793. *The Preparation of 4-Amino- and Other Pteridines.**

By R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens.

An improved preparation of 4 : 5 : 6-triaminopyrimidine from 4 : 6-diaminopyrimidine-2-sulphinic acid and its condensation with glyoxal to give 4-aminopteridine are described. Several 2-substituted 4-amino- and 4-substituted 2-amino-pteridines have also been prepared.

A large quantity of 4-aminopteridine was required and was prepared by condensation of 4 : 5 : 6-triaminopyrimidine with glyoxal.[1] If the pH of the reaction mixture is controlled, this condensation always proceeds satisfactorily, regardless of the age of the glyoxal.[1] Of the various routes available for the preparation of 4 : 5 : 6-triaminopyrimidine, oxidation of 4 : 5 : 6-triamino-2-mercaptopyrimidine to 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid and desulphination with mineral acid [2] proved most expedient for large-scale working.

* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[2] Hoffer, Jubilee Vol., Emil Barell, 1946, p. 428.

A great disadvantage of this route is the poor yield obtained in the reduction of 4 : 6-diamino-2-mercapto-5-nitrosopyrimidine to the 5-amino-compound. Since 4 : 6-diaminopyrimidine can be nitrated in high yield [3] to give 4 : 6-diamino-5-nitropyrimidine, which in turn has been reduced [4] to give 4 : 5 : 6-triaminopyrimidine, we examined the possibility of preparing 4 : 6-diaminopyrimidine by oxidation of the readily available 4 : 6-diamino-2-mercaptopyrimidine to the corresponding sulphinic acid and subsequent desulphination by mineral acid.[2] Further, 4 : 6-diaminopyrimidine is known to give a colour reaction with nitrous acid,[5] indicating the formation of a 5-nitroso-compound, so that an alternative route might become available for the triamine.

Oxidation of 4 : 6-diamino-2-mercaptopyrimidine by hydrogen peroxide gave the sulphinic acid in high yield, but no 4 : 6-diaminopyrimidine was at first isolated after refluxing the acid in N-sulphuric acid, although sulphur dioxide was liberated in the usual way. It was then found that dry alcoholic hydrogen chloride smoothly decomposed 4 : 6-diaminopyrimidine-2-sulphinic acid at room temperature, to give 4 : 6-diaminopyrimidine hydrochloride in good yield. As both 4 : 6-diaminopyrimidine and its hydrochloride are readily soluble in water, conversion of this desulphination product into its free base (for subsequent nitration) by ordinary chemical means was troublesome, but was most satisfactorily effected by passage down a column of Amberlite IRA-400 (OH) resin. The pyrimidine base was nitrated and reduced and gave 4 : 5 : 6-triaminopyrimidine in excellent yield. 4 : 6-Diamino-5-nitrosopyrimidine was prepared directly from 4 : 6-diaminopyrimidine hydrochloride by treatment of a hydrochloric acid solution of the latter with sodium nitrite, and with sodium dithionite gave the expected 4 : 5 : 6-triaminopyrimidine, though in lower overall yield than was obtained from the nitro-compound.

Since the nitration procedure was to be preferred, a further study of the acid desulphination of pyrimidine-2-sulphinic acids was made, with the object of avoiding the use of ion-exchange resins, and especially to discover why the 4 : 6-diamino-compound behaved differently from the 4 : 5 : 6-triamino-compound. The assumption was made that the mechanism of desulphination of 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid is (I) ⟶ (II) ⟶ (III). The 4-amino-group of 4 : 5-diaminopyrimidine being the more basic,[6] it would be expected that in acid solutions 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid would first accept a proton to give the resonance-stabilised cation (I) and that the acceptance of a second proton to give (II) would provide the necessary conditions for heterolytic cleavage of the C–S bond, yielding the ion (III), sulphur dioxide, and a proton. In acid solution, the ion (III) will then give the 4 : 5 : 6-triaminopyrimidine cation.

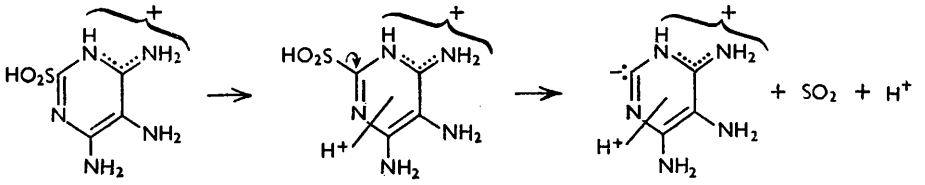
Although an amino-group in the 5-position of the pyrimidine nucleus has only feebly basic properties,[7] it seems reasonable to presume that the monocation (I) derived from 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid will more readily accept the second proton than will the monocation (IV) derived from 4 : 6-diaminopyrimidine 2-sulphinic acid, so that in the latter case desulphination occurs less readily. It follows therefore that, if on treatment of 4 : 6-diaminopyrimidine-2-sulphinic acid with boiling N-sulphuric acid the cation (IV) does not readily accept a second proton, cleavage of the C–S bond will be inhibited and decomposition may be expected to occur in the manner accepted for aromatic sulphinic acids : [8]

