Amidinoacetamides in the Synthesis of Pyrazines and Pteridines

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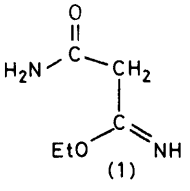
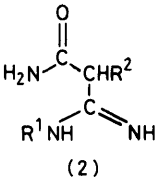
2-(Substituted amidino)-2-aminoacetamides were cyclised with 1,2-dicarbonyl reagents to 3-(substituted amino)-pyrazine-2-carboxamides which were converted, where possible, into the corresponding 1-substituted pteridin-4(1*H*)-ones and 1-substituted pteridine-2,4(1*H*)-diones.

THE preparation of pyrazine intermediates, suitable for conversion into pteridines, has received considerable attention in recent years.[1,2] In a previous paper [3] it was noted that 2-amidino-2-aminoacetamide (2g) constitutes a large part of the skeletal backbones of pyrimidines, imidazoles, and purines. This acetamide derivative also constitutes a part of the skeletal framework of pyrazines and pteridines, and this fact has already been utilised [1] in the synthesis of 3-aminopyrazine-2-carboxamide (3a) and a number of derivatives by the condensation of 2-amidino-2-aminoacetamide dihydrochloride with 1,2-dicarbonyl reagents in aqueous ammonia. We have extended this method by treating 2-(substituted amidino)-2-aminoacetamide monohydrochlorides with symmetrical 1,2-dicarbonyl reagents in suitable basic conditions to provide 3-(substituted amino)pyrazine-2-carboxamides. Benzyl, cyclohexyl, and 2-hydroxyethyl groups were used as substituents and the pyrazine intermediates were converted, where possible, into the corresponding pteridinones and lumazines.

The 2-alkylamidinoacetamide (2a—c) hydrochlorides



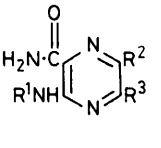
(1)



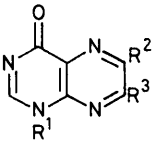
(2)

	R^1	R^2
a;	$PhCH_2$	H
b;	C_6H_{11}	H
c;	$HO[CH_2]_2$	H
d;	$PhCH_2$	PhN_2
e;	C_6H_{11}	PhN_2
f;	$HO[CH_2]_2$	PhN_2
g;	H	NH_2
h;	$PhCH_2$	NH_2
i;	C_6H_{11}	NH_2
j;	$HO[CH_2]_2$	NH_2

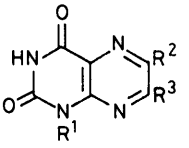
were prepared [3] from ethyl carbamoylacetimidate (1) hydrochloride, a modified preparation of which is described. Molecular-sieve dried solvents were found to be satisfactory and a reaction temperature of 5—10 instead of 0 °C gave a yield of 90.0% (*cf.* 57% [4]). The material could be stored under vacuum for at least 9 months without serious deterioration, and these facts increase the attraction of this substance as a starting material. The 2-alkylamidino-2-phenylazoacetamide (2d—f) hydrochlorides were prepared by vacuum evaporation of solutions of the appropriate phenylazo bases in aqueous methanolic hydrogen chloride.[3] A more direct route was by coupling the amidinoacetamide (2a—c) hydrochloride with benzenediazonium chloride and precipitating the phenylazo salt by adjusting the pH to 5.



(3)



(4)



(5)

	R^1	R^2	R^3
a;	H	H	H
b;	$PhCH_2$	H	H
c;	C_6H_{11}	H	H
d;	$PhCH_2$	Me	Me
e;	C_6H_{11}	Me	Me
f;	$PhCH_2$	$[CH_2]_4$	
g;	C_6H_{11}	$[CH_2]_4$	
h;	$PhCH_2$	Ph	Ph
i;	C_6H_{11}	Ph	Ph

