature overnight, washed with saturated aqueous sodium bicarbonate (20 ℓ) and then water (20 ℓ) and dried (sodium sulphate). Solvent was removed under reduced pressure to leave a yellow-green oil (8.2 kg) which was used without further purification (estimated purity by pmr 70%).

7-Methoxy-5-methylimidazo[1,2-*c*]pyrimidin-2-yl)phenylmethanone (**1a**).

A stirred solution of 6-methoxy-2-methyl-4-pyrimidinamine (2.1 g) [7] in dry tetrahydrofuran was treated with 3-bromo-1-phenyl-1,2-propanedione (70%, 5.4 g) in dry ether (5 ml). After stirring overnight the mixture was chilled and the precipitate was filtered off. A suspension of the salt in dry ethanol was refluxed for 1.5 hours and then chilled. Solid material was filtered off and shaken with a mixture of aqueous sodium carbonate and chloroform.

Table 2

Pyrrolo[2,3-*d*]pyrimidines



Compound	R_1	R_2	R_3	Yield (%)	mp (°C)	Recrystallization Solvent	Formula	Analysis (%) Calcd./Found C	H	N
11a	H	O	H	81	>300	M/C	$C_{15}H_{13}N_3O_3$	63.6 63.2	4.6 4.7	14.8 14.5
11b	H	S	H	95	>300	M/C	$C_{15}H_{13}N_3O_2S$ (+0.25 H_2O)	59.3 59.5	4.5 4.4	13.8 13.7
11c	CH_3	O	H	68	240-241	E	$C_{16}H_{15}N_3O_3$	64.6 64.4	5.1 5.15	14.1 14.0
11d	—	CH_3O	H	63	212-214	E	$C_{16}H_{15}N_3O_3$	64.6 64.5	5.1 5.1	14.1 14.1
11e	—	CH_3S	H	84	210-211	M	$C_{16}H_{15}N_3O_2S$	61.3 61.3	4.8 4.85	13.4 13.5
11f	H	O	CH_3	52	>300	M/C	$C_{16}H_{15}N_3O_3$	64.6 64.3	5.1 5.1	14.1 14.1
11g	CH_3	O	CH_3	57	234-235	M	$C_{17}H_{17}N_3O_3$	65.6 65.5	5.5 5.5	13.5 13.5
11h	—	CH_3O	CH_3	89	155-156	M	$C_{17}H_{17}N_3O_3$	65.6 65.25	5.5 5.6	13.5 13.2
11i	—	CH_3S	CH_3	85	168-169	M	$C_{17}H_{17}N_3O_2S$	62.4 62.5	5.2 5.3	12.8 12.8

Solvents: C = Dichloromethane, E = Ethyl acetate, M = Methanol.

Table 3

Spectral Data for Pyrrolo[2,3-d]pyrimidines

Compound	IR (cm^{-1})	Solvent	^{1}H-NMR (τ) R_1	R_2	R_3	C_2H_5 (J = 7 Hz)	5-H	C_6H_5
11a	1710, 1638, 1620, 1587	D	—	—	—	6.16 q 8.91 t	3.07	2.05-2.75
11b	1640, 1620	Insoluble						
11c	1692, 1660, 1626, 1612, 1560	C	6.38	—	—	5.94 q 8.77 t	2.68	2.05-2.30 (2H) 2.30-2.58 (3H)
11d	1675, 1625, 1570	C	—	5.96	−0.06	5.89 q 8.75 t	2.73 d (J = 3 Hz)	1.98-2.24 (2H) 2.38-2.62 (3H)
11e	1690, 1612, 1550	C	—	7.42	0.03	5.82 q 8.66 t	2.75 d (J = 3 Hz)	1.95-2.30 (2H) 2.35-2.65 (3H)
11f	1728, 1642, 1622, 1605	Insoluble						
11g	1698, 1659, 1621, 1560	C	6.21	—	5.88	5.96 q 8.80 t	2.90	2.10-2.35 (2H) 2.35-2.62 (3H)
11h	1690, 1632, 1580	C	—	6.02	5.92	5.93 q 8.78 t	2.88	2.10-2.30 (2H) 2.40-2.63 (3H)
11i	1690, 1630	C	—	7.33	5.88	5.81 q 8.65 t	2.85	2.15-2.25 (2H) 2.40-2.60 (3H)

Solvents: C = Deuteriochloroform, D = DMSO-d_6.