$$3R{\cdot}SO_2H \longrightarrow R{\cdot}SO_2{\cdot}SR + R{\cdot}SO_3H + H_2O$$

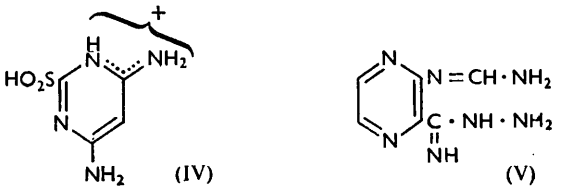
[mechanistically, this may proceed by disproportionation (cf. Kharasch [9])]. The pyrimidinesulphonic acid corresponding to $R{\cdot}SO_3H$ would be hydrolysed under these conditions [10] to 4 : 6-diamino-2-hydroxypyrimidine. There is the further possibility of radical decomposition. We may expect to find in this reaction, then, loss of sulphur dioxide and

[3] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 355.
[4] Robins, Dille, Willits, and Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.
[5] Lythgoe, Todd, and Topham, *J.*, 1944, 315.
[6] Gabriel and Colman, *Ber.*, 1899, **32**, 2929; Forrest and Walker, *J.*, 1949, 79.
[7] Whittaker, *J.*, 1951, 1565.
[8] Otto, *Ber.*, 1876, **9**, 1639; Pauly and Otto, *Ber.*, 1877, **10**, 2181; 1878, **11**, 2070, 2073; von Braun and Weissbach, *Ber.*, 1930, **63**, 2836.
[9] Kharasch, *Chem. Rev.*, 1946, **39**, 269.
[10] Greenbaum and Holmes, *J. Amer. Chem. Soc.*, 1954, **76**, 2899.

the formation of 4 : 6-diaminopyrimidine, 4 : 6-diamino-2-hydroxypyrimidine, and some complex compounds of the disulphoxide type. A closer experimental examination of this reaction proved this to be so, for 4 : 6-diaminopyrimidine and 4 : 6-diamino-2-hydroxypyrimidine were isolated and identified; a compound agreeing in composition with that of the disulphoxide type was isolated, but its constitution was not rigidly established.



(I) (II) (III)



(IV) (V)

If on the other hand the acid strength of the medium for the desulphination of 4 : 6-diaminopyrimidine-2-sulphinic acid is increased, the monocation (IV) may be forced to accept a second proton and normal desulphination should occur. By decomposing the sulphinic acid with 20N-sulphuric acid in the cold, quantitative conversion into 4 : 6-diaminopyrimidine sulphate was achieved; this sulphate could be nitrated without conversion into the free base. Similarly, 20N-sulphuric acid may be used to convert 4 : 5 : 6-triaminopyrimidine-2-sulphinic acid into 4 : 5 : 6-triaminopyrimidine sulphate. Concentrated hydrochloric acid also converted 4 : 6-diaminopyrimidine-2-sulphinic acid into 4 : 6-diaminopyrimidine hydrochloride in high yield. These reactions are extremely rapid and the isolated compounds are free from by-products.

4 : 6-Diamino-5-nitropyrimidine was satisfactorily reduced with hydrogen and Raney nickel or sodium dithionite or iron and hydrochloric acid. The overall yield of 4-aminopteridine by the route outlined was greater than 30%.

When heated with aqueous ammonia to 170° 4-aminopteridine was quantitatively converted into ammonium 2-aminopyrazine-3-carboxylate (cf. Taylor [11]). Heating the pteridine with hydrazine led to a crystalline compound giving the analytical figures for 2-amidrazono-3-formamidinopyrazine (V). It was also noted that 4-aminopteridine formed a complex with oxalic acid from which the base could be regenerated by action of ammonia.

Interest in the biological properties of 4-aminopteridine lead to the preparation of many other pteridines; these were synthesised by conventional methods,[12] and preparations of some of the new compounds are reported in the Experimental section.

Experimental

N.B. : Difficulty was encountered in obtaining good analytical results for some of the compounds prepared, in spite of repeated crystallisations.[12]

The term " spirit " in the text refers to industrial methylated spirits.

4 : 5 : 6-*Triaminopyrimidine-2-sulphinic Acid.*—4 : 5 : 6-Triamino-2-mercaptopyrimidine sulphate (174 g.) was dissolved in 2N-sodium hydroxide (1070 ml.) and cooled to <10°.

[11] Taylor, Ciba Foundation Symposium, " The Chemistry and Biology of Pteridines," Churchill Ltd., London, 1954, p. 2.

[12] Albert, *Quart. Rev.*, 1952, **6**, 197.