The 2-amino-2-benzyl- (2h) and 2-amino-2-cyclohexyl-amidinoacetamide (2i) hydrochlorides were obtained by reduction of the phenylazo hydrochlorides with hydrogen over palladised charcoal at room temperature and pressure. The by-product, aniline, was removed by trituration of the vacuum-dried residues with ether. Unfortunately reduction of the 2-(2-hydroxyethyl-amidino)-2-phenylazoacetamide (2f) hydrochloride gave an unidentified red solid and failure to obtain the required intermediate prevented further investigation of the hydroxyethyl group as substituent. An alternative route is being investigated. Neutralisation of an aqueous solution of 2-amino-2-benzylamidinoacetamide (2h) hydrochloride and glyoxal hydrogen sulphite adduct with aqueous ammonia precipitated a pale yellow solid which fluoresced in u.v. light. This material was identical with 3-benzylaminopyrazine-2-carboxamide

[1] O. Vogl and E. C. Taylor, *J. Amer. Chem. Soc.*, 1959, **81**, 2472.

[2] G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocyclic. Chem.*, 1972, **14**, 99.

[3] W. F. Keir and H. C. S. Wood, *J.C.S. Perkin I*, 1976, 1847.

[4] E. Shaw, *J. Org. Chem.*, 1965, **30**, 3371.

(3b) prepared by the unambiguous reduction of 1-benzyl-3-hydroxy-1-pyrazolo[3,4-*b*]pyrazine with Raney nickel.[5] The other pyrazines prepared in this work had u.v., i.r., and n.m.r. spectra (Tables 1 and 2) similar to those of the pyrazine (3b) and were consequently assigned similar structures. Each n.m.r. spectrum showed one of the amide protons to be considerably deshielded, indicating hydrogen bonding with a ring nitrogen atom. The secondary amino-protons were distinguished from the amide protons by a much slower exchange with deuterium, and in the benzylamino

TABLE 1

U.v. spectra

Compound	$\lambda_{max.}$/nm †	log ε	pH	Solvent
(3b)	257, 368	4.13, 3.67	4.84	
	249, 360	4.22, 3.74	0.13	
(3c)	260, 376	4.19, 3.73	4.64	
	251, 360	4.22, 3.80	0.15	
(3d)	258, 380	4.26, 3.97	0.15 [a]	
(3e)	258, 386	4.12, 3.85	0.15 [a]	
(3f)	257, 380	4.21, 3.95	0.15 [a]	
(3g)	257, 384	4.25, 3.93	0.15 [a]	
(3h)	240, 290, 392	4.15, 4.33, 4.00		MeOH [b]
(3i)	241, 292, 398	4.09, 4.32, 3.96		MeOH [b]
(4b)	*260*, 324, *346*	*3.41*, 3.95, *3.57*	4.58	
	301, 307	*3.92*, 3.95	0.6	
(4c)	*238*, *260*, 326, *344*	*4.14*, *3.48*, 3.94, *3.68*	4.58	
	298, 306	*3.9*, 3.96	0.6	
(4d)	232, *268*, 323 *340*	4.35, *3.59*, 4.11 *3.95*	4.64	
	266, *302*, 309, *319*	3.65, 4.05, 4.09 *3.93*	0.16	
(4f)	230, 330, *345*	3.94, 4.10, *3.90*	4.64	
	265, *304*, 316	*3.70*, *3.96*, 4.06	0.15	
(4h)	255, 280, 369	4.10, 4.11, 4.15		MeOH [b]
(4i)	258, 280, 368	4.10, 4.11, 4.15		MeOH [b]
(5b)	241, *286*, 336	4.09, *3.44*, 3.75	9.57	
	232, 250, 328, *340*	4.01, 3.91, 3.91, *3.81*	4.64	
(5d)	244, *280*, 345	4.08, *3.45*, 3.87	9.60	
	232, 245, 337, *345*	4.10, 3.99, 3.95, *3.81*	4.64	
(5f)	244, *280*, 338	4.20, *3.45*, 3.80	9.57	
	236, 250, 330, *340*	4.00, 3.92, 3.93, *3.83*	4.64	
(5h)	285, 369	4.20, 4.02		MeOH [b]

[a] Solubility difficulties at higher pH values. [b] Solubility difficulties in aqueous solvents.

† Inflections in italics.

pyrazines this deuteriation was synchronous with collapse of the PhCH_2 doublet to a singlet.