The organic layer was evaporated and the residue was chromatographed (silica; ethyl acetate) to give **1a** as yellow crystals (2.7 g, 67%), mp 165-167°; ir: ν max 1645 and 1635 cm^{-1}; ^{1}H nmr (deuteriochloroform): τ 1.55 (2H, m, phenyl 2-H and 6-H), 1.97 (1H, s, 3-H), 2.30-2.65 (3H, m, phenyl H), 3.32 (1H, s, 8-H), 6.08 (3H, s, OCH_3), 7.21 (3H, s, 5-CH_3).

Anal. See table 1.

Compounds **1b-d** were prepared in the same way from the corresponding 4-pyrimidinamines [7,8].

(5,7-Dimethoxyimidazo[1,2-c]pyrimidin-2-yl)phenylmethanone (**1e**).

Prepared as for **1a** from 2,6-dimethoxy-4-pyrimidinamine [8] except that the intermediate salt was cyclised by stirring for 1 hour in methanol at 60°; ir: ν max 1650 and 1630 cm^{-1}; ^{1}H nmr (deuteriochloroform): τ 1.65-1.90 (2H, m, phenyl 2-H and 6-H), 2.00 (1H, s, 3-H), 2.35-2.60 (3H, m, phenyl H), 3.62 (1H, s, 8-H), 5.80 (3H, s, 5-OCH_3), 6.10 (3H, s, 7-OCH_3).

Anal. See table 1.

2-Benzoyl-7-methoxyimidazo[1,2-c]pyrimidin-5-one (**2a**).

A stirred solution of 2,6-dimethoxy-4-pyrimidinamine (10 g) [8] in dry tetrahydrofuran (25 ml) was treated with a solution of 3-bromo-1-phenylpropane-1,2-dione (70%, 21 g) in dry ether (50 ml). After stirring overnight ether (20 ml) was added. The mixture was chilled and crystalline material (10 g) was filtered off. The solid was refluxed in ethanol under nitrogen for 2 hours after which the solution was cooled, diluted with ether (30 ml) and chilled in ice to crystallize **2a** as a yellow solid (4.4 g) mp 209-211°; ir: ν max 1700 and 1640 cm^{-1}. A further 1.4 g was obtained by chromatographing the residue obtained from evaporation of the filtrate (silica; ethyl acetate).

Anal. See table 1.

Compound **2f** was prepared in the same way from 2-methoxy-6-(methylthio)-4-pyrimidinamine.

Alkylation Products from 2-Benzoyl-7-methoxyimidazo[1,2-c]pyrimidin-5-one **2b-2e**.

A solution of **2a** (26.9 g) in dry dimethylformamide (200 ml) was treated with sodium hydride (70%, 3.8 g) and stirred for 1 hour. Iodoethane (17.2 g) was added dropwise over 10 minutes, the mixture was stirred for 2 hours and then poured into water. After standing overnight solid material (15.1 g) was filtered off and chromatographed (silica; 2% methanol in chloroform) to give the following compounds.

a) 2-Benzoyl-1-ethyl-7-methoxyimidazo[1,2-c]pyrimidin-5-one (**3**).

Compound **3** was obtained as yellow crystals (0.9 g), mp 222-224°; ir: ν max 1670 and 1615 cm^{-1}; ^{1}H nmr (deuteriochloroform): τ 2.08 (1H, s, 3-H), 2.10-2.60 (5H, m, phenyl H), 4.44 (1H, s, 8-H), 5.72 (2H, q, J = 7 Hz, ethyl CH_2), 6.07 (3H, s, OCH_3), 8.60 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.6; H, 5.1; N, 14.1. Found: C, 64.5; H, 5.1; N, 14.1.

Further elution of the above then gave:

b) 2-Benzoyl-6-ethyl-7-methoxyimidazo[1,2-c]pyrimidin-5-one (**2c**).

Compound **2c** was obtained as yellow crystals, (13.0 g, 44%), mp 159-160°; ir: ν max 1700 and 1640 cm^{-1}; ^{1}H nmr (deuteriochloroform): τ 1.75-1.95 (2H, m, phenyl 2-H and 6-H), 1.86 (1H, s, 3-H), 2.38-2.58 (3H, m, phenyl H), 4.10 (1H, s, 8-H), 5.88 (2H, q, J = 7 Hz, ethyl CH_2), 6.08 (3H, s, OCH_3), 8.70 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. See table 1.

