643. *Pteridine Derivatives. Part III.*[1] *Bisdihydropurinyls.*

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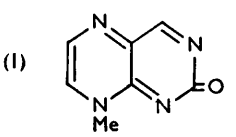
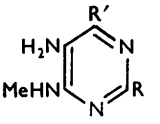
Condensation of 5-amino-2-hydroxy-4-methylaminopyrimidine with glyoxal gave bis-(8 : 9-dihydro-2-hydroxy-9-methylpurin-8-yl) (III; R = OH, R′ = H), and not the expected *N*-alkylpteridone (I). Analogous dihydropurinyls were obtained from glyoxal and other 5-amino-4-methylpyrimidines. Syntheses of several azomethines from glyoxal and 5- or 4-aminopyrimidines are reported. The condensation of 2 : 4 : 5-triamino-6-hydroxypyrimidine with chloral has been re-investigated, and a new synthesis of xanthopterin is described.

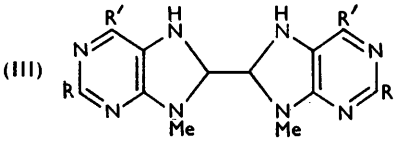
In an attempt to synthesise 2 : 8-dihydro-8-methyl-2-oxopteridine (I), it was observed that condensation of 5-amino-2-hydroxy-4-methylaminopyrimidine (II; R = OH, R′ = H) with glyoxal gave a sparingly soluble, high-melting solid, which had none of the properties

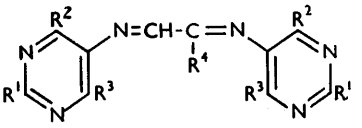

(I)


(II)

normally associated with *N*-alkylpteridones.[1] This compound, $(C_6H_7ON_4)_n$, was readily soluble in dilute acid or alkali, and was precipitated unchanged from either on neutralisation. Insolubility prevented determination of the molecular weight, and an attempt to prepare a more soluble derivative by methylation was unsuccessful.

Analogous compounds were obtained by condensation of glyoxal with 5-amino-4-methylaminopyrimidine (II; R = R′ = H), 5-amino-4 : 6-bismethylaminopyrimidine (II; R = H, R′ = NHMe), or 5-amino-4-chloro-6-methylaminopyrimidine (II; R = H, R′ = Cl). The chloro-compound was sufficiently soluble in camphor to permit deter-


(III)

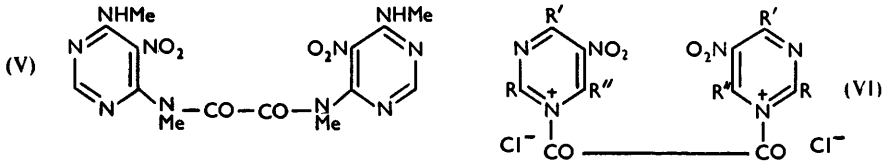

(IV)

mination of the molecular weight which indicated that two pyrimidine nuclei had combined with one glyoxal molecule. Comparison of the ultraviolet absorption spectrum of any one of the insoluble compounds with that of the corresponding pyrimidine (Fig. 1) indicated that the pyrimidine nuclei were not linked by a conjugated system. We therefore propose structures (III) for these materials.

We have excluded the alternative azomethine structure (IV; R^3 = NHMe, R^4 = H) by synthesis of an authentic azomethine (IV; $R^1 = R^2 = NMe_2$, $R^3 = R^4$ = H) from glyoxal and 5-amino-2 : 4-bisdimethylaminopyrimidine. This compound was bright red,

[1] Part II, Albert, Brown, and Wood, *J.*, 1956, 2131.

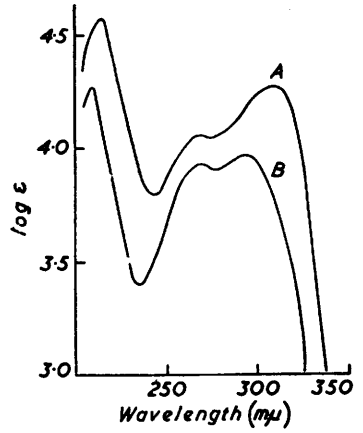
the ultraviolet absorption spectrum (Fig. 2) was distinct from that of the bisdihydropurinyls, and dilute acid readily hydrolyses it to the original pyrimidine, though the bisdihydropurinyls were unaffected by similar treatment. Neither 5-aminopyrimidine



nor 5-amino-4 : 6-dichloropyrimidine reacts with glyoxal under the conditions of the above condensations. This is in agreement with the results of Whittaker,[2] who condensed *p*-nitrobenzaldehyde with 5-aminopyrimidine only under drastic conditions. The presence of at least one electron-releasing group, in addition to the 5-amino-group, appears to be essential for such reactions.

