Synthesis of Polynuclear Heterocycles. Part 4.[1] Imidazo[4,5-*g*][3,1]-benzoxazinones, Imidazo[4,5-*g*]quinazolinones, Imidazo[4,5-*g*]quinazolinediones, and Imidazo[4,5-*f*]indazolinones

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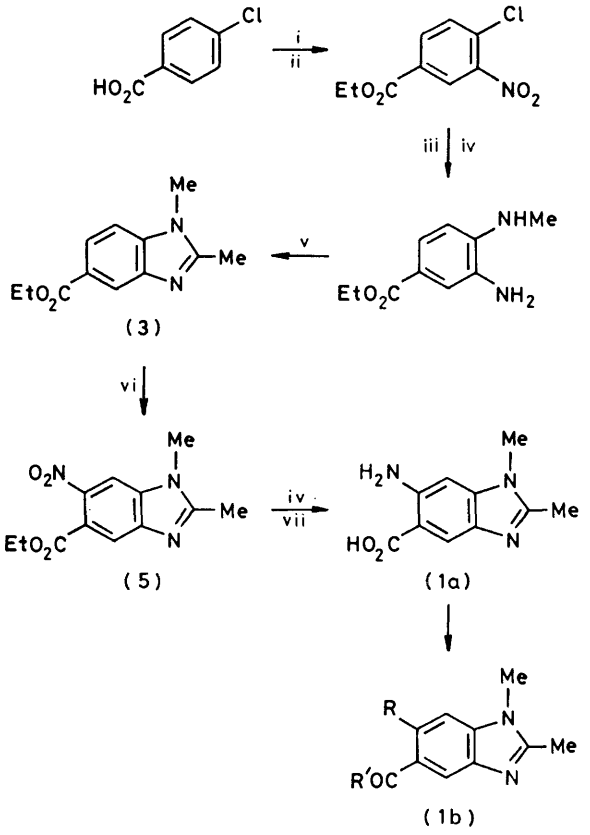
Several new, 1,2-disubstituted 6-aminobenzimidazole-5-carboxylic acids and their ethyl esters have been prepared. The amino-acids react with acyl halides in pyridine solution to give 7-arylimidazo[4,5-*g*][3,1]benzoxazin-5-ones, with urea or potassium cyanate to give imidazo[4,5-*g*]quinazoline-5,7-diones, and with formamide to give imidazo-[4,5-*g*]quinazolin-5-ones. 6-Amino- and 6-acylamino-imidazo[4,5-*g*]quinazolin-5-ones have been synthesised by reacting the acylated amino-esters with hydrazine, or by cyclising the derived amino-hydrazides with an acylating agent. Imidazo[4,5-*f*]indazolin-5-ones are obtained by the action of ethanolic hydrazine hydrate on 6-azido-5-ethoxycarbonylbenzimidazoles.

In continuation of our work [1,2] on the synthesis of ring systems fused linearly or 5,6 to the benzimidazole nucleus we now report on the preparation of the hitherto unknown heterocyclic systems, imidazo[4,5-*g*][3,1]benzoxazin-5-ones (7) and (8a—d), imidazo[4,5-*f*]indazolin-5-ones (13) and (14a—d), imidazo[4,5-*g*]quinazolin-5,7-diones (11) and (12), and of several examples (9) and

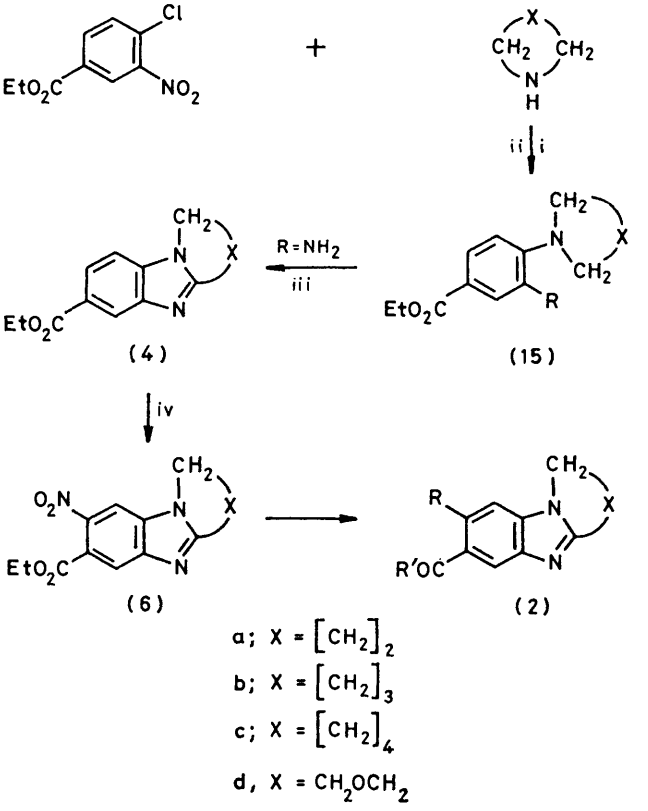


Scheme 1 Reagents: i, HNO_3 (*d* 1.5); ii, EtOH–H_2SO_4; iii, $MeNH_2$–EtOH; iv, Raney Ni–H_2; v, Ac_2O; vi, H_2SO_4–HNO_3; vii, conc. HCl

(10) of the only recently reported [3a,b] imidazo[4,5-*g*]-quinazolin-5-one system.

† 6-Amino-5-ethoxycarbonylbenzimidazole dihydrochloride has been described recently.[3b]

Obvious precursors for the synthesis of these heterocycles are the 6-aminobenzimidazole-5-carboxylic acids



Scheme 2 Reagents: i, EtOH; ii, Raney Ni–H_2; iii, HCO_2H–H_2O_2; iv, as from corresponding stage in Scheme 1

(1a) and (2; R = NH_2 R′ = OH). Surprisingly, however, no examples of aminobenzimidazolecarboxylic acids, in which both the amine and carboxy groups are located on the carbocyclic ring of the benzimidazole nucleus, could be found in the literature.† Likely intermediates for the synthesis of the required amino-acids are the equally unknown benzimidazole-5-carboxylic acids, or more usefully their ethyl esters (3) and (4a—d) (prepared as indicated in Schemes 1 and 2), providing that nitration can be effected at the 6-position.