6% Hydrogen peroxide (696 ml.) was slowly added with stirring so that the temperature did not exceed 20° (ice-water cooling) during 45 min.; stirring was continued for a further 30 min. and the mixture filtered. Acidification of the filtrate with glacial acetic acid (100 ml.) precipitated the sulphinic acid which was washed with water, then methanol, and air-dried, to give an off-white friable powder (98 g., 85%) identical with that described by Hoffer.[2] If a precipitate does not appear during the oxidation, the sulphinic acid must be purified by dissolving it in 3% ammonia solution (860 ml.), filtering from insoluble impurity, and reprecipitation with acetic acid; the yield is the same as above.

4 : 5 : 6-*Triaminopyrimidine Sulphate.—Hoffer's procedure.*[2] 4 : 5 : 6-Triaminopyrimidine-2-sulphinic acid (50 g.) was boiled under reflux in N-sulphuric acid (1100 ml.) for 2 hr., by which time evolution of sulphur dioxide had ceased. The hot solution was filtered from a little sulphur, and the filtrate cooled to 0° overnight. The crystalline product was removed, washed with a little cold water, then methanol and finally with ether, and air-dried to give crude 4 : 5 : 6-triaminopyrimidine sulphate (46 g.). The material was purified by heating it to incipient boiling with water (460 ml.) and ammonia (46 ml.; *d* 0·880), cooling to room temperature, removing the insoluble impurity, and reprecipitating the sulphate by addition of 50% v/v sulphuric acid (20 ml.). In this way, almost white 4 : 5 : 6-triaminopyrimidine sulphate (40 g.) was obtained. Recrystallisation from water gave white plates (Found : C, 20·4; H, 4·95; N, 29·05. Calc. for $C_4H_7N_5,H_2SO_4,H_2O$: C, 19·9; H, 4·6; N, 29·05%). Cf. also p. 4110.

4-*Aminopteridine.*—4 : 5 : 6-Triaminopyrimidine sulphate (50 g.) was dissolved in N-sodium hydroxide (415 ml.) at 70—75°. The pH of this solution should be 9·5—10·5. To the solution of the base was added a solution of glyoxal (25 g. of commercial 50% material) in water (250 ml.) at 70—75° with stirring and the mixture was placed on a steam-bath for 1 hr. After cooling to 0°, the crude 4-aminopteridine was removed, washed with water, and crystallised from 100 parts of water (charcoal) to give an off-white product (20 g.) m. p. 309—311° (decomp.) (ultraviolet absorption spectra in neutral and acid solution were identical with those described by Albert, Brown, and Cheeseman.[1] Infrared absorption, Nujol mull, gave peaks at 3400, 3180, 1658, 1580, 1550, and 1520 cm.$^{1-}$) (Found : C, 49·5; H, 3·4; N, 47·6. Calc. for $C_6H_5N_5$: C, 49·0; H, 3·4; N, 47·5%). The following figures give the yields of crude 4-aminopteridine, in parentheses, when the condensation was done at different pH : pH 11·9 (49·2%); pH 10·5 (79·5%); pH 7·2 (33·6%); pH 6·9 (61·5%).

4-Aminopteridine (1 g.) was dissolved in warm N-oxalic acid (27·2 ml.) and filtered and the filtrate allowed to cool, to give a granular *oxalate* (1·35 g.) which crystallised from water [Found : C, 43·6; H, 3·8; N, 39·9. $(C_6H_5N_5)_2,(CO_2H)_2$ requires C, 43·75; H, 3·15; N, 36·5%].

4 : 6-*Diaminopyrimidine-2-sulphinic Acid.*—To a solution of 4 : 6-diamino-2-mercaptopyrimidine (50 g.) in 2N-sodium hydroxide (220 ml.) was added 3% hydrogen peroxide solution (750 ml.) at <20° (cooling). Stirring was continued for a further 30 min. and the clear pale yellow solution acidified with acetic acid (*ca.* 50 ml.). The precipitate was washed with water, methanol, and then ether and air-dried, to give an off-white amorphous *acid* (58 g., 95%), m. p. 168—170° (decomp.). For analysis, a sample was dissolved in dilute aqueous ammonia and reprecipitated with acetic acid (Found : C, 27·8; H, 3·8; N, 32·1. $C_4H_6O_2N_4S$ requires C, 27·6; H, 3·5; N, 32·2%). The above oxidation, on 100 g. scale, gave a 98% yield.

4 : 6-*Diaminopyrimidine Hydrochloride.*—(*a*) 4 : 6-Diaminopyrimidine-2-sulphinic acid (50 g.) was shaken for 30 min. in dry ethanol (500 ml.) containing dry 2·5N-ethanolic hydrogen chloride (150 ml.). The mixture was cooled to 0° and after 1 hr. the crystals were removed, washed with ether, and dried to give pale yellow needles (23 g.), m. p. 196—198°. Concentration of the original filtrate to 250 ml., followed by addition of ether (750 ml.), gave a further crop of almost white needles (15 g.), m. p. 188°. Recrystallisation from spirit gave white needles, m. p. 203—204° identical with a specimen of hydrochloride prepared from authentic 4 : 6-diaminopyrimidine (Found : C, 33·3; H, 4·8; N, 38·1; Cl, 24·1. $C_4H_6N_4,HCl$ requires C, 32·8; H, 4·8; N, 3·82; Cl, 24·2%). Ultraviolet absorption max. in EtOH : 221 (ε 24,500) and 265 mμ (ε 1167).