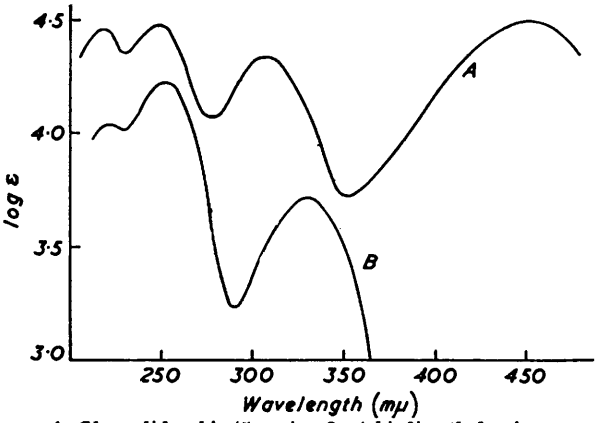
An attempt was made to synthesise a bisdihydropurinyl also by reaction of oxalyl

FIG. 1. *Absorption spectra in ethanol.*



A, Bis-(6-chloro-8 : 9-dihydro-9-methylpurin-8-yl).
B, 5-Amino-6-chloro-4-methylaminopyrimidine.

FIG. 2. *Absorption spectra in ethanol.*



A, Glyoxylidenebis-(5-amino-2 : 4-bisdimethylaminopyrimidine).
B, 5-Amino-2 : 4-bisdimethylaminopyrimidine.

chloride with 4 : 6-bismethylamino-5-nitropyrimidine to give the amide (V), which on reduction and cyclisation would give a bispurin-8-yl derivative. The product, although giving analyses as for the dihydrochloride of (V), was hydrolysed to the original pyrimidine by boiling water or cold dilute sodium hydrogen carbonate solution. Reduction in the presence of platinum oxide or Raney nickel gave 5-amino-4 : 6-bismethylaminopyrimidine. A compound with similar properties, and presumably with a similar structure, was obtained by reaction of oxalyl chloride with 2 : 4-bisdimethylamino-5-nitropyrimidine. We therefore propose the quaternary salt structures (VI; R = H, R′ = R″ = NHMe; and R = R′ = NMe_2, R″ = H, or the 3-isomer) for these products.

Purrmann,[3] in an attempt to synthesise xanthopterin, condensed 2 : 4 : 5-triamino-6-hydroxypyrimidine with chloral, and obtained a strongly fluorescing material, $C_{10}H_{12}O_3N_{10}$, of unknown structure. Repetition of this reaction in acetate buffer gave an apparently identical material, isolated as the crystalline sodium salt. The ultraviolet absorption spectrum of this compound (see Table) resembles that of the azomethine (IV), and differs from those of the bisdihydropurinyls and the azomethines formed by condensation of glyoxal with a 4-aminopyrimidine. We assigned structure (IV; $R^1 = R^3 = NH_2$,

[2] Whittaker, *J.*, 1951, 1565.
[3] Purrmann, *Annalen*, 1941, **548**, 284.

Absorption spectra (in water).

Substance	$\lambda_{max.}$ (mμ)	ε	pH
5-Amino-2-hydroxy-4-methylaminopyrimidine	222; 294	8850; 5280	1
Bis-(8 : 9-dihydro-2-hydroxy-9-methylpurin-8-yl)	233; 330	20,150; 11,000	1
5-Amino-4-methylaminopyrimidine	205; 288	14,300; 8700	7
Bis-(8 : 9-dihydro-9-methylpurin-8-yl)	209; 305	29,500; 15,300	7
5-Amino-4 : 6-bismethylaminopyrimidine	224; 286 [a]	25,100; 10,250	—
Bis-(8 : 9-dihydro-9-methyl-6-methylaminopurin-8-yl)	227; 292 [a]	46,400; 21,400	—
Azomethine (IV; $R^1 = R^3 = NH_2$, $R^2 = R^4 = OH$)	<220; 230; 258; 410	>17,300; 17,340; 15,340; 33,340	13
4-Amino-2 : 6-dihydroxypyrimidine	220; 266	1600; 3580	13
Glyoxylidenebis-(4-amino-2 : 6-dihydroxypyrimidine)	222; 245; 274	15,590; 12,160; 12,800	13
6-Amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine	<220; 266	>2890; 20,950	7
Glyoxylidenebis-(6-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine)	<220; 240; 274	>16,100; 13,980; 18,980	7

[a] In ethanol.