(5-Ethoxy-7-methoxyimidazo[1,2-c]pyrimidin-2-yl)phenylmethanone (**1f**).

The filtrate was extracted with ethyl acetate to give material which was chromatographed to yield a small amount (100 mg) of (5-ethoxy-7-methoxyimidazo[1,2-c]pyrimidin-2-yl)phenylmethanone (**1f**), mp 116-118°; ir: ν max 1658 and 1640 cm^{-1}; ^{1}H nmr

(deuteriochloroform): τ 1.65-1.87 (2H, m, phenyl 2-H and 6-H), 1.98 (1H,s, 3-H), 2.35-2.60 (3H, m, phenyl H), 3.63 (1H, s, 8-H), 5.34 (2H, q, J = 7 Hz, ethyl CH_2), 6.12 (3H, s, OCH_3), 8.50 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. See table 1.

Compounds **2b**, **2d**, **2e**, **2g** and **2h** were obtained in the same way as **2c**.

Ethyl *N*-(4-Tolyl)amidinoacetate (**4a**) (*cf* ref [9]).

A solution of dry phenol (62 g) in dry ethyl cyanoacetate was cooled to −20° and treated with dry hydrogen chloride over 2 hours. After standing at room temperature for 2 days ether was added and the mixture cooled and stirred. Filtration gave ethyl 3-amino-3-phenoxypropionate hydrochloride (62 g, 39%) as colourless crystals, mp 122-123°.

A mixture of *p*-toluidine (5 g) and ethyl 3-amino-3-phenoxypropionate hydrochloride (11.6 g) was heated in refluxing ethyl acetate for 1 hour and then cooled. Dilution with ether enabled filtration of **4a** hydrochloride (10.1 g, 82%), mp 138-140°.

The following hydrochlorides of *N*-substituted ethyl amidinoacetate were prepared in a similar manner by using the appropriate aniline: *N*-(4-ethylphenyl) (**4b**), mp 169-170°; *N*-(3,4-dimethylphenyl) (**4c**), mp 157-159°; *N*-(4-acetylphenyl) (**4b**), mp 189-191° dec; and *N*-(4-chlorophenyl) (**4e**), mp 146-148°.

The free bases were obtained as oils by neutralizing aqueous solutions of the salts with aqeuous ammonium hydroxide and extracting with ether.

Ethyl 5-Benzoyl-2-(*p*-tolylamino)pyrrole-3-carboxylate (**5a**).

A solution of **4a** (5 g) and 3-bromo-1-phenylpropane-1,2-dione (70%, 9 g) in tetrahydrofuran (40 ml) was allowed to stand at room temperature overnight. The solvent was removed under reduced pressure and the residue was refluxed for 4 hours in ethanol (50 ml). Cooling and addition of ether enabled filtration of **5a** (3.9 g, 41%) as pale yellow crystals (from ethyl acetate-petroleum ether), mp 144-145°; ir: ν max 3320, 3200-3100, 1675, 1610 and 1600 cm^{-1}; ^1H nmr (deuteriochloroform): τ 0.95 (1H, broad s, 1-H; disappears rapidly with deuterium oxide), 1.50 (1H, s, side-chain NH; disappears slowly with deuterium oxide), 2.10-2.30 (2H, m, benzoyl 2- and 6-H), 2.40-2.65 (3H, m, benzoyl 3-, 4- and 5-H), 2.70-2.85 (4H, m, tolyl-H), 2.90 (1H, d, J = 3 Hz, 4-H; s after deuterium oxide), 5.73 (2H, q, J = 7 Hz, ethyl CH_2), 7.65 (3H, s, CH_3), 8.67 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.4; H, 5.8; N, 8.0. Found: C, 72.45; H, 5.8; N, 8.0.

Starting from the corresponding amidinoacetates the following 2-substituted ethyl 5-benzoylpyrrole-2-carboxylates were likewise prepared:

2-(4-Ethylanilino) **5b**, (46%), was obtained as pale yellow crystals (from ethyl acetate-petroleum ether), mp 142-143°.

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.9; H, 6.1; N, 7.7. Found: C, 73.0; H, 6.1; N, 7.7.