(*b*) The sulphinic acid (5 g.) was added portion-wise to hydrochloric acid (15 ml.; *d* 1·18) at room temperature. The reaction was vigorous and sulphur dioxide was freely evolved. Hydrochloric acid was removed from the resulting slurry under reduced pressure, and the residue washed with acetone, then ether, to give 4 : 6-diaminopyrimidine hydrochloride (4·05 g.), m. p. 195°. Recrystallisation of a sample from spirit raised the m. p. to 201—202° (undepressed when mixed with an authentic sample).

4 : 6-*Diaminopyrimidine.*—A solution of 4 : 6-diaminopyrimidine hydrochloride (**38** g.) in water (380 ml.) was allowed to percolate through a column of Amberlite IRA-400 (OH) resin (150 g.), and the column eluted with water (6 l.). As the eluate was found to have a pH of 5 it

was again allowed to percolate through the regenerated column. Removal of the water from the second eluate gave 4 : 6-diaminopyrimidine (26 g.) as colourless needles, m. p. 273—274°.

Desulphination of 4 : 6-*Diaminopyrimidine-2-sulphinic acid with* N-*Sulphuric Acid.*—4 : 6-Diaminopyrimidine-2-sulphinic acid (10 g.) was boiled under reflux with N-sulphuric acid (230 ml.) for 1 hr., the clear solution was treated with charcoal and filtered, and the filtrate cooled to 0° for 24 hr. The precipitate was washed and dried, to give colourless needles of 4 : 6-diamino-2-hydroxypyrimidine sulphate (4·65 g.) (Found: C, 25·05; H, 4·9; N, 28·55; S, 8·5. Calc. for $C_4H_6ON_4,\frac{1}{2}H_2SO_4,H_2O$: C, 24·9; H, 4·7; N, 29·0; S, 8·3%). The infrared spectrum of this compound was identical with that of 4 : 6-diamino-2-hydroxypyrimidine sulphate prepared from authentic 4 : 6-diamino-2-hydroxypyrimidine.[13]

The original filtrate from the above preparation was heated to boiling and treated with barium hydroxide (36·2 g. of octahydrate) in hot water (50 ml.). After filtration and washing of the barium sulphate, the filtrate was cooled and saturated with carbon dioxide to precipitate barium carbonate. This was removed and the filtrate evaporated to dryness at reduced pressure to a white solid residue (3·67 g.). Extraction of the residue with boiling spirit gave, after concentration, colourless needles (1·12 g.) of 4 : 6-diaminopyrimidine, m. p. and mixed m. p. 274—275°. The spirit-insoluble residue (0·73 g.) crystallised from water as a white *substance*, m. p. <330° (Found: C, 29·3; H, 4·0; N, 34·1. $C_8H_{10}O_2N_8S_2,H_2O$ requires C, 28·9; H, 3·6; N, 33·7%). A similar product was obtained on reaction of the sulphinic acid with Amberlite IR-120 (H) in water at 80°.

4 : 6-*Diaminopyrimidine Sulphate.*—(a) *Reference compound.* 4 : 6-Diamino-2-mercaptopyrimidine (30 g.) was desulphurised by Brown's method [3] to give 4 : 6-diaminopyrimidine (15·7 g.), m. p. 267—268°. This material (1 g.) was dissolved in sulphuric acid (2 ml.; *d* 1·84) with cooling and the clear solution poured into excess of spirit, to precipitate 4 : 6-*diaminopyrimidine sulphate*, m. p. 181—185° (decomp.) (Found: C, 21·4; H, 3·65; N, 25·2. $C_4H_6N_4,H_2SO_4,H_2O$ requires C, 21·2; H, 4·5; N, 24·7%). Repeated recrystallisation of this sulphate from aqueous alcohol gave another stable *sulphate*, m. p. 247° (decomp.), containing only half a mol. of sulphuric acid (Found: C, 27·25; H, 5·0; N, 32·2. $C_4H_6N_4,\frac{1}{2}H_2SO_4,H_2O$ requires C, 27·1; H, 5·1; N, 31·6%).

(b) *By desulphination.* 4 : 6-Diaminopyrimidine-2-sulphinic acid (9 g.) was added to 20N-sulphuric acid (36 ml.) with stirring at room temperature. The mixture evolved sulphur dioxide and thickened. When addition was complete, the mixture was heated to 90°, then cooled, and acetone added to give a total volume of 250 ml. The precipitated sulphate was removed, washed with acetone, then ether, and dried to give off-white crystals (11·5 g., 98%), m. p. 183—184°.