In each preparation, paper chromatography showed the presence of only one fluorescent product. Thus the condensation of 2-amino-2-benzylamidinoacetamide (2h) hydrochloride with biacetyl and cyclohexane-1,2-dione in aqueous ammonia provided, respectively, the pyrazines (3d) and (3f). Similarly, the condensations of 2-amino-2-cyclohexylamidinoacetamide (2i) hydrochloride with glyoxal hydrogen sulphite adduct, biacetyl, and cyclohexane-1,2-dione yielded, respectively, the pyrazines (3c), (3e), and (3g). The insolubility in water and relative unreactivity of benzil prevented the use of aqueous ammonia as neutralising agent in the preparation of diphenylpyrazines (3h—i). The addition of sodium acetate, however, to a methanolic solution or suspension of the hydrochloride and benzil gave, after 48 h, a precipitate of the diphenylpyrazine, but the yield in each case was relatively poor. Dimethyl- (3d), tetrahydrobenzo- (3f), and diphenyl-benzylaminopyrazine (3h) were converted into the pteridin-4(1*H*)-ones (4d), (4f), and (4h), respectively, by heating under reflux in formic acid–acetic anhydride for 1.5—2 h. Reaction progress was followed by u.v. and t.l.c.; longer periods resulted in lower yields. Conversion of the unsubstituted benzylaminopyrazine (3b) was incomplete with the above reagent, acetic formic anhydride,[6] triethyl orthoformate–acetic anhydride, and diethoxymethyl acetate were equally ineffective. Heating for 1 h, however, with diethoxy-*NN*-dimethylformamide gave a satisfactory conversion into 1-benzylpteridin-4(1*H*)-one (4b). These results appeared to reflect the activating effect of the substituent groups in the pyrazine nucleus overcoming the secondary amino group's reduced reactivity towards formylation, due to the large size of the benzyl group. The cyclohexylaminopyrazines were, as expected, even more unreactive towards formylation, but diethoxy-*NN*-dimethylformamide converted unsubstituted (3c) and diphenyl-cyclohexylaminopyrazine (3i) into the pteridinones (4c) and (4i), respectively. Unfortunately, this reagent caused decomposition of dimethyl- (3e) and tetrahydrobenzo-cyclohexylaminopyrazine (3g), and the other reagents gave incomplete conversions of these pyrazines.

The pyrazines showed a similar variation in reactivity towards ethoxycarbonylation. The unsubstituted benzylaminopyrazine (3b) required heating under reflux for 30 h with ethyl chloroformate for satisfactory conversion into the ethoxycarbonyl intermediate, whereas the dimethyl- (3d), tetrahydrobenzo- (3f), and diphenyl-benzylaminopyrazine (3h) required only 3—6 h. Boiling with aqueous sodium carbonate effected ring closure to the corresponding pteridine-2,4(1*H*)-diones. None of the cyclohexylaminopyrazines reacted appreciably with ethyl chloroformate itself and ethyl chloroformate–triethylamine and dioxan–ethyl chloroformate–sodium carbonate were no more successful.

EXPERIMENTAL

M.p.s were determined with an Electrothermal apparatus. U.v. spectra were determined with a Unicam SP 1800A spectrophotometer, i.r. spectra with a Perkin-Elmer 157G spectrophotometer (Nujol mulls), and n.m.r. spectra with a Perkin-Elmer R10 (100 MHz) spectrometer ($CDCl_3$ as solvent; Me_4Si as internal standard). Reaction mixtures were analysed by t.l.c. on Eastman Chromagram sheets and by paper chromatography on Whatman No. 1 paper (ascending technique). Spots were detected under u.v. light and the development system was butan-1-ol–5N-acetic acid (7 : 3).

Ethyl Carbamoylacetimidate (1) *Hydrochloride*.—A stirred suspension of cyanoacetamide (1 mol) in dioxan (640 ml), ether (100 ml), and ethanol (63 ml) [the solvents were stored

[5] E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Amer. Chem. Soc.*, 1958, **80**, 421.

[6] L. I. Krimen, *Org. Synth.*, 1970, **50**, 1.

