Pyrimidines. Part XXIII.[1] Synthesis of Pyrimido[4,5-*b*][1,4]oxazines by Reaction of 4,5-Diaminopyrimidine Derivatives with α-Halogeno-ketones

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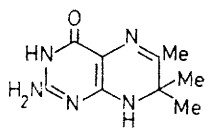
Condensation of certain 4,5-diaminopyrimidine derivatives with α-bromoisopropyl methyl ketone is shown to give pyrimido[4,5-*b*][1,4]oxazines and not the expected dihydropteridine derivatives. Similar condensations with a number of different α-halogeno-aldehydes and α-halogeno-ketones have been studied, and the factors which control the nature of the product have been determined. Some preliminary studies of the chemical reactivity of pyrimido-[4,5-*b*][1,4]oxazines have been carried out.

SEVERAL workers [2-6] have reported that condensation of a 4,5-diaminopyrimidine with an α-halogeno-aldehyde or -ketone gives a dihydropteridine derivative. In many cases the dihydropteridine has not been isolated, since such compounds are readily oxidized to give the fully aromatic pteridine.



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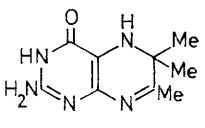

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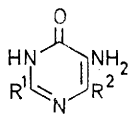
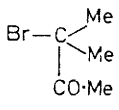


(3) $R^1 = R^2 = NH_2$
(4) $R^1 = NH_2$, $R^2 = NMe_2$
(5) $R^1 = NH_2$, $R^2 = NHMe$
(6) $R^1 = NH_2$, $R^2 = NH{\cdot}C_6H_{11}$
(7) $R^1 = H$, $R^2 = NH_2$
(8) $R^1 = NH_2$, $R^2 = H$



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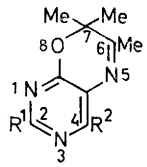

(10) $R^1 = NH_2$, $R^2 = NH_2$
(11) $R^1 = NH_2$, $R^2 = NMe_2$
(12) $R^1 = NH_2$, $R^2 = NHMe$
(13) $R^1 = NH_2$, $R^2 = NH{\cdot}C_6H_{11}$
(14) $R^1 = H$, $R^2 = NH_2$
(15) $R^1 = R^2 = NHAc$

Independent studies in Stuttgart and in Glasgow of the synthesis of the blocked dihydropteridines (1) and (2) involved condensation of 2,4,5-triaminopyrimidin-6(1*H*)-one (3) with α-bromoisopropyl methyl ketone (9). Unexpectedly, the product was not a dihydropteridine, but a derivative (10) of pyrimido[4,5-*b*][1,4]oxazine. Hitchings and his co-workers [7,8] have described some aspects of the synthesis of this ring system, but no other work on it has been reported; we have therefore studied the chemistry of these compounds in detail.

The identification of the product (10) as 2,4-diamino-6,7,7-trimethylpyrimido[4,5-*b*][1,4]oxazine was based on the following observations. The compound was insoluble in alkali, and the u.v. spectrum (Table 1) showed no evidence of any acidic grouping. This eliminates the

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[3] C. W. Waller, B. L. Hutchings, J. H. Mowat, E. L. R. Stokstad, J. H. Boothe, R. B. Angier, J. Semb, Y. Subbarow, D. B. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, and J. P. Sickels, *J. Amer. Chem. Soc.*, 1948, **70**, 19; M. E. Hultquist, E. Kuh, D. B. Cosulich, M. J. Fahrenbach, E. H. Northey, D. R. Seeger, J. P. Sickels, J. M. Smith, R. B. Angier, J. H. Boothe, B. L. Hutchings, J. H. Mowat, J. Semb, E. L. R. Stokstad, Y. Subbarow, and C. W. Waller, *ibid.*, p. 23; D. R. Seeger, D. B. Cosulich, J. M. Smith, and M. E. Hultquist, *ibid.*, 1949, **71**, 1753; B. Roth, J. M. Smith, and M. E. Hultquist, *ibid.*, 1950, **72**, 1914.

[4] M. Viscontini and S. Huwyler, *Helv. Chim. Acta*, 1965, **48**, 764.

[5] M. Viscontini and A. Bobst, *Helv. Chim. Acta*, 1966, **49**, 1815.

[6] F. Weygand, V. Schmied-Kowarzik, A. Wacker, W. Rupp, *Chem. Ber.*, 1950, **83**, 460.

[7] P. B. Russell, G. B. Elion, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1949, **71**, 474.

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isomeric dihydropteridines (1) and (2). Similar reaction of 4,5-diaminouracil (16) and its 3-methyl derivative (17) with α-bromoisopropyl methyl ketone (9) gave analogous products, (21) and (22), thus eliminating the remaining three possible isomeric structures (23), (24), and (25).

Other 4,5-diaminopyrimidines (4)—(7) also reacted with the ketone (9) to give pyrimido[4,5-*b*][1,4]oxazines (11)—(14). The *N*(3)-methyl derivative (22) showed sample prepared by condensation of 4,5-diamino-1-methyluracil (18) with the ketone (9). The u.v. spectra of the cations of the *N*-methyl derivatives (22) and (26) are similar however (Table 1), as would be expected from protonation on N-1 and N-3 respectively.

4,5-Diaminopyrimidine-6(1*H*)-thione (27) also reacted with the ketone (9); the product in this case was the pyrimido[4,5-*b*][1,4]thiazine (28). In principle, this

TABLE 1

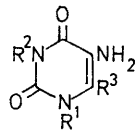
Physical constants of 7*H*-pyrimido[4,5-*b*][1,4]oxazines