$R^2 = R^4 = OH$) to this compound. Treatment with dilute mineral acid gives xanthopterin, presumably by cleavage of the azomethine linkage followed by ring closure. Condensation of 2 : 4 : 5-triamino-6-hydroxypyrimidine with chloral in acid solution gives xanthopterin in 36% yield: this compares favourably with other more lengthy syntheses of xanthopterin.[4]

Experimental

Yields of substances that have no definite m. p. refer to the stage when they appeared homogeneous in paper chromatography in butanol–5N-acetic acid (7 : 3) on being viewed in ultraviolet light of wavelengths 254 and 365 mμ.

Bis-(8 : 9-dihydro-2-hydroxy-9-methylpurin-8-yl).—5-Amino-2-hydroxy-4-methylaminopyrimidine [5] (2·67 g.) was dissolved in water (55 c.c.) at 50°, and glyoxal (2·67 g. of 50% aqueous solution) in water (27 c.c.) was added. A bright yellow precipitate was formed almost immediately, and this rapidly changed colour to buff. The mixture was heated at 50° for 15 min., and the solid (2·3 g., 80%) was collected, washed with warm water, and dried. A sample was purified by dissolution in dilute hydrochloric acid, filtering, and addition of dilute sodium hydroxide solution to pH 9—10; *bis-(8 : 9-dihydro-2-hydroxy-9-methylpurin-8-yl)* was precipitated as pale yellow needles, m. p. >300° (Found: C, 47·9; H, 5·0; N, 36·8. $C_{12}H_{14}O_2N_8$ requires C, 47·7; H, 4·7; N, 37·1%). The bisdihydropurinyl is soluble in dilute alkali; it could not be methylated by using diazomethane, methyl sulphate and alkali, or methyl iodide and potassium carbonate.

Bis-(8 : 9-dihydro-9-methylpurin-8-yl).—5-Amino-4-methylaminopyrimidine [6] (0·69 g.) was dissolved in boiling water (3 c.c.), and a solution of solid polyglyoxal (0·161 g.) in boiling water (4 c.c.) was added. The solution was refluxed for 1 hr., and chilled overnight. The solid (0·58 g., 80%) was collected and recrystallised from ethanol–water, to give the *bisdihydropurinyl* as colourless needles, m. p. *ca.* 270° (decomp.) (Found: C, 53·2; H, 5·0; N, 41·2. $C_{12}H_{14}N_8$ requires C, 53·3; H, 5·2; N, 41·5%).

Bis-(6-chloro-8 : 9-dihydro-9-methylpurin-8-yl).—5-Amino-6-chloro-4-methylaminopyrimidine [6] was condensed with polyglyoxal as above to give the *bischlorodihydropurinyl* as colourless needles (65%), m. p. *ca.* 270° (decomp.) [Found: C, 42·5; H, 3·8; N, 32·9; Cl, 20·8%; *M* (Rast), 320, 340. $C_{12}H_{12}N_8Cl_2$ requires C, 42·5; H, 3·6; N, 33·1; Cl, 20·9%; *M*, 339].

5-Amino-4 : 6-bismethylaminopyrimidine.—4 : 6-Bismethylamino-5-nitropyrimidine [6] (0·45 g.) in ethanol (50 c.c.) was hydrogenated over Raney nickel at room temperature and pressure. The catalyst was filtered off and washed with hot ethanol. The combined filtrates were taken to dryness *in vacuo*, and the residue sublimed at 110° (bath)/0·005 mm., to give *5-amino-4 : 6-bismethylaminopyrimidine*, m. p. 150° (decomp.) (Found: C, 47·3; H, 7·2; N, 45·5. $C_6H_{11}N_5$ requires C, 47·0; H, 7·2; N, 45·7%).

Bis-(8 : 9-dihydro-9-methyl-6-methylaminopurin-8-yl).—(*a*) To the above crude ethanolic solution of 5-amino-4 : 6-bismethylaminopyrimidine was added polyglyoxal (0·075 g.) in water

[4] Albert and Wood, *J. Appl. Chem.*, 1952, **2**, 591; Korte and Fuchs, *Chem. Ber.*, 1953, **86**, 114.
[5] Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[6] *Idem, ibid.*, 1954, **4**, 72.