TABLE 2

I.r. and ^{1}H n.m.r. spectra

	$\nu_{max.}$/cm^{-1}	τ
(3b)	3 460s, 3 290m, 3 200m, 3 130m, 1 695s, 1 585s, 1 530m, 1 510s	5.35 (2 H, d, *J* 7 Hz, C*H*$_2$Ph [a]), 4.2br and 2.3br, (2 H, CO·NH$_2$ [b]), 2.83 and 1.85 (2 H, ABq, *J* 2.5 Hz, H-5 and -6), 2.72 (5 H, m, Ph), 1.1br (1 H, NH [b])
(3c)	3 460s, 3 340w, 3 260m, 3 210m, 3 130m, 1 688s, 1 585s, 1 519s	8.4 (10 H, m, [CH$_2$]$_5$), 6.05 (1 H, m, CH), 4.0br and 2.3br (2 H, CONH$_2$ [b]), 2.4 and 1.85 (2 H, ABq, *J* 2.5 Hz, H-5 and H-6), 1.45br (1 H, NH [b])
(3d)	3 460s, 3 320m, 3 250m, 3 160m, 1 680s, 1 575s, 1 540w, 1 500s	7.65 (3 H, s, CH$_3$), 7.6 (3 H, s, CH$_3$), 5.3 (2 H, d, *J* 7 Hz, C*H*$_2$Ph [a]), 4.6br and 2.35br (2 H, CONH$_2$ [b]), 2.7 (5 H, m, Ph), 1.4br (1 H, NH [b])
(3e)	3 460m, 3 440m, 3 330m, 3 260m, 3 180m, 3 100m, 1 670s, 1 585s, 1 490s	8.4 (10 H, m, [CH$_2$]$_5$), 7.7 (3 H, s, CH$_3$), 7.6 (3 H, s, CH$_3$), 6.1 (1 H, m, CH), 4.05br, 2.35br (2 H, CONH$_2$ [b]), 1.8br (1 H, NH [b])
(3f)	3 470s, 3 320m, 3 250m, 3 170m, 1 680s, 1 575s, 1 540w, 1 500s	8.15 (4 H, m, CH$_2$[C*H*$_2$]$_2$CH$_2$), 7.35 (4 H, m, C*H*$_2$[CH$_2$]$_2$C*H*$_2$), 5.3 (2 H, d, *J* 7 Hz, C*H*$_2$Ph [a]), 4.4br and 2.3br (2 H, CONH$_2$ [b]), 1.4br (1 H, NH [b])
(3g)	3 450s, 3 320m, 3 260m, 3 180m, 3 100w, 1 665s, 1 580s, 1 495s	8.2 (14 H, m, CH$_2$[C*H*$_2$]$_2$CH$_2$ and [CH$_2$]$_5$), 7.15 (4 H, m, C*H*$_2$[CH$_2$]$_2$C*H*$_2$), 5.9 (1 H, m, CH), 3.8br and 2.2br (2 H, CONH$_2$ [b]), 1.6br (1 H, NH [b])
(3h)	3 440s, 3 280m, 3 220m, 3 150m, 1 670s, 1 560s	5.15 (2 H, d, *J* 7 Hz, C*H*$_2$Ph [a]), 4.5br and 2.2br (2 H, CONH$_2$ [b]), 2.65 (15 H, m, 3 × Ph), 1.05br (1 H, NH [b])
(3i)	3 440s, 3 220m, 3 250m, 3 180m, 1 670s, 1 570s, 1 540m, 1 500m	8.35 10 (H, m, [CH$_2$]$_5$), 5.85 (1 H, m, CH), 4.45br and 2.15br (2 H, CONH$_2$), 2.65 (10 H, m, 2 × Ph), 1.45br (1 H, NH [b])
(4b)	1 675s, 1 650s, 1 592s, 1 545m, 1 525m, 1 485m	4.55 (2 H, s, C*H*$_2$Ph), 2.65 (5 H, m, Ph), 1.45 (1 H, s, H-2), 1.25 and 1.1 (2 H, ABq, *J* 2.5 Hz, H-5 and -6)
(4c)	1 672s, 1 655m, 1 605m, 1 550w, 1 535m, 1 490s	8.2 (10 H, m, [CH$_2$]$_5$), 4.95 (1 H, m, CH), 1.48 (1 H, s, H-2), 1.25 and 1.1 (2 H, ABq, *J* 2.5 Hz, H-5 and -6)
(4d)	1 660s, 1 645s, 1 600s, 1 560m, 1 530m, 1 490s	7.3 (6 H, s, 2 × CH$_3$), 4.4 (2 H, s, C*H*$_2$Ph), 2.7 (5 H, m, Ph), 1.4 (1 H, s, H-2)
(4f)	1 660s, 1 650m, 1 600s, 1 558m, 1 530m, 1 490s	8.05 (4 H, m, CH$_2$[C*H*$_2$]$_2$CH$_2$), 6.95 (4 H, m, C*H*$_2$[CH$_2$]$_2$C*H*$_2$), 4.52 (2 H, s, C*H*$_2$Ph), 2.7 (5 H, s, Ph), 1.55 (1 H, s, H-2)
(4h)	1 650s, 1 635m, 1 590s, 1 545m, 1 520m, 1 500m	4.45 (2 H, s, C*H*$_2$Ph), 2.6 (15 H, m, 3 × Ph), 1.45 (1 H, s, H-2)
(4i)	1 670s, 1 590s, 1 580s, 1 540s, 1 500m, 1 490m	8.3 (10 H, m, [CH$_2$]$_5$), 4.95 (1 H, m, CH), 2.7 (10 H, m, 2 × Ph), 1.5 (1 H, s, H-2)
(5b)	3 180m, 3 060m, 1 718s, 1 680s, 1 550m, 1 495s	4.55 (2 H, s, C*H*$_2$Ph), 2.65 (5 H, m, Ph), 1.5 and 1.4 (2 H, ABq, *J* 10 Hz, H-6 and -7), −2.6br (1 H, NH [b])
(5d)	3 180m, 3 070m, 1 730s 1 698s, 1 555m, 1 495s	7.4 (6 H, s, 2 × CH$_3$, 4.6 (2 H, s, C*H*$_2$Ph), 2.7 (5 H, m, Ph), 0.45br (1 H, NH [b])
(5f)	3 180m, 3 060m, 1 710s, 1 690s, 1 558s, 1 498s	8.1 (4 H, m, CH$_2$[C*H*$_2$]$_2$CH$_2$), 7.0 (4 H, m, C*H*$_2$[CH$_2$]$_2$C*H*$_2$), 4.6 (2 H, s, C*H*$_2$Ph), 2.7 (5 H, m, Ph), −0.05br (1 H, NH [b])
(5h)	3 140m, 3 040m, 1 720s, 1 695s, 1 640m, 1 540s	4.5 (2 H, s, C*H*$_2$Ph), 2.7 (15 H, m, 3 × Ph), 1.0br (1 H, NH [b])