2-(3,4-Dimethylanilino) **5c**, (55%), was obtained as pale yellow crystals (from ethyl acetate-petroleum ether), mp 135-137°.

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.9; H, 6.1; N, 7.7. Found: C, 73.2; H, 6.2; N, 7.7.

2-(4-Acetylanilino) **5d**, (13%), was obtained as cream coloured crystals (from chromatography in ethyl acetate on alumina), mp 174-175°.

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.2; H, 5.4; N, 7.4. Found: C, 70.0; H, 5.4; N, 7.4.

2-(4-Chloroanilino) (**5e**), (22%), was obtained as yellow crystals (from chromatography in ethyl acetate-petroleum ether (4:1) on silica), mp 171-173°.

Anal. Calcd. for $C_{20}H_{17}ClN_2O_3$: C, 65.1; H, 4.65; Cl, 9.6; N, 7.6. Found: C, 65.2; H, 4.8; Cl, 10.1; N, 7.5.

Ethyl 2-Amino-5-benzoylpyrrole-3-carboxylate (**7**).

A solution of 3-bromo-1-phenylpropane-1,2-dione (70%, 23 g) in tetrahydrofuran (23 ml) was added to a stirred solution of ethyl amidinoacetate [5] (11 g) in tetrahydrofuran (110 ml) on an ice bath at a rate such that the temperature remained below 15°. After allowing the solution to warm to room temperature the solvent was removed under reduced pressure. The residue was dissolved in methanol (110 ml) and the solution was refluxed under nitrogen for 2 hours. After cooling to 0° addition of ethyl acetate enabled filtration of **7** (10.5 g, 48%) as yellow crystals (from methanol-chloroform), mp 230°; ir: ν max 3470, 3350, 3240, 1696 and 1638 cm^{-1}; ^1H nmr (DMSO-d_6): τ 2.17-2.65 (5H, m, phenyl H), 3.22 (1H, s, 4-H), 3.85 (2H, s, NH_2), 5.86 (2H, q, J = 7 Hz, ethyl CH_2), 8.79 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.5; N, 10.85. Found: C, 64.85; H, 5.5; N, 10.8.

2-Amino-5-benzoylpyrrole-3-carboxylic Acid.

A solution of **7** (8 g) and sodium hydroxide (3 g) in aqueous ethanol (50%, 150 ml) was refluxed overnight and the ethanol was removed under reduced pressure. Addition of acetic acid precipitated the acid (6 g, 84%) as a pale green solid, mp 210° dec which was used without purification.

Ethyl 2-Amino-5-hydroxy-6-phenylpyridine-3-carboxylate (**8**).

Addition of potassium carbonate (1 mole) to the refluxing methanol solution during the preparation of **7** followed by removal of the solvent under reduced pressure and partitioning the residue between ethyl acetate and water gave, on evaporation of the ethyl acetate, compound **8** (50%) as bright yellow crystals (from methanol), mp 190°; ir: ν max 3460, 3300, 1655, 1620 and 1585 cm^{-1}; ^1H nmr (DMSO-d_6): τ 1.75-2.05 (2H, m, phenyl 2-H and 6-H), 2.22 (1H, s, 4-H), 2.40-2.75 (3H, m, phenyl 3-, 4- and 5-H), 3.41 (2H, s, NH_2), 5.72 (2H, q, J = 7 Hz, ethyl CH_2), 8.70 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.1; H, 5.5; N, 11.0. Found: C, 65.1; H, 5.5; N, 10.8.

5-Benzoyl-2-pyrrolamine (**9a**).

Addition of concentrated hydrochloric acid to the hot aqueous ethanolic solution obtained during preparation of 2-amino-5-benzoylpyrrole-3-carboxylic acid caused an exothermic reaction with effervescence. The solution was concentrated under reduced pressure, diluted with water and neutralized with potassium carbonate to precipitate **9a** (92%). Alternatively, the acid can be heated overnight in refluxing pyridine to give a quantitative yield of **9a** as yellow crystals (from ethyl acetate), mp 185-187°; ir: ν max 3430, 3330, 3200 broad and 1634 cm^{-1}; ^1H nmr (DMSO-d_6): τ 2.20-2.70 (5H, m, phenyl H), 3.30-3.50 (1H, m, 4-H), 4.0-5.0 (2H, broad, NH_2), 4.55-4.72 (1H, m, 3-H).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.4; N, 15.0. Found: C, 70.8; H, 5.5; N, 15.0.