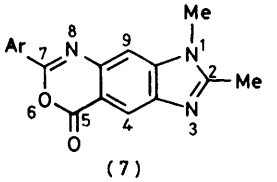
In a recent review[4] it has been pointed out that relatively little is known concerning the directing influence of substituents on the benzimidazole nucleus towards incoming electrophiles. In fact, no examples of the nitration of benzimidazole-5-carboxylic acids or their derivatives could be found other than an early report by Pinnow and Samaan[5] that 2-oxobenzimidazole-5-carboxylic acid with cold mixed acids, or with boiling concentrated nitric acid, undergoes dinitration accompanied by decarboxylation to give 4,6-dinitrobenzimidazolone. However, on the basis of the known behaviour[6,7] towards electrophilic substitution of benzimidazoles bearing electron-withdrawing substituents at the 5(6)-position, it was expected that nitration would proceed mainly at the 6(5)-position and possibly at the 4(7)-position. In the event esters, (3) and (4a—d), on treatment with a mixture of concentrated sulphuric acid and fuming nitric acid at room temperature, gave the nitro-esters (5) and (6a—d), respectively, in high yields (70%). In each instance the product was confirmed as the 6-nitro-isomer by its ^{1}H n.m.r. spectrum, which not only showed *para*-coupled aromatic protons (4- and 7-H), but also demonstrated the absence of any 4-nitro isomer. Subsequent hydrolysis and catalytic reduction of the nitro-esters gave the required amino-acids (1a) and (2; R = NH_2, R′ = OH).

We have shown[8] that the reaction of anthranilic acids with acyl halides in pyridine solution is a general method of preparing 3,1-benzoxazin-4-ones. Application of this reaction to the aminobenzimidazole-5-carboxylic acids (1a) and (2; R = NH_2, R′ = OH) using benzoyl chloride as the acyl halide, led to high yields (60—90%) of the imidazo[4,5-*g*][3,1]benzoxazin-5-ones (7 and 8a—d; Ar = Ph). Similarly, *o*-nitro- and *p*-chloro-benzoyl chloride yield the *o*-nitrophenyl and *p*-chlorophenyl derivatives (7 and 8a—d; Ar = *o*-$NO_2C_6H_4$ and *p*-ClC_6H_4), respectively.

Several methods[9] are available for the conversion of *o*-aminobenzoic acids to quinazolin-4-ones the most practicable of which involves heating the amino-acid with formamide,[10] or better, with a mixture of formamide and ammonium acetate.[11] Such treatment of the aminobenzimidazolecarboxylic acids (1a) and (2b; R = NH_2, R′ = OH) gave the desired imidazo[4,5-*g*]quinazolin-5-ones (9 and 10; R = R′ = H). The yields were good (60—70%) in the presence of ammonium acetate and poor (20%) in its absence. In a similar manner the amino-esters (1b and 2b; R = NH_2, R′ = OEt) cyclised to the same imidazo[4,5-*g*]quinazolin-5-ones readily and in excellent yields (80—90%) with formamide and ammonium acetate and only slowly and in poor yield with formamide alone. These methods complement the recently reported syntheses[3a,b] of imidazo[4,5-*g*]quinazolines.

Imidazo[4,5-*g*]quinazoline-5,7-diones (11) and (12) were obtained by heating the amino-acids (1a) and (2b; R = NH_2, R′ = OH) or their ethyl esters with an aqueous ethanolic solution of urea.[12] Alternatively, the imidazoquinoline-5,7-diones were obtained by reacting the amino-acids or their ethyl esters with potassium cyanate and then cyclising the resulting ureas (1b and 2b; R = $NHCONH_2$, R′ = OH or OEt) with hot dilute hydrochloric acid.[12]

A useful route to the pharmacologically important[13] 3-aminoquinazolin-4-one system involves treating *o*-acylaminobenzoates with hydrazine.[14] Alternatively,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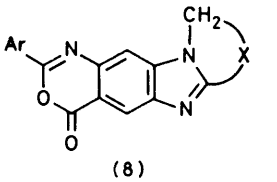
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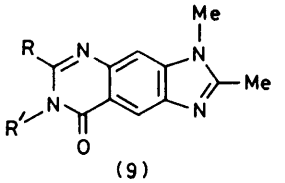
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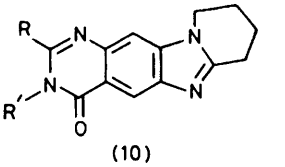
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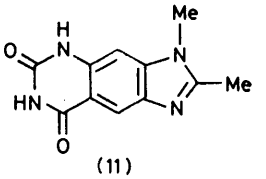
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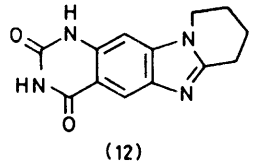
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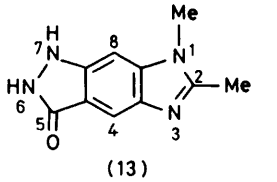
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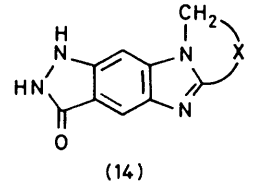
(14)

a; X = $[CH_2]_2$

b; X = $[CH_2]_3$

c; X = $[CH_2]_4$

d; X = CH_2OCH_2

the corresponding *o*-aminobenzohydrazides may be cyclised using an acylating agent. Both these methods have been employed successfully for the synthesis of 6-amino- and 6-acylamino-imidazo[4,5-*g*]-quinazolin-5-ones. For example, the formyl and acetyl derivatives (1b and 2b; R = NHCHO and NHAc, R′ = OEt) of the amino-esters (1b and 2b; R = NH_2, R′ = OEt) when heated under reflux with ethanolic hydrazine hydrate gave the 6-aminoimidazo[4,5-*g*]-quinazolin-5-ones (9 and 10; R = H and Me, R′ = NH_2) in good yield. The amino-hydrazides (1b and 2b; R = NH_2, R′ = $NHNH_2$) obtained by heating the amino-esters with ethanolic hydrazine, with hot 98% formic acid, or with boiling acetic anhydride also cyclised to give 6-aminoimidazo[4,5-*g*]quinazolin-5-ones, this time as the acyl derivatives (9 and 10; R = H, R′ = NHCHO and R = Me, R′ = NHAc) which were

identical to the products obtained by heating the 6-aminoimidazo[4,5-*g*]quinazolinones (9 and 10; R = H and Me, R′ = NH_2) with formic acid and acetic anhydride respectively.