	pK_a in water (20°)	U.v. spectrum [a] $\lambda_{max.}$ (mμ)			log ε			pH	Species [b]
2,4-Diamino-6,7,7-trimethyl (10)	4·32 ± 0·01	279	314		4·20	4·01		2	+
		277	309		4·14	3·98		7	0
2-Amino-4-dimethylamino-6,7,7-trimethyl (11)	4·41 ± 0·01	243	291		4·04	4·24		2	+
		239	287	(310)	4·18	4·18	(3·97)	7	0
2-Amino-4-methylamino-6,7,7-trimethyl (12)	4·51 [c] ± 0·05	283	314		4·22	3·94		1	+
		278	315		4·13	3·95		7	0
2-Amino-4-cyclohexylamino-6,7,7-trimethyl (13)		284	314		4·30	3·99		1	−
		276	318		4·10	3·81		7	
4-Amino-6,7,7-trimethyl (14)	3·26 [c] ± 0·1	267	315		3·98	3·70		1	+
		228	263	305	4·08	3·75	3·68	7	0
2,4-Diacetamido-6,7,7-trimethyl (15)	2·95 [c] ± 0·05	223	295		4·39	4·26		1	+
		230	294		4·35	4·28		7	0
4-Amino-6,7,7-trimethyl-2(3*H*)-one (21)	3·53 ± 0·02	270	(300)		4·22	(3·92)		0	+
	9·20 ± 0·08	279	307		4·21	3·98		7	0
		277	307		4·22	4·01		14	−
4-Amino-3,6,7,7-tetramethyl-2(3*H*)-one (22)	3·69 ± 0·02	273	(300)		4·20	(3·91)		1	+
		282	(300)		4·24	(4·02)		7	0
4-Amino-1,6,7,7-tetramethyl-2(1*H*)-one (26)	4·67 ± 0·01	271	305		4·18	3·91		1	+
		217	273	(300)	4·21	4·19	(3·81)	7	0
2,4-Diamino-6,7-dimethyl- (31)	4·61 ± 0·02	279	314		4·18	3·99		2	+
		277	310		4·12	3·95		7	0
2,4-Diamino-6,7-diphenyl- (32)	4·03 [c] ± 0·07	294	355		4·16	4·25		0	+
		241	288	367	4·17	3·97	4·27	7	0
2,4-Diamino-6-phenyl- (33)	4·11 [c] ± 0·02		293	353		4·12	4·25	1	+
		236	285	364	4·16	3·99	4·27	7	0
4-Amino-6,7-dimethyl-2(3*H*)-one (35)	3·41 ± 0·06	270	(300)		4·16	(3·86)		1	+
	9·21 ± 0·05	278	307		4·16	3·95		7	0
		278	309		4·12	3·94		13	−
4-Amino-3,6,7-trimethyl-2(3*H*)-one (36)	3·74 ± 0·08	272	(300)		4·17	(3·89)		2	+
		281	(300)		4·21	(4·00)		7	0
4-Amino-3-methyl-6,7-diphenyl-2(3*H*)-one (37)	3·22 [c] ± 0·06	293	344		4·27	4·14		1	+
		232	293	354	4·19	4·17	4·28	7	0
4-Amino-6-phenyl-2(3*H*)-one (38)	3·32 [c] ± 0·07		290	348		4·08	4·14	1	+
	8·77 [c] ± 0·22	225	290	350	4·19	3·95	4·23	7	0
		233	268	365	4·19	4·07	4·16	13	−
2,4-Diamino-7,8,9,9a-tetrahydro-6*H*-pyrimido-[4,5-*b*]-[1,4]benzoxazine (51)	4·35 [c] ± 0·05	270	318		4·08	3·79		1	+
		278	318		4·12	3·93		7	0
4-Amino-7,8,9,9a-tetrahydro-6*H*-pyrimido[4,5-*b*][1,4]-benzoxazin-2(3*H*)-one (52)	3·68 [c] ± 0·02	269	304		4·20	3·83		1	+
	9·83 [c] ± 0·13	277	314		4·13	3·85		7	0
		278	315		4·17	3·96		13	−
2,4-Diamino-6,7-dihydro-6,7,7-trimethyl-5*H*- (57)	5·04 [c] ± 0·13	(250)	295		(3·72)	3·80		1	+
		243	284		3·84	3·82		7	0
2,4-Diacetamido-6,7-dihydro-6,7,7-trimethyl-5*H*- (58)	2·82 [c] ± 0·1		293			4·10		0	+
			270	(305)		4·03	(3·85)	6	0
2,4-Diamino-6,7-dihydro-6,7,7-trimethyl-5-nitroso-5*H*- (59)	3·37 [c] ± 0·09	283	301		4·04	4·02		0	+
		280	310		3·93	3·91		5	−

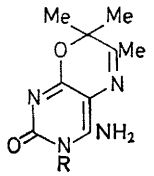
[a] Inflections in parentheses. [b] + Cation, 0 neutral molecule, − anion. [c] Determined by spectrophotometric method (B. N. Mattoo, *Trans. Faraday Soc.*, 1958, **54**, 19); other pK_a values by potentiometric titration.

the increase in solubility usually associated with *N*-methylation, but the m.p. was unusually high compared with that of the parent substance (21). In an attempt to establish the structure of the *N*(3)-methyl derivative (22) by direct interconversion, the 2-oxo compound (21) was treated with dimethyl sulphate at pH 9. A single product was obtained and identified as the isomeric *N*(1)-methyl derivative (26) by comparison with a reaction could have given a dihydropteridine [*e.g.* (29)], but this possibility was excluded since the n.m.r. spectrum of the product in deuteriochloroform showed a singlet at τ 3·95 (2H, 4-NH_2). A dihydropteridine (29) would have shown two singlets for the protons on N-3 and N-5. The basic pK_a of the pyrimidothiazine (28) was almost identical with that of the corresponding pyrimido-oxazine (14), thus further supporting the pro-

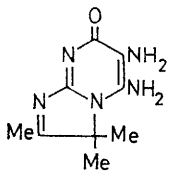
posed structure. Pyrimido[4,5-*b*]thiazines were first described by Rose [9] in 1952. Since then several workers [10] have described syntheses of the ring system, and we have therefore not studied its chemistry further.



(16) $R^1 = R^2 = H$, $R^3 = NH_2$
(17) $R^1 = Me$, $R^2 = H$, $R^3 = NH_2$
(18) $R^1 = H$, $R^2 = Me$, $R^3 = NH_2$
(19) $R^1 = R^2 = R^3 = H$
(20) $R^1 = R^2 = H$, $R^3 = Me$



(21) R = H
(22) R = Me



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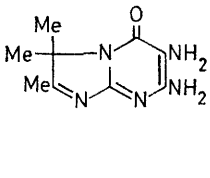

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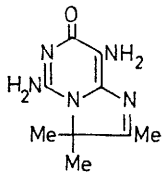

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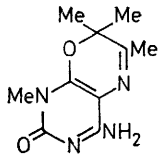
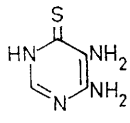


(26)

5-Aminopyrimidin-6(1*H*)-ones (8), (19), and (20), which did not have a 4-amino-group, did not appear to react with the bromo-ketone (9). We concluded that for reaction to occur, the group in position 4 must be such that a lone pair of electrons can conjugate with the vinylogous carbonyl in position 6 (see Scheme).



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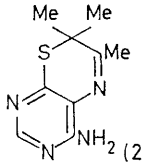

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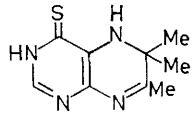

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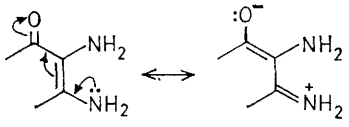


SCHEME

The formation of pyrimido[4,5-*b*]oxazines thus formally involves nucleophilic attack by the oxygen at position 6 of the pyrimidine molecule on the α-carbon atom of the halogeno-ketone, with consequent alkylation of the oxygen atom.

In an attempt to define more precisely the types of α-halogeno-aldehyde and -ketone which lead to pyrimido-[4,5-*b*]oxazines on the one hand, and to dihydropteridines on the other, we have studied the reactions between a number of different α-halogeno-aldehydes and -ketones and 4,5-diaminopyrimidines.