4 : 5 : 6-*Triaminopyrimidine Sulphate.*—(a) *Iron–hydrochloric acid reduction.* The *wet* 4 : 6-diamino-5-nitropyrimidine obtained by nitration of 4 : 6-diaminopyrimidine (25 g.; Brown [3]) was suspended in water (1600 ml.), iron reduced by hydrogen (32 g.), and concentrated hydrochloric acid (2 ml.) were added, and the mixture was heated on a boiling-water bath for 2½ hr. with vigorous stirring. The mixture was filtered, and the filtrate acidified with 50% v/v sulphuric acid (160 ml.), and cooled to give 4 : 5 : 6-triaminopyrimidine sulphate (41 g.).

(b) *Sodium dithionite reduction.* Finely ground 4 : 6-diamino-5-nitropyrimidine (7·5 g.) was suspended in water (150 ml.) at 80° and sodium dithionite (37·5 g.) added with vigorous stirring. After 10 min., the mixture was gently boiled for 5 min., then filtered to remove unchanged nitrocompound (0·3 g.). Acidification of the filtrate with 50% v/v sulphuric acid (75 ml.) gave 4 : 5 : 6-triaminopyrimidine sulphate (7·7 g.); a further quantity (1·3 g.) was obtained from the mother-liquors after boiling to remove sulphur dioxide. Recrystallisation of the combined products from dilute sulphuric acid gave white plates (7·73 g.) of 4 : 5 : 6-triaminopyrimidine sulphate.

(c) *By desulphination.* 4 : 5 : 6-Triaminopyrimidine-2-sulphinic acid (9 g.) was added to 20N-sulphuric acid (36 ml.). After cooling, acetone (200 ml.) was added and the white solid (12·4 g.) removed. Recrystallisation from water (100 ml.) containing 2N-sulphuric acid (25 ml.) gave white plates of 4 : 5 : 6-triaminopyrimidine sulphate (8·2 g.).

4 : 6-*Diamino-5-nitrosopyrimidine.*—A solution of 4 : 6-diaminopyrimidine hydrochloride (2 g.) in N-hydrochloric acid (48 ml.) was cooled to between 0° and −5°. Sodium nitrite (1·41 g.) in water (15 ml.) was added during 20 min. with cooling to <0°. The solution was stirred for a further hour, whilst being allowed to come to room temperature, before addition of solid sodium hydrogen carbonate to pH 8. The light blue, solid *nitroso-compound* was filtered off, washed with cold water, and reduced without drying. A sample for analysis was obtained as

[13] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3112.

fine blue plates from water (Found : C, 34·7; H, 3·6; N, 50·9. $C_4H_5ON_5$ requires C, 34·5; H, 3·6; N, 50·35%).

The moist nitroso-compound was suspended in water (20 ml.) at 60°, and sodium dithionite (5 g.) added portionwise, giving a clear orange solution. This was heated to the b. p., acidified with 50% v/v sulphuric acid (15 ml.), boiled for a few minutes, and cooled to room temperature. The precipitated solid was removed, washed with water, spirit, and ether, and dried to give 4 : 5 : 6-triaminopyrimidine sulphate as pale yellow needles (1·8 g.).

2-Aminopyrazine-3-carboxylic Acid.—4-Aminopteridine (20 g.), ammonia (400 ml.; *d* 0·88), and water (600 ml.) were heated together in an autoclave at 165—170° for 1 hr., then allowed to cool overnight. The resulting solution was evaporated to dryness under reduced pressure to give a bright yellow solid (21·6 g.), m. p. 226° (decomp.). Crystallisation from 50% aqueous acetone gave pale yellow needles of ammonium 2-aminopyrazine-3-carboxylate, m. p. 232° (decomp.) (Found : C, 38·9; H, 5·1; N, 36·5. $C_5H_8O_2N_4$ requires C, 38·5; H, 5·2; N, 35·9%). Ultraviolet absorption max. in H_2O : 242 (ε 10,050) and 340 mμ (ε 6020). A solution of this salt in water, adjusted to pH 2·5 by addition of hydrochloric acid, gave needles of 2-aminopyrazine-3-carboxylic acid, m. p. 203—204° (decomp.), identical (infrared comparison) with a specimen prepared by the method of Weijlard, Tishler, and Erickson.[14]

Action of Hydrazine on 4-Aminopteridine.—4-Aminopteridine (0·27 g.) was refluxed for 10 min. in 90% hydrazine hydrate (5 ml.), forming a deep red solution. After cooling, the solution was diluted with water and extracted with ethyl acetate, evaporation of which gave pale yellow crystals, m. p. 170—172°. Recrystallisation from *cyclo*hexane–ethanol gave *2-amidrazono-2-formamidinopyrazine* as yellow needles, m. p. 173—174° (Found : C, 40·4; H, 4·9; N, 54·3. $C_6H_9N_7$ requires C, 40·2; H, 5·1; N, 54·7%).