The formation of indazoles and indazolinones by the action of ethanolic hydrazine hydrate on *o*-azidoketones and -esters has recently been reported.[15] We have also observed this intriguing reaction [16] and subsequently have suggested a mechanistic rationale to explain indazolinone formation.[17] The process is general and can be used to synthesise substituted indazolinones from the appropriately nuclear-substituted *o*-azidobenzoates.[18] As a further demonstration of the synthetic utility of this simple cyclisation we have reacted the 6-azidobenzimidazole esters (1b and 2a—d; R = N_3, R′ = OEt) with an excess of hydrazine hydrate in boiling ethanol. As expected cyclisation occurred and the new heterocyclic systems (13) and (14a—d), based on the imidazo[4,5-*f*]indazolin-5-one nucleus, were obtained in good yield (50—65%). The products, however, were difficult to purify and satisfactory analysis samples were obtained only after repeated vacuum sublimation.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured for solutions in deuteriochloroform unless otherwise stated, with a Varian A60A instrument (tetramethylsilane as internal standard). I.r. spectra were measured for Nujol mulls with a Perkin-Elmer 227 spectrophotometer; u.v. spectra were measured for 10^{-5}M solutions in chloroform with a Unicam SP 800 instrument.

5-Ethoxycarbonyl-1,2-dimethylbenzimidazole (3).—4-Chloro-3-nitrobenzoic acid, m.p. 180°,[19] obtained (82% yield) by nitration of 4-chlorobenzoic acid, was esterified using an excess of ethanol, and concentrated sulphuric acid as catalyst. The ethyl ester, m.p. 60° (lit.,[20] 59°), was condensed with ethanolic methylamine at room temperature to give ethyl 4-methylamino-3-nitrobenzoate, m.p. 101° (lit.,[21] 102°), which on reduction with Raney nickel and hydrogen gave the 3-amino-derivative, which was not isolated but was converted directly to 5-ethoxycarbonyl-1,2-dimethylbenzimidazole by heating under reflux with an excess of acetic anhydride (120 ml) for 12 h. The mixture was poured into water (150 ml), boiled, and when cool, basified by addition of solid sodium carbonate. The *ester* (3) was obtained as a buff precipitate which crystallised from light petroleum (b.p. 100—120°) as plates, m.p. 133° (Found: C, 66.4; H, 6.55; N, 12.75. $C_{12}H_{14}N_2O_2$ requires C, 66.05; H, 6.45; N, 12.8%); ν(C=O) 1 700 cm^{-1}; δ 1.45 (3 H, t, CH_3), 4.45 (2 H, q, CH_2), 2.7 (3 H, s, CMe), 3.85 (3 H, s, NMe), 7.3 (1 H, d, J_p 1 Hz 7-H), 8.05 (d) and 8.12 (d) (1 H, J_o 8, J_m 1.5 Hz, 6-H), and 8.45 (1 H, d, J_m 1.5 Hz, 4-H).

Preparation of Benzimidazole Esters (4a—d). *General Method.*—(a) *Ethyl 3-nitro-4-piperidinobenzoate* (15a; R = NO_2). To a stirred solution of piperidine (18 g) in benzene (100 ml) was added dropwise over 30 min a solution of ethyl 3-nitro-4-chlorobenzoate (23 g) in benzene (100 ml). The mixture was stirred at room temperature for 24 h and then filtered to remove the precipitated piperidine hydrochloride. The filtrate was extracted with water (3 × 50 ml), dried ($MgSO_4$), and then evaporated to dryness to yield ethyl 3-nitro-4-piperidinobenzoate as a viscous, orange oil. For details of this ester and similar compounds see Table 1.

Reduction of the nitro-amino esters (15a—d) was accomplished smoothly and in good yield using Raney nickel and hydrogen in a Baskerville stainless steel autoclave at room temperature and 50 atm. hydrogen gas pressure. Some of the amino-esters were obtained as dark oils which were cyclised without further purification. For details see Table 1.

(b) *Cyclisation of amino-esters* (15a—d; R = NH_2). *General method.*[22] To a solution of the amino-ester (5 g) in formic acid (98%; 30 ml) was added hydrogen peroxide (30%; 15 ml) and the mixture was warmed on a water-bath at 100°. After the vigorous exothermic reaction had subsided (*ca.* 10 min) the solution was heated at 100° for a further 20 min and then poured into cold water (50 ml). The aqueous solution was made basic with solid sodium carbonate whereupon the benzimidazole ester precipitated from the solution. For details of esters prepared by this method see Table 2.

TABLE 1

Nitro-esters (15; R = NO_2) and amino-esters (15; R = NH_2)

		M.p.	Yield	Found (%)				Required (%)		
R	X	(B.p.) (°C)	(%)	C	H	N	Formula	C	H	N
NO_2	$[CH_2]_2$ [a]	80°	95	59.6	6.2	10.7	$C_{13}H_{16}N_2O_4$	59.1	6.1	10.6
NO_2	$[CH_2]_3$ [b]	(198 at 3 Torr)	92							
NO_2	$[CH_2]_4$ [c]	94	80	61.8	6.75	9.35	$C_{15}H_{20}N_2O_4$	61.6	6.9	9.6
NO_2	CH_2OCH_2 [c]	57	88	55.65	5.85	10.0	$C_{13}H_{16}N_2O_5$	55.7	5.75	10.0
NH_2	$[CH_2]_3$ [d]	84	92	68.2	8.0	11.1	$C_{14}H_{20}N_2O_2$	67.7	8.1	11.3
NH_2	CH_2OCH_2 [e]	144	88	62.0	7.0	11.0	$C_{13}H_{18}N_2O_3$	62.4	7.25	11.2

[a] Crystallised from light petroleum (b.p. 40—60°) as yellow needles. [b] R. J. W. Le Fèvre and E. E. Turner, *J. Chem. Soc.*, 1927, 1113. [c] Crystallised from light petroleum (b.p. 60—80°) as yellow needles. [d] Crystallised from light petroleum (b.p. 40—60°) as needles. [e] Crystallised from light petroleum (b.p. 100—120°) as prisms.