Other α-Halogeno-ketones.—α-Bromoethyl methyl ketone (30) reacted with 2,4,5-triaminopyrimidin-6(1*H*)-one (3) to give a mixture of 2,4-diamino-6,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazine (31) and the 6,7-dimethylpteridine (39). The ketone (30) reacted in similar fashion with the diaminouracil derivatives (16) and (17) to give, in each case, a mixture of the pyrimido[4,5-*b*]-oxazine (35) or (36) and the appropriate pteridinedione (46) or (47). The pyrimido-oxazine was the major product in these experiments and, in some cases, the pteridine was identified only by comparison with authentic material on paper chromatograms. The pteridine is formed presumably by oxidation of an intermediate dihydropteridine.

Pyrimido[4,5-*b*]oxazines such as (31), with a hydrogen atom at position 7, could exist in a tautomeric form (34). This possibility was excluded, however, by the n.m.r. spectrum of (31), which showed a quadruplet at τ 4·5, assigned to the 7-hydrogen atom, split by the adjacent methyl group, and a doublet at τ 8·2 assigned to the 7-methyl group.

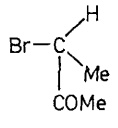
Other α-halogeno-ketones, in which the α-carbon atom carried a single hydrogen atom, reacted in a similar fashion. Thus desyl chloride (α-chloro-α-phenylacetophenone) (50) with the 4,5-diaminopyrimidines (3) and (17) gave pyrimido[4,5-*b*]oxazines (32) and (37) as the major products, together with small amounts of the 6,7-diphenylpteridines (40) and (48). α-Bromocyclohexanone, with the pyrimidines (3) and (16), also gave pyrimido-oxazines (51) and (52) as the major products, together with traces of the pteridines (53) and (54).

It thus appears that, in general, the major products to be expected from reaction of α-halogeno-ketones in which the α-carbon atom carries a *single* hydrogen with 4,5-diaminopyrimidin-6(1*H*)-ones are pyrimido[4,5-*b*]-oxazines and not dihydropteridines.

We have extended these studies to α-halogeno-ketones in which the α-carbon atom carries two hydrogen atoms, and have confirmed an earlier report [6] that bromoacetone reacts with 2,4,5-triaminopyrimidin-6(1*H*)-one (3) to give 7-methylpteridine (41). The mother liquors from this reaction did not contain any pyrimido-oxazine. Similar condensation of bromomethyl ethyl ketone with the pyrimidine (3) gave a mixture of two isomeric pteridines (43) and (44), and again no pyrimido-oxazine.

It thus seems that α-halogeno-ketones in which the

[9] F. L. Rose, *J. Chem. Soc.*, 1952, 3448.
[10] M. Ishidate and H. Yuki, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 131; E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, 1964, **29**, 2121; T. S. Safonova and M. P. Nemeryuk, *Khim. geterotsikl. Soedinenii*, 1965, **1**, 149 (*Chem. Abs.*, 1965, **63**, 5642c); M. P. Nemeryuk and T. S. Safonova, *ibid.*, 1966, **3**, 470 (*Chem. Abs.*, 1966, **65**, 8903c).



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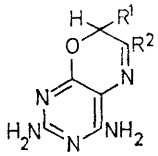
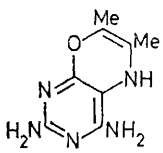


(31) $R^1 = R^2 = Me$
(32) $R^1 = R^2 = Ph$
(33) $R^1 = H$, $R^2 = Ph$



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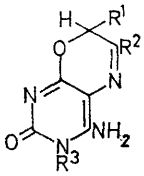
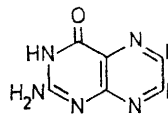
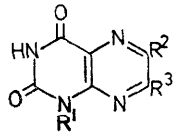


(35) $R^1 = R^2 = Me$, $R^3 = H$
(36) $R^1 = R^2 = R^3 = Me$
(37) $R^1 = R^2 = Ph$, $R^3 = Me$
(38) $R^1 = R^3 = H$, $R^2 = Ph$



(39) $R^1 = R^2 = Me$
(40) $R^1 = R^2 = Ph$
(41) $R^1 = H$, $R^2 = Me$
(42) $R^1 = Ph$, $R^2 = H$
(43) $R^1 = Et$, $R^2 = H$
(44) $R^1 = H$, $R^2 = Et$
(45) R^1 or $R^2 = Ph$, R^1 or $R^2 = H$



(46) $R^1 = H$, $R^2 = R^3 = Me$
(47) $R^1 = R^2 = R^3 = Me$
(48) $R^1 = Me$, $R^2 = R^3 = Ph$
(49) $R^1 = H$, R^2 or $R^3 = Ph$, R^2 or $R^3 = H$

α-carbon atom carries *two* hydrogen atoms do indeed react with 4,5-diaminopyrimidines to give pteridines, and most of the previously reported examples [2-6] of such reactions were of this type. Caution must be exercised, however, in the application of this generalization, since α-chloroacetophenone reacts with the pyrimidines (3) and (16) to give pyrimido-oxazines (33) and (38) as the major products, and only small amounts (detectable by paper chromatography) of the corresponding pteridines (45) and (49).

α-Chloroacetophenone does give a pteridine derivative when the 6-oxo-group of the pyrimidine is protected, for example by a methyl group. Thus 2,4,5-triamino-6-methoxypyrimidine (55) with α-chloroacetophenone gave 2-amino-4-methoxy-7-phenylpteridine (56) in good yield. α-Bromoisopropyl methyl ketone (9), however, did not react with this pyrimidine.

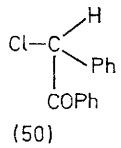
α-Halogeno-aldehydes.—The reaction of α-halogeno-aldehydes with 4,5-diaminopyrimidines is the basis of the early syntheses of folic acid.[2,3] In view of the unexpected results obtained with certain α-halogeno-ketones we have examined comparable reactions with α-halogeno-aldehydes.

Reaction of α-bromoisobutyraldehyde with 2,4,5-triaminopyrimidin-6(1*H*)-one (3) did not give any well defined product. This may be owing to the ease with which this bromo-aldehyde polymerizes to give a trimer.[11] Reaction of α-bromopropionaldehyde, as its diethyl acetal, with the same pyrimidine gave a 7-methylpteridine (41) in moderate yield; the position of the methyl group was confirmed by oxidation to the pteridine-7-carboxylic acid. α-Bromophenylacetaldehyde also reacted with the pyrimidine (3) to give, in high yield, 2-amino-6-phenylpteridin-4(3*H*)-one (42). The position of the phenyl group was confirmed, in this case, by comparison of the u.v. spectrum of the product with that of an authentic specimen.[12]

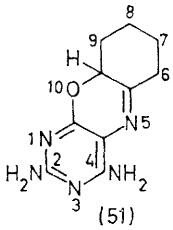
It thus appears that condensation of 4,5-diaminopyrimidines with α-halogeno-aldehydes, in general, gives pteridine derivatives.