4-Amino-2-methylpteridine.—4 : 5 : 6-Triamino-2-methylpyrimidine [5] (3 g.) was dissolved in boiling 2N-sulphuric acid (25 ml.), and the solution cooled to give the crystalline sulphate. After being washed with acetone and air-dried, the sulphate was dissolved in N-sodium hydroxide (40 ml.) at 70—75° and the pH of the solution adjusted, if necessary to 9—10. Glyoxal (2 g.; 50% commercial syrup) in water (20 ml.) at 75° was added and the mixture was allowed to cool to room temperature; the crude *pteridine* was removed, crystallised from water (charcoal), and dried to give off-white needles (2·4 g.), m. p. 234—235° (Found : C, 52·3; H, 4·2. $C_7H_7N_5$ requires C, 52·2; H, 4·4%). Ultraviolet absorption max. in EtOH : 247 (ε 13,800) and 340 mμ (ε 4880).

2-Substituted 4 : 6-Diamino-5-phenylazopyrimidines.—The compounds in Table 1 were prepared by condensation of the appropriate amidine hydrochloride with phenylazomalononitrile by the method of Lythgoe, Todd, and Topham.[5]

TABLE 1. *2-Substituted 4 : 6-diamino-5-phenylazopyrimidines.*

2-Subst.	M. p.	Colour	Solvent for recryst.	Yield [a] (%)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Et	263—264°	Orange	Ethanol	23	59·3	6·0	$C_{12}H_{14}N_6$	59·5	5·8
Pr^n	255—256	Light brown	,,	45	60·6	6·2	$C_{13}H_{16}N_6$	60·9	6·3
Bu^n	262	Golden	Spirit	33	61·5	6·3	$C_{14}H_{18}N_6$	62·2	6·7
Bu^i	260—261	Golden-yellow	,,	47	62·6	6·6	$C_{14}H_{18}N_6$	62·2	6·7
Ph	294—295	Orange	Pyridine	67	66·3	5·0	$C_{16}H_{14}N_6$	66·2	4·9
CH_2Ph	275	Orange	,,	55	66·7	5·2	$C_{17}H_{16}N_6$	67·1	5·3
p-Cl·C_6H_4·CH_2	277	Orange	Et acetate	70	60·4	4·6	$C_{17}H_{15}N_6Cl$	60·3	4·5
p-C_6H_4Me ...	306—307	Red	Pyridine	80	67·0	5·5	$C_{17}H_{16}N_6$	67·1	5·3

[a] Based on the substituted amidines.

2-Substituted 4 : 5 : 6-Triaminopyrimidines.—The compounds in Table 2 were prepared by reduction of the preceding azo-compounds.

2-Substituted 4-Aminopteridines.—Condensation of the above triaminopyrimidines with glyoxal in the manner already described gave the 2-substituted 4-aminopteridines described in Table 3.

4-Amino-2-methoxypteridine.—4 : 6-Diamino-2-chloro-5-nitropyrimidine (1·5 g.), methanol (60 ml.), and potassium hydroxide (1·5 g.) were boiled under reflux for 30 min.; after cooling, the cream-coloured solid was removed, washed with water, then methanol, and dried to give a crystalline product, m. p. 263° (1·05 g.). This product (1·0 g.) was suspended in dry ethanol (150 ml.) and reduced with hydrogen at 40—50°/50 atm. in presence of Raney nickel for 12 hr.

[14] Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.

After removal of catalyst from the hot mixture, the filtrate was concentrated to small bulk (25 ml.) and the dark solution boiled with charcoal and filtered. The filtrate was boiled with 50% glyoxal (0·63 g.) in water (10 ml.) for ½ hr., then evaporated under vacuum, and the residue crystallised from spirit (charcoal) to give 4-*amino*-2-*methoxypteridine* (0·25 g.), m. p. 222—225°. From spirit this formed very pale yellow crystals (0·16 g.), m. p. 224—225° (Found: C, 47·6; H, 4·2; N, 40·1. $C_7H_7ON_5$ requires C, 47·5; H, 4·0; N, 39·6%).

4-*Amino*-2-*di*-n-*butylaminopteridine*.—4 : 6-Diamino-2-chloro-5-nitropyrimidine (0·5 g.), di-*n*-butylamine (1 ml.), and dry ethanol (5 ml.) were refluxed for 3 hr. After cooling, the mixture was diluted with ether and filtered from a little starting material, and the filtrate washed with water. The ether solution was dried ($MgSO_4$), then evaporated to an orange gum which with

TABLE 2. 2-*Substituted* 4 : 5 : 6-*triaminopyrimidines*.