Nitration of 5-Ethoxycarbonylbenzimidazoles. General Method.— *5-Ethoxycarbonyl-1,2-dimethyl-6-nitrobenzimidazole* (5). To a cold, stirred solution of 5-ethoxycarbonyl-1,2-dimethylbenzimidazole (5 g) in concentrated sulphuric acid (25 ml) was added dropwise over 10 min, fuming nitric acid (*d* 1.5; 50 ml). The nitration mixture was allowed to stir at room temperature for 1 h and was then poured into crushed ice (100 g). The resulting slurry was made alkaline by the addition of ammonia solution (15%) and the nitro-ester collected by filtration. *5-Ethoxycarbonyl-1,2-dimethyl-6-nitrobenzimidazole* (4.2 g, 70%) crystallised from ethanol as pale yellow needles, m.p. 165° (Found: C, 54.7; H, 4.6; N, 15.7. $C_{12}H_{13}N_3O_4$ requires C, 54.75; H, 5.0; N, 15.95%); ν(C=O) 1 730 cm^{-1}; δ 1.38 (3 H, t, Me), 4.45—4.8 (2 H, q, CH_2), 2.67 (3 H, s, CMe), 3.83 (3 H, s, NMe), and 7.93br (2 H, s, ArH). In CF_3CO_2D solution the aromatic proton signals appear at δ 8.29 (1 H, s) and 8.6

(1 H, s). For details of other 5-ethoxycarbonyl-6-nitrobenzimidazoles see Table 2.

Hydrolysis of 5-Ethoxycarbonyl-6-nitrobenzimidazoles to 6-Nitrobenzimidazole-5-carboxylic Acids. General Method.—*1,2-Dimethyl-6-nitrobenzimidazole-5-carboxylic acid* (1b; R = NO_2, R^1 = OH). A solution of 5-ethoxycarbonyl-1,2-dimethyl-6-nitrobenzimidazole (10 g) in concentrated hydrochloric acid (100 ml) was heated under reflux for *ca.* 4 h. The mixture was cooled, diluted with water (50 ml), and the product collected by filtration. *1,2-Dimethyl-6-nitrobenzimidazole-5-carboxylic acid* (8 g, 90%) crystallised from aqueous ethanol as prisms, m.p. 345° (Found: C, 51.0; H, 3.9; N, 17.6. $C_{10}H_9N_3O_4$ requires C, 51.05; H, 3.85; N, 17.85%); ν(C=O) 1 700br cm^{-1}; δ([$^2H_6$]DMSO) 2.65 (3 H, s, CMe), 3.88 (3 H, s, NMe), and 8.0 (1 H, s) and 8.41 (1 H, s) (ArH). For details of other 6-nitrobenzimidazole-5-carboxylic acids see Table 2.

amino-acids were therefore converted directly to the oxazinones as outlined below.

Preparation of Imidazo[4,5-g][3,1]*benzoxazin-4-ones. General Method.*—*1,2-Dimethyl-7-phenylimidazo*[4,5-g][3,1]*benzoxazin-5-one* (7; Ar = Ph). To a solution of 6-amino-1,2-dimethylbenzimidazole-5-carboxylic acid (1 g) in pyridine (10 ml) was added benzoyl chloride (1.2 g). The mixture was shaken for 5 min, then set aside for a further 25 min. The pyridine solution was then poured into cold water (50 ml) and the resulting precipitate filtered off and dried. *1,2-Dimethyl-7-phenylimidazo*[4,5-g][3,1]*benzoxazin-5-one* (0.9 g, 64%) crystallised from 2-ethoxyethanol as needles, m.p. 260—263° (Found: C, 69.2; H, 4.6; N, 14.25. $C_{17}H_{13}N_3O_2$ requires C, 70.1; H, 4.5; N, 14.4%); ν(C=O) 1 760 cm^{-1}; $\lambda_{max.}$ 273 (log ε 4.71), 317 (4.38), and 325 (4.36) nm; *m/e* 291 (M^+).

1,2-Dimethyl-7-(o-nitrophenyl)imidazo[4,5-g][3,1]*benzox-*

TABLE 2

Benzimidazole esters (4a—d), nitro-esters (6a—d), nitro-acids (2a—d; R = NO_2, R′ = OH), amino-esters (2a—d; R = NH_2, R′ = OEt), acylamino-esters (2b; R = NHacyl, R′ = OEt), and amino-hydrazide (2b; R = NH_2, R′ = $NHNH_2$)