Chemical Reactivity of Pyrimido[4,5-b]*oxazines.*—Since little is known of the chemistry of this system, some preliminary experiments were carried out with 2,4-diamino-6,7,7-trimethylpyrimido[4,5-*b*][1,4]oxazine (10).

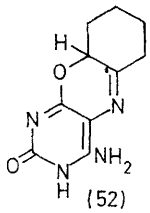
[11] C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, 1957, **79**, 3448.



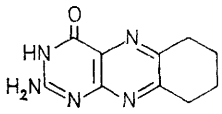
(50)



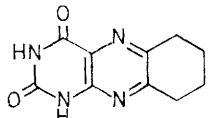
(51)



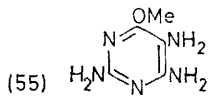
(52)



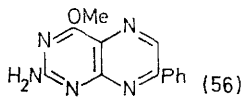
(53)



(54)



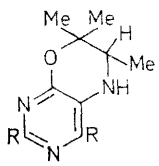
(55)



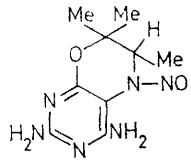
(56)

Hydrogenation over platinum oxide gave a dihydro-derivative (57), in which the C=N group in the oxazine ring had been reduced. This dihydro-compound (57), on treatment with sodium nitrite and hydrochloric acid, gave an *N*-nitroso-derivative (59) which, in agreement with results of Nübel and Pfleiderer [13] for *N*-substituted *N*-nitrosopyrimidines, could not be cyclized to a triazolopyrimido-oxazine.

Acetylation of the pyrimido-oxazine (10) with acetic anhydride at 100° gave a diacetate (15), which, unlike the parent substance, was very soluble in water and ethanol. Catalytic hydrogenation of the diacetate gave its dihydro-derivative (58), which could also be prepared under mild conditions by acetylation of the original dihydro-compound (57).



(57) R = NH_2
(58) R = NHAc



(59)

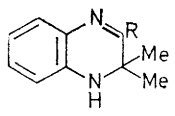
The pyrimido-oxazines could be converted into

[12] H. G. Petering and J. A. Schmitt, *J. Amer. Chem. Soc.*, 1949, **71**, 3977; R. B. Angier, *J. Org. Chem.*, 1963, **28**, 1398.
[13] G. Nübel and W. Pfleiderer, *Chem. Ber.*, 1965, **98**, 1060.

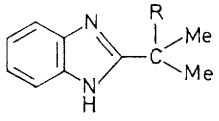
pteridines in two different ways. The first involved refluxing with a 1,2-dicarbonyl compound. Thus with biacetyl the pyrimido-oxazines (10), (21), and (22) gave the corresponding 6,7-dimethylpteridines (39), (46), and (47) in good yield. Other 1,2-dicarbonyl compounds reacted in similar fasion (see Experimental section).

Hitchings and his co-workers [7] have described the conversion of a pyrimido-oxazine into a pteridine by treatment with ammonia in an autoclave. We have confirmed this observation by treatment of the 6-phenylpyrimido-oxazine (33) with aqueous ammonia at 120°; the 6-phenylpteridine (42) was formed together with traces of the 7-phenylisomer.

Model Experiments with o-*Phenylenediamine.*—In the early stages of the work some model experiments with *o*-phenylenediamine were carried out. Condensation of the diamine with α-bromoisopropyl methyl ketone (9) gave 1,2-dihydro-2,2,3-trimethylquinoxaline (60). The reaction between *o*-phenylenediamine and α-bromoisobutyraldehyde was more complex. When the reaction was carried out in ethanol, two products were obtained, one of which (a liquid) could not be obtained completely pure. On the basis of its spectral properties, it was tentatively formulated as a dihydroquinoxaline (61), analogous to that obtained from the ketone (9).



(60) R = Me
(61) R = H



(62) R = OEt
(63) R = OMe
(64) R = Br

The second product, a crystalline solid, had a u.v. spectrum almost identical with that of 2-methylbenzimidazole. The n.m.r. spectrum indicated the presence of an ethyl group, and we therefore formulate this compound as the 2-substituted benzimidazole (62). The ethoxy-group presumably arises by solvolysis of an intermediate bromo-compound (64). In support of this hypothesis, repetition of the reaction with methanol as solvent gave, as the second product, the methoxy-analogue (63).

EXPERIMENTAL

The purity of substances without a definite m.p. was checked by chromatography (ascending) on paper (Schleicher and Schull no. 20436 G1), with (A) butan-1-ol–5N-acetic acid (2 : 1), (B) propan-1-ol–1% aqueous ammonia (2 : 1), (C) 4% sodium citrate, and (D) 3% ammonium chloride as solvents. Spots were located by filtered u.v. light (254 and 365 mμ).

U.v. spectra were determined with either a Cary recording spectrophotometer (model 14 PM-50) or a Perkin-Elmer instrument (model 137 UV). N.m.r. spectra were run with a Perkin-Elmer R10 spectrometer at 40 MHz, with tetramethylsilane as internal standard.

4,5-*Diaminopyrimidines.*—Most of these were prepared by published methods: 2,4,5-triaminopyrimidin-6(1*H*)-one (3); [14] 2,5-diamino-4-dimethylaminopyrimidin-6(1*H*)-one (4) by reduction of the corresponding 5-nitro-compound; [15] 2,5-diamino-4-methylaminopyrimidin-6(1*H*)-one (5) by reduction of the corresponding 5-nitro-compound: [15,16] 4,5-diaminopyrimidin-6(1*H*)-one (7); [17] 2,5-diaminopyrimidin-6(1*H*)-one (8); [18] 4,5-diaminouracil (16); [19] 4,5-diamino-3-methyluracil (17); [20] 4,5-diamino-1-methyluracil (18); [21] 5-aminouracil (19); [22] 5-amino-4-methyluracil (20); [23] 4,5-diaminopyrimidine-6(1*H*)-thione (27); [24] 2,4,5-triamino-6-methoxypyrimidine (55).[25]

2-*Amino*-4-*cyclohexylamino*-5-*nitropyrimidin*-6(1H)-*one.*—To finely powdered 2-amino-4-chloro-5-nitropyrimidin-6(1*H*)-one [26] (5 g.) suspended in ethanol (60 ml.) was added cyclohexylamine (5 g.) and the suspension was refluxed for 1 hr. The mixture was cooled and the crystalline solid which separated was collected and washed with ethanol (2 × 20 ml.) and ether (20 ml.). Recrystallisation from dilute sodium hydroxide, followed by treatment of the resulting salt with dilute hydrochloric acid gave the *cyclohexylaminopyrimidine* (5·5 g., 81%) as plates (Found: C, 47·6; H, 6·5; N, 27·7. $C_{10}H_{15}N_5O_3$ requires C, 47·4; H, 6·0; N, 27·7%).

The corresponding 5-aminopyrimidine (6) was prepared by catalytic reduction of the 5-nitro-derivative over Raney nickel in aqueous solution. The catalyst was filtered off and the filtrate was added directly to hydrochloric acid. Concentration *in vacuo*, followed by refrigeration, gave the 5-aminopyrimidine as the hydrochloride, which was collected and used without further purification.