2-Subst.	M. p.	Solvent [a]	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	Redn. [b]
Et	272°	H_2O	87	46·5	7·2	45·3	$C_6H_{11}N_5$	47·0	7·2	45·7	1
Pr^n	171—172	CH	90	50·4	7·9	41·1	$C_7H_{13}N_5$	50·3	7·8	41·9	2
Bu^n	151—152	EtOH–CH	90	52·8	8·6	38·9	$C_8H_{15}N_5$	53·0	8·3	38·6	2
Bu^i	176	C_6H_6	75	52·7	8·3	—	$C_8H_{15}N_5$	53·0	8·3	—	2
Ph	189—190	H_2O	64	[c]	[c]	35·4	$C_{10}H_{11}N_5$	—	—	34·8	3
CH_2Ph	223—224	,,	62	60·7	6·05	33·4	$C_{11}H_{13}N_5$	61·4	6·1	32·5	3
p-Cl·C_6H_4·CH_2	244—245	,,	90	53·3	4·9	—	$C_{11}H_{12}N_5Cl$	52·9	4·85	—	4
p-C_6H_4Me ...	210—211	,,	53	61·9	6·3	—	$C_{11}H_{13}N_5$	61·4	6·1	—	3

[a] CH = *cyclo*hexane. [b] Methods of reduction: 1, Hydrogen and Adams catalyst at room temperature and atmospheric pressure in ethanol. 2, Hydrogen and Raney nickel at 100°/70 atm. in ethanol. 3, Zinc and acetic acid.[13] 4, Palladium–charcoal–hydrogen in formic acid (Davold and Lowy, *J. Amer. Chem. Soc.*, 1952, **74**, 1563). [c] *Sulphate*, m. p. 238—242° (Found: N, 21·7. $C_{10}H_{11}N_5,H_2SO_4,H_2O$ requires N, 22·1%).

TABLE 3. 2-*Substituted* 4-*aminopteridines*.

No.	2-Subst.	M. p.	Solvent [a]	Yield (%)	Ultraviolet spectrum max. (mμ)	ε	Solvent
1	Et	170°	C_6H_6	55 [c]	245, 336	16,900, 5880	H_2O
2	Pr^n	145—146	,,	49	247, 335	17,900, 5920	EtOH
3	Bu^n	136—137	C_6H_4–CH	44	247, 340	20,600, 6550	,,
4	Bu^i	156	C_6H_6	44	247, 339	19,000, 5540	,,
5	Ph	240—241	H_2O	38 [d]	204, 271, 342	21,200, 19,700 6850	H_2O
6	CH_2Ph	188—189	[b]	63 [e]	247, 337	19,000, 5780	EtOH
7	*p*-Cl·C_6H_4·CH_2	185—186	[b]	17	248, 335	21,700, 6450	,,
8	*p*-C_6H_4Me	269—270	Spirit	58	204, 254, 285, 349	25,900, 13,650, 28,400, 8800	,,

No.	Found (%) C	H	N	Formula	Required (%) C	H	N
1	55·3	5·2	39·85	$C_8H_9N_5$	54·8	5·2	40·0
2	57·4	5·9	36·7	$C_9H_{11}N_5$	57·1	5·9	37·0
3	59·4	6·6	34·45	$C_{11}H_{13}N_5$	59·1	6·45	34·5
4	59·1	6·2	32·9	$C_{11}H_{13}N_5$	59·1	6·45	34·5
5	64·9	4·3	—	$C_{12}H_9N_5$	64·6	4·1	—
6	—	—	29·7	$C_{13}H_{11}N_5$	—	—	29·5
7	57·9	3·6	24·8	$C_{13}H_{10}N_5Cl$	57·5	3·7	25·8
8	66·0	4·75	30·5	$C_{13}H_{11}N_5$	65·8	4·7	29·5

[a] CH = *cyclo*Hexane. [b] Purified by dissolution in 0·5N-HCl and repptn. by aq. NH_3. [c–e] Material of m. p. (*c*) 155—160°, (*d*) 235—236°, (*e*) 183—185°.

light petroleum (b. p. 40—60°) gave pale yellow needles (0·35 g.), m. p. 88—90°. The product (0·35 g.) was reduced in methanol (20 ml.) by hydrogen and Adams catalyst at room temperature and pressure. After removal of the catalyst, the colourless solution rapidly became orange-yellow, and 50% glyoxal (0·15 g.) in water (10 ml.) was added. The solution was refluxed for 1¼ hr., then evaporated, and the residue extracted with ethyl acetate. Evaporation of the ethyl acetate gave a gum which was chromatographed in benzene on acid-washed alumina. Elution with light petroleum–benzene (1 : 9) and evaporation of the eluate gave bright yellow

crystals (0·13 g.), m. p. 110—112°. Recrystallisation from aqueous spirit gave *4-amino-2-di-n-butylaminopteridine* as pale yellow needles, m. p. 110—112° (Found: C, 60·9; H, 7·7; N, 30·9. $C_{14}H_{22}N_6$ requires C, 61·4; H, 8·0; N, 30·6%).