[a] Singlet on deuteriation. [b] Removed by deuteriation.

for 24 h over molecular sieves (4 Å; 8—12 mesh) before use] was cooled to 5 °C (ice–salt bath) in an apparatus which excluded moisture. Dry hydrogen chloride was passed in at such a rate that the temperature of the mixture was maintained at 5—7 °C. Cyanoacetamide dissolved gradually but after about 1.5—2 h dissolution of the starting material was accompanied by precipitation of the product. Refrigeration overnight yielded white crystals; a sample of the mixture was withdrawn and filtered, and the crystals were washed with dry ether, and the i.r. spectrum was examined for lack of C:N absorption. A maximum of 72 h refrigeration usually resulted in satisfactory conversion. The crystals were filtered off, washed with dry ether and dried *in vacuo* (NaOH). The hydrochloride (90.0%) had m.p. 114—115° (decomp.) [lit.,[4] 112—113° (decomp.)].

2-Alkylamidino-2-phenylazoacetamide (2d—f) *Hydrochlorides*.—(*a*) The phenylazo base [3] (2d—f) (0.01 mol) was dissolved in methanol (25 ml) and 4N-hydrochloric acid added (*ca.* 5 ml) until the solution was strongly acidic to litmus. After stirring for 1 h, the solution was evaporated *in vacuo* to provide an almost quantitative yield of the salt as orange-yellow crystals. The *hydrochloride* (2d) had m.p. 185—187° (decomp.) (from aqueous ethanolic hydrogen chloride). The *hydrochloride* (2e) had m.p. 219—222° (decomp.) (from aqueous ethanolic hydrogen chloride). The *hydrochloride* (2f) had m.p. 175—177° (from ethanol and ether).