α-*Halogeno-aldehydes and -ketones.*—These were also prepared by published methods: α-bromoisopropyl methyl ketone (9); [27] α-bromoethyl methyl ketone (30); [28] α-chloro-α-phenylacetophenone (desyl chloride) (50); [29] α-bromocyclohexanone; [30] bromoacetone; [31] α-bromomethyl ethyl ketone; [28] α-chloroacetophenone; [32] α-bromoisobutyraldehyde; [11] α-bromopropionaldehyde (as the diethyl acetal); [33] α-bromophenylacetaldehyde.[34]

7H-*Pyrimido*[4,5-b][1,4]*oxazines.*—These were prepared,

[14] A. Albert and H. C. S. Wood, *J. Appl. Chem.*, 1953, **3**, 521.
[15] W. Pfleiderer and H. Walter, *Annalen*, 1964, **677**, 113.
[16] H. S. Forrest and R. Lohrmann, *J. Chem. Soc.*, 1964, 460.
[17] P. D. Landauer and H. N. Rydon, *J. Chem. Soc.*, 1953, 3721.
[18] T. B. Johnson and C. O. Johns, *Amer. Chem. J.*, 1905, **34**, 554.
[19] W. R. Sherman and E. C. Taylor, *Org. Synth.*, 1963, Coll. Vol. IV, 247.
[20] T. Ukai, Y. Yamamato, and S. Kanetomo, *J. Pharm. Soc. Japan*, 1954, **74**, 674 (*Chem. Abs.*, 1954, **48**, 10,743e).
[21] W. Pfleiderer, *Chem. Ber.*, 1957, **90**, 2272.
[22] D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 1957, 4997.
[23] R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 2418.
[24] G. B. Elion and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1954, **76**, 4027.
[25] B. Roth, J. M. Smith, and M. E. Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2869.
[26] A. Stuart, D. W. West, and H. C. S. Wood, *J. Chem. Soc.*, 1964, 4769.
[27] A. Faworski and A. Wanscheidt, *J. Russ. Phys. Chem. Soc.*, 1913, **44**, 1339 (*Chem. Zentr.*, 1913, **1**, 1007).
[28] J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 1948, 272.
[29] A. M. Ward, *Org. Synth.*, 1932, **12**, 20.
[30] R. Belcher, W. Hoyle, and T. S. West, *J. Chem. Soc.*, 1958, 2743.
[31] P. A. Levene, *Org. Synth.*, 1930, **10**, 12.
[32] H. Korten and R. Scholl, *Ber.*, 1901, **34**, 1901.
[33] J. R. Johnson, A. A. Larsen, A. D. Holley, and K. Gerzon, *J. Amer. Chem. Soc.*, 1947, **69**, 2364.
[34] T. L. Jacobs and W. R. Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 5500.

in general, by condensation of the appropriate pyrimidine with the α-halogeno-ketone in aqueous ethanol. Two typical preparations, which differ only in the method of isolation of the product, are given. Other variations in the conditions, together with yields, analytical data, *etc.* are given in Table 2.

Method A: 2,4-*diamino*-6,7,7-*trimethylpyrimido*[4,5-b][1,4]*oxazine* (10). 2,4,5-Triaminopyrimidin-6(1*H*)-one dihydrochloride (4·3 g., 0·02 mol.) in hot water (30 ml.) was mixed with α-bromoisopropyl methyl ketone (6·6 g., 0·04 mol.) in ethanol (30 ml.). The mixture was refluxed for 45 min., cooled, and after 12 hr. at 0° the yellow crystals (4·1 g.) were collected, washed with ethanol, and dried at 100°. The crude product was dissolved in boiling water (*ca.* 160 ml.), treated with charcoal, and the pH of the filtrate was adjusted to 7 with concentrated ammonia. The *pyrimido-oxazine* (2·8 g., 68%) separated as yellow crystals m.p. 250—251° (decomp.).

Method B: 2-*amino*-4-*methylamino*-6,7,7-*trimethylpyrimido*[4,5-b][1,4]*oxazine* (12). 2,5-Diamino-4-methylaminopyrimidin-6(1*H*)-one dihydrochloride (2·5 g., 0·009 mol.) in water (15 ml.) was mixed with a solution of α-bromoisopropyl methyl ketone (3·3 g., 0·02 mol.) in ethanol (20 ml.), and the mixture was refluxed for 90 min. The pH of the clear, hot solution was adjusted to 6 with conc. ammonia. The solution was cooled, and the yellow crystals (1·1 g.) which separated were collected, washed with a little water, and dried at 100°. The crude product was recrystallized (charcoal) from boiling water (*ca.* 85 ml.); the methylaminopyrimido-oxazine (0·74 g., 37%) was obtained as bright yellow crystals, m.p. 217—219° (decomp.).

Identification of Pteridine By-products.—In those cases (see Table 2) in which a pteridine derivative was formed it was identified by direct comparison with authentic material on paper chromatograms. In one case, the pteridine was isolated (see later) before identification.