2-Amino-4-methylpteridine.—2 : 4 : 5-Triamino-6-methylpyrimidine [15] (1 g.) was refluxed with a solution of glyoxal sodium hydrogen sulphite (2·24 g.) in water (22 ml.) for 80 min. The hot solution was filtered and the filtrate cooled, giving a brown solid. After being washed with alcohol the solid was shaken with N-sodium hydroxide (16 ml.) for 30 min., then filtered off, washed with water, and crystallised from water. *2-Amino-4-methylpteridine* (0·35 g.) separated as small yellow needles, slow decomp. from 290° (Found: C, 52·3; H, 4·3; N, 44·1. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·5%). Ultraviolet absorption max. in H_2O: 226 (ε 28,000), 260 (ε 7800), and 368 mμ (ε 7100).

4-Alkyluracils.—The following compounds were prepared from the appropriate 2-thiouracils (cf. Anderson, Halverstadt, Miller, and Roblin [16]) by Brown's method [17] (yields are in parentheses): 4-Ethyluracil, (90%), m. p. 201—203°; Robinson and Tomlinson [18] give m. p. 205°. 4-n-*Propyluracil* (81%), colourless needles (from water), m. p. 217—219° (Found: C, 54·6; H, 6·4. $C_7H_{10}O_2N_2$ requires C, 54·5; H, 6·5%). 4-iso*Propyluracil* (71%), colourless plates (from water), m. p. 199—200° (Found: N, 18·4. $C_7H_{10}O_2N_2$ requires N, 18·2%).

6-Alkyl-2 : 4-diamino-5-nitropyrimidines.—Nitration of the appropriate uracil according to Gabriel and Colman's method [19] followed by treatment with phosphorus oxychloride and diethylaniline [20] and amination in phenol [21] gave the following compounds: 2 : 4-*Diamino-6-ethyl-5-nitropyrimidine* (35%), yellow rhombs (from alcohol), m. p. (double) 179° and 191° (Found: C, 39·1; H, 5·0; N, 38·0. $C_6H_9O_2N_5$ requires C, 39·3; H, 4·95; N, 38·2%). 2 : 4-*Diamino-5-nitro-6-n-propylpyrimidine* (29%), pale yellow plates (from alcohol), m. p. 162—164° (Found: C, 42·9; H, 5·55; N, 36·1. $C_7H_{11}O_2N_5$ requires C, 42·6; H, 5·6; N, 35·5%). 2 : 4-*Diamino-5-nitro-6-iso*propylpyrimidine (24%), rhombs (from alcohol), m. p. 152—154° (Found: C, 42·3; H, 5·45; N, 35·3%).

6-Alkyl-2 : 4 : 5-triaminopyrimidines.—Hydrogenation of the nitropyrimidines in methanol with Raney nickel [22] gave 2 : 4 : 5-*triamino-6-ethylpyrimidine* (57%), pale yellow prisms (from methanol), m. p. 244—248° (Found: C, 46·9; H, 7·3; N, 44·8. $C_6H_{11}N_5$ requires C, 47·0; H, 7·2; N, 45·7%), 2 : 4 : 5-*triamino-6-n-propylpyrimidine* (77%), colourless rhombs (from ethanol), m. p. 183—186° (Found: C, 50·55; H, 7·6; N, 40·7. $C_7H_{13}N_5$ requires C, 50·3; H, 7·8; N, 41·9%), and 2 : 4 : 5-triamino-6-*iso*propylpyrimidine (91%), a pale blue unstable solid, m. p. 158—160°.

4-Alkyl-2-aminopteridines.—Condensation of the appropriate triaminopyrimidine with glyoxal sodium hydrogen sulphite as described for 2-amino-4-methylpteridine gave the following compounds: *2-Amino-4-ethylpteridine* (4%), long orange needles (from water), m. p. 186—188° (Found: C, 54·6; H, 5·3; N, 40·5. $C_8H_9N_5$ requires C, 54·8; H, 5·2; N, 40·0%). Ultraviolet absorption max. in H_2O: 226 (ε 26,700), 259 (ε 7300), and 369 mμ (ε 7150). *2-Amino-4-n-propylpteridine* (40%), pale brown plates (from ethanol), m. p. 183—184° (Found: C, 56·8; H, 5·6; N, 35·1. $C_9H_{11}N_5$ requires C, 57·1; H, 5·9; N, 37·0%). Ultraviolet absorption max. in H_2O: 227 (ε 24,100), 260 (ε 6000), and 368 mμ (ε 5400). *2-Amino-4-isopropylpteridine* (62%), fine yellow needles (from water), m. p. 162—164° (Found: C, 57·1; H, 5·7; N, 37·45%). Ultraviolet absorption max. in H_2O: 226 (ε 21,000), 259 (ε 6700), and 368 mμ (ε 5800).

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GLAXO LABORATORIES LTD.,
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