Compound	R	R′	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
(4a) [a]			139°	62	67.7	6.2	11.9	$C_{13}H_{14}N_2O_2$	67.8	6.15	12.15
(6a) [b]			124	78	56.8	4.8	15.0	$C_{13}H_{13}N_3O_4$	56.7	4.75	15.25
(2a) [c]	NO_2	OH	302	89	53.5	3.7	16.5	$C_{11}H_9N_3O_4$	53.4	3.7	17.0
(2a) [d]	NH_2	OEt	257	73	63.4	6.2	17.1	$C_{13}H_{15}N_3O_2$	63.65	6.15	17.15
(4b) [a]			124	75	68.9	6.6	11.3	$C_{14}H_{16}N_2O_2$	68.85	6.6	11.45
(6b) [b]			114	80	58.6	5.0	14.5	$C_{14}H_{15}N_3O_4$	58.15	5.2	14.5
(2b) [c]	NO_2	OH	305	92	54.9	4.3	16.1	$C_{12}H_{11}N_3O_4$	55.15	4.25	16.1
(2b) [d]	NH_2	OEt	220	85	64.5	6.8	16.6	$C_{14}H_{17}N_3O_2$	64.85	6.6	16.2
(2b) [d]	NHCHO	OEt	190	80	62.8	6.1	14.1	$C_{15}H_{17}N_3O_3$	62.7	5.95	14.6
(2b) [d]	NHAc	OEt	248	85	63.7	6.5	14.0	$C_{16}H_{19}N_3O_3$	63.8	6.35	13.95
(2b) [e]	NH_2	$NHNH_2$	287	87	58.05	5.9	28.5	$C_{12}H_{15}N_5O$	58.75	6.15	28.55
(4c) [a]			108	58	69.7	7.0	10.5	$C_{15}H_{18}N_2O_2$	69.75	7.0	10.85
(6c) [b]			142	65	59.0	5.5	13.8	$C_{15}H_{17}N_3O_4$	59.35	5.65	13.85
(2c) [c]	NO_2	OH	306	88	56.6	4.8	15.5	$C_{13}H_{13}N_3O_4$	56.7	4.75	15.25
(2c) [d]	NH_2	OEt	170	82	65.65	6.9	15.3	$C_{15}H_{19}N_3O_2$	65.9	7.0	15.35
(4d) [a]			138	52	63.1	5.7	11.3	$C_{13}H_{14}N_2O_3$	63.4	5.75	11.4
(6d) [b]			134	67	53.4	4.6	14.3	$C_{13}H_{13}N_3O_5$	53.6	4.5	14.4
(2d) [c]	NO_2	OH	310	89	49.9	3.5	16.1	$C_{11}H_9N_3O_5$	50.2	3.45	15.95
(2d) [d]	NH_2	OEt	238	88	59.8	5.8	16.1	$C_{13}H_{15}N_3O_3$	59.75	5.8	16.1

[a] Crystallised from aqueous ethanol as prisms. [b] Crystallised from ethanol as pale yellow needles. [c] Crystallised from aqueous ethanol as prisms. [d] Crystallised from ethanol as prisms. [e] Crystallised from water as prisms.

Preparation of 6-Amino-5-ethoxycarbonylbenzimidazoles and 6-Aminobenzimidazole-5-carboxylic Acids. General Method.— *6-Amino-5-ethoxycarbonyl-1,2-dimethylbenzimidazole* (1b; R = NH_2, R′ = OEt). A solution (in the case of the nitro-acids, a suspension) of 5-ethoxycarbonyl-1,2-dimethyl-6-nitrobenzimidazole (10 g) in ethanol (200—400 ml) was reduced using Raney nickel and hydrogen (50 atm) in a Baskerville stainless steel autoclave at room temperature for 12 h. After removal of the nickel catalyst by filtering the mixture through a bed of anhydrous $MgSO_4$, the excess of solvent was removed to give *6-amino-5-ethoxycarbonyl-1,2-dimethylbenzimidazole* as a brown solid (75%) which crystallised from ethanol as prisms, m.p. 224° (Found: C, 61.5; H, 6.5; N, 18.1. $C_{12}H_{15}N_3O_2$ requires C, 61.8; H, 6.5; N, 18.0%); ν(NH_2) 3 460 and 3 300 cm^{-1}, ν(C=O) 1 700 cm^{-1}; δ 1.2—1.4 (3 H, t, Me), 2.45 (3 H, s, CMe), 3.5 (3 H, s, NMe), 4.1—4.5 (2 H, q, CH_2), 5.3—5.6 (2 H, NH_2), and 6.3 (1 H, s) and 8.15 (1 H, s) (ArH); *m/e* 233 (M^+). For details of other 6-amino-5-ethoxycarbonylbenzimidazoles see Table 2.

The 6-aminobenzimidazole-5-carboxylic acids were obtained as grey-green solids of indistinct m.p. (*ca.* 300°) and good elemental analyses were not obtained. The

azin-5-one (7; Ar = *o*-$NO_2C_6H_4$) obtained (80%) as above using *o*-nitrobenzoyl chloride, crystallised from 2-ethoxyethanol as pale yellow plates, m.p. 280° (Found: C, 60.4; H, 3.95; N, 16.3. $C_{17}H_{12}N_4O_4$ requires C, 60.7; H, 3.6; N, 16.65%); ν(C=O) 1 750 cm^{-1}. Similarly *7-(p-chlorophenyl)-1,2-dimethylimidazo*[4,5-g][3,1]*benzoxazin-5-one* (7; Ar = *p*-ClC_6H_4) was prepared (72%) using *p*-chlorobenzoyl chloride and crystallised from 2-ethoxyethanol as needles, m.p. 314° (Found: C, 62.4; H, 3.85; N, 12.85. $C_{17}H_{12}ClN_3O_2$ requires C, 62.7; H, 3.7; N, 12.9%); ν(C=O) 1 755 cm^{-1}. Details of other aryl-substituted imidazo[4,5-*g*][3,1]benzoxazin-5-ones are given in Table 3.

Preparation of Imidazo[4,5-g]*quinazolin-5-ones* (9) *and* (10).—*Method A.* A mixture of the 6-aminobenzimidazole-5-carboxylic acid (1 g) in water (10 ml) was heated under reflux with formamide (25 ml) for 12 h. On cooling the mixture the imidazo[4,5-*g*]quinazolin-5-one precipitated (yields *ca.* 20%) and was purified by crystallisation from dimethylformamide.

Method B. The 6-amino-5-ethoxycarbonylbenzimidazole (2 g) in ethanol (15 ml) solution was heated under reflux with formamide (40 ml) for 24 h. On cooling the mixture

the product, identical to that obtained by method A, crystallised out in yields of 20—25%.

Method C. A solution of the amino-ester (2.5 g) in ethanol (250 ml) was heated under reflux with formamide (50 ml) and a solution of ammonium acetate (3 g) in water (50 ml) for 24 h. The imidazo[4,5-*g*]quinazolinone crystallised from the cold reaction mixture in good yield (60%), and was purified as in method A.

from ethanol, m.p. 165° (Found: C, 59.2; H, 6.0; N, 15.3. $C_{13}H_{15}N_3O_3$ requires C, 59.75; H, 5.8; N, 16.1%). Details of other acyl derivatives are given in Table 2.