TABLE 2

Preparation of 7*H*-pyrimido[4,5-*b*][1,4]oxazines

	Method	Reflux time (min.)	Yield (%)	M.p.	Formula	Found (%) C	H	N	Cl	Requires (%) C	H	N	Cl	Pteridine by-product
2,4-Diamino-6,7,7-trimethyl (10)	A	45	68	250—251° (decomp.)	$C_9H_{13}N_5O$	52·1	6·25	33·6		52·15	6·3	33·8		No
2-Amino-4-dimethylamino-6,7,7-trimethyl (11)	A	90	25	192—193	$C_{11}H_{17}N_5O$	56·05	6·8	29·85		56·15	7·3	29·75		No
2-Amino-4-methylamino-6,7,7-trimethyl (12)	B	90	55	217—219 (decomp.)	$C_{10}H_{15}N_5O$	54·15	6·75	31·65		54·3	6·85	31·65		No
2-Amino-4-cyclohexylamino-6,7,7-trimethyl (13)	B	120	50	212 (decomp.)	$C_{15}H_{23}N_5O$	62·4	8·0	24·2		62·35	8·0	24·25		No
4-Amino-6,7,7-trimethyl (14)	B	150	57	228—230	$C_9H_{12}N_4O$	56·7	6·3	29·3		56·25	6·3	29·15		No
4-Amino-6,7,7-trimethyl-2(3*H*)-one (21)	B	90	80	253—255 (decomp.)	$C_9H_{12}N_4O_2$	51·95	5·85	26·75		51·9	5·8	26·9		No
4-Amino-3,6,7,7-tetramethyl-2(3*H*)-one (22)	B	120	75	330 (decomp.)	$C_{10}H_{14}N_4O_2$	53·80	6·31	25·51		54·04	6·35	25·21		No
4-Amino-1,6,7,7-tetramethyl-2(1*H*)-one (26)	A	90	45	196	$C_{10}H_{14}N_4O_2$	53·85	6·3	25·6		54·04	6·35	25·21		No
2,4-Diamino-6,7-dimethyl- (31) (hydrochloride)	A	120	58	271—273 (decomp.)	$C_8H_{11}N_5OHCl$	42·05	5·4	30·05	15·85	41·85	5·25	30·5	15·45	Yes
2,4-Diamino-6,7-diphenyl- (32)	A [a]	360	63	282 (decomp.)	$C_{18}H_{15}N_5O$	67·85	4·9	21·75		68·15	4·75	22·05		Yes
2,4-Diamino-6-phenyl- (33)	A [b]	360	77	>360	$C_{12}H_{11}N_5O$	60·75	4·6	28·35		59·75	4·6	29·05		Yes
4-Amino-6,7-dimethyl-2(3*H*)-one (35)	B	90	77	246—247 (decomp.)	$C_8H_{10}N_4O_2$	49·15	4·9	29·05		49·5	5·2	28·85		Yes
4-Amino-3,6,7-trimethyl-2(3*H*)-one (36)	B	90	35	234—236	$C_9H_{12}N_4O_2$	52·0	5·35	26·75		51·9	5·8	26·9		Yes
4-Amino-3-methyl-6,7-diphenyl-2(3*H*)-one (37)	B [a]	300	57	230—232	$C_{19}H_{16}N_4O_2$	68·85	4·9	16·4		68·65	4·85	16·85		Yes
4-Amino-6-phenyl-2(3*H*)-one (38)	A [b]	240	81	327—330 (decomp.)	$C_{12}H_{10}N_4O_2$	59·50	3·85	23·45		59·5	4·15	23·15		Yes
2,4-Diamino-7,8,9,9a-tetrahydro-6*H*-pyrimido[4,5-*b*][1,4]-benzoxazine (51)	A	150	66	>360	$C_{10}H_{13}N_5O$	54·70	5·70	31·70		54·8	6·0	31·95		Yes
4-Amino-7,8,9,9a-tetrahydro-6*H*-pyrimido-[4,5-*b*][1,4]benzoxazin-2(3*H*)-one (52)	B	150	50	253—254 (decomp.)	$C_{10}H_{12}N_4O_2$	54·85	5·55	25·85		54·55	5·5	25·45		Yes

[a] Purified by solution in hot dimethylformamide (charcoal), and addition of water to the hot solutions. [b] Sodium acetate was added to the reaction mixture.

Isolation of 2-*Amino*-6,7-*dimethylpteridin*-4(3H)-*one* (39).—The mother liquors from the preparation of 2,4-diamino-6,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazine (31) were adjusted to pH 8—9, and air was bubbled through for 15 hr. at room temperature. Acetic acid was added to adjust the pH to 4—5, and the precipitate was collected, washed with cold water, and dried at 100° to give the pteridine (18%) as a pale brown powder, m.p. >360°, identical (u.v. spectrum and paper chromatography) with an authentic specimen.

Methylation of 4-*Amino*-6,7,7-*trimethyl*-7H-*pyrimido*-[4,5-b][1,4]*oxazin*-2(3H)-*one* (21).—A solution of the pyrimido-oxazinone (4·2 g., 0·02 mol.) in N-sodium hydroxide (24 ml.) was warmed to 40° with stirring. A solution of freshly distilled dimethyl sulphate (3 ml.) in methanol (10 ml.) was added dropwise during 45 min. The pH of the solution was maintained at 9 by the dropwise addition of N-sodium hydroxide. The mixture was stirred for a further 45 min., then neutralized with acetic acid. The precipitate was filtered off, washed with ethanol, and dried at 70—80°. Recrystallisation from boiling water (charcoal) gave the N(1)-*methyl derivative* (2·15 g., 48%) as colourless crystals, m.p. 195—196° (Found: C, 53·85; H, 6·4; N, 24·95%), identical with an authentic sample of 4-amino-1,6,7,7-tetramethyl-7*H*-pyrimido[4,5-*b*][1,4]-oxazin-2(1*H*)-one (26) (see Table 2).

4-*Amino*-6,7,7-*trimethyl*-7H-*pyrimido*[4,5-b][1,4]*thiazine* (28).—To a solution of 4,5-diaminopyrimidine-6(1*H*)-thione (0·7 g., 0·005 mol.) in dimethylformamide (25 ml.) was added α-bromoisopropyl methyl ketone (1·6 g., 0·01 mol.). The mixture was warmed at 90° for 20 min. with stirring. On cooling, yellow crystals separated, and were collected and dried. The crude product, dissolved in a little methanol was treated with charcoal, and the filtrate was evaporated to dryness to give the *pyrimidothiazine* (0·4 g., 40%) as beige crystals, m.p. 150—154° (Found: C, 52·0; H, 5·65; N, 26·5; S, 14·9. $C_9H_{12}N_4S$ requires C, 51·7; H, 5·8; N, 26·8; S, 15·35%), pK_a 3·31 ± 0·06 (spectrophotometric determination), $\lambda_{max.}$ [pH 1 (cation)] 223 (log ε 4·03), 257 (4·20), 281 (3·88), and 328 (3·72) mμ, $\lambda_{max.}$ [pH 7 (neutral molecule)] 257 (log ε 4·31) and 323 (3·55) mμ.

2-*Amino*-7-*methylpteridin*-4(3H)-*one* (41).—(*a*) To a solution of 2,4,5-triaminopyrimidin-6(1*H*)-one dihydrochloride (6·42 g., 0·03 mol.) and sodium acetate (10·5 g.) in water (45 ml.) was added bromoacetone (8·22 g., 0·06 mol.) in ethanol (40 ml.) and the mixture was refluxed for 2 hr. The crystals which separated were filtered from the hot solution, washed with water and with ethanol, and dried at 100° to give the 7-methylpteridine (2·1 g., 41%).

(*b*) To a solution of 2,4,5-triaminopyrimidin-6(1*H*)-one dihydrochloride (2·14 g., 0·01 mol.) in water (15 ml.) and ethanol (20 ml.) was added α-bromopropionaldehyde diethyl acetal (4·5 g., 0·025 mol.). Hydrochloric acid (2 drops) was added and the mixture was heated for *ca.* 2 min., until a clear solution was formed. Sodium acetate was added to adjust the pH to 6, and the mixture was refluxed for 2 hr. The microcrystalline product (0·5 g., 28%) was collected as in (*a*).

The identity of the 7-methylpteridine was confirmed by permanganate oxidation [6] to give the pteridine-7-carboxylic acid, identical with an authentic specimen.