1-(5-Benzoyl-2-pyrrolyl)-3-ethylthiourea (**9b**).

A mixture of 2-amino-5-benzoylpyrrole-3-carboxylic acid (6 g) and ethyl isothiocyanate (4 g) was heated for 1 hour in refluxing

pyridine (30 ml) and the solution evaporated to dryness under reduced pressure. The residue was triturated with ether and then ethyl acetate to crystallize **9b** (4 g, 56%) as a yellow solid (from ethyl acetate), mp 182-184°; ir: ν max 3300 broad and 1645 cm^{-1}; ^1H nmr (DMSO-d_6 + deuterium oxide): τ 2.13-2.68 (5H, m, phenyl H), 3.24 (1H, d, J = 3.5 Hz, pyrrole 4-H), 3.96 (1H, d, J = 3.5 Hz, pyrrole 3-H), 6.53 (2H, q, J = 7 Hz, ethyl CH_2), 8.87 (3H, t, J = 7 Hz, ethyl CH_3).

Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.5; H, 5.5; N, 15.4; S, 11.7. Found: C, 61.6; H, 5.5; N, 15.1; S, 11.4.

Ethyl 5-Benzoyl-2-(3-ethylureido)pyrrole-3-carboxylate (**10a**).

A mixture of **7** (4 g) and ethyl isocyanate (2 g) was heated overnight in refluxing pyridine and the solvent was removed under reduced pressure. Trituration of the residue with ether crystallized **10a** (5 g) as a light brown solid used directly in the preparation of **11a**. A small sample was recrystallized from methanol as a colourless solid, mp 158-160°; ir: ν max 3340, 3290, 1700, 1680 and 1610 cm^{-1}; ^1H nmr (DMSO-d_6): τ −0.50 (1H, broad, 1-H), 0.57 (1H, s, urea 1-H), 2.00-2.50 (6H, m, phenyl H and urea 3-H), 3.04 (1H, d, J = 3 Hz, 4-H; s after addition of deuterium oxide), 5.75 (2H, q, J = 7 Hz, OCH_2), 6.60-7.03 (2H, m, NCH_2), 8.74 and 8.89 (2 × 3H, 2 × t, J = 7 Hz, 2 × CH_3).

Anal. Calcd. for $C_{17}H_{19}N_3O_4$: C, 61.9; H, 5.9; N, 12.7. Found: C, 62.0; H, 5.8; N, 12.8.

Ethyl 5-Benzoyl-2-(3-ethylthioureido)pyrrole-3-carboxylate (**10b**).

Reaction of **7a** with ethyl isothiocyanate as in the preparation of **10a** gave **10b** (60%) as a brown solid used directly in the preparation of **11b**.

6-Benzoyl-3-ethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**11a**).

A mixture of **10a** (5 g) and sodium hydride (80%, 0.5 g) was heated overnight in refluxing dimethylformamide (40 ml). The solution was diluted with water, filtered and treated with acetic acid to precipitate **11a** (3.5 g, 81%) as a light brown solid (Tables 2 and 3).

6-Benzoyl-3-ethyl-2-thioxo-1,2,3,7-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-one (**11b**).

A mixture of **10b** (17 g) and sodium hydride (80%, 1.7 g) was heated for 2 hours in refluxing pyridine and the solution was evaporated to dryness under reduced pressure. The residue was diluted with water and the solution was filtered. Treatment with acetic acid precipitated **11b** (14 g, 95%) as a light brown solid (Tables 2 and 3).

Details of the syntheses and physical properties of the following compounds are given in Scheme 1 and Table 2 and spectral data are given in Table 3:

6-Benzoyl-3-ethyl-1-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidin-2,4(3*H*,7*H*)-dione (**11c**).

6-Benzoyl-3-ethyl-2-methoxy-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (**11d**).

6-Benzoyl-3-ethyl-2-(methylthio)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]-pyrimidin-4-one (**11e**).

6-Benzoyl-3-ethyl-7-methyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**11f**).

6-Benzoyl-3-ethyl-1,7-dimethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**11g**).

6-Benzoyl-3-ethyl-2-methoxy-7-methyl-3,7-dihydro-4*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (**11h**).

6-Benzoyl-3-ethyl-2-(methylthio)-7-methyl-3,7-dihydro-4*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (**11i**).

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