Preparation of 6-*Aminoimidazo*[4,5-g]*quinazolin-5-ones* (9 *and* 10; R = H and Me, R′ = NH_2). *General Method.*—A solution of the 6-acylamino-5-ethoxycarbonylbenzimidazole (1 g) in propan-2-ol (25 ml) and hydrazine hydrate (10 ml) was heated under reflux for 12 h. On cooling, the

TABLE 3

Aryl-substituted imidazo[4,5-*g*][3,1]benzoxazin-5-ones (8a—d)

Compound	Ar	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
(8a)	C_6H_5 [a]	310	58	71.3	4.5	13.9	$C_{18}H_{13}N_3O_2$	71.25	4.3	13.85
(8b)	C_6H_5 [b]	305	80	71.9	4.8	13.4	$C_{19}H_{15}N_3O_2$	71.9	4.75	13.25
(8b)	o-$NO_2C_6H_4$ [c]	280	62	62.8	4.1	15.3	$C_{19}H_{14}N_4O_4$	63.0	3.9	15.45
(8c)	C_6H_5 [d]	240	65	72.3	5.2	12.8	$C_{20}H_{17}N_3O_2$	72.5	5.15	12.7
(8c)	o-$NO_2C_6H_4$ [c]	228	80	63.3	4.5	14.5	$C_{20}H_{16}N_4O_4$	63.8	4.3	14.9
(8d)	C_6H_5 [e]	290	55	68.1	4.3	13.2	$C_{18}H_{13}N_3O_3$	67.7	4.1	13.15
(8d)	o-$NO_2C_6H_4$ [c]	285	45	59.4	3.4	15.5	$C_{18}H_{12}N_4O_5$	59.35	3.3	15.4

[a] Crystallised from 2-ethoxyethanol as needles; ν(C=O) 1 750 cm^{-1}; $\lambda_{max.}$ 273.5 (log ε 4.71), 318 (4.33), and 325 (4.30) nm. [b] Crystallised from 2-ethoxyethanol as needles; ν(C=O) 1 745 cm^{-1}; $\lambda_{max.}$ 273.5 (log ε 4.70), 318 (4.32), and 326 (4.30) nm. [c] Crystallised from 2-ethoxyethanol as pale yellow prisms. [d] Crystallised from 2-ethoxyethanol as needles; ν(C=O) 1 750 cm^{-1}; $\lambda_{max.}$ 275 (log ε 4.70), 318 (4.35), and 326 (4.34) nm. [e] Crystallised from 2-ethoxyethanol as needles; ν(C=O) 1 740 cm^{-1}; $\lambda_{max.}$ 272 (log ε 4.83), 317 (4.09), and 322 (4.08) nm.

1,2-*Dimethylimidazo*[4,5-g]*quinazolin-5-one* (9; R = R′ = H) crystallised as needles, m.p. >360° (Found: C, 61.0; H, 4.7; N, 26.1. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.15%); δ(CF_3CO_2D) 3.18—3.27 (3 H, s, CMe), 4.26—4.29 (3 H, s, NMe), 8.3 (1 H, s) and 9.2 (1 H, s) (ArH), and 9.7 (1 H, s, 7-H); *m/e* 203 (M^+).

Imidazo[4,5-g]*quinazolin-5-one* (10; R = R′ = H) crystallised as needles, m.p. >360° (Found: C, 65.3; H, 5.2; N, 23.0. $C_{13}H_{12}N_4O$ requires C, 65.0; H, 5.0; N, 23.3%); δ(CF_3CO_2D) 2.2—2.6 (4 H, m), 3.4—3.7 (2 H, m) and 4.4—4.8 (2 H, m) (piperidine ring), 8.62 (1 H, s) and 9.15 (1 H, s) (ArH), and 9.55 (1 H, s, quinazoline ring).

Acylation of 6-*Amino-5-ethoxycarbonylbenzimidazoles* (1b *and* 2b; R = NH_2, R′ = OEt).—The amino-esters were acetylated and formylated by standard procedures using acetic anhydride and 98% formic acid respectively. 5-*Ethoxycarbonyl-6-formamido-1,2-dimethylbenzimidazole* (1b; R = NHCHO, R′ = OEt) was obtained as prisms (76%) mixture deposited the aminoimidazo[4,5-*g*]quinazolinone as a white solid which crystallised from propan-2-ol as needles. For details of the 6-aminoimidazo[4,5-*g*]quinazolin-5-ones so prepared see Table 4.

Preparation of 6-*Aminobenzimidazole-5-carbohydrazide.* (1b; R = NH_2, R′ = $NHNH_2$). *General Method.*—A solution of the 6-amino-1,2-dimethyl-5-ethocycarbonylbenzimidazole (2 g) in ethanol (10 ml) and hydrazine hydrate (10 ml) was heated under reflux for 12 h. On cooling the solution the *hydrazide* precipitated, and was purified by crystallisation from water (82%), m.p. 275° (Found: C, 54.6; H, 5.7; N, 31.6. $C_{10}H_{13}N_5O$ requires C, 54.8; H, 5.95; N, 31.95%). For other hydrazides see Table 2.