2-*Amino*-6(*and* 7)-*ethylpteridin*-4(3H)-*ones* (43 and 44).—To a solution of 2,4,5-triaminopyrimidin-6(1*H*)-one dihydrochloride (4·3 g., 0·02 mol.) and sodium acetate (4 g.) in water (40 ml.) was added ethanol (30 ml.), and the mixture was warmed to 40° with stirring. Bromomethyl ethyl ketone (6 g., 0·04 mol.) was added dropwise during 20 min. to the stirred suspension, and the resulting mixture was refluxed for 90 min. The solution was cooled and the crystalline product was collected, washed with water and methanol, and dried at 100°. The crude product was dissolved in N-sodium hydroxide (33 ml.), then treated with charcoal, and boiling acetic acid (20 ml.) was added slowly to the hot, filtered solution. The yellow micro-crystalline product was shown by paper chromatography to consist of a mixture of the isomeric 6- and 7-*ethylpteridines* (1·2 g., 31%), m.p. >360° (Found: C, 50·1; H, 4·65; N, 36·8. $C_8H_9N_5O$ requires C, 50·25; H, 4·75; N, 36·65%), pK_a (of the isomeric mixture) 2·28 ± 0·01 and 8·04 ± 0·02 (spectrophotometric determination), $\lambda_{max.}$ [pH 0 (cation)] 245sh (log ε 3·85) and 317 (3·97) mμ, $\lambda_{max.}$ [pH 5 (neutral molecule)] 234 (log ε 4·12), 273 (4·07), and 340 (3·88) mμ, $\lambda_{max.}$ [pH 13 anion)] 252 (log ε 4·28) and 356 (3·91) mμ.

2-*Amino*-4-*methoxy*-7-*phenylpteridine* (56).—2,4-Diamino-6-methoxy-5-nitrosopyrimidine (1·7 g., 0·01 mol.) was suspended in a mixture of water and ethanol (1 : 1; 30 ml.). Raney nickel was added and the mixture was hydrogenated until uptake was complete. The resulting solution was filtered, and immediately a solution of α-chloroacetophenone (2 g., 0·013 mol.) in ethanol (20 ml.) was added, followed by sodium acetate (2 g.) in water (20 ml.). The mixture was refluxed under nitrogen for 2·5 hr. with stirring. Methanol (100 ml.) was added to the resulting red solution, which was then cooled; the crystalline product was collected, washed with a little water, and dried at 40° (*in vacuo*). The crude product was treated, in hot methanol (280 ml.), with charcoal, and to the hot filtrate water (100 ml.) was added dropwise. The 4-*methoxypteridine* (0·98 g., 40%) separated as yellow needles, m.p. 235° (decomp.) (Found: C, 61·4; H, 4·5; N, 27·9. $C_{13}H_{11}N_5O$ requires C, 61·65; H, 4·4; N, 27·65%), pK_a 4·10 ± 0·04 (spectrophotometric determination), $\lambda_{max.}$ [pH 1 (cation)] 282sh (log ε 3·65) and 360 (4·39) mμ, $\lambda_{max.}$ [pH 7 (neutral molecule)] 238 (log ε 4·32), 267 (4·05), 293sh (3·76), and 375 (4·08) mμ.

2-*Amino*-6-*phenylpteridin*-4(3H)-*one* (42).—(*a*) 2,4,5-Triaminopyrimidin-6(1*H*)-one dihydrochloride (5 g., 0·02 mol.) and sodium acetate (8 g.) were dissolved in water (20 ml.). To the boiling solution was added dropwise during 20 min. a solution of α-bromophenylacetaldehyde (20 g., 0·1 mol.) in ethanol (80 ml.). The mixture was refluxed for a further 90 min. then cooled, and the yellow crystalline precipitate was collected, washed with water and ethanol, and dried. The crude product was dissolved in hot 0·5N-sodium hydroxide (110 ml.) and treated with charcoal; neutralization gave the 6-phenylpteridine (2·4 g., 44%) as yellow crystals, m.p. >360° (Found: C, 59·5; H, 3·8; N, 28·0. Calc. for $C_{12}H_9N_5O$: C, 60·25; H, 3·8; N, 29·3%).

The u.v. spectrum of the product agreed with that given by Angier,[12] and, more significantly, the ratio of the extinction coefficients at pH 1 ($\varepsilon_{276}/\varepsilon_{351}$ = 2·14) agreed well with the literature value (2·1) for the 6-phenyl isomer, and was distinct from that (0·3) quoted for the 7-phenyl isomer.

(*b*) The 6-phenylpteridine (42) was also formed when 2,4-diamino-6-phenyl-7*H*-pyrimido[4,5-*b*][1,4]oxazine was heated in an autoclave for 4 hr. at 120° with aqueous ammonia.

2,4-*Diamino*-6,7-*dihydro*-6,7,7-*trimethyl*-5H-*pyrimido*-[4,5-b][1,4]*oxazine* (57).—2,4-Diamino-6,7,7-trimethyl-pyrimido[4,5-*b*][1,4]oxazine hydrochloride (13·1 g., 0·05

mol.) was suspended in water (400 ml.), platinum oxide (0·1 g.) was added, and the mixture was hydrogenated at room temperature. Uptake was slow, but after 2·5 hr. had reached the theoretical value. After filtration, the solution was concentrated to *ca.* 15 ml., the pH was adjusted to 3, and the solution was heated to 100° (the precipitate redissolved). On cooling, the *hydrochloride* (11·5 g., 87%) of the *dihydropyrimido-oxazine* separated as colourless crystals, m.p. 239—240° (decomp.) (Found: C, 41·15; H, 6·7; Cl, 13·4; N, 26·7. $C_9H_{15}N_5O,HCl,H_2O$ requires C, 41·0; H, 6·85; Cl, 13·45; N, 26·6%).

The hydrochloride (11 g.) was dissolved in hot water (50 ml.), and conc. ammonia was added (to pH 7). The colourless product was collected, and gave the free base (5·2 g.), m.p. 218—220 [from boiling water (charcoal)].

2,4-*Diamino*-6,7-*dihydro*-6,7,7-*trimethyl*-5-*nitroso*-5H-*pyrimido*[4,5-b][1,4]*oxazine* (59).—The dihydropyrimido-oxazine (57) (2·1 g.) was suspended in water (10 ml.) and conc. hydrochloric acid was added (to pH 2·5). The mixture was cooled to 0° and stirred while a solution of sodium nitrite (0·77 g.) in water (10 ml.) was added dropwise. After 1 hr. the yellow product was filtered off and dried at 40° *in vacuo*. It was recrystallised from boiling water (85 ml.) (charcoal) to give the N-*nitroso-derivative* (1·08 g., 45%) as yellow crystals, m.p. 255° (decomp.) (Found: C, 45·35; H, 5·8; N, 35·1. $C_9H_{14}N_6O_2$ requires C, 45·35; H, 5·9; N, 35·3%).

2,4-*Diacetamido*-6,7,7-*trimethyl*-7H-*pyrimido*[4,5-b][1,4]-*oxazine* (15).—2,4-Diamino-6,7,7-trimethylpyrimido[4,5-*b*]-[1,4] oxazine (2·2 g., 0·0106 mol.) was refluxed for 30 min. in acetic anhydride (50 ml.). The resulting clear solution was concentrated to *ca.* 5 ml.; yellow crystals separated. These were recrystallised from hot ethyl acetate (8 ml.) (charcoal) to give the 2,4-*diacetamido-derivative* (0·9 g., 29%) as yellow crystals, m.p. 165—167° (Found: C, 53·5; H, 5·85; N, 23·05; N-Ac, 29·1. $C_{13}H_{17}N_5O_3$ requires C, 53·6; H, 5·9; N, 24·05; N-Ac, 29·55%).