(*b*) A solution of benzenediazonium chloride, prepared by careful addition of aqueous sodium nitrite (7.6 g in 80 ml) to aniline (9.3 g) in 6N-hydrochloric acid (50 ml) so that the temperature was maintained at 5—10 °C, was added at room temperature to a vigorously stirred solution of the alkylamidinoacetamide (2a—c) hydrochloride (0.1 mol) in water (100 ml). Concentrated aqueous sodium acetate was added until the pH was 5. After 15—20 min, orange-yellow crystals had precipitated which were filtered off.* The filtrate was stirred with external cooling (ice-bath) and after 2—3 h more crystals were collected. The combined precipitates were washed with cold water. The hydrochloride was identical (mixed m.p. and i.r. spectra) with material obtained by method (*a*). The cyclohexyl (2e) salt was best prepared by method (*a*) since difficulty was experienced in preventing initial separation as an oil.

2-Alkylamidino-2-aminoacetamide (2h—i) *Hydrochlorides*.—A mixture of palladised charcoal (10%; 3.0 g) and the 2-alkylamidino-2-phenylazoacetamide(2d—e) hydrochloride (0.03 mol) in methanol (150 ml) and water (50 ml) was

* Removal of the first precipitate of crystals was necessary, especially in the case of the benzyl (2d) salt, otherwise further cooling produced an oil.

hydrogenated at room temperature and pressure with vigorous agitation until the theoretical quantity of hydrogen had been absorbed. After removal of the catalyst, the filtrate was evaporated *in vacuo* (40 °C) and the gummy residue was triturated with ether (4 × 50 ml) to provide white crystals. 2-*Amino*-2-*benzylamidinoacetamide* (2 h) *hydrochloride* (68.4%) had m.p. 155—156° (decomp.) (from aqueous ethanol and ether) (Found: C, 49.3; H, 6.2; N, 22.85. $C_{10}H_{15}ClN_4O$ requires C, 49.5; H, 6.2; N, 23.1%). 2-*Amino*-2-*cyclohexylamidinoacetamide* (2i) *hydrochloride* (87.0%) had m.p. 208—210° (decomp.) (from ethanol) (Found: C, 46.25; H, 8.25; N, 23.75. $C_9H_{19}ClN_4O$ requires C, 46.05; H, 8.1; N, 23.9%).

3-*Alkylaminopyrazine*-2-*carboxamides* (3b—c).—Concentrated ammonium hydroxide solution was added dropwise to a stirred solution of the 2-alkylamidino-2-aminoacetamide (2h—i) hydrochloride (0.01 mol) and glyoxal hydrogen sulphite adduct monohydrate (0.01 mol) in water (30 ml). A pale-yellow solid gradually separated and addition was continued until the pH was 8—9. The mixture was stirred for 48 h, the pH being maintained at 8—9 by frequent additions of the base. After refrigeration, the pale yellow crystals were filtered off and washed with water. 3-Benzylaminopyrazine-2-carboxamide (3b) (60.0%) had m.p. 125—126° (from ethanol), and was identical (mixed m.p. and i.r. and u.v. spectra) with an authentic sample.[5] 3-*Cyclohexylaminopyrazine*-2-*carboxamide* (3c) (56.0%) had m.p. 128—129° (from aqueous ethanol) (Found: C, 59.9; H, 7.15; N, 25.45. $C_{11}H_{16}N_4O$ requires C, 60.0; H, 7.3; N, 25.45%).