Preparation of 6-*Acylaminoimidazo*[4,5-g]*quinazolin-5-ones* (9 *and* 10; R = H *and* Me, R′ = NHCHO *and* NHAc).—The 6-aminobenzimidazole 5-carbohydrazide (2 g) was heated under reflux in acetic anhydride (25 ml) for 12 h. The mixture was diluted with water (25 ml), cooled, and

TABLE 4

6-Amino- and 6-acylamino-imidazo[4,5-*g*]quinazolin-5-ones (9) and (10)

Compound	R	R′	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
(9)	H	NH_2 [a]	290 *	72	50.7	5.5	26.8	$C_{11}H_{15}N_5O_3$	49.8	5.66	26.4
(9)	H	NHCHO [b]	262	76	56.3	4.4	26.9	$C_{12}H_{11}N_5O_2$	56.0	4.3	27.2
(9)	Me	NH_2 [c]	284	80	59.05	5.4	28.1	$C_{12}H_{13}N_5O$	59.2	5.4	28.8
(9)	Me	NHAc [d]	292	84	59.2	5.0	23.9	$C_{14}H_{15}N_5O_2$	58.95	5.3	24.55
(10)	H	NH_2 [e]	310	75	60.95	5.3	27.5	$C_{13}H_{13}N_5O$	61.15	5.15	27.4
(10)	H	NHCHO [f]	272	81	59.0	5.0	24.1	$C_{14}H_{13}N_5O_2$	59.35	4.6	24.7
(10)	Me	NH_2 [g]	338	83	62.5	5.7	26.0	$C_{14}H_{15}N_5O$	62.45	5.6	26.0
(10)	Me	NHAc [h]	301	85	61.3	6.0	22.1	$C_{16}H_{17}N_5O_2$	61.7	5.5	22.5

* Satisfactory analysis not obtained; compound may be a dihydrate.

[a] δ(CF_3CO_2D) 3.17 (3 H, s, CMe), 4.25 (3 H, s, NMe), 8.55 (1 H, s) and 9.15 (1 H, s) (ArH), and 9.7 (1 H, s, quinazoline ring); *m/e* 229 (M^+). [b] δ(CF_3CO_2D) 2.8 (3 H, s, CMe), 3.2 (3 H, s, NMe), 8.65 (1 H, s) and 8.75 (1 H, s) (ArH), 9.1 (1 H, s, quinazoline ring), and 9.52 (1 H, s, CHO); *m/e* 285 (M^+). [c] δ(CF_3CO_2D) 3.15 (3 H, s, CMe), 3.25 (3 H, s, 7-Me), 4.23 (3 H, s, NMe), and 8.33 (1 H, s) and 9.05 (1 H, s) (ArH); *m/e* 243 (M^+). [d] δ(CF_3CO_2D) 2.7 (3 H, s, CMe), 3.05 (3 H, s, COMe), 3.18 (3 H, s, 7-Me), 4.25 (3 H, s, NMe), and 8.55 (1 H, s) and 9.2 (1 H, s) (ArH); *m/e* 305 (M^+). [e] δ(CF_3CO_2D) 2.2—2.6 (4 H, m), 3.4—3.7 (2 H, m) and 4.4—4.8 (2 H, m) (piperidine ring), 8.55 (1 H, s) and 9.15 (1 H, s) (ArH), and 9.75 (1 H, s, quinazoline ring); *m/e* 255 (M^+). [f] δ(CF_3CO_2D) 2.15—2.5 (4 H, m), 3.4—3.7 (2 H, m) and 4.5—4.8 (2 H, m) (piperidine ring), 8.65 (1 H, s) and 8.85 (1 H, s) (ArH), 9.1 (1 H, s, quinazoline ring), and 9.5 (1 H, s, CHO); *m/e* 283 (M^+). [g] δ(CF_3CO_2D) 2.0—2.7 (4 H, m), 3.3—3.7 (2 H, m) and 4.35—4.8 (2 H, m) (piperidine ring), 3.25 (3 H, s, CMe), and 8.32 (1 H, s) and 9.0 (1 H, s) (ArH); *m/e* 269 (M^+). [h] δ(CF_3CO_2D) 2.25—2.6 (4 H, m), 3.4—3.7 (2 H, m) and 4.5—4.8 (2 H, m) (piperidine ring), 2.75 (3 H, s, COMe), 3.08 (3 H, s, CMe), and 8.55 (1 H, s) and 9.1 (1 H, s) (ArH); *m/e* 311 (M^+).

then basified by addition of solid sodium carbonate. The crude *N*-acetyl derivatives (9 and 10; R = Me, R′ = NHAc) which precipitated were purified by crystallisation from a mixture of amyl alcohol and ethylene glycol.

In a similar manner the amino-hydrazides were cyclised to the *N*-formyl derivatives (9 and 10; R = H, R′ = NHCHO) with boiling 98% formic acid. The formyl derivatives crystallised from amyl alcohol. For details of these compounds see Table 4.

The acylamino-derivatives prepared as above were identical to those obtained by heating the 6-aminoimidazo-[4,5-*g*]quinazolin-5-ones (9 and 10; R = H and Me, R′ = NH_2) with acetic anhydride and 98% formic acid respectively. Yields of 90 and 80% respectively were obtained.

Preparation of Imidazo[4,5-g]*quinazoline-5,7-diones* (11) *and* (12).—*Method A*. To a suspension of the 6-aminobenzimidazole-5-carboxylic acid (1 g) in water (15 ml) was added a solution of urea (2 g) in water (15 ml). The mixture was heated under reflux for 12 h, then cooled to give the crude imidazo[4,5-*g*]quinazoline-5,7-dione in almost quantitative yield. The products were purified by crystallisation from ethylene glycol.

Method B. To a solution of the 6-amino-5-ethoxycarbonylbenzimidazole (2.5 g) in ethanol (30 ml) was added an aqueous solution of urea (6 g in 15 ml of water). The solution was then heated under reflux for 48 h and on cooling deposited a product (40—50%) identical to that obtained by Method A.

Method C. The aminobenzimidazole ester (2 g) dissolved in water (20 ml) containing a few drops of concentrated hydrochloric acid was stirred at room temperature with a solution of potassium cyanate (1 equiv.) in water (25 ml) for 12 h. Basification (Na_2CO_3) of the mixture, followed by chloroform extraction gave the 6-ureido-derivative in 90—95% yield, which was not purified but which was cyclised directly to the imidazo[4,5-*g*]quinazoline-5,7-dione by heating under reflux with dilute hydrochloric acid for 2 h. The products were identical to those obtained by Methods A and B.