2,4-*Diacetamido*-6,7-*dihydro*-6,7,7-*trimethyl*-5H-*pyrimido*-[4,5-b][1,4]*oxazine* (58).—2,4-Diamino-6,7-dihydro-6,7,7-trimethyl-5*H*-pyrimido[4,5-*b*][1,4]oxazine (1 g., 0·005 mol.) and acetic anhydride (30 ml.) were set aside at room temperature for 60 hr. The solution was evaporated to dryness, and the residue was dissolved in boiling ethyl acetate (30 ml.). On cooling, the *diacetyl derivative* separated, and gave colourless crystals (0·54 g., 36%), m.p. 170—174° (from boiling water) (Found: C, 53·55; H, 6·45; N, 23·85; N-Ac, 29·0. $C_{13}H_{19}N_5O_3$ requires C, 53·25; H, 6·55; N, 23·9; N-Ac, 29·35%).

The same compound was formed by catalytic reduction of the 2,4-diacetamido-derivative (15), as for the reduction of the parent compound (10).

Reaction of 7H-*Pyrimido*[4,5-b][1,4]*oxazines with* 1,2-*Dicarbonyl Derivatives*.—(*a*) To the 2,4-diamino-6,7,7-trimethylpyrimido-oxazine (10) (2·62 g., 0·01 mol.) dissolved in boiling water (25 ml.) was added biacetyl (4 ml.), and the mixture was refluxed for 2·5 hr. The solid which separated was identified as 2-amino-6,7-dimethylpteridin-4(3*H*)-one (1·4 g., 73%) by comparison with an authentic specimen.

In similar fashion the following pyrimido-oxazines were refluxed with the stated 1,2-dicarbonyl derivative to give the appropriate pteridine. The oxazinopyrimidine was in each case dissolved in N-hydrochloric acid.

(*b*) The 2-oxo-derivative (21) with biacetyl gave 6,7-dimethylpteridine-2(1*H*),4(3*H*)-dione (73%), m.p. >360° identical with an authentic specimen.

(*c*) The 3-methyl-2-oxo-derivative (22) with biacetyl gave 1,6,7-trimethylpteridine-2(1*H*),4(3*H*)-dione (38%), m.p. 338° (decomp.), identical with an authentic specimen.

(*d*) The 2-oxo-derivative (21) with ethyl pyruvate gave a mixture (26%) of 6-methylpteridine-2(1*H*),4(3*H*),7(8*H*)-trione and 7-methylpteridine-2(1*H*),4(3*H*),6(5*H*)-trione, identified by chromatographic comparison with authentic specimens.

(*e*) The 2-oxo-derivative (21) with methylglyoxal gave 7-methylpteridine-2(1*H*),4(3*H*)-dione (84%), m.p. >330° (Found: C, 46·8; H, 3·45; N, 31·6. Calc. for $C_7H_6N_4O_2$: C, 47·2; H, 3·4; N, 31·45%).

1,2-*Dihydro*-2,2,3-*trimethylquinoxaline* (60).— *o*-Phenylenediamine (16·2 g., 0·15 mol.) was dissolved in ethanol (130 ml.), α-bromoisopropyl methyl ketone (49·5 g., 0·3 mol.) was added, and the mixture was refluxed for 90 min. The clear hot solution was neutralised with N-sodium hydroxide; yellow crystals separated immediately. These were collected, washed with water, and sublimed at 120°/0·001 mm. to give the *dihydroquinoxaline* (17·8 g., 68%) as needles, m.p. 142—145° (Found: C, 75·8; H, 8·0; N, 15·85. $C_{11}H_{14}N_2$ requires C, 75·85; H, 8·1; N, 16·1%), pK_a 4·18 ± 0·03 (spectrophotometric determination), $\lambda_{max.}$ [pH 0 (cation)] 233 (log ε 4·28), 251sh (4·01), 287 (3·53), and 395 (3·25) mμ, $\lambda_{max.}$ [pH 7 (neutral molecule)] 275sh (log ε 3·39) and 330 (3·36) mμ, τ ($CDCl_3$) 2·6—3·6 (m, aryl H), 6·3 (NH), 7·87 (Me), and 8·73 (*gem*-Me_2).

Reaction of o-*Phenylenediamine with* α-*Bromoisobutyraldehyde*.—(a) *In ethanol*. *o*-Phenylenediamine (5 g., 0·046 mol.) was dissolved in the minimum quantity of ethanol, and freshly distilled α-bromoisobutyraldehyde (10 g., 0·065 mol.) was added. The mixture was refluxed for 1 hr. under nitrogen and then evaporated to dryness. The residue was dissolved in water; the solution was made strongly acid with conc. hydrochloric acid and then extracted with ether (3 × 100 ml.) (extracts discarded). Aqueous sodium hydroxide was added to the residual solution, and the brown precipitate was collected and dried. Careful fractional distillation [110° (bath)/10^{-3} mm.] yielded a yellow oil and a residual yellow solid.

Attempts to purify the oil were not completely successful, but repeated distillation gave an impure specimen of 1,2-dihydro-2,2-dimethylquinoxaline (61), $\lambda_{max.}$ (pH 1) 242 and 293 mμ, τ (DCl) 2·4—3·1 (m, aryl H), 6·6 (s, vinyl H), and 8·5 (s, *gem*-Me_2).

The solid gave 2-(α-*ethoxyisopropyl*)*benzimidazole* (62) as needles, m.p. 229—230° (from benzene) (Found: C, 71·05; H, 7·9; N, 14·0. $C_{12}H_{16}N_2O$ requires C, 70·6; H, 7·9; N, 13·7%), $\lambda_{max.}$ (MeOH) 246 (log ε 4·25), 267sh (4·20), 273 (4·40), and 283 (4·35) mμ [*cf.*[35] 2-methylbenzimidazole, $\lambda_{max.}$ (MeOH) 246 (log ε 4·05), 274 (4·05), and 284 (4·15) mμ], τ (DCl) 1·9—2·5 (m, aryl H), 6·25 (q, O·CH_2·CH_3), 7·9 (s, *gem*-Me_2), and 8·44 (t, O·CH_2·CH_3).

(b) *In methanol*. In this case the residual yellow solid, on recrystallisation, gave 2-(α-*methoxyisopropyl*)*benzimidazole* (63) as needles, m.p. 237° (Found: C, 69·65; H, 7·4; N, 14·7. $C_{11}H_{14}N_2O$ requires C, 69·5; H, 7·4; N, 14·75%), τ (DCl) 2·0—2·5 (m, aryl H), 6·43 (s, OMe), and 7·97 (s, *gem*-Me_2).

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