3-*Alkylamino*-5,6-*dimethylpyrazine*-2-*carboxamides* (3d—e).—A solution of the 2-alkylamidino-2-aminoacetamide (2h—i) hydrochloride (0.01 mol) in water (20 ml) was added to a solution of biacetyl (redistilled; 0.01 mol) in ethanol (6 ml) and the mixture was stirred and cooled to 10 °C. Concentrated ammonium hydroxide solution was added dropwise, the temperature being maintained at 10 °C by external cooling, and a procedure similar to the above yielded pale yellow crystals. 3-*Benzylamino*-5,6-*dimethylpyrazine*-2-*carboxamide* (3d) (80.0%) had m.p. 186—187° (from chloroform and ethanol) (Found: C, 65.85; H, 6.0; N, 21.4. $C_{14}H_{16}N_4O$ requires C, 65.6; H, 6.3; N, 21.85%). 3-*Cyclohexylamino*-5,6-*dimethylpyrazine*-2-*carboxamide* (3e) (74.0%) had m.p. 159—161° (from chloroform and light petroleum) (Found: C, 62.85; H, 8.35; N, 21.95. $C_{13}H_{20}N_4O$ requires C, 62.9; H, 8.1; N, 22.55%).

3-*Alkylamino*-5,6,7,8-*tetrahydrobenzo*[b]*pyrazine*-2-*carboxamides* (3f—g).—A solution of the 2-alkylamidino-2-aminoacetamide (2h—i) hydrochloride (0.01 mol) in water (20 ml) was added to a solution of cyclohexane-1,2-dione (0.01 mol) in ethanol (6 ml) and concentrated ammonium hydroxide was added dropwise at room temperature to the stirred mixture. A similar procedure to the above yielded yellow crystals. 3-*Benzylamino*-5,6,7,8-*tetrahydrobenzo*[b]*pyrazine*-2-*carboxamide* (3f) (80.4%) had m.p. 181—182° (from chloroform and ethanol) (Found: C, 67.65; H, 6.5; N, 19.35. $C_{16}H_{18}N_4O$ requires C, 68.05; H, 6.4; N, 19.85%). 3-*Cyclohexylamino*-5,6,7,8-*tetrahydrobenzo*[b]*pyrazine*-2-*carboxamide* (3g) (70.0%) had m.p. 133—135° (from aqueous ethanol) (Found: C, 66.15; H, 8.05; N, 19.8. $C_{15}H_{22}N_4O$ requires C, 65.65; H, 8.1; N, 20.4%).

3-*Alkylamino*-5,6-*diphenylpyrazine*-2-*carboxamides* (3h—i).—Sodium acetate trihydrate (3 g) was added to a stirred suspension of the 2-alkylamidino-2-aminoacetamide (2h—i) hydrochloride (0.01 mol) and benzil (0.01 mol) in methanol (50 ml). Dissolution was followed by gradual precipitation of a yellow solid. After 48 h, filtration provided bright yellow-green crystals which were washed with water. 3-*Benzylamino*-5,6-*diphenylpyrazine*-2-*carboxamide* (3h) (21.2%) had m.p. 177—178° (from chloroform and light petroleum) (Found: C, 75.5; H, 5.5; N, 14.75. $C_{24}H_{20}N_4O$ requires C, 75.8; H, 5.25; N, 14.75%). 3-*Cyclohexylamino*-5,6-*diphenylpyrazine*-2-*carboxamide* (3i) (18.0%) had m.p. 185—186° (from aqueous ethanol) (Found: C, 74.65; H, 6.55; N, 14.55. $C_{23}H_{24}N_4O$ requires C, 74.2; H, 6.45; N, 15.05%).

Pteridin-4(1H)-*ones* (4d, f, *and* h).—The pyrazine (3d, f, or h) (0.002 mol) was added to a mixture of formic acid (98%; 10 ml) and acetic anhydride (redistilled; 10 ml) and the pale yellow solution was heated under reflux for 1½—2 h. (Cyclisation was followed by t.l.c. and u.v. spectroscopy; longer periods were shown to be inadvisable.) Evaporation *in vacuo* gave a syrup and repeated concentrations with added water and finally with ethanol afforded yellow crystals. 1-*Benzyl*-6,7-*dimethylpteridin*-4(1H)-*one* (4d) (60.2%) had m.p. 205—207° (from chloroform and light petroleum) (Found: C, 67.5; H, 5.35; N, 21.1. $C_{15}H_{14}N_4O$ requires C, 67.65; H, 5.3; N, 21.05%). 1-*Benzyl*-6,7,8,9-*tetrahydrobenzo*[g]*pteridin*-4(1H)-*one* (4f) (56%) had m.p. 218—219° (from ethanol and ethyl acetate) (Found: C, 70.2; H, 5.6; N, 19.0. $C_{17}H_{16}N_4O$ requires C, 69.85; H, 5.5; N, 19.15%). 1-*Benzyl*-6,7-*diphenylpteridin*-4(1H)-*one* (4h) (58.5%) had m.p. 269—270° (from ethanol) (Found: C, 76.7; H, 4.6; N, 14.2. $C_{25}H_{18}N_4O$ requires C, 76.9; H, 4.6; N, 14.35%).