1,2-*Dimethylimidazo*[4,5-g]*quinazoline-5,7-dione* (11) crystallised from ethylene glycol, m.p. >360° (Found: C, 57.3; H, 4.5; N, 24.1. $C_{11}H_{10}N_4O_2$ requires C, 57.4; H, 4.35; N, 24.35%); ν(C=O) 1 740 and 1 670 cm^{-1}, ν(NH) 3 180 cm^{-1}; δ(CF_3CO_2D) 3.2 (3 H, s, CMe), 4.25 (3 H, s, NMe), and 8.4 (1 H, s) and 9.15 (1 H, s) (ArH); *m/e* 230 (M^+).

Imidazo[4,5-g]*quinazoline-5,7-dione* (12) crystallised as prisms from ethylene glycol, m.p. >360° (Found: C, 60.0; H, 4.9; N, 21.4. $C_{13}H_{12}N_4O_2$ requires C, 60.95; H, 4.7; N, 21.85%); ν(C=O) 1 720 and 1 700 cm^{-1}, ν(NH) 3 220 cm^{-1}; δ(CF_3CO_2D) 2.2—2.6 (4 H, m), 3.3—3.6 (2 H, m) and 4.35—4.7 (2 H, m) (piperidine ring), and 7.85 (1 H, s) and 8.85 (1 H, s) (ArH); *m/e* 256 (M^+).

Preparation of 6-Azido-5-ethoxycarbonylbenzimidazoles. General Method.—*6-Azido-1,2-dimethyl-5-ethoxycarbonylbenzimidazole*. (1b; R = N_3, R′ = OEt). A solution of 6-amino-1,2-dimethyl-5-ethoxycarbonylbenzimidazole (2.6 g) in 4M-hydrochloric acid (60 ml) was diazotised at 0° using sodium nitrite (1.3 g) in water (10 ml). The diazonium chloride solution was stirred at 0° for 15 min after the addition of sodium nitrite and then filtered. The filtrate was added dropwise over 15 min to a solution of sodium azide (4 g) and sodium acetate (60 g) in water (200 ml). Filtration of the reaction mixture gave *6-azido-5-ethoxy carbonyl-1,2-dimethylbenzimidazole* (2.3 g, 90%), which crystallised from diethyl ether, m.p. 91° (decomp. 136°); ν(N_3) 2 115 cm^{-1}, ν(C=O) 1 700 cm^{-1}; δ 1.2—1.6 (3 H, t, Me), 2.6 (3 H, s, CMe), 3.7 (3 H, s, NMe), 4.2—4.5 (2 H, q, CH_2), and 6.9 (1 H, s) and 8.1 (1 H, s) (ArH); *m/e* 259 (M^+).

The azido-esters were purified by chromatography

TABLE 5

Imidazo[4,5-*f*]indazolin-5-ones (14a—d)

Compound	M.p. °C	Yield %	Found (%) C	H	N	Formula	Required (%) C	H	N
(14a) [a]	335	38				$C_{11}H_{10}N_4O$	61.7	4.7	26.15
(14b) [b]	360	40	63.4	5.4	24.0	$C_{12}H_{12}N_4O$	63.15	5.3	24.55
(14c) [c]	350	55	63.9	6.1	22.6	$C_{13}H_{14}N_4O$	64.45	5.8	23.1
(14d) [d]	360	50	56.45	4.4	23.9	$C_{11}H_{10}N_4O_2$	57.4	4.4	24.3

[a] Satisfactory analysis could not be obtained even after repeated vacuum sublimation at 265° (0.03 Torr); ν(C=O) 1 645br cm^{-1}; δ(CF_3CO_2D) 3.1—3.4 (2 H, s), 3.7—3.9 (2 H, s) and 4.8 (2 H, s) (pyrrolidine ring), and 7.9 (1 H, s) and 8.6 (1 H, s, ArH); *m/e* 214 (M^+). [b] Sublimed at 270° (0.01 Torr); ν(C=O) 1 640br cm^{-1}; δ(CF_3CO_2D) 2.5br (4 H, s), 3.55br (2 H, s), and 4.6br (2 H, s) (piperidine ring) and 7.9 (1 H, s) and 8.6 (1 H, s) (ArH); *m/e* 228 (M^+). [c] Sublimed at 285° (0.02 Torr); ν(C=O) 1 640br cm^{-1}; δ (CF_3CO_2D) 2.3 (6 H, m), 3.6br (2 H, s), and 4.7br (2 H, s) (perhydroazepine ring) and 7.9 (1 H, s) and 8.6 (1 H, s) (ArH); *m/e* 242 (M^+). [d] Sublimed at 260° (0.02 Torr); ν(C=O) 1 650br cm^{-1}; δ(CF_3CO_2D) 4.5br (4 H, s) and 5.4br (2 H, s) (morpholine ring) and 7.9 (1 H, s) and 8.6 (1 H, s) (ArH); *m/e* 230 (M^+).

(Et_2O–Al_2O_3) and were characterised by i.r., ^1H n.m.r., and mass spectroscopy, details of which are given in Supplementary Publication No. SUP 22411 (3 pp.).*

Preparation of Imidazo[4,5-f]*indazolin-5-ones* (13) *and* (14a—d). *General Method.*—*1,2-Dimethylimidazo*[4,5-f]*indazolin-5-one* (13). A solution of 6-azido-1,2-dimethyl-5-ethoxycarbonylbenzimidazole (2 g) and hydrazine hydrate (5 mol equiv.) in ethanol (15 ml) was heated under reflux for 5 h. On cooling, the solution deposited the product as a yellow solid, which was washed with ethanol and purified by sublimation (190° and 0.05 Torr). 1,2-*Dimethylimidazo*-[4,5-f]*indazolin-5-one* (0.7 g, 42%) was obtained as pale yellow crystals, m.p. 348° (decomp.) (Found: C, 59.3; H, 5.07; N, 26.95. $C_{10}H_{10}N_4O_2$ requires C, 59.4; H, 5.0; N, 27.7%); ν(C=O) 1 640br cm^{-1}; δ(CF_3CO_2D) 3.3 (3 H, s, CMe), 4.3 (3 H, s, NMe), and 8.0 (1 H, s) and 8.6 (1 H, s) (ArH); *m/e* 202 (M^+). Details of other imidazo[4,5-*f*]-indazolinones are given in Table 5.

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

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