(10 c.c.), and the mixture was heated on the steam-bath for 10 min. The solution was concentrated *in vacuo* to *ca.* 5 c.c., and chilled overnight to give the *bisdihydropurinyl* as colourless needles (from ethanol), m. p. 260° (decomp.) (Found: C, 50·9; H, 5·5; N, 43·2. $C_{14}H_{20}N_{10}$ requires C, 51·2; H, 6·1; N, 42·7%).

(*b*) Bis-(6-chloro-8 : 9-dihydro-9-methylpurin-8-yl) (0·05 g.) and 33% ethanolic methylamine (1 c.c.) were heated in a sealed tube for 5 hr., at 125°, then cooled. The solid, recrystallised from ethanol, gave the bisdihydropurinyl, m. p. 258° (decomp.).

2 : 4-*Bisdimethylamino-5-nitropyrimidine*.—2 : 4-Dichloro-5-nitropyrimidine [7] (1 g.) was suspended in ethanol (20 c.c.), and 33% ethanolic dimethylamine (3 c.c.) was added dropwise. The solution was stirred for 30 min., then filtered, and the filtrate was taken to dryness. The residue was sublimed and recrystallised from light petroleum (b. p. 60—80°), to give 2 : 4-*bisdimethylamino-5-nitropyrimidine* (1 g., 92%) as yellow needles, m. p. 88—92° (Found: C, 45·7; H, 5·5; N, 33·7. $C_8H_{13}O_2N_5$ requires C, 45·5; H, 6·2; N, 33·2%).

5-*Amino*-2 : 4-*bisdimethylaminopyrimidine*.—The above nitro-compound was hydrogenated over Raney nickel in the usual way, to give 5-*amino*-2 : 4-*bisdimethylaminopyrimidine* as white needles, m. p. 92—96°, after sublimination at 90° (bath)/0·01 mm. (Found: C, 53·7; H, 7·9; $C_8H_{15}N_5$ requires C, 53·0; H, 8·3%). The mixed m. p. with 5-nitro-derivative was 66—84°.

Azomethine of Glyoxal and 5-*Amino*-2 : 4-*bisdimethylaminopyrimidine*.—5-Amino-2 : 4-bisdimethylaminopyrimidine (0·2 g.) was dissolved in a mixture of hot water (10 c.c.) and ethanol (3 c.c.), and a solution of polyglyoxal (0·038 g.) in hot water (5 c.c.) added, yielding a precipitate at once. The mixture was heated on the steam-bath for 2 min., and cooled, giving *glyoxylidenebis*-(5-*amino*-2 : 4-*bisdimethylaminopyrimidine*) as bright red needles (from aqueous ethanol), m. p. 195—199° (Found: C, 56·7; H, 6·7; N, 36·7. $C_{18}H_{28}N_{10}$ requires C, 56·2; H, 7·3; N, 36·5%). The azomethine was immediately hydrolysed by cold N-hydrochloric acid.

5-*Aminopyrimidine*.—Hydrogenation of 5-amino-4 : 6-dichloropyrimidine, in the presence of magnesium oxide and palladium–charcoal, gave 5-aminopyrimidine, m. p. 169—171°. Whittaker [2] obtained this compound in a similar manner from 5-amino-2 : 4-dichloropyrimidine.

Neither 5-aminopyrimidine nor 5-amino-4 : 6-dichloropyrimidine [6] reacted with glyoxal when refluxed for several hours in water or ethanol.

Oxalylbis-1-(4 : 6-*bismethylamino-5-nitropyrimidinium Chloride*).—To a solution of 4 : 6-bismethylamino-5-nitropyrimidine (0·5 g.) in dry boiling benzene (200 c.c.) was added a solution of redistilled oxalyl chloride (0·11 c.c.) in dry benzene (10 c.c.). The solution was refluxed for 30 min., during which a precipitate was gradually formed. The pale yellow *quaternary salt* (0·43 g., 65%), collected and dried *in vacuo*, had m. p. 255° (decomp.) (Found: C, 34·5; H, 4·5; N, 28·5; Cl, 14·7. $C_{14}H_{18}O_6N_{10}Cl_2$ requires C, 34·1; H, 3·7; N, 28·4; Cl, 14·4%).