Pteridin-4(1H)-*ones* (4b, c, *and* i).—The pyrazine (3b, c, or i) (0.002 mol) was heated for 1 h under reflux with diethoxy-*NN*-dimethylformamide (10 ml). The solution was refrigerated and filtered to yield pale yellow crystals which were washed with cold ethanol. 1-*Benzylpteridin*-4(1H)-*one* (4b) (60%) had m.p. 214—215° (from ethanol) (Found: C, 65.65; H, 4.5; N, 23.75. $C_{13}H_{10}N_4O$ requires C, 65.55; H, 4.25; N, 23.5%). 1-*Cyclohexylpteridin*-4(1H)-*one* (4c) (65%) had m.p. 270—271° (from ethanol) (Found: C, 63.1; H, 6.25; N, 24.35. $C_{12}H_{14}N_4O$ requires C, 62.6; H, 6.15; N, 24.35%). 1-*Cyclohexyl*-6,7-*diphenylpteridin*-4(1H)-*one* (4i) (53.8%) had m.p. 286—287° (decomp.) (from aqueous ethanol) (Found: C, 75.65; H, 5.9; N, 14.35. $C_{24}H_{22}N_4O$ requires C, 75.6; H, 5.5; N, 14.7%).

Pteridine-2,4(1H)-*diones* (5b, d, f, *and* h).—A solution of the pyrazine (3b, d, f, or h) (0.005 mol) in ethyl chloroformate (20 ml) was refluxed for 30 h [(3b)], 3 h [(3d and f)], or 6 h [(3h)]. The solution was evaporated *in vacuo* and the excess of reagent was removed by repeated concentration *in vacuo* with added ethanol. The yellow residue was refluxed for 1 h with saturated aqueous sodium carbonate (20 ml) or in the case of (3h) with saturated ethanolic sodium ethoxide (20 ml). Acidification of the cooled solution to pH 3—4 with 2N-hydrochloric acid gave crystals which were filtered off and washed with water. 1-*Benzylpteridine*-2,4(1H)-*dione* (5b) (55.4%) had m.p. 235—237° [from chloroform and light petroleum (charcoal)] (Found: C, 61.2; H, 4.05; N, 21.55. $C_{13}H_{10}N_4O_2$ requires C, 61.4; H, 4.0; N, 22.05%). 1-*Benzyl*-6,7-*dimethylpteridine*-2,4(1H)-*dione* (5d) (59.0%) had m.p. 235—236° [from chloroform and light petroleum (charcoal)] (Found: C, 63.65; H, 5.2; N, 19.6. $C_{15}H_{14}N_4O_2$ requires C, 63.8; H, 5.0; N, 19.85%). 1-*Benzyl*-5,6,7,8-*tetrahydrobenzo*[g]*pteridine*-2,4(1H)-*dione* (5f) (60.3%) had m.p. 223—225° [from ethanol (charcoal)] (Found: C, 65.95; H, 5.35; N,

18.05. $C_{17}H_{16}N_4O_2$ requires C, 66.2; H, 5.25; N, 18.15%). 1-*Benzyl*-6,7-*diphenylpteridine*-2,4(1H)-*dione* (5h) (50.5%) had m.p. 197—200° [from chloroform and light petroleum (charcoal)] (Found: C, 74.35; H, 4.7; N, 13.4. $C_{25}H_{18}N_4O_2$ requires C, 73.9; H, 4.45; N, 13.3%).

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