4 : 6-Bismethylamino-5-nitropyrimidine did not react when fused with oxalic acid for 30 min. at 160°.

Oxalylbis-1(or 3)-(2 : 4-*bisdimethylamino-5-nitropyrimidinium Chloride*).—2 : 4-Bisdimethylamino-5-nitropyrimidine with oxalyl chloride in ether gave the *pyrimidinium salt* as yellow crystals, m. p. 154—158° (Found: C, 39·2; H, 5·0; N, 25·2. $C_{18}H_{26}O_6N_{10}Cl_2$ requires C, 39·3; H, 4·8; N, 25·5%).

Condensation of 2 : 4 : 5-*Triamino*-6-*hydroxypyrimidine with Chloral*.—(*a*) Triaminohydroxypyrimidine sulphate monohydrate (2 g.) and crystalline sodium acetate (6 g.) were dissolved in water (100 c.c.) containing sodium dithionite (50 mg.). Chloral hydrate (1·4 g.) was added and the mixture kept at room temperature for 2 days. The yellow precipitate (1·3 g.) was collected, washed with water, and dissolved in boiling 2N-sodium hydroxide (25 c.c.). On cooling, *sodium* N-(2 : 4-*diamino*-6-*hydroxypyrimidin*-5-*yl*)-α-(2 : 4-*diamino*-6-*hydroxypyrimidin*-5-*ylimino*)*acetimidoate* (IV; $R^1 = R^3 = NH_2$, $R^2 = OH$; $R^4 = ONa$) crystallised as yellow needles (Found: C, 35·3; H, 3·4; N, 40·5. $C_{10}H_{11}O_3N_{10}Na$ requires C, 35·1; H, 3·2; N, 40·9%).

This azomethine (0·15 g.) was heated in 2N-hydrochloric acid (10 c.c.) on the steam-bath for 30 min. Ammonia was added to pH 4·8, and after refrigeration crude xanthopterin (0·08 g.) was collected and purified as below, to give material with an identical absorption spectrum.

(*b*) Triaminohydroxypyrimidine sulphate monohydrate (2 g.) was dissolved in a mixture of concentrated sulphuric acid (24 c.c.) and water (4 c.c.). Chloral hydrate (1·4 g.) was added, and the mixture was heated on the steam-bath for 1 hr., whereafter evolution of hydrogen chloride had largely ceased. The cooled solution was poured on cracked ice (100 g.), and the pH taken to 4·8 with ammonia. After refrigeration overnight, the yellow-brown precipitate was collected, washed successively with water, ethanol, and ether, and dried *in vacuo*. The

[7] Brown, *J. Appl. Chem.*, 1952, **2**, 239

xanthopterin (0·55 g., 36%) was purified *via* the crystalline barium salt as described by Korte and Fuchs.[4] Light absorption in water (pH 13): $\lambda_{max.}$ 255 and 392 mμ (log ε 4·26 and 3·84 respectively).

Azomethine from Glyoxal and 4-Amino-2 : 6-dihydroxypyrimidine.—Polyglyoxal (0·23 g.) in warm water (20 c.c.) was added to a solution of 4-amino-2 : 6-dihydroxypyrimidine [8] (1 g.) in boiling water (200 c.c.), a precipitate being formed almost immediately. The mixture was refluxed for 1 hr., and the solid (0·35 g.) was collected at 95—100°. This material was purified by dissolving it in hot 2N-sodium carbonate (20 c.c.), to give a red solution from which *glyoxylidenebis-(4-amino-2 : 6-dihydroxypyrimidine)*, m. p. >360°, was precipitated with dilute hydrochloric acid (Found: C, 43·7; H, 2·9; N, 30·0. $C_{10}H_8O_4N_6$ requires C, 43·5; H, 2·9; N, 30·4%).

Azomethine from Glyoxal and 6-Amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine.—Similar condensation of glyoxal with the pyrimid-dione [9] gave *glyoxylidenebis-(6-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine)* as colourless needles (68%) (from water), m. p. >300° (Found: C, 50·6; H, 4·4; N, 25·3. $C_{14}H_{16}O_4N_6$ requires C, 50·6; H, 4·9; N, 25·3%).

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[8] Ruttink, *Rec. Trav. chim.*, 1946, **65**, 764.
[9] Speer and Raymond, *J. Amer. Chem. Soc.*, 1953, **75**, 114.